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Synthesis and Applications of Lithium, Sodium and Potassium Organometallics in Continuous Flow

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Erklärung

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1) "Preparation of Functionalized Aryl, Heteroaryl, and Benzylic Potassium Organometallics Using Potassium Diisopropylamide in Continuous Flow"

   J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed*. **2020**, *59*, 12321 – 12325. (Hot Paper, Cover Picture)

2) "Continuous Flow Preparation of (Hetero)benzylic Lithiums via Iodine-Lithium Exchange Reaction under Barbier Conditions"

   N. Weidmann, J. H. Harenberg, P. Knochel, *Org. Lett.* **2020**, *22*, 5895 – 5899.

3) "Continuous Flow Sodiation of Substituted Acrylonitriles, Alkenyl Sulfides and Acrylates"

   J. H. Harenberg, N. Weidmann, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed*. **2021**, *60*, 731 – 735.

4) "(2-Ethylhexyl)sodium: A Hexane-Soluble Reagent for Br/Na-Exchanges and Directed Metalations in Continuous Flow"

   J. H. Harenberg, N. Weidmann, A. J. Wiegand, C. A. Hoefer, R. R. Annapureddy, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 14296 – 14301.

5) "Continuous Flow Preparation of Benzylic Sodium Organometallics"

   J. H. Harenberg, R. R. Annapureddy, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed*. **2022**, *61*, e202203807.

6) "In Situ Quench Reactions of Enantioenriched Secondary Alkyllithium Reagents in Batch and Continuous Flow Using an I/Li-Exchange"

   A. Kremsmair, H. R. Wilke, J. H. Harenberg, B. R. G. Bissinger, M. M. Simon, N. Alandini, P. Knochel, *Angew. Chem. Int. Ed.* **2023**, *62*, e202214377.

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7) "Halogen-Lithium Exchange of Sensitive (Hetero)aromatic Halides under Barbier Conditions in a Continuous Flow Set-Up,"

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8) "Continuous-Flow Reactions Mediated by Main Group Organometallics"

J. H. Harenberg, N. Weidmann, P. Knochel, *Synlett*, **2021**, *31*, 1880 – 1887.

9) "Preparation and reactions of polyfunctional magnesium and zinc organometallics in organic synthesis"

A. Kremsmair, J. H. Harenberg, K. Schwärzer, A. Hess, P. Knochel, *Chem. Sci*. **2021**, *12*, 6011 – 6019.

10) "Organometallic Synthesis in Flow"

J. H. Harenberg, B. Heinz, D. Djukanovic, N. Weidmann, R. R. Annapureddy, B. Martin, P. Knochel, in *Comprehensive Organometallic Chemistry IV* (Eds.: G. Parkin, K. Meyer, D. O'hare), Elsevier, Oxford, **2022**, pp. 331.

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11) *BASF International Summer Course*, **2022**, Ludwigshafen, Germany.

12) *19th Austrian Chemistry Days*, **2022**, Vienna, Austria.

Abbrevations:

°C	degree Celsius
A	absorbance
Å	Ångström
A	area
a	interfacial area
Ac	acetyl
aq.	*aqueous*
Ar	undefined aryl substituent
ATR	attenuated total reflection
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BPR	back pressure regulator
Bpy	2,2´-dipyridyl
Bu	butyl
C	concentration
calcd.	calculated
CCDC	Cambridge crystallographic data centre
CIPE	complex induced proximity effect
cm	centimetre
conc.	concentrated
CTFR	copper tube flow reactors
Cy	cyclohexyl
d	doublet
D	molecular diffusivity
d.r.	diastereomeric ratio

Da_{II}	second Damköhler number
DCM	dichloromethane
d_h	hydraulic diameter
DIPEA	*N*,*N*-di*iso*propylethylamine
DMEA	*N*,*N*-dimethylethylamine
DMF	*N*,*N*-dimethylformamide
DMU	*N*,*N*′-dimethylurea
D*o*M	directed *ortho* metalation
DTBB	4,4'-di-*tert*-butylbiphenyl
e. g.	for example
E_A	activation energy
ee	enantiomeric excess
EI	electron impact ionization
EPR	Electron paramagnetic resonance
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
Et_2O	diethylether
Et_3N	triethylamine
EtOAc	ethyl acetate
eV	electronvolt
E-X	electrophile
FEP	fluorinatedethylenepropylene
FG	functional group
FT-IR	fourier-transform infrared spectroscopy
g	gram

GC	gas chromatography
GCMS	gas chromatography–mass spectrometry
h	heat transfer coefficient
h	hour
Hal	halogen
Het	undefined heteroaryl substituent
Hex	hexyl
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectra
Hz	hertz
i	*iso*
i. e.	that means
I.D.	inner diameter
Inj	injection
IR	infrared spectroscopy
J	coupling constant
K	kelvin
k	reaction rate constant
KDA	potassium diisopropylamide
kg	kilogram
kV	kilovolt
L	diffusion distance
l	length
L	liter
LDA	lithium diisopropylamide
m	meter

M	molarity
m	multiplet
m. p.	melting point
mA	milliampere
mbar	millibar
Me	methyl
Me_6Tren	tris[2-(dimethylamino)ethyl]amine
Mes	mesityl
Met	undefined metal
MFC	mass flow controller
mg	milligram
MHz	mega hertz
min	minute
mL	millilitre
mm	millimetre
mmol	millimol
MS	mass spectra
Ms	methanesulfonyl
NaDA	sodium diisopropylamide
NaTMP	sodium 2,2’,6,6’-tetramethylpiperidide
NMR	nuclear magnetic resonance spectroscopy
Np	naphthalenide
o	*ortho*
O.D.	outer diameter
Oct	octyl
p	*para*

Pent	pentyl
PFA	perfluoroalkoxy alkanes
Ph	phenyl
PMDTA	*N*,*N*,*N′*,*N″*,*N″*-pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
PTFE	polytetrafluoroethylene
q	heat flux
q	quartet
r	radius
R	undefined organic substituent
R	universal gas constant
s	*sec*
s	second
s	singulet
sat.	*saturated*
SLAB	super linear alkylbenzene
T	temperature
t	*tert*
t	time
t	triplet
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TLC	thin-layer chromatography

t_m	mixing time
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMPH	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TP	typical procedure
t_r	reaction time
t_{res}	residence time
Ts	toluenesulfonyl
UV	ultraviolet
UV/Vis	Ultraviolet–visible spectroscopy
V	volume
wt%	weight percentage
ε	molar attenuation coefficient
ν	flow rate

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A. INTRODUCTION

1. OVERVIEW

Since the earliest days of organic synthesis, chemists were searching for reactions which result in carbon-carbon or carbon-heteroatom bond formations. Thinking about the terminology of "Organic Synthesis" this is little surprising. Both terms date back to the days of Aristotle and origin from ancient Greek. Whereas organic (οργανον, *organon*) is nowadays seldomly used in its original meaning as "instrument", the meaning of synthesis remained unchanged *syn* (σύν) can be translateted as together and *thesis* (θεσις) translates to put or place,[1] combining those two syllables one realises that the tasks of synthetic chemists are already written in their names.

Almost 200 years ago Friedrich Wöhler discovered that the treatment of lead oxycyanate with ammonia did not result in the expected ammonium cyanate, but instead a new carbon–nitrogen bond was formed and urea was obtained.[2] Within the two centuries after Wöhler´s urea synthesis, which is considered as the onset of organic synthesis,[3] the field expanded and a plethora of methods for the generation of diverse and complex organic compounds has been developed.[4] Organometallic chemistry in general and the Nobel prize awarded transition metal catalysed cross-coupling reactions in particular, established themselves as powerful tools in organic synthesis enabling new kinds of bond formations in polyfunctionalized molecules. Nevertheless, the need for new reactions capable of forming new bonds between carbon and other atoms remains unbroken.[5]

In recent years another challenge arose, especially in times of energy and resource shortages and with the global warming being more apparent, chemistry is determined to become more sustainable.[6] Reaction conditions need to be adapted and well established but unsustainable reagents require replacements.[7] A prime example for such a class of reagents are organolithium compounds. Due to their high reactivity they are ubiquitous in the field of organic synthesis and found applications as nucleophiles in addition,[8] substitution[9] and cross-coupling reactions[10] and as lithiating reagents in either halogen lithium exchanges[11] or directed metalations.[12] However from a green chemistry perspective lithium compounds are problematic. The occurrence of lithium in the earth crust is rather limited and

[1] C. Wentrup, *Eur. J. Org. Chem.* **2022**, *2022*, e202101492.
[2] F. Wöhler, *Ann. Phys.* **1828**, *88*, 253.
[3] K. C. Nicolaou, *Angew. Chem. Int. Ed.* **2013**, *52*, 131.
[4] a) K. C. Nicolaou, S. Rigol, *Nat. Prod. Rep.* **2020**, *37*, 1404; b) N. Wang, Z. Wu, J. Wang, N. Ullah, Y. Lu, *Chem. Soc. Rev.* **2021**, *50*, 9766.
[5] D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383.
[6] I. T. Horváth, *Chem. Rev.* **2018**, *118*, 369.
[7] N. A. Stini, P. L. Gkizis, C. G. Kokotos, *Green Chem.* **2022**, *24*, 6435.
[8] H. Yamataka, K. Yamada, K. Tomioka, in *PATAI'S Chemistry of Functional Groups*, **2009**.
[9] L. H. Sommer, W. D. Korte, *J. Org. Chem.* **1970**, *35*, 22.
[10] S. Hazra, C. C. C. Johansson Seechurn, S. Handa, T. J. Colacot, *ACS Catal.* **2021**, *11*, 13188.
[11] W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1.
[12] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.

its use in other industries, leads to a rapid consumption of the lithium stock.[13] From an economic point of view replacing lithium by a more cost-efficient alternative would likewise be desirable. Especially its use in battery technologies led to a price explosion. The cost of lithium carbonate increased by the factor of 5.4 within the last year from the 16th of July 2021 to the 15th of July 2022.[14]

The heavier alkali metals such as sodium and potassium might offer intriguing alternatives. Other than lithium, sodium and potassium are among the most common elements in the earth crust. Sodium deposits exceed the one of lithium by three orders of magnitude.[15] However apart from the early years of organoalkali chemistry, sodium and potassium organyls received little attention.[16] One of the major drawbacks in organosodium and organopotassium chemistry is the poor solubility and stability of most sodium and potassium organyls in commonly used hydrocarbon solvents. Furthermore, frequently used ethereal solvents such as tetrahydrofuran (THF) are no suitable alternative since they lead to decomposition if the solution is not stored at cryogenic temperatures.[17] In order to replace the comparably easy to handle lithium chemistry, the heavier alkalimetal reagents need to be soluble in organic solvents and either be stable enough to store and transport or readily producible by on-demand procedures.[18]

However, aforementioned obstacles in sustainability cannot be overcome solely by developing new atom economic reactions but also require a look into the working methods in organic chemistry. Whereas the analytical capabilities improved significantly over the last decades, the equipment used for the manipulation of organic compounds did not develop in a similar way and the vast majority of reactions is still conducted in a glass flask. The versatility, thermal resistance and durability of the flask allow convenient synthesis on a milligram or gram scale. If however, reactions are run at bigger quantities, flasks and related reactor vessels reach their limits.[19] Continuous flow technology avoids problems in scalability and additionally bears characteristics which may increase the sustainability of a reaction. The most obvious contributions this technology brings to the table are the excellent heat transfer attributed to the big surface to volume ratio inherent to most continuous flow reactors, the reduced need for solvents, the increased mass transfer probabilities which avoid local hot spots and therefore reduce unwanted side reactions and decrease possible hazards which origin from exothermic

[13] G. Martin, L. Rentsch, M. Höck, M. Bertau, *Energy Storage Mater.* **2017**, *6*, 171.
[14] Lithium carbonate price: 86 842 ¥/t (16th of July 2021); 469 737 ¥/t (15th of July 2022) https://tradingeconomics.com/commodity/lithium; retrived 15th of July 2022.
[15] N. N. Greenwood, A. Earnshaw, *Chemistry of the Elements*, Elsevier, Amsterdam, **2012**.
[16] a) D. Seyferth, *Organometallics* **2006**, *25*, 2; b) D. Seyferth, *Organometallics* **2009**, *28*, 2; c) T. X. Gentner, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2021**, *60*, 9247.
[17] a) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544; b) Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312.
[18] D. B. Collum, R. A. Woltornist, Y. Ma, R. F. Algera, Y. Zhou, Z. Zhang, *Synthesis* **2020**, *52*, 1478.
[19] a) J.-i. Yoshida, *Flash Chemistry: fast organic synthesis in microsystems* J.-i. Yoshida, John Wiley & Sons, Ltd, Chichester United Kingdom, **2008**; b) M. Rodriguez-Zubiri, F.-X. Felpin, *Org. Process Res. Dev.* **2022**, *26*, 1766; c) H.-L. Qian, S.-T. Xu, X.-P. Yan, *Anal. Chem.* **2023**, *95*, 304.

reactions. Those features render flow chemistry as one of the primary keys for sustainable manufacturing.[20]

[20] a) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; b) L. Rogers, K. F. Jensen, *Green Chem.* **2019**, *21*, 3481; c) M. Kleoff, J. Schwan, M. Christmann, P. Heretsch, *Org. Lett.* **2021**, *23*, 2370.

2. CONTINUOUS FLOW

2.1 Continuous Flow Set-Up

Continuous flow set-ups come in various shapes and sizes. Due to their modularity the reaction set-up can be varied according to the demand of the reaction. The simplest continuous flow devices consist of a reagent delivery system, a mixing device, a reactor and a collection unit. More sophisticated assemblies might include in-line quenching units, pressure regulators or various tools for in-line analytics and purification steps (Figure 1). Applying complex multistep sequences, which contain more than two reagent delivery devices and numerous reactors, a continuous preparation of natural products or pharmaceuticals can be achieved.[21] In the following chapters a brief overview of the different modules and their mode of action is given.

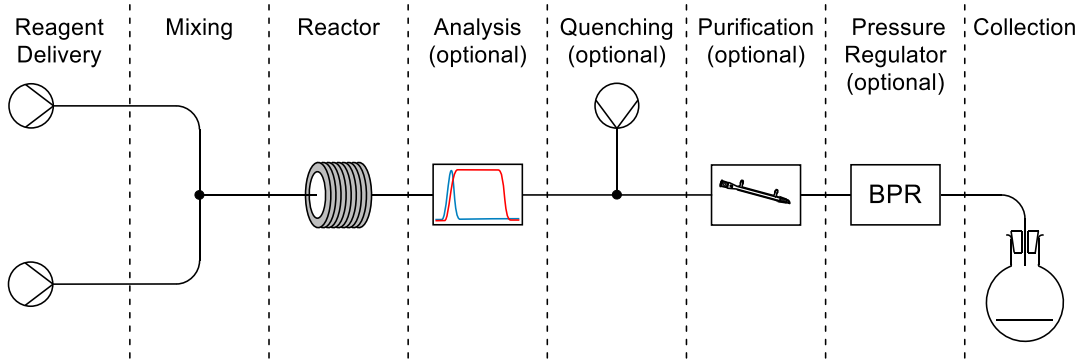


Figure 1: Schematic depiction of a continuous flow set-up.[21]

2.1.1 Reagent delivery

A key role in every continuous flow set-up play the pumping devices. Not only do they provide the system with reagents, but they also regulate stoichiometry and residence time of the reaction. The most common delivery units are syringe, HPLC and peristaltic pumps.

Smaller volumes can be accurately pumped using simple syringe pumps (Figure 2). Noteworthy, the solvents cannot be pumped continuously but instead the reaction time is predefined by the volume of the syringe in use. Moreover, syringe pumps become unreliable at higher pressures. Additionally, they require a large amount of manual control which might lead to systematic errors and therefore a lower reproducibility.[21]

[21] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.

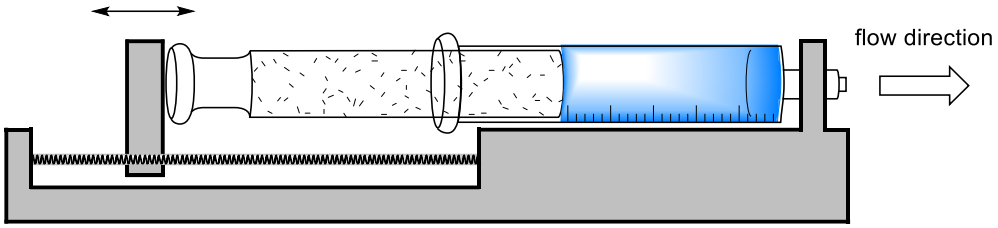


Figure 2: Schematic depiction of a syringe pump.[22]

The basic elements of an HPLC piston pumps are a cylindrical pump chamber holding a piston, which is connected to a moving cam and a pair of check valves (Figure 3). The piston is moved in and out of the pump chamber through the rotation of the moving cam. During the inlet stroke of the pump the piston is moved out of the chamber resulting in a zone of low pressure. Therefore, the outlet check valve is settled on its seat, whereas the inlet valve is lifted and solution might enter the chamber. During the outlet stroke the piston is pushed into the pump chamber pressuring the aforementioned. The inlet valve is pressed onto its seat, while the outlet valve is lifted and the solution is forced out of the chamber.[23] Those systems are able to pressurize closed systems, are physically robust and very precise. However, reagent mixtures are passing directly through the pumping chamber, which leads to an exposure of the system to possibly corrosive chemicals and can ultimately result in fouling and clogging. Additionally, periodic pressure pulses are difficult to avoid due to the nature of the pumping process and the use of volatile solvents may result in pumping problems.[22, 24]

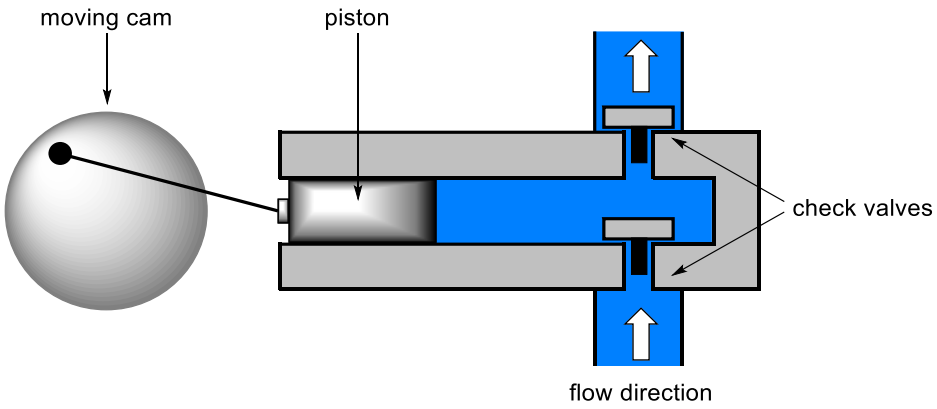


Figure 3: Schematic depiction of a HPLC pump.[22]

Peristaltic pumps consist of a moving rotor, an elastic tubing and a solid housing. The rotor pressurizes the system by pressing the elastic tubing against the walls of the housing (Figure 4). A pressure gradient is generated, the pressure in front of the rotor blade is increased whereas relaxation of the tubing results in a slipstream, which draws further solution into the pump. Similarly, to HPLC pumps a sinusoidal

[22] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.
[23] Dolan J. W., *LCGC North America* **2016**, *34*, 324.
[24] P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1192.

pressure profile is observed in simple peristaltic pumps, especially at higher flow rates. Nonlinear rotor systems overcome this problem by adjusting their rotation rates as they compress the tubing which allows a constant fluid flow rate.[25] Other than in HPLC or syringe pumps the pumping device itself is never in contact with the fluid.[26] The solutions are solely pumped through the elastic tubing which is easily replaced, if clogging or fouling might appear.

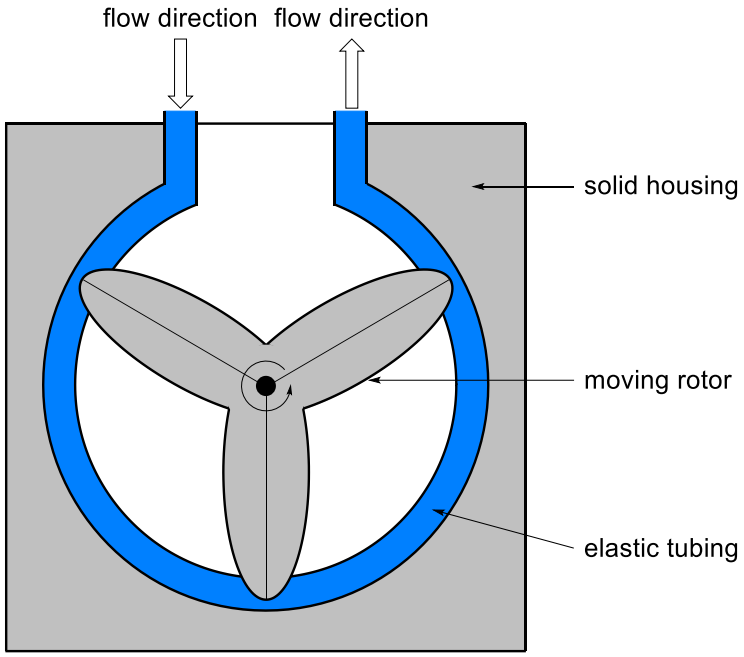


Figure 4: Schematic depiction of a peristaltic pump.[26]

One of the problems of liquid-driven pumping devices is the vast amount of solvent which is needed to transport the reaction solutions. The direct contact of the reaction solution with the solvent of the pre and post run, which is needed to drive the reaction mixture through the system, results in a diffusion profile with areas of hard to predict concentrations in the beginning and back of an injected sample. To ensure the correct stoichiometry of the reagents, the reaction mixture is usually collected only in a steady state and the pre and post run is discarded leading to large amounts of solvent and reagent waste (Figure 5a). To prolong the lifetime of the tubing and pumps, flow systems are usually stored under water or *iso*-propanol. Especially, when air or moisture sensitive reactions, for instance reactions containing organometallic reagents, are performed, the entire system has to be washed with multiple reactor volumes of anhydrous solvent. Which is again leading to a consumption of solvent before the reaction even started. Argon-driven continuous flow set-ups might reduce solvent and reagent waste. Instead of being driven by anhydrous solvent with the help of syringe, HPLC or peristaltic pumps, the sample is transported by a segmented liquid-gas flow which leads to a very distinct sample regime,

[25] P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1192.
[26] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.

since no dissolved reactant can diffuse into the gas phase (Figure 5b). Furthermore, no washing of the reactor set-up is needed, since the system can be stored under inert argon atmosphere. In gas driven set-ups the flow rate is usually controlled through a thermal mass flow controller (MFC). Especially, if reactions are performed in small sample sizes and valuable reagents are transformed for instance in natural product synthesis argon-driven flow platforms might be of great benefit.[27]

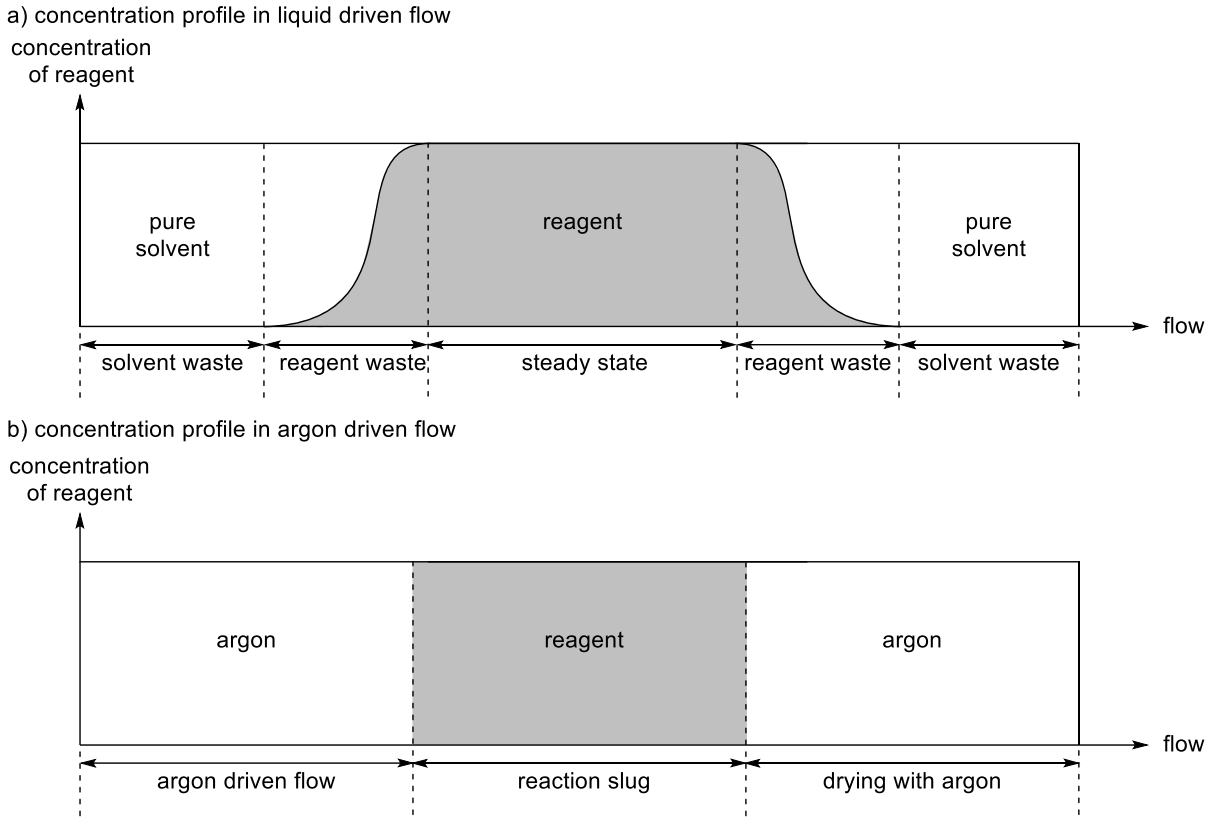


Figure 5: Concentration profile in a) a liquid driven and b) an argon driven flow set-up.[27]

2.1.2 Mixing devices

In most continuous flow assemblies, the reagents, provided by the delivering unit, are blended in a mixing device. Operationally those devices can be divided into active and passive mixing devices. Active mixers apply external energy to enhance mixing, for instance through the use of ultrasonic waves. In passive mixing only internal forces of the solution flow are used and the driving force is diffusion. The structure of passive mixers is more simple and therefore more convenient to produce and handle. The main goal is to use the energy of the stream, to restructure the flow and generate short diffusion pathways, which increase the mixing speed. There are various more or less sophisticated passive mixing devices. The simplest ones are T- or Y-shaped mixers (Figure 6). Since in Y-shaped mixers a laminar flow is usually predominant, mixing depends on molecular diffusion. The diameter of

[27] M. Kleoff, J. Schwan, M. Christmann, P. Heretsch, *Org. Lett.* **2021**, *23*, 2370.

the mixer should be as small as possible, to improve the mixing efficiency. The lower diameter come with the drawback of low production volume in a certain time period.[28]

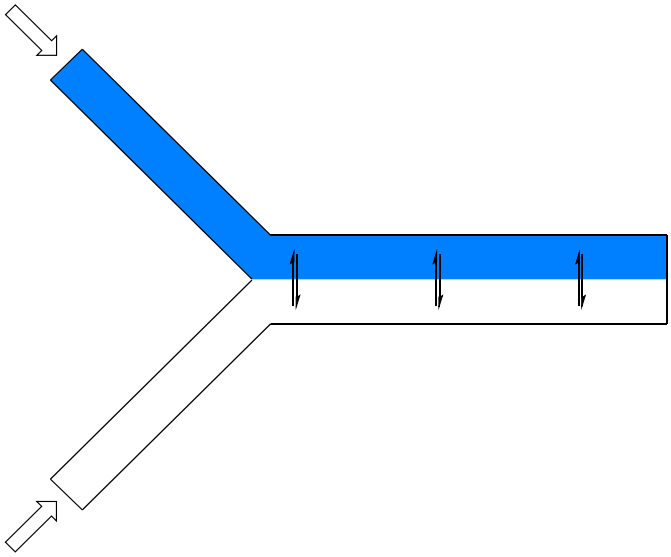


Figure 6: Schematic working principle of a Y-shaped mixer.[28b]

Those drawbacks are overcome, when multilamination micromixers are used. In multilamination mixers the incoming streams are separated in multiple parallel smaller streams, which are stacked in an alternating configuration. Upon interaction with each other the multiple laminae result in an increased overall contact area between the two streams (Figure 7). Moreover, larger volumes can be pumped without a decrease in mixing efficiency.[28b]

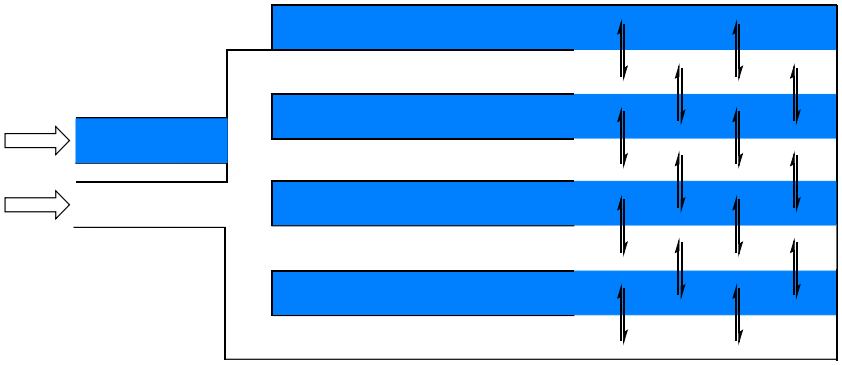


Figure 7: Schematic working principle of a multilamination mixer.[28b]

[28] a) J.-i. Yoshida, *Flash Chemistry: fast organic synthesis in microsystems* J.-i. Yoshida, John Wiley & Sons, Ltd, Chichester United Kingdom, **2008**; b) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.

Even though, their structures are equally simple as in Y-shaped mixers, T-shaped mixers often display better mixing properties. Especially at higher flow rates the predominant laminar flow regime is transformed into an engulfment flow regime leading to a faster achievement of homogeneity in the reaction mixture.[29] Not only in T-shaped mixers the flow rate is playing a key role on the mixing efficiency. In most cases higher flow rates lead to a faster mixing.[30]

Additionally, more advanced micromixers e.g. triangular,[31] split and recombine[32] or chaotic micromixers[33] might be used but are not as easily prepared and often times not commercially available.

2.1.3 Reactors

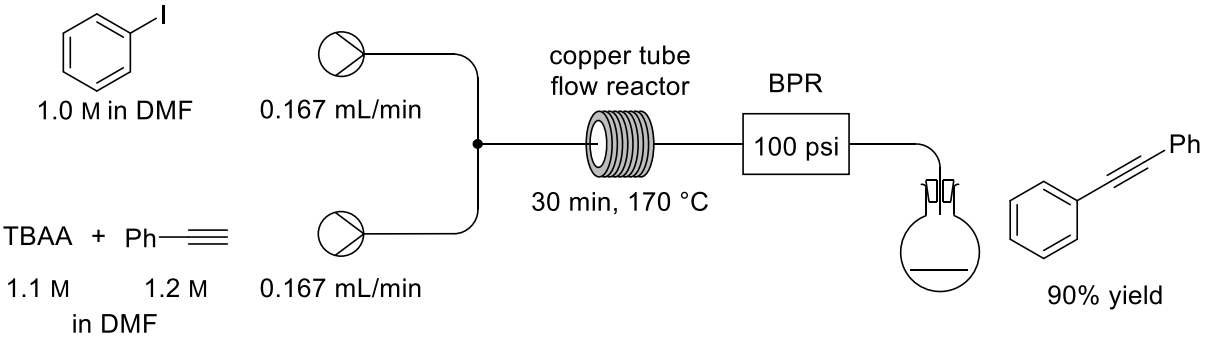
Thanks to their modular construction, continuous flow apparatuses can be easily adjusted for almost any given reaction. Numerous different reactor designs with various working principles are available. They reach from relatively simple coil-, to very complex tube-in-tube or packed-bed reactors. It is important to note, that other than in batch reactors the reaction time, more accurately the residence time in continuous flow reactors, depends on the reactor volume. The residence time (t_{res}) equals the time it takes the reagent mixture from the mixer to the quenching unit (Equation 1). To adjust the residence times, the reagents can either be pumped at a different flow rate (ν) or the reactor volume (V) can be varied. Thus, long reaction times are only seldom viable in continuous flow, lower stream velocities often result in poorer mixing and larger reactors are often not feasible due to high pressure drops and poor residence time distribution.[34]

$$t_{res} = \frac{V}{\nu} \tag{1}$$

Another significant difference between the batch and flow reactors are the concentration changes. In a batch reactor the concentration of a starting material decreases over time whereas the concentration of the product increases. In a continuous flow reactor, the concentration of the starting material and product change along the reactor unit. Concentration of the starting material is high next to the mixer and concentration of the product is high at the quenching or collecting unit. In an ideal steady state the concentration of starting material and product at a certain position in the reactor should be constant at any given time.[35]

[29] D. Bothe, C. Stemich, H.-J. Warnecke, *Chem. Eng. Sci* **2006**, *61*, 2950.
[30] J.-i. Yoshida, *Flash Chemistry: fast organic synthesis in microsystems* J.-i. Yoshida, John Wiley & Sons, Ltd, Chichester United Kingdom, **2008**.
[31] P. Löb, K. S. Drese, V. Hessel, S. Hardt, C. Hofmann, H. Löwe, R. Schenk, F. Schönfeld, B. Werner, *Chem. Eng. Technol.* **2004**, *27*, 340.
[32] a) K. Mae, T. Maki, I. Hasegawa, U. Eto, Y. Mizutani, N. Honda, *Chem. Eng. J.* **2004**, *101*, 31; b) H. Wakami, J.-i. Yoshida, *Org. Process Res. Dev.* **2005**, *9*, 787.
[33] A. D. Stroock, S. K. W. Dertinger, A. Ajdari, I. Mezić, H. A. Stone, G. M. Whitesides, *Science* **2002**, *295*, 647.
[34] P. Bianchi, J. D. Williams, C. O. Kappe, *J. Flow Chem.* **2020**, *10*, 475.
[35] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.

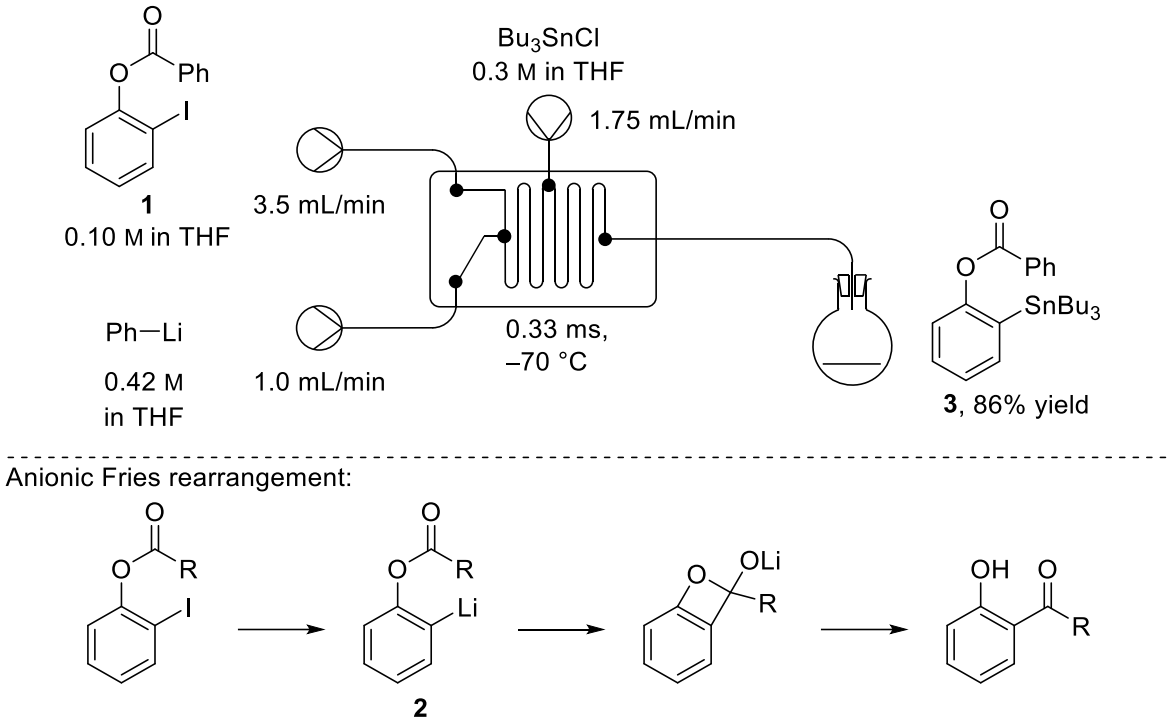
Among all the reaction vessels in continuous flow, coil reactors are the most commonly used reactor types. They are usually made out of tubing from inert polymers such as perfluoroalkoxy alkane (PFA), polytetrafluoroethylene (PTFE) or fluorinated ethylene propylene (FEP) and thus very inexpensive. Because of their low inner diameter and light permeability, polymer based coil reactors are an excellent choice for the performance of photochemical reactions. Stainless steel or other metal coils can be used, if reactions are conducted at high temperatures or pressures.[36] Copper tube flow reactors (CTFR) were applied by Novartis to perform copper catalysed decarboxylation reactions or Sonogashira- and Ullmann-couplings at high pressures and temperatures above the boiling point of DMF, which was used as solvent. In those reactions the CFTR was not only the reaction vessel but also acted as the catalyst (Scheme 1).[37]



Scheme 1: Sonogashira-coupling using a CTFR which acts as reaction vessel and catalyst.[37]

Chip reactors are closely related to coil reactors. Similar to those they are well suited for photochemical transformations, and display an even better heat transfer, which enables an excellent temperature control. Chip reactor technology became even more appealing with the recent progress in 3D-printing technology. Common materials for chip reactors are silicon, glass, different ceramics or stainless steel. Often chip reactors also include the mixing area of the reaction set-up, especially split and recombine mixers are easily prepared *via* 3D-printing.[36,38] Yoshida and co-workers invented a 3D-serpentine microchannel chip reactor for reactions, which require ultrafast mixing. Thus, they were able to perform I/Li-exchanges on *ortho*-iodophenyl esters (**1**), which are usually rapidly undergoing anionic Fries reactions. Ultra-fast mixing and extremely short residence times of 0.33 ms until the addition of the electrophile solution, enabled them to outpace this intramolecular Fries rearrangement and instead trap the lithium species **2** with different electrophiles, leading to the *ortho* substituted phenyl esters **3**. The custom made chip reactor was essential to perform reactions at such short residence times while still maintaining the temperature of –70 °C (Scheme 2).[39]

[36] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.
[37] Y. Zhang, T. F. Jamison, S. Patel, N. Mainolfi, *Org. Lett.* **2011**, *13*, 280.
[38] M. D. Symes, P. J. Kitson, J. Yan, C. J. Richmond, G. J. Cooper, R. W. Bowman, T. Vilbrandt, L. Cronin, *Nat. Chem.* **2012**, *4*, 349.
[39] H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691.



Scheme 2: I/Li-exchange on *ortho*-iodophenyl esters (**1**) using a custom made 3D-serpentine microchannel chip reactor. Mechanism of the competing anionic Fries rearrangement.[40]

As mentioned above, both coil- as well as chip-reactors are excellent choices to conduct photochemical reactions. According to the Lambert-Beer law, the light absorbance (A) is proportional to the concentration of the absorbing species (c) and the optical path length (l), with ε being the molar attenuation coefficient (Equation 2). Therefore, it is very challenging to scale photochemical reactions especially under batch conditions. By increasing the size of the reaction vessel the optical pathway is also prolonged. Due to that, the centre of the flask is not properly irradiated. In a continuous flow reactor, the optical pathways are very small, ensuring a uniform irradiation of the solution. Additionally, the reaction can be easily scaled by simply prolonging the pumping period.[41] Longer reactions times can be obtained by using oscillatory flow reactors, in which the flow direction is changed periodically. Those reactors maintain the benefits of flow chemistry, without the need of large reactor volumes for increased reaction times. [42]

$$A = \varepsilon c l \tag{2}$$

Efficient biphasic reactions rely on a high interfacial surface area on which reactions can take place or molecules can diffuse from one media to another. Various microreactors have been developed to make liquid-liquid, gas-liquid and solid-liquid reaction systems more viable. Most of them have an increased

[40] H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691.
[41] L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag, T. Noel, *Chem. Rev.* **2022**, *122*, 2752.
[42] a) H.-W. Hsieh, C. W. Coley, L. M. Baumgartner, K. F. Jensen, R. I. Robinson, *Org. Process Res. Dev.* **2018**, *22*, 542; b) P. Bianchi, J. D. Williams, C. O. Kappe, *J. Flow Chem.* **2020**, *10*, 475.

interfacial surface area compared to batch reactors. The easiest way of performing reactions between a gas and a liquid or two immiscible solvents, is in a round bottom flask. In those batch reactors the interfacial area (a) is rather small, and further decreases with increasing reactor volume. The volume (V) of a sphere increases with the radius (r) to the power of three, whereas the area of a circle (A) only increases with r^2 (Figure 8a, Equation 3, Table 1)).

$$a[m^2m^{-3}] = \frac{A}{V} = \frac{\pi r^2}{4/3\pi r^3} \quad (3)$$

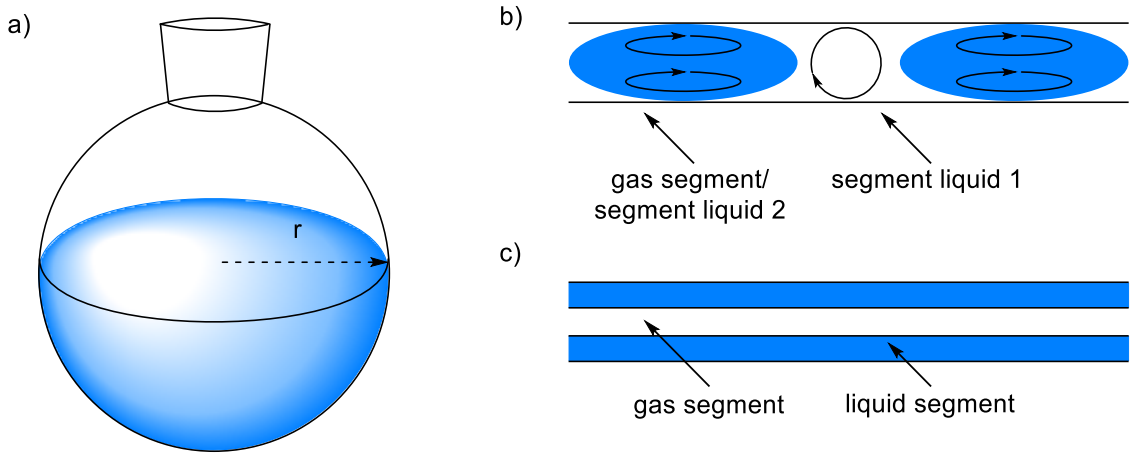


Figure 8: a) Interfacial area in a round bottom flask with a certain headspace. b) Schematic depiction of a segmented flow including toroidal currents. c) Schematic depiction of an annular flow.[43]

Tube reactors in which a segmented flow (Figure 8b) is apparent display interfacial areas which are by at least one magnitude bigger and do not decrease with larger volumes. The same holds true for annular flow regimes (Figure 8c). The interfacial areas of different gas-liquid reactors are shown in table 1. In segmented flow regimes, where gas bubbles are separated by liquid segments, toroidal currents occur in both the gaseous as well as the liquid layer and thus lead to improved homogeneity and mass transfer as can be seen in figure 8b.[43]

Table 1: Interfacial areas (a) of different reactor types.[43, 44]

Entry	Reactortype	a [m^2m^{-3}]
1	Round bottom flask (100 mL)	46
2	Round bottom flask (250 mL)	35
3	Tube reactor horizontal and coiled	50-700
4	Tube reactor vertical	100-2000
5	Gas-liquid microchannel contactor (Chen and Co-workers)	3400-9000

[43] C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2015**, *20*, 327.
[44] J. Yue, G. Chen, Q. Yuan, L. Luo, Y. Gonthier, *Chem. Eng. Sci* **2007**, *62*, 2096.

Differently from the afore described single channel microreactors, tube-in-tube reactors, invented by the group of Ley, consist of two adjacent channels, which are separated from each other by a chemically resistant semipermeable membrane.[45] In most gas-liquid reactors of this type, one channel is surrounded by the other to ensure the biggest possible surface area. Whereas one channel is filled with liquid, the other one is supplied via a MFC with the desired gas. The membranes of the inner tubing are usually made of hydrophobic Teflon AF-2400 and only permeable for gases. The applied gas will diffuse into the liquid until the liquid layer is saturated. Those type of systems have been applied for various different gases such as H_2, CO, CO_2, O_2, O_3, NH_3.[46] Kappe and co-workers used a Teflon AF-2400 tube-in-tube reactor to saturate a solution of acetonitrile with on-demand generated highly toxic HCN, which they subsequently used for hydrocynation reactions of e.g. imines and styrenes.[47] Apart from tube-in-tube reactors or single channel reactors, falling film reactors are another possibility for the performance of gas-liquid reactions.[46b]

Other than reactions with liquids or gases the handling of solids in microreactors is extremely challenging, since they may aggregate or deposit on the reactor walls, which might ultimately lead to clogging and prevent the fluids from flowing.[48] When heterogeneous catalysts or reagents are used, flow chemists often apply packed-bed reactors. Those reactors consist of a certain volume, in which a solid material is embedded between two filter units which only let the liquid stream pass. A plethora of different solid reagents reaching from immobilized enzymes and organo catalysts over heterogeneous metal catalysts to metallic reagents such as Mg or Zn can be loaded into such a bed reactor. Thus, different cartridge or column materials can be found in different set-ups. Immobilized enzymes or biocatalysts are often bound to polymers, also glass beads or silica are among others often times used as carrier materials. The columns commonly consist of stainless steel or glass.[49]

Packed-bed reactors offer certain advantages over heterogeneous reactions in batch. They avoid the need for additional filtration steps as long as the solid substrate is not leaching, reduce the manual handling of possible toxic or pyrophoric reagents, but most importantly they allow to work at higher local concentrations than obtainable in batch.[50] When for instance working with an expensive transition metal catalyst most batch reactions use sub stoichiometric amounts of catalyst, since the catalyst is either discarded or has to be recovered in tedious purification processes after the transformation is done. When performing the same reaction in a packed-bed reactor, the catalyst is usually present in higher

[45] M. O'Brien, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2010**, *12*, 1596.
[46] a) C. A. Hone, C. O. Kappe, *Chem. Eur. J.* **2020**, *26*, 13108; b) C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2015**, *20*, 327.
[47] M. Kockinger, C. A. Hone, C. O. Kappe, *Org. Lett.* **2019**, *21*, 5326.
[48] T. Noël, *Organometallic Flow Chemistry*, 1 ed., Springer, Cham, Switzerland, **2016**.
[49] G. Lin, H. Qiu, *Chem. Eur. J.* **2022**, *28*, e20220006.
[50] a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796; b) G. V. Ramaotsoa, I. Strydom, J.-L. Panayides, D. Riley, *React. Chem. Eng.* **2019**, *4*, 372; c) D. Cantillo, C. O. Kappe, *ChemCatChem* **2014**, *6*, 3286.

stoichiometry towards the reagent. Whereas the catalyst is highly concentrated in the reactor bed, the reagent solution is usually relatively diluted. Thus, when looking at the concentrations in the reactor at a given time the catalyst is present in exceedingly larger amount than the reagent. Because of this high catalyst to reagent ratio in the reactor residence times can be reduced significantly, leading to more efficient processes.[51] Furthermore, scale-up is easily done by simply pumping for longer time periods.[52] In an ideal scenario, the high local concentration of catalyst is maintained no matter the runtime. As long as the catalyst is not poisoned, deactivated in another way or leaching from the reactor, the same batch of catalyst could be used for an indefinite number of runs.

The nature and size of the heterogeneous particles is of immense importance. On the one hand, big particles display low surface to volume ratios and therefore sometimes insufficient conversions, since the heterogeneous reactions occur on the interphase. Small particles on the other hand often lead to clogging of the filter.[53]

Bed reactors might be classified into various groups. In a classic packed-bed reactor (Figure 9a), the particles are restricted in their movement. In fluidized-bed reactors (Figure 9b), the particles are floating in the liquid stream. Mixed-bed reactors (Figure 9c), behave like a combination of the two aforementioned reactors. The particles at the bottom of the reactor are moving very little, whereas particles at the top are floating through the liquid flow.[53] Additionally, immobilized reactors come in the form of monoliths, or wall coated reactors.[54]

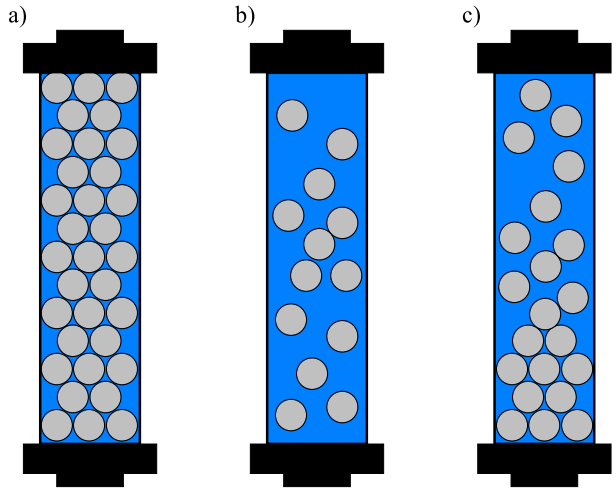


Figure 9: Schematic depiction of different bed reactors: a) Packed-bed reactor. b) Fluidized-bed reactors. c) Mixed-bed reactors.[53]

[51] E. Masson, E. M. Maciejewski, K. M. P. Wheelhouse, L. J. Edwards, *Org. Process Res. Dev.* **2022**, *26*, 2190.
[52] T. Ichitsuka, N. Suzuki, M. Sairenji, N. Koumura, S. y. Onozawa, K. Sato, S. Kobayashi, *ChemCatChem* **2019**, *11*, 2427.
[53] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.
[54] G. Lin, H. Qiu, *Chem. Eur. J.* **2022**, *28*, e20220006.

All of those bed reactors have in common, that the calculation of the residence time as well as the residence time distribution becomes increasingly more difficult and is better measured then calculated.[55]

2.1.4 Optional devices

Apart from the aforementioned essential parts and the collecting unit, a continuous flow set-up might consist of a plethora of additional and optional units. Assemblies using an **in-line quench** allow a more precise control over the reaction time, than simply collecting the reaction stream in a flask, in which the reaction might proceed. Reactions where the quench happens in a subsequent flask are often referred to as semi-batch or semi-continuous processes.[55, 56]

Back pressure regulators (BPR) apply a constant upstream pressure to the system and therefore enable the use of low boiling solvents at temperatures above their boiling point. Thus, instead of a high boiling solvent a low boiling solvent with advantageous properties can be superheated to accelerate the reaction. Pressurising and superheating continuous flow systems is additionally effective, since in contrary to most batch reactions flow assemblies eliminate the problems related to reaction headspaces. Due to the avoidance of a gaseous layer in the reactor, volatile reagents and solvents are not able to evaporate which would lead to a change in reagent concentrations.[57] Furthermore, BPRs lead to a better control of the flow rates and increase reproducibility. The working principle of a BPR is shown in figure 10. An external reference pressure on the tubing is applied to generate a resistance which introduce an upstream pressure.[55]

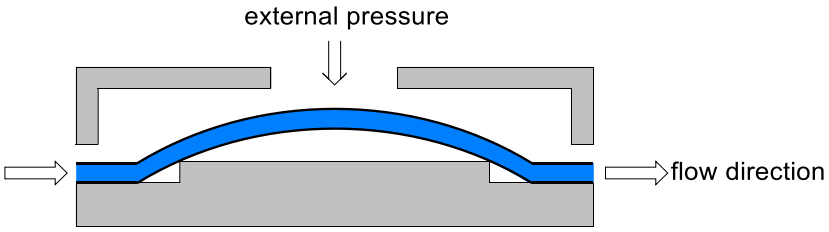


Figure 10: Schematic depiction of a back pressure regulator.[55]

Continuous flow technology offers excellent conditions for reaction screenings and kinetic/mechanistic studies, since reaction parameters, such as temperature, pressure, reaction time, stoichiometry and mixing might be precisely controlled. To further enhance these possibilities a wide range of **analytical tools** might be used for in-line analytics and reaction tracking. Thus precise real time data can be acquired without the need of taking aliquots. FTIR, Raman, UV-Vis and NMR-spectroscopy methods can be used for in-line analysis of the reaction mixture. Even though, the use of benchtop NMRs is more

[55] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.
[56] N. G. Anderson, *Org. Process Res. Dev.* **2001**, *5*, 613.
[57] N. Zaborenko, M. W. Bedore, T. F. Jamison, K. F. Jensen, *Org. Process Res. Dev.* **2011**, *15*, 131.

common, highfield NMR machines have recently been used to perform 2D NMR experiments in-line.[58] Thermal imaging cameras might be used to quantify reaction and mixing enthalpies.[59]

Online analytics in continuous flow avoid the manual collection of samples aliquots, thus reducing worktime and the possibility of human errors. Online analytics might include methods like gas chromatography (GC), mass spectroscopy (MS), high-performance liquid chromatography (HPLC), fluorescence or X-ray spectroscopy.[58b] Those real time measurements accelerate screening processes immensely and allow adjustments to the reaction parameters during an ongoing experiment or synthesis.[60]

Especially in multistep synthesis, the need for **in-line purifications** is often times given. Most purification devices consist of semipermeable membranes. Those can either be hydrophobic to perform liquid-liquid separations or in case of gas-liquid separations, the in chapter 2.1.3 described tube-in–tube reactor can be converted into a gas separator. Scavenger cartridges have frequently been applied in in-line purifications. Recently, automated in-line flash chromatography has been implemented. The set-up consists of multiple chromatography columns. While one chromatography system is engaged in an active chromatography run the others are washed and loaded with a feed of the crude reaction mixture. After a run is done the systems are automatically interchanged.[61] Continuous crystallizations and simulated moving-bed chromatography are momentarily only interesting for industrial scale.[58b]

[58] a) M. Bazzoni, C. Lhoste, J. Bonnet, K. E. Konan, A. Bernard, P. Giraudeau, F. X. Felpin, J. N. Dumez, *Chem. Eur. J.* **2023**; b) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.
[59] M. Zhang, Y. Feng, L. Lou, H. Zhang, J. Wang, Y. Yang, *Org. Process Res. Dev.* **2022**, *26*, 1506.
[60] M. Rodriguez-Zubiri, F.-X. Felpin, *Org. Process Res. Dev.* **2022**, *26*, 1766.
[61] C. G. Thomson, C. Banks, M. Allen, G. Barker, C. R. Coxon, A. L. Lee, F. Vilela, *J. Org. Chem.* **2021**, *86*, 14079.

2.2 Why Using Flow Chemistry?

Yoshida, one of the pioneers of flow chemistry, made the assumption that chemists run reactions in centimetre sized flasks and over timespans of minutes or hours because those are scales which are convenient to handle. Our hands are similarly sized and it is easier to control reactions in a time span of minutes than it is in seconds or even smaller magnitudes. However, at the molecular level reactions take place within pico- or even femtoseconds and the size of most molecules is on a nanometre scale. Even though those scales are still far from being reached, the use of microreactors in flow chemistry offers an alternative which is in closer proximity to the molecular scale (Figure 11).[62]

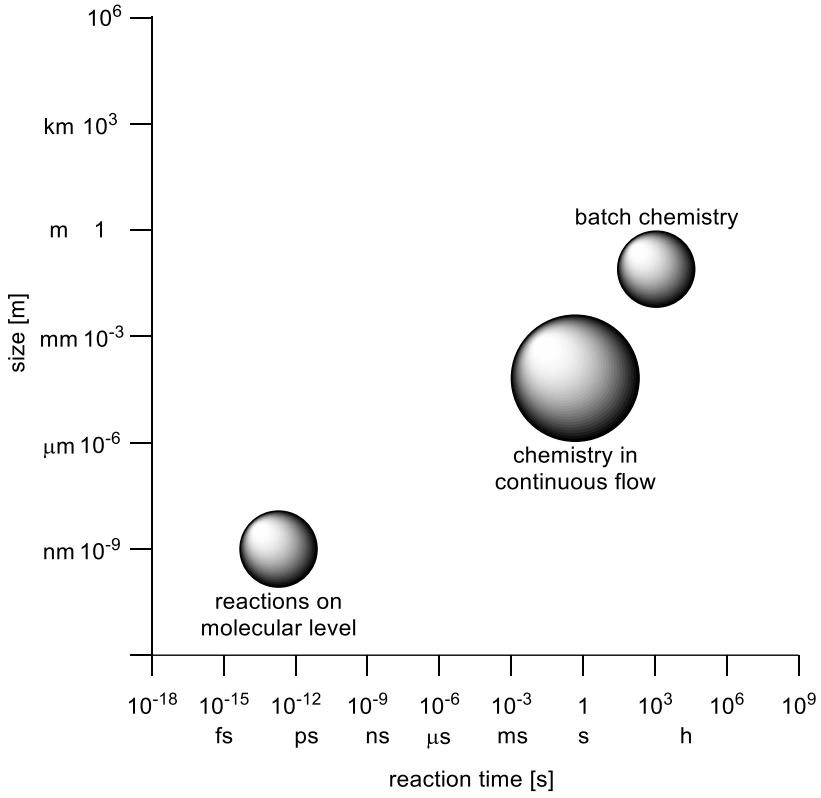


Figure 11: Relationship between reaction time and size in chemical reactions.[62]

The question arises what are the benefits of those decreased reaction times and reactor volumes and which limitations come with those characteristics?

2.2.1 Mass transport

Mass transfer rates play a key role in the kinetics and selectivity of chemical reactions. The ratio between the mixing time (t_m) and the reaction time (t_r) is defined as the second Damköhler number

[62] J.-i. Yoshida, *Flash Chemistry: fast organic synthesis in microsystems* J.-i. Yoshida, John Wiley & Sons, Ltd, Chichester United Kingdom, **2008**.

(Da_{II}) (Equation 4), which indicates whether a reaction is reaction rate controlled ($Da_{II} < 1$) or mass transfer controlled ($Da_{II} > 1$).

$$Da_{II} = \frac{t_m}{t_r} \tag{4}$$

Mass transfer controlled reaction might lead to the formation of unwanted side products and underline the enormous importance of efficient mixing in chemical reactions.[63]

As a simplification synthetic chemists often consider reactions in solution as homogenous. This only holds true for reactions where $Da_{II} < 1$. In a hypothetical reaction, the two starting materials A and B are transformed into a product P (Equation 5), which might undergo a competitive reaction with another equivalent B to give the unwanted side product S (Equation 6).

$$A + B \xrightarrow{k_1} P \tag{5}$$

$$B + P \xrightarrow{k_2} S \tag{6}$$

If it is further assumed that $k_1 \gg k_2$, one would expect that P is formed as the major product as long as the ratio between A and B is approximately one. Experimental examples often contradict this assumption and the side product S is formed in larger quantities than P. Those reactions show, that reaction selectivities are not only determined purely by the reaction rates but also by the degree to which the components are mixed. If the solutions of A and B are poorly mixed (Figure 12a), A will react with B in a first reaction interval at their peripheries and an area with a high concentration of P emerges between the areas where A and B are highly concentrated (Figure 12b). In a subsequent interval, B can only react with A, if it diffuses though the zone of high P-concentration without being trapped by a molecule of P. Otherwise it would form the unwanted side product S according to equation 6 (Figure 12c). In an extreme case of a strongly mixing controlled reaction where $Da_{II} \gg 1$ all the product P will be converted into S even though the reaction rates (k_1 and k_2) seem to favour the formation of the desired Product P.[64] This phenomenon, in which a mixing problem masks the kinetically based selectivities, is referred to as disguised chemical selectivity.[65]

[63] T. Noël, *Organometallic Flow Chemistry*, 1 ed., Springer, Cham, Switzerland, **2016**.
[64] a) A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae, J.-i. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11666; b) P. Rys, *Angew. Chem. Int. Ed.* **1977**, *16*, 807.
[65] P. Rys, *Acc. Chem. Res.* **1976**, *9*, 345.

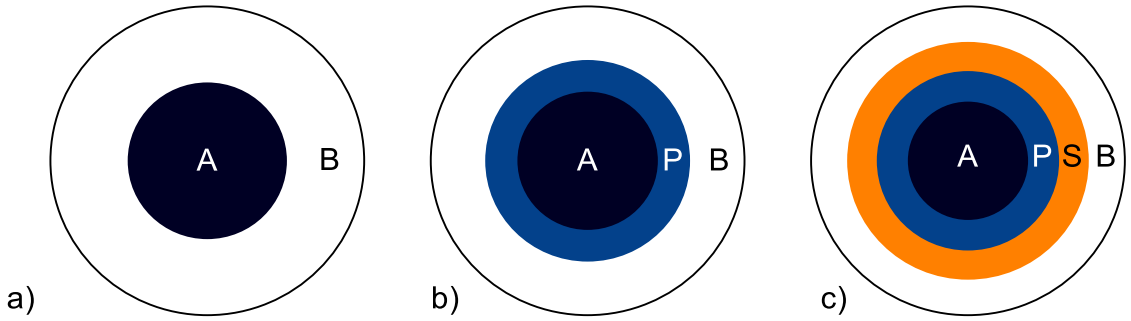


Figure 12: Schematic evolution of mixing controlled competitive consecutive reactions.[66]

As mentioned above, disguised chemical selectivity might lead to the formation of unwanted side reactions and therefore reduced efficiencies of the planned synthesis. According to equation 4 two approaches might be taken to decrease Da_{II}. Either the mixing time (t_m) might be reduced using more sophisticated mixers or the reaction time has to be prolonged (t_r). In batch chemistry the second strategy is the more common. According to the Arrhenius equation (equation 7) lowering the reaction temperature (T) decreases the reaction rate (k) and therefore slows down the reaction (with A being the pre-exponantial factor and R being the universal gas constant). Thus, cooling of the reaction vessel leads to a lower ratio of t_m to t_r and might suppress unwanted side reactions.[67]

$$k = Ae^{-\frac{E_A}{RT}} \tag{7}$$

Since the mixing time (t_m) is correlated with the diffusion distance (L), according to equation 8 decreasing the reactor size is a further approach to lower Da_{II} (D being the molecular diffusivity).

$$t_m = \frac{L^2}{D} \tag{8}$$

Micromixer technology in continuous flow intrinsically utilizes the latter strategy. The smaller diameters of the mixers, tubing and reactors offer additional levers which are lowering the Damköhler number and therefore shift the reaction towards a reaction rate controlled regime. These facts support Yoshida´s claim that smaller reaction vessels might be more suitable to study chemical reactions.[68]

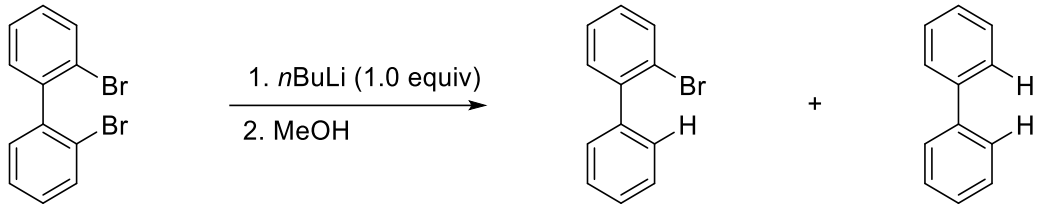
Similarly, to the hypothetical reaction above, the monolithiation of dibromoaryls through halogen-lithium-exchange and the subsequent dilithiation might be considered as competitive consecutive reactions. Yoshida used this reaction as an excellent example to demonstrate the effect of both aforementioned strategies to lower the Damköhler number and achieve reaction rate controlled conditions.

[66] A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae, J.-i. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11666.
[67] T. Noël, *Organometallic Flow Chemistry*, 1 ed., Springer, Cham, Switzerland, **2016**.
[68] J.-i. Yoshida, *Flash Chemistry: fast organic synthesis in microsystems* J.-i. Yoshida, John Wiley & Sons, Ltd, Chichester United Kingdom, **2008**.

In the present example 2,2′-dibromobiphenyl (**4**) displays the starting material A and *n*BuLi acts as starting material B which form a monolithiated intermediate representing P. Similarly, to how B was trapped by P and gave the unwanted sideproduct S in figure 12, the monolithitaed species is able to undergo a second bromine-lithium-exchange with *n*BuLi resulting in an undesired dilithiated species. Upon quenching with MeOH the monolithiated species results in the product **5**, whereas the dilithiated species gives the unwanted side product **6**. Performing the reaction at 24 °C in a batch reactor led to a reaction outcome in which the undesired dilithiated species was formed in a higher quantity than the monolithiated species (Table 2, entry 1). Considering the kinetically based selectivities monolithiated intermediate would be expected as the major product.[69] Following the approach of increasing the selectivity by reducing the temperature and therefore the reaction speed. Yoshida et al. lowered the reaction temperature stepwise and indeed achieved significantly increased ratios of **5**/**6** of up to 19:1 (entries 2-6).

The best result however was observed, when the reaction was conducted under microflow conditions. Here the second Damköhler number was decreased by reducing the mixing time (t_m), utilizing very short diffusion distances (L) instead of prolonging the reaction time (t_r). The reaction gave excellent selectivities even at 0 °C (entry 6).[70]

Table 2: Lithiation of 2,2′-dibromobiphenyl (**4**) under batch and continuous flow conditions.



4 **5** **6**

Entry	Reaction vessel	T [°C]	Yield **5** [%]	Yield **6** [%]	Ratio **5**/**6**
1	macro batch (20 mL)	24	14	34	0.41
2	macro batch (20 mL)	0	36	25	1.44
3	macro batch (20 mL)	-27	48	18	3.43
4	macro batch (20 mL)	-48	69	4	17.25
5	macro batch (20 mL)	–78	76	4	19.00
6	microflow	0	88	3	29.33

Even though flow chemistry does not change the kinetics of a chemical reaction,[71] this example shows the dramatic effect mixing can have on reaction selectivites and how continuous flow and microreactor technology might be utilized to overcome disguised chemical selectivity.

[69] T. Noël, *Organometallic Flow Chemistry*, 1 ed., Springer, Cham, Switzerland, **2016**.
[70] A. Nagaki, N. Takabayashi, Y. Tomida, J.-i. Yoshida, *Org. Lett.* **2008**, *10*, 3937.
[71] J.-i. Yoshida, *Chem. Commun.* **2005**, 4509.

2.2.2 Heat transfer

Temperature screenings are a crucial part of every reaction optimization. Not only does the temperature affect the reaction velocity but it also determines the selectivity of a reaction as it was already mentioned in the chapter above.[72]

To ensure a reliable reaction outcome, the temperature of a reaction should be maintained in a constant range. Since almost every chemical reaction produces or consumes heat, an exchange with the environment has to take place, in order to achieve approximately isothermal conditions.[73] Especially when dealing with strongly exothermic reactions, efficient heat transfer becomes essential. Extensive heat generation with inadequate heat removal might lead to runaway reactions and ultimately explosions.[72] Thus, heat transfer has to be considered during the reactor design, to guarantee reproducible results and safe handling.[73]

The temperature in the reactor is maintained constant as long as the rate (β) between the heat generation and the heat removal is ≤ 1 (equation 9).

$$\beta = \frac{heat\ generation\ rate}{heat\ removal\ rate} = \frac{-r\Delta H_R d_h}{6\Delta T_{ad} h_{in}} \leq 1 \tag{9}$$

In equation 9 $-r\Delta H_R$ is the rate of heat generation, d_h is the hydraulic diameter, depicting the reaction vessels dimension, ΔT_{ad} depicts the adiabatic temperature rise and h is the heat transfer coefficient. The heat transfer coefficient (h) is defined as the proportionality constant between the heat flux q, which in terms is defined as the rate of heat transfer per unit area (dA), and the temperature difference of the liquid with the surrounding solid surface ΔT (equation 10).[74]

$$h = \frac{q}{\Delta T} = \frac{dQ/dA}{\Delta T} \tag{10}$$

From the equations 9 and 10 beneficial characteristics of the high surface to volume ratios inherent to micro channel reactors become evident. Both small channel diameters as well as high surface areas between reaction mixture with the channel walls result in low β-values allowing a precise temperature control through efficient heat transfer.[75]

Heat transfer difficulties in batch chemistry are usually circumvented by performing the reaction at rather inefficient conditions such as low temperatures, low reagent concentrations or dropwise addition of reagents. Microreactor technology might enable more sustainable and productive preparations

[72] T. Noël, *Organometallic Flow Chemistry*, 1 ed., Springer, Cham, Switzerland, **2016**.
[73] R. A. Kashid Madhvanand N., Kiwi-Minsker Lioubov, *Microstructured Devices for Chemical Processing*, Wiley, Weinheim, **2014**, pp. 179.
[74] F. P. Incropera, D. P. Dewitt, Bergman T. L., Lavine A. S., *Fundamentals-of-Heat-and-Mass-Transfer*, John Wiley and Sons, Hoboken, **2006**.
[75] J. J. Brandner, W. Benzinger, U. Schygulla, K. Schubert, *Microgravity Science and Technology* **2007**, *19*, 41.

avoiding high energy consumptions due to cryogenic temperatures and large amounts of solvent waste.[76]

2.2.3 Safety

Following the increased demand for sustainability, one of the major goals in developing new methods in synthetic chemistry needs to be step efficiency and atom economy. However, a variety of easily accessible and synthetically interesting small molecules such as phosgene, carbon monoxide or diazo compounds are avoided in conventional chemistry, especially at larger scales because of their hazardous nature. Chemical reactions can be dangerous because of various reasons: 1) They may be highly exothermic and therefore accumulate large amounts of heat and become uncontrollable. 2) They may involve toxic or cancerogenic reagents. 3) They may involve unstable species, which are difficult to handle or even explosive.[77]

As mentioned above, the increased heat- and mass-transfer capabilities of continuous flow compared to batch reactors enable the safe handling of exothermic reactions even at larger scales and at higher temperatures.[78] Furthermore, the closed systems and small reactor volumes of the microreactor technology limit the hazards of explosive or toxic reagents.[77] Kappe and co-workers used a continuous flow reaction set-up for the in situ generation of explosive hydrazoic acid. Other than round bottom flasks, most microreactors avoid vapour head spaces and thus decrease the danger of accumulating volatile hydrazoic acid.[79] In situ generations in continuous flow are frequently used to avoid storage, handling and transport of hazardous chemicals.

The group of Seeberger performed $AlMe_3$ mediated amide formations in continuous flow at temperatures of 125 °C using a backpressure regulator to allow the superheating of THF, which was used as solvent. $AlMe_3$ is known to be extremely pyrophoric and the temperature of the reaction exceeded the boiling point of the solvent significantly. Nevertheless, the reactions proceeded safely and the pharmaceutically active substances rimonabant und efaproxial were produced efficiently.[80]

Nitration reactions are considered as some of the most dangerous industrial processes. Especially on larger scale, those highly exothermic reactions can lead to uncontrolled heating and even explosions. The reduced working volume in microreactors limits the hazard of a runaway reaction.[81] Durcy and Roberge performed an almost solvent free nitration of phenols, which did not require the presence of H_2SO_4. They observed a better heat exchange and a very rapid radical propagation in the confined

[76] R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 7502.
[77] M. Movsisyan, E. I. Delbeke, J. K. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892.
[78] Z. Dong, Z. Wen, F. Zhao, S. Kuhn, T. Noël, *Chemical Engineering Science: X* **2021**, *10*, 100097.
[79] B. Gutmann, J. P. Roduit, D. Roberge, C. O. Kappe, *Angew. Chem. Int. Ed.* **2010**, *49*, 7101.
[80] T. Gustafsson, F. Ponten, P. H. Seeberger, *Chem. Commun* **2008**, 1100.
[81] P. Plouffe, A. Macchi, D. M. Roberge, *Org. Process Res. Dev.* **2014**, *18*, 1286.

volume. The higher selectivity was especially visible through a 10-fold decrease in polymeric side products compared to the batch results. Thus, the reaction got more efficient in comparison to nitrations in a flask and additionally the small internal volume ensures a small chemical inventory at any given time therefore resulting in an improved safety.[82]

2.2.4 Scalability

Even though, extending the scale of a continuous flow process can be easily achieved by prolonging the pumping period of a previously optimized process, the small reaction volumes require exceedingly long process times for the production of compounds beyond a gram scale. That might not be a problem for the laboratory scale but if compounds need to be produced on a kilogram or even bigger scale simply running processes for a longer time might not be feasible anymore. Still scalability remains one of the advantages of continuous flow processing which is most cited.[83] Especially, tubular reactor volumes are easily scaled up by either increasing the number of tube reactors, or by enhancing the diameter of the tubing. Changing the diameter of the tubing is however problematic for various reasons: heat transfer becomes less efficient due to the smaller surface to volume ratio; diffusion pathways increase and so increases the mixing time; in case of photochemical reactions the optical pathway is also prolonged. Due to the change of all those characteristics, the process requires additional optimization times and loses lots of advantages of microflow technology. A second option is to increase the number of microreactors. This can either be achieved by external numbering, in which another flow system of the same kind is set up, or by internal numbering in which only certain parts of the unit are multiplied. Internal numbering is the more cost efficient method since usually it only requires the acquisition of new reactors while keeping the number of pumping, monitoring and collecting equipment constant. Using a single reagent feed this parallelisation approach requires precise control of flow distribution to ensure that all reactor tubes are provided with equal amounts of reagent and work similarly. To cover industrial needs sizing and numbering up have to be combined, since multiplication of microreactors might require thousands of reactors to achieve sufficient process volumes and therefore is extremely expensive and the technical difficulties in achieving an even flow distribution become significantly more challenging. Process intensification possible through continuous flow technology might further help to reach higher production scales.[84]

2.2.5 Sustainability

Additionally, continuous flow technology leads to a more sustainable chemistry. Reactions can be run at noncryogenic temperatures and higher concentrations due to the efficient heat and mass transfer.

[82] L. Ducry, D. M. Roberge, *Angew. Chem. Int. Ed.* **2005**, *44*, 7972.
[83] M. Berton, J. M. de Souza, I. Abdiaj, D. T. McQuade, D. R. Snead, *J. Flow Chem.* **2020**, *10*, 73.
[84] a) L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag, T. Noel, *Chem. Rev.* **2022**, *122*, 2752; b) Z. Dong, Z. Wen, F. Zhao, S. Kuhn, T. Noël, *Chemical Engineering Science: X* **2021**, *10*, 100097.

Therefore, energy and material consumptions might be decreased significantly. The smaller reaction volumes and other increased safety measurements (see chapter 2.2.3) allow the implication of hazardous chemicals in synthetic routes, which might reduce the step count and increase the atom economy in the synthesis of the target molecules.[85] Especially on larger scales those energy and resource savings add up.

[85] M. Movsisyan, E. I. Delbeke, J. K. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892.

3. Organometallic Chemistry

Organometallic reagents are characterized by a direct bond between a partial negatively charged carbon atom and a partial positively charged metal atom. The polarity of this $C^{\delta-}M^{\delta+}$-bond is mostly determined by the electronegativity difference (ΔEN) between the carbon atom and the corresponding metal. Since, the reactivity of organometallic species is also depended on the ΔEN, the Pauling scale might give first insights into the reactivity of a metal organyl. Thus, metallic elements with low electronegativities (EN) lead to stronger polarized and more reactive organometallic reagents (Figure 13) Following this logic, the highly ionic and reactive character of the alkali metal organyls becomes apparent.[86]

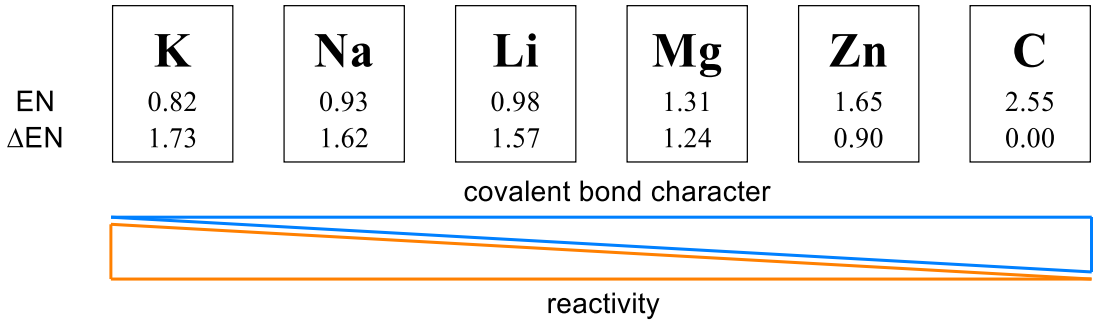


Figure 13: Correlation between EN-values according to Pauling to reactivity and stability of the C–M bond. ΔEN towards the EN of Carbon.[87]

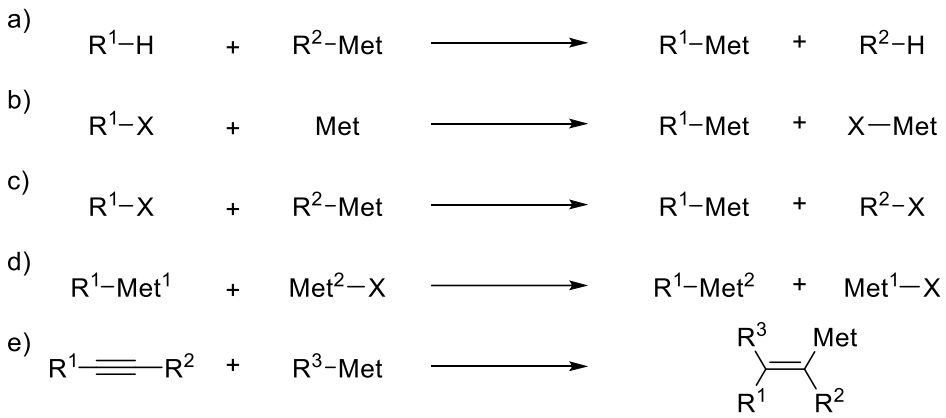
Even though, those values give a first impression it has to be noted that the electronegativity-values are changing among other things with the oxidation numbers and in case of the carbon atom also with the degree of hybridization. Because electrons in the s-orbital experience a stronger attraction towards the atoms core than those in the p-orbitals, the electronegativity rises when the s-character is increased: EN (Csp^3) = 2.55, EN (Csp^2) = 2.75, EN (Csp) = 3.29. Those changes explain the increasing acidity of carbon atoms with a higher s-character and further show why the metal species with a higher s-character at the carbon are of higher polarity. Furthermore, the EN differs according to the substituents on the C-atom.[86] The high reactivity of strongly polarized organyls towards electrophiles is often accompanied with a low functional group tolerance, especially if the functional groups have an electrophilic character. Another correlation is the often decreased stability of such metalorganic reagents. Thus, reaction conditions and reagents need to be fine-tuned, to on one side be reactive enough to undergo transformations with the desired electrophile, but on the other side leave other functional groups untouched. Often the tolerance of sensitive functionalities is achieved by choosing less reactive organometallics such as zinc, or magnesium (so called Grignard reagents) derivatives.[88] Nevertheless, even highly polarized organometallic reagents e.g. alkalimetal reagents are capable to tolerate

[86] C. Elschenbroich, F. Hensel, H. Hopf, *Organometallchemie, Vol. 6*, Teubner Verlag, Wiesbaden, **2008**.
[87] A. L. Allred, *Journal of Inorganic and Nuclear Chemistry* **1961**, *17*, 215.
[88] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.

functional groups for instance at cryogenic temperatures,[89] when prepared under Barbier conditions[90] or at extremely fast reaction times under continuous flow conditions.[91] The following chapter is supposed to answer the question: How to prepare and handle organometallic reagents, especially functionalized, highly reactive alkaliorganyls?

3.1 Preparation of Organometallic Reagents

Five of the most common ways to prepare organometallic reagents are: 1) Directed metalation via deprotonation (Scheme 3a); 2) Insertion through reduction of a C–X bond (Scheme 3b); 3) Synthesis via a X/metal exchange on a C–X bond (Scheme 3c, with X being a hetroatom in both cases); 4) Synthesis via transmetalation of another organometallic reagent (Scheme 3d); 5) Carbometalation or hydrometalation on an alkene or alkyne (Scheme 3e). The following chapters will focus on the first four methods, since they are the most relevant for the work in hand.



Scheme 3: Approaches towards the synthesis of organometallic reagents: a) Directed metalation; b) Oxidative insertion; c) Heteroatom metal exchange; d) Transmetalation; e) Carbo-/Hydrometalation.

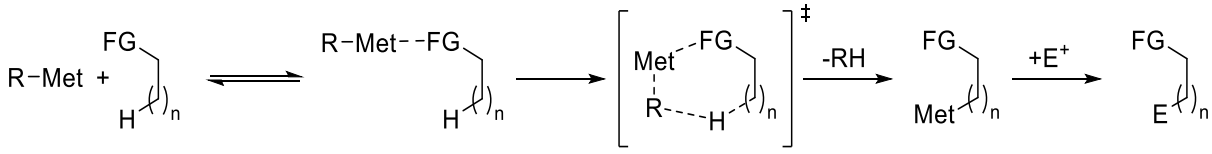
The choice of the synthesis pathways is usually depended on the availability of the starting material, the regioselectivity, as well as the functional group tolerance. For instance, halogen-metal exchange reactions are not feasible on substrates with electrophilic functional groups and oxidative insertions are not advisable on substrates labile to reductions. In case of alkali metal and magnesium organyls the

[89] a) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983; b) D. C. Harrowven, H. S. Poon, *Tetrahedron Lett.* **1994**, *35*, 9101.
[90] a) C. Gómez, F. F. Huerta, M. Yus, *Tetrahedron* **1998**, *54*, 1853; b) C. Gómez, F. F. Huerta, M. Yus, *Tetrahedron* **1997**, *53*, 13897.
[91] a) D. Ichinari, Y. Ashikari, K. Mandai, Y. Aizawa, J. I. Yoshida, A. Nagaki, *Angew. Chem. Int. Ed.* **2020**, *59*, 1567; b) A. Nagaki, H. Yamashita, K. Hirose, Y. Tsuchihashi, J. I. Yoshida, *Angew. Chem. Int. Ed.* **2019**, *58*, 4027; c) A. Nagaki, K. Sasatsuki, S. Ishiuchi, N. Miuchi, M. Takumi, J. I. Yoshida, *Chem. Eur. J.* **2019**, *25*, 4946; d) H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691. e) P. Knochel, F. Kopp, M. Yus, F. Foubelo, H. Ila, T. J. Korn, O. Baron, S. I. Krasovskiy, M. Shimizu, T. Hiyama, E. Fouquet, A. Herve, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel, S. Matsubara, X. Yang, N. Gommermann, L.-F. Huang, T.-Y. Luh, M. Werner, A. Koch, K. H. Dötz, I. Marek, F. Mahuteau-Betzer, Cahiez Gérard, G. R. Stephenson, J. Périchon, C. Gosmini, *Handbook of Functionalized Organometallics - Applications in Synthesis, Vol. 1*, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2005**.

field is mainly dominated by halogen-metal exchanges and directed metalation in which a base deprotonates a carbon hydrogen bond. This is however just true for the laboratory scale since all bases and exchange reagents are ultimately prepared from the metals.[92]

3.1.1 Directed metalation via deprotonation

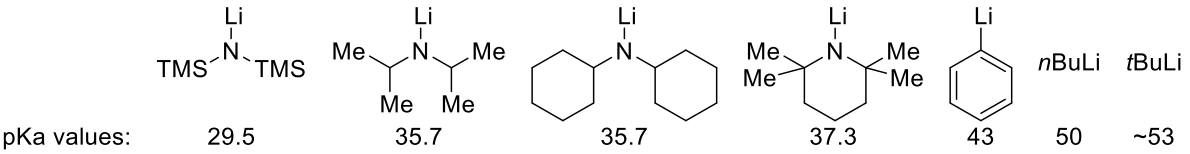
The permutation between a metal species and a proton on a hydrocarbon is commonly referred to as a metalation. They only proceed if the C-H bond is more acidic than the newly formed bond between the proton and base.[92] Other than to oxidative insertions or halogen-metal exchanges, they do not require a prefunctionalization of the substrate with a halogen but instead transform a previously inert C-H bond into a highly reactive carbon-metal species. Directed metalations can be considered as two step mechanisms: First the metal base coordinates to a Lewis basic functional group, subsequently the proton next to the metal directing group is replaced by the corresponding metal of the base. The formation of a premetalation complex, which facilitates deprotonation, is called complex-induced proximity effect (CIPE) (Scheme 4).



Scheme 4: Reaction mechanism of a functional group (FG) directed metalation via CIPE.[93a]

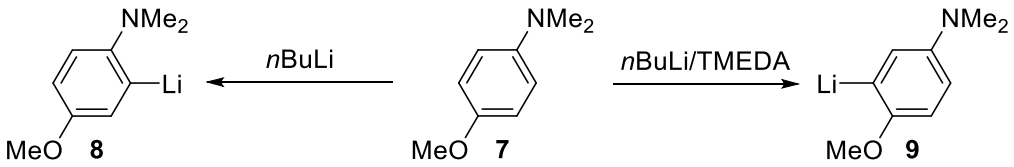
Bases in directed metalations can be of different nature. They may consist of carbon metal bonds, metal amides, metal alkoxides or in case of the Lochmann-Schlosser bases of mixtures of alkoxides or metal amides and alkali metal organyls. Alkylmetal species are generally of the highest thermodynamic basicity but in some cases metal amides such as 2,2,6,6-methylpiperidinyl metal (TMPMet), metal dicyclohexyl amide (Cy_2NMet), metal diisopropylamide (MetDA) or metal hexamethyldisilazide (MetHMDS) might display a higher kinetic basicity and therefore lead to faster conversions of the substrates. Their acidity is strongly dependent on the metal ion and the aggregation state. Furthermore, the pK_a-values are hard to determine and literature reports differ significantly (Scheme 5).[93]

[92] M. Schlosser, P. Knochel, T. Hiyama, H.-J. Knölker, S. Bräse, *Organometallics in Synthesis - Third Manual*, John Wiley & Sons, Inc., Hoboken, **2013**.
[93] a) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; b) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470.



Scheme 5: Lithium bases and the pK_a-values of their conjugated acids. From left to right LiHMDS, LDA, Cy_2NLi, TMPLi, Phenyllithium, *n*BuLi, *t*BuLi.[94]

The aforementioned metal amide bases have the additional advantage, that they are of low nucleophilicity and allow the deprotonation of substrates bearing electrophilic functional groups, such as carbonyls during enolate formations.[95] Additionally, they are unable to undergo halogen or chalcogen metal exchange reactions, which are commonly observed using alkyl- or arylmetal bases especially when Br- or I-substituents are present in the substrate. The low kinetic basicity of alkylmetals can be overcome by addition of metal coordinating reagents. For instance the metalation of unsubstituted benzene by *n*BuLi is relativly slow when conducted in hydrocarbon solvents, even though the p*K*a values (benzene: 43; *n*butane: 50)[96] clearly indicate that the metalation should proceed smoothly. The reaction rate might be accelerated by addition of coordinating tetrahydrofuran (THF) or the bidentate ligand tetramethyl ethylene diamine (TMEDA). Those coordinate to the lithium and thus break the in hydrocarbon solution present hexameric structure of *n*BuLi accountable for its low kinetic basicity.[97] As the name of this chapter already implies most metalation reactions are directed by functional groups either through coordination or by increasing the acidity of the adjacent protons. Directed *ortho* metalation (DoM) of 4-methoxy-*N*,*N*-dimethylaniline (**7**) nicely shows the effect of coordination versus acidity. In hydrocarbon solution and without the presence of coordinating additives, the lithiation takes place next to the more Lewis basic dimethyl amino group (**8**). If TMEDA is added to the base, the alkyllithium complex becomes less Lewis acidic and deprotonation occurs at the more acidic proton *ortho* to the stronger electronegative methoxy group (**9**) (Scheme 6).[98]



Scheme 6: Metalation of 4-methoxy-*N*,*N*-dimethylaniline with pure *n*BuLi in hydrocarbons and with *n*BuLi in the presence of TMEDA.[98]

[94] a) R. R. Fraser, T. S. Mansour, *J. Org. Chem.* **1984**, *49*, 3442; b) M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Vol. 6*, John Wiley & Sons, Hoboken, **2007**.
[95] a) T. X. Gentner, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2021**, *60*, 9247; b) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470.
[96] M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Vol. 6*, John Wiley & Sons, Hoboken, **2007**.
[97] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.
[98] J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**.

The stabilizing effects of directing groups was reported, doing *s*-BuOH quenching experiments with *para*- and *ortho*-anisyllithium. Calorimetric studies showed that the quench of the para substituted lithium species is 3.6 kcal/mol more exothermic and thus significantly less stabilized.[99] One of the disadvantages in metalation reactions is the sometimes challenging prediction of regioselectivity, which might lead to tedious screenings of reaction conditions and unwanted metalation sides. Computational methods might give first indications into the preferred position of deprotonation, especially for bases, such as TMPZnCl·LiCl, where thermodynamic effects play a more important role. Metalation sites of kinetically dominated bases such as TMPLi are more challenging to predict.[100]

Apart from DoMs, metalations on aromatic substrates bearing an alkyl substituent can also proceed at the benzylic position. If this alkyl group is in *ortho* position to a directing group those types of deprotonations are called lateral metalations. Other than in *ortho* metalations where the carbon metal bond is in plane with the aromatic ring and thus acidification is most efficient by inductive effects, the metalation of the benzylic side is best promoted by conjugative effects (Figure 14).[101]

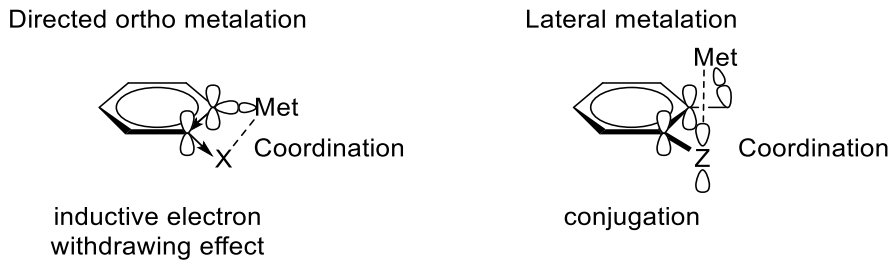


Figure 14: Factors favouring directed *ortho* metalation and lateral metalation.[101]

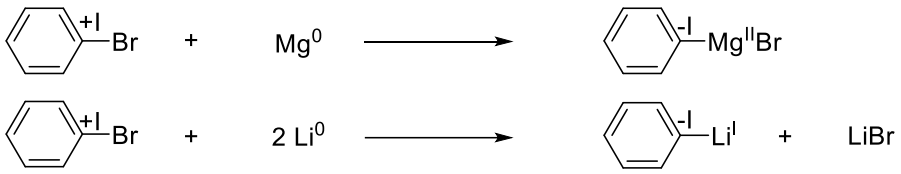
Deprotonations of hydrocarbons bearing no heteroatoms are known but rather scarce. They usually require strong bases such alkylalkali metal species in the presence of TMEDA or superbases of the Lochmann-Schlosser type.[102]

3.1.2 Oxidative insertion by C-heteroatom bond reduction

In an oxidative addition a new metal carbon bond is formed by cleaving a bond between an organic residue and a heteroatom. During this process the oxidation state of the metal is increased and a total of two electrons is transferred to the carbon centre which is thereby formally reduced. Thus, the insertion of a magnesium atom into a carbon halide bond leads from a Mg^0 to Mg^{II}-atom after insertion into the C–X bond (Scheme 7).[103] During oxidative additions of alkali metals two equivalents of the metal are

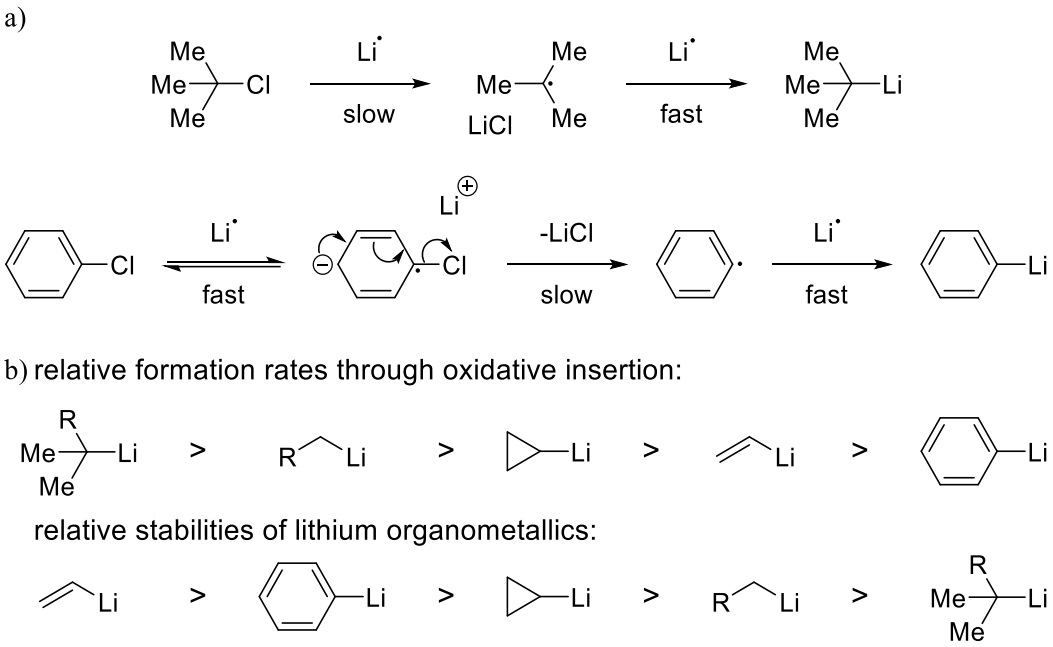
[99] a) G. W. Klumpp, M. J. Sinnige, *Tetrahedron Lett.* **1986**, *27*, 2247; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.
[100] M. Balkenhohl, H. Jangra, I. S. Makarov, S.-M. Yang, H. Zipse, P. Knochel, *Angew. Chem.* **2020**, *132*, 15102.
[101] J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**.
[102] L. Lochmann, M. Janata, *Cent. Eur. J. Chem.* **2014**, *12*, 537.
[103] a) J. F. Hartwig, *Organotransition metal chemistry: From bonding to catalysis, Vol. 2010th edition*, University Science Books, Mill Valley, **2010**; b) F. A. Carey, R. J. Sundeberg, *Organische Chemie: Ein weiterführendes Lehrbuch, Vol. 3*, VCH Verlagsgesellschaft mbH, Weinheim, **1995**.

needed, since the oxidation state of +II is only very seldom obtained. During a reaction turnover one equivalent of the desired alkali metal organyl and one equivalent of the corresponding alkali metal halide is formed (Scheme 7).



Scheme 7: Oxidative insertion into phenyl bromide using magnesium or lithium as metallic reagents.

Interestingly, the mechanism for the formation of alkali metal organyls differs significantly between alkyl and aryl halides, even though both proceed via a single electron transfer (SET) (Scheme 8a). Due to the radical intermediates emerging in the rate limiting (slowest) step of the mechanisms the relative rates of formation diverge from the results expected, if considering the anion stability. Instead of the anion stability the reaction rate is dependent on the stability of the radical formed as an intermediate (Scheme 8b).[104]



Scheme 8: a) Mechanisms of the reductive lithiation of phenyl chloride and *t*butyl chloride. b) Formation rates of different lithium species via reductive lithiations, relative stabilities of the lithium organometallics.[104, 105]

[104] J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**.
[105] D. E. Applequist, D. F. O'Brien, *J. Am. Chem. Soc.* **1963**, *85*, 743.

Oxidative insertions are often facilitated by the presence of arenes such as naphthalene or 4,4´-di-*t*butylbiphenyl. The arenes act as acceptors for the alkali metal valence electrons and subsequently reduce the alkyl halide to an alkyl radical, thus accelerating the rate limiting step of the reduction.[106]

3.1.3 Halogen-metal exchange

Halogen-metal exchanges are reactions in an equilibrium, thus the organohalide and the exchange reagent have to be chosen carefully. As a general rule when reacting an organometallic with an aryl or alkyl halide the more stable and less basic organometallic reagent is formed (Figure 15).[106b]

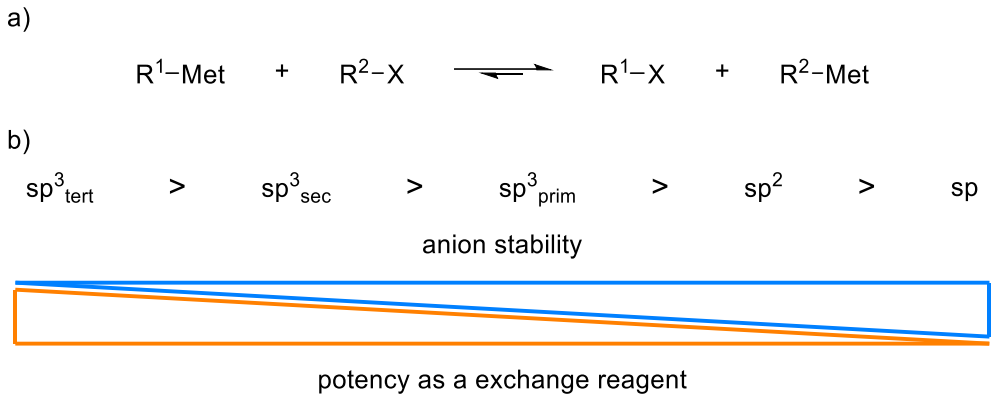
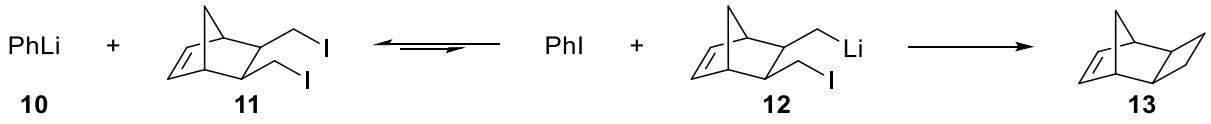


Figure 15: a) Reaction equation of a halogen-metal exchange with the carbanion stability of $R^2 > R^1$. b) Anion stability of differently hybridized and substituted carbanions.

Derivations from the above shown reactivity scale might be observed due to coordinating, mesomeric or inductive effects which might alter the stability and thus acidity of a carbanion. Furthermore, the equilibrium of the reaction can be shifted by consumption of the less stable reagent. For instance, the sp^2-hybridized PhLi (**10**) is able to undergo exchange reactions with the sp^3-carbon of the primary alkyl iodide species **11** depicted in Scheme 9. Thermodynamically the exchange is unfavourable but the subsequent substitution reaction removes the alkyllithium reagent **12** from the equilibrium and thus allows formation of the cyclobutane **13** in good yields.[107]

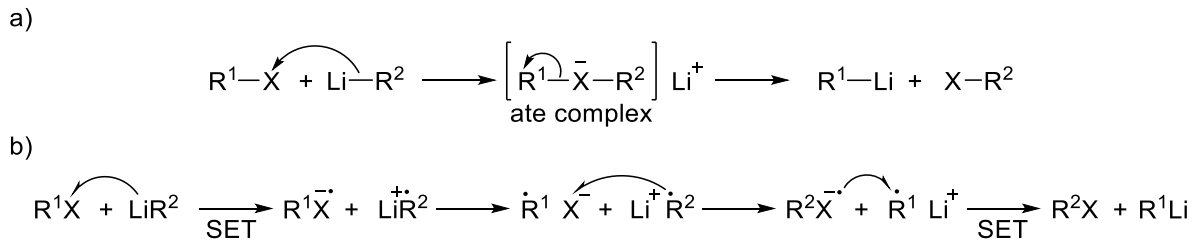


Scheme 9: Thermodynamically unfavored I/Li-exchange on alkyl iodide **11** with phenyl lithium (**10**).[107]

[106] a) D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2000**, *2000*, 225; b) J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**.
[107] R. R. Sauers, S. B. Schlosberg, P. E. Pfeffer, *J. Org. Chem.* **1968**, *33*, 2175.

The characteristics of the reactions are strongly influenced by the halogen atom of the starting materials. Whereas the I/Li-exchange is almost instantaneous and is in some cases able to outcompete the protonation of *t*BuLi with MeOH,[108] exchanges with bromine are significantly slower, and chlorine or fluorine exchanges are extremely scarce.[109]

Halogen-metal exchange reactions are considered to proceed through one of two mechanisms. Either radical intermediates are present or the exchange passes an ate complex. In the latter, the organometallic species acts as a nucleophile attacking the organohalide resulting in a reversible formation of an ate complex, which subsequently dissociates into the products (Scheme 10a). During the radical mechanism a SET from the organometallic to the alkyl or aryl halide occurs leading to a radical cation of the metal species and a radical anion of the halide. Those species form to two carbon centred radicals which can subsequently disproportionate into newly generated organometallics and organo halides (Scheme 10b).[110]

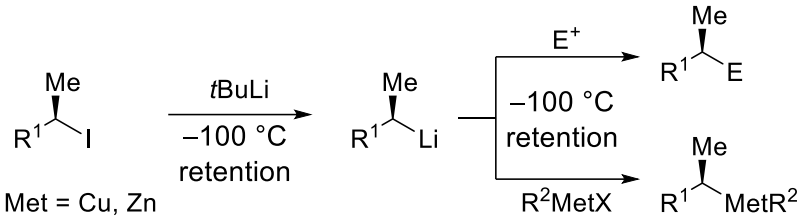


Scheme 10: Halogen-lithium exchange mechanisms: a) Nucleophilic mechanism via an ate complex. b) Radical mechanism.[110]

In halogen/lithium exchanges most aryl bromides and iodides as well as primary alkyl iodides react via an ate complexes. For secondary alkyl iodides both reaction pathways have been described, whereas alkyl bromides seem to follow the radical mechanism.[111]

Halogen lithium exchange reactions are stereoretentive on vinylhalides. In a series of papers Knochel and co-workers showed that stereoretention is also given when performing exchange reactions between optically enriched secondary alkyl iodides without heteroatom stabilization and *t*BuLi at low temperatures. The resulting enantio- or diastereoenriched lithium compounds could subsequently be transmetalated or directly quenched with electrophiles without losing the stereo information (Scheme 11).[112]

[108] W. F. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861.
[109] J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**.
[110] W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1.
[111] D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2000**, *2000*, 225.
[112] a) A. Kremsmair, J. Skotnitzki, P. Knochel, *Chem. Eur. J.* **2020**, *26*, 11971; b) J. Skotnitzki, V. Morozova, P. Knochel, *Org. Lett.* **2018**, *20*, 2365; c) V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5516; d) J. Skotnitzki, A. Kremsmair, D. Keefer, F. Schüppel, B. Le Cacher de Bonneville, R. de Vivie-Riedle, P. Knochel, *Chem. Sci.* **2020**, *11*, 5328; e) J. Skotnitzki, L. Spessert, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 1509; f) J. Skotnitzki, A. Kremsmair, D. Keefer, Y. Gong, R. de Vivie-Riedle,



Scheme 11: Stereoretentive I/Li-exchange reaction on secondary alkyl iodides.[112]

Whereas, exchanges between halides and alkali metal organyls have been reported by Gilman and Wittig in the first half of the last century[113] and have been thoroughly studied and used in organic synthesis, the halogen-magnesium exchanges seemed to be more challenging. Especially Br/Mg-exchanges were limited due to side reactions and the need of high temperatures decreasing functional group tolerance. Only in 2004 the Knochel group developed an efficient exchange reagent for the performance of halogen-magnesium exchanges which was capable to perform Br/Mg-exchanges at low temperatures and in the presence of sensitive functional groups. Key to this development was the addition of stoichiometric amounts of LiCl to the Grignard reagent. Nowadays this broadly applied *i*PrMgCl·LiCl species is commonly known as Turbo-Grignard.[114] Similar exchanges are possible with other heteroatoms, most prominently chalcogens and tin.[115]

3.1.4 Transmetalation

As mentioned before the reactivity of an organometallic species is strongly influenced by the metallic element present in the carbon metal bond. Probably the most convenient way to alter or adjust the reactivity of the organometallic is the replacement of one metal by another via so called transmetalation. Transmetalations are defined as the transfer of a ligand from one metal to another. The ligands can be carbon ligands such as alkyl, aryl, alkenyl, or allyl residues but also hetero atom ligands for instance halogens or pseudohalogens. Already in 1861 Frankland reported the first transmetalation reaction by transferring alkyl groups from dialkyl zinc species to mercury, tin, lead, antimony and arsen.[116]

There are multiple different forms of transmetalations, which mainly differ in the nature of the ligand accepting metal species. The method reported by Frankland in which an organometallic reagent reacts with a neutral metal is often referred to as redox transmetalation, since the receiving metal is oxidized while the ligand donating metal atom is reduced (Scheme 12a). In the second, nowadays more common

P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 320; g) K. Moriya, M. Simon, R. Mose, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10963; h) V. Morozova, K. Moriya, P. Mayer, P. Knochel, *Chem. Eur. J.* **2016**, *22*, 9962.

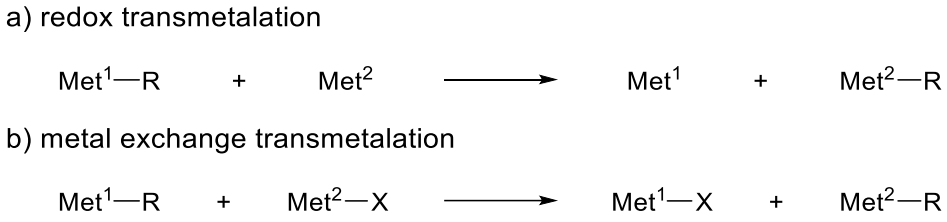
[113] a) G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903; b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106.

[114] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; b) J. M. Gil-Negrete, E. Hevia, *Chem. Sci.* **2021**, *12*, 1982.

[115] a) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, *37*, 2620; b) C. Rim, D. Y. Son, *Arkivoc* **2006**, *2006*, 265.

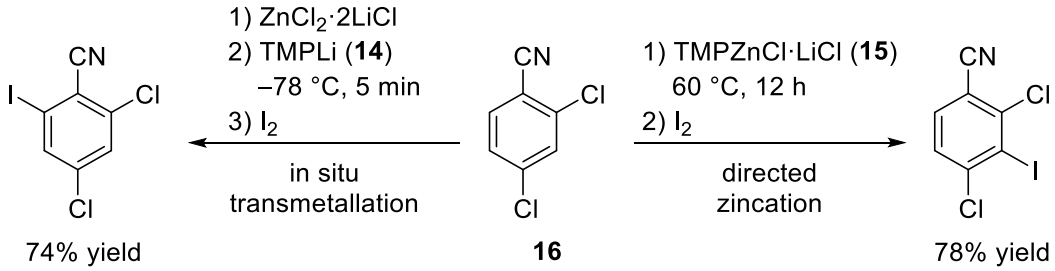
[116] E. Frankland, *Q. J. Chem. Soc.* **1861**, *13*, 177.

type of transmetalation, an organic residue of the less electronegative metal is exchanged with a halogen or pseudohalogen ligand of a more electronegative metal (Scheme 12b). The driving force in these reactions are the formation of a more covalent and thus more stable metal organic species and a more ionic salt which is thermodynamically favoured due to its higher lattice energy.[117]



Scheme 12: a) Redox transmetalation. b) Metal exchange transmetalation.

Highly reactive organolithium reagents are consequently readily transmetalated to the less reactive organomagnesium or zinc species by the addition of magnesium and zinc salts. Knochel and co-workers were able to utilize this characteristic for the in situ transmetalation of reactive aryllithium species which were obtained by directed lithiation, with TMPLi (**14**) in the presence of copper, magnesium or zinc salts. Using this approach, they were able to access aryl zinc species which on the one hand are hard to obtain because of the long metalation times of most zinc amides and on the other hand contained functional groups not tolerated by organolithium compounds. Furthermore, the metalation with the kinetic base TMPLi and in situ transmetalation led to different regioselectivities than directed metalations with the less powerful base TMPZnCl·LiCl (**15**) as can be seen in the metalation of 2,4-dichlorobenzonitrile (**16**) (Scheme 13).[118]



Scheme 13: In situ trapping metalation of 2,4-dichlorobenzonitrile (**16**) with TMPLi (**14**) in the presence of $ZnCl_2$·2LiCl and its effect on the regioselectivity.[118]

Similarly, transmetalation between two organometallics can occur. Upon mixing an organozinc with an organolithium species the less electronegative lithium will be bound to the more stabilized carbanion, whereas the less stabilized carbanion tends to form a more covalent bond with the zinc atom.

[117] a) K. Osakada, in *Current Methods in Inorganic Chemistry*, *Vol. 3* (Eds.: H. Kurosawa, A. Yamamoto), Elsevier, **2003**, pp. 233; b) S. C. Rasmussen, *ChemTexts* **2021**, *7*, 1.
[118] A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.

3.2 Alkali Metal Compounds

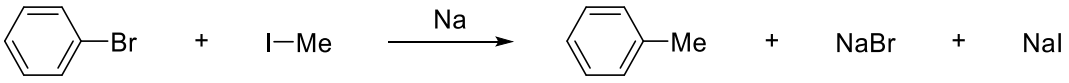
According to Manfred Schlosser, one of the pioneers in the chemistry of potassium and sodium organometallics, "an alkali metal attached to a carbon skeleton can be viewed like a joker in a card game destined to be traded in against something else."[119] Even though this statement might be an exaggeration, it nicely shows the special role alkali metal reagents play in organometallic chemistry. Their high reactivity inherent to the high polarity of the carbon metal bond allows a plethora of reactions even with very unreactive electrophiles. Furthermore, they enable the transmetalation and thus fine tuning to organometallics of almost every other metal. This interchangeability and reactivity towards electrophiles renders them as one of the most versatile classes of organometallics.

Among the alkali metals lithium drew by far the most attention, reports on sodium and potassium species are scarce and mainly deal with Lochmann-Schlosser super bases.[120] Since this work is dealing mainly with sodium, the chemistry of lithium compounds will only be covered in continuous flow in chapter 3.3 and the chemistry of potassium compounds as well as Lochmann-Schlosser bases will just be covered very briefly.

Already in 1858 Wanklyn prepared the first alkali metal organyls even though those species were not monometallic but sodium and potassium zincates, which he obtained from mixing the alkali metals with diethyl zinc.[121] He was able to react those reagents with carbon monoxide thus performing the first carbonylation of an organometallic species.[122] Wurtz performed reactions between alkyl halides and elemental sodium, forming mixtures of different alkyl coupling products, which resulted from reactions of the intermediate alkylsodium species with another alkyl halide (Scheme 14a).[123]

a) Wurtz reaction

b) Wurtz-Fittig reaction



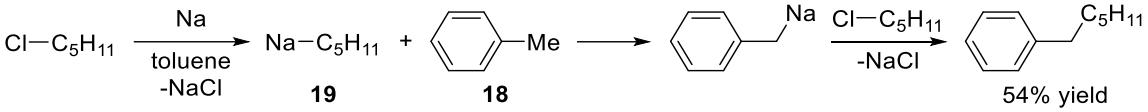
17 **18**

Scheme 14: a) Unselective Wurtz reaction. b) Wurtz-Fittig reaction between an aryl bromide and alkyl iodide leading to a more selective product formation.[123, 124]

[119] M. Schlosser, P. Knochel, T. Hiyama, H.-J. Knölker, S. Bräse, *Organometallics in Synthesis - Third Manual*, John Wiley & Sons, Inc., Hoboken, **2013**.
[120] A. Mordini, M. Valacchi, in *Science of Synthesis Category 1, Organometallics, Vol. 8b*, Georg Thieme Verlag KG, Stuttgart, **2006**.
[121] J. A. Wanklyn, E. Frankland, *Proc. R. Soc.* **1858**, *9*, 341.
[122] D. Seyferth, *Organometallics* **2006**, *25*, 2.
[123] A. Wurtz, *Ann. Chim. Phys.* **1855**, *44*, 275.

Because of their low selectivity those reactions are synthetically not very useful, nevertheless they were important milestones for the understanding of organometallic chemistry, since they helped ending the radical theory. Fittig showed that similar coupling reactions are also possible between bromobenzene (**17**) and alkyl iodides, in those cases he obtained toluene (**18**) and ethylbenzene (Scheme 14b).[124] The so called Wurtz-Fittig reaction found more application in organic chemistry since it avoids complex product mixtures. Aryl halides react more rapidly with elemental sodium than alkyl halides and the resulting arylsodium species are subsequently able to selectively couple to the alkyl halides.[125]

In the 1940s, the group of Morton reported in a series of publications the use of organosodium compounds such as amylsodium (**19)** for the directed metalation of weakly acidic protons of benzene, alkylbenzenes[126] and olefins (Scheme 15).[127] However, the preparation of sodium organyls required long reaction times, high speed stirring, high sodium concentrations and even when using large excess of substrates, the yields remained relatively low. Those reasons together with the poor solubility of most sodium organometallics led to a decrease in interest in organosodium chemistry.[125, 128]



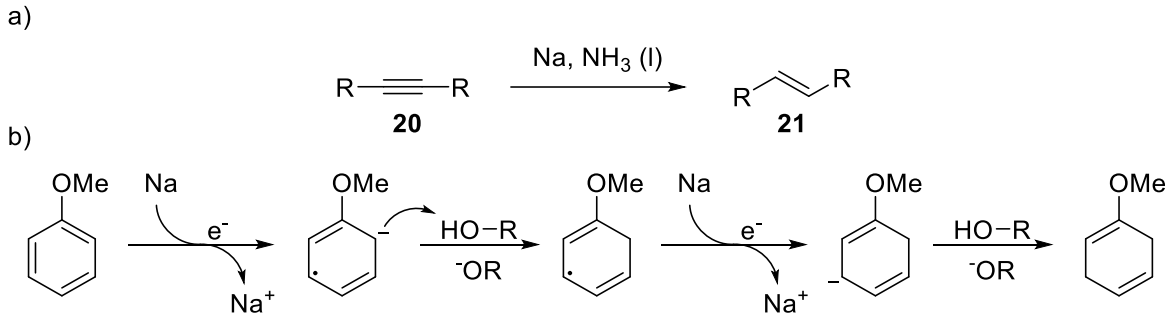
Scheme 15: Deprotonation of toluene (**18**) by amylsodium (**19**).[126]

Approaches to solubilize the alkylsodium species included screenings for different alkyl residues and mixing with different additives. Upon addition of TMEDA to pentylsodium (**19**) in hexane the heterogenous mixture turned into a suspension but solubilisation was not observed.[129]

After those developments the use of sodium in organic chemistry was mainly focused on reductions of different functional groups and carbon-carbon multiple bonds. As such metallic sodium can reduce alkynes **20** to the corresponding trans-alkenes **21** (Scheme 16a).[130] Most recognition was probably achieved by the Birch reduction in which elemental sodium is used in liquid ammonia and the presence

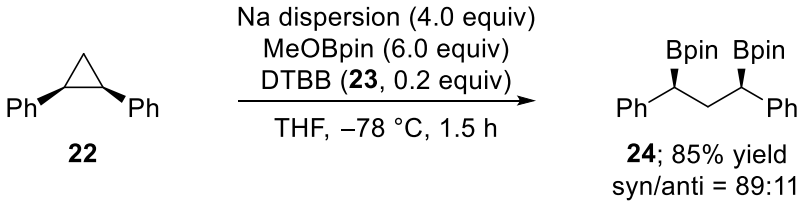
[124] B. Tollens, R. Fittig, *Justus Liebigs Annalen der Chemie* **1864**, *131*, 303.
[125] D. Seyferth, *Organometallics* **2006**, *25*, 2.
[126] a) A. A. Morton, E. L. Little, Jr., W. O. Strong, Jr., *J. Am. Chem. Soc.* **1943**, *65*, 1339; b) A. A. Morton, F. Fallwell, *J. Am. Chem. Soc.* **1938**, *60*, 1429.
[127] a) A. A. Morton, E. L. Little, *J. Am. Chem. Soc.* **1949**, *71*, 487; b) A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little, R. L. Letsinger, *J. Am. Chem. Soc.* **1950**, *72*, 3785; c) A. A. Morton, E. J. Lanpher, *J. Org. Chem.* **1955**, *20*, 839.
[128] a) A. Mordini, M. Valacchi, in *Science of Synthesis Category 1, Organometallics, Vol. 8b*, Georg Thieme Verlag KG, Stuttgart, **2006**; b) A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 340.
[129] G. B. Trimitsis, A. Tuncay, R. D. Beyer, K. J. Ketterman, *J. Org. Chem.* **1973**, *38*, 1491.
[130] a) D. J. Mathre, W. C. Guida, *Tetrahedron Lett.* **1980**, *21*, 4773; b) K. N. Campbell, L. T. Eby, *J. Am. Chem. Soc.* **1941**, *63*, 216.

of an amine or alcohol to reduce aromatic compounds (Scheme 16b).[131] Apart from those reductive reactions and the use of sodium alkoxides, sodium hydride and other inorganic sodium salts, sodium, similarly to potassium, was widely replaced in organic chemistry by lithium which is more convenient to handle.



Scheme 16: a) Reduction of alkyne **20** to trans alkene **21** with metallic sodium in liquid ammonia. b) Mechanism of the Birch-Reduction, solvent in b) is also liquid ammonia.[131b]

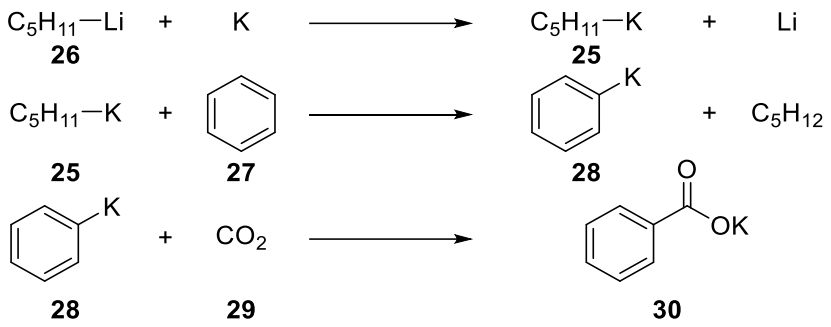
The groups of Yorimitsu and Azzena used reductive C-C, C-S, or C-O bond cleavages for the preparation of organosodium species. Arylcyclopropanes **22** were reductively opened by using a sodium dispersion in the presence of 4,4′-di-*tert*-butylbiphenyl (DTBB, **23**) and the corresponding electrophile. DTBB acts as an electron transfer catalyst in this type of reaction. This ring-opening procedure gave the 1,3-difuncionalized products **24** in good yields even though the ratio between the syn- and the anti-product was strongly dependent on the starting materials and electrophiles (Scheme 17).[132]



Scheme 17: 1,3-Difunctoinalization of Arylcyclopropanes via reductive ring-opening using sodium metal.[132]

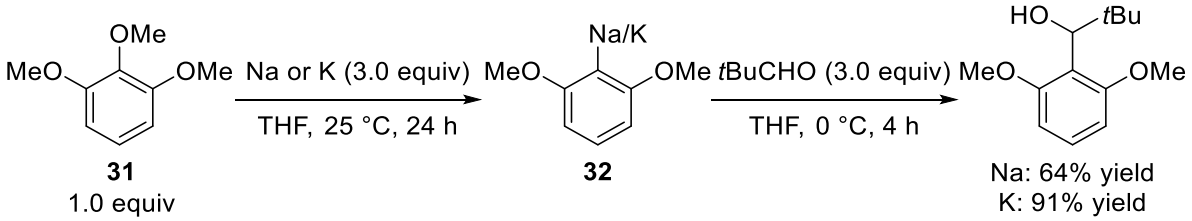
Redox transmetalations have been used for the in situ generation of alkylpotassium species **25** from alkyllithium reagents **26** for the metalation of benzene (**27**). In this procedure a solution of alkyllithium **25** in pentane was treated with benzene (**27**) and metallic potassium. Upon reductive transmetalation the resulting potassium species **25** was able to metalate the present benzene (**27**) and the phenylpotassium (**28**) was quenched with carbon dioxide (**29**) to give benzoic acid (**30**) (Scheme 18).[133]

[131] a) A. J. Birch, *Journal of the Chemical Society (Resumed)* **1944**, 430; b) H. E. Zimmerman, P. A. Wang, *J. Am. Chem. Soc.* **1990**, *112*, 1280; c) S. Asako, I. Takahashi, T. Kurogi, Y. Murakami, L. Ilies, K. Takai, *Chem. Lett.* **2021**, *51*, 38.
[132] H. Yorimitsu, S. Wang, A. Kaga, *Synlett* **2020**, *32*, 219.
[133] D. Bryce-Smith, E. E. Turner, *Journal of the Chemical Society (Resumed)* **1953**, 861.



Scheme 18: Reductive transmetalation of alkyllithium species with metallic potassium and subsequent metalation of benzene.[134]

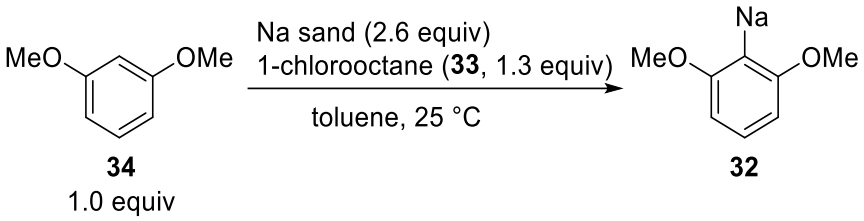
Reductive C-O bond cleavage was reported on 1,2,3-methoxyarenes **31**. Upon reaction with potassium or sodium the methoxy group in 2-position can be cleaved selectively and the resulting alkali metal organyls **32** react with various electrophiles (Scheme 19). The proposed mechanism also proceeds through single electron transfers and an intermediate aryl radical.[135]



Scheme 19: Reductive C-O bond cleavage on 1,2,3-methoxy arenes **31** and subsequent electrophile quench.[135c]

Mioskowski reported a one pot procedure for the directed *ortho* metalation of methoxy substituted benzenes. They were able to perform reductive insertions of sodium into 1-chlorooctane (**33**) in toluene in the presence of the methoxyarenes **34**. Directed *ortho* metalation with in situ generated octylsodium base and subsequent quench with different electrophiles gave the expected products (Scheme 20). Of importance for this procedure was the slow addition of 1-chlorooctane to the reaction mixture, which avoided Wurtz coupling products of the alkane. Mioskowski and co-workers proposed that the oxidative insertion as well as the DoM take place at the metallic surface of the used sodium sand.[136]

[134] D. Bryce-Smith, E. E. Turner, *Journal of the Chemical Society (Resumed)* **1953**, 861.
[135] a) U. Azzena, T. Denurra, E. Fenude, G. Melloni, G. Rassu, *Synthesis* **1989**, *1989*, 28; b) U. Azzena, G. Dettori, M. V. Idini, L. Pisano, G. Sechi, *Tetrahedron* **2003**, *59*, 7961; c) U. Azzena, T. Denurra, G. Melloni, A. M. Piroddi, *J. Org. Chem.* **1990**, *55*, 5386.
[136] a) A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 340; b) J.-M. Becht, A. Gissot, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2004**, *45*, 9331.



Scheme 20: One-pot oxidative insertion directed *ortho*-sodiation procedure for the formation of methoxy substituted benzoic acids.[137]

They were further able to show that biaryls can be produced in a similar fashion. Dropwise addition of chloro- or fluoroarenes instead of carbon dioxide at room temperature led after reaction times of ten minutes to the desired biaryl species. The regioisomers which were obtained when using substituted chloro- or fluoroarenes indicated a mechanism via aryne intermediates.[138]

Finally, after 125 years since the beginning of the alkylsodium chemistry, the first hydro carbon soluble alkylsodium species were reported. They all have the specific structure **35** shown in Figure 16a in common.[139] Even though the probably biggest drawback of alkylsodium chemistry was overcome by this finding, these readily prepared and soluble sodium organyls were never broadly applied in organic synthesis. Only 2-ethylhexylsodium (**36**) found niche applications as polymerisation starter[140] and NMR investigations were performed by the same group in order to study its behaviour when mixed with alkyllithium species (Figure 16b).[141] David Collum, who among others reanimated the field of organosodium chemistry in the past 10 years stated: "We examined the efficacy of 2-ethylhexylsodium as a hydrocarbon-soluble alkylsodium and found it functional but inconvenient to manipulate."[142]

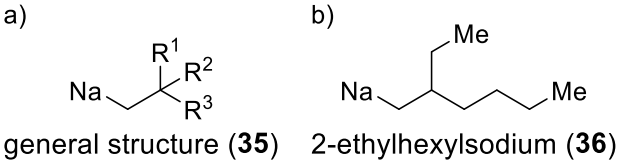
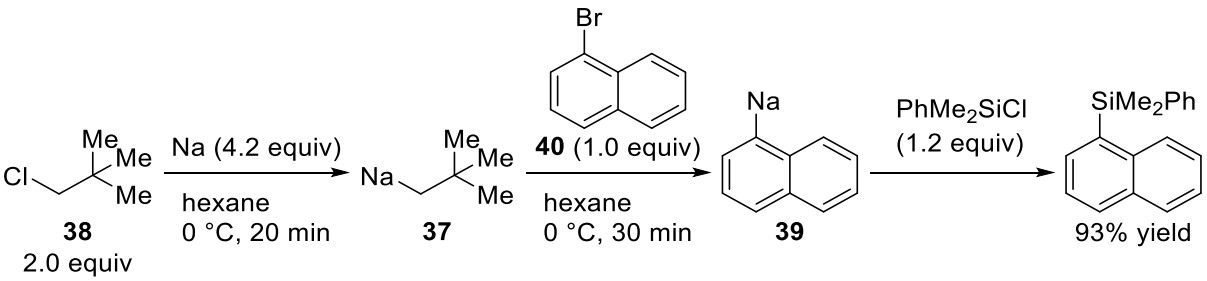


Figure 16: a) General structure of hydrocarbon soluble alkylsodium species **35** with R^1 and R^2 being independent straight hydrocarbon chains (C_2H_5 to C_5H_{11}) and R^3 being either a hydrogen or an alkyl chain (CH_3 to C_3H_7). b) 2-Ethylhexylsodium (**36**), the most investigated compound of this class.[139, 141]

[137] A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 340.
[138] J.-M. Becht, A. Gissot, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2004**, *45*, 9331.
[139] S. H. Eidt, D. B. Malpass, **1981**, *EP 0041306 A1*.
[140] a) A. A. Arest-Yakubovich, N. I. Pakuro, I. V. Zolotareva, E. V. Kristal'nyi, R. V. Basova, *Polymer International* **1995**, *37*, 165; b) A. A. Arest-Yakubovich, B. I. Nakhmanovich, G. I. Litvinenko, *Polymer* **2002**, *43*, 7093.
[141] S. G. Sakharov, N. I. Pakuro, A. A. Arest-Yakubovich, L. V. Shcheglova, P. V. Petrovskii, *J. Organomet. Chem.* **1999**, *580*, 205.
[142] D. B. Collum, R. A. Woltornist, Y. Ma, R. F. Algera, Y. Zhou, Z. Zhang, *Synthesis* **2020**, *52*, 1478.

Thus, alkylsodium species remained significantly underdeveloped until the group of Asako and Takai showcased the utility of neopentylsodium (**37**). Through a sodium insertion into the halide carbon bond of neopentyl chloride (**38**) using a dispersion of the alkali metal, they obtained the alkylsodium species (**37**) which they used as a halogen sodium exchange reagent for the preparation of sodium arenes (**39**) and alkenes from the corresponding bromides (**40**) and iodides (Scheme 21).[143]



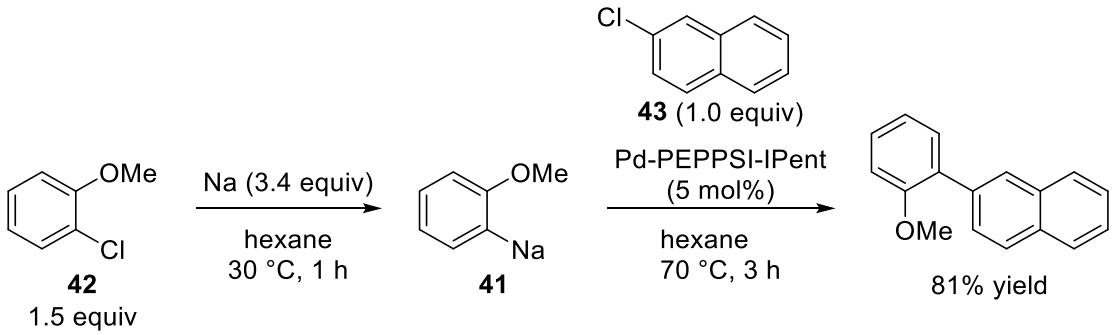
Scheme 21: Generation of neopentylsodium (**37**) from neopentyl chloride (**38**) with sodium dispersion and subsequent Br/Na-exchange.[143]

The reasoning behind the choice for neopentyl chloride (**38**) as a starting material for the exchange reagent was built on the four following points: 1) The halide should be readily available to prevent tedious synthetic steps; 2) The halide should be primary. Literature reports showed, that secondary and tertiary halides are transformed less efficiently into the corresponding alkylsodium species and are more susceptible to β-hydride elimination; 3) The halide should bear a bulky substituent to kinetically reduce Wurtz-type coupling; 4) Ultimately it should not bear a hydrogen atom in β-position to fully exclude β-hydride elimination. All those points however did not tackle the drawback of the poor solubility of the neopentylsodium (**37**). The scope of the electrophile quenches after the halogen sodium exchange was limited to silyl chlorides, deuterations and transmetalation reactions.[143] It might be assumed that the reason for this is the presence of elemental sodium in the reaction mixture. This could have detrimental effects on electrophiles, such as for instance carbonyls, which are prone to reduction as can for instance be seen in the Bouveault-Blanc reaction.[144] Thus, the low solubility of neopentylsodium, which did not allow a satisfying separation from strongly reductive sodium metal significantly decreased the applicability of the procedure.

In an earlier paper the same group already reported the generation of arylsodium species **41** via two electron reduction of aryl chlorides **42** and their use in in palladium catalysed cross-couplings. They were able to either perform Suzuki-Miyaura or Negishi coupling after transmetalation with zinc salts or

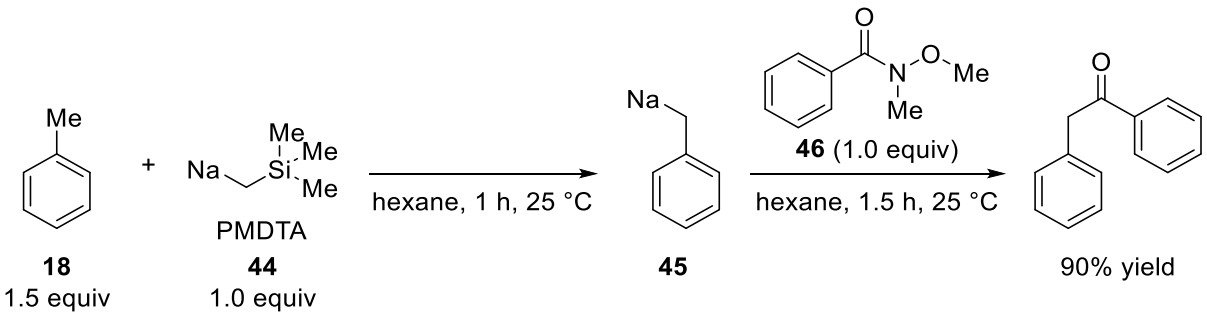
[143] S. Asako, I. Takahashi, H. Nakajima, L. Ilies, K. Takai, *Communications Chemistry* **2021**, *4*, 76.
[144] a) L. Bouveault, G. Blanc, *Bull. Soc. Chim. Fr* **1903**, *136*, 1676; b) J. An, D. N. Work, C. Kenyon, D. J. Procter, *J. Org. Chem.* **2014**, *79*, 6743.

borate esters. But most interestingly they applied the arylsodium species without transmetalation in palladium catalysed Murahashi type couplings (Scheme 22).[145]



Scheme 22: Preparation of 2-sodium anisol (**41**) by oxidative insertion and subsequent Pd-catalyzed Murahasi crosscoupling with 2-chloronaphtalene (**43**).[145a]

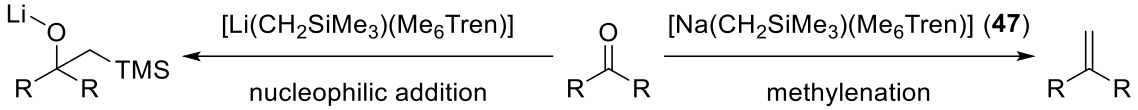
Most recently Hevia and co-workers used $NaCH_2SiMe_3$·PMDTA (**44**) as a base for lateral sodiations of alkyl benzenes such as **18** and subsequently used benzylic sodium species like **45** in quench reactions with Weinreb-amides (**46**) (Scheme 23).[146] It was reported before that the addition of multidentate amide ligands disaggregates the otherwise polymeric structure of $NaCH_2SiMe_3$ and that the resulting $NaCH_2SiMe_3$·PMDTA (**44**) is soluble in hexane.[147] $NaCH_2SiMe_3$ was obtained according to the Schlosser method in a rather tedious procedure by mixing $LiCH_2SiMe$ with NaO*t*Bu in hexane followed by a gravity filtration yielding a filter cake of insoluble $NaCH_2SiMe_3$ which subsequently was dried under vacuum than taken up in fresh hexane together with PMDTA to give a clear solution. Similar reagents of the structure $MetCH_2SiMe_3$, with Met being Na, K, Rb or Cs, have been used before for the lateral metalation of alkyl benzenes.[148]



Scheme 23: $NaCH_2SiMe_3$·PMDTA (**44**) mediated benzylic sodiation.[146]

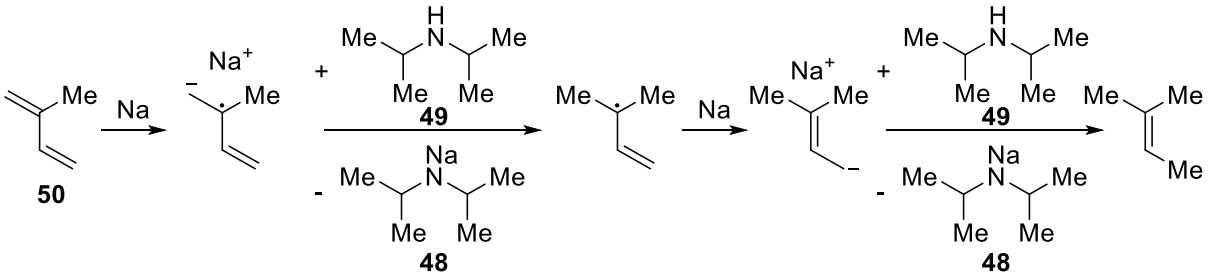
[145] a) S. Asako, H. Nakajima, K. Takai, *Nat. Catal.* **2019**, *2*, 297; b) S. Hazra, C. C. C. Johansson Seechurn, S. Handa, T. J. Colacot, *ACS Catal.* **2021**, *11*, 13188.
[146] D. Anderson, A. Tortajada, E. Hevia, *Angew. Chem. Int. Ed.* **2023**, e202218498.
[147] a) S. E. Baillie, W. Clegg, P. García-Álvarez, E. Hevia, A. R. Kennedy, J. Klett, L. Russo, *Chem. Commun.* **2011**, *47*, 388; b) W. Clegg, B. Conway, A. R. Kennedy, J. Klett, R. E. Mulvey, L. Russo, *Eur. J. Inorg. Chem.* **2011**, *2011*, 721.
[148] A. J. Hart, D. H. O'Brien, C. R. Russell, *J. Organomet. Chem.* **1974**, *72*, C19.

A similar reagent [Na(CH_2SiMe_3)(Me_6Tren)] (**47**) was shown to undergo methylenation reactions instead of the nucleophilic additions observed for the lithium equivalent when reacted with carbonyl compounds such as ketones and amides. This procedure represents an intriguing alternative to the commonly used and often times toxic methylenation methods (Scheme 24). [149]



Scheme 24: Methylenation of carbonyls using [Na(CH_2SiMe_3)(Me_6Tren)] (**47**).[149]

This revival of the synthetic sodium chemistry was initiated by David Collum and his group and their thorough studies of sodium diisopropylamide (NaDA, **48**) the sodium equivalent of LDA. Following up on the reports of Gilman[150] and Morton[151] which show that some alkylsodium species are soluble and stable in trialkylamine solvents.[152] They were able to show that NaDA (**48**) is readily produced in *N*,*N*-dimethylethylamine (DMEA) from di*iso*propylamine (**49**) and sodium in the presence of isoprene (**50**).[153] Earlier reports by Wakefield reported the same synthesis with the variation that cyclohexane was used as a solvent, consequently a mixture containing precipitated NaDA (**48**) was obtained.[154] The mechanism of this alkali amide formation is closely related to the one of the Birch reduction, isoprene (**50**) acts as electron acceptor and its resulting anions deprotonate the amine (Scheme 25).[155]

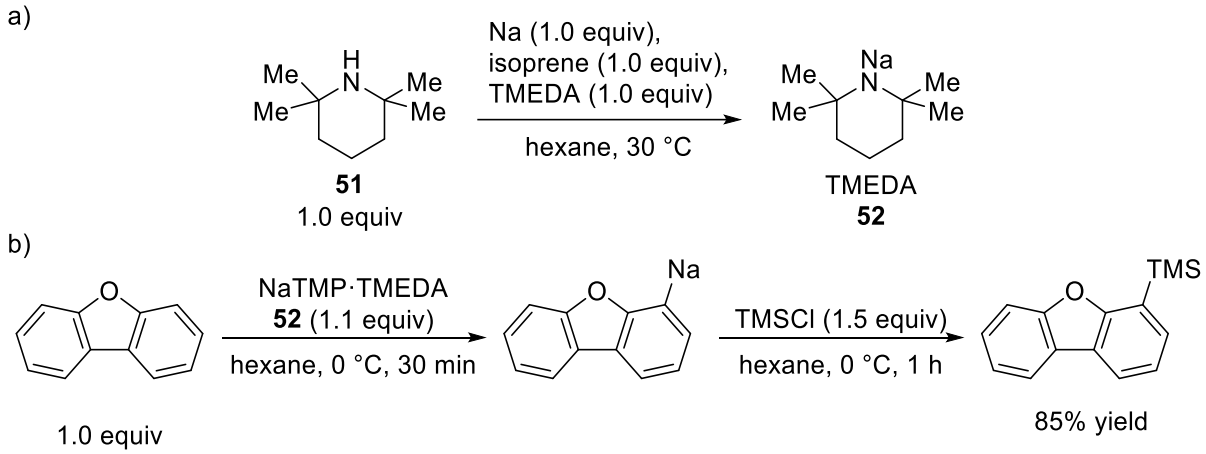


Scheme 25: Mechanism of the NaDA (**48**) preparation using isoprene (**50**) as electron acceptor.

Amide bases of sodium and potassium have been studied before, especially the group of Mulvey prepared and crystallized a plethora of different Na/K derivatives of TMPH (**51**) and di*iso*propylamine (**49**). Most of them were however prepared via the Lochmann-Schlosser method by addition of alkoxides to the lithium amide. Furthermore, Mulvey showed more interest in the structure of these bases than in their synthetic utility.

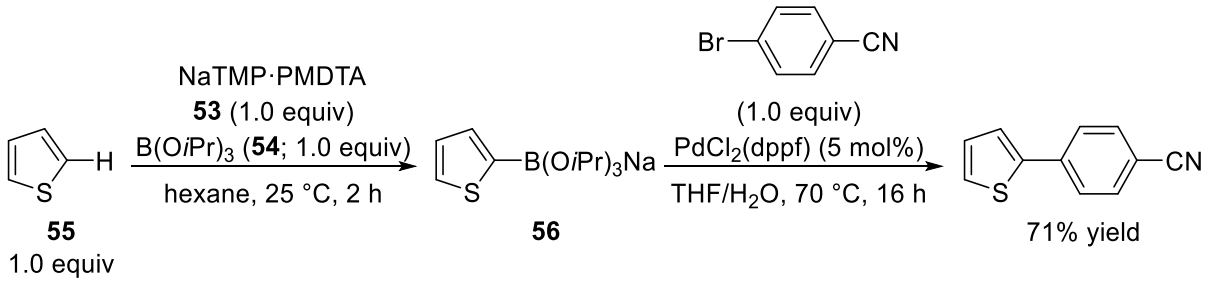
[149] N. Davison, C. L. McMullin, L. Zhang, S.-X. Hu, P. G. Waddell, C. Wills, C. Dixon, E. Lu, *J. Am. Chem. Soc.* **2023**, *145*, 6562.
[150] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109.
[151] A. A. Morton, F. K. Ward, *J. Org. Chem.* **1960**, *25*, 120.
[152] D. B. Collum, R. A. Woltornist, Y. Ma, R. F. Algera, Y. Zhou, Z. Zhang, *Synthesis* **2020**, *52*, 1478.
[153] Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312.
[154] D. Barr, A. J. Dawson, B. J. Wakefield, *Chem. Commun.* **1992**, 204.
[155] F. Gaudemar-Bardone, M. Gaudemar, *Synthesis* **1979**, *1979*, 463.

The reports of Collum led to further investigations of other groups. An almost identical lithium free preparation of NaTMP·TMEDA (**52**) was reported by Asako and Takai. In the presence of 1.0 equiv TMEDA, the preparation proceeded smoothly in hexane. Interestingly NaTMP·TMEDA (**52**) appears to be soluble in hydrocarbons. The authors applied the resulting sodium amide **52** as base in Wittig reactions and directed metalations of heteroarenes (Scheme 26).[156]



Scheme 26: a) Preparation of NaTMP·TMEDA (**52**). b) Directed *ortho* sodiation with NaTMP·TMEDA (**52**).[156]

Following up on those findings Hevia et al. were using NaTMP·TMEDA (**52**) or NaTMP·PMDTA (**53**) in the presence of B(O*i*Pr)$_3$ (**54**) for sodium mediated borylation of arenes such as **55.** The obtained aryl boronates **56** where subsequently used in Suzuki-Miyaura couplings. The Lewis acidic B(O*i*Pr)$_3$ (**54**) seems to have a significant impact on the metalation efficacy since without additive or with different boron species the yield of the metalated or borylated product (**56**) drops significantly (Scheme 27).[157]

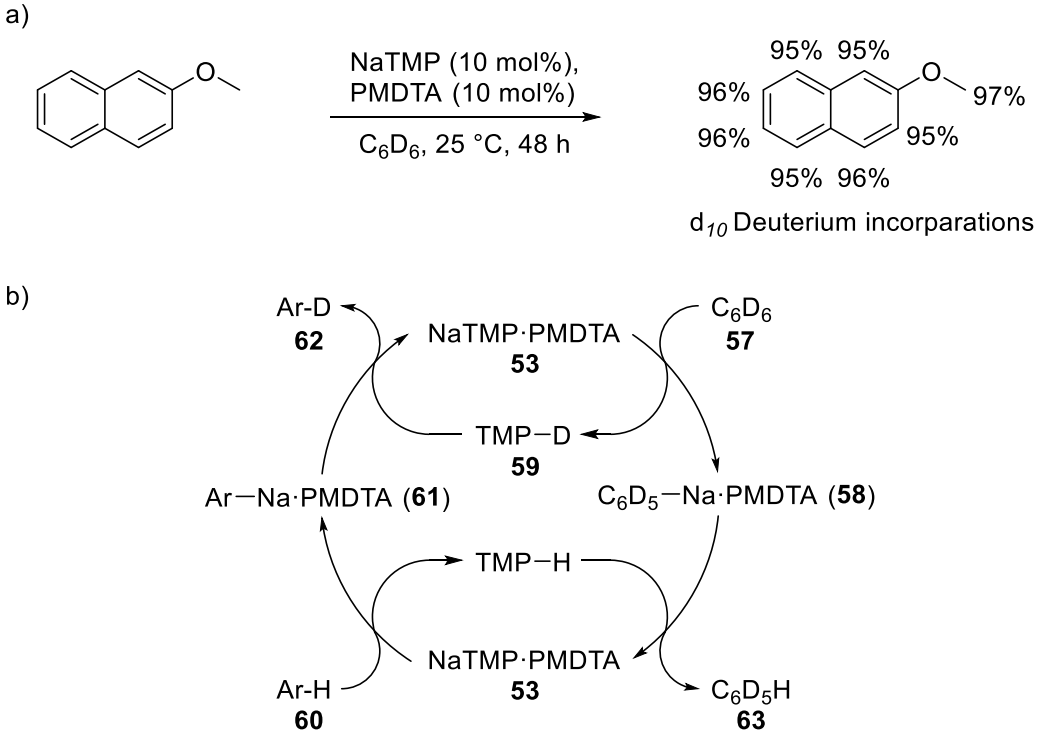


Scheme 27: Deprotonation of heteroarenes **55** with NaTMP·PMDTA (**53**) in the presence of B(O*i*Pr)$_3$ (**54**) and subsequent Suzuki-Miyaura cross-coupling.[157]

The same authors reported a perdeuteration of arenes using catalytic amounts of NaTMP·PMDTA (**53**) in benzene-d_6 (**57**) (Scheme 28a). The reaction proceeds best when an excess of the deuterium source in this case C_6D_6 (**57**) is present. The deuterated benzene **57** is metalated by NaTMP·PMDTA (**53**) resulting in phenylsodium-d_5 (**58**) and TMPD (**59**). In a second cycle, NaTMP **53** is also sodiating the

[156] S. Asako, M. Kodera, H. Nakajima, K. Takai, *Adv. Synth. Catal.* **2019**, *361*, 3120.
[157] L. Bole, A. Tortajada, E. Hevia, *Angew. Chem. Int. Ed.* **2022**.

arene **60**. This partial sodiation now enables a proton/deuterium metal permutation on the sodiated arenes **61** resulting in Ar-D (**62**) and C_6D_5H (**63**) respectively. During this step the catalytic cycle is closed by reformation of NaTMP **53** (Scheme 28b). Interestingly the use of the ligand had a severe influence on the deuteration levels. When THF was used instead of polydentate amine ligands the percentage of deuteration decreased significantly, thus showing the importance of the increased kinetic basicity of NaTMP obtainable by addition of PMDTA and TMEDA[158]



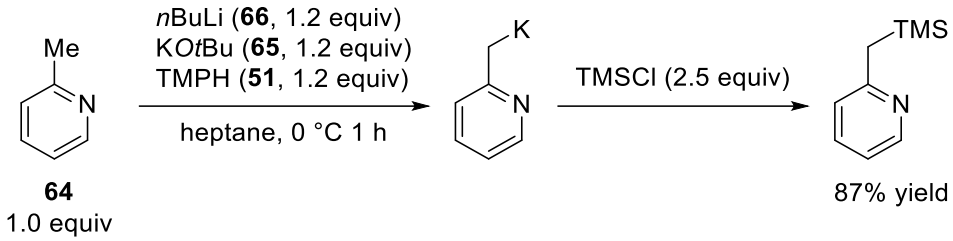
Scheme 28: a) NaTMP·PMDTA (**53**) mediated perdeuteration of arenes. b) Proposed catalytic cycle of the NaTMP·PMDTA (**53**) mediated perdeuteration.[158]

Crystal structures of sodium and potassium amide bases have drawn the attention of inorganic chemists several years prior to the synthetic applications in organic chemistry.[159] Thus, Mulvey and others were able to synthesize various amide species and subject them to X-ray diffraction studies. Those alkali

[158] A. Tortajada, E. Hevia, *J. Am. Chem. Soc.* **2022**, *144*, 20237.
[159] a) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470; b) D. R. Armstrong, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2011**, *17*, 8820.

metal amides include: NaDA·TMEDA,[160] KDA·TMEDA,[161] differently solvated NaTMP species[162] and KTMP·TMEDA.[163]

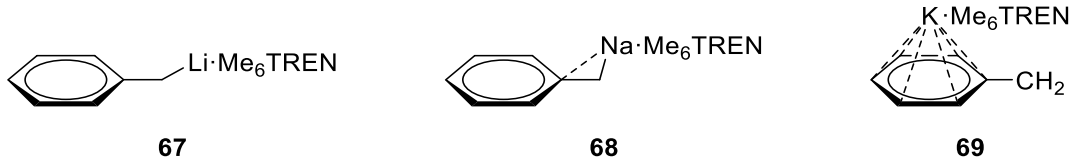
O´Shea and co-workers used Schlosser-type mixed metal Li/KTMP base for the benzylic metalation of unactivated alkyl substituted arenes and were able to perform various quenches including silylations, alkylations and couplings with benzyl bromides. The base was prepared in presence of the methylarene **64** by subsequent addition of KO*t*Bu (**65**) followed by *n*BuLi (**66**) and TMPH (**51**) to the reaction mixture (Scheme 29).[164]



Scheme 29: Lateral metalation of 2-picoline (**64**) with mixed metal Li/KTMP.[164]

Interestingly, when metalating toluene with different alkali metals in the presence of tris(*N*,*N*-dimethyl-2-aminoethyl)amine (Me_6TREN), the behaviour of the alkali metal reagents varies significantly. Upon metalation with LiTMP in the presence of Me_6TREN toluene was lithiated in benzylic position. The benzylic metal species of the heavier alkali metals sodium and potassium were obtained using super basic Lochmann-Schlosser bases (*t*BuONa/*n*BuLi and *t*BuOK/*n*BuLi) and subsequent addition of Me_6TREN. X-ray diffraction studies gave insights into the positioning of the alkali metal cation. Whereas in the benzylic lithium species the metal atom is bound via a Li–C σ bond to the benzylic carbon and shows no significant interaction with the phenyl ring (**67**), a trend towards more interaction with the phenyl ring with increasing cation size is observable. Similar to the lithium species, the sodium structure is also a monomeric one but in addition to the Na–C σ bond the position of the sodium cation in the crystal structure indicates a π-interaction with the electrons of the aromatic ring (**68**). The biggest difference is observable for the potassium reagent (**69**). No interaction with the benzylic carbon atom is observable instead the cation is coordinated exclusively to the π-system (Figure 17).[165]

[160] P. C. Andrews, N. D. R. Barnett, R. E. Mulvey, W. Clegg, P. A. O'Neil, D. Barr, L. Cowton, A. J. Dawson, B. J. Wakefield, *J. Organomet. Chem.* **1996**, *518*, 85.
[161] W. Clegg, S. Kleditzsch, R. E. Mulvey, P. O'Shaughnessy, *J. Organomet. Chem.* **1998**, *558*, 193.
[162] a) B. Gehrhus, P. H. Hitchcock, A. R. Kennedy, M. F. Lappert, R. E. Mulvey, P. J. A. Rodger, *J. Organomet. Chem.* **1999**, *587*, 88; b) D. R. Armstrong, P. García-Álvarez, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2011**, *17*, 6725; c) D. R. Armstrong, D. V. Graham, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Chem. Eur. J.* **2008**, *14*, 8025.
[163] D. R. Armstrong, D. V. Graham, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Chem. Eur. J.* **2008**, *14*, 8025.
[164] a) A. Manvar, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2015**, *80*, 8727; b) M. Blangetti, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2012**, *77*, 2870.
[165] M. G. Davidson, D. Garcia-Vivo, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2011**, *17*, 3364.



67 **68** **69**

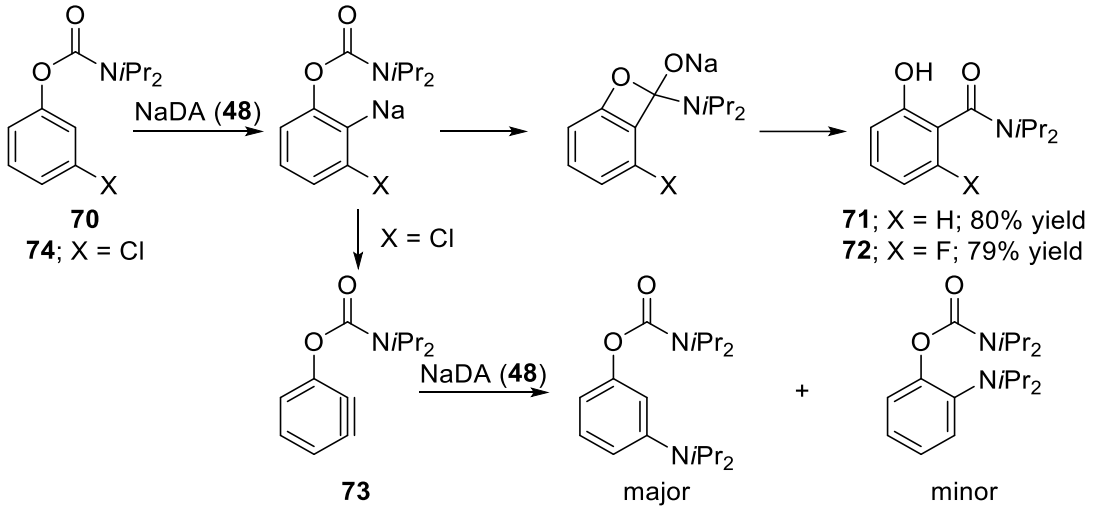
Figure 17: Schematic depiction of the σ/π bonding preferences of alkali metal cations in toluene.[166]

Similar observations have been made in the presence of THF. In these studies sodium is likewise bound to the benzylic and the ipso carbon of toluene. Furthermore, benzylic species of caesium and rubidium were included. Both the rubidium and the caesium cations coordinated to the phenyl ring. A major difference is however the change from a 1D to 2D coordination polymer observed in benzylcaesium. Other than for rubidium the caesium interacts with both the α-carbon as well as the aromatic ring.[167] Sigma/pi bonding preferences of alkali metal cations to biarylmethyl anions have been studied likewise.[168] Those cation-π interactions can be utilized in metalation reactions. Alkali metal HMDS bases are for instance not able to metalate toluene, but by addition of caesium salts which coordinate to the aromatic π-system toluene becomes slightly polarized. The acidity of the benzylic group is increased and deprotonation can take place.[169]

According to Collum and co-workers, NaDA exclusively forms dimers in which the sodium atom is four times coordinated, when dissolved in trialkylamines and THF. Those structures are similar to the solid state crystal structures mentioned above. The use of DMEA as a solvent does not only increase the solubility but also increases the ability of NaDA to be stored. Whereas the half-life of NaDA (**48**) in DMEA is two months, metalation and subsequent decomposition of commonly used ethereal solvents such as THF reduces the half-life time to one hour.[170] A plethora of different reactions with NaDA dissolved in DMEA were performed and compared with the reactivities of LDA. Elimination of alkyl and alkenyl halides gave the corresponding alkenes and alkynes. Furthermore, it overcame the problem of competitive S_N2 reactions, in which the amide replaces the halide, frequently observed for eliminations with LDA.[171] In particular metalations and various elimination reactions on alkylhalides and epoxides were accelerated up to 1000-fold in the presence of PMDTA.[172] Directed sodiation of arylcarbamates **70** proceeded smoothly and resulted after Snieckus-Fries rearrangement in the corresponding *ortho*-hydroxylbenzamides **71** and **72**. However, in the presence of chloride atoms in

[166] M. G. Davidson, D. Garcia-Vivo, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2011**, *17*, 3364.
[167] L. Brieger, C. Unkelbach, C. Strohmann, *Chem. Eur. J.* **2021**, *27*, 17780.
[168] A. Rae, K. M. Byrne, S. A. Brown, A. R. Kennedy, T. Krämer, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2022**, *28*, DOI: 10.1002/chem.202104260.
[169] T. X. Gentner, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2021**, *60*, 9247.
[170] R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 7921.
[171] Y. Ma, R. F. Algera, R. A. Woltornist, D. B. Collum, *J. Org. Chem.* **2019**, *84*, 10860.
[172] Y. Ma, R. A. Woltornist, R. F. Algera, D. B. Collum, *J. Am. Chem. Soc.* **2021**, *143*, 13370.

meta position to the carbamate benzyne formation is observable and the yield of the desired phenol drops significantly (Scheme 30).[173]



Scheme 30: *Ortho*-sodiation of arylcarbamates and subsequent Snieckus-Fries rearrangement and the competitive formation of benzyne **73** in case of 3-chlorophenyl di*iso*propylcarbamate **74**.[173]

Similar problems were observed when trying to prepare *ortho*-halo arylsodiums in directed metalations of haloarenes (Figure 18).[174]

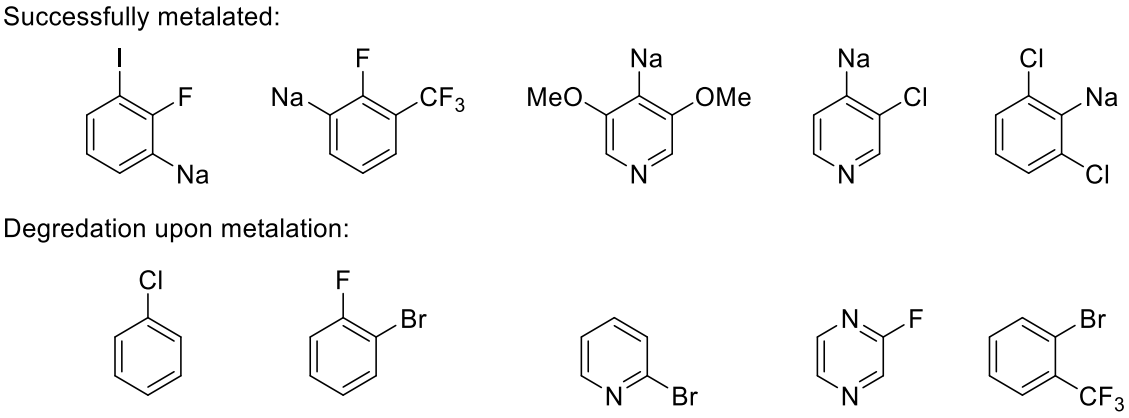


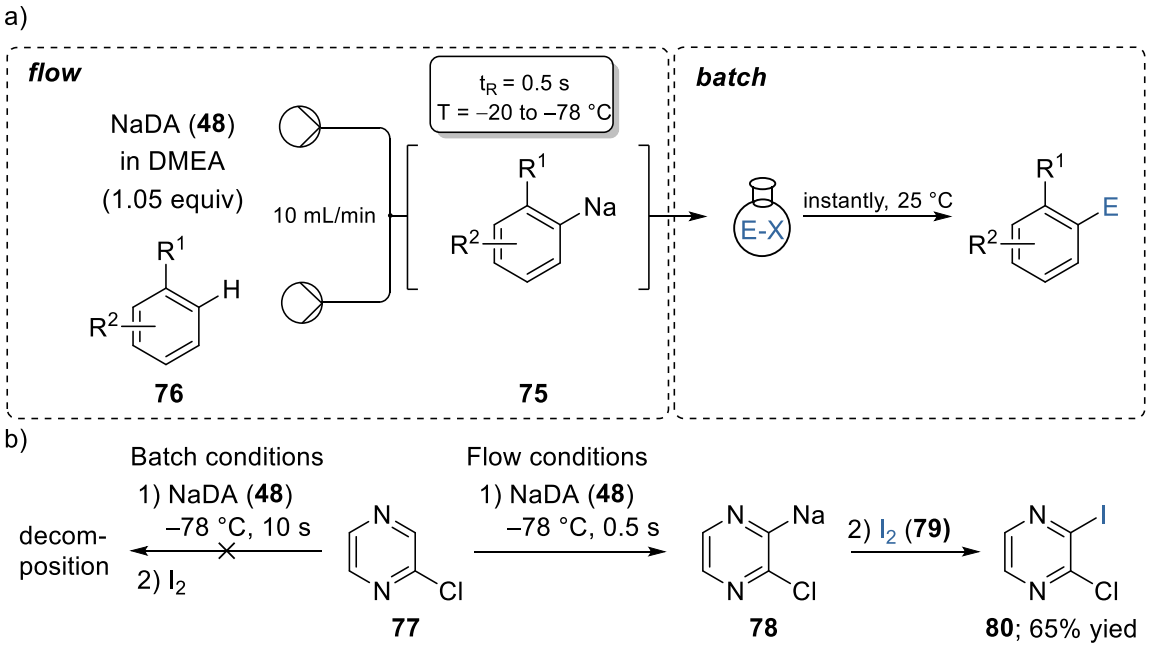
Figure 18: Directed *ortho* metalation of arenes and its limitations using NaDA under Batch conditions.[174]

Those nicely reported limitations in the metalation of halogen bearing aromatics led Weidmann et al. to the assumption, that directed metalations using NaDA in DMEA might benefit from subsecond reaction times available under continuous flow conditions as can be seen in the following chapter.[175]

[173] Y. Ma, R. A. Woltornist, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2019**, *84*, 9051.
[174] R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197.
[175] N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748.

3.3 Organometallic Chemistry in Continuous Flow

Indeed, the flow procedure invented in the Knochel group, broadens the substrate scope substantially. Preparation of NaDA (**48**) in DMEA in batch and subsequent continuous flow metalation within half a second and at –20 to –78 °C gave the corresponding sodiated arenes **75**. The reaction solution was then injected into a round bottom flask charged with an electrophile under argon atmosphere (Scheme 31a).[176]



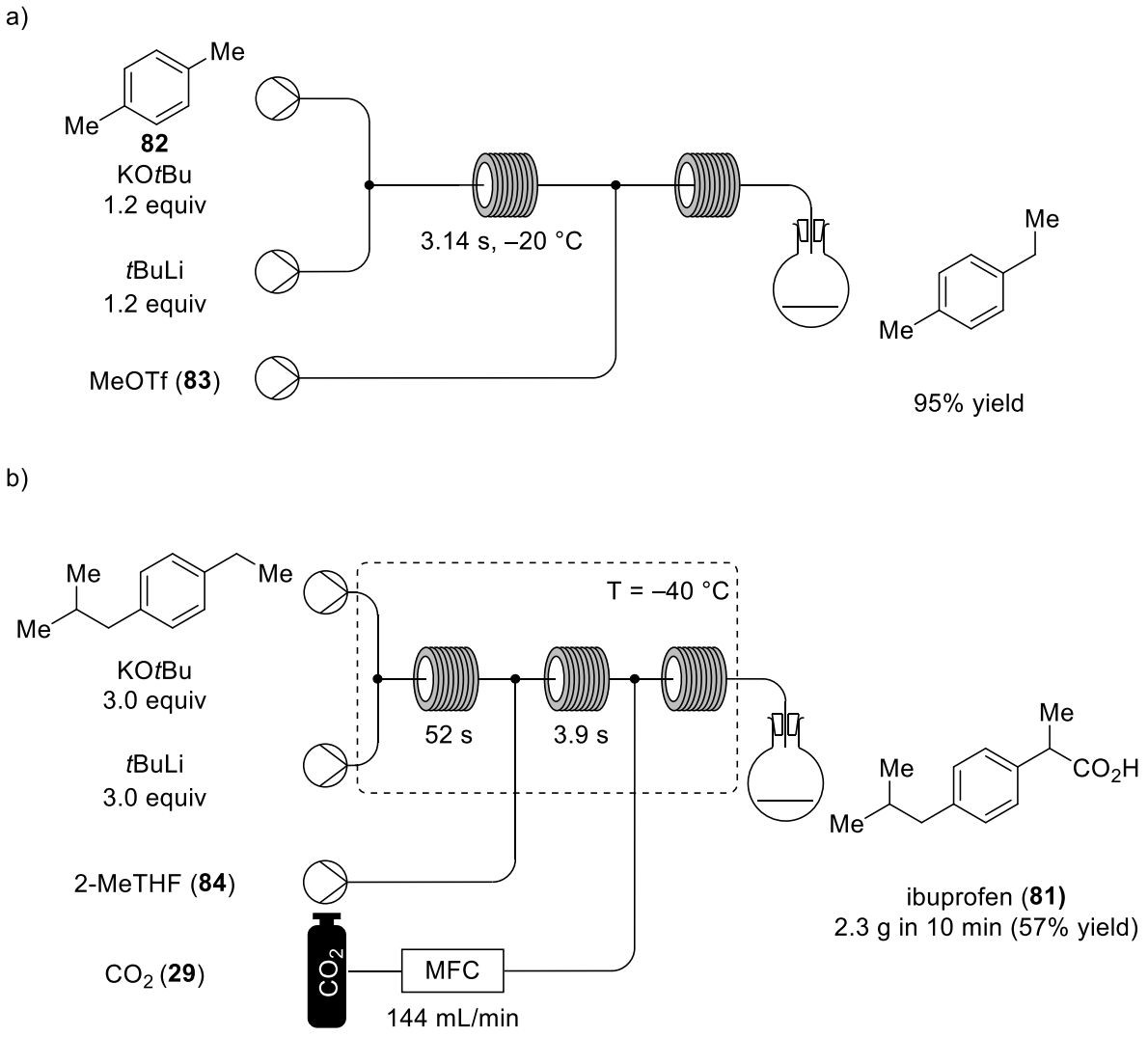
Scheme 31: a) General scheme of the continuous flow sodiation of arenes **76** and hetero arenes using NaDA (**48**). b) Comparison studies between batch and flow sodiation of 2-chloropyrazine (**77**).[176]

When applying continuous flow conditions, they were able to successfully metalate and quench various (hetero)arenes such as for instance 2-chloropyrazine which were unattainable under batch conditions. Presumably the sodiated heterocycle **78** is not stable and decomposes within the 10 s reaction time. Decreasing the residence time to 0.5 s led upon batch quench with I_2 (**79**) to the functionalized product **80** in 65% yield (Scheme 31b). Additionally, they were able to show the increased reaction scope by sodiation of various starting materials which decomposed under NaDA mediated deprotonation in a round bottom flask according to Collum and Co-workers. [176, 177]

In 1991 Schlosser reported a one-pot procedure for the synthesis of Ibuprofen including three subsequent metalations of *para*-xylene with the *n*BuLi/KO*t*Bu-superbase. However, this procedure was lacking reproducibility as many other publications state.[178] Similar to these publications, ibuprofen (**81**)

[176] N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748.
[177] R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197.
[178] a) M. Schlosser, H. Geneste, *Chem. Eur. J.* **1998**, *4*, 1969; b) F. Faigl, M. Schlosser, *Tetrahedron Lett.* **1991**, *32*, 3369.

was prepared from *p*-xylene (**82**) by three consecutive metalations with a similar in situ generated superbase (Scheme 32).[179]



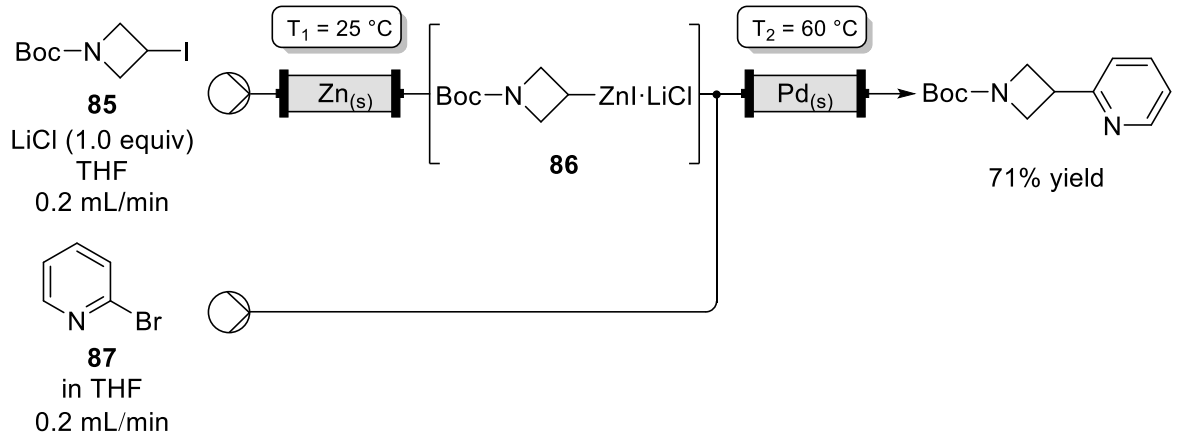
Scheme 32: a) First step of the continuous flow synthesis of Ibuprofen (**81**) from *p*-xylene (**82**). b) Third step of the continuous flow synthesis of ibuprofen (**81**) from *p*-xylene (**82**).[179]

The authors used the intermediate mixed potassium/lithium species for in-line Wurtz-type couplings with methyltriflate (**83**) (Scheme 32a) and *iso*-propyl iodide in the first two reaction steps. For the biphasic carboxylation in the third step the set-up was adjusted. First the concentration and the number of equivalents of base in the first reactor was increased. Since diluted reaction mixtures showed enhanced efficiency in the biphasic reaction step additional 2-MeTHF (**84**) was added via a third pump. Carbon dioxide (**29**) was introduced via a mass flow controller (MFC). 2.3 g of the desired ibuprofen (**81**) were obtained in 57% yield within 10 min total runtime (Scheme 32b).[180]

[179] H.-J. Lee, H. Kim, D.-P. Kim, *Chem. Eur. J.* **2019**, *25*, 11641.
[180] H.-J. Lee, H. Kim, D.-P. Kim, *Chem. Eur. J.* **2019**, *25*, 11641.

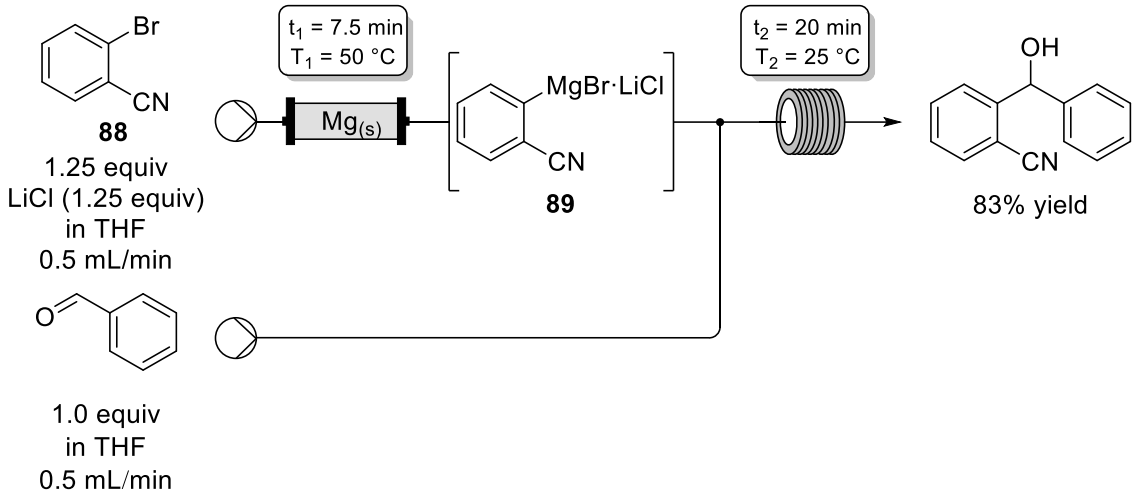
Apart from the aforementioned publications, the use of sodium and potassium organyls under continuous flow conditions is very rare.[181] The low solubility of these metal species and most of their bases precludes them for microreactor technologies which are in themselves prone to clogging. In chapter 2.1.3 the use of packed-bed reactors is mentioned as a way to conduct biphasic solid-liquid reactions. Those reactors charged with elemental magnesium and zinc were applied for oxidative additions of the respective metal into carbon halide bonds.[182] Most work in this field has been done by Alcázar and co-workers.[183] They reported an oxidative insertion of zinc into alkylic or benzylic carbon halide bonds such as in **85**. In some cases THF soluble LiCl was included in the starting material mixture which is known to have beneficial influence in oxidative insertion reactions due to its solubilizing effects.[184] The resulting organozinc halides **86** were subsequently used in palladium catalysed Negishi-cross-coupling reactions with aryl halides such as **87**. The cross-coupling reaction took place in a second packed reactor charged with the SiliaCat DPP-Pd catalyst and was heated to 60 °C (Scheme 33). The metallic zinc required activation before it could be used for oxidative insertions. Those activations were achieved by pumping TMSCl in THF at a flow rate of 1.0 mL/min followed by 1,2-dibromoethane at the same flow rate.[183a]

[181] a) K. Hashimoto, N. Kumagai, M. Shibasaki, *Org. Lett.* **2014**, *16*, 3496; b) G. Vilé, G. Schmidt, S. Richard-Bildstein, S. Abele, *J. Flow Chem.* **2018**, *9*, 19.
[182] a) S. H. Lau, S. L. Bourne, B. Martin, B. Schenkel, G. Penn, S. V. Ley, *Org. Lett.* **2015**, *17*, 5436; b) S. Ley, A. Hafner, *Synlett* **2015**, *26*, 1470; c) E. Watanabe, Y. Chen, O. May, S. V. Ley, *Chem. Eur. J.* **2020**, *26*, 186; d) M. Goldbach, E. Danieli, J. Perlo, B. Kaptein, V. M. Litvinov, B. Blümich, F. Casanova, A. L. L. Duchateau, *Tetrahedron Lett.* **2016**, *57*, 122; e) N. Sotto, C. Cazorla, C. Villette, M. Billamboz, C. Len, *J. Org. Chem.* **2016**, *81*, 11065; f) A. Herath, V. Molteni, S. Pan, J. Loren, *Org. Lett.* **2018**, *20*, 7429; g) M. Tissot, N. Body, S. Petit, J. Claessens, C. Genicot, P. Pasau, *Org. Lett.* **2018**, *20*, 8022; h) Y. Deng, X. J. Wei, X. Wang, Y. Sun, T. Noel, *Chem. Eur. J.* **2019**, *25*, 14532.
[183] a) N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737; b) L. Huck, M. Berton, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar, *Green Chem.* **2017**, *19*, 1420; c) L. Huck, A. de la Hoz, A. Diaz-Ortiz, J. Alcazar, *Org. Lett.* **2017**, *19*, 3747; d) I. Abdiaj, C. R. Horn, J. Alcazar, *J. Org. Chem.* **2019**, *84*, 4748.
[184] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.



Scheme 33: Continuous flow generation of organo zinc reagent **86** via oxidative insertion into organo halide bonds of **85** and subsequent Negishi-cross-coupling using a supported palladium catalyst.[185]

Grignard reagents were prepared in a similar on-demand procedure via insertion of magnesium into organo halide bonds. The aryl or alkyl halides **88** passed a previously activated magnesium column in the presence of LiCl. The resulting Grignard reagents **89** were either used directly for in-line electrophile quenches or quenches under batch conditions (Scheme 34).[186]



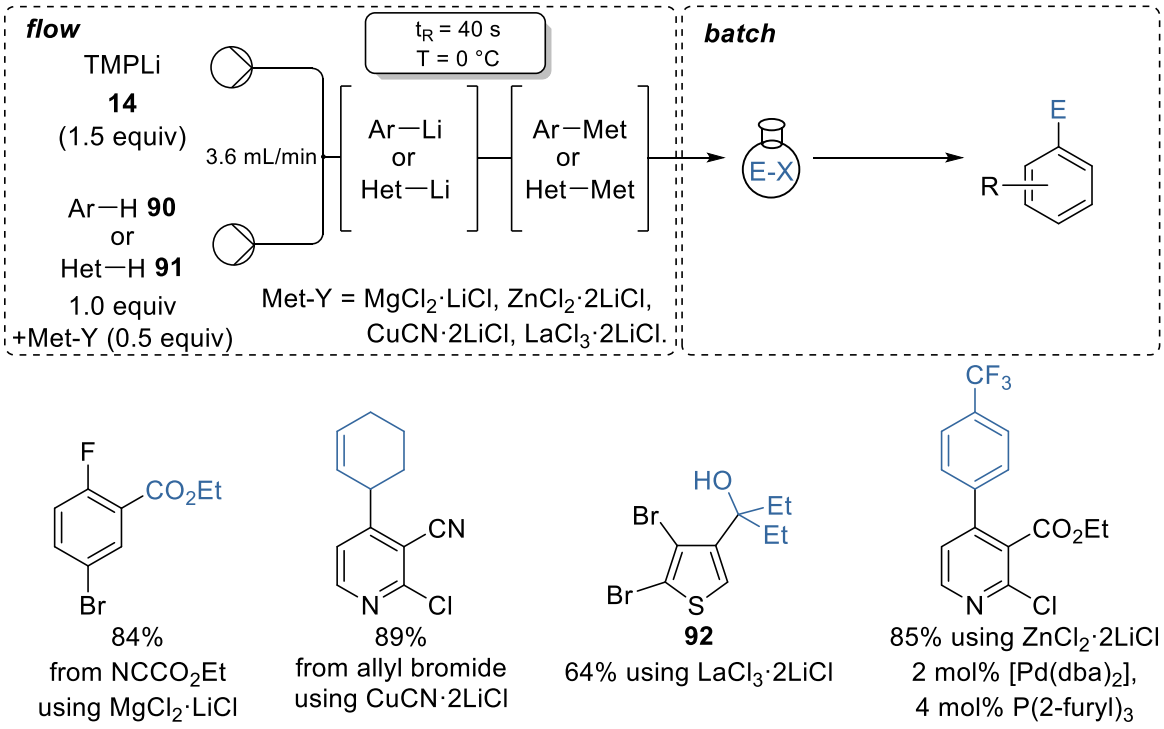
Scheme 34: Continuous flow generation of organo magnesium reagent **89** via oxidative insertion into organo halide bonds and subsequent electrophile quenche.[186]

The Knochel group reported different approaches towards polyfunctional magnesium and zinc reagents under continuous flow conditions via in situ trapping reactions. In those, an organolithium reagent is generated either via metalation using TMPLi or via halogen lithium exchange in the presence of metal halides. Thus, the reactions benefit from the high basicity of lithium bases and extremely fast reaction speeds of halogen lithium exchanges, while the in situ trapping with for instance zinc and magnesium

[185] N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737.
[186] L. Huck, A. de la Hoz, A. Diaz-Ortiz, J. Alcázar, *Org. Lett.* **2017**, *19*, 3747.

lead to a higher functional group tolerance. Azides, nitriles, isothiocyanates and esters are tolerated by this procedure.

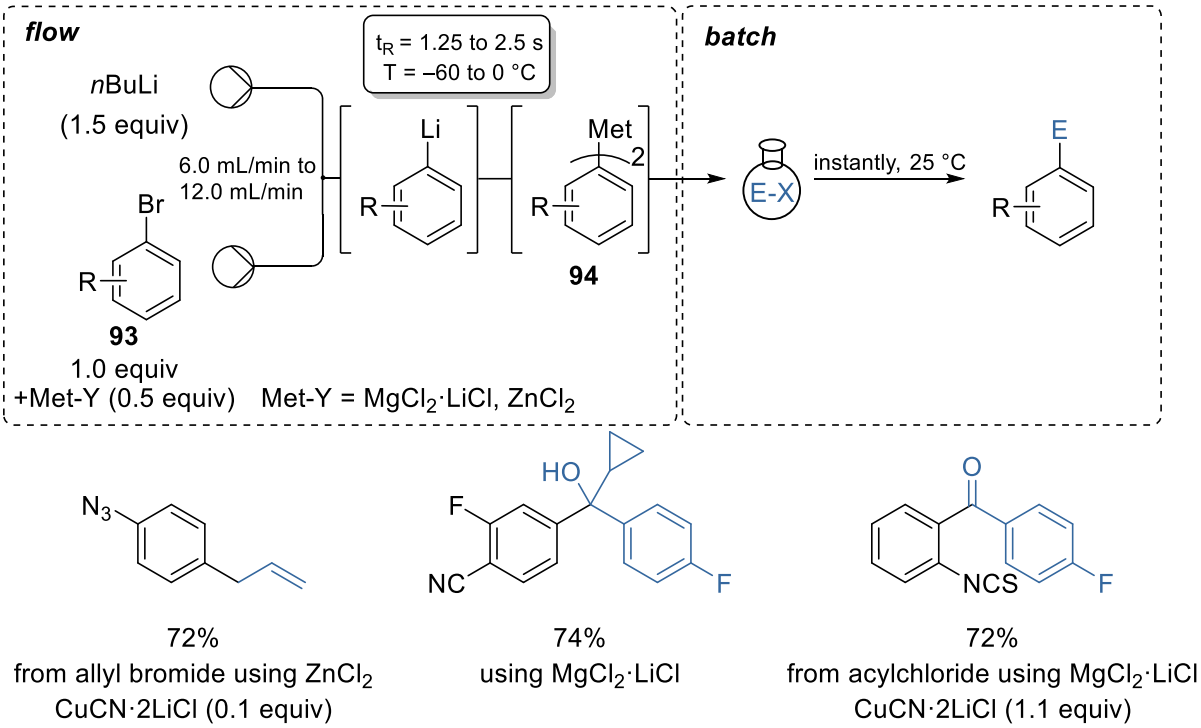
As an extention to the in 3.1.4 mentioned batch procedure of Frischmuth,[187] Becker et al. reported an in situ trapping metalation using TMPLi (**14**), which was able to lithiate under continuous flow conditions different arenes (**90**) or heteroarenes (**91**) premixed with Mg, Zn or La halides or with CuCN·2LiCl. Thus metalations which are usually not or at least problematic to achieve with Mg, La, Zn or Cu amide bases were accessible while sensitive functional groups such as esters were tolerated. In various cases, the reaction gave metalations at unusual kinetically controlled sides and was conducted at convenient reaction conditions of 0 °C and 40 s residence time. Those temperatures are rather unusual for directed lithitaions which are usually conducted at cryogenic temperatures. The resulting metal organics were suitable for different electrophile quenchings and thus this method allows an efficient in situ fine tuning of usually hard to obtain metallic species. Organolanthanum reagents are known to display a high reactivity towards carbonyl electrophiles due to their oxophilic nature[188] and thus the reaction of the thiophene lanthanum species with an enolizible ketone gave the corresponding alcohol **92** upon batch quench in good yields (Scheme 35).[189]



Scheme 35: In situ trapping metalation-transmetalation using magnesium, zinc and lanthanum halides as well as copper cyanide.[189]

[187] A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.
[188] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
[189] M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501.

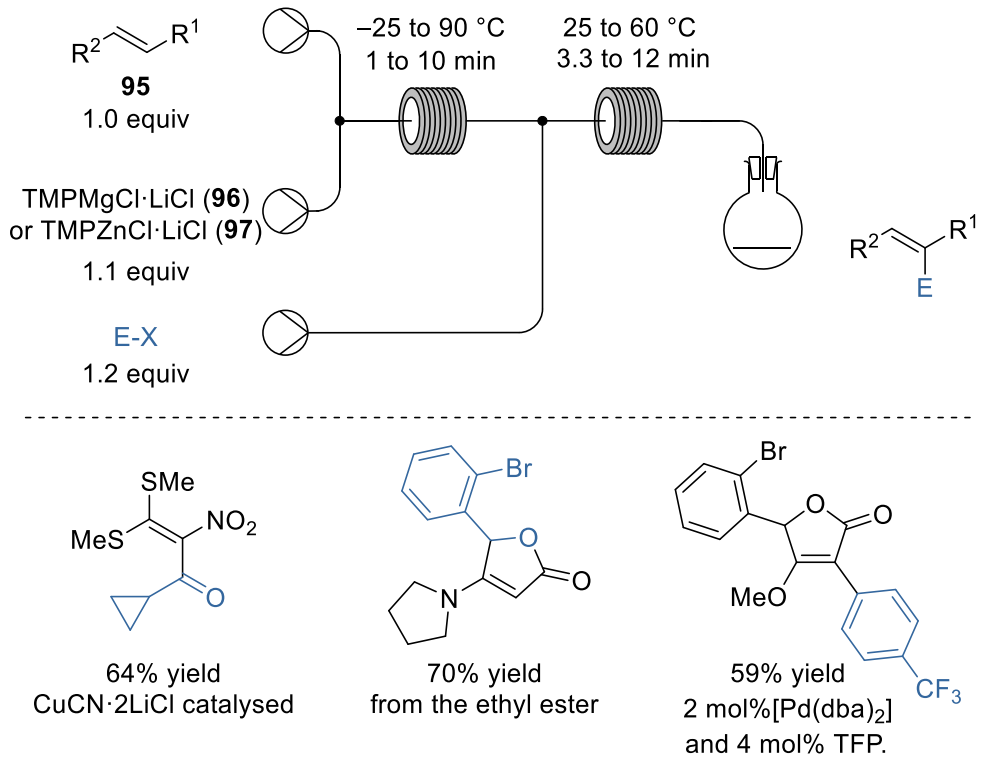
Ketels et al. were able to use a similar procedure for halogen lithium exchanges on sensitive bromo- and iodo-(hetero)arenes **93** in the presence of premixed $ZnCl_2$, $MgCl_2$·LiCl solution. A broad range of functional groups which are usually not tolerated by lithium organometallics were applicable. The resulting diorganomagnesium and diorganozinc reagents **94** were used in electrophilic quenches and cross-coupling reactions (Scheme 36).[190]



Scheme 36: In situ trapping halogen–lithium exchange using magnesium and zinc halides.[190a]

Metalations of functionalized alkenes (**95**) were reported using TMPMgCl·LiCl (**96**) or TMPZnCl·LiCl (**97**) under continuous flow conditions. In batch similar reactions are carried out at cryogenic temperatures, since the corresponding metal species are prone to anionic polymerizations. When conducting those reactions in continuous flow, the magnesiation and zincation of acrylates, acrylonitriles and nitroolefins takes place between –25 °C to 90 °C depending on the starting materials and amide bases. Unsurprisingly, TMPZnCl·LiCl (**97**) mediated metalations were conducted at higher temperatures. In-line electrophile quenches in chip or coil reactors[191] both resulted in highly functionalized alkenes. The product stream was afterwards collected in a flask filled with a saturated aqueous NH_4Cl solution (Scheme 37).[192]

[190] a) M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770; b) M. Ketels, D. Ziegler, P. Knochel, *Synlett* **2017**, *28*, 2817.
[191] T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933.
[192] M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828.

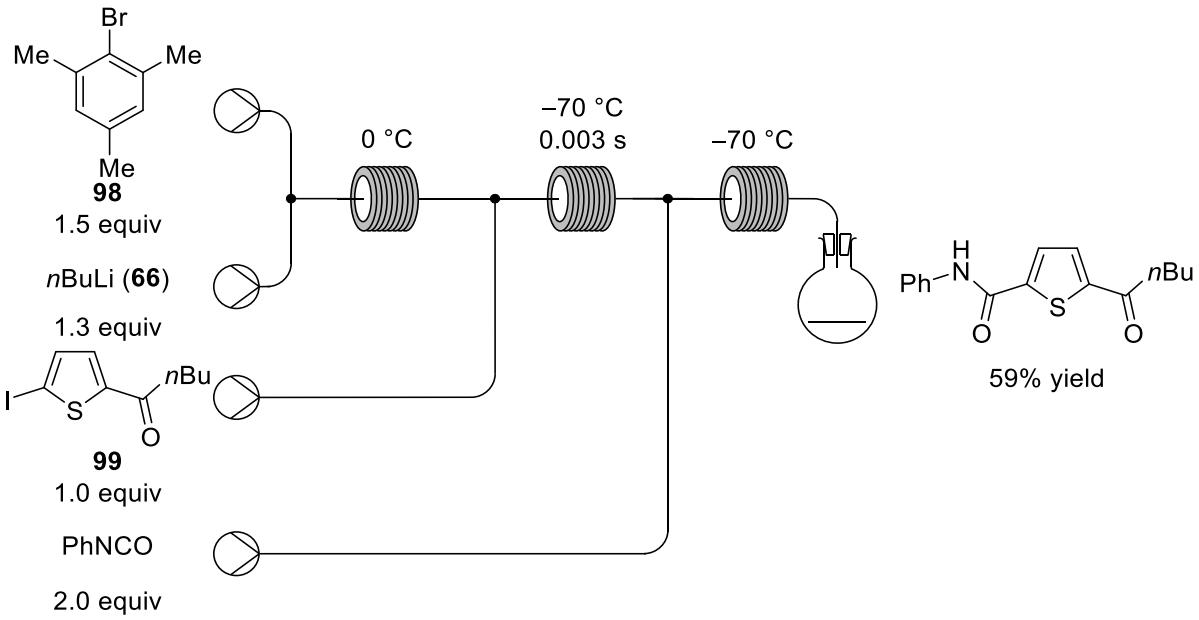


Scheme 37: Continuous flow magnesiation and zincation of acrylates, acrylonitriles and nitroolefines.[193]

The pioneering work of Yoshida, Nagaki et al. showed the potential continuous flow chemistry can unlock especially for highly reactive intermediates. High reactivity usually goes hand in hand with poor chemo- and/or regioselectivity and requires complex protecting group strategies. The group of Yoshida overcame the need for protecting groups by using extremely short residence times and small reaction volumes. They called this approach "flash chemistry". This flash chemistry approach allowed the generation of organolithium compounds bearing sensitive functional groups which can be considered impossible under batch conditions.[194]

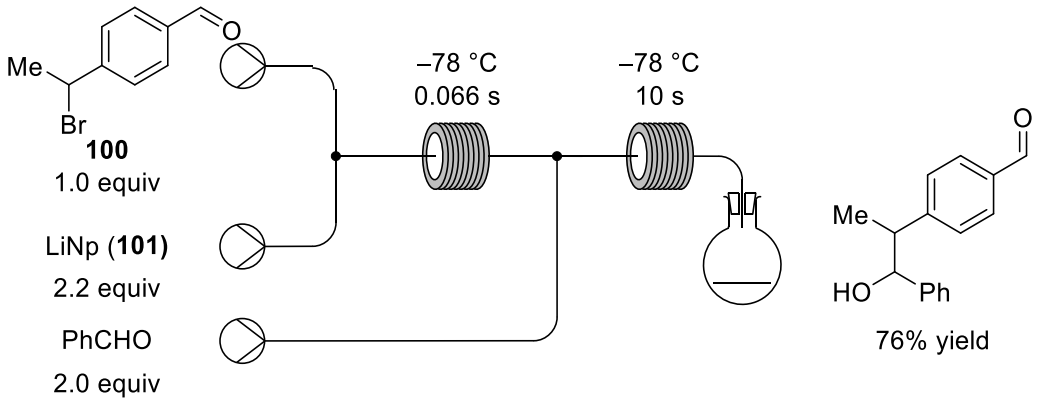
Thus halogen lithium exchange using *s*BuLi on *ortho*-bromobenzoates gave the resulting metal species within 0.01 s which were directly quenched with various electrophiles to give the *ortho*-functionalized esters.[195] Similarly, organolithium species containing even more electrophilic ketones were generated in a protecting group free procedure involving a first Br/Li-exchange between *n*BuLi (**66**) and mesityl bromide (**98**). The resulting mesityllithium is used as an exchange reagent for I/Li-exchanges with ketone bearing iodoarenes such as **99** in the same multi pump continuous flow set-up. After an extremely short residence time of 0.003 s the resulting aryllithium species is quenched in another mixer with the corresponding electrophile (Scheme 38).[196]

[193] M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828.
[194] M. Colella, A. Nagaki, R. Luisi, *Chem. Eur. J.* **2020**, *26*, 19.
[195] A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2008**, *47*, 7833.
[196] H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264.



Scheme 38: Br/Li-I/Li-exchange sequence for the generation of aryllithium reagents bearing unprotected enolisable ketones via a flash chemistry approach.[197]

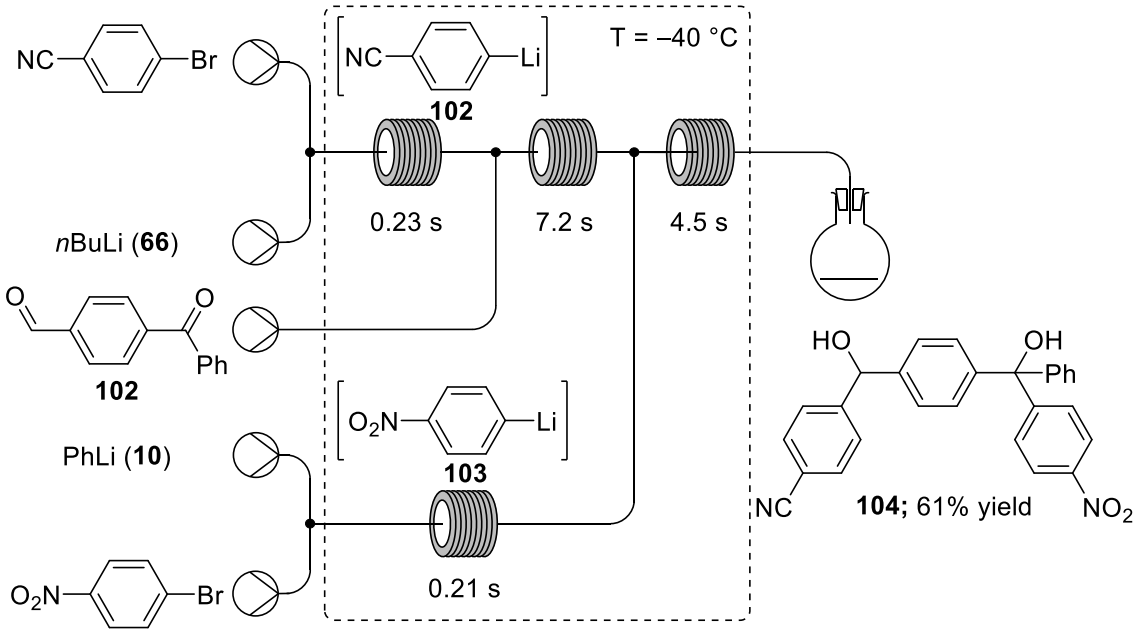
Using lithium naphthalenide (LiNp) or lithium 4,4′-di-*tert*-butylbiphenylide (LiDTBB) the same group were able to perform reductive lithiations into sterically demanding halides or into such bearing electrophilic ester, nitrile or epoxide groups. Apart from their possibility to react with the nucleophilic lithium species they can additionally be reduced by elemental alkali metals.[198] Performing such oxidative insertions into benzylic halides like **100** with help of LiNp (**101**) even tolerated aldehydes in addition to ester- and ketogroups (Scheme 39). Not only do these protocols exclude the need for protecting groups but in case of the oxidative insertion into the benzylic halides they also avoid Wurtz-type couplings which are often observed in batch since benzylic halides are good electrophiles.[199]



Scheme 39: Oxidative insertion into benzylic halides in the presence of sensitive functional groups.[199]

[197] H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264.
[198] A. Nagaki, H. Yamashita, K. Hirose, Y. Tsuchihashi, J. I. Yoshida, *Angew. Chem. Int. Ed.* **2019**, *58*, 4027.
[199] A. Nagaki, Y. Tsuchihashi, S. Haraki, J. Yoshida, *Org Biomol Chem* **2015**, *13*, 7140.

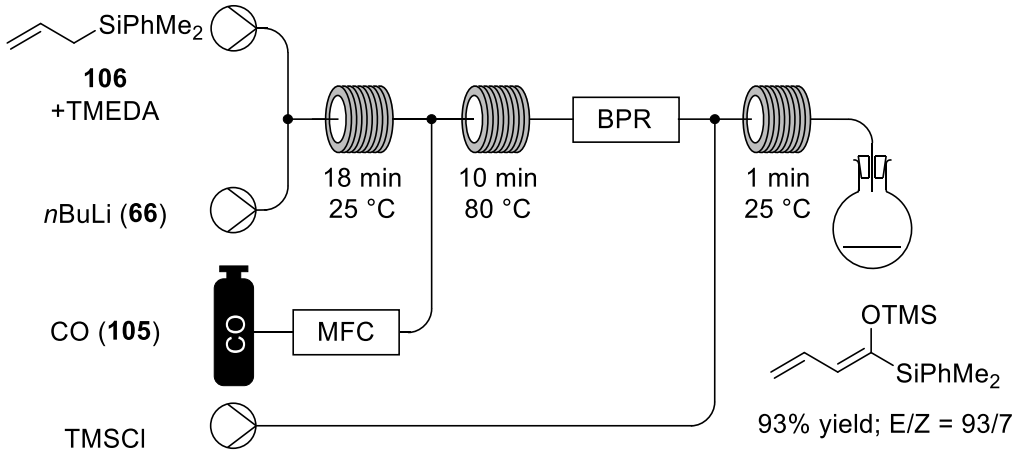
Furthermore, Yoshida was able to utilize high mixing efficiency of flow reactors for selective electrophilic additions to bifunctional electrophiles such as 4-benzoylbenzaldehyde (**102**). Even though, aldehydes are more electrophilic than ketones batch reactions lead to mixtures of products when reacted with PhLi (**10**). By performing the reactions in continuous flow, they were able to increase the chemoselectivity significantly. High flow rates favoured the desired attack on the aldehyde moiety. A multistep continuous flow set-up enabled a reaction sequence in which a nitrile bearing lithium species (**103**) was first added to the aldehyde **102** and subsequently *p*-nitrophenyllithium (**103**) attacked selectively the ketone. The resulting diol **104** was obtained in 61% yield despite including two lithium species which both carry sensitive functional groups (Scheme 40).[200]



Scheme 40: Chemoselective addition of functionalized aryllithium species in continuous flow.[200]

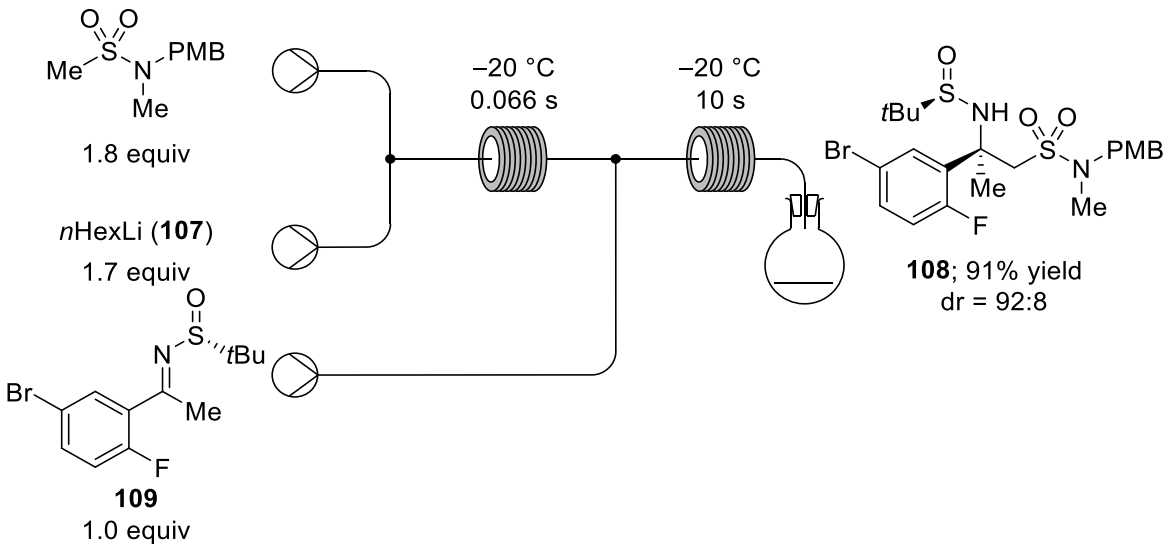
Fukuyama et al. used toxic carbon monoxide (**105**) for the carbonylation of allylic lithium species obtained by continuous flow lithiations of alkenes **106** with *n*BuLi (**66**) in the presence of TMEDA (Scheme 41).[201]

[200] A. Nagaki, K. Imai, S. Ishiuchi, J. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914.
[201] T. Fukuyama, T. Totoki, I. Ryu, *Org. Lett.* **2014**, *16*, 5632.



Scheme 41: Allylic lithiation using *n*BuLi (**66**) in the presence of TMEDA followed by carbonylation using CO gas (**105**).[201]

When performing metalation reactions in continuous flow *n*BuLi is often replaced by *n*HexLi, especially when multistep synthesis are supposed to follow the deprotonation step. The reason for that is that other than hexane, the butane occuring as a byproduct of the lithiation is gaseous, which might in larger quantities cause problems in the downstream process. Chemists at Merck applied HexLi (**107**) as a base for the metalation of acidic protons in the synthesis of a precursor to the Alzheimer´s disease drug candidate verubecestat (MK-8931) (**108**). Due to the competetive deprotonation of the chiral ketimine **109**, the yields of the addition product **108** were comparably low in batch. In flow the Mannich-type reaction outcompetes the proton transfer and thus leads to improved yields of **108** even at kilogram scales (Scheme 42).[202]



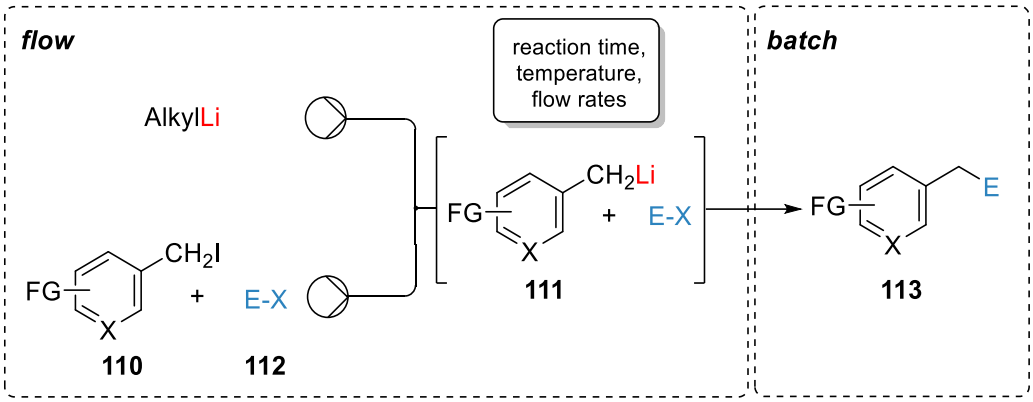
Scheme 42: Continuous flow approach towards the synthesis of a verubecestat (MK-8931) precursor (**108**).[202]

[202] D. A. Thaisrivongs, J. R. Naber, J. P. McMullen, *Org. Process Res. Dev.* **2016**, *20*, 1997.

4. OBJECTIVES

Continuous flow conditions have proven to be a beneficial addition to the field of organometallic chemistry. Especially highly reactive and in many cases hazardous organolithium compounds profit from the improved mixing and safety properties.

The resulting increased chemoselectivity prompted us to attempt halogen/lithium exchanges on benzylic iodides under Barbier conditions. These reactions are challenging in classic batch chemistry because of the electrophilic character of the benzylic iodide and the nucleophilc character of the alkyllithium exchange reagents, which might lead to a plethora of side reactions. The most noteworthy of those are: 1) The substitution of the iodide by the alkyl nucleophile; 2) The addition of the alkyllithium exchange reagent to the electrophile present under Barbier conditions; 3) The Wurtz-type homocoupling occurring after the I/Li-exchange on the benzylic iodide (**110**) followed by an attack of the resulting benzylic lithium species (**111**) on another molecule of the unreacted benzylic iodide. We thought, that transferring this Barbier-type reaction into continuous flow might benefit the reaction selectivity. Thus, premixing of (hetero)benzylic iodide (**110**) with a carbonyl electrophile (**112**) was supposed to lead to the desired products (**113**) in a more distinct ratio, after highly efficient mixing with an alkyllithium exchange reagent in a T-shaped mixer.(Scheme 43).[203]

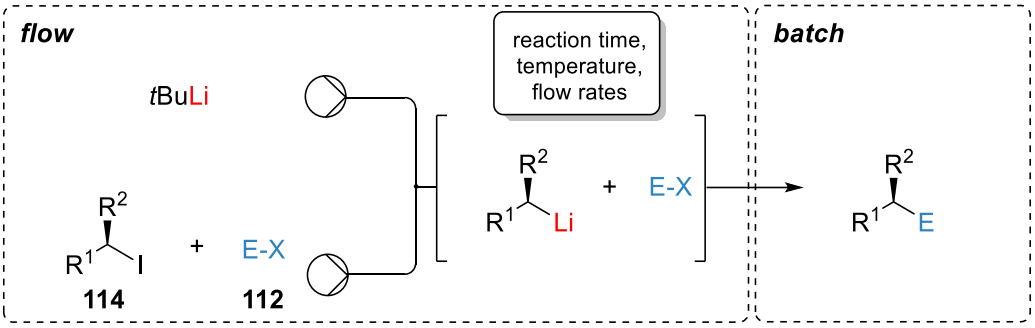


Scheme 43: Barbier-type I/Li-exchange on benzylic iodides (**110)** in the presence of carbonyl electrophiles (**112**) in continuous flow.

Over the last decade the Knochel group reported a number of stereoretentive I/Li-exchange reactions on chiral secondary alkyl iodides (**114**) using *t*BuLi (see chapter 3.1.3), which were followed by either transmetalations or direct electrophile quenches. While those reactions are excellent proof of principle studies, they remain of pure academic interest. The need for cryogenic temperatures as well as decreased yields and loss of stereoselectivity at larger reaction scales limit the applicability of these procedures. Furthermore, these reactions were difficult to reproduce when conducted by a chemist with little

[203] This project was developed in cooperation with Dr. Niels Weidmann, see: N. Weidmann, Dissertation, LMU München.

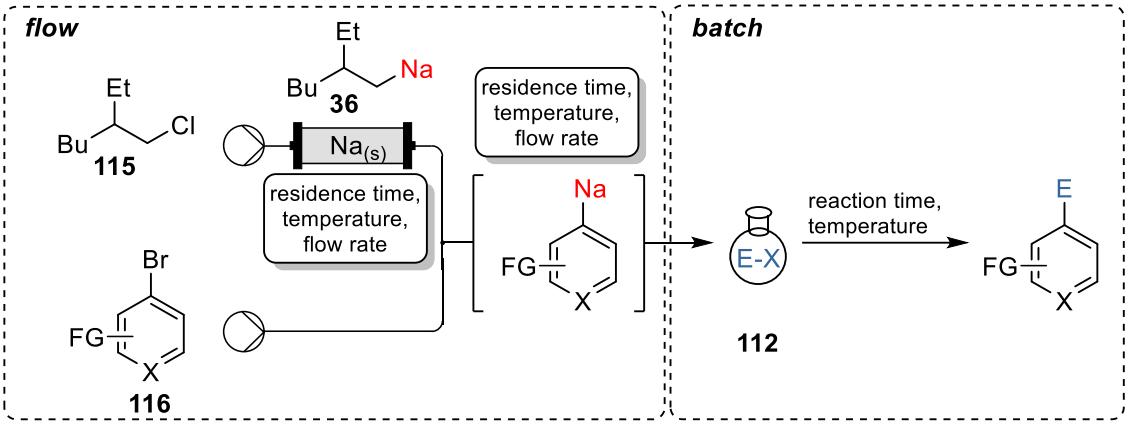
experience in the field. Wilke and Kremsmair developed in situ quenching methods in which either the electrophile or a magnesium salt was present during the I/Li-exchange. We envisioned that a Barbier-type continuous flow procedure similar to the one described above might enable stereoretentive I/Li-exchange reactions at a gram scale, while performing the reaction at higher temperatures. Simultaneously the reproducibility might be enhanced due to automating (Scheme 44).[204]



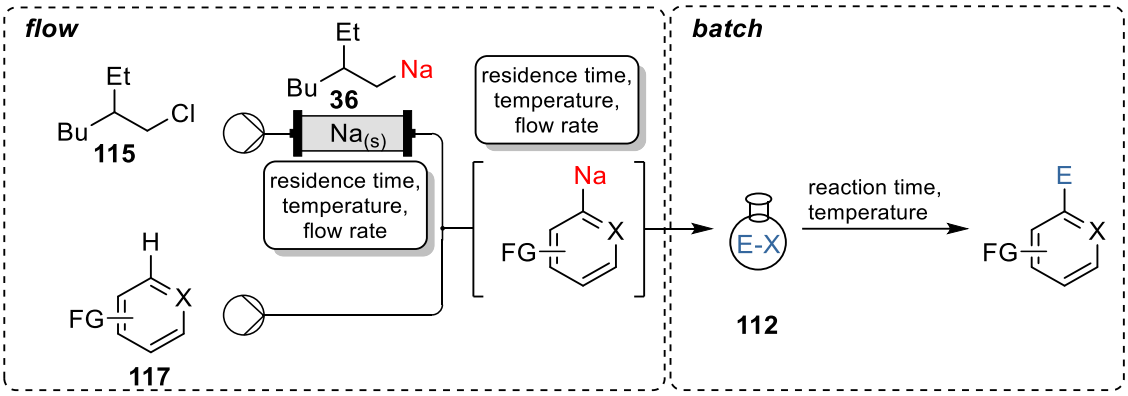
Scheme 44: Stereoretentive Barbier-type I/Li-exchange on chiral secondary iodides (**114**) in the presence of various electrophiles (**112**) in continuous flow.

In comparison to halogen–lithium exchanges, halogen–sodium exchanges are scarcely described. Asako, Takai et al. reported a halogen–sodium exchange using neopentyl sodium (**37**).[205] But while possessing various beneficial characteristics, this exchange reagent comes with the drawback of its low solubility in hydrocarbon solvents and thus was used in the presence of metallic sodium, possibly hampering a lot of reactions. The groups of Collum,[206] Asako and Takai considered using the hydrocarbon soluble (2-ethylhexyl)sodium (**36**) but decided against it, since it is according to them hard to handle and showed decreased stability in comparison to neopentyl sodium (**37**). Inspired by magnesium and zinc packed-bed reactors of Alcázar,[207] we thought that an on-demand preparation of (2-ethylhexyl)sodium (**36**) from 3-(chloromethyl)heptane (**115**) using a sodium packed-bed reactor might overcome a lot of these disadvantages. Thus, we intended to develop a procedure in which the alkyl chloride **115** was supposed to be transformed in a sodium packed-bed reactor into the corresponding alkylsodium **36**. The high local sodium concentration in the bed reactor was thought to be advantageous in avoiding Wurtz-type homocoupling. Since the packed-bed reactor is engulfed by two filters, we expected that the alkylsodium solution would be free of elemental sodium. Furthermore, the procedure was supposed to decrease the hazards of handling sodium to a minimum. Subsequent in-line Br/Na-exchanges (Scheme 45) or directed sodiation (Scheme 46) on (hetero)arenes of type **116** and **117** should circumvent the problems associated with storage and handling of alkylsodium species.

[204] This project was developed in cooperation with Dr. Alexander Kremsmair and Henrik R. Wilke see: A. Kremsmair, Dissertation, LMU München and H. R. Wilke master thesis, LMU München.
[205] S. Asako, I. Takahashi, H. Nakajima, L. Ilies, K. Takai, *Communications Chemistry* **2021**, *4*, 76.
[206] D. B. Collum, R. A. Woltornist, Y. Ma, R. F. Algera, Y. Zhou, Z. Zhang, *Synthesis* **2020**, *52*, 1478.
[207] a) N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737; b) L. Huck, A. de la Hoz, A. Diaz-Ortiz, J. Alcazar, *Org. Lett.* **2017**, *19*, 3747.



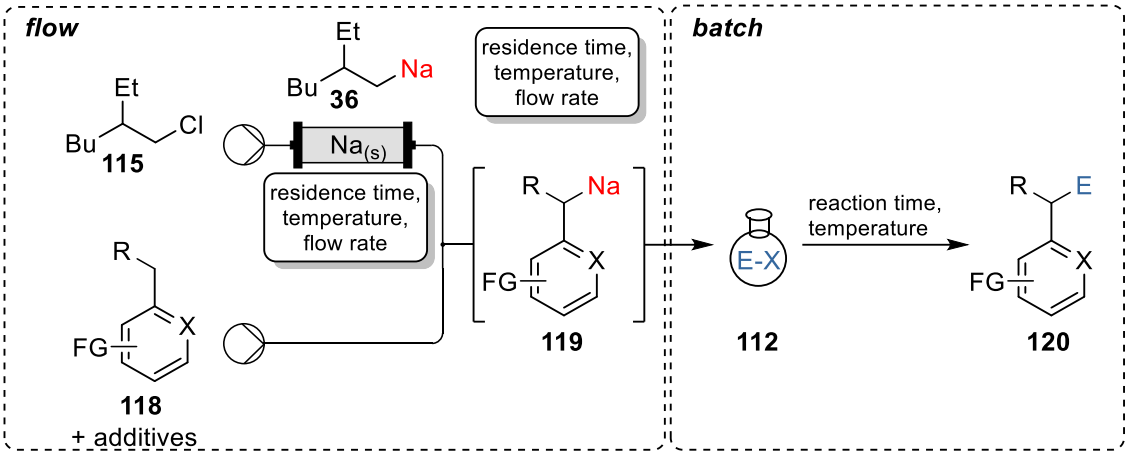
Scheme 45: On-demand generation of (2-ethylhexyl)sodium (**36**) using a sodium packed-bed reactor followed by an in-line Br/Na-exchange on bromo(hetero)arenes of type **116** and subsequent batch quench with various electrophiles (**112**).



Scheme 46: On-demand generation of (2-ethylhexyl)sodium (**36**) using a sodium packed-bed reactor followed by a directed in-line sodiation of (hetero)arenes of type **117** and subsequent batch quench with various electrophiles (**112**).

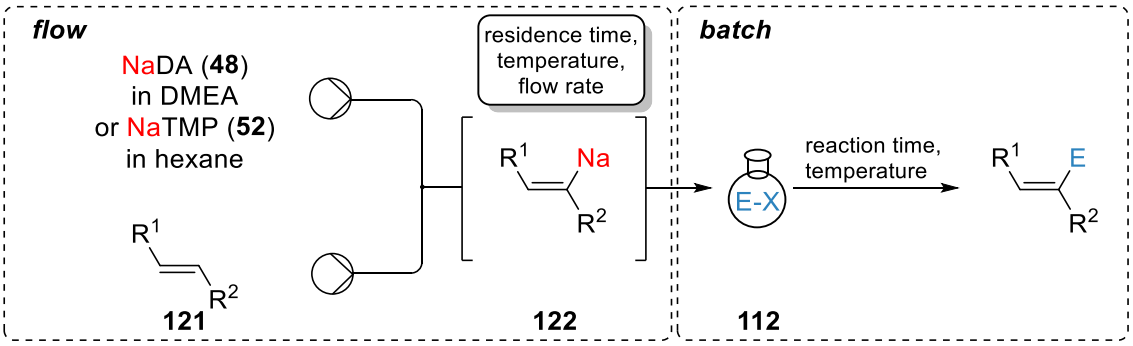
In a similar fashion, we opted to perform lateral sodiations and metalations of alkylarenes (**118**) in the benzylic position using the on-demand generated (2-ethylhexyl)sodium (**36**). The reactivity of these highly reactive benzylic sodium reagents (**119**) towards a broad range of electrophiles (**112**) should be explored. Since the very early times of alkali metal chemistry, the potential of alkylsodium reagents to undergo Wurtz-type couplings has been apparent.[208] Thus, we were especially interested in these S_N2-type reactions which would enable a transition metal free pathway for the installation of alkyl residues on arenes, in case of secondary alkyl halide reaction partners even in a stereoselective manner. We envisioned an on-demand generation of the alkylsodium base **36** followed by an in-line sodiation of the benzylic position. Electrophile quenches were expected to lead to the functionalized products (**120**) (Scheme 47).[209]

[208] a) A. Wurtz, *Ann. Chim. Phys.* **1855**, *44*, 275; b) A. Wurtz, *Ann. Chim. Phys.* **1855**, *96*, 364.
[209] This project was developed in cooperation with Dr. Rajasekar Reddy Annapureddy.



Scheme 47: On-demand generation of (2-ethylhexyl)sodium (**36**) using a sodium packed-bed reactor followed by a lateral in-line sodiation of alkyl(hetero)arenes (**118**) and subsequent batch quench with elecrophiles of type **112**.

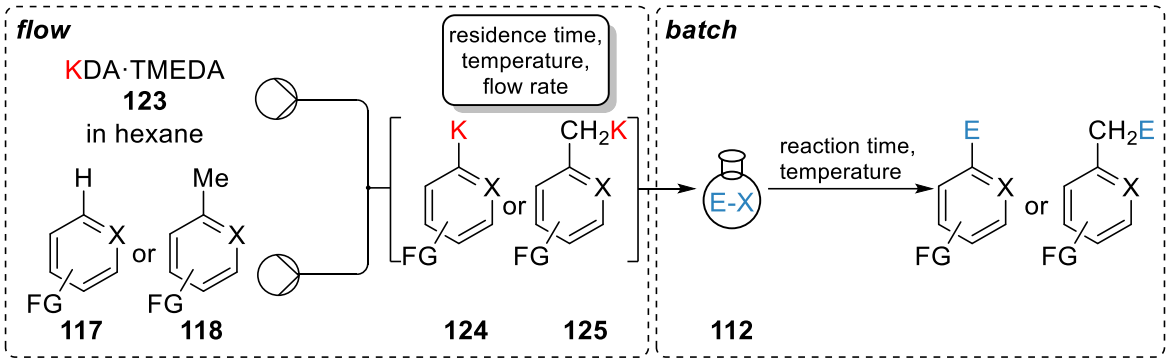
The newly sparked interest in sodium amide bases, which were rediscovered by the group of Collum, led Weidmann et al. to transfer the directed sodiatons of heteroarenes using DMEA soluble NaDA (**48**) into a continuous flow set-up and as such they were able to expand the substrate scope significantly.[210] Following up on this approach and as well on the directed magnesiations and zincations of alkenyl reagents in continuous flow which were reported at a similar time by the Knochel group,[211] a continuous flow procedure for the directed sodiation of alkenyl reagents (**121**) should be developed. We envisioned that the higher basicity of the sodium amide bases as well as the higher reactivity of the resulting sodium intermediates (**122**) might lead to a broadened scope of starting materials and potential electrophiles of type **112** (Scheme 48).[212]



Scheme 48: Directed sodiation of alkenyl starting materials **121** with DMEA soluble NaDA (**48**) or hexane soluble NaTMP (**52**) in continuous flow followed by batch quench of the resulting alkenylsodium species (**122**) by various electrophiles (**112**) in Batch.

[210] N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748.
[211] M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828.
[212] This project was developed in cooperation with Dr. Niels Weidmann, see: N. Weidmann, Dissertation, LMU München. Some results in of this project were already included in the master thesis of Johannes H. Harenberg, see: J. H. Harenberg, master thesis, LMU München

Ultimately, we considered that a generation of lithium free potassium amide base might be possible in a method similar to the one of Collums NaDA preparation. Thus, a potassium amide base which are commonly prepared via the Schlosser method by mixing TMPH (**51**) with KO*t*Bu (**65**) and an alkyllithium reagent[213] should be prepared from elemental potassium and di*iso*propylamine (**49**) in the presence of isoprene (**50**). The resulting potassium amide base **123** should be used for directed and lateral metalations of functionalized (hetero)arenes (**117**) and methyl substituted (hetero)arenes (**118**). We predicted that the resulting aryl- and benzylpotassium reagents (**124** and **125**) show an even further increased reactivity due to the higher ΔEN of the K–C bond and thus should enable batch quenching with a range of challenging electrophiles (**112**) (Scheme 49).[214]



Scheme 49: Directed and lateral metalation of (hetero)arenes (**117**) and methyl substituted (hetero)arenes (**118**) under continuous flow conditions using KDA (**123**). Subsequent batch quench of the resulting aryl- and benzylpotassium (**124** and **125**) species with various electrophiles (**112**).

[213] a) P. Fleming, D. F. O'Shea, *J. Am. Chem. Soc.* **2011**, *133*, 1698; b) M. Blangetti, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2012**, *77*, 2870.
[214] This project was developed in cooperation with Dr. Niels Weidmann, see: N. Weidmann, Dissertation, LMU München.

B. RESULTS AND DISCUSSION

1. Continuous Flow Preparation of (Hetero)Benzylic Lithiums via Iodine-Lithium Exchange Reaction under Barbier Conditions[215]

1.1 Introduction

Organolithiums are widely used in organic syntheses.[216] Because of the high polarity of the carbon−lithium bond, they react readily with various electrophiles.[217] Generation of lithium intermediates and control of their reactivity and selectivity are ongoing tasks.[218] A great improvement has been achieved by performing these organometallic reactions in continuous flow.[219] Yoshida and co-workers successfully generated highly reactive lithium species via exchange reactions, direct metalation, or insertion, which were quenched within milliseconds by various electrophiles using custom-made microreactors allowing ultrafast mixing and very short residence times (Scheme 50a).[220] We recently reported an efficient method of in situ trapping transmetalation using *n*BuLi as the exchange reagent for a halogen−lithium exchange reaction in the presence of $MgCl_2 \cdot LiCl$, resulting in the more stable organomagnesium species, which were subsequently quenched with various electrophiles.[221]

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[215] Adapted with permission from N. Weidmann, J. H. Harenberg, P. Knochel, *Org. Lett.* **2020**, *22*, 5895. Copyright 2020 American Chemical Society. https://doi.org/10.1021/acs.orglett.0c01991. This project was developed in cooperation with Dr. Niels Weidmann, see: N. Weidmann, Dissertation, LMU München.

[216] a) J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**; b) *Science of Synthesis, Vol. 8a,b* V. Snieckus, M. Majewski, Georg Thieme Verlag, Stuttgart Germany, **2005**; c) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

[217] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; b) B. Goldfuss, *Synthesis* **2005**, *2005*, 2271.

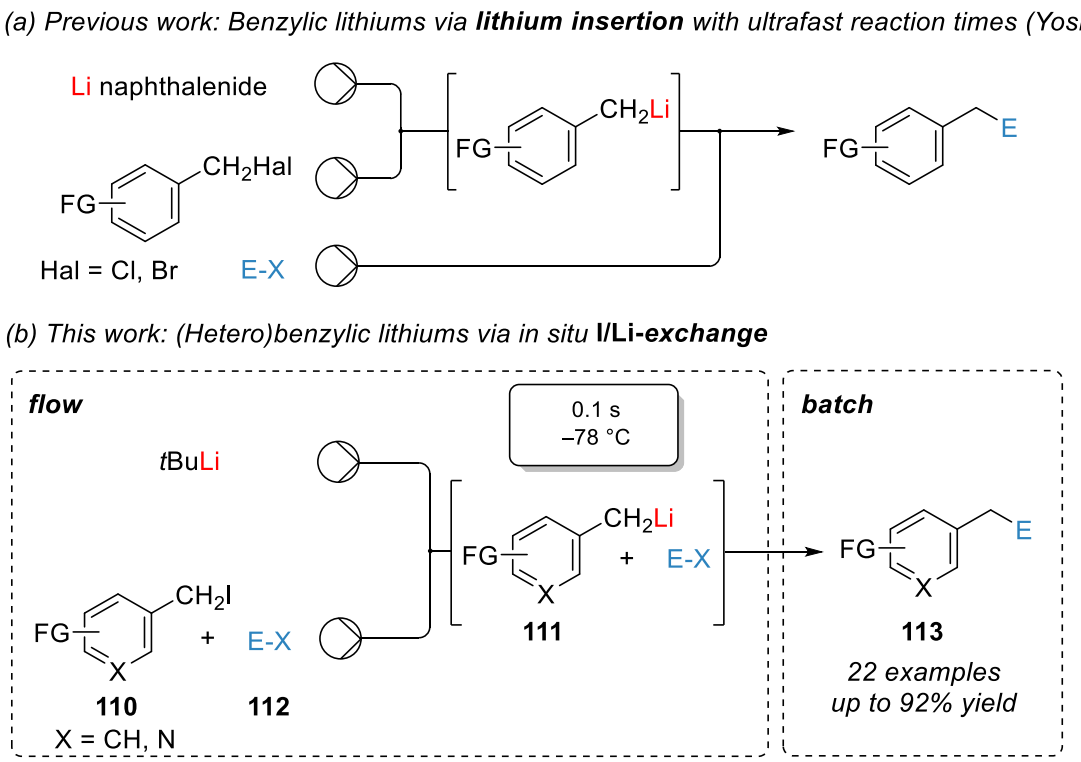
[218] a) A. Nagaki, H. Yamashita, K. Hirose, Y. Tsuchihashi, J. I. Yoshida, *Angew. Chem. Int. Ed.* **2019**, *58*, 4027; b) A. P. Pulis, A. Varela, C. Citti, P. Songara, D. Leonori, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2017**, *56*, 10835; c) F. H. Lutter, M. S. Hofmayer, J. M. Hammann, V. Malakhov, P. Knochel, in *Organic Reactions*, **2019**, pp. 63; d) J. Skotnitzki, A. Kremsmair, D. Keefer, Y. Gong, R. de Vivie-Riedle, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 320; e) J. Skotnitzki, A. Kremsmair, P. Knochel, *Synthesis* **2020**, *52*, 189; f) V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5516; g) L. Degennaro, A. Nagaki, Y. Moriwaki, G. Romanazzi, M. M. Dell'Anna, J.-i. Yoshida, R. Luisi, *Open Chem.* **2016**, *14*; h) G. Dilauro, A. Francesca Quivelli, P. Vitale, V. Capriati, F. M. Perna, *Angew. Chem. Int. Ed.* **2019**, *58*, 1799; i) S. Ghinato, G. Dilauro, F. M. Perna, V. Capriati, M. Blangetti, C. Prandi, *Chem. Commun.* **2019**, *55*, 7741; j) M. Dell'Aera, F. M. Perna, P. Vitale, A. Altomare, A. Palmieri, L. C. H. Maddock, L. J. Bole, A. R. Kennedy, E. Hevia, V. Capriati, *Chem. Eur. J.* **2020**, *26*, 8742.

[219] a) E. Comer, M. G. Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8160; b) G. A. Price, A. Hassan, N. Chandrasoma, A. R. Bogdan, S. W. Djuric, M. G. Organ, *Angew. Chem. Int. Ed.* **2017**, *56*, 13347; c) E. Comer, M. G. Organ, *Chem. Eur. J.* **2005**, *11*, 7223; d) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102.

[220] a) A. Nagaki, K. Sasatsuki, S. Ishiuchi, N. Miuchi, M. Takumi, J. I. Yoshida, *Chem. Eur. J.* **2019**, *25*, 4946; b) H. J. Lee, H. Kim, J. I. Yoshida, D. P. Kim, *Chem. Commun* **2018**, *54*, 547; c) H. Kim, Y. Yonekura, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2018**, *57*, 4063; d) H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691; e) A. Nagaki, Y. Tsuchihashi, S. Haraki, J. Yoshida, *Org Biomol Chem* **2015**, *13*, 7140.

[221] a) M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770; b) M. Ketels, D. Ziegler, P. Knochel, *Synlett* **2017**, *28*, 2817.

Although substituted benzylic lithiums were previously prepared by halogen–lithium exchange or insertion reactions from the corresponding benzylic halides, their synthesis is often accompanied by side reactions such as Wurtz homocouplings.[222] Furthermore, iodine–lithium exchange on alkyl iodides is virtually instantaneous, outcompeting even the deprotonation of MeOH.[223] On the basis of those facts, we envisioned that the need for an ultrafast in-line quench or in situ trapping with metal salts could be overcome by adding an electrophile to the starting material solution (Barbier conditions). Herein we report an iodine–lithium exchange reaction on benzylic iodides of type **110** in the presence of carbonyl electrophiles of type **112** in a microflow reactor setup.[224] The resulting benzylic lithium species of type **111** were instantaneously trapped in a Barbier-type reaction by electrophiles of type **112** already present in the reaction solution, affording the desired secondary and tertiary alcohols of type **113** (Scheme 50b).



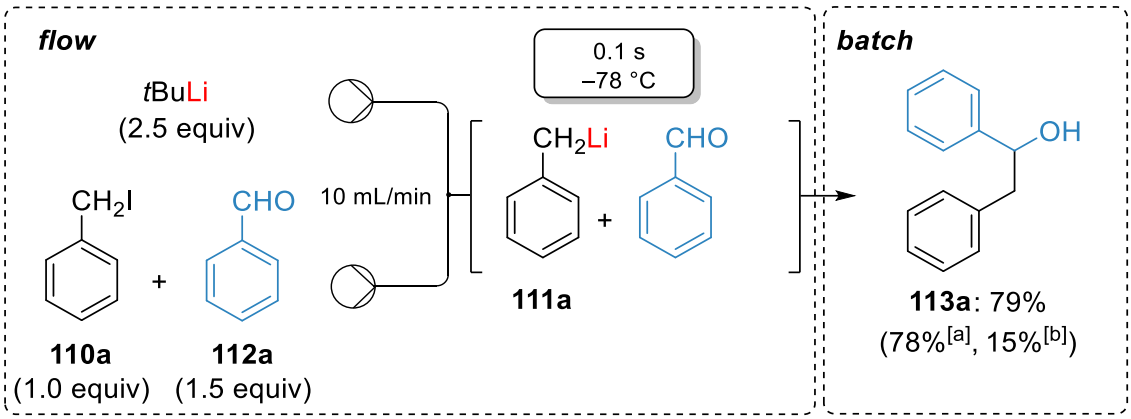
Scheme 50: (a) Lithium insertion into benzylic halides using ultrafast in-line electrophile quench.[224a] (b) Iodine-lithium exchange on (hetero)benzylic iodides under Barbier conditions.

[222] a) W. E. Parham, L. D. Jones, Y. A. Sayed, *J. Org. Chem.* **1976**, *41*, 1184; b) S. Warren, P. Wyatt, M. McPartlin, T. Woodroffe, *Tetrahedron Lett.* **1996**, *37*, 5609; c) L. Kupracz, A. Kirschning, *Adv. Synth. Catal.* **2013**, *355*, 3375; d) H. Gilman, H. McNinch, D. Wittenberg, *J. Org. Chem.* **1958**, *23*, 2044.
[223] a) W. F. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861; b) C. A. Stein, T. H. Morton, *Tetrahedron Lett.* **1973**, *14*, 4933.
[224] For applications of benzyllithiums in flow, see: a) A. Nagaki, Y. Tsuchihashi, S. Haraki, J. Yoshida, *Org. Biomol. Chem.* **2015**, *13*, 7140. For usage of benzyllithiums under Barbier conditions, see: b) C. Gómez, F. F. Huerta, M. Yus, *Tetrahedron* **1997**, *53*, 13897; c) C. Gómez, F. F. Huerta, M. Yus, *Tetrahedron* **1998**, *54*, 1853.

1.2 Optimization of the Reaction Conditions

We first examined the generation of benzyllithium (**111a**) under Barbier-type conditions from benzyl iodide (**110a**) (65 mg, 0.20 mmol, 1.0 equiv) using *n*BuLi (0.25 mmol, 1.25 equiv) as the exchange reagent in the presence of benzaldehyde (**112a**) (32 mg, 0.30 mmol, 1.5 equiv) at 0 °C using a combined flow rate of 2.0 mL/min, resulting in 50% GC yield with a significant amount of *n*BuLi addition product to benzaldehyde and Wurtz-type homocoupling (Table 3, entry 1).[225]

Decreasing the reactor volume had no impact on the conversion and GC yield (entry 2). Investigation of various lithium bases (e.g., *s*BuLi, *t*BuLi, *n*HexLi, neopentyllithium)[225] revealed a significant increase in the GC yield when *t*BuLi was used (74%; entry 3). We further optimized the reaction conditions by increasing the flow rate and lowering the temperature, resulting in an 87% GC yield (−78 °C, 10 mL/min combined flow rate, 0.02 mL reactor volume, 0.1 s; entry 8). Entries 1−11 demonstrate the strong mixing dependence of the iodine−lithium exchange using benzylic iodides. In accordance with the literature,[226] higher flow rates and smaller reactor diameters resulted in more efficient mixing, favoring the exchange reaction. Coordinating additives such as *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDTA) afforded secondary alcohol **113a** in only 10−13% GC yield (entries 9 and 10) with the Wurtz-type coupling as a major side reaction.[227] Using *n*BuLi as the exchange reagent under the optimized conditions led to decreased conversion and GC yield (entry 11).



Scheme 51: General set-up for the iodine-lithium exchange of benzylic iodides with *t*BuLi and in situ Barbier trapping with carbonyl-containing electrophiles under continuous flow conditions. [a] Isolated yield of a scale-up on a 4.00 mmol scale. [b] Performing the reaction under Barbier conditions (–40 °C, 30 min) in batch.[228]

[225] For detailed flow screening conditions, including the major side products, see page 158.
[226] a) A. Soleymani, H. Yousefi, I. Turunen, *Chem. Eng. Sci* **2008**, *63*, 5291; b) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.
[227] For detailed screening of coordinating ligands, see page 161.
[228] For detailed information on the batch reaction see page 185.

Table 3: Optimization of reaction conditions for iodine-lithium exchange of benzylic iodide (**110a**) with lithium bases and in situ Barbier-type reaction with benzaldehyde (**112a**) enabled by continuous flow.

entry	base [equiv]	t [s]	$V_{reactor}$ [mL]	flow rate [mL/min]	T [°C]	conv. [%]	GC-yield [%]
1	*n*BuLi (1.25)	150	5	2	0	67	50
2	*n*BuLi (1.25)	30	1	2	0	64	48
3	*t*BuLi (2.5)	30	1	2	0	89	74
4	*t*BuLi (2.5)	2.5	0.02	2	–78	90	84
5	*t*BuLi (2.5)	30	1	2	–78	90	83
6	*t*BuLi (2.5)	6	1	10	–20	95	72
7	*t*BuLi (2.5)	6	1	10	–78	95	80
8	***t*BuLi (2.5)**	**0.1**	**0.02**	**10**	**–78**	**94**	**87[a,b]**
9	*t*BuLi (2.5)[c]	0.1	0.02	10	–78	100	13
10	*t*BuLi (2.5)[d]	0.1	0.02	10	–78	100	10
11	*n*BuLi (1.25)	0.1	0.02	10	–78	79	68

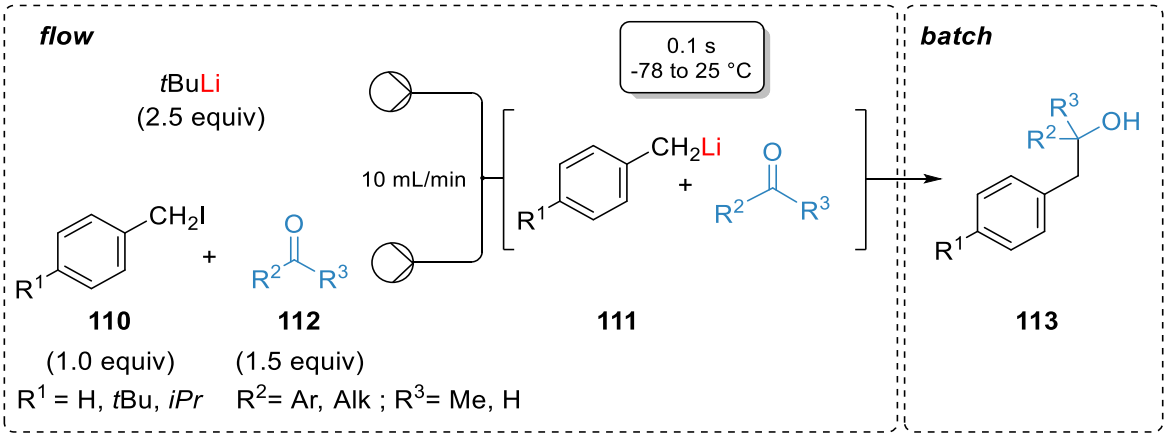
[a] Isolated yield of analytically pure product on a 0.20 mmol scale: 79%. [b] Isolated yield of a scale-up on a 4.00 mmol scale: 78%. [c] TMEDA (2.5 equiv) was added. [d] PMDTA (2.5 equiv) was added.

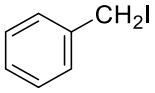
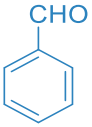
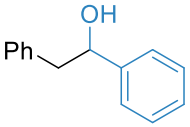
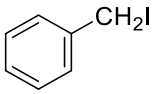
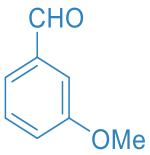
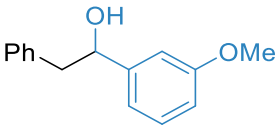
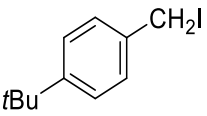
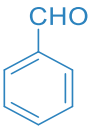
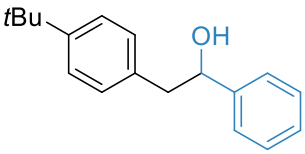
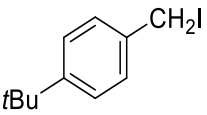
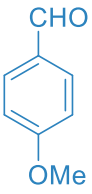
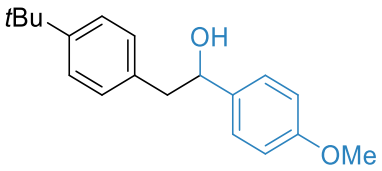
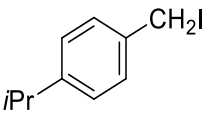
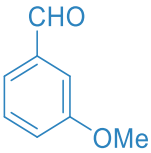
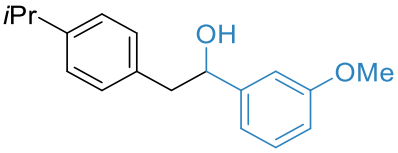
1.3 In Situ Generation of Benzylic Lithium Species via I/Li-Exchange under Barbier Conditions in Continuous Flow

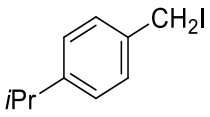
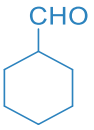
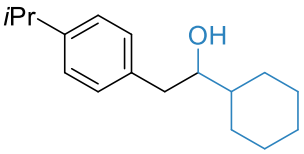
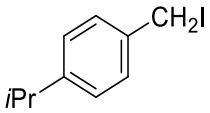
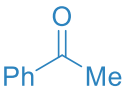
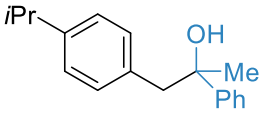
Under the optimized reaction conditions (Table 3, entry 8 and Scheme 51), the desired alcohol **113a** was obtained in 79% isolated yield. A scale-up was possible without further optimization of the reaction conditions by increasing the run time from 12 s (0.20 mmol scale) to 240 s (4.00 mmol scale), resulting in a 78% isolated yield. Interestingly, performing the reaction under batch conditions led to a significantly decreased yield of 15%.[229] Having these optimized conditions in hand, we investigated the scope of various carbonyl derivatives and substituted benzylic iodides (Table 4).[230]

[229] For detailed batch screening conditions see page 185.
[230] A temperature screening was conducted separately for each reaction.

Table 4: In situ exchange reaction and subsequent Barbier-type reaction of (sterically demanding) benzylic iodides of type **110** leading via reactive benzylic lithium species of type **111** to functionalized alcohols of type **113**.



entry	Benzylic iodide	E-X	Product of type **113**
			
1	**110a**	**112a**	**113a**: 79%[b]
			
2	**110a**	**112b**	**113b**: 63%[b]
			
3	**110b**	**112a**	**113c**: 65%[b]
			
4	**110b**	**112c**	**113d**: 56%[b]
			
5	**110c**	**112b**	**113e**: 71%[c]

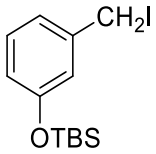
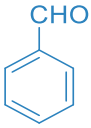
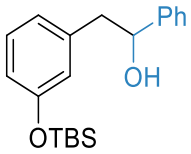
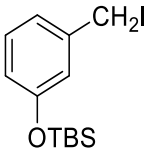
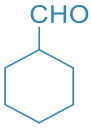
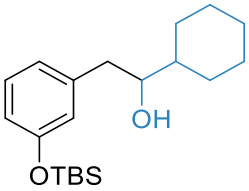
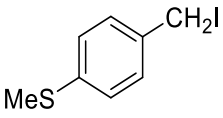
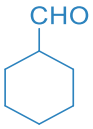
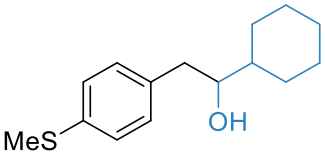
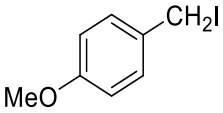
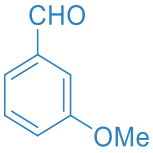
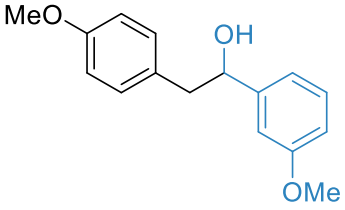
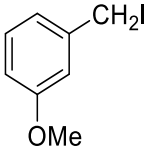
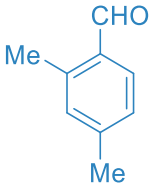
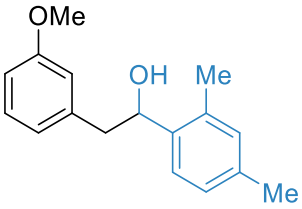
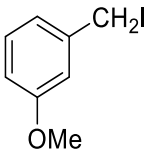
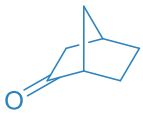
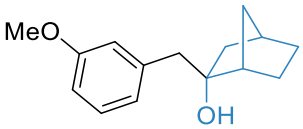
entry	Benzylic iodide	E-X	Product of type **113**
			
6	**110c**	**112d**	**113f**: 76%[d]
			
7	**110c**	**112e**	**113g**: 68%[c]

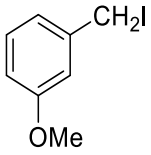
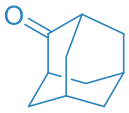
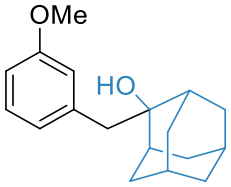
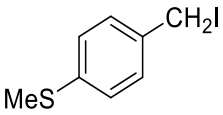
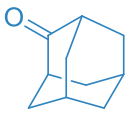
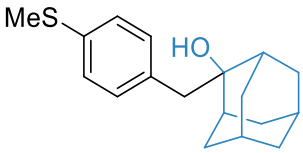
[a] Yield of analytically pure isolated product. [b] T= –78 °C. [c] T= –20 °C. [d] T= 25 °C

Benzyllithium (**111a**) was generated in the presence of *m*-anisaldehyde (**112b**), resulting in a 63% isolated yield of secondary alcohol **113b** (entry 2). However, using aliphatic aldehydes such as 2-ethylbutanal or noncyclic ketones such as 2-hexanone under Barbier-type reaction conditions afforded the desired aliphatic alcohols in lower GC yields, possibly as a result of enolization of the aldehydes or ketones. Alkyl-substituted substrates such as 4-*tert*butylbenzyl iodide (**110b**) and 4-*iso*propylbenzyl iodide (**110c**) afforded the desired benzylic alcohols **113c**–**f** after in situ quenching with aromatic and aliphatic aldehydes in 56–76% isolated yield (entries 3–6). Remarkably, addition to ketones, which is typically slower than addition to aldehydes,[231] was also possible without a significant loss of yield using **110c** and acetophenone (**112e**), affording tertiary alcohol **113g** in 68% isolated yield (entry 7). We then subjected electron-rich benzylic iodides bearing a TBS-substituted alcohol, thioether, or methoxy substituent to the optimized flow conditions (Table 5).

[231] A. Nagaki, Y. Tsuchihashi, S. Haraki, J. Yoshida, *Org. Biomol. Chem.* **2015**, *13*, 7140.

Table 5: In situ exchange reaction and subsequent Barbier-type reaction of electron-rich benzylic iodides of type **126** leading via reactive benzylic lithium species of type **127** to functionalized alcohols of type **128**.

entry	Benzylic iodide	E-X	Product of type **128**
			
1	**126a**	**112a**	**128a**: 50%[b]b
			
2	**126a**	**112d**	**128b**: 62%[c]
			
3	**126b**	**112d**	**128c**: 68%[d]
			
4	**126c**	**112b**	**128d**: 67%[e]
			
5	**126d**	**112f**	**128e**: 53%[d]
			
6	**126d**	**112g**	**128f**: 59%, *d.r.*>99:1[d]

entry	Benzylic iodide	E-X	Product of type **128**
			
7	**126d**	**112h**	**128g**: 85%[c] (40%)[f]
			
8	**126b**	**112h**	**128h**: 76%[d]

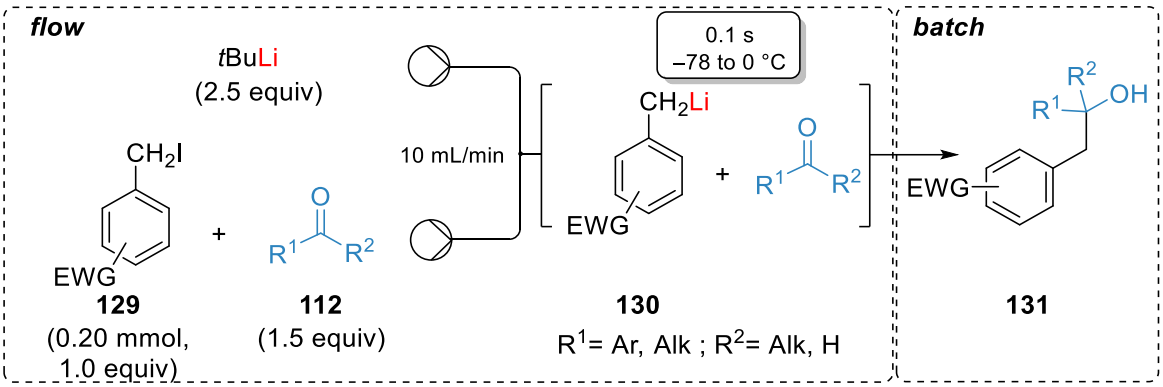
[a] Yield of analytically pure isolated product. [b] T= –40 °C. [c] T= –78 °C. [d] T= –30 °C. [e] T= –20 °C [f] Performing the reaction under Barbier conditions (–20 °C, 30 min) in batch.[232]

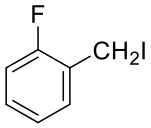
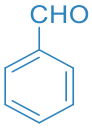
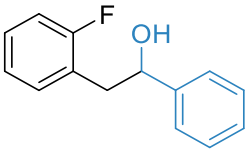
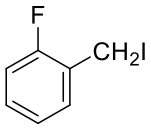
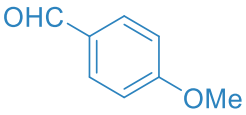
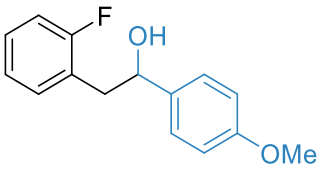
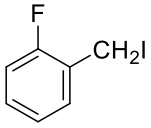
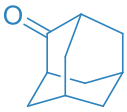
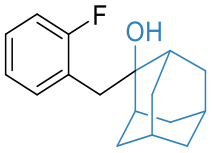
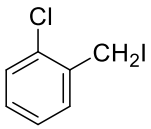
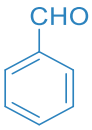
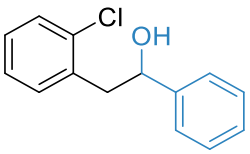
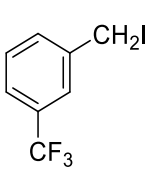
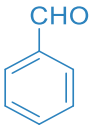
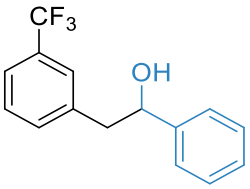
3-OTBS-substituted benzylic iodide **126a** was lithiated at −40 °C within 0.1 s, providing secondary alcohol **128a** in 50% isolated yield after an in situ quench with **112a** (entry 1). Alternatively, benzylic organolithium **127a** reacted with cyclohexyl carboxaldehyde (**112d**), leading to aliphatic alcohol **128b** in 62% isolated yield (entry 2). Flow lithiation of thioether-substituted benzylic iodide **126b** and in situ trapping with **112e** led to the desired carbinol **128c** in 68% isolated yield (entry 3). *m*- and *p*-methoxysubstituted benzylic organolithiums (**127c** and **127d**) were prepared from the corresponding iodides (**126c** and **126d**) and afforded secondary benzylic alcohols **128d** and **128e** in 53−67% isolated yield (entries 4 and 5). Furthermore, Barbier-type reactions with sterically demanding ketones such as norcamphor (**112g**) and adamantanone (**112h**) were possible without further optimization of the flow conditions, affording tertiary alcohols **128f**−**h** in 59−85% isolated yield (entries 6−8). Using Barbier conditions in batch led to **128g** in only 40% isolated yield,[232] which is significantly lower than the 85% yield obtained under continuous flow conditions.

To further extend the scope of the lithiation protocol, we applied this method to electron-deficient benzylic substrates (Table 6). 2-Fluoro- and 2-chloro-substituted benzylic iodides (**129a** and **129b**) were converted to the corresponding lithiated species **130a** and **130b** within 0.1 s. Trapping the intermediates of type **130** with aldehyde **112a** or **112c** or ketone **112h** gave the desired alcohols **131a**−**d** in 44−80% yield (entries 1−4). The presence of a trifluoromethyl group at the *meta* position was also tolerated, affording the secondary alcohol **131e** in 64% isolated yield after reaction with **112a** using Barbier conditions (entry 5).

[232] For detailed batch screening conditions see page 184.

Table 6: In situ exchange reaction and subsequent Barbier-type reaction of electron-poor benzylic iodides of type **129** leading via reactive lithium species of type **130** to functionalized alcohols of type **131**.

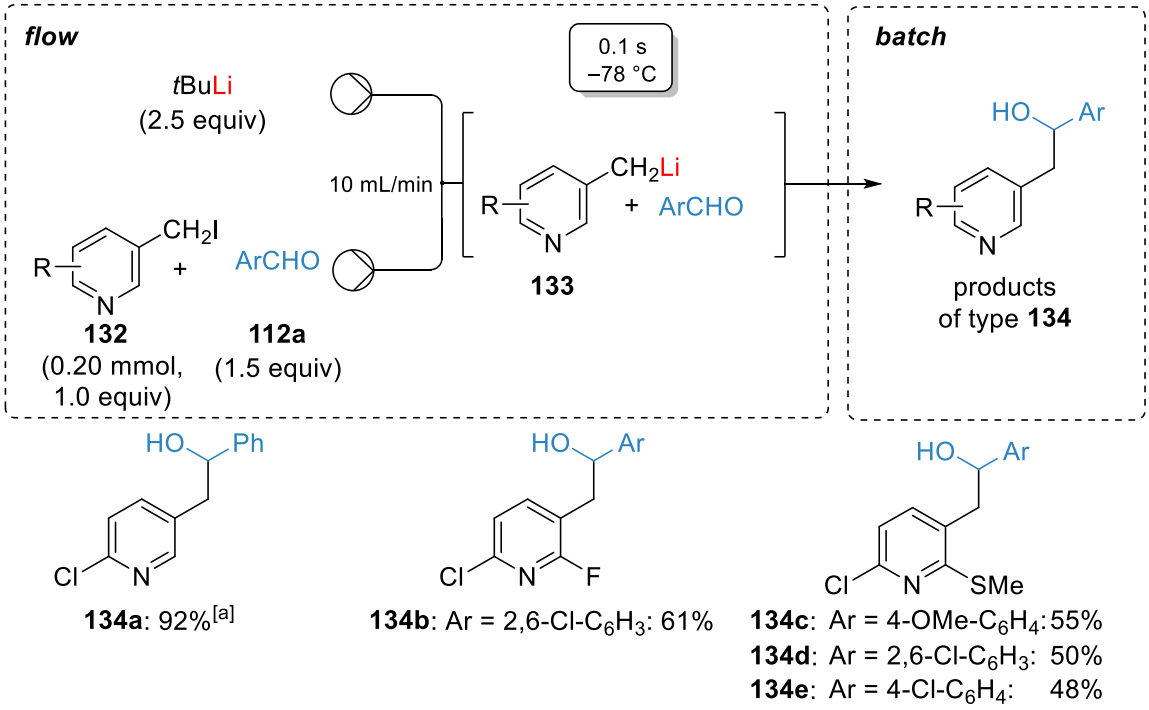


entry	Benzylic iodide	E-X	Product of type **131**
			
1	**129a**	**112a**	**131a**: 70%[b]
			
2	**129a**	**112c**	**131b**: 53%[b]
			
3	**129a**	**112h**	**131c**: 44%[c]
			
4	**129b**	**112a**	**131d**: 80%[b]
			
5	**129c**	**112a**	**131e**: 64%[b]

[a] Yield of analytically pure isolated product. [b] T= –78 °C. [c] T= 0 °C

1.4 In Situ Generation of Heterobenzylic Lithium Species via I/Li-Exchange under Barbier Conditions in Continuous Flow

Having in mind that functionalization of heteroaromatics is an important synthetic goal[233] and that heterocycles are among the most important structural motifs in current research because of their wide range of bioactive properties and frequent use in agrochemical and pharmaceutical chemistry, we turned our attention to heterobenzylic iodides (Scheme 51).[234]



Scheme 51: In situ exchange reaction and subsequent Barbier-type reaction of heterobenzylic iodides of type **132** leading via highly reactive lithium species of type **133** to functionalized alcohols of type **134**. [a] No product detected under various batch conditions.[235]

[233] a) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; c) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667; d) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; e) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, *37*, 2620.

[234] a) *Modern Arene Chemistry* D. Astruc, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2002**; b) T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347; c) G. A. Bhat, J. L. G. Montero, R. P. Panzica, L. L. Wotring, L. B. Townsend, *J. Med. Chem.* **1981**, *24*, 1165; d) C. B. Vicentini, D. Mares, A. Tartari, M. Manfrini, G. Forlani, *J. Agric. Food Chem* **2004**, *52*, 1898; e) D. S. Ziegler, L. Klier, N. Müller, K. Karaghiosoff, P. Knochel, *Synthesis* **2018**, *50*, 4383; f) B. Heinz, M. Balkenhohl, P. Knochel, *Synthesis* **2019**, *51*, 4452.

[235] For detailed batch screening conditions see page 187.

We found that readily prepared 2-chloro-5-(iodomethyl)pyridine (**132a**)[236] reacted instantaneously with *t*BuLi (2.5 equiv) to give the corresponding pyridylmethyllithium **133a**. In the presence of **112a**, benzylic alcohol **134a** was obtained in 92% isolated yield, whereas no product was detected by GC−MS under various batch conditions.[237] 6-Chloro-2-fluoro-3(iodomethyl)pyridine (**132b**) was lithiated at −78 °C within 0.1 s, affording the desired secondary alcohol **134b** in 61% yield via Barbier trapping with 2,6-dichlorobenzaldehyde (**112i**). Furthermore, flow lithiation of 6-chloro-3-(iodomethyl)-2-(methylthio)pyridine (**132c**) led to the corresponding pyridylmethyllithium **133c**, which was instantaneously quenched in situ by various aromatic aldehydes to afford secondary alcohols **134c**−**e** in 48−55% yield.[238]

1.5 Conclusion

In summary, we have reported a convenient method for the generation and efficient quenching of (hetero)benzylic lithium species via an iodine−lithium exchange reaction on readily available benzylic iodides using *t*BuLi as the exchange reagent. The highly reactive (hetero)benzyllithiums were trapped in situ by carbonyl-containing electrophiles using Barbier conditions in a commercially available continuous flow set-up. A general scale-up was possible by increasing the run time without further optimization.

[236] a) N. M. Barl, E. Sansiaume-Dagousset, G. Monzón, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422; b) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824.
[237] For detailed batch screening conditions see page 187.
[238] For the preparation of heterobenzylic iodides, see page 196. The reaction of various other heterobenzylic iodides, such as quinolines and pyrimidines, were investigated. However, the GC yield of the Barbier-type flow exchange reaction dropped significantly.

2. In Situ Quench Reactions of Enantioenriched Secondary Alkyllithium Reagents in Batch and Continuous Flow Using an I/Li-Exchange[239]

2.1 Introduction

The enantioselective synthesis of small molecules has attracted increasing interest in pharmaceutical and agrochemical research.[240] Especially, the preparation of enantioenriched organometallics is an important goal as it gives straightforward access to numerous enantiopure compounds after quenching with electrophiles.[241] Nevertheless, many reported chiral maingroup organometallics bear a heteroatom in α-position for stabilization, preventing fast epimerization.[242] Therefore, we investigated a general preparation of optically enriched non-heteroatom stabilized organometallics.[243] Recently, we have reported the preparation of chiral non-heteroatom stabilized[244] secondary alkyllithiums (**135**) from the corresponding iodides (**114**) *via* an I/Li-exchange with *t*-BuLi. The resulting organolithium species[245] were either directly quenched with electrophiles (**112**) or trapped after stereoretentive

[239] Adapted with permission from A. Kremsmair, H. R. Wilke, J. H. Harenberg, B. R. G. Bissinger, M. M. Simon, N. Alandini, P. Knochel, *Angew. Chem. Int. Ed.* **2023**, *62*, e202214377. Copyright 2023 Angewandte Chemie International Edition published by Wiley-VCH. https://doi.org/10.1002/anie.202214377. This project was developed in cooperation with Dr. Alexander Kremsmair and Henrik R. Wilke see: A. Kremsmair, Dissertation, LMU München and H. R. Wilke master thesis, LMU München. The majority of the work for this project was done by H. R. Wilke and A. Kremsmair, the author of the dissertation in hand conducted all the screenings and reactions in continuous flow. For sake of clarity this dissertation nevertheless contains the entire publication.

[240] a) H.-J. Federsel, *Nature Reviews Drug Discovery* **2005**, *4*, 685; b) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem. Int. Ed.* **2006**, *45*, 4732; c) N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348; d) J. R. Cossy, in *Comprehensive Chirality* (Eds.: E. M. Carreira, H. Yamamoto), Elsevier, Amsterdam, **2012**, pp. 1; e) P. Jeschke, *Pest Management Science* **2018**, *74*, 2389; f) C. W. Lindsley, *ACS Chemical Neuroscience* **2019**, *10*, 1115.

[241] a) R. W. Hoffmann, B. Hölzer, O. Knopff, K. Harms, *Angew. Chem. Int. Ed.* **2000**, *39*, 3072; b) A. Basu, S. Thayumanavan, *Angew. Chem. Int. Ed.* **2002**, *41*, 716; c) R. E. Gawley, *Overview of Carbanion Dynamics and Electrophilic Substitutions in Chiral Organolithium Compounds* R. E. Gawley, **2010**; d) G. Eppe, D. Didier, I. Marek, *Chem. Rev.* **2015**, *115*, 9175.

[242] a) W. C. Still, C. Sreekumar, *J. Am. Chem. Soc.* **1980**, *102*, 1201; b) H. J. Reich, M. D. Bowe, *J. Am. Chem. Soc.* **1990**, *112*, 8994; c) H. J. Reich, K. J. Kulicke, *J. Am. Chem. Soc.* **1995**, *117*, 6621; d) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2282; e) D. Hoppe, *Synthesis* **2009**, *2009*, 43; f) P. J. Rayner, P. O'Brien, R. A. J. Horan, *J. Am. Chem. Soc.* **2013**, *135*, 8071.

[243] Pioneering work of Letsinger first demonstrated the preparation of secondary alkyllithiums from the corresponding secondary alkyl iodides using an I/Li-exchange and their extensive racemization at low temperatures: R. L. Letsinger, *J. Am. Chem. Soc.* **1950**, *72*, 4842.

[244] For recent examples of stabilized oxygen-bearing lithium compounds see: a) J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2007**, *46*, 7491; b) T. Hémery, R. Huenerbein, R. Fröhlich, S. Grimme, D. Hoppe, *J. Org. Chem.* **2010**, *75*, 5716; c) D. Leonori, V. K. Aggarwal, *Acc. Chem. Res.* **2014**, *47*, 3174; d) R. Rasappan, V. K. Aggarwal, *Nat. Chem.* **2014**, *6*, 810; e) S. Monticelli, W. Holzer, T. Langer, A. Roller, B. Olofsson, V. Pace, *ChemSusChem* **2019**, *12*, 1147.

[245] The addition of *t*-BuLi to an alkyl iodide produces first an ate-intermediate $[Alk–I–t–Bu]^-Li^+$ which then collapses to the alkyllithium species. Although conceivable, it is unlikely that this high energy intermediate plays a role in reactions with electrophiles. See: a) H. J. Reich, N. H. Phillips, I. L. Reich, *J. Am. Chem. Soc.* **1985**, *107*, 4101; b) W. B. Farnham, J. C. Calabrese, *J. Am. Chem. Soc.* **1986**, *108*, 2449; c) H. J. Reich, D. P. Green, N. H. Phillips, *J. Am. Chem. Soc.* **1989**, *111*, 3444; d) H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130.

transmetalations[246] leading to various products of type **136** (Scheme 52a, left).[247] However, the drawback of such approaches was the very low temperatures required for the generation of the organolithium species (−100 °C). Furthermore, the functional group tolerance was limited and the scale-up of these reaction sequences proved to be difficult affording poor yields and low optical purities. Thus, we have found that an in situ quench (ISQ, also known as Barbier conditions)[248] of chiral alkyl iodides in the presence of a suitable magnesium reagent with *t*-BuLi allowed the performance of the I/Li-exchange at up to −50 °C with high stereoretention (up to 99%) providing, upon transmetalation, several chiral secondary Grignard reagents.[249] Yet, the resulting chiral alkylmagnesiums proved to be unreactive towards some important classes of electrophiles (**112**) including enolizable or sterically hindered ketones.

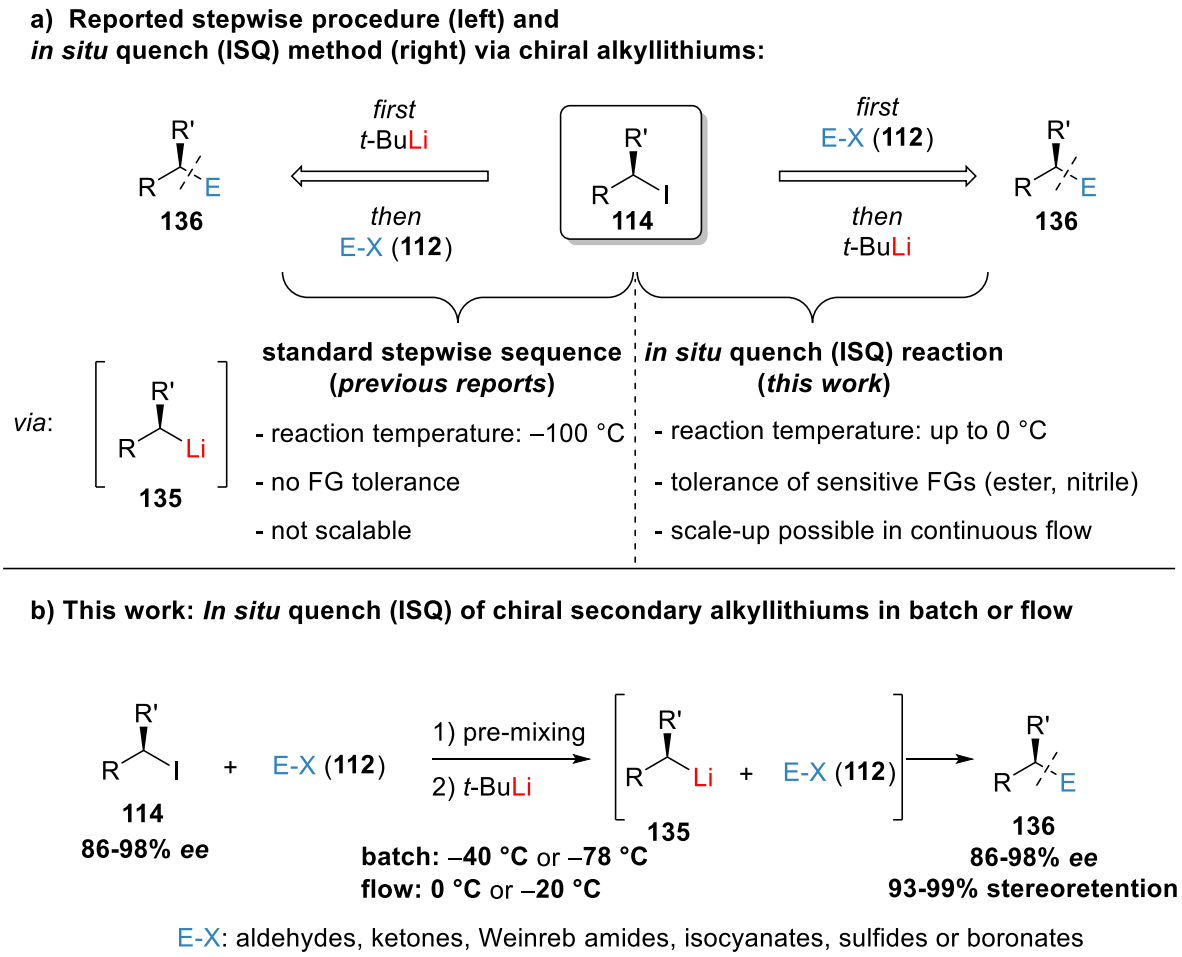
Hence, we envisioned an ISQ-reaction involving the treatment of enantioenriched secondary alkyl iodides (**114**) in the presence of electrophiles (**112**) using *t*-BuLi at −78 °C or higher temperatures (Scheme 52a, right). These conditions combined with the use of a continuous flow set-up might allow even higher temperatures and previously impossible reaction scales. These perspectives would greatly improve the practicability of our method. Herein, we report such an in situ quench (ISQ) reaction of chiral alkyllithiums (**135**), including for the first time highly functionalized substrates, in the presence of a broad range of electrophiles such as aldehydes, ketones, Weinreb amides, isocyanates, sulfides, or boronates (**112**) after the addition of *t*-BuLi at −78 °C or even −40 °C. This allowed the facile preparation of diversely functionalized products of type **136** with high enantiomeric purity (up to 98% *ee*) via intermediate alkyllithiums of type (**135**, Scheme 52b). Furthermore, we were able to transfer the reaction into continuous flow conditions, in which it was scaled up to a 40-fold.

[246] For transmetalations to alkylcoppers see: a) K. Moriya, M. Simon, R. Mose, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10963; b) V. Morozova, K. Moriya, P. Mayer, P. Knochel, *Chem. Eur. J.* **2016**, *22*, 9962; c) V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5516; d) J. Skotnitzki, V. Morozova, P. Knochel, *Org. Lett.* **2018**, *20*, 2365; e) J. Skotnitzki, A. Kremsmair, D. Keefer, F. Schüppel, B. Le Cacher de Bonneville, R. de Vivie-Riedle, P. Knochel, *Chem. Sci.* **2020**, *11*, 5328; f) A. Kremsmair, J. Skotnitzki, P. Knochel, *Chem. Eur. J.* **2020**, *26*, 11971. For transmetalations to mixed alkylcopper-zinc reagents see: g) J. Skotnitzki, L. Spessert, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 1509; h) J. Skotnitzki, A. Kremsmair, B. Kicin, R. Saeb, V. Ruf, P. Knochel, *Synthesis* **2020**, *52*, 873. For transmetalations to alkylzincs see: i) J. Skotnitzki, A. Kremsmair, D. Keefer, Y. Gong, R. de Vivie-Riedle, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 320.

[247] a) S. Seel, G. Dagousset, T. Thaler, A. Frischmuth, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 4614; b) G. Dagousset, K. Moriya, R. Mose, G. Berionni, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 1425; c) K. Moriya, D. Didier, M. Simon, J. M. Hammann, G. Berionni, K. Karaghiosoff, H. Zipse, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 2754; d) J. Skotnitzki, A. Kremsmair, P. Knochel, *Synthesis* **2020**, *52*, 189.

[248] a) C. Blomberg, *The Barbier Reaction and Related One-Step Processes*, Springer Verlag, Berlin, Heidelberg, **1993**; b) S. Goto, J. Velder, S. El Sheikh, Y. Sakamoto, M. Mitani, S. Elmas, A. Adler, A. Becker, J.-M. Neudörfl, J. Lex, H.-G. Schmalz, *Synlett* **2008**, *2008*, 1361; c) A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.

[249] A. Kremsmair, H. R. Wilke, M. M. Simon, Q. Schmidt, K. Karaghiosoff, P. Knochel, *Chem. Sci.* **2022**, *13*, 44.



Scheme 52: Previous standard sequence and highly stereoretentive ISQ-reactions involving secondary alkyllithium intermediates.

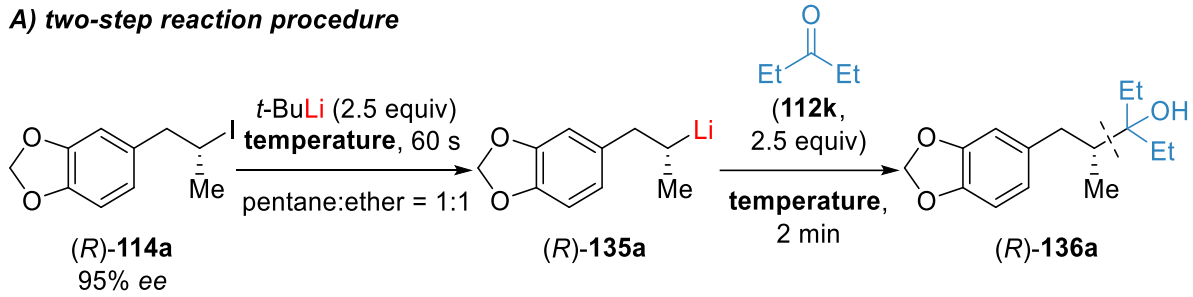
2.2 Optimization for the Barbier Type I/Li-Exchange in Batch

In preliminary experiments, we have converted the chiral secondary alkyl iodide (*R*)-**114a** (95% *ee*) into the corresponding organolithium (*R*)-**135a** at −100 °C (addition of (*R*)-**114a** to *t*-BuLi within 60 s) resulting, after immediate quench with diethyl ketone (**112k**, 2.5 equiv), in the formation of the alcohol (*R*)-**136a** in 67% GC-yield and 92% *ee* (Table 7b, entry 1). Increasing the reaction temperature to −78 °C or −40 °C led to significant racemization of (*R*)-**136a** showing the limitations of the former two-step procedure (entries 2 and 3 of Table 7a). In contrast, using the ISQ-procedure and mixing the iodide (*R*)-**114a** (95% *ee*, 1.0 equiv) with Et_2CO (**112k**, 2.5 equiv) in 3:2 pentane:ether and adding *t*-BuLi (2.1 M in pentane) within 10 s at −78 °C provided (*R*)-**136a** in 60% isolated yield and 93% *ee* (entry 4, Table 7b). A temperature increase to −60 °C led to (*R*)-**136a** in 52% GC-yield and still 92% *ee* (entry 5). A slight erosion of enantioselectivity was observed at −40 °C, providing (*R*)-**136a** in 54% GC-yield and 90% *ee* (entry 6). A significant decrease in optical purity of (*R*)-**136a** was observed when the

reaction was done at −20 °C (44% GC-yield, 86% *ee*, entry 7) or at 0 °C (41% GC-yield, 69% *ee*, entry 8). Changing the amount of electrophile used in the ISQ-procedure led to lower yields of (*R*)-**136a**.[250]

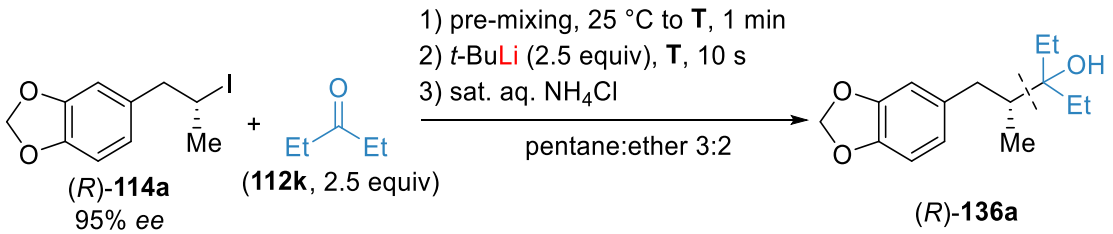
Table 7: Preparation of the enantioenriched alcohol (*R*)-**136a** using a two-step sequence via alkyllithium (*R*)-**135a** followed by the addition of diethyl ketone (**112k**, method **A**) or via the in situ generation of (*R*)-**135a** in the presence of **112k** (method **B**).

A) two-step reaction procedure



Entry	Temperature (T) [°C]	GC-Yield of (*R*)-**136a**[a]	*ee* of (*R*)-**136a**[b]
1	−100	67%	92%
2	−78	61%	53%
3	−40	54%	0%

B) in situ quench (ISQ) procedure



Entry	Temperature (T) [°C]	GC-Yield of (*R*)-**136a**[a]	*ee* of (*R*)-**136a**[b]
4	**−78**	**60%**[c]	**93%**
5	−60	52%	92%
6	−40	54%	90%
7	−20	44%	86%
8	0	41%	69%

[a] The yield was determined by GC-analysis; [b] The enantiomeric excess (% *ee*) was determined by chiral HPLC-analysis; [c] Yield of isolated analytically pure product.

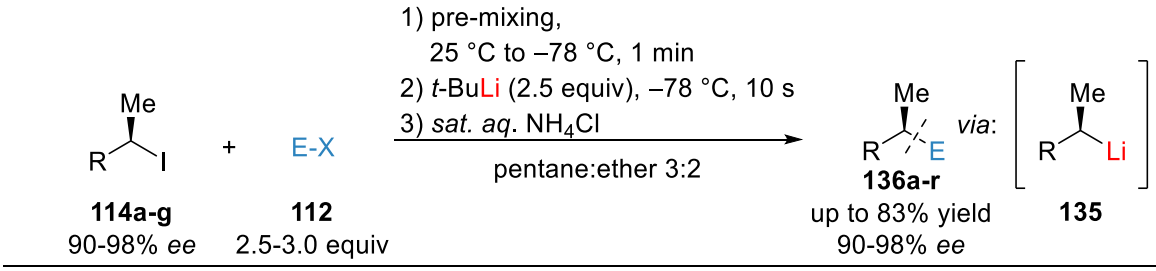
[250] For further information, see page 209.

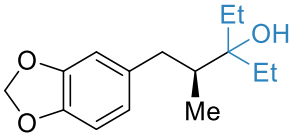
2.3 In Situ Generation of Chiral Secondary Alkyllithium Species in the Presence of Various Electrophiles under Batch Conditions

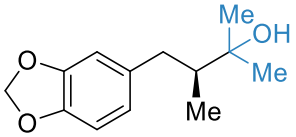
Based on these preliminary experiments, we have designed a general procedure for the in situ quench of various functionalized chiral secondary alkyl iodides of type **114** in the presence of electrophiles (E-X) of type **112** such as ketones, boronates, Weinreb amides, disulfides, aldehydes and isocyanates leading to functionalized chiral products of type **136** (Scheme 53). Thus, mixing (*S*)-**114a** and diethyl ketone (**112k**) in pentane:ether and adding *t*-BuLi within 10 s at −78 °C followed by an immediate quench with *sat. aq.* NH_4Cl solution, gave the expected alcohol (*S*)-**136a** in 68% yield and 91% *ee*. Using (*S*)-**114a** in the presence of other enolizable ketones such as acetone (**112l**) or cyclohexanone (**112m**) led to the chiral alcohols (*S*)-**136b** and (*S*)-**136c** in 45-61% yield and 91-92% *ee*. In the case of solid electrophiles such as adamantanone (**112h**), the reaction was performed at −40 °C due to the limited solubility of the reaction mixture at lower temperatures. Nevertheless, the desired alcohol (*R*)-**136d** was isolated in 72% yield and 94% *ee*. Also, transmetalations to boronic acid esters like (*R*)- or (*S*)-**136e** were achieved with high stereoretention in up to 83% yield and up to 92% *ee* starting from (*R*)- or (*S*)-**114a** and methoxyboronic acid pinacol ester (**112n**). Although, the Weinreb amide *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (**112o**) showed only limited solubility under our standard conditions (−78 °C), the ISQ-reaction could be performed at −40 °C providing the α-chiral ketone (*R*)-**136f** in 56% yield and 94% *ee*. Employing the benzothiophene derived alkyl iodides (*R*)- or (*S*)-**114b** in the presence of diethyl ketone (**112k**) and adding *t*-BuLi at −78 °C gave the corresponding alcohols (*R*)- and (*S*)-**136g** in 63-67% yield and 91-96% *ee*. Also, a mixture of the chiral alkyl iodide (*S*)-**114b** and the silyl protected dihydroxyacetone derivative **112p** was only soluble at −40 °C and therefore *t*-BuLi was added at this temperature affording (*S*)-**136h** in 72% yield with high stereoretention (98% *ee*). Electrophiles like Bu_2S_2 (**112q**) or citronellal (**112r**) reacted with (*S*)-**114b** providing the sulfide (*S*)-**136i** (63% yield, 93% *ee*) or (2*S*,5*S*)-**136j** (after oxidation with Dess-Martin periodinane;[251] 48% yield, dr = 92:8, 96% *ee*). Furthermore, the chiral alcohol (*S*)-**136k** was isolated after mixing (*S*)-**114c** with cyclopentadecanone (**112s**) and adding *t*-BuLi at −40 °C in 53% yield and 92% *ee*. Isocyanates like (*R*)-**112t** also proved to be suitable electrophiles when mixed with the secondary alkyl iodide (*S*)-**114d** yielding, under standard conditions, the desired amide (2'*S*,3*R*)-**136l** in 72% yield with dr = 2:98 and 96% *ee*. Moreover, the optically enriched iodides (*R*)- and (*S*)-**114e** underwent the ISQ-reaction with dicyclopropyl ketone (**112u**), di-*iso*-propyl ketone (**112v**) or dicyclohexyl ketone (**112w**, at −40 °C) providing the alcohols **136m-o** in up to 78% yield and up to 96% *ee*. To our delight, chiral secondary alkyl iodides bearing sensitive functional groups like a nitrile (*R*- and *S*-**114f**) or an ester (*R*- and *S*-**114g**) were compatible with this method. Thus, the amides (2'*R*,3*R*)-**136p** (75%, dr = 94:6, 96% *ee*) and (2'*R*,3*S*)-**136p** (82%, dr = 8:92, 96% *ee*) as well as the

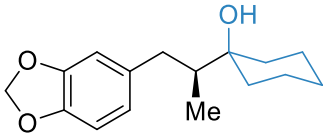
[251] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.

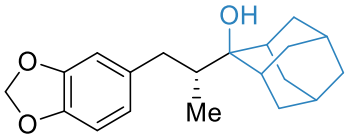
alcohol (*S*)-**136q** (49%, 95% *ee*) were isolated after ISQ-reaction using (*R*)- or (*S*)-**114f** and either (*R*)- or (*S*)-**112t** or (**112v**). Likewise, (*R*)- and (*S*)-**136r** were obtained after reaction of the ester-containing alkyl iodide (*R*)- or (*S*)-**114g** with adamantanone (**112h**), after addition of *t*-BuLi, in up to 53% yield and 94% *ee* at −40 °C.

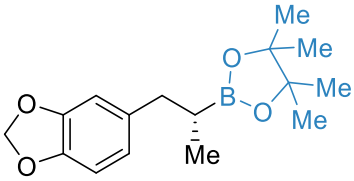


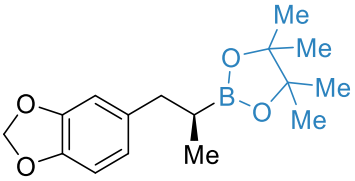

(*S*)-**136a**: 68%, 91% *ee*

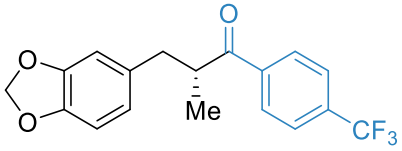

(*S*)-**136b**: 45%, 91% *ee*

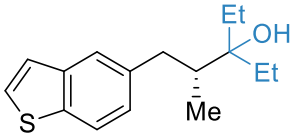

(*S*)-**136c:** 61%, 92% *ee*

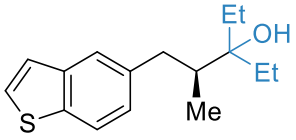

(*R*)-**136d**[a]: 72%, 94% *ee*

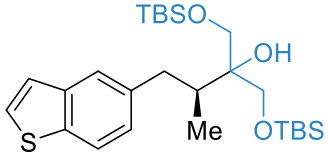

(*R*)-**136e**: 83%, 92% *ee*

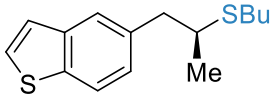

(*S*)-**136e**: 80%, 91% *ee*

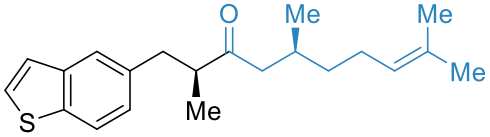

(*R*)-**136f**[a]: 56%, 94% *ee*

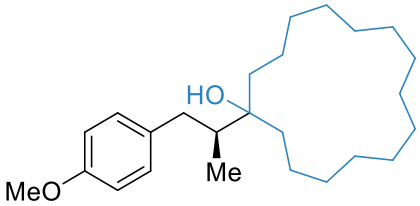

(*R*)-**136g**: 63%, 91% *ee*

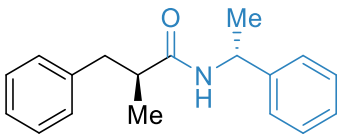

(*S*)-**136g**: 67%, 96% *ee*

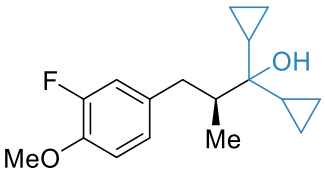

(*S*)-**136h**[a]: 72%, 98% *ee*

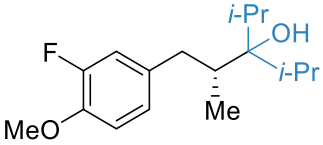

(*S*)-**136i**: 63%, 93% *ee*

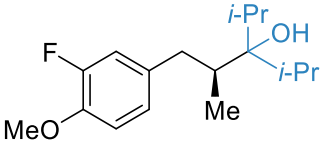

(2*S*,5*S*)-**136j:** 48%, dr = 92:8, 96% *ee*

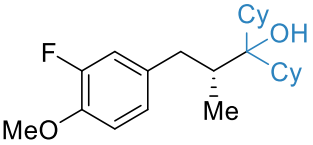

(*S*)-**136k**[a]: 53%, 92% *ee*

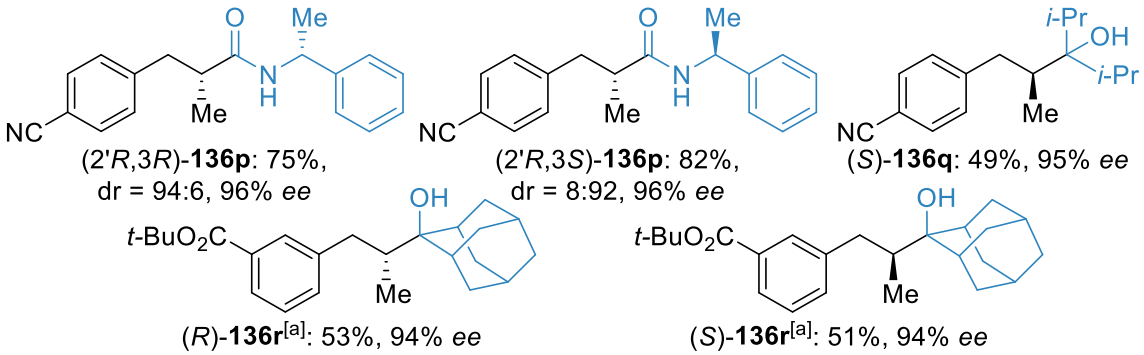

(2'*S*,3*R*)-**136l**: 72%, dr = 2:98, 96% *ee*


(*S*)-**136m**: 78%, 94% *ee*


(*R*)-**136n**: 66%, 90% *ee*

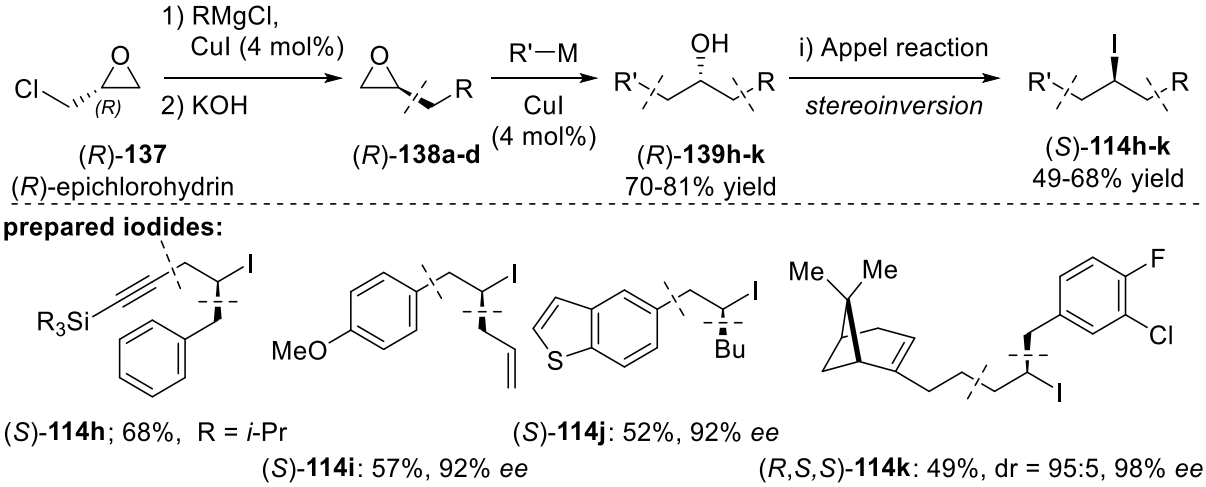

(*S*)-**136n**: 64%, 96% *ee*


(*R*)-**136o**[a]: 69%, 94% *ee*



Scheme 53: Prepared chiral products **136a-r** by in situ quench (ISQ) of optically enriched secondary alkyl iodides **114a-g** in the presence of electrophiles **112** using *t*-BuLi. Yields refer to isolated analytically pure products. The enantiomeric excess (% *ee*) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr = *syn*/*anti*) was determined via GC- or NMR-analysis. [a] The reaction was performed at −40 °C using 3.0 equiv of electrophile.

While the reaction proceeded smoothly with chiral iodides of type AlkCH(Me)I, we have also demonstrated that higher substituted alkyl iodides may be used. The required alkyl iodides were prepared from commercially available (*R*)-epichlorohydrin (*R*-**137**) in a three step sequence (Scheme 54).[252] Thus, (*R*)-**137** was treated with various Grignard reagents (RMgCl) in the presence of 4 mol% CuI[253] affording, after treatment with KOH, chiral epoxides of type **138**. Another ring opening of **138** with Grignard reagents (R'MgCl) or alkynyllithiums in the presence of 4 mol% CuI provided chiral alcohols of type **139** in 70-81% yield (over 3 steps). A stereoinvertive Appel reaction furnished the desired secondary alkyl iodides (*S*)-**114h-k** in 49-68% yield and 92-98% *ee*.

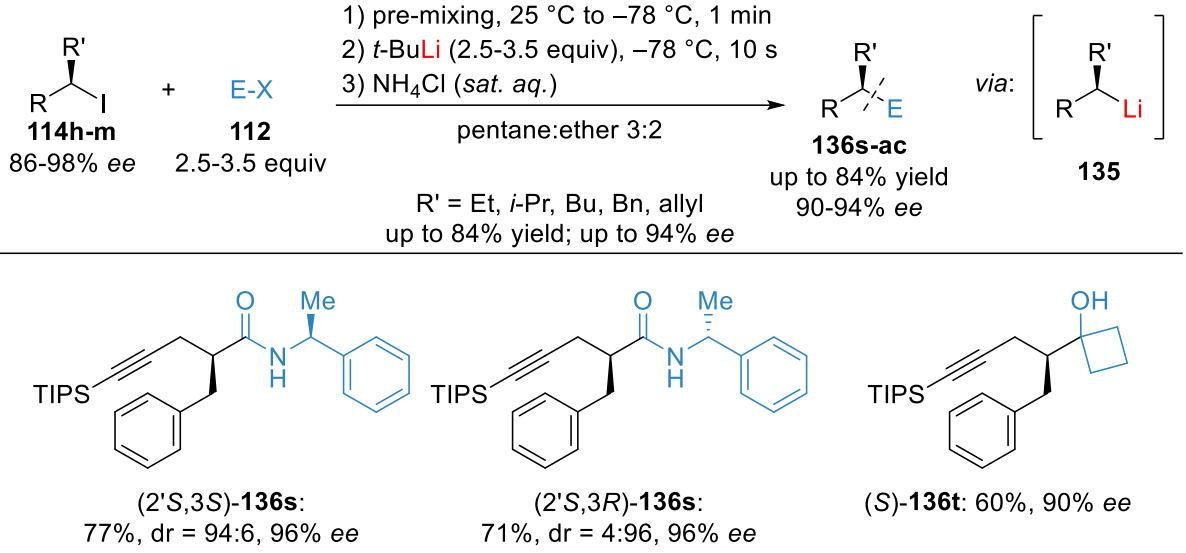


Scheme 54: Modular preparation of optically enriched secondary alkyl iodides (*S*)-**114h-k** from (*R*)-epichlorohydrin (*R*-**137**) via epoxide opening and closure sequences followed by stereoinvertive Appel reaction; i) (1.2 equiv PPh_3, 1.2 equiv I_2, 1.2 equiv *N*-methylimidazole, −10 °C, 30 min).

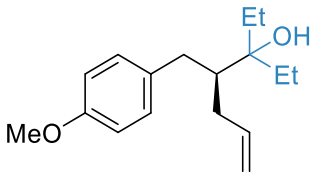
[252] P. Gupta, P. Kumar, *Tetrahedron: Asymmetry* **2007**, *18*, 1688.
[253] a) B. H. Lipshutz, S. Sengupta, in *Organic Reactions, Vol. 41*, **1992**, pp. 135; b) S. Takano, M. Yanase, M. Takahashi, K. Ogasawara, *Chem. Lett.* **1987**, *16*, 2017.

With these chiral secondary alkyl iodides in hand, we performed several ISQ-reactions (Scheme 55). Thus, the chiral homobenzylic secondary alkyl iodide (*S*)-**114h** smoothly underwent the ISQ-reaction in the presence of the isocyanates (*R*)-**112t** or (*S*)-**112t** providing the diastereomerically and enantiomerically enriched amides (2'*S*,3*S*)-**136s** in 77% with dr = 94:6 and 96% *ee* as well as (2'*S*,3*R*)-**136s** in 71%, dr = 4:96, 96% *ee*. Furthermore, ISQ of (*S*)-**114h** with cyclobutanone (**112x**) at −78 °C gave the chiral alcohol (*S*)-**136t** in 60% yield and 90% *ee*. Also, treating the allyl substituted iodide (*S*)-**114i** with diethyl ketone (**112k**), methoxyboronic acid pinacol ester (**112n**) or Bu_2S_2 (**112q**) led to the expected optically enriched alcohol (*S*)-**136u** (78%, 92% *ee*), to the boronic acid ester (*S*)-**136v** (73%, 90% *ee*), or to the sulfide (*S*)-**136w** (57%, 91% *ee*). In the case of the chiral secondary alkyl iodide (*S*)-**114j** bearing a butyl substitutent, we observed that dropwise addition of 2.5 equiv of *t*-BuLi led to low conversion of this iodide to the corresponding alkyllithium reagent. However, raising the amounts of *t*-BuLi and electrophile to 3.5 equiv led to the expected alcohol (*S*)-**136x** and amide (*S*)-**136y** in up to 61% yield with full stereoretention (92% *ee*) when using dicyclopropyl ketone (**112u**) or cyclohexyl isocyanate (**112y**) as electrophiles.

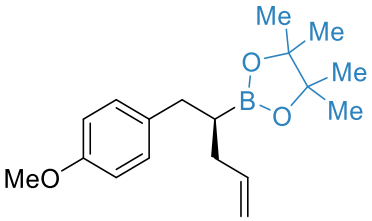
Also the terpene derived optically enriched iodide (*R*,*S*,*S*)-**114k** underwent the ISQ-reaction providing, after mixing with cyclobutanone (**112x**) and addition of *t*-BuLi, the desired alcohol (*R*,*S*,*S*)-**136z** in 59% yield with dr = 92:8 and 98% *ee*. Even the sterically demanding secondary alkyl iodide (*S*)-**114l**, bearing an *iso*-propyl substituent,[254] reacted with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (*R*-**112z**) under high stereoretention providing (2'*S*,3*R*)-**136aa** in 47% yield and dr = 91:9 (95% *ee*). Moreover, the optically enriched alcohols (*R*)- and (*S*)-**136ab** as well as (*R*)- and (*S*)-**136ac** were isolated after this ISQ-reaction from (*R*)- and (*S*)-**114m** in the presence of either adamantanone (**112h**) or dicyclopropyl ketone (**112u**) in up to 84% yield and up to 93% *ee*.



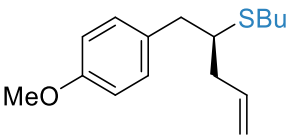
[254] H. Hattori, J. Roesslein, P. Caspers, K. Zerbe, H. Miyatake-Ondozabal, D. Ritz, G. Rueedi, K. Gademann, *Angew. Chem. Int. Ed.* **2018**, *57*, 11020.



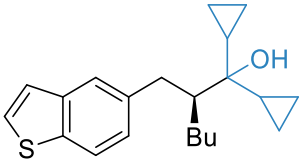
(*S*)-**136u**: 78%, 92% *ee*



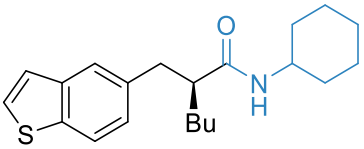
(*S*)-**136v**: 73%, 90% *ee*



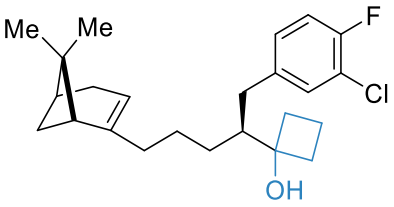
(*S*)-**136w**: 57%, 91% *ee*



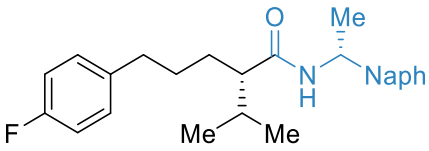
(*S*)-**136x**[a]: 50%, 92% *ee*



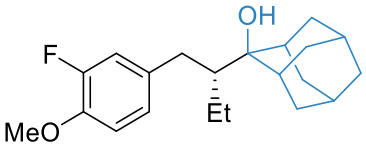
(*S*)-**136y**[a]: 61%, 92% *ee*



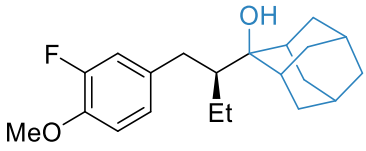
(*R*,*S*,*S*)-**136z:**
59%, dr = 92:8, 98% *ee*



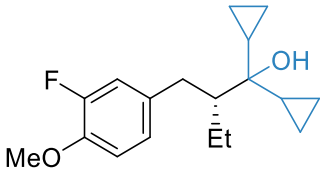
(2'*S*,3*R*)-**136aa**[a,b]:
47%, dr = 91:9, 95% *ee*



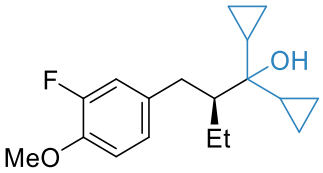
(*R*)-**136ab**: 84% 92% *ee*



(*S*)-**136ab**: 81%, 90% *ee*



(*R*)-**136ac**: 62%, 93% *ee*



(*S*)-**136ac**: 65%, 90% *ee*

Scheme 55: Chiral products **136s-ac** prepared by in situ quench (ISQ) of functionalized optically enriched secondary alkyl iodides **114h-m** in the presence of electrophiles (**112**) using *t*-BuLi at −78 °C. Yields refer to isolated analytically pure products. The enantiomeric excess (% *ee*) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr = *syn*/*anti*) was determined via GC- or NMR-analysis. [a] The reaction was performed using 3.5 equiv of *t*-BuLi and 3.5 equiv of electrophile; [b] Naph = naphthyl.

2.4 In Situ Generation of Chiral Secondary Alkyllithium Species in the Presence of Various Electrophiles under Continuous Flow Conditions

Although these ISQ-procedures provided various highly enantioenriched products, a scale-up above 0.3 mmol was complicated and gave erratic results. Recently, the use of continuous-flow setups and microreactors gained increasing interest in sustainable synthesis[255] especially in terms of safer handling of thermally labile organometallics. Pioneering works by Ley,[256] Yoshida,[257] Organ,[258] and others[259] have popularized the performance of reactions involving highly reactive organometallics in continuous flow.

Therefore, we envisioned that this ISQ-reaction might benefit from the fast mixing properties and the efficient heat transfer of microreactor technology. We utilized a commercial two pump system[260] in which the afforehand prepared solution of *t*-BuLi (0.20 M in hexane)[261] and the premixed solution of alkyl iodides of type **114** (0.08 M) and electrophiles of type **112** (0.20 M in hexane:Et_2O = 2:1) were passed through precooling loops (2.0 mL) using two peristaltic pumps. The streams were combined in a T-shaped mixer and pumped through a coil reactor (1.0 mL). Upon reaching steady state, the reaction mixture was collected in a flask charged with *sat*. *aq*. NH_4Cl (Scheme 56).

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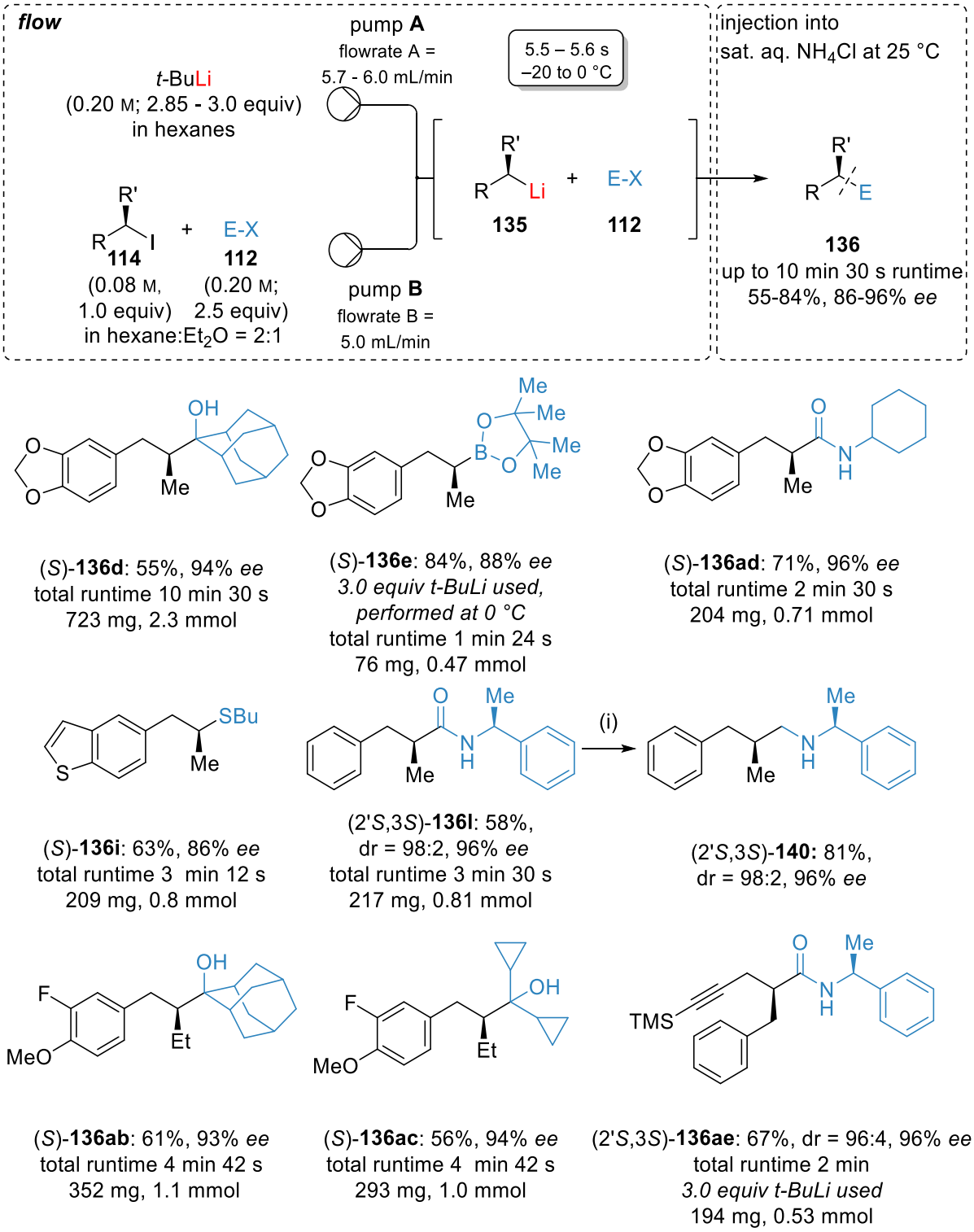
[261] Hexanes was used instead of pentane since the tubing of the peristaltic pumps shows reduced lifetime using pentane.



Scheme 56: Preparation of optically enriched products of type **136** via in situ quench (ISQ) of optically enriched secondary alkyl iodides in the presence of electrophiles (**112**) using *t*-BuLi in continuous flow. Yields refer to isolated analytically pure products. The enantiomeric excess (% *ee*) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr = *syn*/*anti*) was determined via GC- or NMR-analysis. (i) $LiAlH_4$ (3.0 equiv), 0 °C to 50 °C, 14 h.

After a short optimization,[262] based on the previously found conditions, we observed that the continuous flow set-up allowed to raise the reaction temperature at which the ISQ was performed to −20 °C. Best results were obtained when pumping the premixed alkyl iodide and electrophile solution at a flow rate of 5.0 mL/min. Wheras the *t*-BuLi solution was pumped at a flow rate of 5.7 to 6.0 mL/min depending on the substrate. Therefore, the residence time in the coil reactor varied between 5.5 to 5.6 s. Thus, also moderately soluble electrophiles like adamantanone (**112h**) in the presence of the secondary alkyl iodide (*S*)-**114a** were employed and, after mixing with *t*-BuLi, the corresponding alcohol (*S*)-**136d** was isolated in 55% with 94% *ee*. No clogging of the reactor was observed and the reaction mixture was collected for a total of 10 min 30 s, resulting in a 40-fold scale-up in comparison to batch conditions. The high optical purity of (*S*)-**136d** indicated that the elevated temperatures do not lead to any significant epimerization of the intermediate alkyllithium (**135a**). Furthermore, X-ray diffraction analysis of (*S*)-**136d** using Flack parameter method[263] confirmed the (*S*)-configuration and an overall stereoretention.[264] If (*S*)-**114a** was mixed with other electrophiles like boronic acid ester **112n**, the temperature could be increased even further to 0 °C, preventing precipitation in the precooling loop. Under these conditions, the optical purity decreased only slightly and (*S*)-**136e** was obtained in 84% isolated yield and 88% *ee*. Also, (*S*)-**114a** was treated with cyclohexyl isocyanate (**112y**) upon addition of *t*-BuLi and after collecting for 2 min 30 s the desired amide (*S*)-**136ad** was isolated in 71% yield and 96% *ee*. The reactions of (*S*)-**114b**, in the presence of Bu_2S_2 (**112q**), or (*S*)-**114d**, which was mixed with the isocyanate (*S*)-**112t**, and *t*-BuLi provided the sulfide (*S*)-**136i** (63%, 86% *ee*) or the amide (2'*S*,3*S*)-**136l** (58%, dr = 98:2, 96% *ee*). Furthermore, the optically enriched iodides (*S*)-**114m** and (*S*)-**114n** were also compatible with this continuous flow set-up and the scale-up of their reactions with either adamantanone (**112h**) or dicyclopropyl ketone (**112u**) as well as (*S*)-(−)-1-phenylethyl isocyanate (*S*)-**112t** gave (*S*)-**136ab**, (*S*)-**136ac** and (2'*S*,3*S*)-**136ae** in up to 67% yield with up to dr = 96:4 and up to 96% *ee*.

Further post-functionalizations have been achieved by reducing the chiral amide (2'*S*,3*S*)-**136l**[265] to the corresponding amine (2'*S*,3*S*)-**140**[266] with complete retention of the configuration (Scheme 56).[267]

[262] For further information see page 210.
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[265] The other diastereosiomer (2'*S*,3*R*)-**136l** (Scheme 53) was also successfully reduced to the corresponding amine (2'*S*,3*R*)-**140**. For details see page 265.
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2.5 Conclusion

In summary, we have reported a practical and convenient ISQ-procedure for converting various secondary alkyl iodides, including ester or nitrile-functionalized iodides, to highly reactive secondary alkyllithiums in the presence of electrophiles such as ketones, aldehydes, Weinreb amides, isocyanates, boronates and disulfides. A wide range of chiral molecules such as alcohols, ketones, amides, boronic esters and thioethers were obtained with high retention of configuration. Remarkably, these ISQ-reactions were conducted between −78 °C and −40 °C in batch and between −20 °C and 0 °C in continuous flow. This continuous flow set-up also allowed to scale-up this reaction up to 40-fold without further optimization.

3. (2-Ethylhexyl)sodium: A Hexane-Soluble Reagent for Br/Na-Exchanges and Directed Metalations in Continuous Flow[268]

3.1 Introduction

Organosodium reagents are highly reactive organometallics towards various electrophiles due to the very ionic character of the C–Na bond.[269] Despite the appealing chemical properties and the low price, high abundancy and low toxicity of sodium, these compounds have seldomly found applications in organic syntheses.[270] Dimethylethylamine soluble NaDA (sodium diisopropylamide) was prepared by Collum and co-workers as an alternative to the frequently used LDA (lithium diisopropylamide).[271] Recently, Asako and Takai have reported a new method for the preparation of arylsodiums via a Br/Na-exchange using neopentylsodium, which was prepared by the reaction of neopentyl chloride with sodium dispersion (Scheme 57a). This procedure seems to limit the trapping of the resulting arylsodium to R_3SiCl, D_2O and transmetalation reactions.[272] The presence of residual sodium dispersion may hamper the use of more complex electrophiles. In contrast to well established lithium chemistry,[273] the

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use of organosodium reagents remains underexploited in continuous flow due to their poor solubility.[274] We have reported the generation of organosodium and -potassium derivatives in continuous flow using Na- and K-amide bases.[275] In the course of this work, we envisioned a new procedure for generating soluble alkylsodiums in continuous flow expanding pioneering work of Alcázar,[276], Ley,[277] McQuade[276a] and others[278] which established the use of metal-packed-bed reactors for the direct preparation of Mg or Zn organometallics in continuous flow. Herein, we report a new sodium-packed-bed reactor for on-demand generation of the hexanesoluble sodium reagent (2-ethylhexyl)sodium (**36**)[279] from readily available 3-(chloromethyl)heptane (**115**), which was used for performing in-line Br/Na-exchanges as well as directed metalations (Scheme 57b) in continuous flow.

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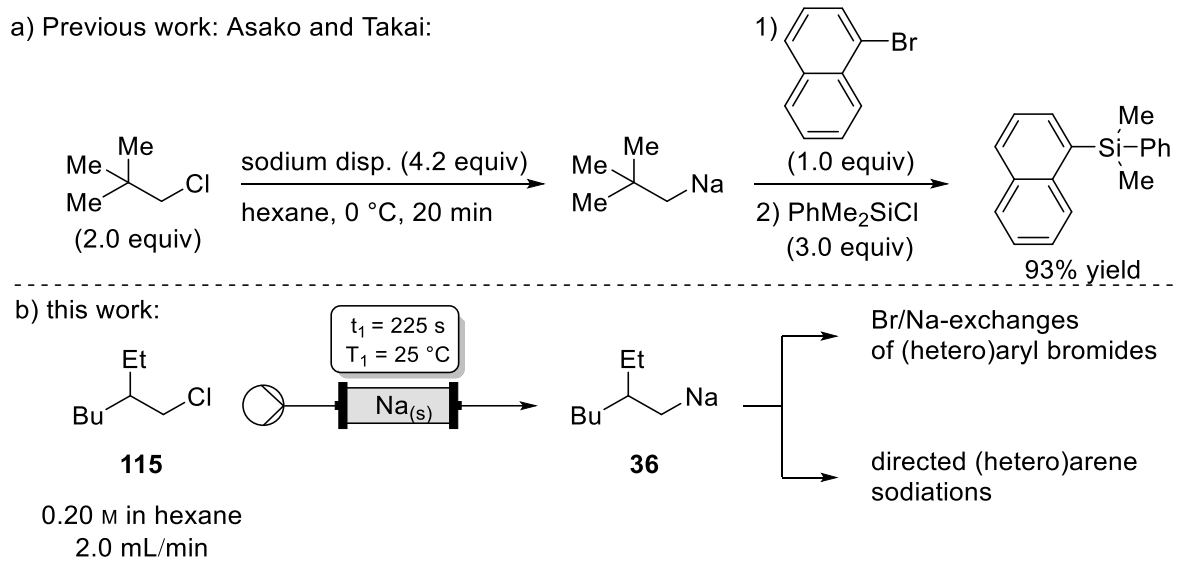

Scheme 57: a) Generation of neopentylsodium in batch and its use in halogen-sodium exchange reactions. b) On-demand continuous flow generation of (2-ethylhexyl)sodium (**36**) and subsequent in-line Br/Na-exchange and directed metalation.

3.2 Preparation of the Sodium-Packed-Bed Reactor and Generation of (2-Ethylhexyl)sodium

To prepare the packed-bed reactor, we charged a glass column (7.5 mL) with sodium particles (3.4 mL, Ø ca. 1 mm).[280,281] The resulting mixed-bed reactor[282] was flushed with dry hexane and was activated using a 0.1 M solution of *i*-PrOH in hexane. Pumping alkyl chloride **115** (0.2 M in hexane, 2.0 mL/min, 25 °C) through the reactor afforded a slightly yellow solution of **36** in hexane (ca. 0.15 M).[283] This soluble alkylsodium species[284] was free of metallic sodium and was directly used for in-line Br/Na-exchanges as well as directed sodiations. Collected aliquots of **36** prepared in continuous flow showed moderate stability (Figure 19), demonstrating the importance of the direct use of the sodium species. This on-demand procedure avoids storage problems of instable **36** and considerably limits hazards of working with metallic sodium. Whereas preparation of **36** in batch led to a dark solution over metallic sodium, the flow procedure resulted in a slightly yellow solution of **36** free of elemental sodium (Figure 19). The airstable dark coloration is already described in the publications of Wurtz and Fittig and has later been attributed by EPR and UV/Vis spectroscopy to colloidal sodium particles of a diameter ~2 nm.[285]

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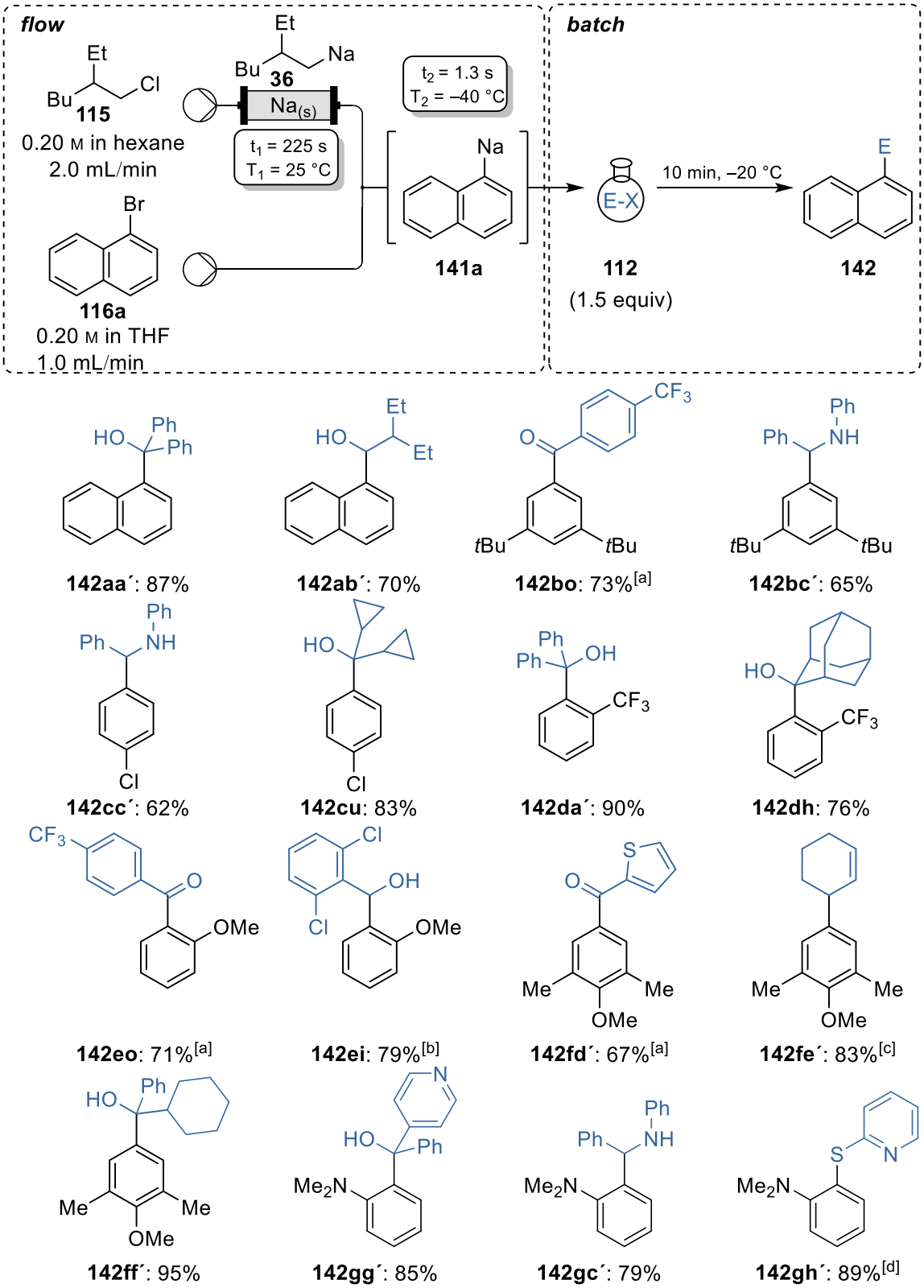
Figure 19. From left to right: (2-Ethylhexyl)sodium (**36**) in hexane prepared in batch over metallic sodium, 5 min after addition of **115**. (2-Ethylhexyl)sodium (**36**) in hexane prepared via a sodium-packed-bed reactor, 5 min after collecting. (2-Ethylhexyl)sodium (**36**) in hexane prepared via a packed-bed sodium reactor, 18 h after collecting.

3.3 Application of the On-Demand Generated (2-Ethylhexyl)sodium in Subsequent In-Line Br/Na-Exchange Reactions

The sodium-packed-bed reactor was used without clogging for ca. 1 h pumping a 0.2 M solution of **115** in hexane with a flow rate of 2.0 mL/min. The soluble organosodium **36** was directly used for Br/Na-exchanges with various aryl bromides of type **116**. Thus, mixing a THF-solution of 1-bromonaphthalene (**116a**, 0.2 M, 1.0 mL/min) with (2-ethylhexyl)sodium (**36**, 0.2 M, 2.0 mL/min) in a T-shaped mixer gave 1-naphthylsodium (**141a**) (−40 °C, 1.3 s).[286]

Subsequent batch-quench of **141a** with benzophenone (**112a´**) or enolisable 2-ethylbutyraldehyde (**112b´**) afforded the desired alcohols (**142aa´-142ab´**) in 70-87% yield (Scheme 58). The resulting arylsodiums reacted instantly with various electrophiles such as ketones, aldehydes, Weinreb-amides, imines, allyl bromides, disulfides and alkyl iodides. Weinreb-amide **112o** and imine **112c´** gave the expected products **142bo** and **142bc´** in 65–73% yield upon Br/Na-exchange on 1-bromo-3,5-di-*tert*-butylbenzene (**116b**). Halogen- and trifluoromethyl-substituted aryl bromides such as **116c** and **116d** furnished after batch quenching the functionalized arenes **142cc´**, **142cu**, **142da´** and **142dh** in 62–90% yield. Electron-rich bromoarenes were well suited for such a Br/Na-exchange in continuous flow affording the polyfunctionalized arenes **142eo**, **142ei**, **142fd´**, **142fe´**, **142ff´, 142gg´**, **142gc´** and **142gh´** in 67–95% yield.

[286] For screening of the Br/Na-exchange reaction conditions, see page 278.

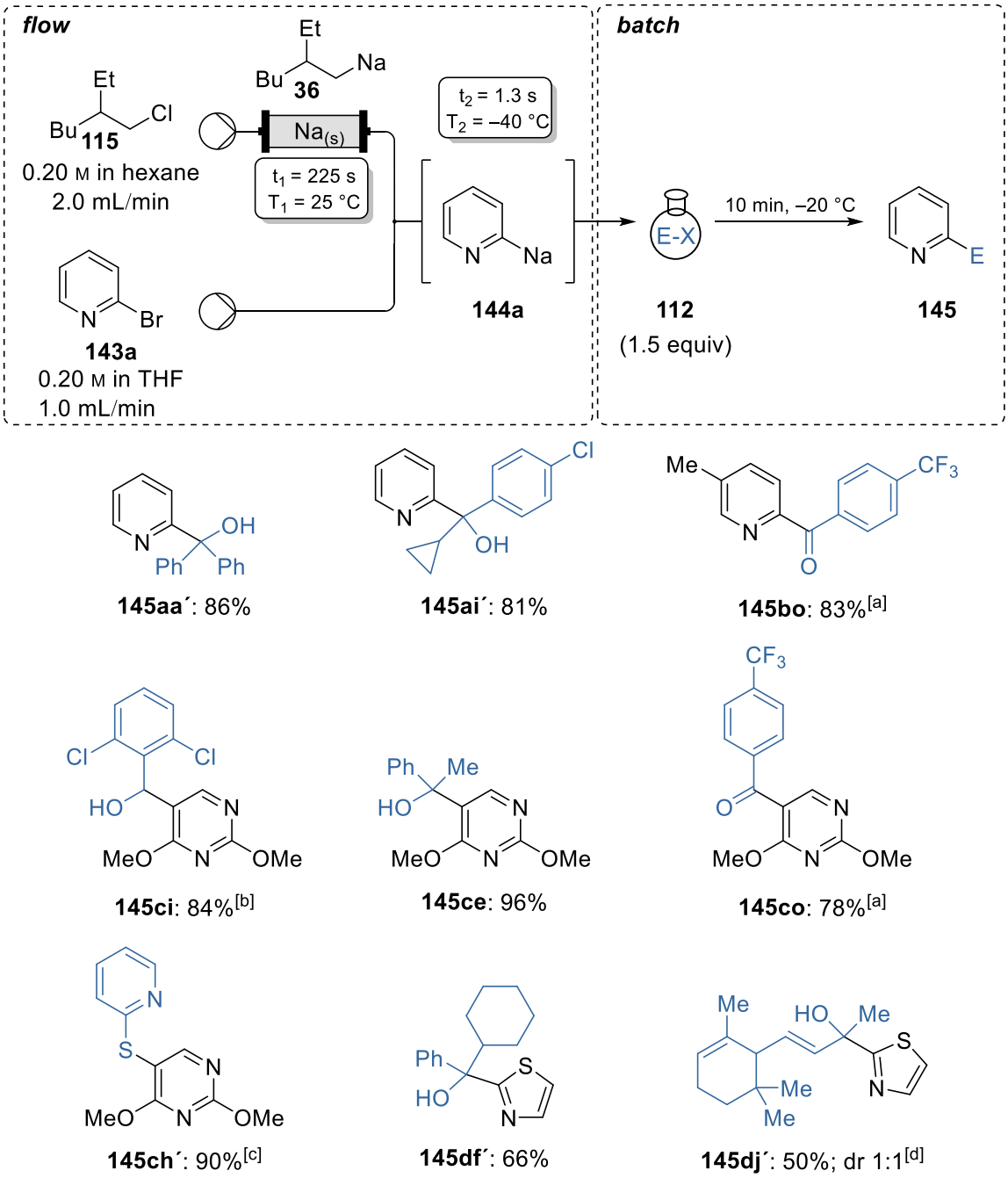


Scheme 58: On-demand preparation of alkylsodium reagent **36** from alkyl chloride **115** followed by Br/Na-exchange on aryl bromides of type **116** leading to arylsodiums of type **141** and subsequent batch quench with electrophiles of type **112** leading to products of type **142**. Yields of analytically pure products. [a] From the Weinreb-amide [b] 2.0 equiv E-X were used. [c] From the allyl bromide with addition of 50 mol% CuCN·2LiCl. [d] From the disulfide.

Nitrogen containing heterocycles are important building blocks in pharmaceutical and agricultural chemistry.[287] Therefore, the functionalization of those scaffolds is an ongoing task in synthetic chemistry.[288] The exchange procedure was extended towards heterocyclic bromides using the optimized reaction conditions. Br/Na-exchange on 2-bromopyridine (**143a**) at −40 °C using a combined flow rate of 3.0 mL/min led to the desired aryl-sodium **144a**, which was subsequently quenched in batch with ketones **112a´** and **112i´** affording the tertiary alcohols **145aa´** and **145ai´** in 81-86% yield (Scheme 59). Similarly, 5-methyl-2-bromopyridine (**143b**) and highly substituted bromopyrimidine **143c** underwent Br/Na-exchanges. Batch quenching using various electrophiles of type **112** led to the functionalized N-heterocycles **145bo**, **145ci**, **145ce**, **145co** and **145ch´** in 78–96% yield. Furthermore, 2-bromothiazole (**143d**) was converted into the corresponding sodium species **144d**, which was quenched with ketone **112f´** resulting in **145df´** (66% yield). Trapping **144d** with a racemic mixture of α-ionone (**122j´**) gave the 1,2-addition product **145dj´** (50% yield, dr 1:1).

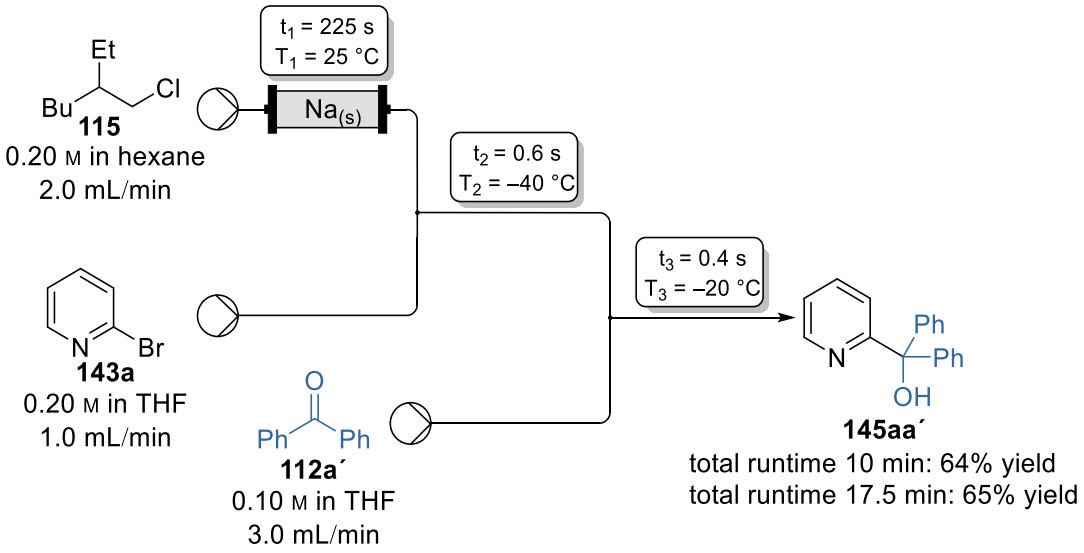
[287] a) *Modern Arene Chemistry* D. Astruc, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2002**; b) T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347; c) G. A. Bhat, J. L. G. Montero, R. P. Panzica, L. L. Wotring, L. B. Townsend, *J. Med. Chem.* **1981**, *24*, 1165; d) C. B. Vicentini, D. Mares, A. Tartari, M. Manfrini, G. Forlani, *J. Agric. Food Chem* **2004**, *52*, 1898.

[288] a) M. Balkenhohl, H. Jangra, I. S. Makarov, S.-M. Yang, H. Zipse, P. Knochel, *Angew. Chem.* **2020**, *132*, 15102; b) K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302; c) H. Chen, M. Farizyan, F. Ghiringhelli, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2020**, *59*, 12213.



Scheme 59: On-demand preparation of alkylsodium reagent **36** from alkyl chloride **115** followed by Br/Na-exchange on heteroaryl bromides of type **143** leading to heteroarylsodiums of type **144** and subsequent batch quench with electrophiles of type **112** leading to products of type **145**. Yields of analytically pure products. [a] From the Weinreb-amide. [b] 2.0 equiv E-X were used. [c] From the disulfide. [d] From racemic α-ionone.

To demonstrate the scalability[289] of the Br/Na-exchange reaction, an in-line electrophile quench was set up. Thus, pumping a solution of **115** (0.2 M, 2.0 mL/min) through the sodium-packed reactor resulted in the sodium exchange reagent **36**. 2-Bromopyridine (**143a**, 0.2 M, 1.0 mL/min) was mixed with the solution of **36** in a T-shaped mixer. After passing through a micro-reactor (0.6 s, −40 °C, combined flow rate: 3.0 mL/min), the pyridylsodium **144a** was trapped in-line with a solution of benzophenone (**112a´**, 0.1 M, 3.0 mL/min). Increasing the runtime 10- or 17.5-fold (2.0 or 3.5 mmol) led to the functionalized pyridine **145aa´** in 64-65% isolated yield (Scheme 60).



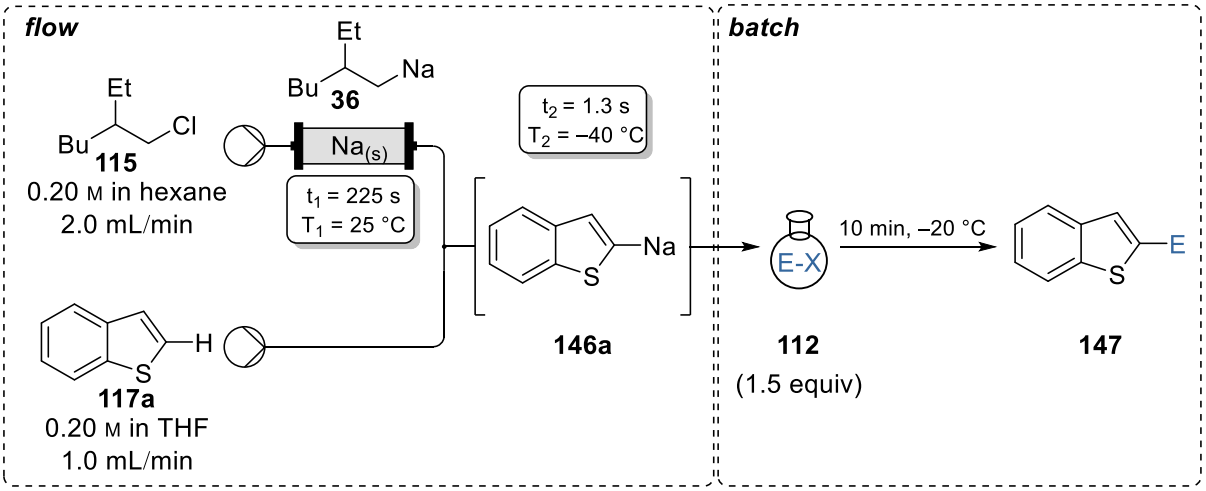
Scheme 60: Scale-up of the Br/Na-exchange reaction using 2-bromopyridine (**143a**), (2-ethylhexyl)sodium (**36**) as exchange reagent and benzophenone (**112a´**) as electrophile, applying in-line quenching conditions

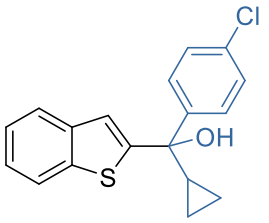
3.4 Application of the On-Demand Generated (2-Ethylhexyl)sodium in Subsequent In-Line Directed Sodiations

Apart from halogen/lithium-exchanges, alkyllithiums are frequently used in directed metalations converting readily available arene starting materials into highly reactive aryllithiums, therefore allowing the functionalization of previously unreactive aromatic C-H bonds.[290] We expected **36** to behave similarly, and indeed without changing the set-up of the continuous flow procedure,

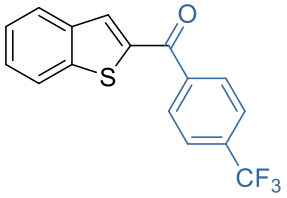
[289] a) M. Kleoff, J. Schwan, L. Boeser, B. Hartmayer, M. Christmann, B. Sarkar, P. Heretsch, *Org. Lett.* **2020**, *22*, 902; b) M. Köckinger, C. A. Hone, B. Gutmann, P. Hanselmann, M. Bersier, A. Torvisco, C. O. Kappe, *Org. Process Res. Dev.* **2018**, *22*, 1553; c) S. Laue, V. Haverkamp, L. Mleczko, *Org. Process Res. Dev.* **2015**, *20*, 480; d) N. Zaborenko, M. W. Bedore, T. F. Jamison, K. F. Jensen, *Org. Process Res. Dev.* **2011**, *15*, 131.
[290] a) J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**; b) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

(2-ethylhexyl)sodium (**36**) was able to metalate benzothiophene (**117a**) resulting in the corresponding sodium species **146a**.[291] Quenching with carbonyl electrophiles **112i´**, **112o**, and **112i** gave the expected products **147ai´**, **147ao** and **147ai** in 73-87% yield (Scheme 61). Imidazole **117b** was metalated similarly and subsequent batch quench gave the products **147bh´**, **147bc´** and **147bh** in 55-79% isolated yield. The electron rich 1,3-dimethoxybenzene (**117c**) was converted to the arylsodium **146c**. Trapping with ketone **112i´** or disulfide **112q** gave the desired products **147ci´** and **147cq** in 86-88% yield. Additionally, transition metal free Wurtz-type coupling,[292] with iodooctane (**5k´**) gave the alkylated product **147ck´** in 46% yield.

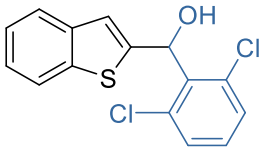




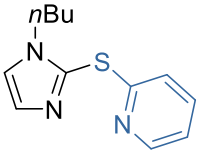
147ai´: 87%



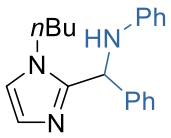
147ao: 85%[a]



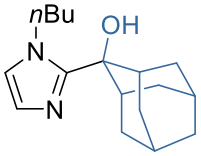
147ai: 73%[b]



147bh´: 79%[c]

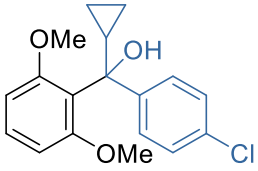


147bc´: 69%

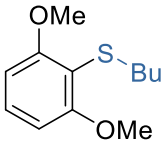


147bh: 55%

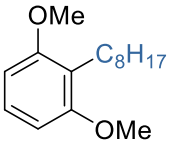
[291] For optimization of the metalation reaction conditions, see page 281.
[292] a) A. Wurtz, *Ann. Chim. Phys.* **1855**, *44*, 275; b) A. Wurtz, *Ann. Chim. Phys.* **1855**, *96*, 364; c) J. W. Morzycki, S. Kalinowski, Z. Łotowski, J. Rabiczko, *Tetrahedron* **1997**, *53*, 10579; d) J. F. Garst, P. W. Hart, *Chem. Commun.* **1975**, 215.



147ci´: 86%



147cq: 88%[c]



147ck´: 46%[d]

Scheme 61: On-demand preparation of alkylsodium reagent **36** from alkyl chloride **115** followed by directed metalation of (hetero)arenes of type **117** leading to (hetero)arylsodiums of type **146** and subsequent batch quench with electrophiles of type **112** leading to products of type **147**. Yields of analytically pure products. [a] From the Weinreb-amide. [b] 2.0 equiv E-X were used [c] From the disulfide. [d] From the alkyl iodide.

3.5 Conclusion

In summary, we have reported the on-demand generation of sodium metal free, hexane-soluble (2-ethylhexyl)sodium from 3-(chloromethyl)heptane using a sodium-packed-bed reactor in a commercially available continuous flow set-up. The procedure avoids storage of alkylsodium species and limits the handling of metallic sodium to a minimum. (2-Ethylhexyl)sodium was used for in-line sodiations and Br/Na-exchange reactions. The resulting arylsodiums were subsequently trapped with various electrophiles such as ketones, aldehydes, Weinreb-amides, imines, allyl bromides, disulfides and alkyl iodides. A reaction scale-up of the Br/Na-exchange using an in-line electrophile quench was reported. Further investigations on the use of alkylsodium reagents are currently under way in our laboratories.

4. CONTINUOUS FLOW PREPARATION OF BENZYLIC SODIUM ORGANOMETALLICS[293]

4.1 Introduction

Among all alkali metal organometallics, lithium compounds have found most applications in organic chemistry.[294] However, the increased use of lithium in battery technologies leads to unpredictable prices[295] and drives the search for using alternative alkali metals for applications in fine organic synthesis.[296] Although sodium is 1200 times more abundant in the earth´s crust[297] and more environmentally friendly,[298] it is underexploited in organic chemistry.[299] This is a result of the high reactivity of sodium organometallics as well as the poor solubility of most organosodiums.[300] Recently, we have reported that the reactivity of organosodiums can be well tuned by continous flow techniques.[301] Also, the findings that (2-ethylhexyl)sodium (**36**) is easily prepared from 3-(chloromethyl)heptane (**115**) using a sodium packed-bed reactor[302] and uniquely soluble in

[293] Adapted with permission from J. H. Harenberg, R. Reddy Annapureddy, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2022**, e202203807. Copyright 2022 Angewandte Chemie International Edition published by Wiley-VCH. https://doi.org/10.1002/anie.202203807. This project was developed in cooperation with Dr. Rajasekar Reddy Annapureddy.

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[295] The price of Li_2CO_3 increased by a factor of 9.4 from 19th of February 2021 (45455 ¥) to 21st of February 2022 (424 641 ¥). https://tradingeconomics.com/commodity/lithium; retrived February 2022.

[296] G. Martin, L. Rentsch, M. Höck, M. Bertau, *Energy Storage Mater.* **2017**, *6*, 171.

[297] N. N. Greenwood, A. Earnshaw, *Chemistry of the Elements*, Elsevier, Amsterdam, **2012**.

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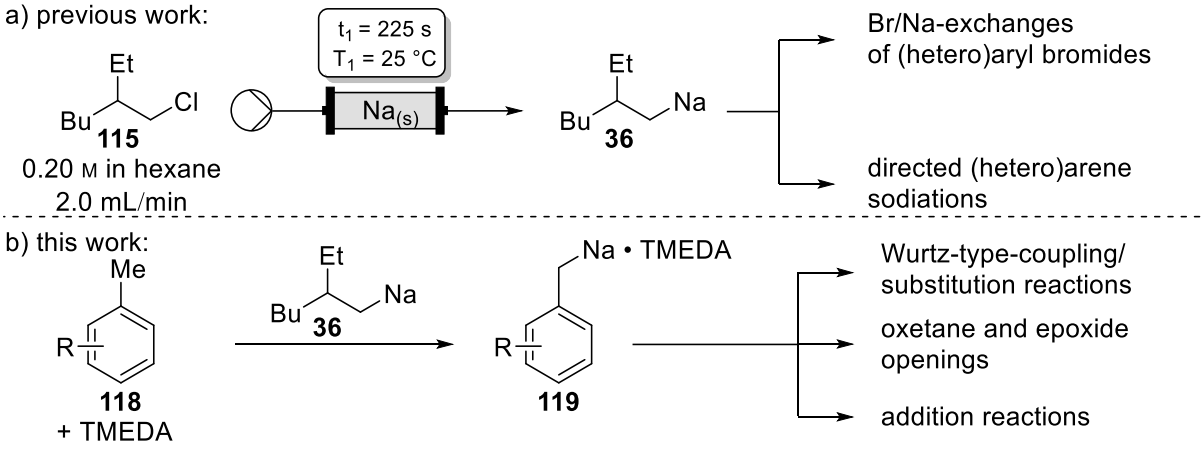
[299] a) T. F. Crimmins, C. M. Chan, *J. Org. Chem.* **1976**, *41*, 1870; b) T. F. Crimmins, E. M. Rather, *J. Org. Chem.* **1978**, *43*, 2170; c) D. Seyferth, *Organometallics* **2006**, *25*, 2; d) D. Seyferth, *Organometallics* **2009**, *28*, 2; e) J.-M. Becht, A. Gissot, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2004**, *45*, 9331; f) L. Ilies, S. Asako, P. B. De, *Synthesis* **2021**, *53*, 3180; g) A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 340.

[300] a) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544; b) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 7921; c) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197; d) D. B. Collum, R. A. Woltornist, Y. Ma, R. F. Algera, Y. Zhou, Z. Zhang, *Synthesis* **2020**, *52*, 1478; e) Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312; f) Y. Ma, R. F. Algera, R. A. Woltornist, D. B. Collum, *J. Org. Chem.* **2019**, *84*, 10860; g) Y. Ma, R. A. Woltornist, R. F. Algera, D. B. Collum, *J. Am. Chem. Soc.* **2021**, *143*, 13370; h) Y. Ma, R. A. Woltornist, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2019**, *84*, 9051; i) R. A. Woltornist, D. B. Collum, *J. Am. Chem. Soc.* **2020**, *142*, 6852; j) R. A. Woltornist, D. B. Collum, *J. Am. Chem. Soc.* **2021**, *143*, 17452; k) Y. Zhou, I. Keresztes, S. N. MacMillan, D. B. Collum, *J. Am. Chem. Soc.* **2019**, *141*, 16865; l) S. Asako, M. Kodera, H. Nakajima, K. Takai, *Adv. Synth. Catal.* **2019**, *361*, 3120; m) S. Asako, H. Nakajima, K. Takai, *Nat. Catal.* **2019**, *2*, 297; n) L. Ilies, S. Asako, P. B. De, *Synthesis* **2021**, *53*, 3180; o) M. Schlosser, *Angew. Chem. Int. Ed.* **1964**, *3*, 287; p) M. Schlosser, *Angew. Chem. Int. Ed.* **1964**, *3*, 362.

[301] a) J. H. Harenberg, N. Weidmann, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 731; b) J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 12321; c) N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748; d) J. H. Harenberg, N. Weidmann, P. Knochel, *Synlett* **2020**, *31*, 1880.

[302] a) N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737; b) M. Berton, L. Huck, J. Alcazar, *Nat Protoc* **2018**, *13*, 324; c) L. Huck, A. de la Hoz, A. Diaz-Ortiz, J. Alcazar, *Org. Lett.* **2017**, *19*, 3747.

n-hexane,[303] make this new reagent ideal for preparing various organosodiums either by a Br/Na-exchange or more attractively by directed sodiation of arenes and heteroarenes (Scheme 62a).[304] Since the lateral metalation of various methyl and alkyl substituted (hetero)arenes has proven to be an excellent method for preparing benzylic alkali metal reagents,[305] we have envisioned to use the new base **36** for the lateral metalation of various substituted arenes of type **118**. Herein, we report the successful preparation of various benzylic sodium species of type **119** as well as their reactivity in nucleophilic substitutions including Wurtz-type couplings,[306] epoxide[307] and oxetane openings[308] and additions to carbonyl electrophiles (Scheme 62b).



Scheme 62: a) On-demand continuous flow generation of (2-ethylhexyl)sodium (**36**) and subsequent in-line Br/Na-exchange and directed metalation. b) Lateral metalations of methylarenes using in continuous flow prepared (2-ethylhexyl)sodium (**36**) and subsequent use of the benzylic sodiums for additive free Wurtz-type-couplings, oxetane, epoxide openings and addition to carbonyl derivatives.

[303] a) A. A. Arest-Yakubovich, B. I. Nakhmanovich, G. I. Litvinenko, *Polymer* **2002**, *43*, 7093; b) S. G. Sakharov, N. I. Pakuro, A. A. Arest-Yakubovich, L. V. Shcheglova, P. V. Petrovskii, *J. Organomet. Chem.* **1999**, *580*, 205.
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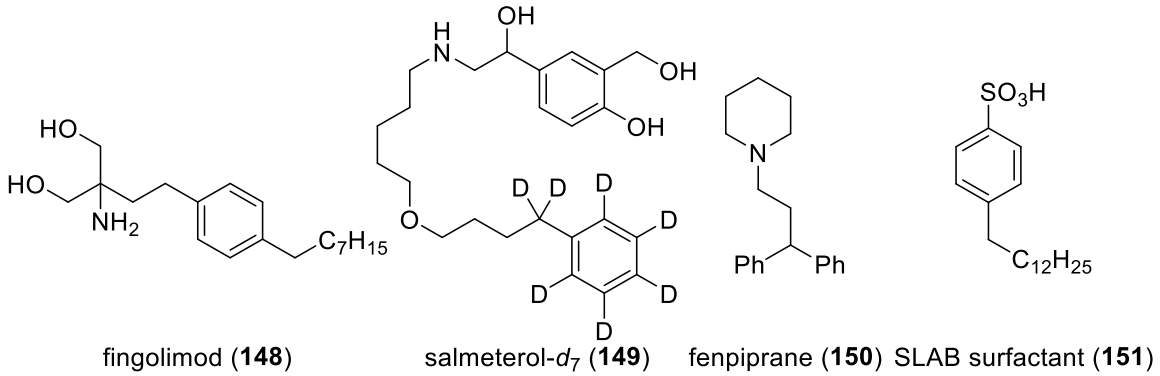
[305] a) R. A. Benkeser, A. E. Trevillyan, J. Hooz, *J. Am. Chem. Soc.* **1962**, *84*, 4971; b) W. T. Smith, D. L. Nickel, *Org. Prep. Proced. Int.* **1975**, *7*, 277; c) G. B. Trimitsis, A. Tuncay, R. D. Beyer, *J. Am. Chem. Soc.* **1972**, *94*, 2152; d) N. Weidmann, J. H. Harenberg, P. Knochel, *Org. Lett.* **2020**, *22*, 5895; e) H. Jiang, S.-C. Sha, S. A. Jeong, B. C. Manor, P. J. Walsh, *Org. Lett.* **2019**, *21*, 1735; f) Z. Wang, Z. Zheng, X. Xu, J. Mao, P. J. Walsh, *Nat. Commun.* **2018**, *9*, 3365; g) F. Yang, D. Zou, S. Chen, H. Wang, Y. Zhao, L. Zhao, L. Li, J. Li, P. J. Walsh, *Adv. Synth. Catal.* **2020**, *362*, 3423.
[306] a) F. Faigl, M. Schlosser, *Tetrahedron Lett.* **1991**, *32*, 3369; b) J. W. Morzycki, S. Kalinowski, Z. Łotowski, J. Rabiczko, *Tetrahedron* **1997**, *53*, 10579; c) A. A. Morton, F. Fallwell, *J. Am. Chem. Soc.* **1938**, *60*, 1429; d) S.-C. Kuo, F. Chen, D. Hou, A. Kim-Meade, C. Bernard, J. Liu, S. Levy, G. G. Wu, *J. Org. Chem.* **2003**, *68*, 4984; e) H. Pines, J. A. Vesely, V. N. Ipatieff, *J. Am. Chem. Soc.* **1955**, *77*, 554; f) M. Takagi, M. Nojima, S. Kusabayashi, *J. Am. Chem. Soc.* **1983**, *105*, 4676; g) S. Thayumanavan, A. Basu, P. Beak, *J. Am. Chem. Soc.* **1997**, *119*, 8209; h) H.-J. Lee, H. Kim, D.-P. Kim, *Chem. Eur. J.* **2019**, *25*, 11641.
[307] a) D. Arnodo, S. Ghinato, S. Nejrotti, M. Blangetti, C. Prandi, *Chem. Commun* **2020**, *56*, 2391; b) E. Vrancken, A. Alexakis, P. Mangeney, *Eur. J. Org. Chem.* **2005**, *2005*, 1354; c) T. Imai, S. Nishida, T. Tsuji, *Chem. Commun.* **1994**, 2353.
[308] a) H. Yorimitsu, S. Wang, A. Kaga, *Synlett* **2021**, *32*, 219; b) A. Maercker, M. Passlack, *Chem. Ber.* **1983**, *116*, 710.

Such benzylic organometallics are potentially important reagents for the synthesis of drug targets such as the immunomodulator fingolimod (**148**), which is approved for the treatment of multiple sclerosis,[309] the β_2 adrenoreceptor agonist salmeterol (**149**) used for the therapy of the asthma disease[310] or other pharmaceuticals such as fenpiprane (**150**). Furthermore, the procedure might enable a straightforward and scalable synthesis of super linear alkylbenzene (SLAB) surfactants like **151**.[311] Herein, we demonstrate that benzylic sodium intermediates prepared by this continuous flow method are well suited for the preparation of **148** to **151** (Scheme 63).



fingolimod (**148**) salmeterol-d_7 (**149**) fenpiprane (**150**) SLAB surfactant (**151**)

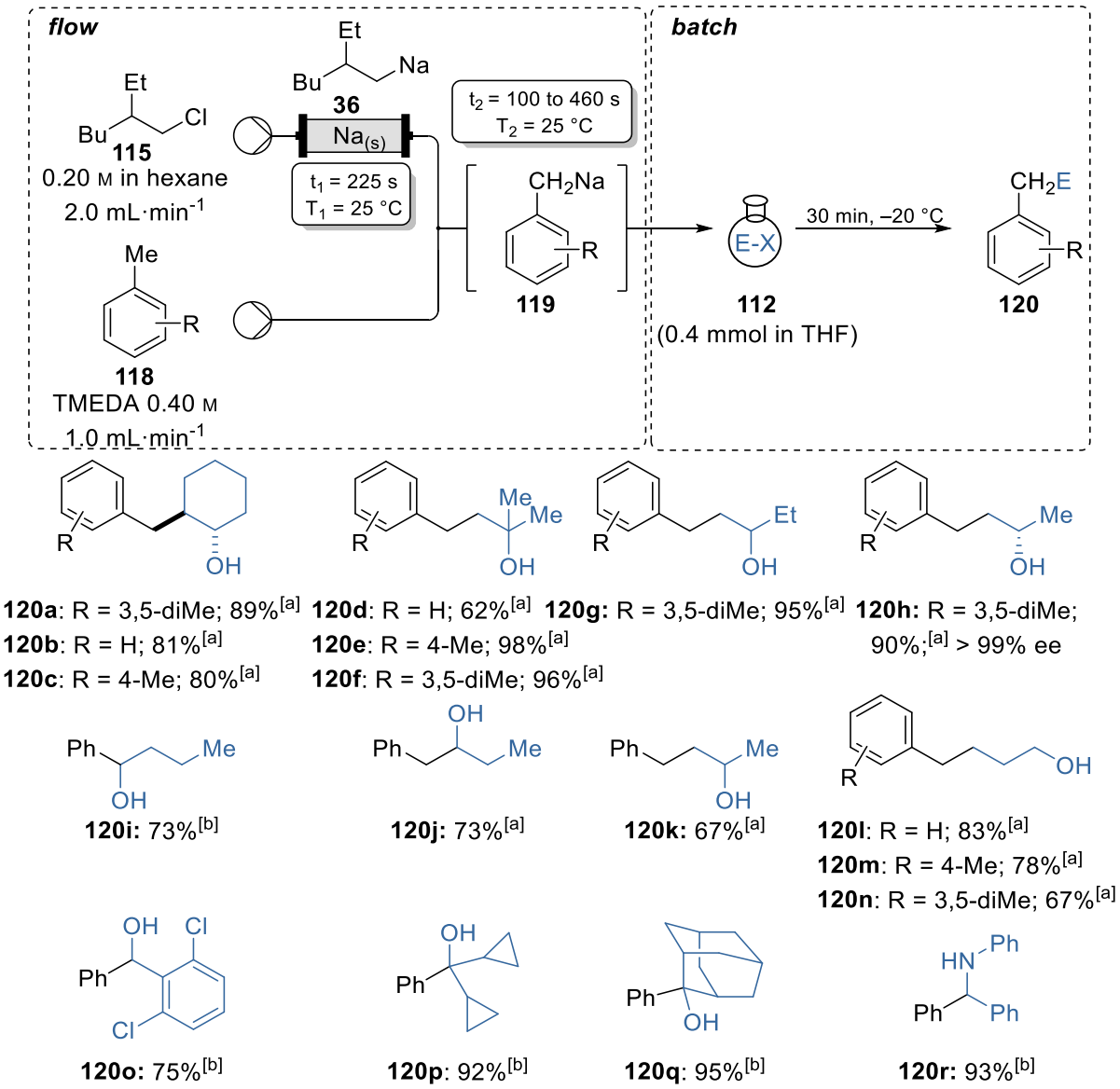
Scheme 63: Pharmaceuticals and super linear alkylbenzene surfactant (SLAB) potentially prepared using benzylic organometallics.

4.2 In-Line Sodiation of Methylarenes Using On-Demand Generated (2-Ethylhexyl)sodium and Subsequent Electrophile Quench Reactions

Thus, in preliminary experiments, we have generated (2-ethylhexyl)sodium (**36**) as a 0.15 M solution in *n*-hexane by pumping alkyl chloride **115** (0.20 M in hexane, 2.0 mL · min^{-1}) through the previously developed sodium packed-bed reactor.[312] Mixing the stream of **36** (2.0 mL · min^{-1}) with a 0.4 M solution of *N*,*N*,*N*´,*N*´-tetramethylethylenediamine (TMEDA) in neat mesitylene (**118a**) (1.0 mL · min^{-1}) in a T-shaped mixer led to an optimum metalation within 460 s at 25 °C producing 3,5-dimethylbenzylsodium (**119a**). Even though the metalation proceeded without TMEDA, its presence accelerated the sodiation and increased dramatically the solubility of the resulting benzylic intermediates.[313,314] A subsequent

[309] a) A. N. Balaev, A. A. Busel, V. E. Fedorov, *Pharm. Chem. J.* **2017**, *51*, 476; b) H. E. Askey, J. D. Grayson, J. D. Tibbetts, J. C. Turner-Dore, J. M. Holmes, G. Kociok-Kohn, G. L. Wrigley, A. J. Cresswell, *J. Am. Chem. Soc.* **2021**, *143*, 15936; c) J. Doubský, S. Rádl, J. Cinibulk, R. Klvaňa, *Org. Process Res. Dev.* **2022**, *26*, 859; d) N. Mulakayala, P. Rao, J. Iqbal, R. Bandichhor, S. Oruganti, *Eur. J. Med. Chem.* **2013**, *60*, 170.
[310] J. Liu, D. Zhou, X. Jia, L. Huang, X. Li, A. S. C. Chan, *Tetrahedron: Asymmetry* **2008**, *19*, 1824.
[311] a) T. B. Gunnoe, W. L. Schinski, X. Jia, W. Zhu, *ACS Catal.* **2020**, *10*, 14080; b) N. I. Saper, A. Ohgi, D. W. Small, K. Semba, Y. Nakao, J. F. Hartwig, *Nat. Chem.* **2020**, *12*, 276.
[312] J. H. Harenberg, N. Weidmann, A. J. Wiegand, C. A. Hoefer, R. R. Annapureddy, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 14296.
[313] Lateral metalation using *n*BuLi requires the presence of TMEDA. See page 324.
[314] a) L. Brieger, C. Unkelbach, C. Strohmann, *Chem. Eur. J.* **2021**, *27*, 17780; b) A. Rae, K. M. Byrne, S. A. Brown, A. R. Kennedy, T. Krämer, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2022**, *28*, e202104260; c) D. B. Collum, *Acc. Chem. Res.* **1992**, *25*, 448; d) H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130.

batch reaction with cyclohexene oxide (**112l´**) produced the ring opening alcohol product **120a** in 89% isolated yield (Scheme 64).[315]



Scheme 64: On-demand preparation of alkylsodium reagent **36** from alkyl chloride **115** followed by in-line sodiations on methyl aryls of type **118** or benzene **118d** leading to benzylic sodiums of type **119** and subsequent batch quench with electrophiles of type **112** leading to products of type **120**. Isolated yields of analytically pure products. [a] t_2 = 460 s; [b] t_2 = 100 s.

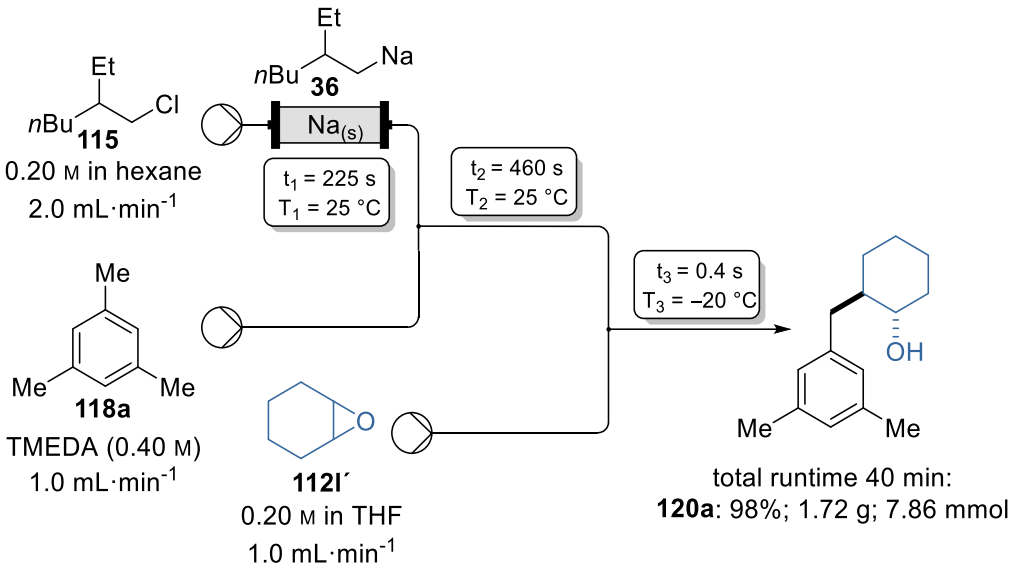
These optimized conditions were extended to continuous flow sodiations of other commonly used methyl substituted arenes, such as toluene (**118b**) and *p*-xylene (**118c**). Batch quench of the resulting benzylic sodium species (**119b**, **119c**) with substituted epoxides led to the secondary and tertiary alcohols **120b**-**120g** in 62–98% isolated yield with a nucleophilic attack on the sterically less hindered

[315] Barbier-type reaction conditions gave a comparable yield of 82%. See page 336.

epoxide carbon. Reaction of **119a** with the enantiopure (*S*)-2-methyloxirane (**112o´**) gave the alcohol **120h** (90% yield, > 99% ee) with complete retention of stereochemistry.

In addition to the lateral metalation of methyl substituted arenes, it was possible to sodiate neat benzene (**118d**) in the presence of TMEDA (0.4 M) using the same flow rates as for the lateral metalation, but a shorter coil reactor resulting in a residence time of 100 s at 25 °C. Thus, quenching of phenylsodium (**119d**) with butyraldehyde (**112p´**) led to alcohol **120i** in 73% yield. In fact, our method allowed the introduction of an alcohol function in α, β, γ, and δ- position to the aromatic ring. Thus, the 1,2-addition of benzylsodium (**119b**) to propionaldehyde (**112q´**) and the Lewis acid free ring openings of epoxide **112r´** and unsubstituted oxetane (**112s´**) proceeded smoothly and led to the phenylbutanols **120i**–**120l** (67–83% yield). The oxetane opening products of mesytylene and *p*-xylene **120m**, **120n** were obtained in 67–78% yield. Batch quench of phenylsodium (**119d**) with aldehyde, ketone and imine electrophiles led to the formation of the desired products **120o**–**120r** in 75–95% yield.

Scalability of this synthesis was shown by transferring the reaction sequence into a continuous flow set-up using a susbsequent in-line quench. Thus, after formation of the solution **119a** in a coiled tube reactor (t_2 = 460s, T_2 = 25 °C) the solution was mixed in a second T-shaped mixer with a solution of **112l´** in THF (0.20 M, 1.0 mL · min^{-1}). Increasing the runtime to 40 min led to a 20-fold scale-up (8.0 mmol) and the desired product **120a** in 98% yield (1.72 g, 7.86 mmol, Scheme 65).



Scheme 65: 20-Fold scale-up of the lateral metalation of mesitylene (**118a**), using (2-ethylhexyl)sodium (**36**) as base and cyclohexene oxide (**112l´**) as electrophile, applying in-line quenching conditions.

4.3 Batch Sodiation of Alkylarenes Using On-Demand Generated (2-Ethylhexyl)sodium and Subsequent Electrophile Quench Reactions

The moderate solubility of more complex benzylic sodium derivatives in hexane led us to develop an alternative procedure, in which the sodiation step took place in batch. In preliminary experiments, addition of on-demand generated solution of **36** for 2 min to a mixture of TMEDA (0.8 mmol) in toluene (**118b**) in batch gave benzylsodium (**119b**). After quenching **119b** with adamantanone (**112h**) or the protected epoxy-propanols **112t´** and **112u´** the desired alcohol products **120s**–**120u** were obtained in 83–94% yield. In case of **120u**, a silyl migration was observed, however a deprotection with TBAF in THF gave the corresponding 1,2-diol **152u** in 94% yield (Scheme 66).

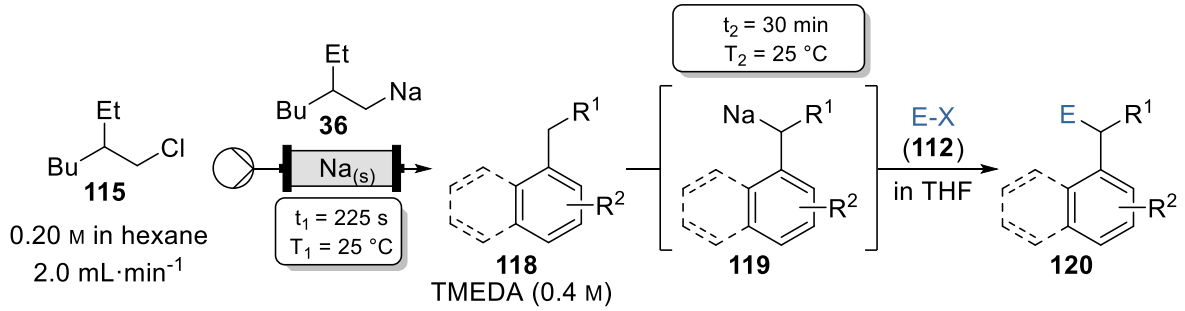
In all above described experiments the methyl arenes of type **118** were used in large excess (solvent !). For more expensive or solid substituted arenes, we designed another more general procedure. Thus, the solution of **36** prepared in continuous flow was added to a mixture of 1-methylnaphthalene (**118e**, 1.0 equiv) and TMEDA (2.0 equiv) in hexane. Stirring for 30 min at 25 °C resulted in benzylsodium **119e**. Batch quench with epoxides, oxetane or ketones gave the alcohols **120v**[316]–**120x** (68–92% yield). Similar results were obtained using **118e** in excess (2.5 equiv) and the electrophiles (1.0 equiv) as limiting reagent, leading to **120v** (98% yield), **120x** (69% yield), and **120y** (81% yield). The procedure was used for the metalation of 1-ethyl-4-methylbenzene (**118f**) which was selectively sodiated at the methyl group. After addition of electrophiles the expected products **120z** and **120aa** were obtained in 93–94% yield. Substituted alkylarenes such as ethylbenzene (**118g**) and tetralin (**118h**) were similarly sodiated and reaction of the secondary benzylsodium species **119g** and **119h** with ketones and epoxides resulted in alcohols **120ab**–**120ah** (52–71% yield).

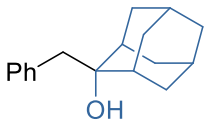
Lateral metalation of methylarenes substituted by halide atoms or methoxy- or amide-functionalities on the aromatic ring (**118i**–**118k**) and quenching with electrophiles led to the functionalized alcohols **120ai**–**120al** (66–86% yield).[317] This sodiation procedure was extended to the metalation of benzylic positions adjacent to functional groups. Thus, benzyl(phenyl)sulfane (**118l**) and phenylacetonitrile (**118m**) were converted into sulfides and nitriles **120am**–**120ao** in 62–90% yield.

Diphenylmethane **118n** was sodiated in a hexane solution or neat.[318] The resulting benzhydrylsodium **119n** was an excellent nucleophile for the Lewis acid free ring opening of epoxides and oxetane (**112s´**) and gave the desired alcohols **120ap**–**120as** in 75–97% yield. The sodiation of benzene (**118d**) in continuous flow gave phenylsodium (**119d**) in high yields, we have extended this metalation to

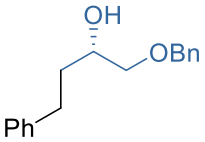
[316] Stereochemistry confirmed by single crystal X-ray diffraction see page 427. Deposition Numbers 2158223 (for **120v**), 2158222 (for **154o**), 2158220 (for **154p**), and 2158221 (for **156a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
[317] J. Clayden, C. Stimson, M. Helliwell, M. Keenan, *Synlett* **2006**, *2006*, 873.
[318] See pages 374 and 391.

benzene-d_6 (**118o**).[319] Indeed, the sodiation of neat **118o** in the presence of TMEDA proceeded smoothly and quenching with adamantanone (**112h**) gave the desired penta-deuterated tertiary alcohol **120at** in 94% yield.



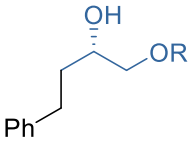


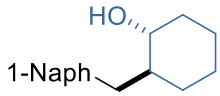
120s: 93%[a]



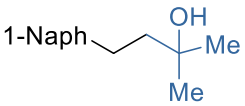
120t: 83%[a]

a) **120u:** R = TBS; 94% r.r. 4.3:1[a]
152u: R = H; 94%

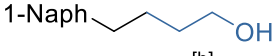




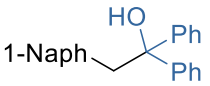
120v: 92%[b]
120v: 98%[c]



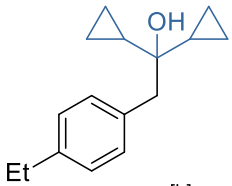
120w: 87%[b]



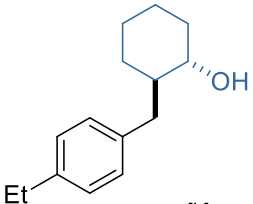
120x: 68%[b]
120x: 69%[c]



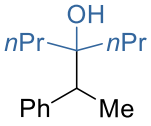
120y: 81%[c]



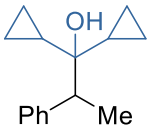
120z: 93%[b]



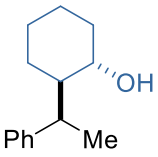
120aa: 94%[b]



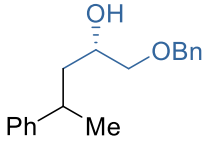
120ab: 61%[a]



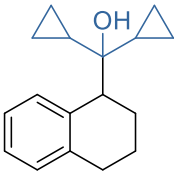
120ac: 56%[a]



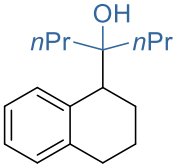
120ad: 71%; d.r. = 2:1[a]



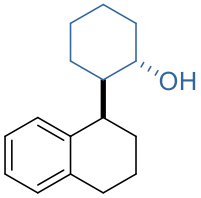
120ae: 61%; d.r. = 1.15:1[a]



120af: 52%[b]

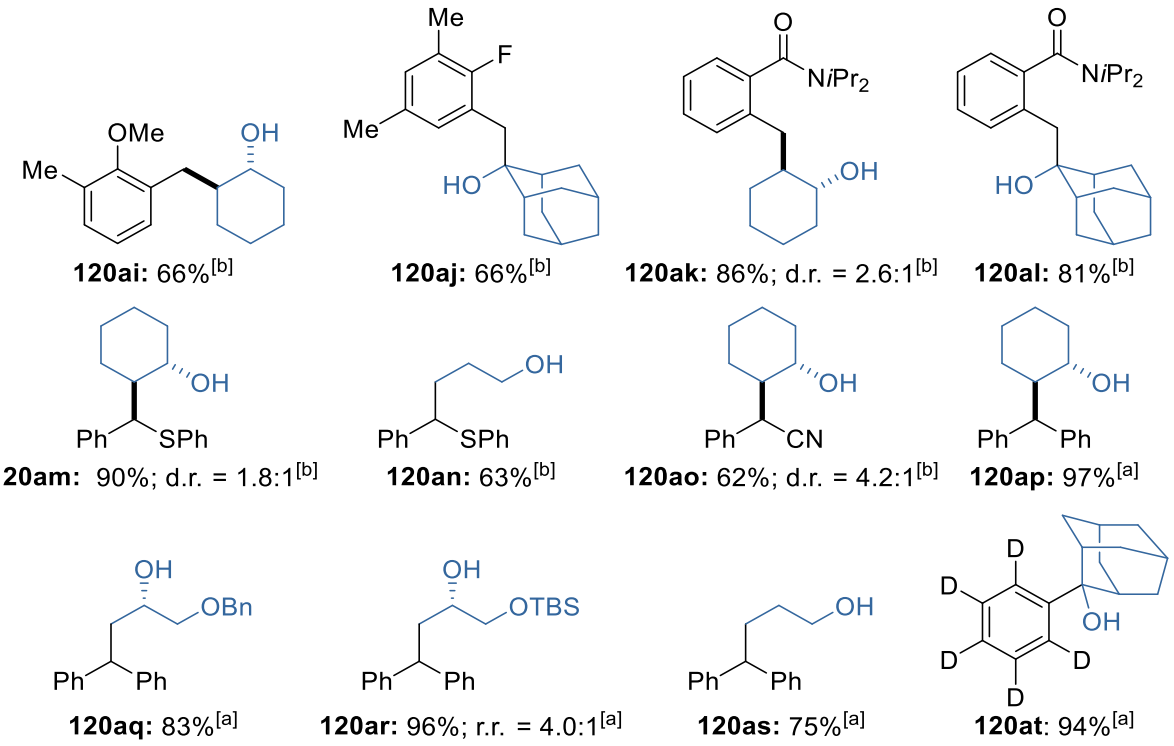


120ag: 54%[b]



120ah: 56%; d.r. = 1.2:1[b]

[319] a) R. Rahimoff, O. Kosmatchev, A. Kirchner, T. Pfaffeneder, F. Spada, V. Brantl, M. Müller, T. Carell, *J. Am. Chem. Soc.* **2017**, *139*, 10359; b) F. Spada, S. Schiffers, A. Kirchner, Y. Zhang, G. Arista, O. Kosmatchev, E. Korytiakova, R. Rahimoff, C. Ebert, T. Carell, *Nat Chem Biol* **2020**, *16*, 1411.



Scheme 66: On-demand preparation of alkylsodium reagent **36** from alkyl chloride **115** followed by batch sodiations on substituted aryls of type **118** or benzene-d_6 (**118n**) leading to benzylic sodiums of type **119** and subsequent quench with electrophiles of type **112** leading to products of type **120**. Yield of analytically pure products. [a] Arene **118** was used neat with TMEDA (2.0 equiv) and electrophile **112** (1.0 equiv in THF); [b] Arene **118** in hexane (1.0 equiv) with TMEDA (2.0 equiv) and electrophile **112** (2.0 equiv in THF); [c] Arene **118** in hexane (2.5 equiv) with TMEDA (2.0 equiv) and electrophile **112** (1.0 equiv in THF) a) Deprotection was achieved with TBAF in THF 94% yield.

4.4 Wurtz-Type-Couplings of Benzylic Sodium Reagents Prepared via Batch Sodiation of Alkylarenes Using On-Demand Generated (2-Ethylhexyl)sodium

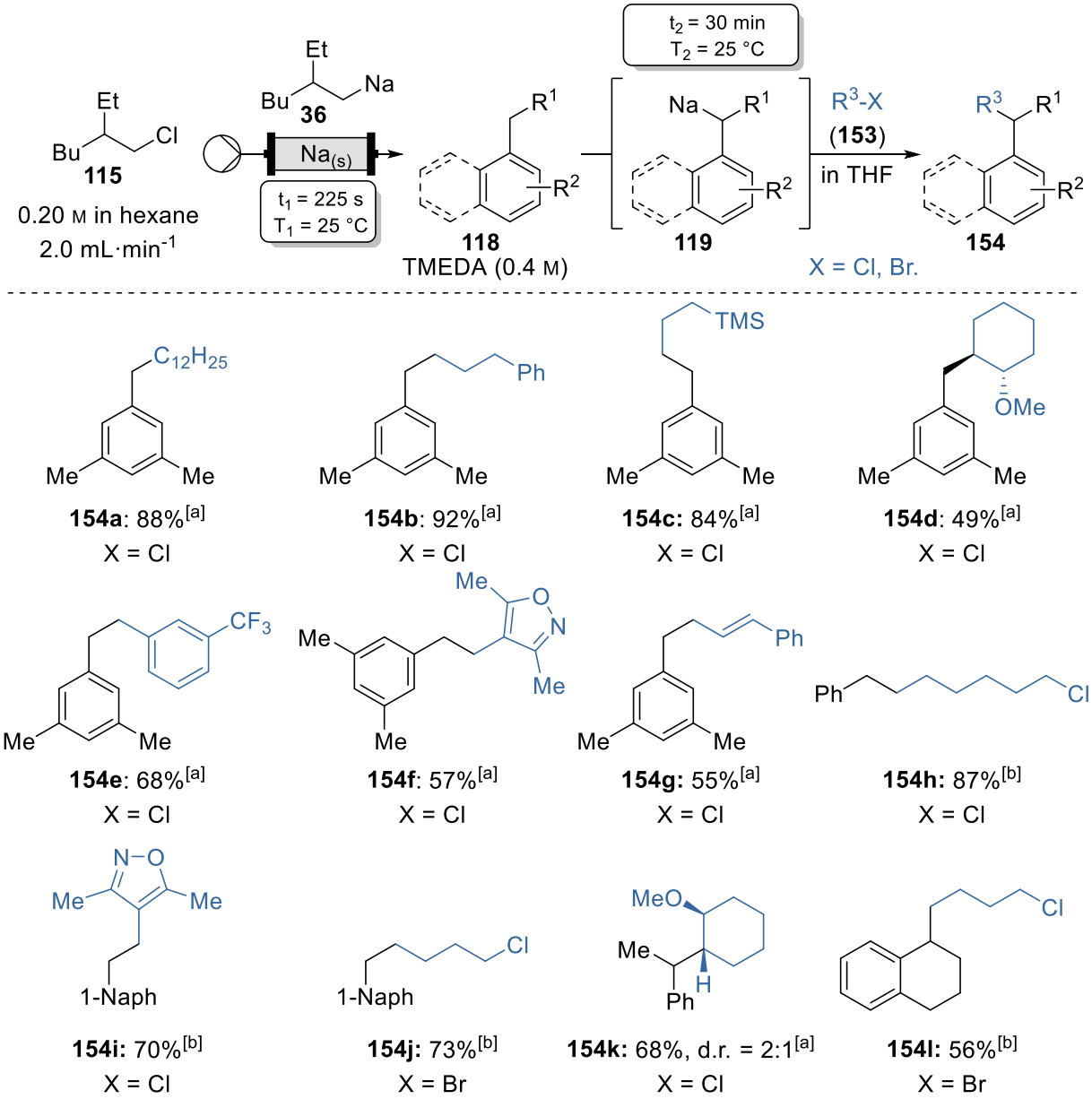
Carbon-carbon bond formation is a major goal of synthetic organometallic chemistry. Most cross-couplings performed required expensive transition metal catalysts and ligands.[320] On another hand, the Wurtz-type-coupling between an alkali metal organyl and an alkyl halide proceeded without transition metal catalysts and is therefore an attractive alternative to conventional cross-couplings. Nevertheless, Wurtz-type couplings are scarce. This is most likely due to their low selectivity and the fact that most reactions of this type are limited to alkyl iodides.[321] We have found that benzylsodiums of type **119** are

[320] a) F. H. Lutter, S. Graßl, L. Grokenberger, M. S. Hofmayer, Y. H. Chen, P. Knochel, *ChemCatChem* **2019**, *11*, 5188; b) A. de Meijere, S. Bräse, M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH, Weinheim, **2014**.

[321] a) F. Faigl, M. Schlosser, *Tetrahedron Lett.* **1991**, *32*, 3369; b) U. Azzena, F. Kondrot, L. Pisano, M. Pittalis, *Appl. Organomet. Chem.* **2012**, *26*, 180; c) M. Blangetti, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2012**, *77*, 2870; d) J. Fässler, J. A. McCubbin, A. Roglans, T. Kimachi, J. W. Hollett, R. W. Kunz, M. Tinkl, Y. Zhang, R. Wang,

excellent nucleophiles for such cross-couplings and are capable of forming Csp^3–Csp^3 bonds with readily accessible electrophiles such as alkyl-, allyl-, and benzyl chlorides. Thus, metalation in continuous flow as well as batch sodiation of neat mesitylene (**118a**) in the presence of TMEDA with on-demand generated **36**, led to **119a**. Subsequent addition of primary alkyl chlorides **153a**–**153c** in THF at –20 °C and stirring of the mixture at 25 °C overnight gave the corresponding alkylbenzenes **154a**–**154c** in 84–92% yield (Scheme 67). Quenching with the secondary *cis*-1-chloro-2-methoxycyclohexane (**153d**) gave the expected substitution on the alkyl chloride with inversion of stereochemistry, indicating a S_N2-type reaction mechanism, and led to the *trans*-product **154d** in 49% yield. Reaction of **119a** with the (hetero)benzyl chlorides **153e** and **153f** led to the 1,2-diarylethanes **154e** and **154f** (57–68%). Allylation with *E*-cinnamyl chloride (**153g**) gave the S_N2-type product and maintained *E*-configuration in the product (**154g**; 55%). Interestingly, allyl bromides gave significantly lower yields and led to a mixture of S_N2- and S_N2'-type products. Benzylsodium (**119b**) and the sodiated intermediate of 1-methylnaphthalene (**118e**) underwent Wurtz-type couplings with benzyl chloride **153e** and alkyl dihalides **153h** and **153i**. Thus, the monosubstituted products (**154h**–**154j**; 73–87%) were obtained. In case of the 1-bromo-3-chlorobutane (**153i**) the bromide was selectively substituted over the chloride. Similarly substituted products (**154k**, **154l**; 56–68%) were obtained from secondary benzylsodium organometallics **119g** and **119h.** Stereo-inversion was observed for the reaction between **119g** and **153d**, leading to the formation of a C-C-bond between two secondary carbons (**154k**).

M. Campbell, V. Snieckus, *J. Org. Chem.* **2015**, *80*, 3368; e) A. Glöckner, H. Bauer, M. Maekawa, T. Bannenberg, C. G. Daniliuc, P. G. Jones, Y. Sun, H. Sitzmann, M. Tamm, M. D. Walter, *Dalton Trans.* **2012**, *41*, 6614; f) F. C. Sassone, F. M. Perna, A. Salomone, S. Florio, V. Capriati, *Chem. Commun* **2015**, *51*, 9459; g) J. F. Garst, P. W. Hart, *Chem. Commun.* **1975**, 215; h) L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Burlington **2005**.

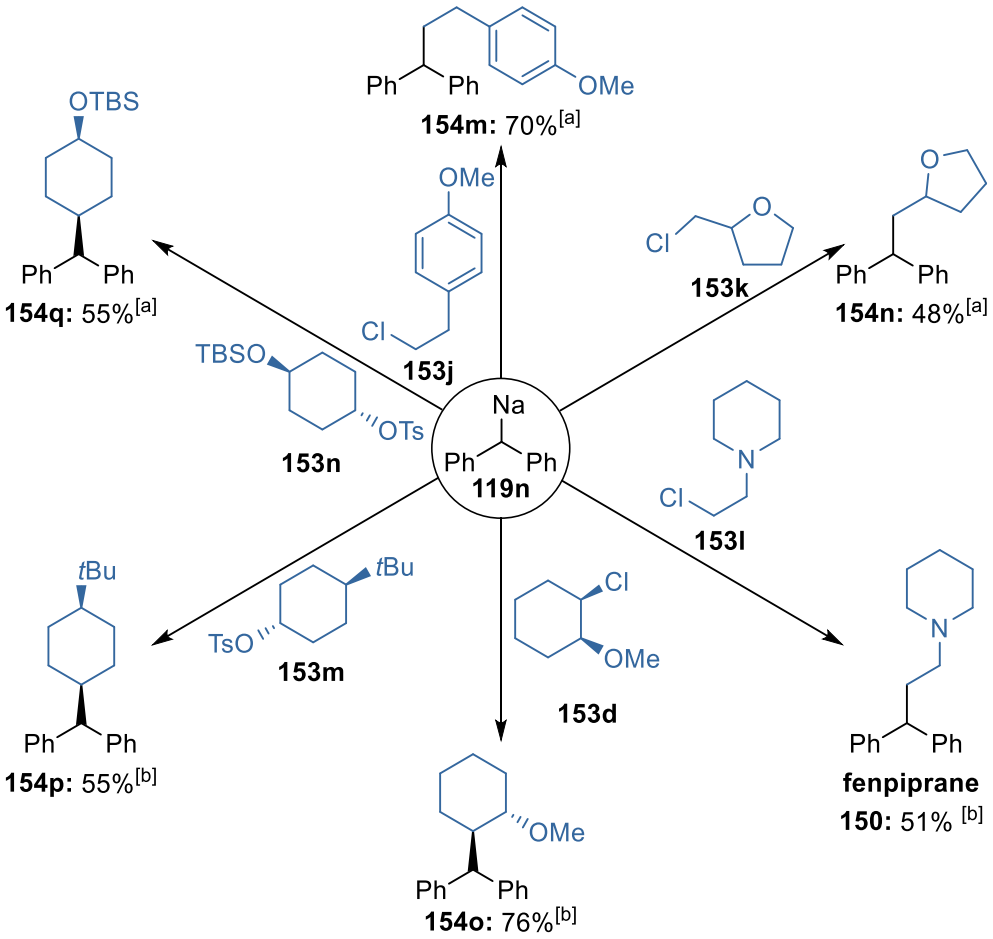


Scheme 67: On-demand preparation of alkylsodium reagent **36** from alkyl chloride **115** followed by batch sodiations on substituted arenes of type **118** leading to benzylic sodiums of type **119** and subsequent quench with electrophiles of type **153** leading to products of type **154**. Yield of analytically pure products. [a] Arene **118** was used neat with TMEDA (0.8 mmol) and alkyl halides of type **153** (0.4 mmol in THF); [b] **118** in hexane (0.4 mmol) with TMEDA (0.8 mmol) and **153** (0.8 mmol in THF).

Benzhydrylsodium (**119n**) was quenched with ether bearing primary alkyl chlorides **153j** and **153k** to give the functionalized Wurtz-type products **154m** and **154n** in 48–70% isolated yield (Scheme 68). Substitution reaction with chloroethylpiperidine **153l** led to the spasmolytic and antiallergic drug fenpiprane **150** (51% yield).[322] Reaction of **119n** with the enantiopure alkyl chloride **153d** resulted in

[322] S. Li, K. Huang, J. Zhang, W. Wu, X. Zhang, *Org. Lett.* **2013**, *15*, 1036; T. Rische, P. Eilbracht, *Tetrahedron* **1999**, *55*, 1915.

the *trans*-cyclohexane **154o** (76%) with full inversion of stereochemistry.[323] Secondary tosylates are also good substrates. We obtained the 1,4-disubstituted cyclohexanes **154p** and **154q** in 55% yield, solely as the *cis* isomers,[324] from the reaction of the *trans*-1,4-disubstituted cyclohexane tosylates **153m** and **153n** with **119n**.[325]

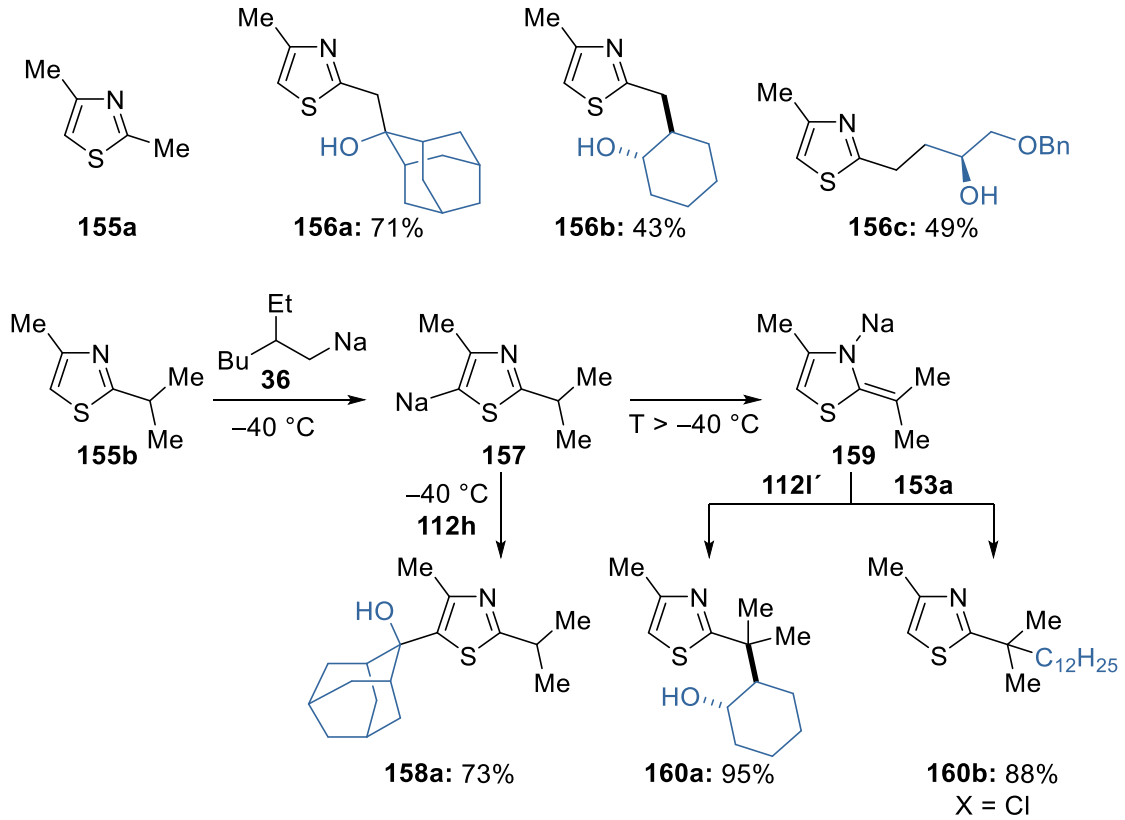


Scheme 68. Wurtz-type reactions of benzhydrylsodium (**119n**) with electrophiles of type **153**. Isolated yields of analytically pure products. [a] Diphenylmethane (**118n**) was used neat with TMEDA (0.8 mmol) and electrophiles **153** as limiting reagent (0.4 mmol in THF); [b] Diphenylmethane (**118n**) was used as limiting reagent in hexane (0.4 mmol) with TMEDA (0.8 mmol) and electrophiles **153** (0.8 mmol in THF).

[323] Stereochemistry confirmed by single crystal X-ray diffraction see page 431.
[324] Stereochemistry confirmed by single crystal X-ray diffraction see page 435.
[325] For stereo- and chemoselectivity studies on the Wurtz-type reaction between **119n** and electrophiles of type **153** see page 420.

4.5 Selectivity Studies of the Metalation with (2-Ethylhexyl)sodium on 2,4-Disubstituted Thiazoles

The treatment of 2,4-dimethylthiazole (**155a**) with (2-ethylhexyl)sodium (**36**) at –40 °C for 30 min enabled a selective lateral sodiation at the methyl group in position 2. Quenching with ketone **112h** and epoxides **112l´** and **112t´** provided the expected thiazoles **156a-c** in 43–71% yield (Scheme 69).[326] Interestingly, in the case of the more sterically hindered 2-isopropyl-4-methylthiazole **155b**, we observed a kinetically controlled ring sodiation at position 5 at –40 °C affording the sodiated thiazole **157**. Quenching with adamantanone (**112h**) provided the alcohol **158a** in 73% yield. The sodiated thiazole **157** isomerized at higher temperatures to the more stable lateral metalation derivative **159** with extensive decomposition in the absence of an electrophile.[327] However, in the presence of cyclohexene oxide (**112l´**) or dodecyl chloride (**153a**), the expected products **160a** and **160b** were obtained in 88–95% yield.

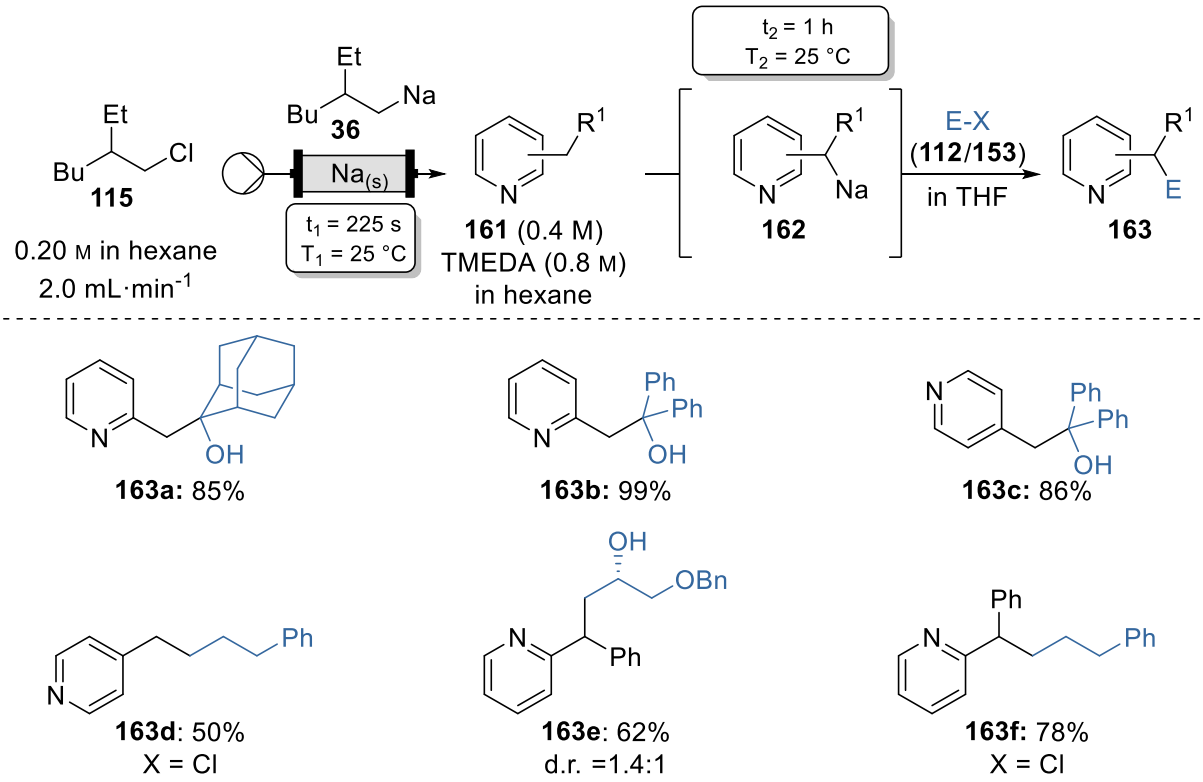


Scheme 69: On-demand preparation of alkylsodium reagent **36** from alkyl chloride **115** followed by batch sodiations on substituted thiazoles of type **155**, leading to sodium species of type **157** and upon migration to **159**. A subsequent quench with electrophiles of type **112** and **153** led to products of type **156**, **158** and **160**. Yields of analytically pure products.

[326] For single crystal X-ray diffraction studies see page 439.
[327] For a temperature screening of the sodiation of **155b** see page 425.

4.6 Batch Sodiation of 6-Membered Alkylheteroarenes Using On-Demand Generated (2-Ethylhexyl)sodium and Subsequent Electrophile Quench Reactions

Similarly, six-membered N-heterocycles were sodiated at the benzylic position at 25 °C within 1 h. Thus, 2- and 4-picoline (**161a**–**161b**) gave the corresponding metalated species **162a**–**162b** which upon quench with ketones **112h** and **112a´** and alkyl chloride **153b** gave the desired heterocyclic products **163a**–**163d** in 50–99% yield (Scheme 70). 2-Benzylpyridine (**161c**) underwent after metalation with (2-ethylhexyl)sodium (**36**) a ring opening reaction with the chiral epoxide **112t´** to give protected glycol **163e** in 62% yield (d.r. = 1.4:1). Wurtz-type coupling of the same benzylic organosodium with (3-chloropropyl)benzene (**153b**) gave the substituted pyridine **163f** in 78% yield.



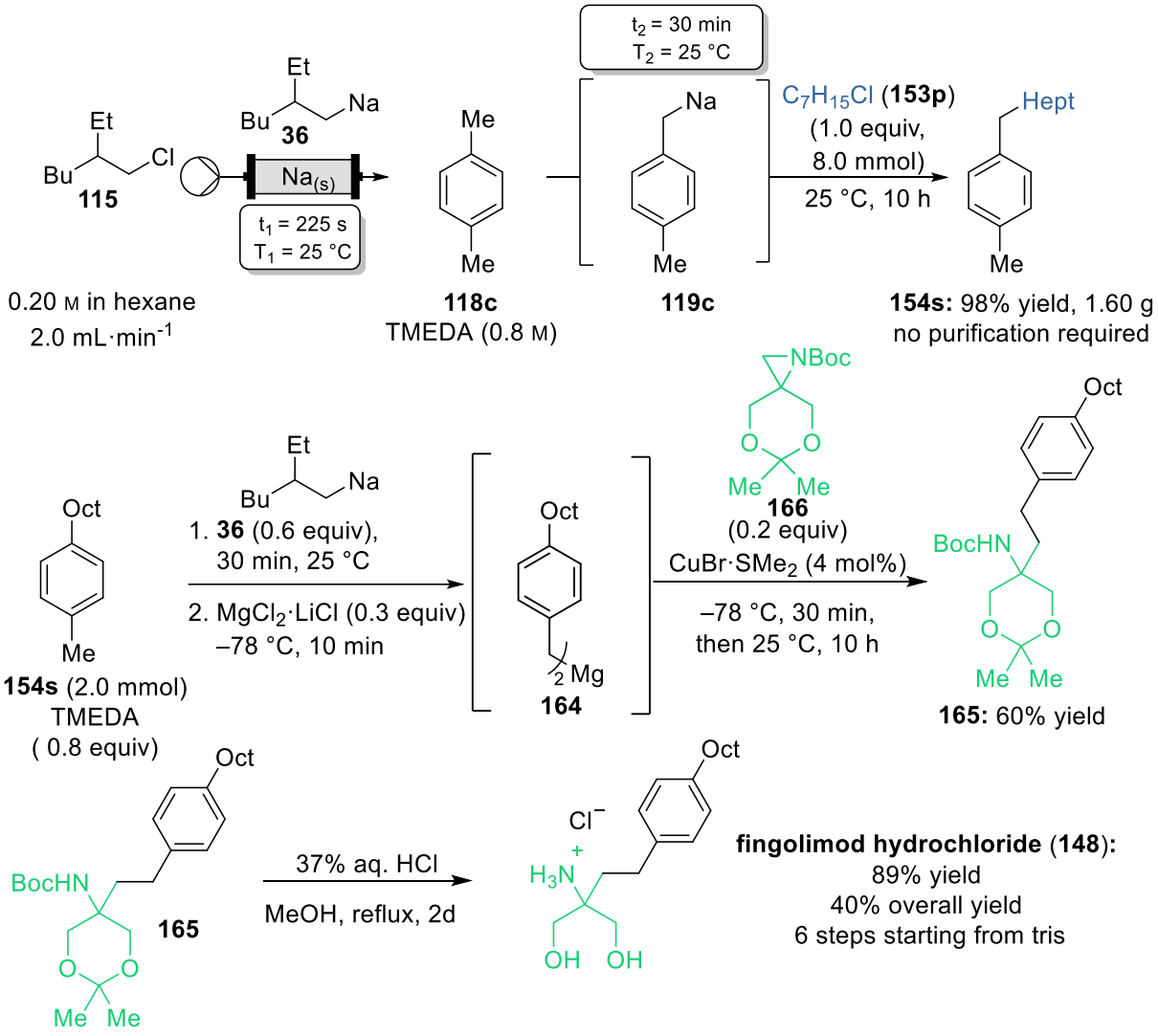
Scheme 70: On-demand preparation of alkylsodium reagent **36** from alkyl chloride **115** followed by batch sodiations on substituted arenes of type **161** leading to heterobenzylic sodiums of type **162** and subsequent quench with electrophiles of type **112** or **153** leading to products of type **163**.

4.7 Synthesis of Fingolimod, Salmeterol-d_7 and a Super Linear Alkylbenzene Surfactant Using the Continuous Flow Preparation of Benzylic Sodium Organometallics

The utility of the lateral sodiation procedure was demonstrated by the straightforward synthesis of industrial relevant compounds (Scheme 71–73). Fingolimod (**148**) and salmeterol (**149**) are among the 100 best selling drugs, both exceeding retail sales of 2 billion USD in 2020.[328] The multiple scleroses therapeutics fingolimod (**148**) has previously been synthesized by various approaches.[329] Most of them require transition metal catalyzed cross-coupling reaction to introduce the octyl group. We envisioned a synthesis starting from inexpensive *p*-xylene (**118c**). The described Wurtz-type coupling reaction allowed to install the octyl chain, and a selective sodiation of the obtained 4-octyltoluene (**154s**), was enabling an aziridine opening to give the protected fingolimod precursor **165**.

On-demand generated (2-ethylhexyl)sodium (**36**) was used for the lateral sodiation of **118c** in the presence of TMEDA. Trapping with 1-chloroheptane (**153p**, 8.0 mmol) resulted in 4-octyltoluene (**154s**) in 98% yield on a gram scale and did not require any purification. Benzylic sodiation of **154s** followed by a transmetalation to magnesium allowed a CuBr·SMe_2-catalyzed aziridine opening of **166** to give the protected tertiary amine **165** in 60% yield. Fingolimod hydrochloride (**148**) was obtained by deprotection of **165** using an *aq.* HCl solution (89% yield). Azridine **166** is conveniently prepared from the readily available *tris*(hydroxymethyl)aminomethane known as tris, commonly used as gel electrophoresis buffer.[329b] Fingolimod (**148**) was obtained in an overall yield of 40% within 6 steps starting from tris (Scheme 71).

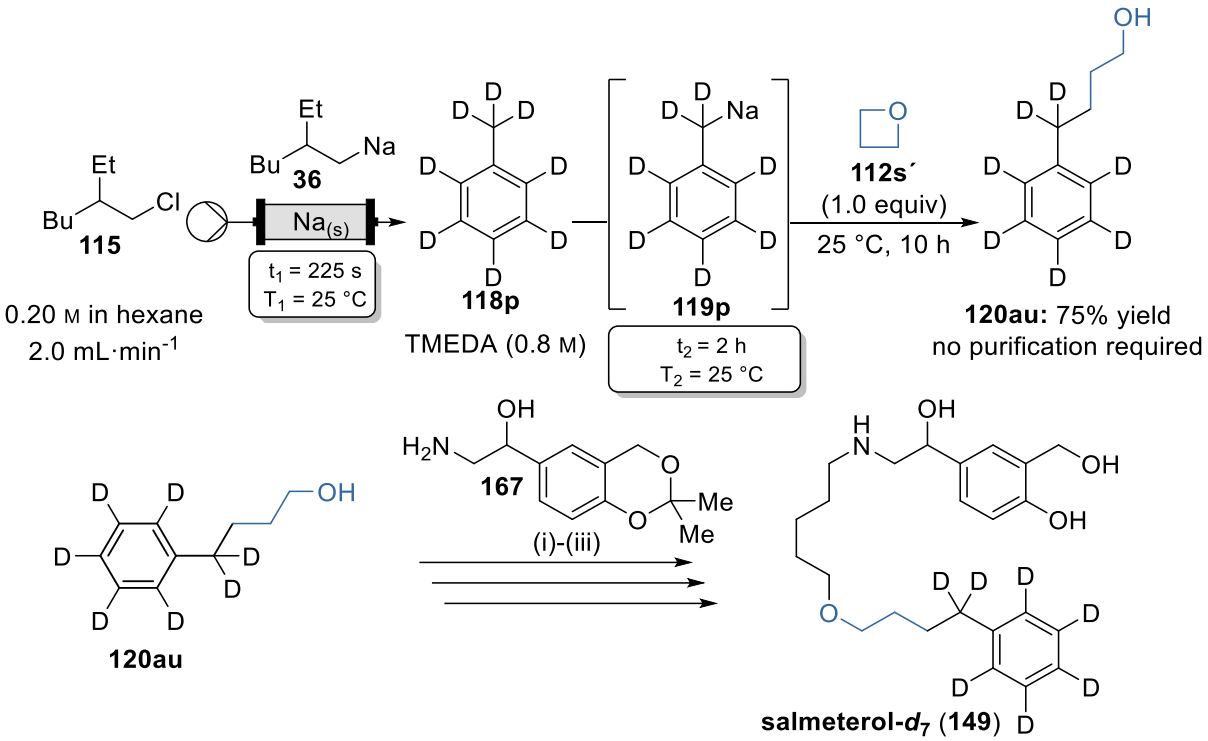
[328] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348.
[329] a) H. E. Askey, J. D. Grayson, J. D. Tibbetts, J. C. Turner-Dore, J. M. Holmes, G. Kociok-Kohn, G. L. Wrigley, A. J. Cresswell, *J. Am. Chem. Soc.* **2021**, *143*, 15936; b) J. Doubský, S. Rádl, J. Cinibulk, R. Klvaňa, *Org. Process Res. Dev.* **2022**, *26*, 859; c) N. Mulakayala, P. Rao, J. Iqbal, R. Bandichhor, S. Oruganti, *Eur. J. Med. Chem.* **2013**, *60*, 170.



Scheme 71: Applications of the lateral sodiation procedure: Synthesis of fingolimod hydrochloride (**148**).

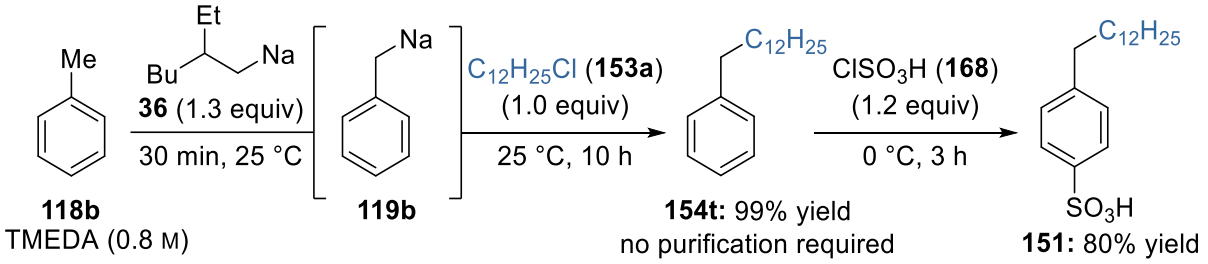
7-Fold isotopically labeled salmeterol-d_7 was easily prepared *via* sodiation of toluene-d_8 (**118p**) with the alkylsodium reagent **36**. The resulting benzylic metal species **119p** gave upon addition of oxetane (**112s´**) the primary alcohol **120au** in 75% yield without the need of a chromatographical purification. Alkylation of **120au** with 1,6-dibromohexane and amination of the resulting product with **167** gave the acetal protected salmeterol precursor. Cleavage of the acetal group gave salmeterol-d_7 (**149**).[330] The synthesis showed the applicability of the dedeuteration by facilitating the introduction of multiple times isotopically labeled groups (Scheme 72).

[330] L. Jiang, C. Lin, Y. Qiu, X. Quan, J. Zhu, H. Shi, *J. Chem. Res.* **2016**, *40*, 564.



Scheme 72: Applications of the lateral sodiation procedure: Synthesis of salmeterol-d_7 (**149**); (i) NaH, 1,6-dibromohexane, NBu_4Br, THF, 25 °C, 64%; (ii) **167**, KI, DMF, 40 °C, 50%; (iii) HCl, THF, 25 °C, 6 h, 77%.

SLAB surfactants are valuable detergents. Compared to their branched counterparts they are easily biodegradable and therefore more environmental friendly. However, the installation of the linear alkyl chain can be challenging as cationic methods often lead to branched structures.[331] As we showed earlier, the introduction of linear alkyl chains using our Wurtz-type procedure is uncomplicated and high yielding. The SLAB-sulfonic acid **151** was readily obtained from toluene by Wurtz-type coupling of sodium species **119b** with 1-cholododecane (**153a**) followed by sulfonation with chlorosulfonic acid (**168**). Again no purification was required for the synthesis of **154t** obtained in quantitative yield (Scheme 73).



Scheme 73: Applications of the lateral sodiation procedure: Synthesis of the SLAB-surfactant **151**.

[331] a) T. B. Gunnoe, W. L. Schinski, X. Jia, W. Zhu, *ACS Catal.* **2020**, *10*, 14080; b) N. I. Saper, A. Ohgi, D. W. Small, K. Semba, Y. Nakao, J. F. Hartwig, *Nat. Chem.* **2020**, *12*, 276; c) W. Zhu, T. B. Gunnoe, *J. Am. Chem. Soc.* **2021**, *143*, 6746.

4.8 Conclusion

In summary, we reported a lateral sodiation of alkyl (hetero)arenes using on-demand generated hexane soluble (2-ethylhexyl)sodium (**36**) in the presence of TMEDA. (2-Ethylhexyl)sodium (**36**) was prepared via a sodium packed-bed reactor and used for metalations at ambient temperature in batch as well as in continuous flow. The resulting benzylic sodium species of type (**119**) were subsequently trapped with various electrophiles including carbonyl compounds, epoxides, oxetane, allyl/benzyl chlorides, alkyl halides and alkyl tosylates. The Wurtz-type reactions with secondary alkyl halides and tosylates proceeded under complete inversion of stereochemistry. A 20-fold reaction scale-up using an in-line quenching procedure with cyclohexene oxide was reported. Furthermore, the utility of the lateral sodiation was shown in the synthesis of pharmaceutical relevant compounds. Thus, fingolimod (**148**) was prepared from *p*-xylene (**118c**) applying the lateral sodiation twice. In addition, multiple times isotopically labeled salmeterol-d_7 (**149**) and fenpiprane (**150**) as well as precursors to super linear alkylbenzene surfactants such as **151** were easily accessible and did not require purification steps. Further investigations on (2-ethylhexyl)sodium and its applications are currently under way in our laboratories.

5. Continuous Flow Sodiation of Substituted Acrylonitriles, Alkenyl Sulfides and Acrylates[332]

5.1 Introduction

The metalation of unsaturated nitriles and sulfides is an important synthetic procedure.[333] After quenching with various electrophiles, highly functionalized unsaturated products are obtained, which may be useful building blocks for biologically active heterocycles and natural products.[334] The batch-metalation of alkenyl nitriles or sulfides with lithium bases is often complicated due to competitive allylic lithiations.[335] The use of stronger, more polar bases like sodium or potassium amides may avoid such limitations. However, the sodiation of such unsaturated compounds is much less explored.[336] Moreover, the use of sodium organometallics is of high interest due to the low price, high abundancy and low toxicity of sodium salts.[337] Recently, arylsodium compounds have been prepared by Collum using NaDA (sodium diisopropylamide) as deprotonating agent[338] and by Asako and Takai, who have investigated the utility of arylsodiums in catalytic cross-couplings.[339] Yoshida, Ley, Organ and others

[332] Adapted with permission from J. H. Harenberg, N. Weidmann, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 731. Copyright 2020 Angewandte Chemie International Edition published by Wiley-VCH. https://doi.org/10.1002/anie.202012085. This project was developed in cooperation with Dr. Niels Weidmann, see: N. Weidmann, Dissertation, LMU München. Some results in this chapter were already included in the master thesis of Johannes H. Harenberg, see: J. H. Harenberg, master thesis, LMU München.

[333] a) F. F. Fleming, Q. Wang, Z. Zhang, O. W. Steward, *J. Org. Chem.* **2002**, *67*, 5953; b) J. Doroszuk, M. Musiejuk, Ł. Ponikiewski, D. Witt, *Eur. J. Org. Chem.* **2018**, *2018*, 6333; c) O. de Lucchi, L. Pasquato, *Tetrahedron* **1988**, *44*, 6755; d) B. M. Trost, A. C. Lavoie, *J. Am. Chem. Soc.* **1983**, *105*, 5075; e) B. Bartels, R. Hunter, C. D. Simon, G. D. Tomlinson, *Tetrahedron Lett.* **1987**, *28*, 2985; f) A. B. Flynn, W. W. Ogilvie, *Chem. Rev.* **2007**, *107*, 4698; g) F. F. Fleming, Q. Wang, *Chem. Rev.* **2003**, *103*, 2035; h) G. Dagousset, C. François, T. León, R. Blanc, E. Sansiaume-Dagousset, P. Knochel, *Synthesis* **2014**, *46*, 3133.

[334] a) S. Sengupta, V. Snieckus, *J. Org. Chem.* **1990**, *55*, 5680; b) M. A. Reed, M. T. Chang, V. Snieckus, *Org. Lett.* **2004**, *6*, 2297; c) E. Block, S. Ahmad, J. L. Catalfamo, M. K. Jain, R. Apitz-Castro, *J. Am. Chem. Soc.* **1986**, *108*, 7045; d) G. Brooks, K. Coleman, J. S. Davies, P. A. Hunter, *The Journal of Antibiotics* **1988**, *41*, 892; e) T. H. Morris, E. H. Smith, R. Walsh, *Chem. Commun.* **1987**, 964.

[335] a) F. F. Fleming, S. Gudipati, J. A. Aitken, *J. Org. Chem.* **2007**, *72*, 6961; b) F. F. Fleming, V. Gudipati, O. W. Steward, *Tetrahedron* **2003**, *59*, 5585; c) B. A. Feit, U. Melamed, R. R. Schmidt, H. Speer, *Tetrahedron* **1981**, *37*, 2143; d) D. C. Harrowven, H. S. Poon, *Tetrahedron Lett.* **1994**, *35*, 9101; e) D. C. Harrowven, H. S. Poon, *Tetrahedron* **1996**, *52*, 1389; f) R. R. Schmidt, J. Talbiersky, P. Russegger, *Tetrahedron Lett.* **1979**, *20*, 4273; g) R. R. Schmidt, R. Hirsenkorn, *Tetrahedron* **1983**, *39*, 2043; h) R. Knorr, E. Lattke, *Chem. Ber.* **1981**, *114*, 2116; i) M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828.

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[337] a) D. Seyferth, *Organometallics* **2006**, *25*, 2; b) D. Seyferth, *Organometallics* **2009**, *28*, 2; c) N. Wiberg, in *Lehrbuch der Anorganischen Chemie*, 102 ed., De Gruyter Verlag, Berlin, **2007**, pp. 1259.

[338] a) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544; b) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197; c) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 7921; d) Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312.

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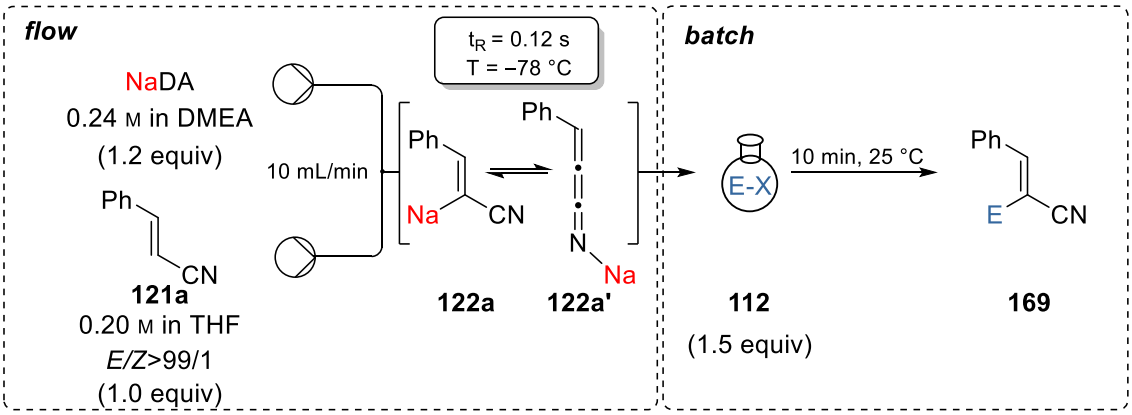
have demonstrated a high functional group tolerance performing challenging metalations in a continuous flow set-up.[340] Based on these studies, we have extended the Collum procedure to the preparation of sodiated aryl and heteroaryl derivatives which are difficult to generate otherwise and decompose upon batch-sodiation.[341] KDA · TMEDA (potassium diisopropylamide · *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) in *n*-hexane was used in continuous flow for similar metalations.[342] Herein, we wish to report that NaDA and NaTMP (TMPH = 2,2,6,6-tetramethylpiperidine) were efficient bases for the regioselective flow-metalation of various substituted acrylonitriles and alkenyl sulfides.[343]

5.2 NaDA Mediated Sodiation of Cinnamonitrile in Continuous Flow

In first experiments, we have optimized the sodiation of cinnamonitrile (**121a**) and have found that metalation with NaDA (0.24 M in DMEA (dimethylethylamine), 1.2 equiv) at −78 °C using a combined flow-rate of 10 mL/min and a 0.02 mL reactor proceeded best with a residence time of 0.12 s affording organosodium **122a**. Subsequent trapping with electrophiles of type **112** such as aldehydes, ketones, disulfides and allylic bromides afforded 2-substituted cinnamonitriles of type **169** with usually high *E*/*Z* ratios (Table 8, entries 1-10). Thus, for a quenching with aromatic aldehydes, we obtained the *Z*-product of type **169** as major product, whereas for more sterically hindered ketones the *E*-product was formed.

Table 8. Sodiation of cinnamonitrile (**121a**) using a microflow reactor and subsequent batch quench of the intermediate sodium organometallic **122a** with various electrophiles of type **112** leading to functionalized cinnamonitriles of type **169**.



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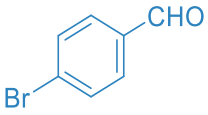
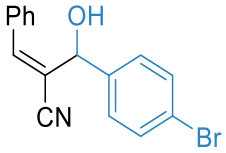
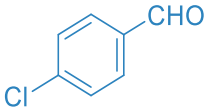
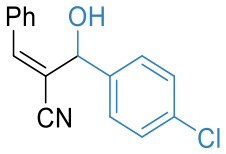
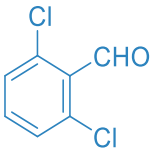
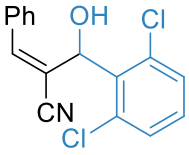
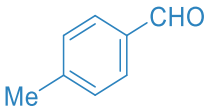
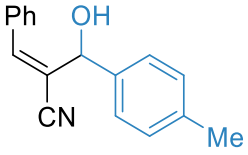
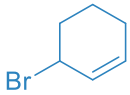
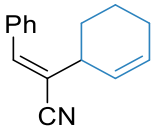
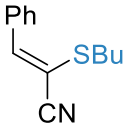
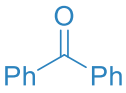
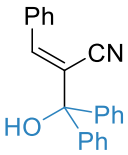
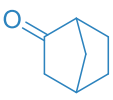
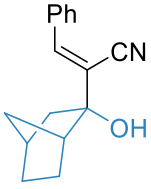
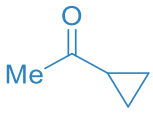
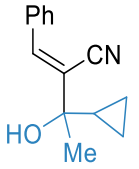
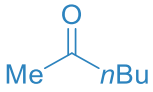
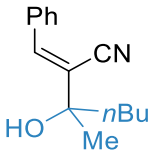
[341] N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748.

[342] J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 12321.

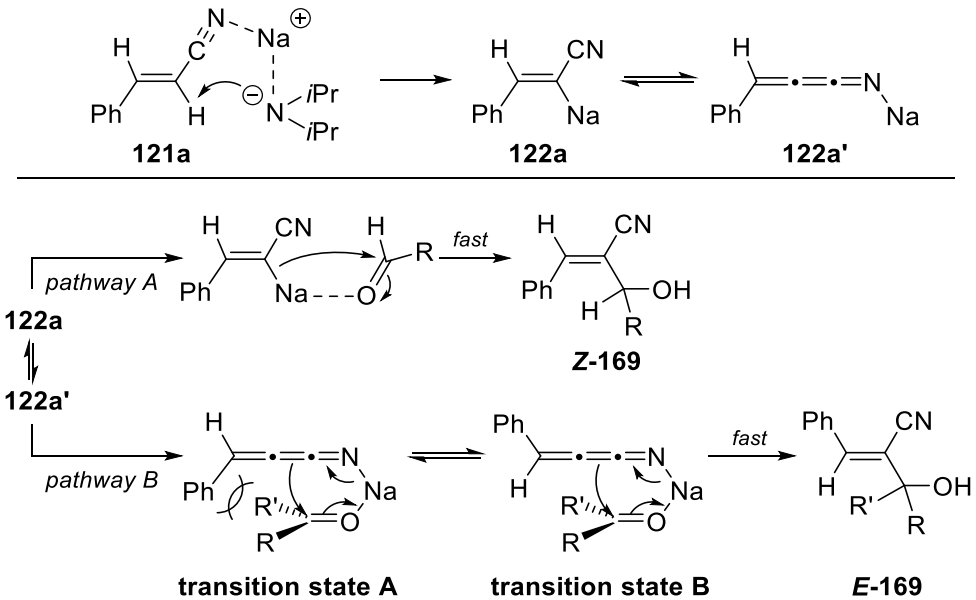
[343] Commercially available equipment from *Uniqsis* was used. For a detailed optimization, see page 448.

entry	electrophile	product[a]
		
1	**112w´**	**169aw´**: 95%, *Z/E*>99/1[b]
		
2	**112x´**	**169ax´**: 92%, *Z/E*>99/1[b]
		
3	**112i**	**169ai**: 74%, *Z/E*=89/11[b]
		
4	**112j**	**169aj**: 93%, *Z/E*>99/1[c]
		
5	**112e´**[d]	**169ae´**: 93%, *E/Z*=9/1[b]
		
6	**112q**	**169aq**: 93%, *Z/E*=54/46
		
7	**112a´**	**169aa´**: 82%, *E/Z*>99/1[c]
		
8	**112g**	**169ag**: 82%, *E/Z*>99/1 *d.r.*>99/1[c]

entry	electrophile	product[a]
9	 **112y´**	 **169ay´**: 78%, *E/Z*>99/1[b]
10	 **112z´**	 **169az´**: 87%, *E/Z*>99/1[b]

[a] Yield of analytically pure product. [b] The *E*- or *Z*- diastereoselectivity was assigned in analogy to related products, for which X-ray data were obtained. [c] The diastereoselectivity was determined by crystal structure analyses, see pages 497–537. [d] 10 mol% CuCN·2LiCl.

The diastereoselectivity of products of type **169** obtained after the addition to a carbonyl electrophile was tentatively explained by assuming that the sodiated nitrile **122a** reacted fast with an aldehyde (RCHO) according to pathway A leading to the allylic alcohol ***Z*-169**. In contrast, by using ketones, an equilibration to the cummulene form **122a'** may occur and the cyclic transition state **A** would be disfavoured due to steric hindrance. *E/Z* isomerization of the cummulene structure **122a'** occurred affording the ***E*-169** product *via* transition state **B** (Scheme 74).

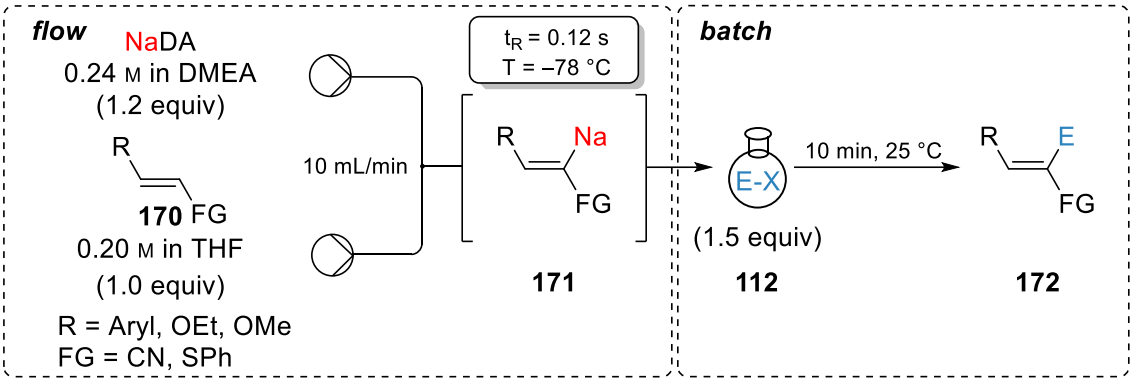


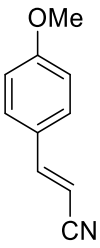
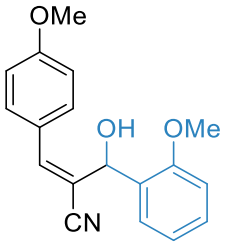
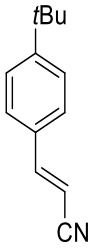
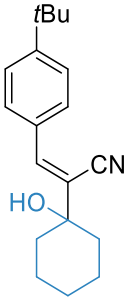
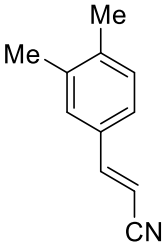
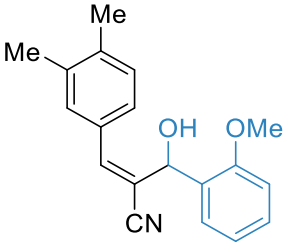
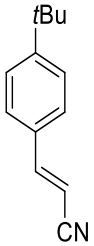
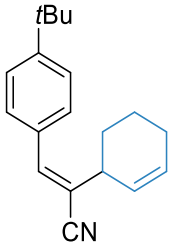
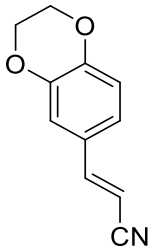
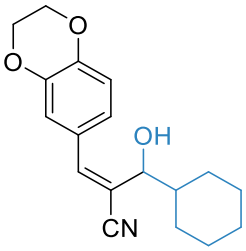
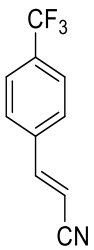
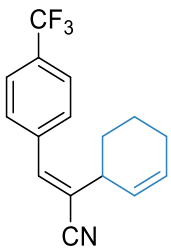
Scheme 74: Tentative mechanism for the stereoselective addition of sodiated phenylacrylonitrile **122a'** to aldehydes or ketones**.**

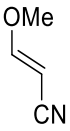
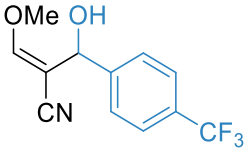
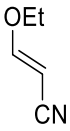
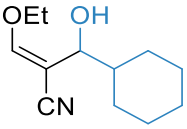
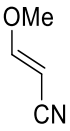
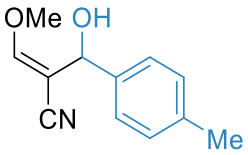
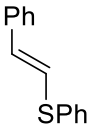
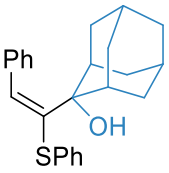
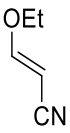
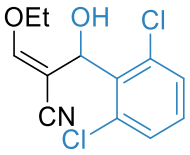
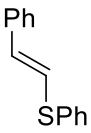
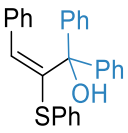
5.3 NaDA Mediated Sodiaton of Substituted Acrylonitriles and Alkenyl Sulfides in Continuous Flow

We have then extended this flow procedure to various functionalized arylacrylonitriles of type **170**. Electron-rich cinnamonitrile derivatives (**170a**-**170d**) were selectively metalated in 2-position using NaDA in a continuous flow set-up within 0.12 s at −78 °C. The resulting organosodiums (**171a-d**) were trapped in batch with various carbonyl electrophiles, such as *m*-anisaldehyde (**112a´´**), cyclohexanecarboxaldehyde (**112d**) or cyclohexanone (**112m**), and with 3-bromocyclohexene (**112e´**) using 10 mol% CuCN·2LiCl as catalyst, affording the desired alcohols (**172aa´´, 172ba´´**, **172cd** and **172dm**) and an allylated cinnamonitrile derivative (**172de´**) in 57-97% yield with diastereomeric ratios up to >99/1 (Table 9, entries 1-5). Similarly, regioselective sodiation of electron-deficient 3-(4-(trifluoromethyl)phenyl)acrylonitrile (**170e**) followed by copper-catalyzed allylation with 3-bromocyclohexene (**112e´**) led to the functionalized phenylacrylonitrile (**172ee´**) in 66% yield with an *E/Z* ratio >99/1. Furthermore, an extension to methoxy- and ethoxyacrylonitriles **170f** and **170g** was possible resulting in secondary alcohols (**172fb´´**, 1**72fj**, 1**72gi** and 1**72gd**) after batch-quench with aromatic aldehydes (**112i**, **112j** and **112b´´**), and aliphatic aldehyde (**112d**) in 91-98% and *Z/E* ratios >99/1 (entries 7-10). An alkenyl sulfide such as phenyl(styryl)sulfane (**170h**) provided the sodium derivative (**171h)** upon metalation with NaDA, which after trapping with sterically demanding ketones such as adamantanone (**112h**) and benzophenone (**112a´**) gave tertiary alcohols (**172hh** and **172ha´**) in 85-95% yield and comparable *E/Z* ratios to the starting material **170h** (entries 11-12).

Table 9: Sodiation of substituted acrylonitriles and alkenyl sulfides of type **170** using a microflow reactor and subsequent batch quench of the intermediate sodium organometallics of type **171** with various electrophiles of type **112** leading to functionalized phenylacrylonitriles and alkenyl sulfides of type **172**.



entry	substrate	product[a]	entry	substrate	product[a]
1	 **170a** *E*/*Z*=76/24	 **172aa´´**: 97%[b] *Z*/*E*=89/11	4	 **170d** *E*/*Z*=79/21	 **172dm**: 67%[c] *E*/*Z*>99/1
2	 **170b** *E*/*Z*=79/21	 **172ba´´**: 84%[c] *Z*/*E*=90/10	5	 **170d**[d] *E*/*Z*=79/21	 **172de´**: 57%[b] *E*/*Z*>99/1
3	 **170c** *E*/*Z*=83/17	 **172cd**: 74%[b] *Z*/*E*>99/1	6	 **170e**[d] *E*/*Z*=78/22	 **172ee´**: 66%[c] *E*/*Z*>99/1

entry	substrate	product[a]	entry	substrate	product[a]
7	 **170f** *E*/*Z*=83/17	 **172fb´´**: 93%[c] *Z*/*E*>99/1	10	 **170g** *E*/*Z*=68/32	 **172gd**: 91%[b] *Z*/*E*>99/1
8	 **170f** *E*/*Z*=83/17	 **172fj**: 98%[c] *Z*/*E*>99/1	11	 **170h** *E*/*Z*=71/29	 **172hh**: 95%[c] *E*/*Z*=77/23
9	 **170g** *E*/*Z*=68/32	 **172gi**: 95%[c] *Z*/*E*>99/1	12	 **170h** *E*/*Z*=71/29	 **172ha´**: 85%[b] *E*/*Z*=68/32

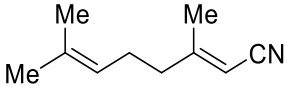
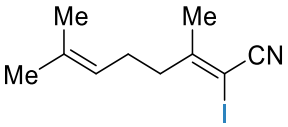
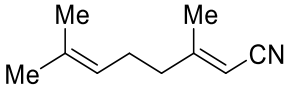
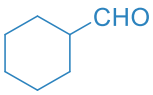
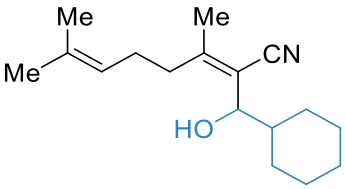
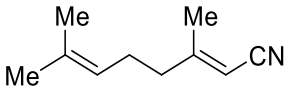
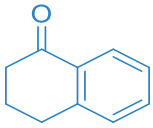
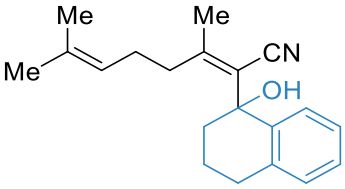
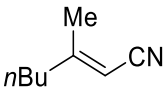
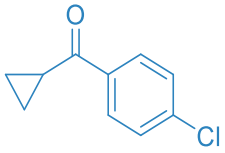
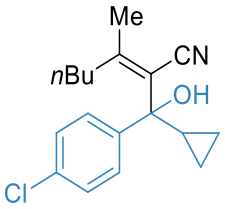
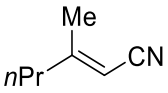
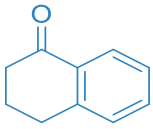
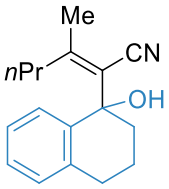
[a] Yield of analytically pure product. [b] The *E*- or *Z*- diastereoselectivity was assigned in analogy to related products, for which X-ray data were obtained. [c] The diastereoselectivity was determined by crystal structure analyses, see pages 497–537. [d] 10 mol% CuCN·2LiCl.

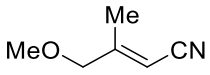
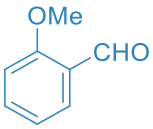
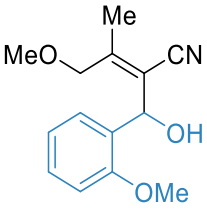
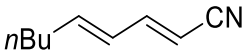
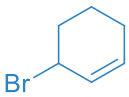
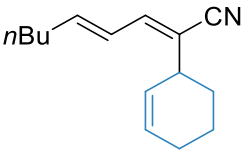
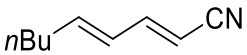
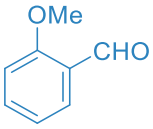
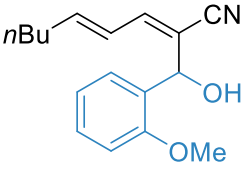
5.4 NaDA Mediated Sodiaton of Alkyl and Alkenyl Substituted Acrylonitriles in Continuous Flow

Extension to alkyl-substituted acrylonitriles such as geranylnitrile (**173a**, *E*/*Z*=50/50) and the related nitrile **173b** (*E*/*Z*=65/35) was possible under the standard sodiation conditions providing after electrophilic quench the desired functionalized nitriles (**175ac´´**, **175ad**, **175ad´´**, **175bi´**) in 60-98% yield as *E*/*Z* mixtures (Table 10, entries 1-4). Interestingly, starting from the diastereomerically pure acrylonitrile **173c** (*E*/*Z*>99/1) the desired product **175cd´´** was obtained in 67% yield (Z/E=58/42) after quench with α-tetralone (**112d´´**) (entry 5) showing the prevalence of the cumulene structure of the sodiated nitriles (see **122a** in Table 8). However, the methoxy-substituted acrylonitrile **173d** (*E*/*Z*=80/20) afforded after continuous flow sodiation and quenching with *o*-anisaldehyde (**112a´´**) the allylic alcohol **175da´´** as single diastereoisomer in 58% yield (*Z*/*E*>99/1) showing the importance of the methoxy group for controlling the stereochemistry of the intermediate sodiated nitrile (entry 6). Also, the dienylnitrile **173e** was sodiated in flow and trapping with an allylic bromide (**112e´**) or an

aldehyde (**112a´´**) furnished the functionalized dienylnitriles (**175ee´** and **175ea´´**) in 74-82% yield (entries 7-8).

Table 10: Sodiation of alkyl- and alkenyl-substituted acrylonitriles of type **173** using a microflow reactor and subsequent batch quench of the intermediate sodium organometallics of type **174** with various electrophiles of type **112** leading to functionalized alkyl- and alkenyl-substituted acrylonitriles of type **175**.

entry	substrate	electrophile	product[a]
			
1	**173a**, *E*/*Z*=50/50	**112c´´**	**175ac´´**: 75%, *Z*/*E*=68/32
			
2	**173a**, *E*/*Z*=50/50	**112d**	**175ad**: 60%, *Z*/*E*=64/36
			
3	**173a**, *E*/*Z*=50/50	**112d´´**	**175ad´´**: 98%, *Z*/*E*=53/47
			
4	**173b**, *E*/*Z*=65/35	**112i´**	**175bi´**: 85%, *Z*/*E*=55/45
			
5	**173c**, *E*/*Z*>99/1	**112d´´**	**175cd´´**: 67%, *Z*/*E*=58/42

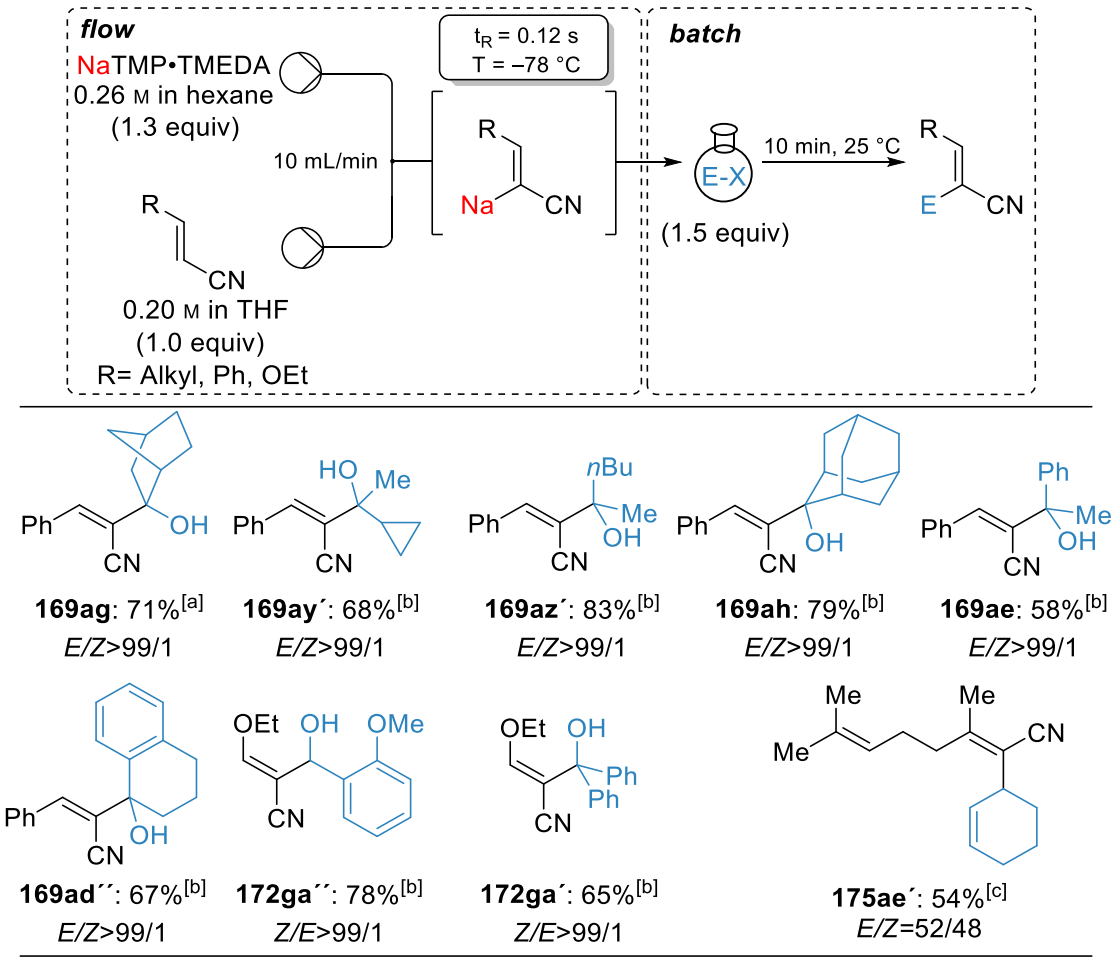
entry	substrate	electrophile	product[a]
			
6	**173d**, *E/Z*=80/20	**112a´´**	**175da´´**: 58%, *Z/E*>99/1
			
7	**173e**, *2E/2Z*=69/31	**112e´**[b]	**175ee´**: 74%, *2E/2Z*=77/23
			
8	**173e**, *2E/2Z*=69/31	**112a´´**	**175ea´´**: 82%. *2Z/2E*=76/24

[a] Yield of analytically pure product. [b] 10 mol% CuCN·2LiCl.

5.5 NaTMP Mediated Sodiaton of Substituted Acrylonitriles in Continuous Flow

Recently, Takai and Asako published a straightforward synthesis of lithium-free sodium 2,2,6,6-tetramethylpiperidide (NaTMP) in *n*-hexane by using sodium dispersion, TMPH, TMEDA and isoprene.[344] This method would allow us to avoid the use of the amine DMEA as solvent and therefore making our method more practical. Using the Takai procedure, we have prepared hexane-soluble NaTMP·TMEDA[345] and have performed an efficient continuous flow sodiation of cinnamonitrile (**121a**) selectively in 2-position within 0.12 s at −78 °C. A subsequent batch trapping of **122a'** with various ketones of type **112** afforded the desired tertiary alcohols of type **169** in 58-83% yield as single regioisomers (Scheme 75). Similarly, ethoxyacrylonitrile **170g** gave, after batch quench with *o*-anisaldehyde (**112a´´**) and benzophenone (**112a´**), the allylic alcohols (**172ga´´** and **172ga´**) in 65-78% yield (*Z/E*>99/1). Further, geranylnitrile (**173a**) provided the organosodium **174a** upon metalation with NaTMP·TMEDA, which after a copper-catalyzed allylation using 3-bromocyclohexene (**112e´**) led to the desired product (**175ae´**) in 54% yield with a *E/Z* ratio of 52/48.

[344] a) S. Asako, M. Kodera, H. Nakajima, K. Takai, *Adv. Synth. Catal.* **2019**, *361*, 3120; b) D. R. Armstrong, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2011**, *17*, 8820; c) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470; d) R. McLellan, M. Uzelac, L. J. Bole, J. M. Gil-Negrete, D. R. Armstrong, A. R. Kennedy, R. E. Mulvey, E. Hevia, *Synthesis* **2019**, *51*, 1207; e) B. Gehrhus, P. H. Hitchcock, A. R. Kennedy, M. F. Lappert, R. E. Mulvey, P. J. A. Rodger, *J. Organomet. Chem.* **1999**, *587*, 88.
[345] For the synthesis of NaTMP·TMEDA, see page 152.

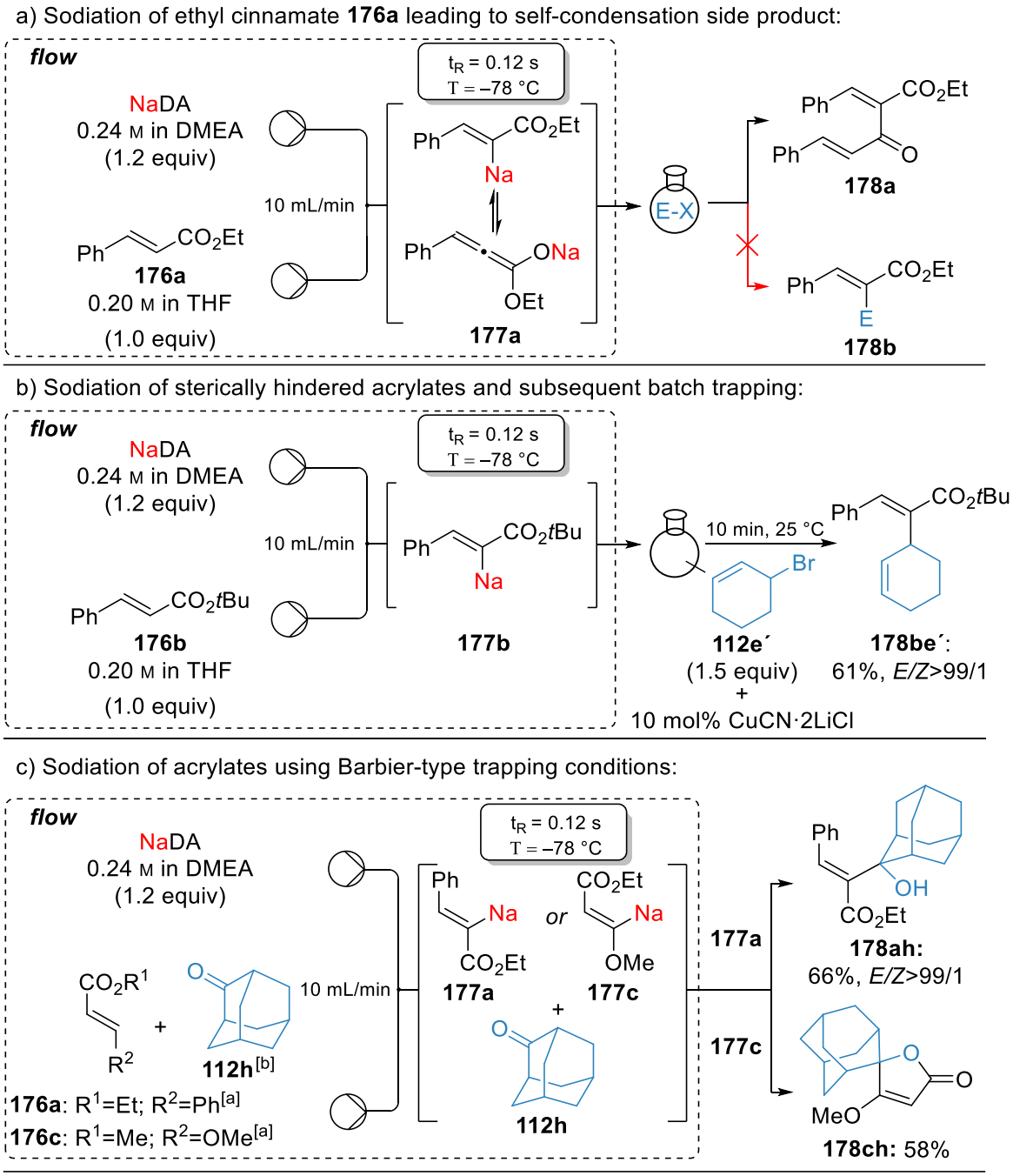


Scheme 75: General set-up for the sodiation of functionalized acrylonitriles with NaTMP·TMEDA in a microflow reactor and subsequent batch quench of the intermediate sodium organometallics with various electrophiles leading to functionalized acrylonitriles. [a] The diastereoselectivity was determined by crystal structure analyses, see pages 497–537. [b] The E- or Z- diastereoselectivity was assigned in analogy to related products, for which X-ray data were obtained. [c] 10 mol% CuCN·2LiCl.

5.6 NaDA Mediated Sodiation of Acrylates in Continuous Flow

However, the sodiation of other acrylates still remained challenging. Applying our standard sodiation method to ethyl cinnamate (**176a**) afforded solely the condensation product **178a** showing that the sodiation of **176a** was possible, but difficult to control. Thus, the intermediate organosodium **177a** reacted instantaneously with another molecule of **176a** before the desired electrophile quench proceeded (Scheme 76a). To prevent this self-condensation reaction, sterically hindered *tert*-butyl cinnamate (**176b**) was used affording organosodium **177b** after continuous flow sodiation. A copper-catalyzed batch allylation with 3-bromocyclohexene (**112e´**) gave the desired product **178be´** in 61% yield with

an *E/Z* ratio >99/1 (Scheme 76b). To overcome the need of sterically hindered esters, we envisioned a Barbier-type in situ trapping[346] of the highly reactive organosodiums of type **177**.



Scheme 76: Sodiation of substituted acrylates of type **176** using a microflow reactor under standard-flow conditions and Barbier conditions. *In situ* quench of the intermediate sodium organometallics of type **177** with adamantanone (**112h**) afforded functionalized acrylates of type **178**. [a] 0.20 M in THF, 1.0 equiv. [b] 0.30 M in THF, 1.5 equiv.

[346] a) M. A. Ganiek, M. V. Ivanova, B. Martin, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 17249; b) M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280; c) N. Weidmann, J. H. Harenberg, P. Knochel, *Org. Lett.* **2020**, *22*, 5895.

Interestingly, ethyl cinnamate (**176a**), which underwent self-condensation side reactions applying our standard flow conditions (Scheme 76a), was sodiated at −78 °C under Barbier-conditions and afforded organosodium **177a**, which was instantaneously trapped by adamantanone (**112h**), outcompeting self-condensation and resulting in the tertiary alcohol **178ah** in 66% yield (*E/Z* >99/1). Similarly, methyl-3-methoxyacrylate (**176c**) was sodiated in 3-position in the presence of adamantanone (**112h**) using NaDA (1.2 equiv) affording the spirolactone **178ch** in 58% yield (Scheme 76c).

5.7 Conclusion

In summary, we have reported the sodiation of substituted acrylonitriles and alkenyl sulfides in a continuous flow set-up using NaDA (sodium diisopropylamide) in $EtNMe_2$ (DMEA) and NaTMP (sodium 2,2,6,6-tetramethylpiperidide) · TMEDA in *n*-hexane. The resulting sodiated acrylonitriles and alkenyl sulfides were subsequently trapped in batch with various electrophiles such as aldehydes, ketones, disulfides and allylic bromides affording functionalized acrylonitriles and alkenyl sulfides. This flow-procedure was successfully extended to other acrylates by using Barbier-type conditions.

6. Preparation of Functionalized Aryl, Heteroaryl, and Benzylic Potassium Organometallics Using Potassium Diisopropylamide in Continuous Flow[347]

6.1 Introduction

Of all the alkali metals, lithium has by far received the most applications in organic synthesis.[348] However, the use of sodium and potassium organometallic intermediates has been explored for more than a century[349] and presents several specific advantages such as enhanced reactivity, low prices and moderate toxicity of these alkali organometallics as well as opportunities for new metalation selectivities.[350] Recently, we have reported that the use of continuous flow techniques[351] considerably facilitates the use of sodium bases such as NaDA (sodium diisopropylamide) for the selective sodiation of aromatics and heterocycles.[352] Herein, we wish to report a new metalation procedure allowing both to perform arene and heteroarene metalations as well as lateral metalations using potassium diisopropylamide (KDA) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in continuous flow in a hexane:tetrahydrofuran (THF) mixture.

[347] Adapted with permission from J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 12321. Copyright 2020 Angewandte Chemie International Edition published by Wiley-VCH. https://doi.org/10.1002/anie.202003392. This project was developed in cooperation with Dr. Niels Weidmann, see: N. Weidmann, Dissertation, LMU München.

[348] a) J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**; b) T. L. Rathman, J. A. Schwindeman, *Org. Process Res. Dev.* **2014**, *18*, 1192; c) G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596; d) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; e) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

[349] a) D. Seyferth, *Organometallics* **2006**, *25*, 2; b) D. Seyferth, *Organometallics* **2009**, *28*, 2; c) G. B. Buckton, *Proc. R. Soc.* **1859**, *9*, 685; d) G. Buckton, *Justus Liebigs Annalen der Chemie* **1859**, *109*, 218; e) W. H. Carothers, D. D. Coffman, *J. Am. Chem. Soc.* **1930**, *52*, 1254; f) J. A. Wanklyn, *Justus Liebigs Annalen der Chemie* **1858**, *108*, 67.

[350] a) Y. Ma, R. A. Woltornist, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2019**, *84*, 9051; b) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544; c) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470; d) M. Schlosser, P. Knochel, T. Hiyama, H.-J. Knölker, S. Bräse, *Organometallics in Synthesis - Third Manual*, John Wiley & Sons, Inc., Hoboken, **2013**; e) M. Schlosser, J. Hartmann, M. Staehle, J. Kramar, A. Walde, A. Mordini, *Chimia* **1986**, *40*, 306.

[351] a) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; b) C. Battilocchio, F. Feist, A. Hafner, M. Simon, D. N. Tran, D. M. Allwood, D. C. Blakemore, S. V. Ley, *Nat. Chem.* **2016**, *8*, 360; c) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463; d) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967; e) B. Gutmann, C. O. Kappe, *J. Flow Chem.* **2017**, *7*, 65; f) J. Britton, T. F. Jamison, *Nat Protoc* **2017**, *12*, 2423; g) G. A. Price, A. R. Bogdan, A. L. Aguirre, T. Iwai, S. W. Djuric, M. G. Organ, *Catal. Sci. Technol.* **2016**, *6*, 4733; h) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796; i) M. Colella, A. Nagaki, R. Luisi, *Chem. Eur. J.* **2020**, *26*, 19.

[352] N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748.

6.2 Optimization of the Preparation of Potassium Amide Bases

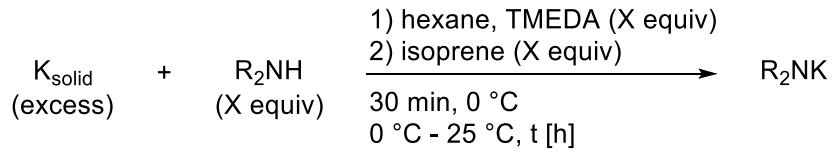
Whereas KDA was usually prepared by the Schlosser method by mixing LDA (lithium diisopropylamide) with *t*BuOK,[353] we have envisioned to prepare this base in the absence of any lithium salts, using a modified procedure of Collum for the preparation of NaDA.[354] Thus, small slices of oil-free solid potassium suspended in hexane were mixed with diisopropylamine. The resulting suspension was cooled to 0 °C and isoprene was added dropwise. After 30 min of stirring at 0 °C, the suspension was warmed to 25 °C leading after 6 h reaction time to a dark solution (Table 11, entries 1-6). The resulting KDA/TMEDA solution was titrated with a standardized solution of 0.40 M *n*-butanol in hexane. In most cases, an excess of potassium (ca. 3 equiv) was used and the KDA/TMEDA yield was calculated based on diisopropylamine (1.0 equiv). We have varied the equivalents of TMEDA and isoprene (entries 1-4) and found that 1.0 equivalent of TMEDA and 0.5 equivalent of isoprene resulted in the best yield after 6 h reaction time (entry 4).[355] Longer stirring did not improve the yield. Such KDA/TMEDA solutions were stable for at least one week at 25 °C. Similar yields were obtained using cyclohexane instead of hexane (entry 5). A quantitative yield was reached by setting potassium as limiting reagent (1.0 equiv) and adding an excess of diisopropylamine (DIPA, 3.0 equiv), TMEDA (3.0 equiv) and isoprene (1.5 equiv; entry 6). Attempts to extend this preparation to 2,2,6,6-tetramethylpiperidine (TMPH) or Cy_2NH led to significantly lower yields (entries 7-8). For subsequent experiments performed in continuous flow, we have used the KDA/TMEDA preparation conditions described in entry 4.

[353] a) The crystal structure of KDA complexed with 1.0 equiv of TMEDA was reported: W. Clegg, S. Kleditzsch, R. E. Mulvey, P. O'Shaughnessy, *J. Organomet. Chem.* **1998**, *558*, 193; b) L. Lochmann, J. Trekoval, *J. Organomet. Chem.* **1979**, *179*, 123; c) L. Lochmann, J. Pospíšil, D. Lím, *Tetrahedron Lett.* **1966**, *7*, 257; d) A. Mordini, D. Peruzzi, F. Russo, M. Valacchi, G. Reginato, A. Brandi, *Tetrahedron* **2005**, *61*, 3349; e) L. Lochmann, M. Janata, *Cent. Eur. J. Chem.* **2014**, *12*, 537; f) for preparation of KTMP using Me_3SiCH_2K see: B. Conway, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, J. G. Álvarez, *Angew. Chem. Int. Ed.* **2010**, *49*, 3182.

[354] Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312.

[355] The crystal structure of KDA complexed with 1.0 equiv of TMEDA was reported: W. Clegg, S. Kleditzsch, R. E. Mulvey, P. O'Shaughnessy, *J. Organomet. Chem.* **1998**, *558*, 193.

Table 11: Optimization of the preparation of potassium amide bases using solid potassium, secondary amides, TMEDA and isoprene in hexane



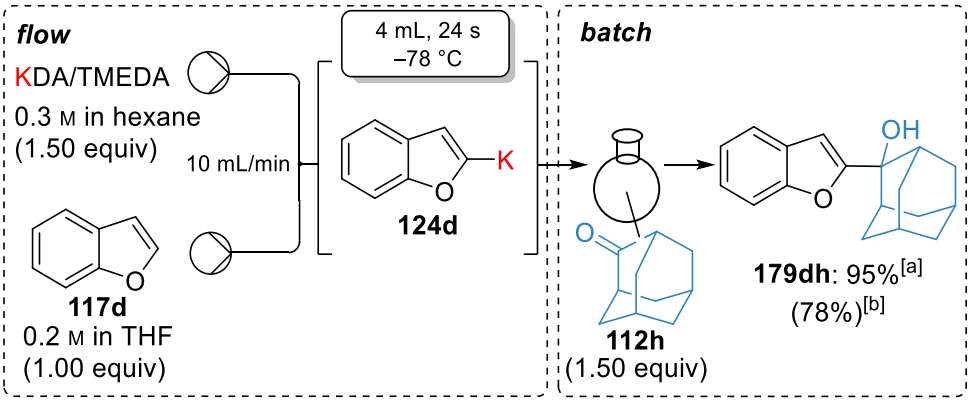
entry	R_2NH 1.0 equiv	TMEDA X equiv	Isoprene X equiv	t [h]	Molarity (K-base)	Yield (%)
1	DIPA	2.7	0.5	6	0.33	33
2	DIPA	1.0	1.0	6	0.40	40
3	DIPA	2.7	1.0	6	0.50	50
4	**DIPA**	**1.0**	**0.5**	**6**	**0.56**	**56**
5	DIPA	1.0	0.5	18	0.57 (0.49)	57 (49)[a]
6	**DIPA**	**3.0**	**1.5**	**18**	**0.33**	**99[b]**
7	TMPH	1.0	0.5	6	0.20	20
8	$HNCy_2$	1.0	0.5	6	0.28	28

[a] Yield of KDA/TMEDA in cyclohexane. [b] Potassium was used as limiting reagent, DIPA was used in excess (3.0 equiv).

6.3 Directed Metalation of (Hetro)arenes with KDA/TMEDA in Continuous Flow

In preliminary experiments, we have optimized the reaction conditions for performing metalations with KDA/TMEDA in hexane and in continuous flow using benzofuran (**117d**) in THF as substrate and adamantanone (**112h**) as quenching reagent. We have varied the temperature, the flow rate and the reactor size (reactor volume) and have found that it was best to perform the metalation at –78 °C using 1.5 equiv of KDA/TMEDA, a 4 mL tube reactor and a combined flow rate of 10 mL/min leading to a reaction time of 24 s for the metalation.[356] The resulting potassium organometallic **124d** was then quenched with adamantanone (**112h**, 1.5 equiv) at –40 °C for 10 min leading after work-up to the tertiary alcohol **179dh** in 95% isolated yield (Scheme 77).

[356] Commercially available equipment from *Uniqsis* was used. For a detailed optimization, see page 543.

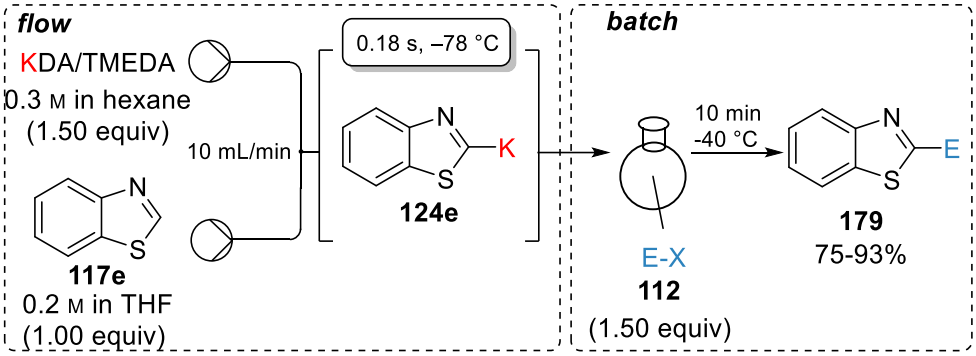


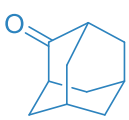
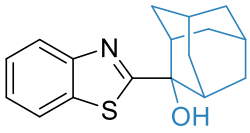
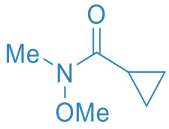
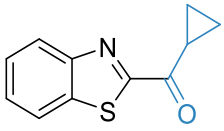
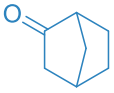
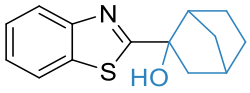
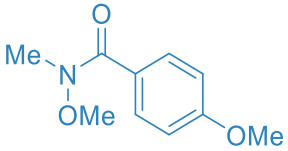
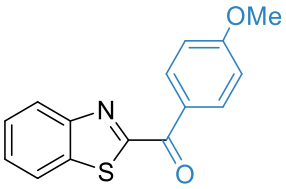
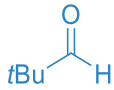
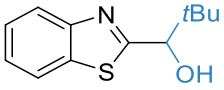
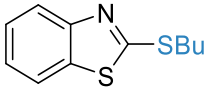
Scheme 77: Metalation of benzofuran (**117d**) with KDA/TMEDA and subsequent trapping with adamantanone (**112h**) in continuous flow. [a]Isolated yield of analytically pure product. [b]Cyclohexane was used as solvent.

These potassium organometallics display a high reactivity and the metalation of benzothiazole (**117e**) under optimum conditions[357] (flow rate: 10 mL/min; reaction time: 0.18 s; reactor volume: 0.03 mL; reaction temperature: –78 °C) furnished a potassium intermediate **124e**, which was trapped with various electrophiles like ketones (adamantanone (**112h**) or norcamphor (**112g**)) leading to the tertiary alcohols **179eh** and **179eg** in 74–77% yield (Table 12, entries 1-2). Using Barbier-type conditions,[358] that is metalation of a mixture of **117e** (1.00 equiv) with **112h** (1.50 equiv) with KDA/TMEDA (1.50 equiv) under the same flow conditions led to the alcohol **179eh** in 74% yield (entry 1). Quenching of **124e** with pivaldehyde (**112e´´**) afforded the alcohol **179ee´´** in 75% yield. Weinreb amides were excellent acylation reagents for potassium organometallics and the trapping of **124e** with **112f´´** and **112g´´** gave the corresponding ketones in 91-93% yield (entries 4-5). Thiolation of **124e** with Bu_2S_2 (**112q**) led to the thioether **179eq** in 92% yield. The corresponding Barbier reaction proceeded in this case with only 47% yield (entry 6).

[357] Optimization studies of the flow conditions were separately conducted for each substrate.
[358] a) P. Barbier, *Compt. Rend.* **1899**, *128*, 110; b) F. A. H. C. Blomberg, *Synthesis* **1977**, 18.

Table 12: Metalation of benzothiazole (**124e**) using KDA/TMEDA in continuous flow and subsequent batch quench with various electrophiles of type **112** leading to functionalized benzothiazole derivatives of type **179**.



#	E–X of type **112**	Product of type **179**	#	E-X of type **112**	Product of type **179**
1	 **112h**	 **179eh**: 77%, (74%)[b]	4	 **112f´´**	 **179ef´´**: 91%
2	 **112g**	 **179eg**: 77%	5	 **112g´´**	 **179eg´´:** 93%
3	 **112e´´**	 **179ee´´:** 75%	6	 **112q**	 **179eq**: 92%, (47%)[b]

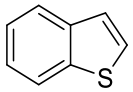
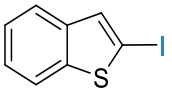
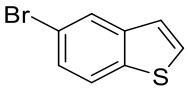
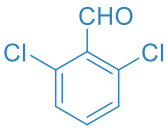
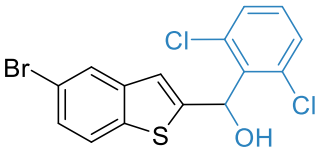
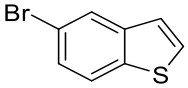
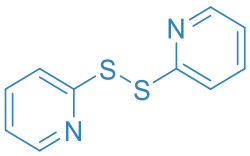
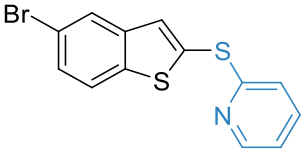
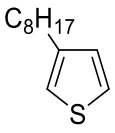
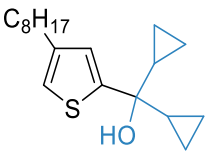
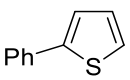
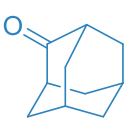
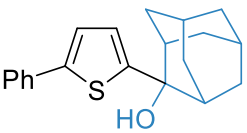
[a] Yield of analytically pure isolated product. [b] Barbier-type reaction using a pre-mixed solution of benzothiazole (1.00 equiv) and electrophile (1.50 equiv), instant quench with NH_4Cl.

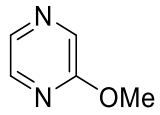
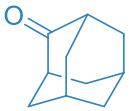
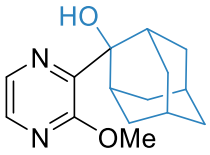
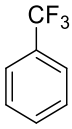
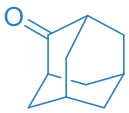
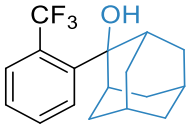
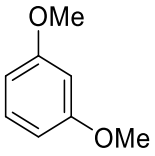
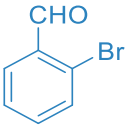
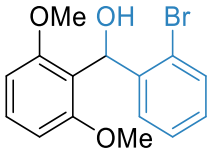
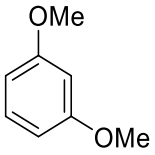
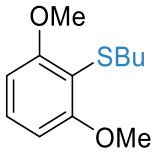
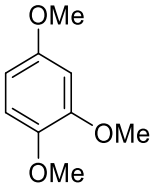
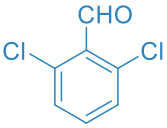
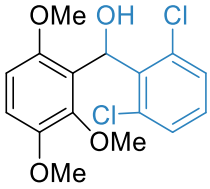
We have extended the reaction scope to various heterocyclic and aromatic substrates. For example, benzothiophene derivatives **117a** and **117f** were metalated with KDA/TMEDA and quenched with iodine (**112c´´**) or the aromatic aldehyde **112i** as well as the disulfide **112h´** leading to the expected products (**179ac´´**, **179fi** and **179fh´**) in 63-98% yield (Table 13, entries 1-3). Complete regioselectivity of the metalation of 3-octylthiophene (**117g**) was observed and addition to dicyclopropyl ketone (**112u**) gave the tertiary alcohol **179gu** in 65% yield (entry 4). Similarly, 2-phenylthiophene **117h** was metalated with KDA/TMEDA and trapped with **112h** affording **179hh** in 80% yield (entry 5). 2-Methoxypyrazine (**117i**) was regioselectively metalated at position 3 with KDA/TMEDA (–78 °C,

0.18 s using a combined flow rate of 10 mL/min). Addition of ketone **112h** gave the desired alcohol **179ih** in 81% yield (entry 6).

Extension to various aromatic substrates was possible. Electron-poor trifluoromethylbenzene (**117j**) was metalated in *ortho*-position with KDA/TMEDA (–78 °C, 24 s reaction time, 10 mL/min combined flow rate) providing after addition of **112h** the alcohol **179jh** in 42% yield (entry 7). Electron-rich substrates such as 1,3-dimethoxybenzene (**117c**) and 1,2,4-trimethoxybenzene (**117k**) were metalated with KDA/TMEDA and gave after batch quenching with aldehydes **112h´´** and **112i** and Bu_2S_2 (**112q**) the corresponding adducts **179ch´´**, **179cq** and **179ki** in 71-82% yield (entries 8-10).

Table 13. Metalation of (hetero)arenes of type **117** using KDA/TMEDA in continuous flow and subsequent batch quench with various electrophiles of type **112** leading to functionalized (hetero)arenes of type **179**.

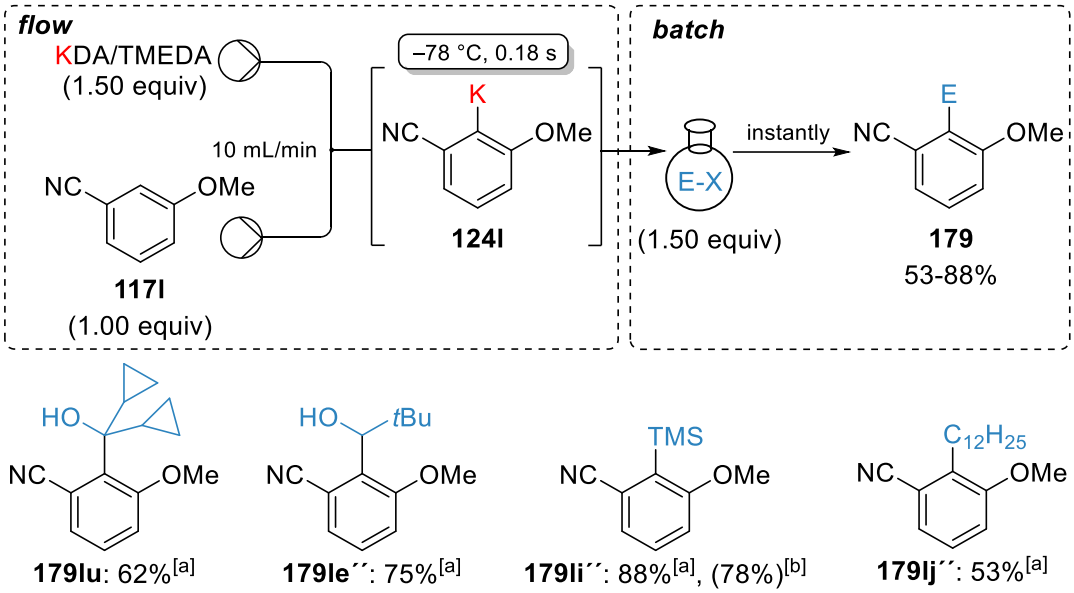
entry	substrate of type **117** T [°C], t [s], flow rate [mL/min]	electrophile of type **112**[a]	product of type **179**[b]
			
1	**117a:** –78, 24, 10	**112c´´**	**179ac´´:** 63%[c]
			
2	**117f:** –78, 0.18, 10	**112i**	**179fi:** 98%
			
3	**117f:** –78, 0.18, 10	**112h´**	**179fh´:** 93%
			
4	**117g:** –78, 0.18, 10	**112u**	**179gu:** 65%
			
5	**117h:** –78, 0.18, 10	**112h**	**179hh:** 80%

entry	substrate of type **117** T [°C], t [s], flow rate [mL/min]	electrophile of type **112**[a]	product of type **179**[b]
6	 **117i:** –78, 0.18, 10	 **112h**	 **179ih:** 81%
7	 **117j:** –78, 24, 10	 **112h**	 **179jh:** 42%
8	 **117c:** –78, 24, 10	 **112h´´**	 **179ch´´:** 82%
9	 **117c:** –78, 24, 10	 **112q**	 **179cq:** 73%
10	 **117k:** –78, 0.18, 10	 **112i**	 **179ki:** 71%

[a] 1.50 equiv of electrophile were used. [b] Yield of analytically pure isolated product. [c] KDA/TMEDA was prepared in cyclohexane. [d] Barbier-type reaction using a pre-mixed solution of 1,3-dimethoxybenzene (**117c**, 28 mg, 0.20 mmol, 1.00 equiv) and adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv), instant quench with NH_4Cl.

Remarkably, aromatic nitriles were tolerated in such metalations and 3-methoxybenzonitrile (**117l**) was deprotonated at position 2 by KDA/TMEDA (–78 °C, reaction time: 0.18 s). The resulting arylpotassium derivative **124l** reacted with various electrophiles (ketone **112u**, pivaldehyde (**112e´´**) and TMS-Cl (**112i´´**)) leading to the expected products **179lu**, **179le´´** and **179li´´** in 62-88% yield. Performing the metalation of **117l** with KDA/TMEDA in batch followed by Me_3SiCl quenching

afforded the product **179li´´** in 78% yield. A Wurtz-type coupling[359] using primary alkyl iodides such as dodecyl iodide (**112j´´**) led to the alkylated 3-methoxybenzonitrile **179lj´´** in 53% yield. (Scheme 78).

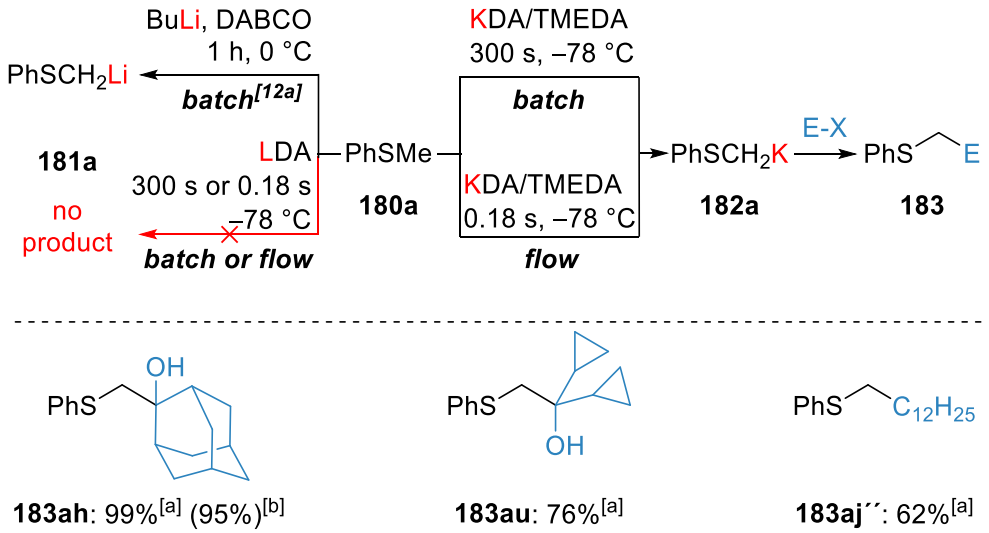


Scheme 78: Metalation of 3-methoxy benzonitrile (**117l**) with KDA/TMEDA in continuous flow and subsequent trapping with various electrophiles. [a] Yield of analytically pure isolated product [b] Yield of analytically pure isolated product obtained under batch conditions.

6.4 Preparation of Benzyilic Potassium Species via Metalation with KDA/TMEDA in Continuous Flow

Then, we turned our attention to substrates able to undergo lateral metalation. Thus, thioanisole (**180a**) was previously lithiated with BuLi and DABCO or HMPA leading to $PhSCH_2Li$ (**181a**).[360] However, LDA did not achieve a lithiation, neither under batch nor under flow conditions.[361] On the other hand, KDA/TMEDA successfully deprotonated **180a** in batch as well as in flow (Scheme 79) affording $PhSCH_2K$ (**182a**), which was quenched with ketones **112h** and **112u** and alkyl iodide **112j´´** resulting in the desired products **183ah**, **183au** and **183aj´´** in 62-99% yield.

[359] A. Wurtz, *Ann. Chim. Phys.* **1855**, *44*, 275; A. Wurtz, *Ann. Chim. Phys.* **1855**, *96*, 364.
[360] a) E. J. Corey, D. Seebach, *J. Org. Chem.* **1966**, *31*, 4097; b) M. F. Semmelhack, J. W. Herndon, *Organometallics* **1983**, *2*, 363; c) The use of TMEDA and 2.2 equiv of *n*BuLi leads to dimetalation of thioanisole: S. Cabiddu, C. Floris, S. Melis, *Tetrahedron Lett.* **1986**, *27*, 4625.
[361] For detailed screening conditions, see page 541.



Scheme 79: Metalation of thioanisole (**180a**) using various lithium and potassium bases under batch and flow conditions. [a] Yield of analytically pure isolated product obtained in continuous flow. [b] Yield of analytically pure isolated product obtained under batch conditions.

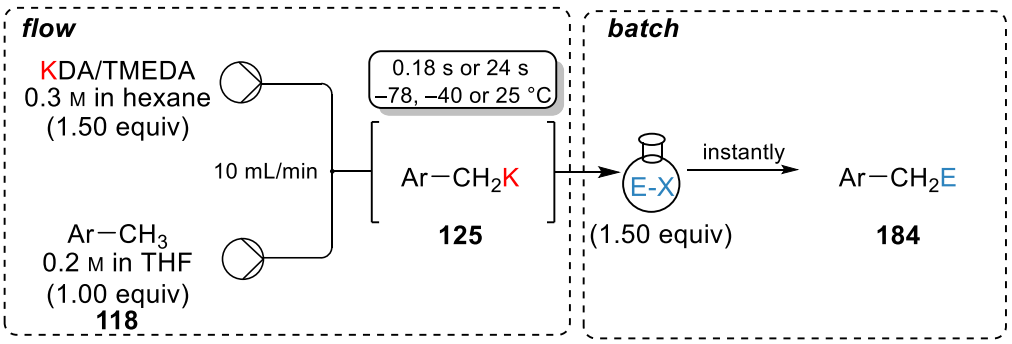
Whereas lateral alkali-metalations of arenes were well described under batch conditions,[362] the corresponding reactions in flow were rare.[363] The use of KDA/TMEDA was quite advantageous for the metalation of methyl-substituted arenes (Scheme 80). Preliminary results show, that a 0.2 M solution of toluene (**118b**) led to unsatisfactory results, however the injection of neat toluene (**118b**) improved considerably the flow metalation with KDA/TMEDA. Interestingly, this metalation was performed at 25 °C (in contrast to previously described metalations of arenes and heteroarenes). In this case, the reaction time was increased to 24 s at a flow rate of 10 mL/min. Under these convenient conditions, a subsequent batch-trapping with ketone **112h** gave **184bh** in 69% yield. Similarly, *p*-xylene (**118c**) provided the mono-potassium derivative **125c**, which after quenching with dodecyl iodide (**112j´´**) or Weinreb amide **112g´´** afforded the products **184cj´´** and **184cg´´** in 95-96% yield. Mesitylene (**118a**) was metalated neat and after quenching with ketone **112i´** and dodecyl iodide (**112j´´**) gave the arenes **184ai´** and **184aj´´** in 89-92% yield. In the case of the Wurtz-type coupling with **112j´´**, the reaction was ten-fold scaled up to a 3 mmol scale,[364] providing **184aj´´** in 93% yield. For 1-methylnaphthalene

[362] a) P. Fleming, D. F. O'Shea, *J. Am. Chem. Soc.* **2011**, *133*, 1698; b) A. Manvar, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2015**, *80*, 8727; c) F. Gualtieri, A. Mordini, S. Pecchi, S. Scapecchi, *Synlett* **1996**, *1996*, 447; d) M. A. J. Miah, M. P. Sibi, S. Chattopadhyay, O. B. Familoni, V. Snieckus, *Eur. J. Org. Chem.* **2018**, *2018*, 440; e) J. Fässler, J. A. McCubbin, A. Roglans, T. Kimachi, J. W. Hollett, R. W. Kunz, M. Tinkl, Y. Zhang, R. Wang, M. Campbell, V. Snieckus, *J. Org. Chem.* **2015**, *80*, 3368; f) S. L. MacNeil, O. B. Familoni, V. Snieckus, *J. Org. Chem.* **2001**, *66*, 3662; g) D. D. Zhai, X. Y. Zhang, Y. F. Liu, L. Zheng, B. T. Guan, *Angew. Chem. Int. Ed.* **2018**, *57*, 1650.

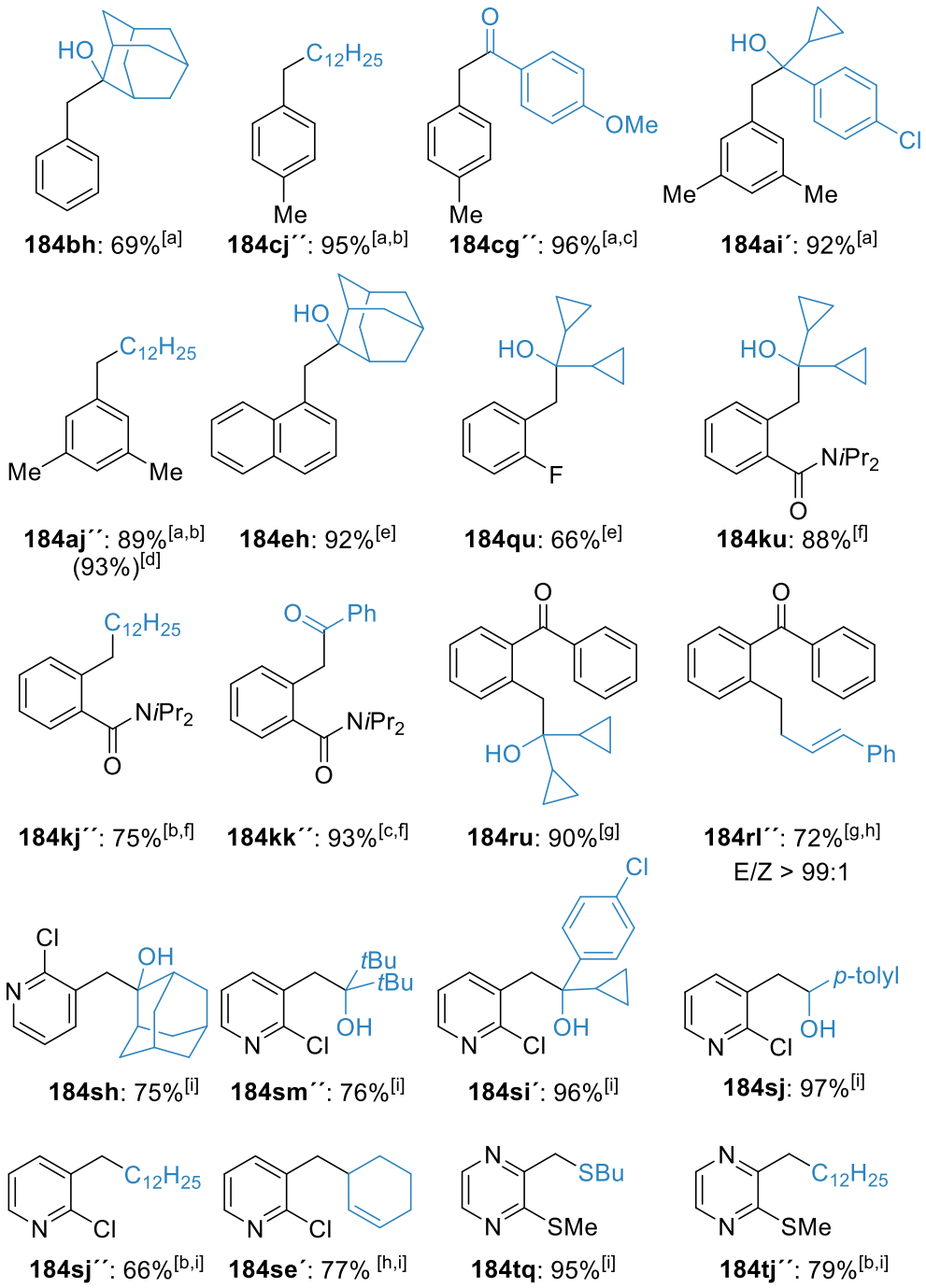
[363] a) F. Venturoni, N. Nikbin, S. V. Ley, I. R. Baxendale, *Org Biomol Chem* **2010**, *8*, 1798; b) J. Y. F. Wong, J. M. Tobin, F. Vilela, G. Barker, *Chem. Eur. J.* **2019**, *25*, 12439; c) H.-J. Lee, H. Kim, D.-P. Kim, *Chem. Eur. J.* **2019**, *25*, 11641.

[364] a) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967; b) A. Hafner, P. Filipponi, L. Piccioni, M. Meisenbach, B. Schenkel, F. Venturoni, J. Sedelmeier, *Org. Process Res. Dev.* **2016**, *20*, 1833.

(**118e**), a 0.2 M solution in THF was used and standard KDA/TMEDA-metalation led after trapping with ketone **112h** to the corresponding naphthylmethyl alcohol **184eh** in 92% yield. Functionalized substrates such as 2-fluorotoluene (**118q**) were metalated at the benzylic position, affording the potassium organometallic **125q**, which after quenching with ketone **112u** led to the tertiary alcohol **184qu** in 66% yield. *N*,*N*-diisopropyl-2-methylbenzamide (**118k**) led upon reaction with KDA/TMEDA at –40 °C (reaction time: 24 s) solely to the lateral metalated species **125k**, completely avoiding *ortho* metalation.[365] Trapping with various electrophiles such as ketone **112u**, alkyl iodide **112j´´** and Weinreb amide **112k´´** gave the expected products **184ku**, **184kj´´** and **184kk´´** in 75-93% yield. Further, ketones were tolerated. For example, lateral metalation of ketone **118r** using KDA/TMEDA proceeded smoothly at –40 °C within 0.18 s using a flow rate of 10 mL/min. Batch trapping with ketone **112u** and cinnamyl bromide (**112l´´**) in the presence of 10% CuCN·2LiCl resulted in the tertiary alcohol **184ru** and the allylated ketone **184rl´´** in 72-90% yield. We further extended the substrate scope to methyl-substituted heterocycles such as 2-chloro-3-methyl-pyridine (**118s**). Metalation of **118s** at the meta-methyl substituent using KDA/TMEDA led to the corresponding organopotassium species **125s**, which after batch quench with various carbonyl electrophiles (**112h**, **112m´´**, **112i´** and **112j**) gave the corresponding alcohols **184sh**, **184sm´´**, **184si´** and **184sj** in 75-97% yield. Trapping **125s** with alkyl iodide **112j´´** and cyclohexyl bromide **112e´** (in the presence of 10% CuCN·2LiCl) led to the corresponding products **184sj´´** and **184se´** in 66-77% yield. Pyrazine **118t** was metalated in continuous flow with KDA/TMEDA. We have found that after metalation at the methyl-substituent the heterobenzylic potassium organometallic **125t** was obtained. Batch trapping with dibutyl disulfide (**112q**) and dodecyl iodide (**112j´´**) gave the functionalized pyrazines **184tq** and **184tj´´** in 79-95% isolated yield.



[365] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) L. Balloch, A. R. Kennedy, R. E. Mulvey, T. Rantanen, S. D. Robertson, V. Snieckus, *Organometallics* **2011**, *30*, 145; c) K. J. Singh, A. C. Hoepker, D. B. Collum, *J. Am. Chem. Soc.* **2008**, *130*, 18008.



Scheme 80: Lateral metalation of methyl-substituted (hetero)arenes using KDA/TMEDA in continuous flow leading to organopotassium species of type **125**. Subsequent batch trapping with various electrophiles afforded functionalized methyl-substituted (hetero)arenes of type **184**. Yields of analytically pure isolated products [a] substrate (neat), E-X (0.30 mmol, 1.00 equiv), KDA/TMEDA (1.10 equiv), 25 °C, 24 s, 10 mL/min. [b] Wurtz-type coupling from the corresponding iodide. [c] from the corresponding Weinreb amide. [d] Scale-up to 2.0 mmol using the optimized flow conditions. [e] 25 °C, 24 s, 10 mL/min [f] –40 °C, 24 s, 10 mL/min. [g] 40 °C, 0.18 s, 10 mL/min. [h] 10 mol% CuCN·2LiCl. [i] –78 °C, 0.18, 10 mL/min.

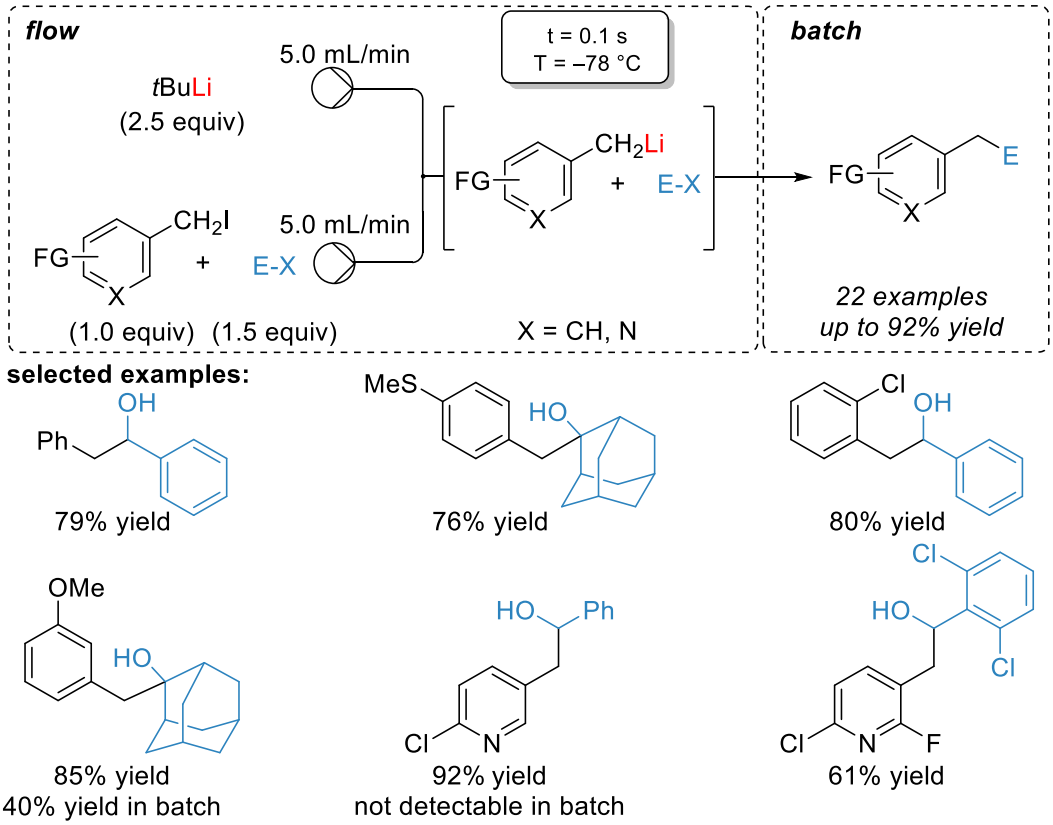
6.5 Conclusion

In summary, we have reported a preparation of the potassium base KDA/TMEDA in the absence of any lithium salts and have demonstrated its utility for the metalation of (hetero)arenes containing sensitive functional groups using a flow set-up. The resulting potassium organometallics react upon batch quench instantly with various electrophiles affording functionalized (hetero)arenes in high yields. This flow procedure was successfully extended to the lateral metalation of methyl-substituted arenes and heteroaromatics resulting in benzylic potassium organometallics, which were trapped with a range of electrophiles. A scale-up was possible without further optimization. Further investigations of flow metalations using KDA/TMEDA are currently under way in our laboratories.

7. SUMMARY

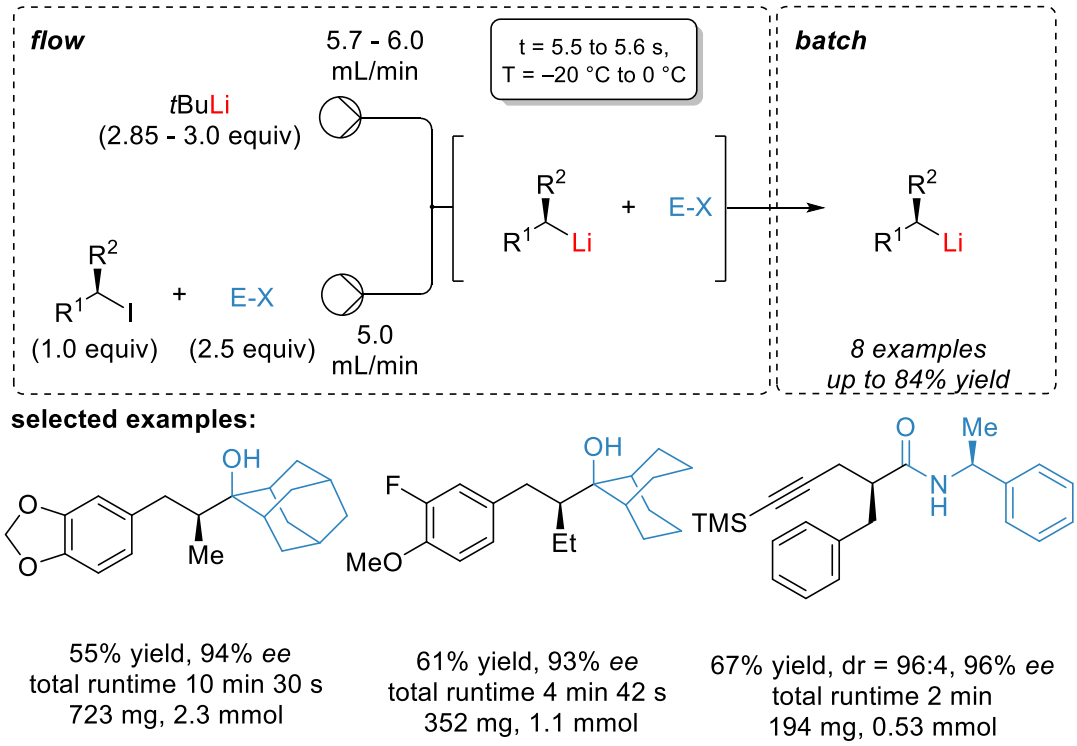
During the cause of these studies we developed a number of different approaches for the generation of highly reactive alkali metal organyls, including organometallic reagents of lithium, sodium and potassium. It was shown that the preparation these types of reagents is not only feasible under but also benefits from continuous flow techniques.

The first part of this thesis focused on I/Li-exchange reactions under Barbier-type conditions. Exchange reactions on benzylic iodides using *t*BuLi as the exchange reagent in the presence of carbonyl electrophiles were reported. Efficient mixing was the key parameter for the preparation of functionalized products and the suppression of unwanted side reactions. In particular, high flow rates and the presence of electrophile in the starting material solution lowered the Wurtz-type homo-coupling which is commonly observed in halogen-lithium exchange reactions or lithium insertions into benzylic halogen bonds. The method was successfully applied in the generation of various electron poor as well as electron rich benzylic lithium species under continuous flow conditions. Additionally, the procedure was extended towards heterobenzylic iodides, which, after premixing with the electrophile, gave upon I/Li-exchange in a microreactor the desired primary and secondary alcohols. Comparison studies in batch showed that especially exchange reactions on the heterobenzylic iodides profited from the continuous flow conditions (Scheme 81).



Scheme 81: I/Li-exchange on (hetero)benylic iodides under Barbier conditions in continuous flow.

With these conditions in hand the goal was set to implement the stereoretentive I/Li-exchanges on secondary alkyl iodides, which were previously reported by the Knochel group, into a continuous flow set-up. Wilke and Kremsmair developed an in situ generation of enantioenriched secondary lithiums via I/Li-exchange in the presence of various electrophiles under batch conditions. Minor adjustments to the continuous flow procedure shown above for the preparation of benzylic lithium reagents indeed allowed for the transfer of the stereospecific I/Li-exchange into a continuous flow set-up. Even though the reactions had to be conducted at higher temperatures, due to solubility problems of the alkyl iodides and electrophiles, a high enantiomeric excess was maintained. It was possible to prolong the runtime of these reactions and thus generate the chiral lithium reagents at a gram scale (Scheme 82). Thus, continuous microreactor technology overcame two of the major limitations of former procedures, which were not scalable and required cryogenic temperatures of up to –100 °C.

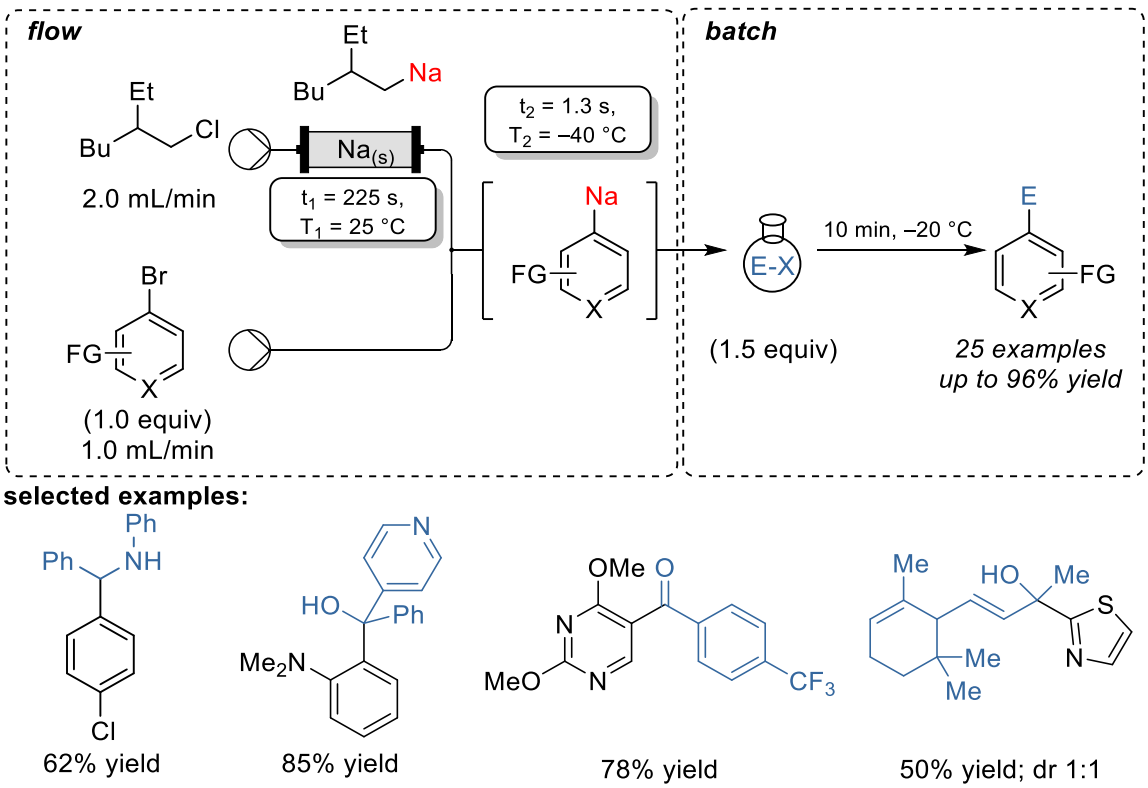


Scheme 82: I/Li-exchange on secondary alkyliodides under Barbier conditions in continuous flow.

The majority of this work dealt with the chemistry of organosodium species, which are significantly less represented in the scientific literature. It was believed that the major reason for that is the poor solubility and thus the resulting inconvenience in the handling of most sodium organometallics. Especially, when conducting reactions in microreactors solubility is of immense importance. Consequently, it was searched for reports on soluble alkylsodium reagents and (2-ethylhexyl)sodium was found to be described as hexane soluble but of limited stability and difficult to handle. An on-demand procedure for the preparation of this reagent via oxidative insertion into the corresponding alkyl chloride using a sodium packed-bed reactor was developed. This on-demand generation circumvented

multiple of the drawbacks associated with (2-ethylhexyl)sodium: 1) The use of the sodium column limited work with hazardous metallic sodium to a minimum. Furthermore, subsequent in-line consumption of the alkylsodium reagent additionally decreased the risk of handling pyrophoric and highly reactive organometallics; 2) Due to the filters engulfing the sodium packed-bed reactor a hexane solution of (2-ethylhexyl)sodium of high purity was obtained. Most importantly the solution was free of metallic sodium which might hamper electrophile quenches and reactions with reagents prone to reduction; 3) The high local concentration of metallic sodium in the packed-bed reactor leads to a decrease in Wurtz-type homocoupling which is often observed in oxidative insertions of sodium into alkyl halides; 4) The on-demand generation and the direct in-line consumption of (2-ethylhexyl)sodium avoids the aforementioned storage problems associated with its stability.

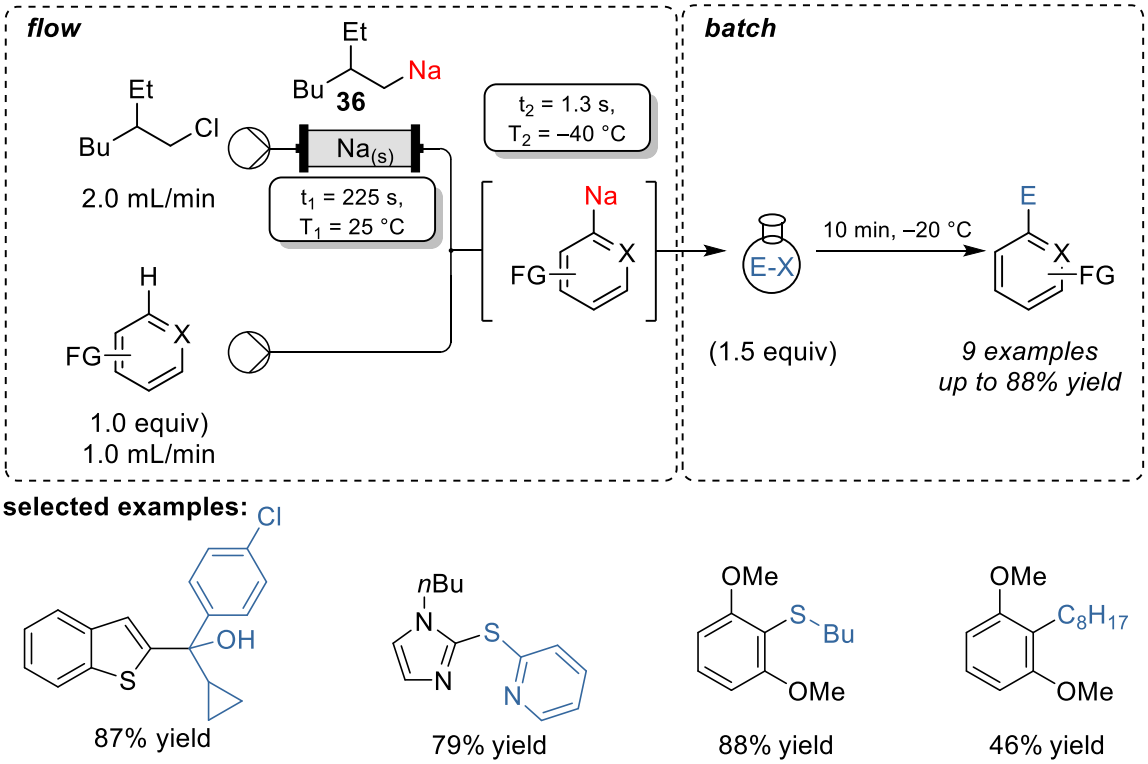
It was possible to use the alkylsodium species for in-line Br/Na-exchanges. The resulting sodium(hetero)arenes were subsequently quenched in batch with a broad range of electrophiles (Scheme 83). Exchange on 2-bromopyridine and subsequent quench in continuous flow using a benzophenone electrophile solution which was delivered via a third pump allowed an efficient scaling of the procedure.



Scheme 83: On-demand generation of (2-ethylhexyl)sodium using a sodium packed-bed reactor followed by an in-line Br/Na-exchange on bromo(hetero)arenes and subsequent batch quench with various electrophiles.

Similar to alkyllithium species, (2-ethylhexyl)sodium was expected to not only be useful as an exchange reagent, but also be a potent base for directed sodiations. In fact, directed sodiations of (hetero)arenes

proceeded smoothly under continuous flow conditions and electrophile quenches in batch led to the desired functionalized products (Scheme 84).

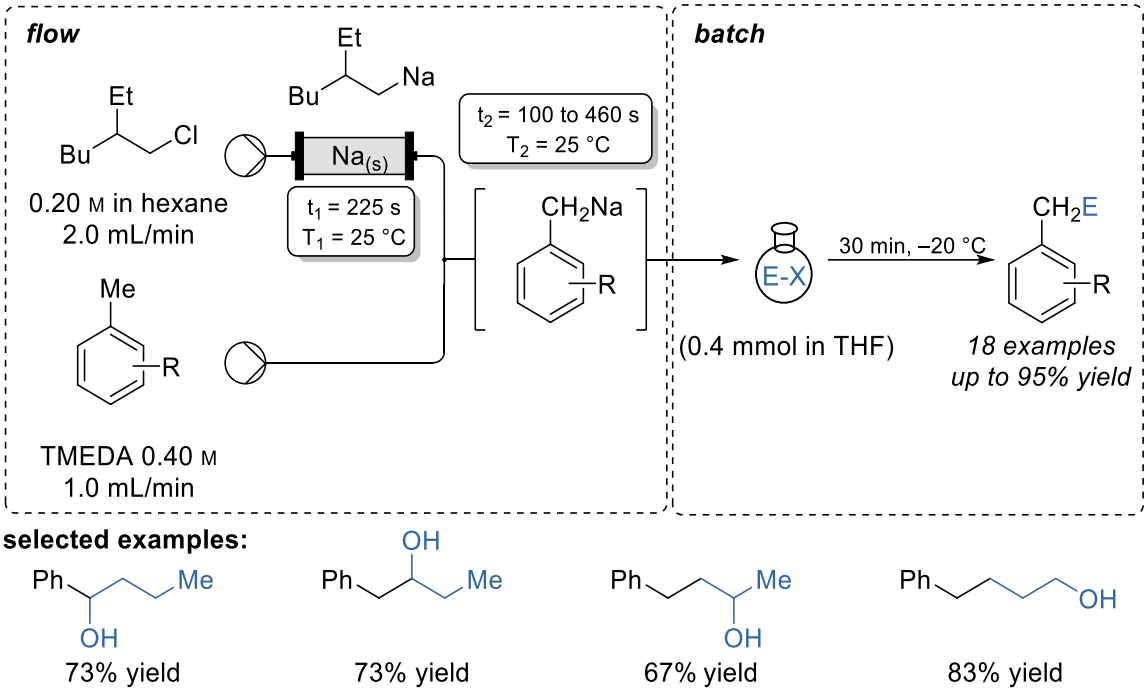


Scheme 84: On-demand generation of (2-ethylhexyl)sodium using a sodium packed-bed reactor followed by a directed in-line sodiation of (hetero)arenes and subsequent batch quench with various electrophile.

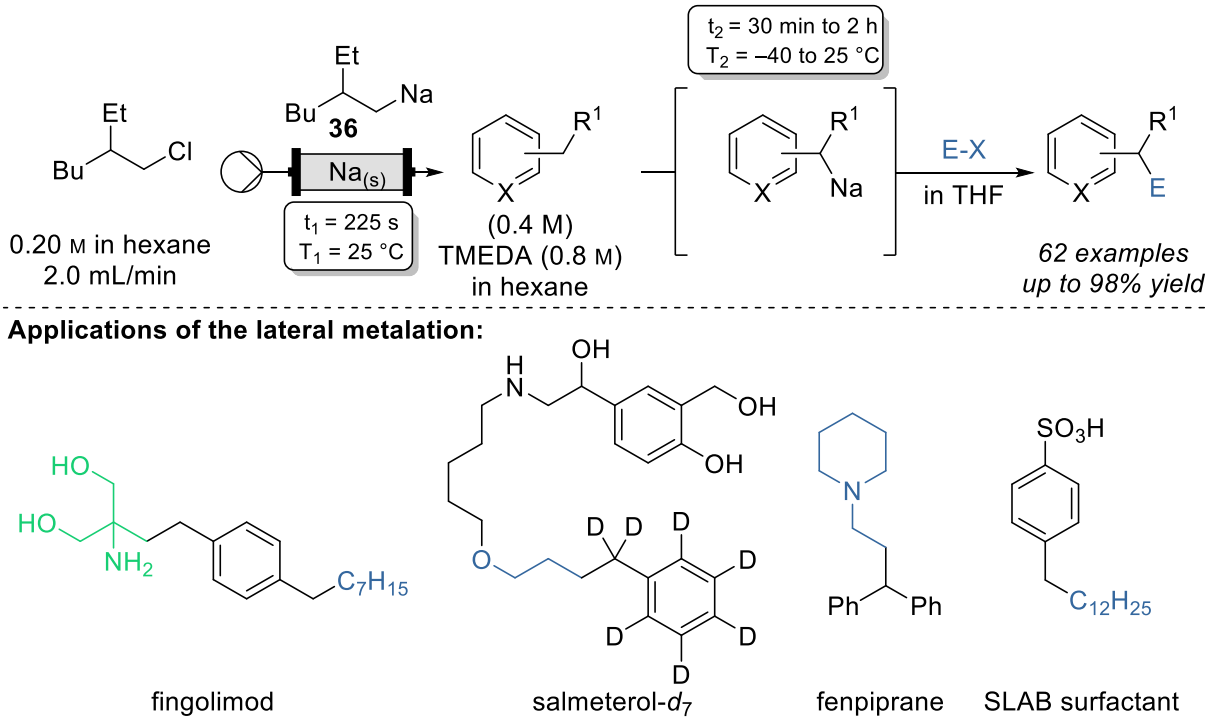
The sodiation procedure was extended to benzylic metalations of alkylarenes. Reactions proceeded at room temperature but required longer reaction times (Scheme 85). The resulting benzylic sodium species showed an excellent reactivity towards electrophiles. Thus, Lewis acid free ring opening reactions on various epoxides as well as oxetane were feasible allowing the generation of a series of phenylbutanols bearing the hydroxyl group in α, β, γ, and δ-position to the aromatic ring. In-line electrophile quenching with cyclohexene oxide using a three pump set-up demonstrated the scalability of the procedure.

The poor solubility of the benzylic sodium reagents in hexane together with the need for longer metalation times rendered the sodiation in continuous flow as rather inconvenient. Especially for more expensive alkylarenes a batch sodiation was developed in which the on-demand generated (2-ethylhexyl)sodium was directly injected into a flask charged with a mixture of alkylarene in the presence of TMEDA (Scheme 86). A plethora of electrophiles were used as quenching reagents. Reactions with alkyl chlorides enabled Wurtz-type coupling reactions, which allow carbon-carbon bond formations between benzylic sodium reagents and inexpensive alkyl halides without the need for transition metal catalysts. Using secondary alkyl chlorides an inversion of the stereochemistry can be observed

indicating a S_N2-type mechanism. The benzylic sodiation was used in the synthesis of several industrial relevant compounds.

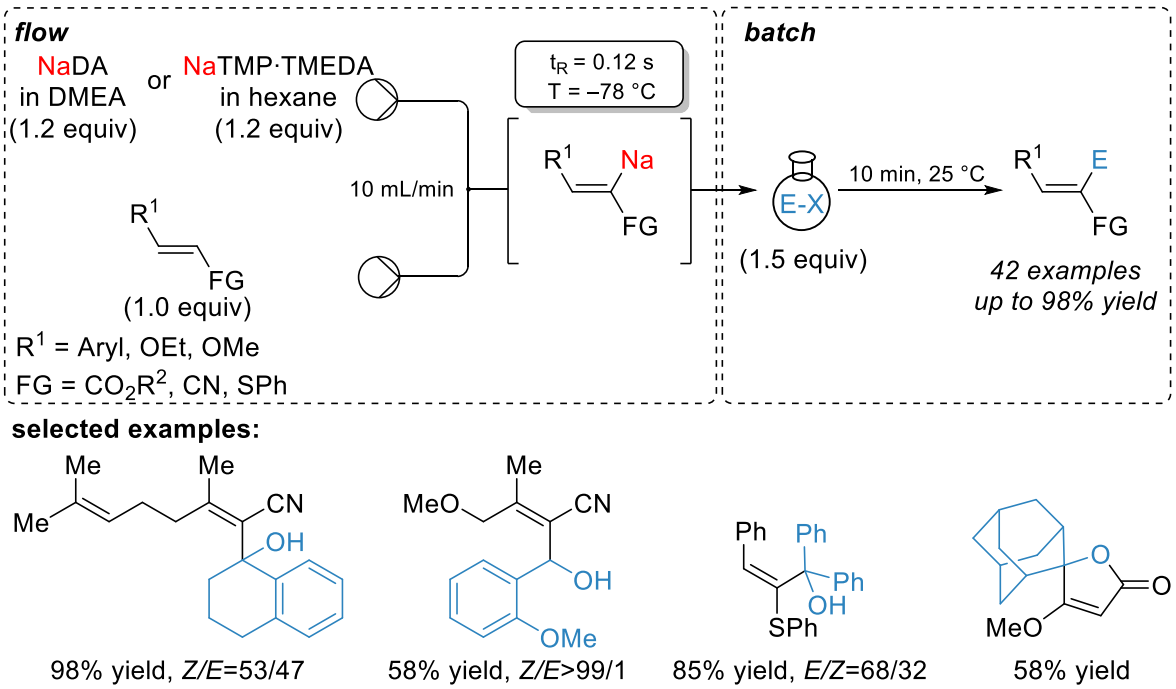


Scheme 85: On-demand generation of (2-ethylhexyl)sodium using a sodium packed-bed reactor followed by a lateral in-line sodiation of methylarenes and benzene, subsequent batch quench with various electrophiles.



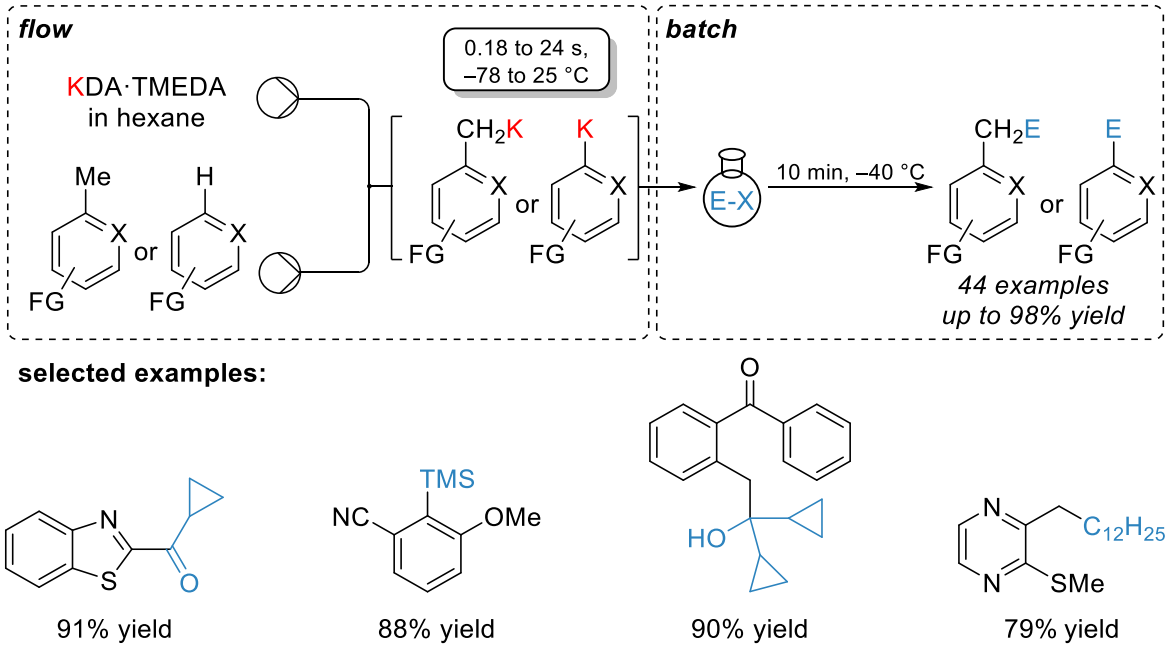
Scheme 86: On-demand generation of (2-ethylhexyl)sodium using a sodium packed-bed reactor followed by a lateral batch sodiation of alkyl substituted (hetero)arenes and subsequent batch quench with various electrophiles. Industrial relevant compounds prepared using the lateral sodiation protocol.

Sodiation of acrylonitriles and alkenyl sulfides was achieved using sodium amide bases. NaDA in DMEA as well as NaTMP·TMEDA in hexane were suitable bases for the directed metalation of these functionalized starting materials under continuous flow conditions. Best results were obtained at short residence times and low temperatures (Scheme 87). Other than in the previously reported magnesiation and zincation of alkenyl substrates, metalation of alkyl substituted acrylonitriles was successful and gave upon batch quench with various electrophiles the highly substituted alkenes. Acrylates were tolerated if either sterically demanding esters were utilized or alternatively by applying Barbier-conditions in which the acrylate was premixed with a suitable electrophile.



Scheme 87: Continuous flow sodiation of substituted acrylonitriles, alkenyl sulfides and acrylates followed by an electrophile quench in batch.

Finally, the last part of this work was focused on a novel preparation of the potassium amide base KDA·TMEDA. Based on Collum´s preparation of NaDA, KDA was generated by mixing finely sliced metallic potassium in hexane with di*iso*propylamine in the presence of isoprene and TMEDA. Different from the vast majority of potassium amide bases, this procedure demonstrates a lithium free generation of the reagent. The hexane soluble KDA·TMEDA was used in continuous flow metalations of (hetero)arenes. The arylpotassium reagents were instantaneously quenched with electrophiles such as ketones, aldehydes, alkylic and allylic halides, disulfides, Weinreb amides and TMSCl. Expanding the procedure to the metalation of methyl substituted arenes allowed a significant extension of the substrate scope. It was possible to metalate starting materials bearing sensitive functional groups such as nitriles and ketones (Scheme 88).



Scheme 88: Preparation of functionalized arylic, heteroarylic and benzylic potassium organometallics using potassium di*iso*propylamide in continuous flow followed by an electrophile quench in batch.

C. EXPERIMENTAL PART

1. GENERAL INFORMATION

The data in the chapters C. 1. to C. 7. has been published as supporting information to the publications of the same name. The original files can be accessed via the following links (last access 03.04.2023):

2. Continuous Flow Preparation of (Hetero)Benzylic Lithiums via Iodine-Lithium Exchange Reaction under Barbier Conditions: https://pubs.acs.org/doi/full/10.1021/acs.orglett.0c01991.

3. In Situ Quench Reactions of Chiral Secondary Alkyllithium Reagents in Batch and Continuous Flow: https://onlinelibrary.wiley.com/doi/full/10.1002/anie.202214377.

4. (2-Ethylhexyl)sodium: A Hexane-Soluble Reagent for Br/Na-Exchanges and Directed Metalations in Continuous Flow: https://onlinelibrary.wiley.com/doi/full/10.1002/anie.202103031.

5. Continuous Flow Preparation of Benzylic Sodium Organometallics: https://onlinelibrary.wiley.com/doi/full/10.1002/anie.202203807

6. Continuous Flow Sodiation of Substituted Acrylonitriles, Alkenyl Sulfides and Acrylates: https://onlinelibrary.wiley.com/doi/full/10.1002/anie.202012085

7. Preparation of Functionalized Aryl, Heteroaryl, and Benzylic Potassium Organometallics Using Potassium Diisopropylamide in Continuous Flow: https://onlinelibrary.wiley.com/doi/full/10.1002/anie.202003392

1.1 Solvents

Hexane was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. Solvents for column chromatography were distilled prior to use.

THF: For the continuous flow preparation of (hetero)benzylic lithiums via iodine-lithium exchange reaction under barbier conditions and continuous flow sodiation of substituted acrylonitriles, alkenyl sulfides and acrylates THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves.

DMEA was continuously refluxed and freshly distilled from sodium benzophenone ketyl under argon and stored under argon.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

All reagents were obtained from commercial sources (Sigma-Aldrich, TCI, Merck, Acros Organics, Fluorochem and Apollo) and used without further purification.

TMEDA was continuously refluxed and freshly distilled from calcium hydride or sodium benzophenone ketyl under argon and stored under argon.

PMDTA was continuously refluxed and freshly distilled from calcium hydride or sodium benzophenone ketyl under argon and stored under argon.

Di*iso*propyl amine was continuously refluxed and freshly distilled from calcium hydride or sodium benzophenone ketyl under argon and stored under argon.

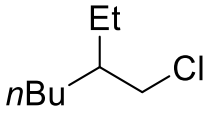
2,2,6,6-tetramethylpiperidine was continuously refluxed and freshly distilled from calcium hydride or sodium benzophenone ketyl under argon and stored under argon.

***n*BuLi** solution in hexane was purchased from Albemarle (Frankfurt) and the concentration was determined by titration against 1,10-phenanthroline in THF using *i*PrOH.

***t*BuLi** solution in hexane was purchased from Albemarle (Frankfurt) and the concentration was determined by titration against 1,10-phenanthroline in THF using *i*PrOH.

CuCN·2LiCl[366] solution (1.00 M in THF) was prepared by drying CuCN (8.96 g, 100 mmol) and LiCl (8.48 g, 200 mmol) in a Schlenk flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (100 mL) was added and stirred until the salts were dissolved.

3-(chloromethyl)heptane (36)



Thionyl chloride (61.7 mL, 0.85 mol, 1.7 equiv) was added over 1 h to a solution of 2-ethylhexan-1-ol (78.5 mL, 0.50 mol, 1.0 equiv) and pyridine (23.0 mL) at 0 °C. The reaction mixture was stirred over night at 55 °C. Afterwards the mixture was quenched with H_2O (100 mL) at 0 °C. The aqueous layer was extracted three times with EtOAc (3×100 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99.5:0.5) afforded the title compound **36** as colorless oil (66.0 g, 0.45 mol, 89% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.58 – 3.49 (m, 2H), 1.59 (m, 1H), 1.51 – 1.12 (m, 8H), 0.90 (m, 6H)
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 48.4, 41.6, 31.0, 29.0, 24.3, 23.0, 14.1, 10.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2928, 2873, 2859, 1458, 1446, 1380, 1294, 782, 768, 724, 683.

[366] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

MS (EI, 70 eV): *m/z* (%) = 83 (41), 70 (15), 57 (100), 55 (29), 41 (71).

HRMS (EI-orbitrap): *m/z:* [M – C_2H_5] calc. for [$C_6H_{12}Cl$]: 119.0628; found 119.0622.

NaDA solution (ca. 1.0 M in DMEA) was prepared according to a slightly modified procedure reported by Collum.[367] Optimized reaction conditions are as follows: Sodium dispersion (5 mL, 58.3 mmol, 30 wt% in toluene, <0.1 mm particle size) was washed with dry DMEA (3×2 mL). Then, dry DMEA (14.4 mL) and dry di*iso*propyl amine (4.2 mL, 29.8 mmol, 1.0 equiv) were added. After cooling the solution to 0 °C, isoprene (1.52 mL, 15.0 mmol, 0.5 equiv) was added dropwise and the solution was allowed to warm to 25 °C over 2 h. The concentration of the resulting yellow NaDA solution was determined by titration with diphenyl acetic acid.

TMPNa solution (ca. 1.0 M in hexane) was prepared according to a slightly modified procedure reported by Takai.[368] Sodium dispersion (1.5 mL, 17.5 mmol, 1.4 equiv, 30 wt% in toluene, <0.1 mm particle size) was washed with dry hexane (3×2 mL). Then, dry hexane (5 mL) and 2,2,6,6-tetramethylpiperidine (TMPH, 2.1 mL, 12.5 mmol, 1.0 equiv) were added. After cooling the solution to 0 °C, isoprene (1.25 mL, 12.5 mmol, 1.0 equiv) was added dropwise and the solution was allowed to warm to 25 °C over 2 h. The concentration of the resulting black TMPNa solution was determined by titration with diphenyl acetic acid.

KDA was prepared by washing an excess of potassium with distilled hexane (3×3.00 mL). Distilled hexane (15.00 mL), TMEDA (3.36 mL, 22.4 mmol, 1.00 equiv) and diisopropylamine (3.15 mL, 22.4 mmol, 1.00 equiv) were added. Isoprene (1.13 mL, 11.2 mmol, 0.5 equiv) was added at 0 °C. After stirring for 30 min at 0 °C, the suspension was allowed to warm to 25 °C over 2 h, stirring for another 4 h at 25 °C gave the KDA base (0.56 M, 56%) as a dark suspension.

Titration of KDA was done using a standardized solution of *n*BuOH (0.4 M) in distilled hexane. KDA (0.5 mL) was added to a flame dried flask equipped with a stir bar. To the black solution the standardized *n*BuOH titration solution was added dropwise under stirring at –20 °C. The endpoint of the titration was reached when the solution turned yellow (Figure 20).

Figure 20: Titration of KDA a) base before titration; b) titration mixture after reaching the endpoint.

[367] Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312.
[368] S. Asako, M. Kodera, H. Nakajima, K. Takai, *Adv. Synth. Catal.* **2019**, *361*, 3120.

1.3 Typical Procedure 1 (TP1): Preparation and Activation of the Sodium-Packed-Bed Reactor

A 50 ml round bottom flask was charged with an oval shaped stirring bar (length: 2.5 cm; width: 1.2 cm) and sodium dispersion (30 wt% in toluene, particle size <0.1 mm, 10 mL). The sodium dispersion was stirred for 4 h at 300 to 400 rpm (Figure 21). An ovendried Omnifit® Labware glass column (length: 25 cm; inner diameter: 6.6 mm, figure 22) was closed at one side with a nonadjustable PTFE endpiece. The column was charged with the previously stirred sodium dispersion (particle size ca. 1 mm) using a 10 mL syringe without a cannula until the sodium metal reached a height of 10 cm (≙ 3.4 mL of sodium, Figure 23). The adjustable PTFE endpiece was used to close the column and was adjusted to give the maximum height of 22 cm (≙ V_{R1} = 7.5 mL). The packed-bed reactor was then installed in the flow setup, attaching the ETFE nut of the inlet to the tubing (V_{pre1} = 0.60 mL) connected to the pump and the nut of the outlet to the precooling loop (V_{pre2} = 0.35 mL) connected to the T-shaped mixer. The packed-bed reactor was placed upright (the inlet of the reactor facing downwards, Figure 24) in an *i*-PrOH bath to maintain a temperature of 25 °C. After washing with *n*-hexane (runtime: 10 min; flow rate: 2.0 mL/min), the sodium was activated by pumping a solution of *i*-PrOH (0.1 M in *n*-hexane; runtime: 2 min; flow rate: 5.0 mL/min) through the packed-bed reactor. A solution of 3-(chloromethyl)heptane (**115**, 0.2 M in *n*-hexane; flow rate: 2.0 mL/min) was pumped through the column. After 15 min, an aliquot was taken and analyzed by GC to monitor full conversion of the 3-(chloromethyl)heptane (**115**) to the corresponding organosodium derivative and steady state.

Figure 21: Packed-bed reactor filled with sodium particles of appropriate size.

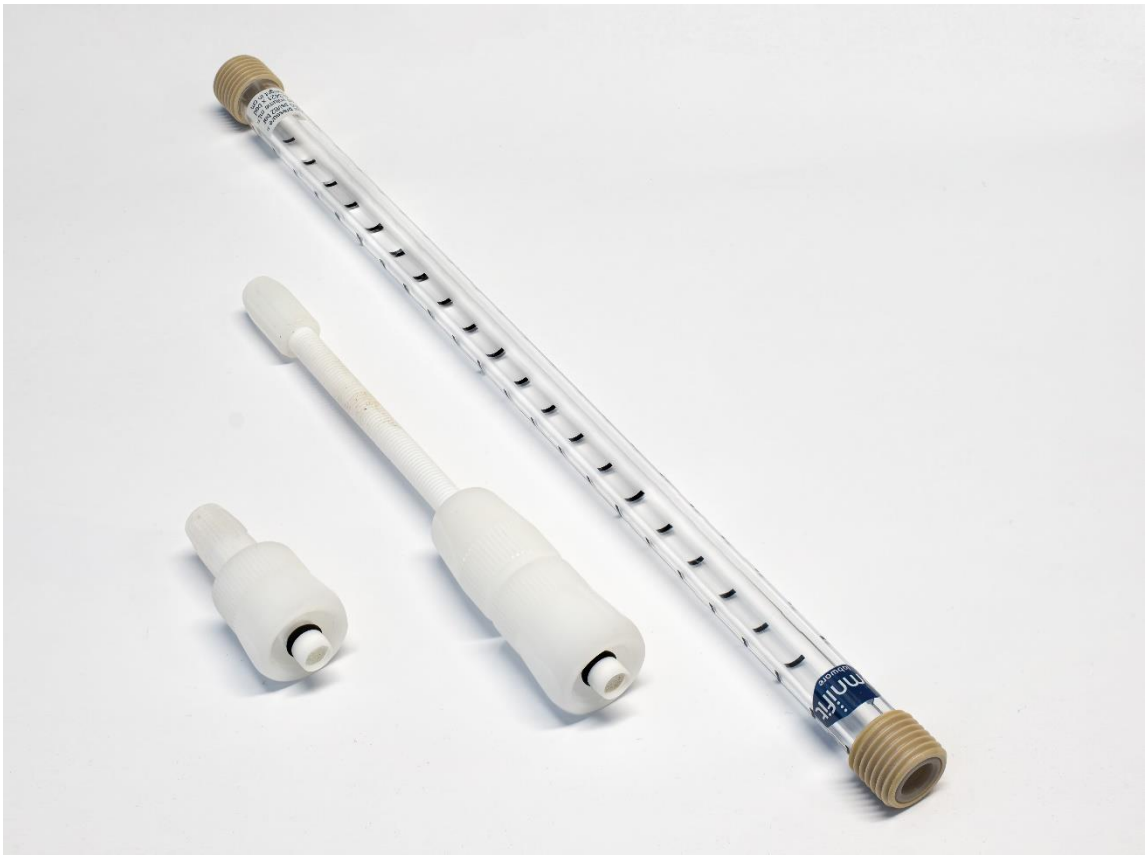


Figure 22: From left to right: nonadjustable PTFE endpiece with ETFE nut; adjustable PTFE endpiece with ETFE nut; Omnifit® Labware glass column.

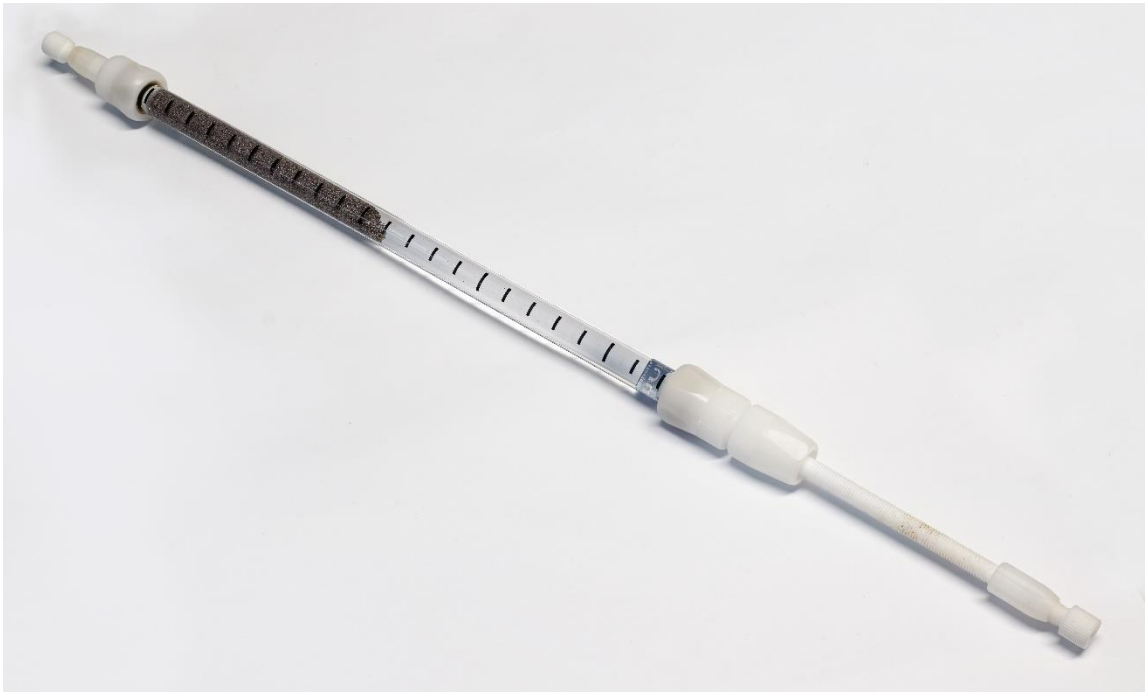


Figure 23: Closed packed-bed reactor filled with sodium particles. Adjustable endpiece set to give the maximum volume of V_{R1} = 7.5 mL.

Figure 24: Packed-bed sodium reactor in an *i*-PrOH bath connected *via* a nonadjustable endpiece (bottom) to the tubing (V_{pre1}) attached to the pump. Adjustable endpiece (top) connected to the tubing (V_{pre2}) attached to the T-shaped mixer.

1.3 Chromatography

Flash column chromatography was performed using SiO_2 60 (0.040-0.063 mm, 230-400 mesh ASTM) from Merck. Thin layer chromatography (TLC) was performed using aluminum plates covered with SiO_2 (Merck 60, F-254). Spots were visualized under UV light.

1.4 Analytical Data

Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. NMR spectra were recorded on Bruker ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δH: 7.26; δC: 77.16). For the observation of the observed signal multiplicities, the following abbreviations were used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet) and m (multiplet). Melting points are uncorrected and were measured on a Büchi B.540 apparatus. Infrared spectra were recorded from 4000-400 cm^{-1} on a Nicolet 510 FT-IR or a Perkin-Elmer 281 IR spectrometer. Absorption bands are reported in wavenumbers (cm^{-1}). Gas chromatography (GC) was performed with instruments of the type Hewlett-Packard 6890

or 5890 Series II, using a column of the type HP 5 (Hewlett-Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm, film thickness: 0.25 µm). The detection was accomplished using a flame ionization detector. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a Finnigan MAT95Q or Finnigan MAT90 instrument for electron impact ionization (EI) and electrospray ionization (ESI). For the combination of gas chromatography with mass spectroscopic detection, a GC-MS of the type Hewlett-Packard 6890 / MSD 5793 networking was used (column: HP 5-MS, Hewlett-Packard; 5% phenylmethylpolysiloxane; length: 15 m, diameter 0.25 mm; film thickness: 0.25 µm). Optical rotation values were recorded in a Perkin Elmer 241 or anton Paar MCP 200 polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

Thereby, the wavelength λ is reported in nm and the measuring temperature ϕ in °C. α represents the recorded optical rotation, c the concentration of the analyte in 10 mg/mL and d the length of the cuvette in dm. Thus, the specific rotation is given in $10^{-1}\cdot deg\cdot cm^2\cdot g^{-1}$.Usage of the sodium D line (λ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the experimental section.

1.5 Single Crystal X-ray Diffraction Studies

Single crystals of crystaline compounds, suitable for X-ray diffraction, were obtained by slow evaporation of solvents from the solutions. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-Kα radiation (λ = 0.71071 Å). Data collection and data reduction were performed with the CrysAlisPro software.[369] Absorption correction using the multiscan method) was applied. Alternativly, the X-ray intensity data were measured on a 'D8 Venture' system equipped with a 'Bruker D8 Venture TXS' 'rotating-anode X-ray tube' ('Mo Kα', λ = 0.71073 Å) and a 'multilayer mirror optics' monochromator. Data collection[370], data reduction[371] and cell refinement[372] were performed with the Bruker specific software. Absorption correction using the

[369] Program package CrysAlisPro 1.171.38.46 (Rigaku OD, 2015).
[370] Program package 'Bruker Instrument Service v3.0.21'.
[371] Program package ‘SAINT V8.18C (Bruker AXS Inc., 2011)’.
[372] Program package ‘APEX2 v2012.4-3 (Bruker AXS)’.

multiscan method was applied. The structures were solved with SHELXS-97,[373] refined with SHELXL-97[374] and finally checked using PLATON.[375]

[373] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany
[374] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany
[375] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands

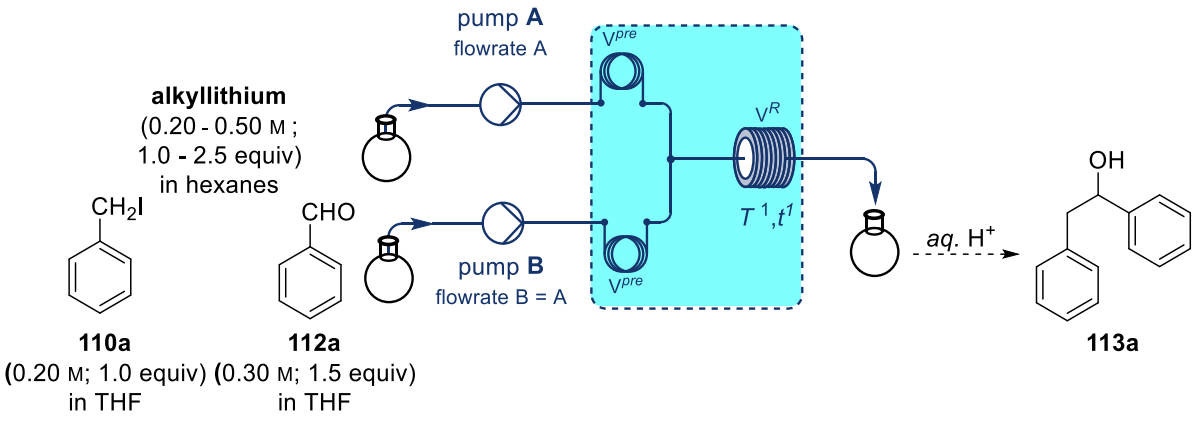
2. Continuous Flow Preparation of (Hetero)Benzylic Lithiums via Iodine-Lithium Exchange Reaction under Barbier Conditions

General remarks on flow and subsequent batch quenching reactions

Tetradecane (nC$_{14}$H$_{30}$) was used as internal standard. All flasks were heat gun dried (650 °C) under vacuum and backfilled with argon after cooling. Syringes, which were used to transfer reagents and solvents, were purged with argon three times prior to use. Batch quenching reactions were carried out with magnetic stirring. Flow reactions were performed on the commercially available flow system (Vapourtec E-series Integrated Flow Chemistry System with 3rd Pump Kit). Hexane solutions of *t*BuLi and THF solutions of the corresponding reagents were kept in flasks with rubber septa under an argon atmosphere during the reactions. All reactions were performed in coiled tube reactors. Coiled reactors were made from PFA or PTFE Teflon (I.D. = 0.8 mm or 0.25 mm, O.D. = 1.6 mm) tubing and T-pieces (I.D. = 0.5 mm) were used as mixers. Prior to performing reactions, the systems were dried by flushing with dry THF or hexane (flow rate of all pumps: 1.00 mL/min; run-time: 30 min).

2.1 Reaction Screenings

2.1.1 Screening of reaction conditions:



Scheme 89: General scheme for the optimization screening of **113a**.

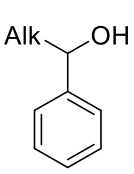
All reactions were conducted with the same starting material solution. This results in a direct comparability of the values for the Wurtz-type product, conversion of starting material and desired product **113a**. The values for the addition of alkyllithium to the aldehyde **112a** as well as the substitution product of alkyllithium at the benzyl iodide are not directly comparable.

Table 14: Optimization screening of product **113a.**

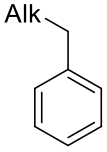
entry	base [equiv]	t [s]	$V_{reactor}$ [mL]	flow rate [mL/min]	T [°C]	E+Alk[a]	SM+Alk[a]	Wurtz-type side product[a]	conv. [%]	GC-yield [%]
1	*n*BuLi (1.25)	150	5	2	0	2.66	0.35	0.14	67	50
2	*n*BuLi (1.25)	150	5	2	–20	2.86	0.30	0.15	70	53
3	*n*BuLi (1.25)	150	5	2	–40	2.81	0.26	0.16	73	57
4	*n*BuLi (1.25)	150	5	2	–78	3.53	0.16	0.32	76	73
5	*n*BuLi (1.25)	30	1	2	0	2.29	0.35	0.15	64	48
6	*n*BuLi (1.25)	30	1	2	–20	2.48	0.28	0.13	66	49
7	*n*BuLi (1.25)	30	1	2	–40	2.61	0.25	0.13	68	53
8	*n*BuLi (1.25)	30	1	2	–78	3.16	0.14	0.20	71	59
9	*n*BuLi (1.25)	2.5	0.02	2	0	3.62	0.22	0.15	73	61
10	*n*BuLi (1.25)	2.5	0.02	2	–20	3.61	0.22	0.15	72	62
11	*n*BuLi (1.25)	2.5	0.02	2	–40	4.06	0.21	0.15	73	61
12	*n*BuLi (1.25)	2.5	0.02	2	–78	3.70	0.19	0.14	70	64
13	*n*BuLi (1.25)	30	5	10	0	3.83	0.21	0.16	78	62
14	*n*BuLi (1.25)	30	5	10	–20	3.91	0.19	0.16	81	66
15	*n*BuLi (1.25)	30	5	10	–40	4.12	0.14	0.25	83	75
16	*n*BuLi (1.25)	30	5	10	–78	4.06	0.05	0.33	87	78
17	*n*BuLi (1.25)	6	1	10	0	4.25	0.20	0.15	77	66
18	*n*BuLi (1.25)	6	1	10	–20	4.33	0.16	0.15	78	74
19	*n*BuLi (1.25)	6	1	10	–40	4.09	0.11	0.19	81	76
20	*n*BuLi (1.25)	6	1	10	–78	4.08	0.06	0.29	86	78
21	*n*BuLi (1.25)	0.1	0.02	10	0	4.33	0.17	0.14	75	70
22	*n*BuLi (1.25)	0.1	0.02	10	–20	4.30	0.16	0.15	77	70
23	*n*BuLi (1.25)	0.1	0.02	10	–40	4.26	0.12	0.15	77	71
24	*n*BuLi (1.25)	0.1	0.02	10	–78	4.01	0.10	0.16	79	68
25	*t*BuLi (2.5)	150	5	2	0	2.63	1.25	0.39	94	62
26	*t*BuLi (2.5)	150	5	2	–20	3.07	1.26	0.38	95	73
27	*t*BuLi (2.5)	150	5	2	–40	3.14	1.18	0.32	94	80
28	*t*BuLi (2.5)	150	5	2	–78	3.02	1.11	0.34	94	86
29	*t*BuLi (2.5)	30	1	2	0	2.81	1.36	0.43	89	74
30	*t*BuLi (2.5)	30	1	2	–20	2.93	1.25	0.36	92	75
31	*t*BuLi (2.5)	30	1	2	–40	3.48	1.33	0.35	92	82
32	*t*BuLi (2.5)	30	1	2	–78	3.33	1.15	0.27	90	83

entry	base [equiv]	t [s]	$V_{reactor}$ [mL]	flow rate [mL/min]	T [°C]	E+Alk[a]	SM+Alk[a]	Wurtz-type side product[a]	conv. [%]	GC-yield [%]
33	*t*BuLi (2.5)	2.5	0.02	2	0	3.62	1.31	0.28	92	76
34	*t*BuLi (2.5)	2.5	0.02	2	–20	3.60	1.29	0.28	91	75
35	*t*BuLi (2.5)	2.5	0.02	2	–40	3.64	1.30	0.30	93	77
36	*t*BuLi (2.5)	2.5	0.02	2	–78	4.01	1.37	0.28	90	84
37	*t*BuLi (2.5)	30	5	10	0	3.61	1.28	0.38	95	77
38	*t*BuLi (2.5)	30	5	10	–20	3.47	1.25	0.35	93	75
39	*t*BuLi (2.5)	30	5	10	–40	3.35	1.11	0.25	96	80
40	*t*BuLi (2.5)	30	5	10	–78	3.64	1.05	0.35	97	97
41	*t*BuLi (2.5)	6	1	10	0	3.29	1.24	0.36	93	75
42	*t*BuLi (2.5)	6	1	10	–20	3.58	1.26	0.37	95	72
43	*t*BuLi (2.5)	6	1	10	–40	3.68	1.26	0.34	95	82
44	*t*BuLi (2.5)	6	1	10	–78	3.59	1.27	0.35	95	80
45	*t*BuLi (2.5)	0.1	0.02	10	0	3.70	1.29	0.32	94	81
46	*t*BuLi (2.5)	0.1	0.02	10	–20	3.65	1.27	0.32	94	81
47	*t*BuLi (2.5)	0.1	0.02	10	–40	4.13	1.29	0.36	96	87
48	***t*BuLi (2.5)**	0.1	**0.02**	**10**	**–78**	**4.03**	**1.22**	**0.34**	**94**	**87**
49	*t*BuLi (2.5)[b]	0.1	0.02	10	–78	0.27	0.20	1.65	100	13
50	*t*BuLi (2.5)[c]	0.1	0.02	10	–78	0.00	0.11	1.78	100	10
51	*s*BuLi (1.1)	0.1	0.02	10	–78				75	59
52	*n*HexLi (1.1)	0.1	0.02	10	–78				68	57
53	neopentyl Li (1.1)	0.1	0.02	10	–78				83	62

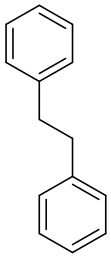
[a] The values were calculated according to $x = \frac{\text{GC value}}{\text{Standard value}}$. [b] TMEDA (2.5 equiv) was added to the *t*BuLi solution. [c] PMDTA (2.5 equiv) was added to the *t*BuLi solution.



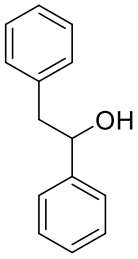
alkyllithium addition to electrophile (E+Alk)



alkyllithium substitution of iodide (SM+Alk)

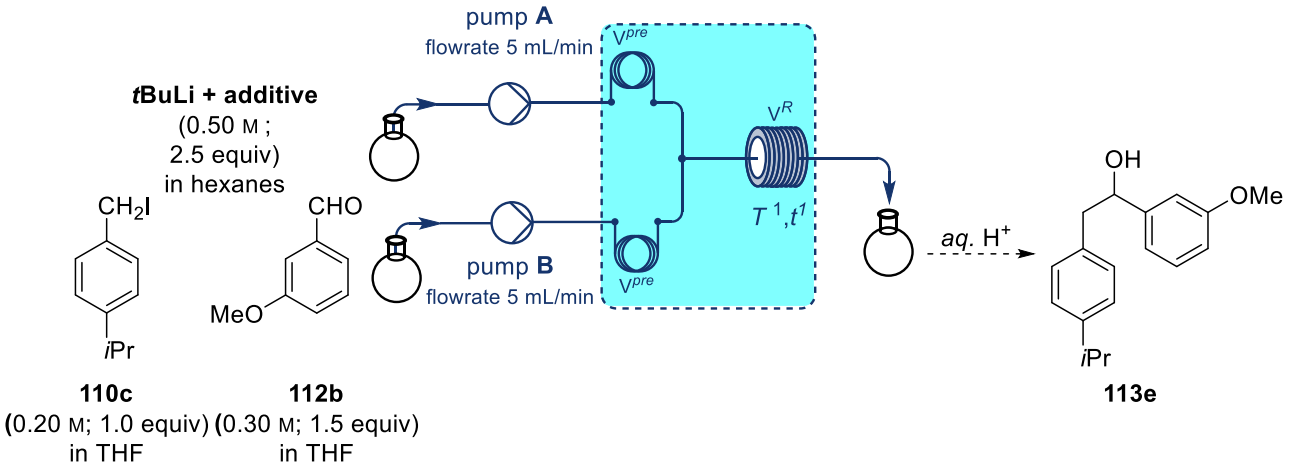


Wurtz-type side product



product (**113a**)

2.1.2 Screening of different additives:

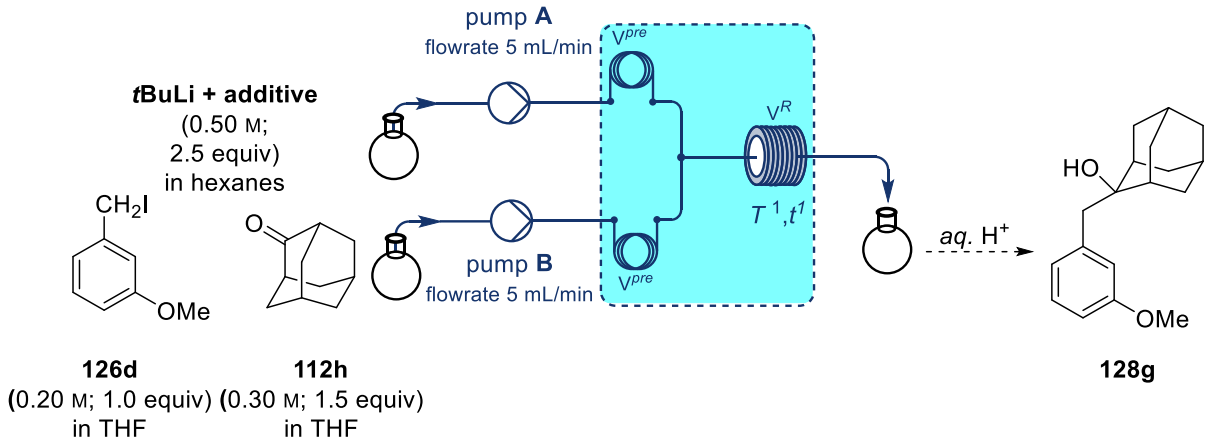


Scheme 90: General scheme for the additive screening of Barbier-type reaction of **110c** and **112b** affording product **113e**.

Table 15: Additive screening of Barbier-type reaction of **110c** and **112b** affording product **113e**.

entry	base [equiv]	additive	t [s]	T [°C]	E+Alk[a]	SM+Alk[a]	Wurtz-type side product[a]	conv. [%]	GC-yield [%]
1	*t*BuLi (2.5)	TMEDA	0.1	–20	0.57	0.09	3.74	100	4
2	*t*BuLi (2.5)	TMEDA	0.1	–40	0.69	0.10	3.68	100	4
3	*t*BuLi (2.5)	TMEDA	0.1	–78	0.57	0.09	3.74	100	4
4	*t*BuLi (2.5)	PMDTA	0.1	–20	0.15	0.01	3.93	100	2
5	*t*BuLi (2.5)	PMDTA	0.1	–40	0.13	0.01	4.15	100	3
6	*t*BuLi (2.5)	PMDTA	0.1	–78	0.13	0.00	4.39	100	3
7	*t*BuLi (2.5)	-	0.1	–78	0.74	1.91	0.71	100	71

[a] The values were calculated according to $x = \frac{\text{GC value}}{\text{Standard value}}$.



Scheme 91: General scheme for the additive screening of Barbier-type reaction of **126d** and **112h** affording product **128g**.

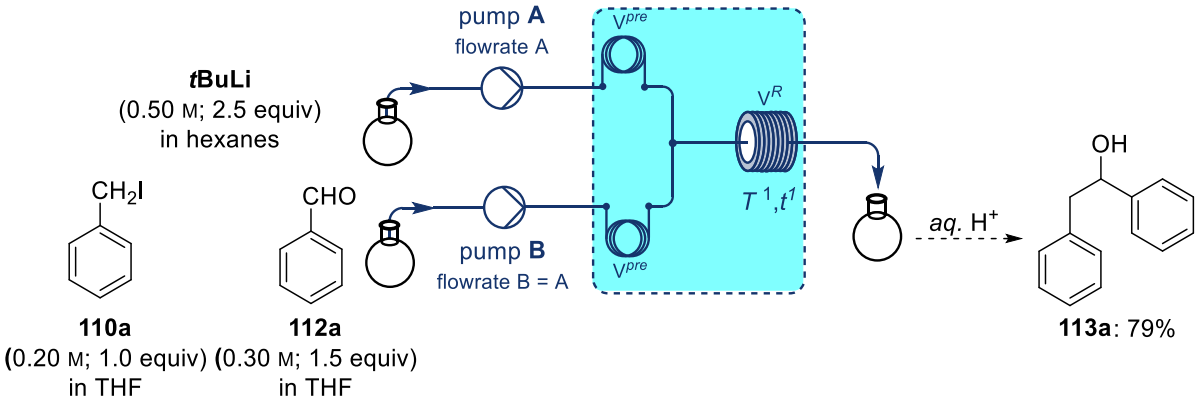
Table 16: Additive screening of Barbier-type reaction of **126d** and **112h** affording product **128g**.

entry	base [equiv]	additive	t [s]	T [°C]	E+Alk[a]	SM+Alk[a]	Wurtz-type side product[a]	conv. [%]	GC-yield [%]
1	*t*BuLi (2.5)	TMEDA	0.1	–20	0.10	0.07	2.46	100	12
2	*t*BuLi (2.5)	TMEDA	0.1	–40	0.12	0.07	2.71	100	13
3	*t*BuLi (2.5)	TMEDA	0.1	–78	0.14	0.07	2.72	100	11
4	*t*BuLi (2.5)	PMDTA	0.1	–20	0.03	0.01	2.33	100	5
5	*t*BuLi (2.5)	PMDTA	0.1	–40	0.04	0.00	2.32	99	5
6	*t*BuLi (2.5)	PMDTA	0.1	–78	0.03	0.00	2.22	98	5
7	*t*BuLi (2.5)	-	0.1	–78	0.09	1.28	0.98	96	85

[a] The values were calculated according to $x = \frac{\text{GC value}}{\text{Standard value}}$.

2.2 Typical Procedures

Typical procedure 1 (TP2) using a Vapourtec E-series Integrated Flow Chemistry System (Scheme 92): Preparation of 1,2-Diphenylethan-1-ol (113a)

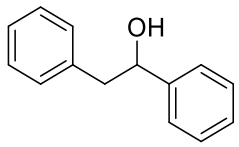


Scheme 92: Vapourtec E-series Integrated Flow Chemistry System for the iodine-lithium exchange of (hetero)benzylic substrates with *t*BuLi in the presence of various carbonyl compounds.

A solution of benzyl iodide (**110a**, 0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113a** as a white amorphous solid (31 mg, 0.16 mmol, 79% yield).

2.3 Preparation of Products

1,2-Diphenylethan-1-ol (113a)



According to the **TP2**, a solution of benzyl iodide (**110a**, 0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113a** as a white amorphous solid (31 mg, 0.16 mmol, 79% yield).

In addition, a convenient scale-up of the reaction according to **TP2** was demonstrated. A solution of benzyl iodide (**110a**, 0.20 M, 4.00 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 6.00 mmol, 1.5 equiv) in THF (total volume: 20.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 10.0 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×100 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113a** as a white amorphous solid (619 mg, 3.12 mmol, 78% yield).

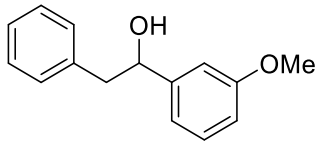
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 – 7.15 (m, 10H), 4.91 (dd, *J* = 8.5, 4.9 Hz, 1H), 3.13 – 2.88 (m, 2H), 1.97 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.9, 138.2, 129.6 (2C), 128.7 (2C), 128.6 (2C), 127.8, 126.8, 126.0 (2C), 75.5, 46.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3294, 3026, 2922, 2855, 1495, 1453, 1445, 1072, 1039, 1026, 1016, 952, 778, 760, 741, 696.

MS (EI, 70 eV): *m/z* (%) = 107 (59), 92 (100), 91 (41), 79 (71), 77 (23).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{14}H_{12}$ 180.0939; Found 180.0930.

m.p. (°C): 63.9 – 66.4.

1-(3-Methoxyphenyl)-2-phenylethan-1-ol (113b)



According to the **TP2**, a solution of benzyl iodide (**110a**, 0.20 M, 0.20 mmol, 1.0 equiv) and *m*-anisaldehyde (**112b**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113b** as a colorless amorphous solid (28 mg, 0.13 mmol, 63% yield).

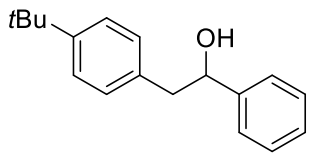
^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.29 (td, *J* = 7.1, 1.0 Hz, 2H), 7.25 – 7.21 (m, 2H), 7.21 – 7.18 (m, 2H), 6.94 – 6.89 (m, 2H), 6.83 – 6.79 (m, 1H), 4.87 (dd, *J* = 8.6, 4.7 Hz, 1H), 3.79 (d, *J* = 0.8 Hz, 3H), 3.06 – 2.93 (m, 2H), 1.96 (s, 1H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 159.8, 145.7, 138.1, 129.7 (2C), 129.6, 128.7 (2C), 126.8, 118.3, 113.3, 111.4, 75.4, 55.4, 46.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3294, 3026, 2922, 2855, 1495, 1453, 1445, 1316, 1072, 1039, 1026, 1016, 952, 917, 778, 760, 741, 696.

MS (EI, 70 eV): *m/z* (%) = 137 (16), 136 (16), 109 (12), 71 (26), 70 (10), 71 (17), 57 (30), 56 (19), 45 (14), 43 (100), 42 (37), 41 (27).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{15}H_{16}O_2$ 228.1150; Found 228.1126.

m.p. (°C): 72.4 – 74.8.

2-(4-(*Tert*-butyl)phenyl)-1-phenylethan-1-ol (113c)



According to the **TP2**, a solution of 1-(*tert*-butyl)-4-(iodomethyl)benzene (**110b**, 0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113c** as a white amorphous solid (33 mg, 0.13 mmol, 65% yield).

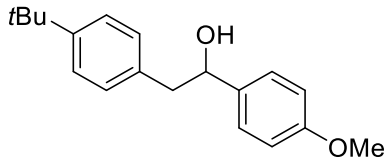
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.43 – 7.38 (m, 3H), 7.38 – 7.34 (m, 3H), 7.33 – 7.27 (m, 1H), 7.21 – 7.15 (m, 2H), 4.90 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.10 – 2.87 (m, 2H), 1.92 (s, 1H), 1.33 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 149.7, 144.1, 135.2, 129.3 (2C), 128.6 (2C), 127.7, 126.0 (2C), 125.7 (2C), 75.4, 45.8, 34.6, 31.5 (3C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3560, 2951, 1509, 1493, 1453, 1360, 1269, 1049, 1028, 910, 817, 755, 731, 699.

MS (EI, 70 eV): *m/z* (%) = 148 (24), 134 (11), 133 (100), 117 (12), 107 (14), 105 (11), 79 (19).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{18}H_{20}$ 236.1565; Found 236.1557.

m.p. (°C): 58.0 – 60.9.

2-(4-(*Tert*-butyl)phenyl)-1-(4-methoxyphenyl)ethan-1-ol (113d)



According to the **TP2**, a solution of 1-(*tert*-butyl)-4-(iodomethyl)benzene (**110b**, 0.20 M, 0.20 mmol, 1.0 equiv) and *p*-anisaldehyde (**112c**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification

(silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113d** as a white amorphous solid (32 mg, 0.11 mmol, 56% yield).

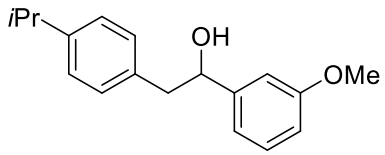
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.30 (m, 4H), 7.20 – 7.14 (m, 2H), 6.93 – 6.87 (m, 2H), 4.85 (ddd, *J* = 8.8, 4.5, 2.2 Hz, 1H), 3.82 (s, 3H), 3.05 – 2.88 (m, 2H), 1.93 (d, *J* = 2.6 Hz, 1H), 1.32 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.2, 149.6, 136.3, 135.3, 129.2 (2C), 127.3 (2C), 125.6 (2C), 113.9 (2C), 75.0, 55.4, 45.7, 34.6, 31.5 (3C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3557, 2952, 1608, 1509, 1249, 1178, 1106, 1047, 1028, 878, 829, 814.

MS (EI, 70 eV): *m/z* (%) = 266 (11), 251 (13), 148 (11), 137 (52), 88 (16), 73 (13), 70 (16), 61 (20), 45 (13), 43 (100).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{19}H_{24}O_2$ 284.1776; Found 284.1751.

m.p. (°C): 66.2 – 67.6.

2-(4-Isopropylphenyl)-1-(3-methoxyphenyl)ethan-1-ol (113e)



According to the **TP2**, a solution of 1-(iodomethyl)-4-isopropylbenzene (**110c**, 0.20 M, 0.20 mmol, 1.0 equiv) and *m*-anisaldehyde (**112b**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -20 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113e** as a colorless oil (30 mg, 0.14 mmol, 71% yield).

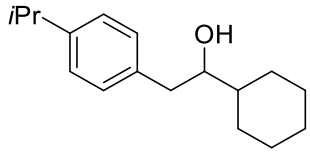
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.21 (m, 1H), 7.18 – 7.10 (m, 4H), 6.96 – 6.91 (m, 1H), 6.90 (t, *J* = 2.1 Hz, 1H), 6.80 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.83 (dd, *J* = 9.1, 4.3 Hz, 1H), 3.77 (s, 3H), 3.02 – 2.82 (m, 3H), 1.95 (d, *J* = 2.5 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.8, 147.4, 145.8, 135.4, 129.6, 129.5 (2C), 126.8 (2C), 118.3, 113.3, 111.3, 75.4, 55.4, 45.9, 33.9, 24.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3421, 2958, 2870, 2835, 1601, 1586, 1513, 1488, 1463, 1456, 1434, 1383, 1362, 1339, 1318, 1257, 1190, 1149, 1040, 1020, 997, 876, 864, 842, 815, 783, 763, 727, 695.

MS (EI, 70 eV): *m/z* (%) = 137 (25), 134 (72), 120 (10), 119 (100), 117 (12), 109 (58), 94 (18), 91 (12).

HRMS (EI-orbitrap): *m/z:* $[M - OH]^+$ calcd for $C_{18}H_{21}O^+$ 253.1587; Found 253.1589.

1-Cyclohexyl-2-(4-isopropylphenyl)ethan-1-ol (113f)



According to the **TP2**, a solution of 1-(iodomethyl)-4-isopropylbenzene (**110c**, 0.20 M, 0.20 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (**112d**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, 25 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113f** as a white amorphous solid (38 mg, 0.15 mmol, 76% yield).

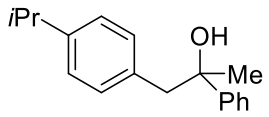
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.21 – 7.11 (m, 4H), 3.56 (ddt, *J* = 9.0, 5.7, 3.0 Hz, 1H), 2.94 – 2.81 (m, 2H), 2.56 (dd, *J* = 13.7, 9.7 Hz, 1H), 1.92 (dtt, *J* = 12.6, 3.3, 1.7 Hz, 1H), 1.84 – 1.73 (m, 3H), 1.73 – 1.64 (m, 1H), 1.50 – 1.38 (m, 2H), 1.34 – 1.03 (m, 11H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.1, 136.5, 129.4 (2C), 126.8 (2C), 77.1, 43.3, 40.5, 33.9, 29.4, 28.2, 26.7, 26.5, 26.3, 24.2, 24.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3314, 2957, 2928, 2919, 2891, 2844, 1514, 1445, 1418, 1335, 1293, 1105, 1084, 1057, 1030, 1005, 891, 866, 847, 838, 812.

MS (EI, 70 eV): *m/z* (%) = 134 (64), 119 (60), 95 (19), 91 (11), 88 (14), 73 (11), 70 (15), 61 (26), 39 (13).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{17}H_{26}O$ 246.1984; Found 246.1976.

m.p. (°C): 54.6 – 55.9.

1-(4-Isopropylphenyl)-2-phenylpropan-2-ol (113g)



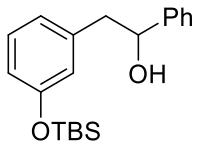
According to the **TP2**, a solution of 1-(iodomethyl)-4-isopropylbenzene (**110c**, 0.20 M, 0.20 mmol, 1.0 equiv) and acetophenone (**112e**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -20 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **113g** as a colorless oil (27 mg, 0.14 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 – 7.40 (m, 2H), 7.37 – 7.31 (m, 2H), 7.26 – 7.23 (m, 1H), 7.12 – 7.06 (m, 2H), 6.96 – 6.92 (m, 2H), 3.14 – 2.95 (m, 2H), 2.86 (p, *J* = 6.9 Hz, 1H), 1.87 (s, 1H), 1.56 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.9, 147.4, 134.0, 130.7 (2C), 128.2 (2C), 126.7, 126.4 (2C), 125.1 (2C), 74.5, 50.1, 33.8, 29.6, 24.1, 24.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3448, 3057, 3025, 2960, 2870, 1514, 1494, 1456, 1446, 1420, 1373, 1363, 1284, 1263, 1218, 1177, 1142, 1100, 1065, 1050, 1028, 1021, 940, 910, 866, 843, 811, 764, 747, 721, 698.

MS (EI, 70 eV): *m/z* (%) = 134 (61), 121 (80), 119 (100), 117 (24), 115 (14), 91 (20), 43 (39).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{18}H_{22}O$ 236.1565; Found 236.1559.

2-(3-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-phenylethan-1-ol (128a)



According to the **TP2**, a solution of *tert*-butyl(3-(iodomethyl)phenoxy)dimethylsilane (**126a**, 0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed

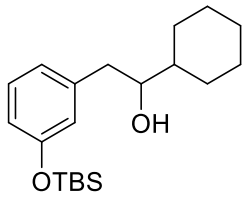
a 0.02 mL reactor tube (0.1 s, -40 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **128a** as a colorless oil (27 mg, 0.10 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26 – 7.23 (m, 3H), 7.21 – 7.17 (m, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.70 (dt, *J* = 7.6, 1.3 Hz, 1H), 6.62 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1H), 6.57 (t, *J* = 2.1 Hz, 1H), 4.78 (dd, *J* = 8.3, 5.1 Hz, 1H), 2.99 – 2.69 (m, 2H), 1.17 – 1.14 (m, 1H), 0.88 (s, 9H), 0.07 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.9, 143.8, 139.6, 129.6, 128.5 (2C), 127.7, 126.0 (2C), 122.6, 121.4, 118.5, 75.4, 46.1, 25.8 (3C), 18.3, -4.3 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031, 2955, 2929, 2857, 1602, 1584, 1485, 1472, 1463, 1442, 1390, 1362, 1272, 1252, 1158, 1043, 1028, 1004, 977, 939, 887, 872, 837, 779, 755, 696, 665.

MS (EI, 70 eV): *m/z* (%) = 310 (20), 269 (12), 253 (66), 222 (100), 178 (10), 165 (54), 149 (10), 107 (13), 75 (10).

HRMS (EI-orbitrap): *m/z:* $[M - OH]^+$ calcd for $C_{20}H_{27}OSi^+$ 311.1826; Found 311.1829.

2-(3-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-cyclohexylethan-1-ol (128b)



According to the **TP2**, a solution of *tert*-butyl(3-(iodomethyl)phenoxy)dimethylsilane (**126a**, 0.20 M, 0.20 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (**112d**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **128b** as a colorless oil (35 mg, 0.12 mmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.19 – 7.13 (m, 1H), 6.81 (dt, *J* = 7.6, 1.4 Hz, 1H), 6.71 (ddt, *J* = 6.8, 3.2, 1.7 Hz, 2H), 3.55 (ddd, *J* = 9.2, 5.5, 3.5 Hz, 1H), 2.83 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.54 (dd,

J = 13.5, 9.4 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.83 – 1.66 (m, 4H), 1.41 (dtt, *J* = 11.6, 6.1, 3.0 Hz, 1H), 1.31 – 1.11 (m, 6H), 0.98 (s, 9H), 0.19 (s, 6H).

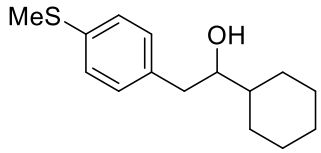
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.9, 140.8, 129.6, 122.5, 121.3, 118.2, 77.0, 43.2, 40.9, 29.5, 28.1, 26.7, 26.5, 26.3, 25.8 (3C), 18.3, -4.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2854, 1602, 1584, 1485, 1472, 1463, 1444, 1390, 1362, 1306, 1276, 1252, 1158, 1099, 1085, 1034, 1004, 978, 955, 891, 837, 779, 717, 696, 665.

MS (EI, 70 eV): *m/z* (%) = 223 (12), 222 (100), 183 (24), 181 (99), 177 (14), 166 (10), 165 (57), 164 (10), 163 (14), 149 (13), 75 (11).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{20}H_{34}O_2Si$ 334.2328; Found 334.2320.

1-Cyclohexyl-2-(4-(methylthio)phenyl)ethan-1-ol (128c)



According to the **TP2**, a solution of (4-(iodomethyl)phenyl)(methyl)sulfane (**126b**, 0.20 M, 0.20 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (**112d**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -30 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **128c** as a slightly yellow oil (34 mg, 0.14 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.24 – 7.19 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 3.54 (s, 1H), 2.83 (dd, *J* = 13.7, 3.4 Hz, 1H), 2.56 (dd, *J* = 13.7, 9.4 Hz, 1H), 2.47 (s, 3H), 1.90 (d, *J* = 12.5 Hz, 1H), 1.83 – 1.63 (m, 4H), 1.48 – 1.33 (m, 2H), 1.33 – 1.00 (m, 5H).

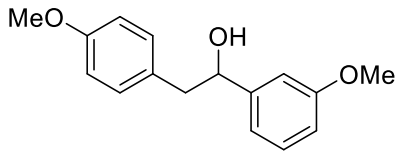
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 136.3, 136.2, 130.0 (2C), 127.2 (2C), 77.0, 43.3, 40.3, 29.5, 28.1, 26.7, 26.4, 26.7, 16.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3331, 3259, 2930, 2917, 2882, 2848, 1492, 1446, 1435, 1424, 1404, 1108, 1098, 1083, 1059, 1038, 1018, 1010, 972, 956, 890, 844, 835, 802, 662.

MS (EI, 70 eV): *m/z* (%) = 138 (100), 137 (28), 123 (99), 122 (11), 91 (30).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{15}H_{22}OS$ 250.1391; Found 250.1383.

1-(3-Methoxyphenyl)-2-(4-methoxyphenyl)ethan-1-ol (128d)



According to the **TP2**, a solution of 1-(iodomethyl)-4-methoxybenzene (**126c**, 0.20 M, 0.20 mmol, 1.0 equiv) and *m*-anisaldehyde (**112b**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -20 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **128d** as a colorless oil (35 mg, 0.13 mmol, 67% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.24 (m, 1H), 7.19 – 7.10 (m, 2H), 6.98 – 6.91 (m, 2H), 6.91 – 6.81 (m, 3H), 4.85 (ddd, *J* = 8.7, 4.6, 2.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.06 – 2.87 (m, 2H), 1.98 (d, *J* = 2.7 Hz, 1H).

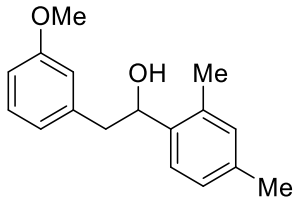
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.8, 158.5, 145.7, 130.6 (2C), 130.0, 129.5, 118.4, 114.1 (2C), 113.3, 111.4, 75.5, 55.4, 55.4, 45.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3422, 3000, 2935, 2835, 1610, 1602, 1585, 1511, 1488, 1464, 1455, 1435, 1318, 1300, 1285, 1242, 1177, 1149, 1108, 1033, 876, 863, 846, 817, 784, 773, 730, 715, 697.

MS (EI, 70 eV): *m/z* (%) = 122 (100), 121 (45), 109 (25), 94 (10).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{16}H_{16}O_2$ 240.1150; Found 240.1144.

1-(2,4-Dimethylphenyl)-2-(3-methoxyphenyl)ethan-1-ol (128e)



According to the **TP2**, a solution of 1-(iodomethyl)-3-methoxybenzene (**126d**, 0.20 M, 0.20 mmol, 1.0 equiv) and 2,4-dimethylbenzaldehyde (**112f**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume:

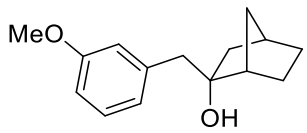
1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -30 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **128e** as a slightly yellow oil (27 mg, 0.11 mmol, 53% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.49 (d, *J* = 7.9 Hz, 1H), 7.28 (s, 1H), 7.15 – 7.07 (m, 1H), 7.04 – 6.98 (m, 1H), 6.91 – 6.78 (m, 3H), 5.13 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.82 (s, 3H), 3.07 – 2.84 (m, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 1.92 (d, *J* = 2.2 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.8, 140.2, 139.2, 137.0, 134.4, 131.2, 129.7, 127.1, 125.3, 121.9, 115.2, 112.1, 71.7, 55.3, 45.2, 21.1, 19.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3414, 2921, 2835, 1602, 1584, 1488, 1465, 1453, 1436, 1378, 1313, 1296, 1256, 1191, 1166, 1152, 1040, 996, 954, 873, 856, 822, 775, 750, 743, 718, 694.

MS (EI, 70 eV): *m/z* (%) = 135 (88), 123 (10), 122 (100), 121 (13), 107 (70), 105 (22), 91 (57), 79 (12), 78 (11), 77 (15), 65 (11).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{17}H_{18}O$ 238.1358; Found 238.1351.

2-(3-Methoxybenzyl)bicyclo[2.2.1]heptan-2-ol (128f)



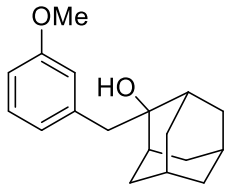
According to the **TP2**, a solution of 1-(iodomethyl)-3-methoxybenzene (**126d**, 0.20 M, 0.20 mmol, 1.0 equiv) and norcamphor (**112g**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -30 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **128f** as a colorless oil (27 mg, 0.12 mmol, 59% yield, *d.r.* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.27 – 7.20 (m, 1H), 6.87 – 6.78 (m, 3H), 3.81 (s, 3H), 2.89 – 2.71 (m, 2H), 2.29 – 2.22 (m, 1H), 2.19 – 2.11 (m, 1H), 1.94 – 1.82 (m, 1H), 1.73 (ddd, *J* = 12.9, 4.6, 2.9 Hz, 1H), 1.70 – 1.45 (m, 3H), 1.40 – 1.22 (m, 3H), 1.12 (dd, *J* = 12.9, 3.3 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.6, 139.4, 129.4, 123.1, 116.4, 111.9, 79.3, 55.3, 48.0, 45.9, 45.8, 38.7, 37.5, 28.8, 22.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3392, 2935, 2838, 1612, 1586, 1512, 1487, 1462, 1446, 1302, 1243, 1174, 1140, 1110, 1076, 1032, 1006, 960, 948, 870, 831, 811, 786, 772, 755, 740, 688.

MS (EI, 70 eV): *m/z* (%) = 122 (100), 121 (16), 111 (19), 93 (13), 91 (22).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{15}H_{20}O_2$ 232.1463; Found 232.1353.

2-(3-Methoxybenzyl)adamantan-2-ol (128g)



According to the **TP2**, a solution of 1-(iodomethyl)-3-methoxybenzene (**126d**, 0.20 M, 0.20 mmol, 1.0 equiv) and adamantanone (**112h**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **128g** as a white amorphous solid (46 mg, 0.17 mmol, 85% yield).

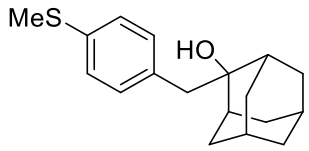
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.19 (m, 1H), 6.86 – 6.76 (m, 3H), 3.80 (s, 3H), 2.97 (s, 2H), 2.17 (dd, *J* = 12.6, 2.9 Hz, 2H), 2.14 – 2.04 (m, 2H), 1.92 (p, *J* = 3.0 Hz, 1H), 1.84 – 1.75 (m, 3H), 1.69 (dd, *J* = 8.3, 3.8 Hz, 4H), 1.57 – 1.48 (m, 2H), 1.45 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.6, 139.0, 129.3, 123.1, 116.4, 111.9, 74.7, 55.3, 44.0, 38.5, 37.0 (2C), 34.7 (2C), 33.1 (2C), 27.6, 27.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3510, 2962, 2942, 2930, 2899, 2853, 1742, 1600, 1590, 1489, 1471, 1462, 1432, 1374, 1260, 1228, 1168, 1123, 1101, 1084, 1061, 1035, 1010, 993, 929, 922, 791, 739, 716, 694.

MS (EI, 70 eV): *m/z* (%) = 255 (16), 254 (78), 151 (51), 122 (52), 121 (15), 91 (15), 88 (13), 73 (11), 70 (14), 61 (27), 45 (15), 43 (100).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{18}H_{22}O$ 254.1671; Found 254.1668.

m.p. (°C): 100.7 – 104.2.

2-(4-(Methylthio)benzyl)adamantan-2-ol (128h)



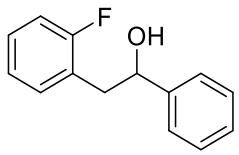
According to the **TP2**, a solution of (4-(iodomethyl)phenyl)(methyl)sulfane (**126b**, 0.20 M, 0.20 mmol, 1.0 equiv) and adamantanone (**112h**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -30 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **128h** as a slightly yellow oil (44 mg, 0.15 mmol, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.23 – 7.13 (m, 4H), 2.95 (s, 2H), 2.47 (s, 3H), 2.19 – 2.12 (m, 2H), 2.12 – 2.03 (m, 2H), 1.91 (p, *J* = 3.1 Hz, 1H), 1.83 – 1.74 (m, 3H), 1.68 (dt, *J* = 18.6, 3.3 Hz, 4H), 1.52 (dq, *J* = 12.6, 1.9 Hz, 2H), 1.36 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 136.4, 134.3, 131.2 (2C), 126.7 (2C), 74.8, 43.4, 38.5, 36.9 (2C), 34.7 (2C), 33.1 (2C), 27.6, 27.4, 16.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3422, 3393, 2943, 2937, 2911, 2904, 2893, 2849, 1495, 1452, 1439, 1402, 1354, 1351, 1287, 1208, 1200, 1196, 1160, 1122, 1096, 1068, 1056, 1042, 1019, 1005, 994, 964, 952, 925, 894, 848, 814, 804, 733, 661.

MS (EI, 70 eV): *m/z* (%) = 151 (48), 138 (100), 137 (10), 91 (16).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{18}H_{22}S$ 270.1442; Found 270.1435.

2-(2-Fluorophenyl)-1-phenylethan-1-ol (131a)



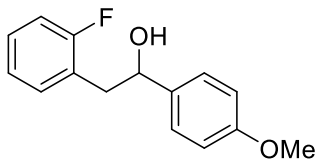
According to the **TP2**, a solution of 1-fluoro-2-(iodomethyl)benzene (**129a**, 0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **131a** as a colorless oil (30 mg, 0.14 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.29 – 7.25 (m, 3H), 7.24 – 7.13 (m, 3H), 6.90 – 6.79 (m, 3H), 4.81 (t, *J* = 6.7 Hz, 1H), 2.93 (d, *J* = 6.6 Hz, 2H), 1.87 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.0 (d, *J* = 245.7 Hz), 143.7, 140.7 (d, *J* = 7.3 Hz), 130.0 (d, *J* = 8.3 Hz), 128.7, 128.0 (2C), 126.0 (2C), 125.3 (d, *J* = 2.8 Hz), 116.5 (d, *J* = 21.0 Hz), 113.6 (d, *J* = 21.0 Hz), 75.3, 45.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3372, 1615, 1588, 1488, 1448, 1248, 1201, 1139, 1075, 1041, 1028, 1010, 960, 948, 913, 868, 778, 755, 738, 698, 690.

MS (EI, 70 eV): *m/z* (%) = 199 (12), 198 (60), 197 (45), 196 (29), 183 (21), 177 (12), 105 (47), 77 (19), 70 (14), 61 (24), 45 (16), 44 (42), 43 (100), 42 (10).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{14}H_{11}F$ 198.0845; Found 198.0803.

2-(2-Fluorophenyl)-1-(4-methoxyphenyl)ethan-1-ol (131b)



According to the **TP2**, a solution of 1-fluoro-2-(iodomethyl)benzene (**129a**, 0.20 M, 0.20 mmol, 1.0 equiv) and *p*-methoxybenzaldehyde (**112c**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled

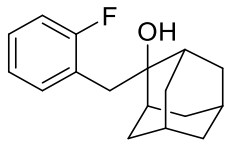
solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **131b** as a yellow oil (26 mg, 0.11 mmol, 53% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30 – 7.19 (m, 3H), 6.95 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.93 – 6.84 (m, 4H), 4.85 (dd, *J* = 7.7, 5.6 Hz, 1H), 3.81 (s, 3H), 3.07 – 2.92 (m, 2H), 1.92 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.8 (d, *J* = 245.7 Hz), 159.2, 140.8 (d, *J* = 7.3 Hz), 135.7, 129.8 (d, *J* = 8.4 Hz), 127.2 (2C), 125.2 (d, *J* = 2.8 Hz), 116.4 (d, *J* = 21.0 Hz), 113.9 (2C), 113.4 (d, *J* = 21.0 Hz), 74.8, 55.3, 45.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3392, 2935, 1612, 1586, 1512, 1487, 1462, 1446, 1302, 1243, 1174, 1140, 1110, 1076, 1032, 1006, 960, 948, 870, 831, 811, 786, 772, 755, 740, 688.

MS (EI, 70 eV): *m/z* (%) = 228 (25), 138 (10), 137 (100), 135 (16), 109 (15), 88 (11), 77 (10), 73 (10), 70 (11), 61 (20), 45 (11), 43 (74).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{15}H_{15}FO_2$ 246.1056; Found 246.1062.

2-(2-Fluorobenzyl)adamantan-2-ol (131c)



According to the **TP2**, a solution of 1-fluoro-2-(iodomethyl)benzene (**129a**, 0.20 M, 0.20 mmol, 1.0 equiv) and adamantanone (**112h**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, 0 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **131c** as a white amorphous solid (23 mg, 0.09 mmol, 44% yield).

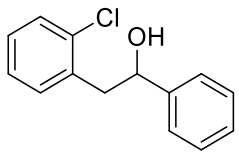
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30 – 7.22 (m, 1H), 7.01 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.99 – 6.90 (m, 2H), 2.99 (s, 2H), 2.21 – 2.11 (m, 2H), 2.04 (d, *J* = 3.1 Hz, 2H), 1.92 (s, 1H), 1.85 – 1.75 (m, 3H), 1.69 (dt, *J* = 17.8, 3.3 Hz, 4H), 1.54 (dt, *J* = 12.6, 1.7 Hz, 2H), 1.38 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.8 (d, *J* = 245.4 Hz), 140.1 (d, *J* = 7.2 Hz), 129.6 (d, *J* = 8.4 Hz), 126.4 (d, *J* = 2.8 Hz), 117.6 (d, *J* = 20.6 Hz), 113.5 (d, *J* = 21.0 Hz), 74.9, 43.8 (d, *J* = 1.8 Hz), 38.5, 37.0 (2C), 34.7 (2C), 33.1 (2C), 27.5, 27.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3478, 2905, 2855, 1616, 1586, 1487, 1444, 1251, 1141, 1098, 1042, 1018, 1010, 994, 927, 786, 747, 718, 688.

MS (EI, 70 eV): *m/z* (%) = 152 (10), 151 (100), 109 (34), 91 (23), 83 (11), 79 (16).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{17}H_{19}F$ 242.1471; Found 242.1464.

m.p. (°C): 79.0 – 81.6.

2-(2-Chlorophenyl)-1-phenylethan-1-ol (131d)



According to the **TP2**, a solution of 1-chloro-2-(iodomethyl)benzene (**129b**, 0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **131d** as white crystals (37 mg, 0.16 mmol, 80% yield).

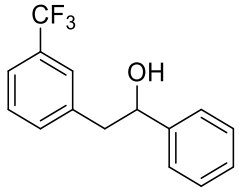
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35 – 7.25 (m, 5H), 7.25 – 7.19 (m, 1H), 7.14 – 7.07 (m, 3H), 4.95 (ddd, *J* = 8.8, 4.3, 2.7 Hz, 1H), 3.14 (dd, *J* = 13.7, 4.4 Hz, 1H), 3.00 (dd, *J* = 13.7, 8.9 Hz, 1H), 1.89 (d, *J* = 3.1 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.0, 136.1, 134.5, 132.2, 129.7, 128.6 (2C), 128.3, 127.8, 126.8, 125.9 (2C), 73.6, 44.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3288, 3260, 3234, 3192, 3061, 3030, 2927, 1472, 1444, 1418, 1400, 1326, 1288, 1203, 1049, 1040, 1030, 1002, 994, 910, 874, 747, 695, 682.

MS (EI, 70 eV): *m/z* (%) = 128 (34), 126 (100), 125 (13), 107 (93), 91 (25), 89 (11), 79 (80), 77 (19).

HRMS (EI-orbitrap): *m/z:* [M – OH]$^+$ calcd for $C_{14}H_{12}Cl^+$ 215.0622; Found 215.0619.

m.p. (°C): 72.3 – 73.1.

1-Phenyl-2-(3-(trifluoromethyl)phenyl)ethan-1-ol (131e)



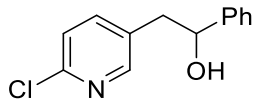
According to the **TP2**, a solution of 1-(iodomethyl)-3-(trifluoromethyl)benzene (**129c**, 0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **131e** as a colorless oil (34 mg, 0.13 mmol, 64% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.38 (m, 1H), 7.37 – 7.32 (m, 2H), 7.32 – 7.20 (m, 6H), 4.90 – 4.72 (m, 1H), 3.10 – 2.88 (m, 2H), 1.86 (d, *J* = 2.8 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.5, 139.1, 133.0 (d, *J* = 1.4 Hz), 130.6 (q, *J* = 32.2 Hz), 128.7, 128.6 (2C), 127.9, 126.3 (q, *J* = 3.8 Hz), 125.9 (2C), 124.2 (q, *J* = 272.6 Hz), 123.4 (q, *J* = 3.8 Hz), 75.2, 45.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1709, 1450, 1421, 1360, 1330, 1221, 1203, 1162, 1121, 1096, 1075, 1052, 1029, 795, 758, 702, 666.

MS (EI, 70 eV): *m/z* (%) = 159 (30), 109 (18), 107 (93), 105 (18), 79 (100), 77 (52).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{15}H_{11}F_3$ 248.0813; Found 248.0809.

2-(6-Chloropyridin-3-yl)-1-phenylethan-1-ol (134a)



According to the **TP2**, a solution of 2-chloro-5-(iodomethyl)pyridine (**132a**, 0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq*. NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **134a** as white crystals (41 mg, 0.18 mmol, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 2.5 Hz, 1H), 7.42 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.38 – 7.27 (m, 5H), 7.21 (dd, *J* = 8.2, 0.7 Hz, 1H), 4.88 (t, *J* = 6.5 Hz, 1H), 3.07 – 2.94 (m, 2H), 2.03 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 150.6, 149.8, 143.2, 140.2, 132.6, 128.8 (2C), 128.3, 126.0 (2C), 123.8, 74.9, 42.0.

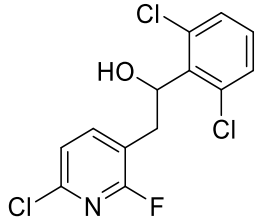
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3345, 2917, 1586, 1568, 1459, 1434, 1407, 1386, 1312, 1302, 1292, 1214, 1202, 1140, 1110, 1092, 1076, 1060, 1027, 1003, 826, 813, 763, 738, 699, 685.

MS (EI, 70 eV): *m/z* (%) = 233 (10), 215 (12), 129 (30), 127 (100), 107 (39), 105 (13), 91 (13), 79 (43), 77 (36).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_{13}H_{12}ClNO$ 233.0607; Found 233.0610.

m.p. (°C): 106.7 – 111.0.

2-(6-Chloro-2-fluoropyridin-3-yl)-1-(2,6-dichlorophenyl)ethan-1-ol (134b)



According to the **TP2**, a solution of 6-chloro-2-fluoro-3-(iodomethyl)pyridine (**132b**, 0.20 M, 0.20 mmol, 1.0 equiv) and 2,6-dichlorobenzaldehyde (**112i**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total

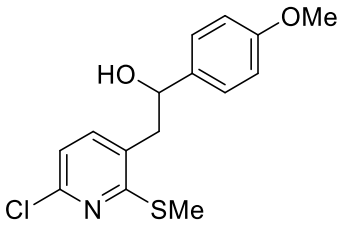
volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **134b** as a yellow oil (39 mg, 0.12 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.65 (dd, *J*=9.3, 7.7, 1H), 7.39 – 7.31 (m, 2H), 7.25 – 7.18 (m, 2H), 5.72 (s, 1H), 3.49 (dd, *J*=14.0, 8.8, 1H), 3.24 (dd, *J*=14.0, 6.2, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.0 (d, *J*=245.4), 147.0 (d, *J*=14.0), 144.2 (d, *J*=5.6, 2C), 136.2 (2C), 134.4, 129.7 (2C), 121.8 (d, *J*=5.1), 118.1 (d, *J*=29.3), 71.5, 34.1 (d, *J*=2.7).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3416, 2931, 1707, 1601, 1565, 1435, 1396, 1315, 1264, 1202, 1182, 1139, 1098, 1088, 1049, 1003, 950, 912, 872, 821, 800, 778, 768, 750, 727, 678.

MS (EI, 70 eV): *m/z* (%) = 177 (27), 175 (40), 147 (29), 145 (100), 111 (23), 109 (12), 75 (17).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{13}H_7Cl_3FN$ 300.9628; Found 300.9623.

2-(6-Chloro-2-(methylthio)pyridin-3-yl)-1-(4-methoxyphenyl)ethan-1-ol (134c)



According to the **TP2**, a solution of 6-chloro-3-(iodomethyl)-2-(methylthio)pyridine (**132c**, 0.20 M, 0.20 mmol, 1.0 equiv) and *p*-methoxybenzaldehyde (**112c**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **134c** as a white amorphous solid (34 mg, 0.11 mmol, 55% yield).

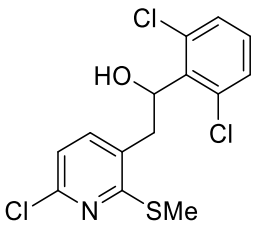
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31 – 7.27 (m, 2H), 7.20 (d, *J*=7.8, 1H), 6.95 – 6.84 (m, 3H), 4.97 (t, *J*=6.6, 1H), 3.81 (s, 3H), 3.02 – 2.92 (m, 2H), 2.59 (s, 3H), 1.95 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.4, 159.3, 149.0, 139.8, 136.0, 130.1, 127.1 (2C), 118.9, 114.0 (2C), 72.2, 55.4, 41.8, 13.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3342, 3284, 2923, 2853, 2838, 1610, 1575, 1549, 1511, 1461, 1439, 1412, 1366, 1343, 1322, 1296, 1246, 1219, 1202, 1178, 1168, 1132, 1073, 1058, 1045, 1026, 1001, 861, 838, 822, 782, 736, 726, 705.

MS (EI, 70 eV): *m/z* (%) = 175 (35), 173 (100), 142 (25), 140 (80), 139 (15), 137 (69), 109 (51), 94 (24), 77 (10).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calcd for $C_{15}H_{14}ClNOS$ 291.0485; Found 291.0480.

m.p. (°C): 86.8 – 89.1.

2-(6-Chloro-2-(methylthio)pyridin-3-yl)-1-(2,6-dichlorophenyl)ethan-1-ol (134d)



According to the **TP2**, a solution of 6-chloro-3-(iodomethyl)-2-(methylthio)pyridine (**132c**, 0.20 M, 0.20 mmol, 1.0 equiv) and 2,6-dichlorobenzaldehyde (**112i**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **134d** as a white amorphous solid (35 mg, 0.10 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.28 (s, 1H), 7.26 (s, 1H), 7.21 (d, *J*=7.8, 1H), 7.13 (dd, *J* =8.5, 7.5, 1H), 6.89 (d, *J*=7.8, 1H), 5.67 (ddd, *J*=9.9, 8.9, 5.9, 1H), 3.44 (dd, *J*=14.4, 8.9, 1H), 3.12 – 3.03 (m, 2H), 2.56 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.9, 149.2, 139.4 (2C), 136.7, 134.5, 129.6, 129.4 (2C), 129.3, 119.0, 71.3, 37.2, 13.7.

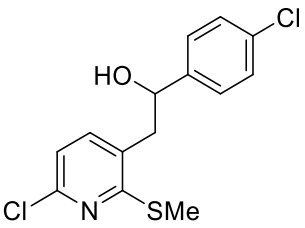
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3402, 2926, 1577, 1554, 1435, 1409, 1364, 1312, 1297, 1248, 1220, 1202, 1170, 1148, 1132, 1087, 1078, 1056, 971, 964, 862, 835, 811, 778, 766, 751, 722, 710, 666.

MS (EI, 70 eV): *m/z* (%) = 330 (11), 328 (11), 264 (10), 191 (25), 189 (79), 177 (17), 176 (16), 175 (25), 174 (46), 173 (19), 172 (52), 145 (16), 144 (11), 143 (53), 141 (100), 140 (13), 136 (11), 127 (13), 126 (23), 115 (13), 111 (14), 90 (13), 75 (16).

HRMS (EI-orbitrap): *m/z:* $[M - H]^+$ calcd for $C_{14}H_{11}Cl_3NOS^+$ 345.9621; Found 345.9623.

m.p. (°C): 115.8 – 120.3.

2-(6-Chloro-2-(methylthio)pyridin-3-yl)-1-(4-chlorophenyl)ethan-1-ol (134e)



According to the **TP2**, a solution of 6-chloro-3-(iodomethyl)-2-(methylthio)pyridine (**132c**, 0.20 M, 0.20 mmol, 1.0 equiv) and 4-chlorobenzaldehyde (**112x´**, 0.30 M, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.50 M in hexane, 0.50 mmol, 2.5 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **134e** as a slightly yellow oil (30 mg, 0.09 mmol, 48% yield).

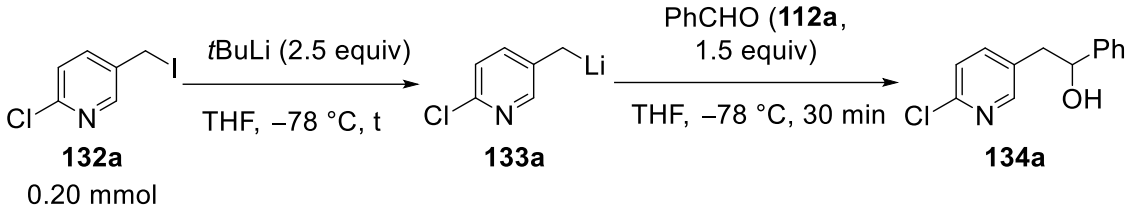
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35 – 7.28 (m, 4H), 7.20 (d, *J*=7.8, 1H), 6.93 (d, *J*=7.8, 1H), 5.00 (dd, *J*=7.8, 5.4, 1H), 2.99 – 2.91 (m, 2H), 2.60 (s, 3H), 2.03 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.3, 149.2, 142.3, 139.9, 133.6, 129.7, 128.8 (2C), 127.2 (2C), 119.0, 71.9, 42.0, 13.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3416, 3004, 2927, 1709, 1576, 1551, 1513, 1492, 1416, 1359, 1247, 1220, 1172, 1134, 1090, 1078, 1014, 860, 832.

MS (EI, 70 eV): *m/z* (%) = 175 (25), 173 (72), 142 (33), 141 (15), 140 (100), 139 (19), 113 (15), 77 (20).

HRMS (EI-orbitrap): *m/z:* $[M + H]^+$ calcd for $C_{14}H_{14}Cl_2NOS^+$ 314.0168; Found 314.0168.

2.4 Batch Screening

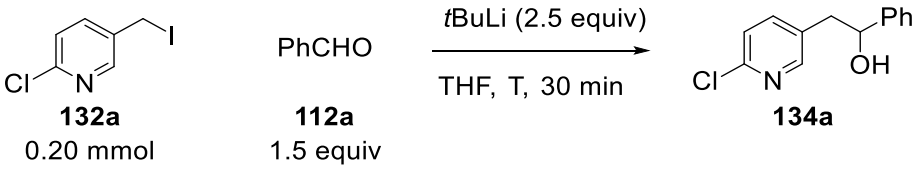
2.4.1 Typical procedure for the sequential batch method



Scheme 93: Sequential batch method using 2-chloro-5-(iodomethyl)pyridine (**132a**) as starting material and benzaldehyde (**112a**) as electrophile.

To 2-chloro-5-(iodomethyl)pyridine (**132a**, 0.20 mmol, 1.0 equiv) in THF (1.0 mL) was added *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv) at -78 °C. The reaction solution was stirred for an indicated time t (t_1 = 1 min, t_2 = 5 min, t_3 = 30 min) at -78 °C. Then, a solution of the benzaldehyde (**112a**, 0.30 mmol, 1.5 equiv) in THF (1.0 mL) was added at -78 °C. The mixture was stirred at -78 °C for further 30 min before it was allowed to warm to 25 °C and quenched with sat. *aq.* NH_4Cl solution. The crude mixture was filtrated over a pipet column containing silica and $MgSO_4$ before it was analysed via GC-analysis.

2.4.2 Typical procedure for the Barbier-type batch method

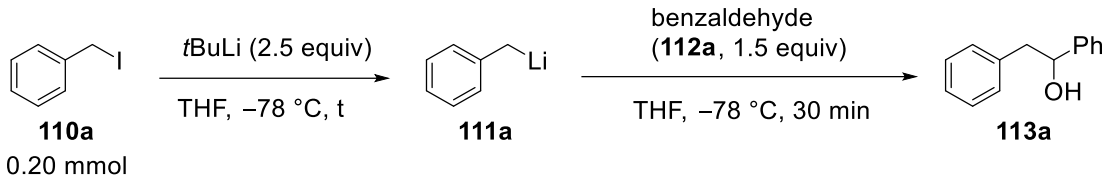


Scheme 94: Barbier-type batch method using 2-chloro-5-(iodomethyl)pyridine (**132a**) as starting material and benzaldehyde (**112a**) as electrophile.

To 2-chloro-5-(iodomethyl)pyridine (**132a**, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 0.30 mmol, 1.5 equiv) in THF (1.0 mL) at an indicated temperature T (T_1 = -20 °C, T_2 = -40 °C, T_3 = -78 °C) was added *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv). The mixture was stirred at the indicated temperature for 30 min before it was quenched with sat. *aq.* NH_4Cl solution. The crude mixture was filtrated over a pipet column containing silica and $MgSO_4$ before it was analaysed via GC-analysis. The aqueous layer was extracted with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. Solvents were removed *in vacuo* and the crude product was purified by flash chromatography using suitable EtOAc and isohexane mixtures.

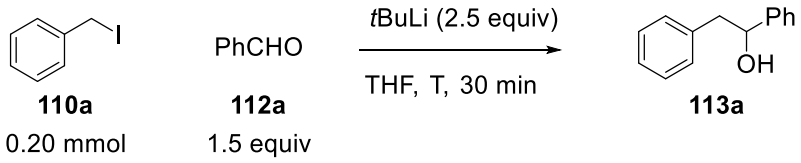
2.4.3 Batch screening results

1,2-Diphenylethan-1-ol (113a)



Scheme 95: Sequential batch approach for the synthesis of **113a**.

According to the typical procedure for the sequential batch approach, to a solution of **110a** (44 mg, 0.20 mmol, 1.0 equiv) in THF (1.0 mL) was added *t*BuLi (1.0 mL, 0.50 mmol, 0.50 M in hexane, 2.5 equiv) at -78 °C the mixture was stirred for an indicated time t (t_1 = 1 min, t_2 = 5 min, t_3 = 30 min) at -78 °C. Then, a solution of benzaldehyde (**112a**, 32 mg, 0.30 mmol, 1.5 equiv) in THF (1.0 mL) was added at -78 °C. The mixture was stirred at -78 °C for further 30 min before it was allowed to warm to 25 °C and quenched with sat. *aq.* NH_4Cl solution.



Scheme 96: Barbier batch approach for the synthesis of **113a**.

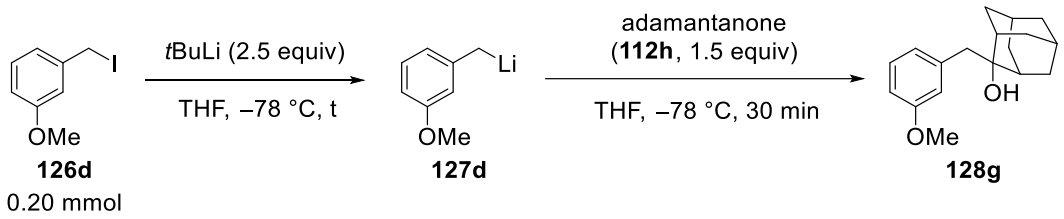
According to the typical procedure for the Barbier-type batch reactions, to a solution of **110a** (44 mg, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 32 mg, 0.30 mmol, 1.5 equiv) in THF (1.0 mL), *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv) was added at an indicated temperature T (T_1 = -20 °C, T_2 = -40 °C, T_3 = -78 °C). The mixture was stirred at the indicated temperature for 30 min before it was quenched with sat. *aq.* NH_4Cl solution. The crude mixture was filtrated over a pipet column containing silica and $MgSO_4$ before it was analaysed via gas chromatography. For entry 5, the aqueous layer was extracted with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. Solvents were removed *in vacuo* and the crude product was purified by flash chromatography using isohexane:EtOAc 9:1. **113a** was obtained as colorless crystals (16 mg, 0.08 mmol, 40% yield).

Table 17: Batch screening of reaction between **110a** and **112a** affording product **113a.**

entry	procedure	t [min]	T [°C]	conv. [%]	GC-yield [%]
1	sequential	1	–78	>95	<5
2	sequential	5	–78	>95	<5
3	sequential	30	–78	>95	<5
4	Barbier-type	30	–20	>95	32
5	Barbier- type	30	–40	>95	40[a]
6	Barbier- type	30	–78	>95	31

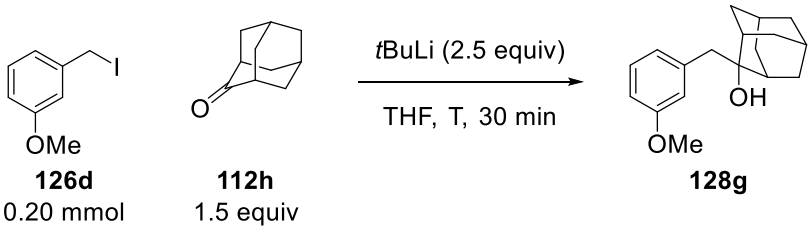
GC-yields were calculated by normation of the isolated yield. [a]Isolated yield.

2-(3-Methoxybenzyl)adamantan-2-ol (128g)



Scheme 97: Sequential batch approach for the synthesis of **128g**.

According to the typical procedure for the sequential batch approach, to a solution of **126d** (50 mg, 0.20 mmol, 1.0 equiv) in THF (1.0 mL) was added *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv) at -78 °C. The mixture was stirred for an indicated time t (t_1 = 1 min, t_2 = 5 min, t_3 = 30 min) at -78 °C. Then, a solution of adamantanone (**112h**, 45 mg, 0.30 mmol, 1.5 equiv) in THF (1.0 mL) was added at -78 °C. The mixture was stirred at – 78 °C for further 30 min before it was allowed to warm to 25 °C and quenched with sat. *aq.* NH_4Cl solution.



Scheme 98: Barbier batch approach for the synthesis of **128g**.

According to the typical procedure for the Barbier-type batch reactions, to a solution of **126d** (50 mg, 0.20 mmol, 1.0 equiv) and adamantanone (**112h**, 45 mg, 0.30 mmol, 1.5 equiv) in THF (1.0 mL), *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv) was added at an indicated temperature T (T_1 = -20 °C,

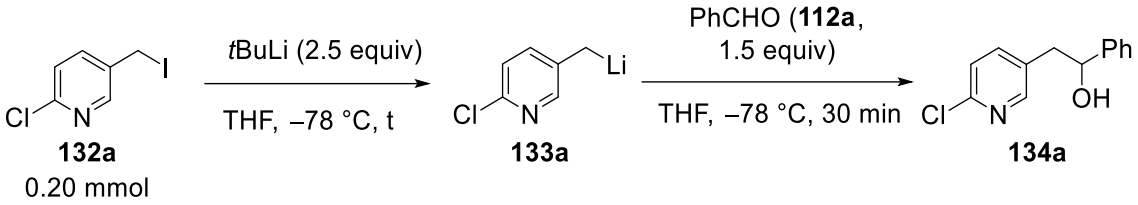
T_2 = -40 °C, T_3 = -78 °C). The mixture was stirred at the indicated temperature for 30 min before it was quenched with sat. *aq.* NH_4Cl solution. The crude mixture was filtrated over a pipet column containing silica and $MgSO_4$ before it was analaysed via gas chromatography. For entry 4, the aqueous layer was extracted with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. Solvents were removed *in vacuo* and the crude product was purified by flash chromatography using isohexane:EtOAc 9:1. **128g** was obtained as colorless crystals (8 mg, 0.03 mmol, 15% yield).

Table 18: Batch screening of reaction between **126d** and **112h** affording product **128g.**

entry	procedure	t [min]	T [°C]	conv. [%]	GC-yield [%]
1	sequential	1	–78	>95	<5
2	sequential	5	–78	>95	<5
3	sequential	30	–78	>95	<5
4	Barbier-type	30	–20	>95	15[a]
5	Barbier- type	30	–40	>95	14
6	Barbier- type	30	–78	>95	13

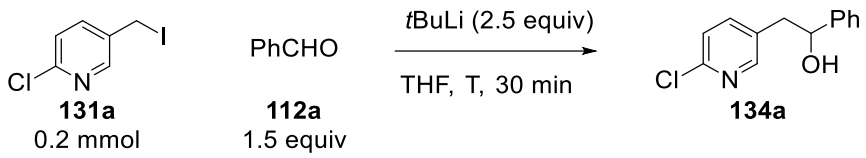
GC-yields were calculated by normation using the isolated yield. [a] Isolated yield.

2-(6-Chloropyridin-3-yl)-1-phenylethan-1-ol (134a)



Scheme 99: Sequential batch approach for the synthesis of **134a**.

According to the typical procedure for the sequential batch approach, to a solution of **132a** (51 mg, 0.20 mmol, 1.0 equiv) in THF (1.0 mL) was added *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv) at -78 °C the mixture was stirred for a time t (t_1 = 1 min, t_2 = 5 min, t_3 = 30 min) at -78 °C. Then, a solution of benzaldehyde (**112a**, 32 mg, 0.30 mmol, 1.5 equiv) in THF (1.0 mL) was added at -78 °C. The mixture was stirred at this temperature for further 30 min before it was allowed to warm to 25 °C and quenched with sat. *aq.* NH_4Cl solution.



Scheme 100: Barbier batch approach for the synthesis of **134a**.

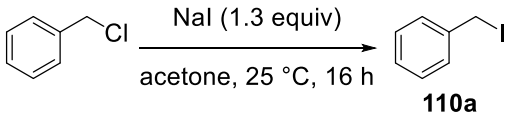
According to the typical procedure for the Barbier-type batch reactions, to a solution of **132a** (51 mg, 0.20 mmol, 1.0 equiv) and benzaldehyde (**112a**, 32 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL), *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv) was added at an indicated temperature T (T_1 = -20 °C, T_2 = -40 °C, T_3 = -78 °C). The mixture was stirred at the indicated temperature for 30 min before it was quenched with sat. *aq.* NH_4Cl solution. The crude mixture was filtrated over a pipet column containing silica and $MgSO_4$ before it was analysed via GC-analysis.

Table 19: Batch screening of reaction between **132a** and **112a** affording product **134a.**

entry	procedure	t [min]	T [°C]	conv. [%]	GC-yield [%]
1	sequential	1	–78	>95	<5
2	sequential	5	–78	>95	<5
3	sequential	30	–78	>95	<5
4	Barbier-type	30	–20	>95	<5
5	Barbier- type	30	–40	>95	<5
6	Barbier- type	30	–78	>95	<5

2.5 Synthesis of Starting Materials

2.5.1 Typical procedure for the preparation of (hetero)benzylic iodides

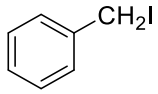


Scheme 101: Finkelstein reaction for the synthesis of benzylic iodides from the corresponding chlorides.

(Chloromethyl)benzene (1.26 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous

layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as a slightly yellow oil (1.79 g, 8.2 mmol, 82% yield), which was stored at -24 °C together with a copper turning.

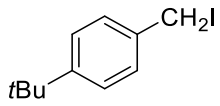
(Iodomethyl)benzene (110a)



(Chloromethyl)benzene (1.26 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as a slightly yellow oil (1.79 g, 8.2 mmol, 82% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41 – 7.36 (m, 2H), 7.33 – 7.21 (m, 3H), 4.46 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.4, 129.0 (2C), 128.9 (2C), 128.0, 5.8.
The spectra matched with those reported in the literature.[376]

1-(*Tert*-butyl)-4-(iodomethyl)benzene (110b)



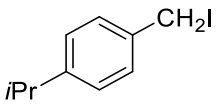
1-(*Tert*-butyl)-4-(chloromethyl)benzene (1.82 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as yellow oil (2.11 g, 7.7 mmol, 77% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 (s, 4H), 4.46 (s, 2H), 1.31 (s, 9H).

[376] Combe, S. H.; Hosseini A.; Song, L.; Hausmann, H.; Schreiner, P. R. *Org .Lett.* **2017**, *19*, 6156.

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.1, 136.3 (2C), 128.6 (2C), 126.0, 34.8 (3C), 31.4, 6.2. The spectra matched with those reported in the literature.[377]

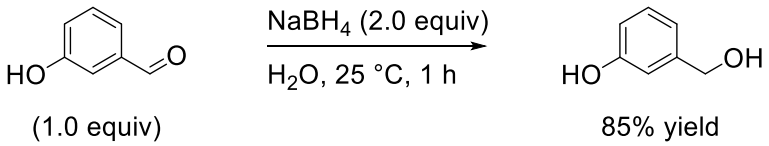
1-(Iodomethyl)-4-*iso*propylbenzene (110c)



1-(Chloromethyl)-4-*iso*propylbenzene (1.68 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq*. $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as brown oil (2.18 g, 8.4 mmol, 84% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 – 7.28 (m, 2H), 7.18 – 7.13 (m, 2H), 4.46 (s, 2H), 2.96 – 2.81 (m, *J*=7.0, 1H), 1.24 (dd, *J*=7.0, 5.5, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.9, 136.7, 128.9 (2C), 127.1 (2C), 34.0, 24.0 (2C), 6.3. The spectra matched with those reported in the literature.[378]

3-(Hydroxymethyl)phenol



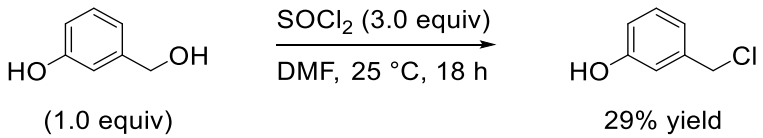
Scheme 102: $NaBH_4$ reduction of 2-hydroxybenzaldehyde.

According to literature[379], 2-hydroxybenzaldehyde (3.96 g, 32.4 mmol, 1.0 equiv) was dissolved in water (90 mL). $NaBH_4$ (2.45 g, 64.8 mmol, 2.0 equiv) was added portionwise and the mixture was stirred for 1 h at 25 °C. The reaction mixture was cooled to 0 °C and 6 M HCl was added until pH 5 was reached. The aqueous layer was extracted with EtOAc (3x50 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvents gave the title compound as colorless oil (3.40 g, 27.4 mmol, 85% yield) which was used without further purification.

[377] Nugent, J.; Arroniz, C.; Shire, B. R.; Sterling, A. J.; Pickford, H. D.; Wong, M. L. J.; Mansfield, S. J.; Caputo, D. F. J.; Owen, B.; Mousseau, J. J.; Duarte, F.; Anderson, E. A. *ACS Catal.* **2019**, *9*, 9568.
[378] Ruso, J. S.; Rajendiran, N.; Kumaran, R. S. *J. Korean Chem. Soc.* **2014**, *58*, 39.
[379] Guiso, M.; Betrow, A.; Marra, C. *Eur. J. Org. Chem.* **2008**, *11*, 1967.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.16 (t, *J*=7.8, 1H), 6.85 (ddd, *J*=7.6, 1.6, 0.9, 1H), 6.80 (t, *J*=2.2, 1H), 6.70 (ddd, *J*=8.1, 2.7, 0.9, 1H), 4.93 (s, 1H), 4.60 (d, *J*=4.9, 2H), 1.65 (t, *J*=5.8, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.0, 142.8, 130.0, 119.3, 114.7, 113.9, 65.2.
The spectra matched with those reported in the literature.[380]

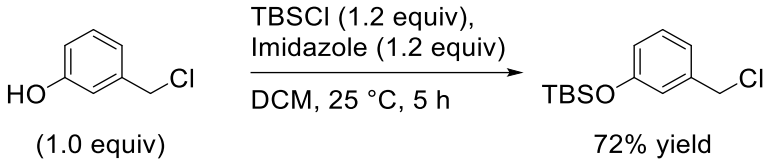
3-(Chloromethyl)phenol



Scheme 103: Chlorination of 3-(hydroxymethyl)phenol using $SOCl_2$.

To a solution of 3-(hydroxymethyl)phenol (3.43 g, 27.6 mmol, 1.0 equiv) in DMF (50.0 mL) was added $SOCl_2$ (6.0 mL, 82.9 mmol, 3.0 equiv) at 0 °C. The reaction mixture was stirred for 18 h at 25 °C. Water (50 mL) was added to the mixture and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with sat. *aq.* LiCl solution (5x100 mL) and dried over $MgSO_4$. Solvents were removed *in vacuo* and the residue was purified by flash column chromatography (isohexane:EtOAc = 9:1) to obtain the title compound as yellow oil (1.15 g, 8.1 mmol, 29% yield).
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.23 (t, *J*=7.9, 1H), 6.96 (dt, *J*=7.6, 1.2, 1H), 6.88 (t, *J*=2.1, 1H), 6.79 (ddd, *J*=8.1, 2.6, 0.9, 1H), 4.54 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.2, 139.1, 130.0, 120.7, 115.6 (2C), 46.1.
The spectra matched with those reported in the literature.[381]

Tert-butyl(3-(chloromethyl)phenoxy)dimethylsilane



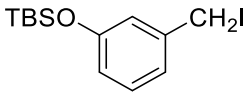
Scheme 104: TBS protection of 3-(Chloromethyl)phenol.

To a solution of 3-(Chloromethyl)phenol (1.15 g, 8.1 mmol, 1.0 equiv) and imidazole (0.66 g, 9.7 mmol, 1.2 equiv) in DCM (40 mL) TBSCl (1. 46 g, 9.7 mmol, 1.2 equiv) was added portionwise. The mixture was stirred for 5 h at 25 °C. After the reaction was completed, water (50 mL) was added and the aqueous layer was extracted with DCM (3x50 mL). The combined organic layers were dried over $MgSO_4$. Solvents were removed *in vacuo* and the crude residue was purified by column chromatography to obtain the title compound as a colorless, amorphous solid (1.50 g, 5.8 mmol, 72% yield).

[380] Aoun, S.; Sierocki, P.; Lebreton, Mathé-Allainmat, M. *Synthesis* **2019**, *51*, 3556.
[381] Pouliot, M.-F.; Mahé, O.; Hamel, J.-D., Desroches, J.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5428.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.21 (t, *J*=7.9, 1H), 6.97 (dt, *J*=7.7, 1.2, 1H), 6.87 (t, *J*=2.1, 1H), 6.79 (ddd, *J*=8.1, 2.5, 1.0, 1H), 4.53 (s, 2H), 0.98 (s, 9H), 0.20 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.9, 138.9, 129.7, 121.4, 120.3, 120.1, 46.1, 25.7 (3C), 18.2, -4.4 (2C).
The spectra matched with those reported in the literature.[382]

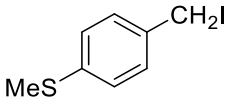
***Tert*-butyl(3-(iodomethyl)phenoxy)dimethylsilane (126a)**



Tert-butyl(3-(chloromethyl)phenoxy)dimethylsilane (2.57 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as a slightly brown amorphous solid (1.95 g, 5.6 mmol, 56% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.14 (t, *J*=7.9, 1H), 6.96 (dq, *J*=7.6, 1.7, 1.3, 1H), 6.85 (t, *J*=2.1, 1H), 6.71 (ddd, *J*=8.1, 2.4, 1.0, 1H), 4.40 (s, 2H), 0.98 (d, *J*=1.1, 9H), 0.20 (d, *J*=1.3, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.9, 140.7, 129.9, 121.8, 120.7, 119.9, 25.8 (3C), 18.3, 5.7 , -4.3 (2C).
The spectra matched with those reported in the literature.[383]

(4-(Iodomethyl)phenyl)(methyl)sulfane (126b)



(4-(Chloromethyl)phenyl)(methyl)sulfane (1.72 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over

[382] Huy, P. H.; Filbrich, I. *Chem. Eur. J.* **2018**, *24*, 7410.
[383] Berkowitz, D., B.; McFadden, J. M.; Sloss, M. K. *J. Org. Chem.* **2000**, *65*, 2907.

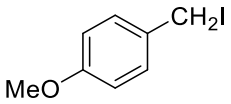
$MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as yellow amorphous solid (2.43 g, 9.2 mmol, 92% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.27 (m, 2H), 7.19 – 7.14 (m, 2H), 4.45 (s, 2H), 2.47 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 138.7, 136.1, 129.3 (2C), 126.8 (2C), 15.8, 5.9.
MS (EI, 70 eV): *m/z* (%) = 137 (100), 122 (25), 121 (12).

HRMS (EI-orbitrap): *m/z:* $[M - H]^+$ calcd for $C_8H_8IS^+$ 262.9386; Found 262.9384.

m.p. (°C): 60.4 – 62.1.

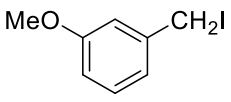
1-(Iodomethyl)-4-methoxybenzene (126c)



1-(Chloromethyl)-4-methoxybenzene (1.56 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as a slightly yellow liquid (2.11 g, 8.5 mmol, 85% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35 – 7.29 (m, 2H), 6.85 – 6.80 (m, 2H), 4.48 (s, 2H), 3.80 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.3, 131.5, 130.2 (2C), 114.4 (2C), 55.5, 6.7.
The spectra matched with those reported in the literature.[384]

1-(Iodomethyl)-3-methoxybenzene (126d)

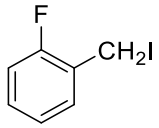


[384] Iranpoor, N.; Firouzabadi, H.; Jamalian, A.; Kazemi, F. *Tetrahedron*, **2005**, *61*, 5699.

1-(Chloromethyl)-3-methoxybenzene (1.56 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq*. $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as slightly yellow liquid (2.01 g, 8.1 mmol, 81% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.21 (t, *J*=7.9, 1H), 6.97 (dt, *J*=7.7, 1.3, 1H), 6.91 (t, *J*=2.1, 1H), 6.79 (ddd, *J*=8.2, 2.6, 0.9, 1H), 4.43 (s, 2H), 3.81 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.8, 140.8, 130.0, 121.2, 114.3, 113.8, 55.4, 5.7.
The spectra matched with those reported in the literature.[385]

1-Fluoro-2-(iodomethyl)benzene (129a)

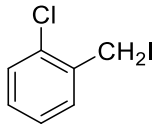


1-(Chloromethyl)-2-fluorobenzene (1.45 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq*. $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as a brown oil (1.84 g, 7.8 mmol, 78% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26 (td, *J*=8.0, 5.9, 1H), 7.15 (dt, *J*=7.7, 1.3, 1H), 7.08 (dt, *J*=9.5, 2.1, 1H), 6.94 (tdd, *J*=8.4, 2.6, 1.0, 1H), 4.42 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.8 (d, *J*=246.8), 141.7 (d, *J*=7.7), 130.5 (d, *J*=8.4), 124.5 (d, *J*=2.9), 115.9 (d, *J*=22.0), 115.1 (d, *J*=21.2), 4.1 (d, *J*=2.2).
The spectra matched with those reported in the literature.[386]

[385] Rafiee, M.; Wang, F.; Hruszkewycz, D. P.; Stahl, S. S. *J. Am. Chem. Soc.* **2018**, *140*, 22.
[386] Ayres, J.A.; Ashford M. W.; Stöckl, Y.; Prudhomme, V.; Ling, K. B.; Platts, J. A.; Morrill, L. C. *Org. Lett.* **2017**, *19*, 3835.

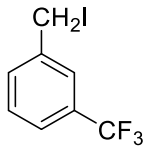
1-Chloro-2-(iodomethyl)benzene (129b)



1-Chloro-2-(chloromethyl)benzene (1.61 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as a slightly yellow oil (2.17 g, 8.6 mmol, 86% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.44 – 7.38 (m, 1H), 7.38 – 7.31 (m, 1H), 7.25 – 7.18 (m, 2H), 4.53 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 136.9, 134.0, 130.7, 130.3, 129.6, 127.5, 2.6.
The spectra matched with those reported in the literature.[387]

1-(Iodomethyl)-3-(trifluoromethyl)benzene (129c)



1-(Chloromethyl)-3-(trifluoromethyl)benzene (1.95 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as yellow amorphous solid (1.52 g, 5.3 mmol, 53% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.62 (q, *J*=1.9, 1H), 7.56 (dt, *J*=7.6, 1.6, 1H), 7.53 – 7.48 (m, 1H), 7.42 (t, *J*=7.7, 1H), 4.47 (s, 2H).

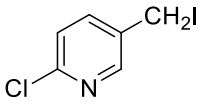
[387] Combe, S. H.; Hosseini A.; Song, L.; Hausmann, H.; Schreiner, P. R. *Org .Lett.* **2017**, *19*, 6156.

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.4, 132.2 (d, *J*=1.4), 131.3 (q, *J*=32.6), 129.5, 125.5 (q, *J*=3.8), 124.8 (q, *J*=3.8), 124.0 (q, *J*=272.3 Hz), 3.6.
MS (EI, 70 eV): *m/z* (%) = 160 (10), 159 (100), 109 (20).

HRMS (EI-orbitrap): *m/z:* $[M - H]^+$ calcd for $C_8H_5F_3I$ 284.9383; Found 284.9380.

m.p. (°C): 32.5 – 33.7.

2-Chloro-5-(iodomethyl)pyridine (132a)



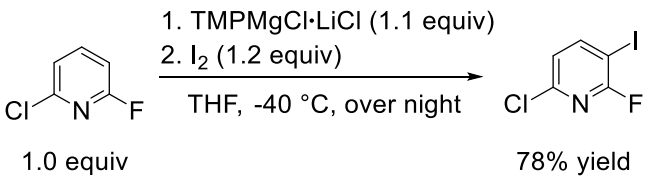
2-Chloro-5-(chloromethyl)pyridine (1.62 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq*. $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as yellow crystalls (1.82 g, 7.2 mmol, 72% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.40 (d, *J*=2.6, 1H), 7.67 (dd, *J*=8.2, 2.6, 1H), 7.28 (d, *J*=8.2, 1H), 4.38 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 150.7, 149.2, 139.4, 134.5, 124.6, -0.8.
MS (EI, 70 eV): *m/z* (%) = 128 (34), 126 (100), 90 (19).

HRMS (EI-orbitrap): *m/z:* [M] calcd for C_6H_5ClIN 251.9066; Found 251.9066.

m.p. (°C): 55.9 – 58.1.

6-Chloro-2-fluoro-3-iodopyridine



Scheme 105: Directed magnesiation of 2-chloro-6-fluoropyridine followed by an I_2 quench.

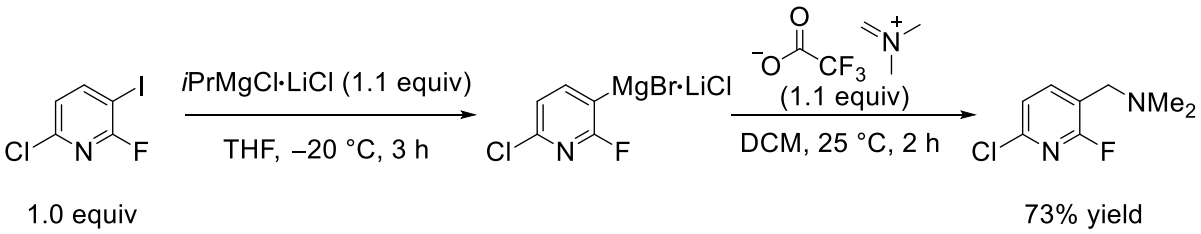
To a solution of 2-chloro-6-fluoropyridine (8.90 g, 67.7 mmol. 1.0 equiv) in THF (37.5 mL) was slowly added TMPMgCl·LiCl solution (1.45 M in THF, 52.0 mL, 75.4 mmol, 1.1 equiv) at -40 °C. The mixture was stirred at – 40 °C for 2 h. A solution of iodine (20.8 g, 82.0 mmol, 1.2 equiv) in THF (40.0 mL) was added slowly to the reaction mixture. The mixture was allowed to warm to 25 °C and stirred for 16 h. The reaction was quenched with sat. *aq.* $Na_2S_2O_3$ (30 mL) solution. The aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and filtrated. Solvents were removed *in vacuo.* Flash chromatographical purification (isohexane → isohexane:EtOAc 9:1) afforded the title compound as a colorless amorphous solid (13.6 g, 52.8 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.08 (t, *J*=8.0, 1H), 7.03 (dd, *J*=8.0, 1.2, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.1 (d, *J*=241.5), 151.8 (d, *J*=3.0), 149.2 (d, *J*=12.6), 123.4 (d, *J*=5.4), 73.3 (d, *J*=41.4).
MS (EI, 70 eV): *m/z* (%) = 259 (32), 257 (100), 158 (11), 130 (14), 110 (11).

HRMS (EI-orbitrap): *m/z:* [M] calcd for C_5H_2ClFIN 256.8904; Found 256.8899.

The spectra matched with those reported in the literature.[388]

1-(6-Chloro-2-fluoropyridin-3-yl)-*N*,*N*-dimethylmethanamine



Scheme 106: I/Mg-exchange and subsequent quench with iminium trifluoroacetate.

According to literature[Error! Bookmark not defined.], to 6-chloro-2-fluoro-3-iodopyridine (7.70 g, 30 mmol, 1.0 e quiv) in THF (30.0 mL) was added *i*PrMgCl·LiCl (1.22 M in THF, 27.0 mL, 33 mmol, 1.1 equiv) at -30 °C. The mixture was stirred at -30 °C for 2 h. To a solution of *N*,*N*,*N´*,*N´*-tetramethyl methylene diamine (4.5 mL, 33 mmol, 1.1 equiv) in DCM (33 mL) at 0 °C was carefully added trifluoroacetic anhydride (4.65 mL, 33 mmol, 1.1 equiv) and stirred for 30 min at 0 °C. The methylene(dimethyl)iminium trifluoroacetate solution was added dropwise at 0 °C to the prepared Grignard reagent and stirred for 2 h at 25 °C. The mixture was quenched with sat. *aq.* $NaHCO_3$ (30 mL). The aqueous phase was extracted with EtOAc (3×30 mL) and the combined organic layer were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent, flash chromatographical purification

[388] Barl, N. M.; Sansiaume-Dagousset, E.; Monzón, G.; Wagner, A. J.; Knochel, P. *Org. Lett.* **2014**, *16*, 2422.

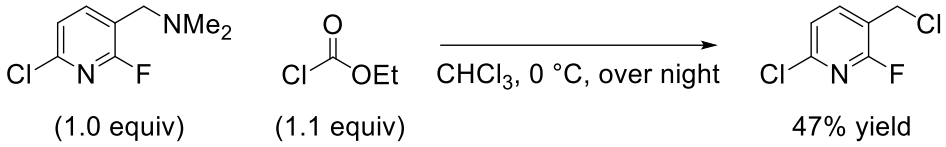
(silica gel, DCM:EtOH = 96:4) afforded the title compound (4.14 g, 22 mmol, 73% yield) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 – 7.82 (m, 1H), 7.23 (dd, *J*=7.8, 1.0, 1H), 3.50 (s, 2H), 2.30 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.6 (d, *J*=245.8), 147.4, 144.13 (d, *J*=5.3), 122.0, 121.9, 55.5 (d, *J*=2.7), 45.2 (2C).
MS (EI, 70 eV): *m/z* (%) = 190 (14), 189 (19), 188 (43), 187 (63), 146 (33), 144 (100), 108 (11), 58 (31).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_8H_{10}ClFN_2$ 188.0517; Found 188.0510.

The spectra matched with those reported in the literature.[389]

6-Chloro-3-(chloromethyl)-2-fluoropyridine



Scheme 107: Deaminative chlorination of 6-chloro-3-(chloromethyl)-2-(methylthio)pyridine.

According to literature[389], to a solution of 6-chloro-3-(chloromethyl)-2-(methylthio)pyridine (4.14 g, 22.0 mmol, 1.0 equiv) in $CHCl_3$ (22 mL) was added ethyl chloroformate (2.3 mL, 24.0 mmol, 1.1 equiv) at 0 °C. The mixture was allowed to slowly warm up to 25 °C and stirred for 16 h. The mixture was quenched with H_2O and the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and filtrated, solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (isohexane → isohexane:EtOAc 9:1). The title compound was obtained as a colorless amorphous solid (2.32 g, 8.6 mmol, 47% yield).

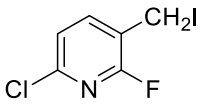
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 (ddd, *J*=9.2, 7.8, 0.6, 1H), 7.29 – 7.25 (m, 1H), 4.59 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.6 (d, *J*=247.6), 148.9 (d, *J*=14.0), 143.3 (d, *J*=4.2), 122.3 (d, *J*=5.2), 118.4 (d, *J*=27.9), 38.0 (d, *J*=1.5).
MS (EI, 70 eV): *m/z* (%) = 179 (11), 146 (33), 144 (100), 108 (10).

HRMS (EI-orbitrap): *m/z:* [M] calcd for $C_6H_4Cl_2FN$ 178.9705; Found 178.9697.

The spectra matched with those reported in the literature.[389]

[389] Barl, N. M.; Sansiaume-Dagousset, E.; Monzón, G.; Wagner, A. J.; Knochel, P. *Org. Lett.* **2014**, *16*, 2422.

6-Chloro-2-fluoro-3-(iodomethyl)pyridine (132b)

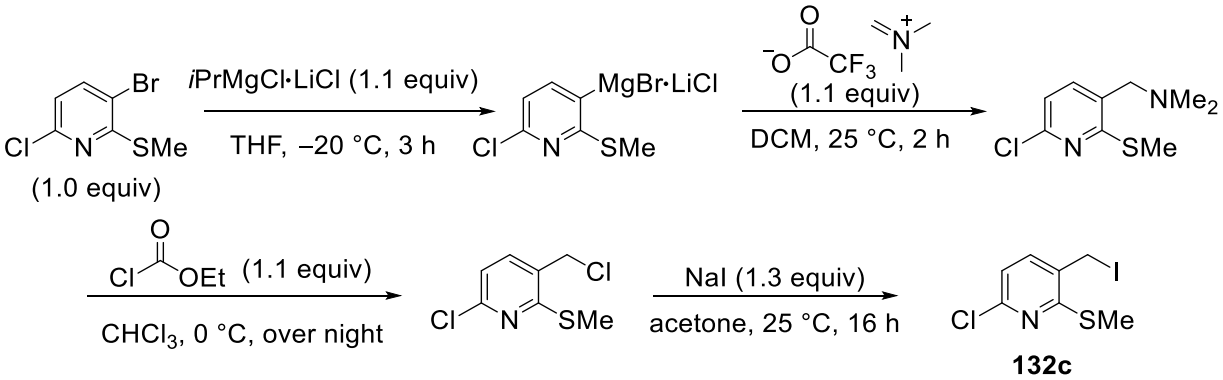


6-Chloro-3-(chloromethyl)-2-fluoropyridine (1.80 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as yellow oil (1.79 g, 6.6 mmol, 66% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 (dd, *J*=9.5, 7.8, 1H), 7.20 (dd, *J*=7.8, 0.9, 1H), 4.35 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.2 (d, *J*=247.9), 148.0 (d, *J*=13.8), 143.1 (d, *J*=4.3), 122.4 (d, *J*=5.2), 120.7 (d, *J*=28.0), -6.7 (d, *J*=1.9).
MS (EI, 70 eV): *m/z* (%) = 146 (33), 144 (100), 108 (11).

HRMS (EI-orbitrap): *m/z:* $[M - H]^+$ calcd for $C_6H_3ClFIN^+$ 269.8977; Found 269.8974.

6-Chloro-3-(iodomethyl)-2-(methylthio)pyridine (132c)



Scheme 108: Reaction sequence for the preparation of 6-Chloro-3-(iodomethyl)-2-(methylthio)pyridine (**132c**).

According to literature[390], to 3-bromo-6-chloro-2-(methylthio)pyridine (3.22 g, 13.5 mmol, 1.0 equiv) in THF (14 mL) was added *i*PrMgCl·LiCl (1.22 M in THF, 12.2 mL, 14.9 mmol, 1.1 equiv) at -30 °C. The mixture was stirred at -30 °C for 2 h. A solution of *N*,*N*,*N´*,*N´*-tetramethyl methylene diamine (2.02

[390] Barl, N. M.; Sansiaume-Dagousset, E.; Monzón, G.; Wagner, A. J.; Knochel, P. *Org. Lett.* **2014**, *16*, 2422.

mL, 14.9 mmol, 1.1 equiv) in DCM (15 mL) was prepared at 0 °C. Trifluoroacetic anhydride (2.09 mL, 14.9 mmol, 1.1 equiv) was carefully added at 0 °C and the mixture was stirred for 30 min. The methylene(dimethyl)iminium trifluoroacetate solution was added dropwise at 0 °C to the prepared Grignard reagent and stirred for 2 h at 25 °C. The mixture was quenched with sat. *aq.* $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of solvent, flash chromatographical purification (silica gel, DCM:EtOH = 95:5) afforded the title compound (2.81 g, 13.0 mmol, 96% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 3.35 (s, 2H), 2.56 (s, 3H), 2.26 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.9, 149.2, 138.6, 130.8, 118.8, 59.7, 45.6 (2C), 13.6.

According to literature[391], to a solution of 6-chloro-3-(chloromethyl)-2-(methylthio)pyridine (2.81 g, 13.0 mmol, 1.0 equiv) in $CHCl_3$ (13 mL) was added ethyl chloroformate (1.36 mL, 14.3 mmol, 1.1 equiv) at 0 °C. The mixture was allowed to slowly warm up to 25 °C and stirred for 16 h. The mixture was quenched with H_2O and the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtrated, solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (isohexane → isohexane:EtOAc 9:1). The title compound was obtained as a colorless amorphous solid (1.91 g, 9.2 mmol, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.54 (d, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 4.57 (s, 2H), 2.62 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.7, 150.7, 138.9, 128.9, 119.3, 41.9, 13.5.

6-Chloro-3-(chloromethyl)-2-(methylthio)pyridine (2.08 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with sat. *aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$. After filtration, a copper turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as slightly yellow crystals (2.10 g, 7.0 mmol, 70% yield), which was stored at -24 °C together with a copper turning.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 (d, *J*=7.9, 1H), 6.97 (d, *J*=7.9, 1H), 4.38 (s, 2H), 2.62 (s, 3H).

[391] Barl, N. M.; Sansiaume-Dagousset, E.; Monzón, G.; Wagner, A. J.; Knochel, P. *Org. Lett.* **2014**, *16*, 2422.

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.3, 150.0, 138.7, 130.7, 119.5, 13.6, -0.1.

MS (EI, 70 eV): *m/z* (%) = 174 (36), 172 (100), 136 (19), 126 (23), 90 (11).

HRMS (EI-orbitrap): *m/z:* [M] calcd for C_7H_7ClINS 298.9032; Found 298.9024.

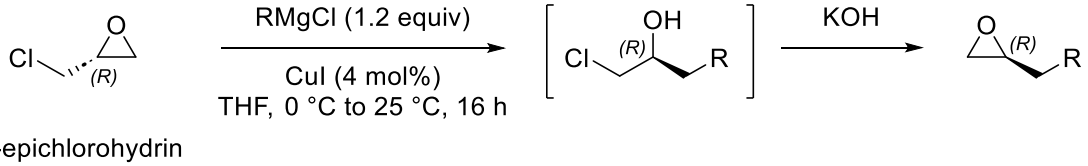
m.p. (°C): 87.5 – 89.9.

3. In Situ Quench Reactions of Chiral Secondary Alkyllithium Reagents in Batch and Continuous Flow

3.1 Typical Procedures

Enantiomerically enriched epoxides (*R*)-**138a-d** were prepared from (*R*)-epichlorohydrin (*R*-**137**) via copper-catalyzed epoxide opening[392] and subsequent base-mediated ring closure[393] according to **TP3**. Enantiomerically pure alcohols **139a-n** were prepared via copper-catalyzed opening of propylene oxide, butylene oxide or chiral epoxides (*R*)-**138a-d**[394] with arylmagnesium reagents[395] (prepared via **TP4**) according to **TP5**. The enantiomerically enriched secondary alkyl iodides **114a-n** were prepared from their corresponding alcohols **139a-n** via *Appel*-reactions[396] according to **TP6**. Optically enriched products **136a-ac** were obtained from the secondary alkyl iodides **114a-n** via I/Li-exchange reaction using *t*-BuLi in the presence of electrophiles **112** as stated in **TP7**. Reactions using a continuous flow set-up were performed according to **TP8**.

3.1.2 Procedure for the preparation of chiral epoxides from (*R*)-epichlorohydrin (TP3)



(*R*)-epichlorohydrin

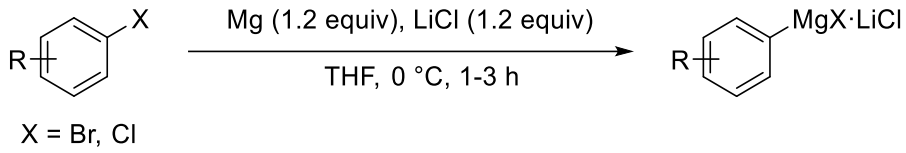
Scheme 109: Procedure for the preparation of chiral epoxides from (*R*)-epichlorohydrin.

According to a modified literature procedure[392] a dry and Ar-flushed flask was charged with the desired magnesium reagent (1.2 equiv) in THF (0.5 M). Then, CuI (4 mol%) was added and the reaction was cooled to 0 °C. (*R*)-epichlorohydrin (*R*-**137**, 1.0 equiv) in THF (0.5 M) was added dropwise over a period of 15 minutes and the reaction was allowed to warm to ambient temperature overnight. A sat. aq. NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was carefully removed under reduced pressure. The remaining crude product was treated with powdered KOH (2.2 equiv based on starting material) in a round bottom flask. For volatile epoxides, a distillation head was attached and the respective epoxide was distilled off. Higher molecular weight epoxides were

[392] P. Gupta, P. Kumar, *Tetrahedron: Asymmetry* **2007**, *18*, 1688–1692.
[393] H. Hattori, J. Roesslein, P. Caspers, K. Zerbe, H. Miyatake-Ondazabal, D. Ritz, G. Rueedi, K. Gademann, *Angew. Chem. Int. Ed.* **2018**, *57*, 11020–11024.
[394] a) B. H. Lipshutz, S. Sengupta *Org. React.* **1992**, *41*, 135–296; b) S. Takano, M. Yanase, M. Takahashi, K. Ogasawara *Chem. Lett.* **1987**, *16*, 2017-2020.
[395] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802–6806.
[396] A. Kremsmair, H. R. Wilke, M. M. Simon, Q. Schmidt, K. Karaghiosoff, P. Knochel, *Chem. Sci.* **2022**, *13*, 44–49.

treated with KOH (2.2 equiv. based on starting material) in a 1:1 mixture of Et_2O/water. The aqueous phase was extracted with Et_2O (2 × 20 mL), the combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed. Epoxides were used without further purification.

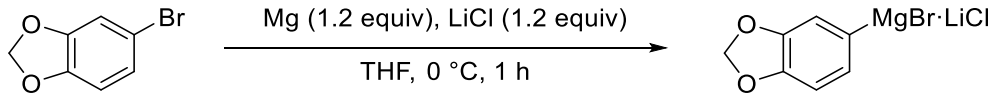
3.1.3 Typical procedure for the preparation of arylmagnesium reagents (TP4)



Scheme 110: Oxidative magnesium insetion into aryl halides in the presence of LiCl.

According to a modified literature procedure,[397] a dry and argon-flushed *Schlenk*-flask was charged with magnesium turnings (1.2 equiv) and anhydrous lithium chloride (1.2 equiv) in THF (1.0 M solution) and cooled to 0 °C. The aryl halide (1.0 equiv) was added and the reaction mixture was stirred for 1-3 h at 0 °C. The concentration of the obtained arylmagnesium species was determined via titration with iodine in THF.

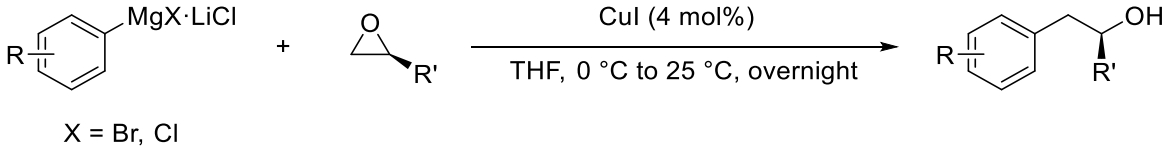
Detailed procedure for the preparation of the corresponding arylmagnesium reagent from 5-bromobenzo[*d*][1,3]dioxole:



Scheme 111: Oxidative magnesium insetion into 5-bromobenzo[*d*][1,3]dioxole in the presence of LiCl.

A dry and argon-flushed *Schlenk*-flask was charged with magnesium turnings (1.46 g, 60 mmol, 1.2 equiv) and anhydrous lithium chloride (2.54 g, 60 mmol, 1.2 equiv) in THF (50 mL, 1.0 M solution) and cooled to 0 °C. The bromobenzo[*d*][1,3]dioxole (6.0 mL, 10.1 g, 50 mmol, 1.0 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. The concentration of the obtained arylmagnesium species was determined via titration with iodine in THF.[398]

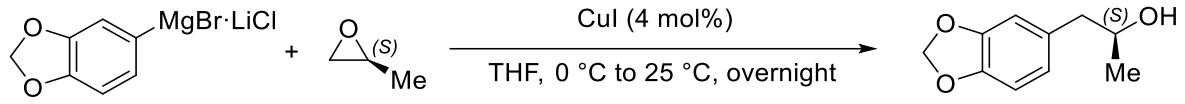
3.1.4 Typical procedure for the preparation of secondary alkyl alcohols (TP5)



Scheme 112: Preparation of secondary alkyl alcohols via CuI mediated ring opening of epoxides.

[397] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802–6806.
[398] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890–891.

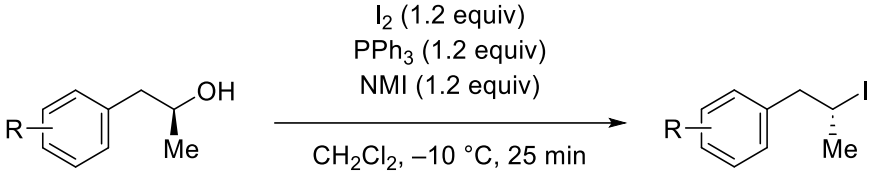
According to a modified literature procedure,[399] a dry and argon-flushed *Schlenk*-flask was charged with a solution of an aryl magnesium reagent (1.2 equiv) and diluted with THF to afford a ca. 0.5 M solution. The mixture was cooled to 0 °C and CuI (4 mol%) was added to the reaction mixture. Then, the chiral epoxide (1.0 equiv, 0.5 M in THF) was added dropwise to the reaction mixture at 0 °C and allowed to warm to room temperature overnight. Thereafter, the mixture was quenched with a sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The remaining crude product was purified by flash column chromatography on silica gel to afford the corresponding alkyl alcohol of type **139**.



Scheme 113: Detailed procedure for the preparation of (*R*)-**139a** from the corresponding arylmagnesium reagent of 5-bromobenzo[*d*][1,3]dioxole, (*R*)-propylene oxide and CuI.

A dry and argon-flushed *Schlenk*-flask was charged with a solution of the aryl magnesium reagent (1 M, 24 mL, 24 mmol, 1.2 equiv) and diluted with THF (24 mL) to afford a ca. 0.5 M solution. The mixture was cooled to 0 °C and CuI (152 mg, 0.8 mmol, 4 mol%) was added to the reaction mixture. Then, (*R*)-propylene oxide (1.4 mL, 1.16 g, 20 mmol, 1.0 equiv) in THF (40 mL) was added dropwise to the reaction mixture at 0 °C and allowed to warm to room temperature overnight. Thereafter, the mixture was quenched with a sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The remaining crude product was purified by flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:3 to afford (*S*)-**139a** (3.06 g, 17 mmol, 85%) as colorless oil.

3.1.5 Typical procedure for the preparation of secondary alkyl iodides (TP6)

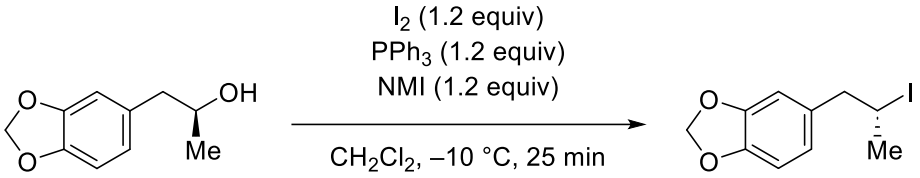


Scheme 114: Preparation of secondary alkyl iodides.

A dry and argon-flushed *Schlenk*-flask was charged with a solution of iodine (1.2 equiv) in CH_2Cl_2 (ca. 0.3 M solution) and cooled to −10 °C. Triphenylphosphine (1.2 equiv) was added in one portion and

[399] a) B. H. Lipshutz, S. Sengupta *Org. React.* **1992**, *41*, 135–296; b) S. Takano, M. Yanase, M. Takahashi, K. Ogasawara *Chem. Lett.* **1987**, *16*, 2017-2020.

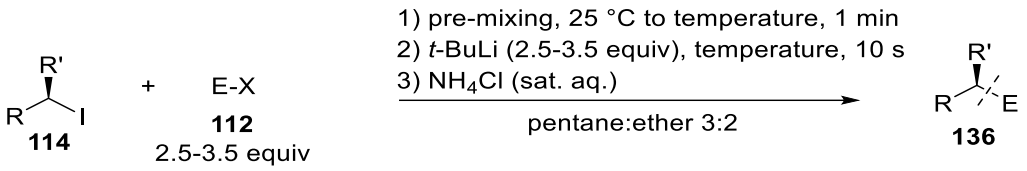
the resulting yellow suspension was stirred for 1 h at −10 °C. Then *N*-methylimidazole (1.2 equiv) was added dropwise. The reaction mixture was further stirred for 10 min after which the corresponding alcohol (**139**, 1.0 equiv, dissolved to 0.5 M in CH_2Cl_2) was added over a period of 15 min. The reaction was further stirred for 10 min at −10 °C and then quenched with freshly prepared sat. aq. $NaHSO_3{\cdot}Na_2S_2O_5$. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure at 30 °C. The resulting oil was triturated with a mixture of *n*-pentane/diethyl ether. The precipitate was filtered off and the filtrate was concentrated under reduced pressure at 30 °C. The remaining crude product was purified by flash column chromatography on silica gel to afford the corresponding chiral secondary alkyl iodide of type **114**.



Scheme 115: Detailed procedure for the preparation of (*R*)-**114a** from (*S*)-**139a**.

A dry and argon-flushed *Schlenk*-flask was charged with a solution of iodine (1.52 g, 6.0 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL, ca. 0.3 M solution) and cooled to −10 °C. Triphenylphosphine (1.57 g, 6.0 mmol, 1.2 equiv) was added in one portion and the resulting yellow suspension was stirred for 1 h at −10 °C. Then *N*-methylimidazole (480 µL, 492 mg, 6.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was further stirred for 10 min after which the corresponding alcohol (*S*-**139a**, 901 mg, 5.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added over a period of 15 min. The reaction was further stirred for 10 min at −10 °C and then quenched with freshly prepared sat. aq. $NaHSO_3{\cdot}Na_2S_2O_5$. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure at 30 °C. The resulting oil was triturated with a mixture of *n*-pentane/diethyl ether. The precipitate was filtered off and the filtrate was concentrated under reduced pressure at 30 °C. The remaining crude product was purified by flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:250 to afford (*R*)-**114a** (913 mg, 3.15 mmol, 63%) as colorless oil.

3.1.6 Typical procedure for the in situ trapping of chiral secondary alkyl iodides in the presence of electrophiles (TP7)



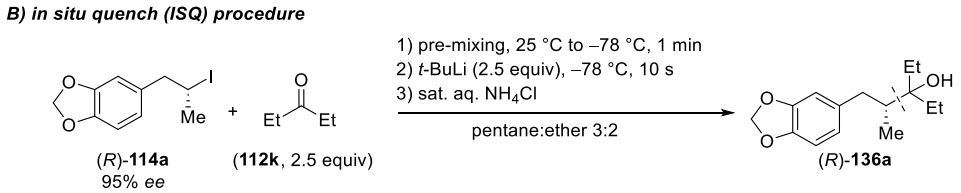
Scheme 116: Procedure for the Barbier type reaction of chiral secondary alkyl.

The secondary alkyl iodide (0.1 mmol, 1.0 equiv) was dissolved in dry diethyl ether (0.16 M) and transferred into a dry and Ar-flushed Schlenk-finger. Then, *n*-pentane (0.125 M) was added and the electrophile (**3**, 2.5-3.5 equiv). The Schlenk finger was put into a dry ice/acetone bath at −78 °C or −40 °C and stirred for 1 min at this temperature. Subsequently, *t*-BuLi (2.5-3.5 equiv, ca. 2.1 M in pentane) was added dropwise over 10 s at −78 °C or −40 °C. The reaction tube was immediately quenched with sat. aq. NH_4Cl solution, diluted with water (2 mL) and diethyl ether (2 mL) before warming to ambient temperature over 10 min. The phases were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The remaining crude product was purified by flash column chromatography on silica gel to afford products of type **136**.

In the case of solid electrophiles or electrophiles, which proved to be insoluble at −78 °C, the reaction was performed at −40 °C in the presence of 3.0 equiv of electrophile.

In case of the products **136x-y** and **136aa** the reaction was performed using 3.5 equiv of *t*-Buli in the presence of 3.5 equiv of electrophile to ensure full conversion of the iodide.

Detailed procedure for the preparation of (*R*)-**136a** from (*R*)-**114a** and **112k**:



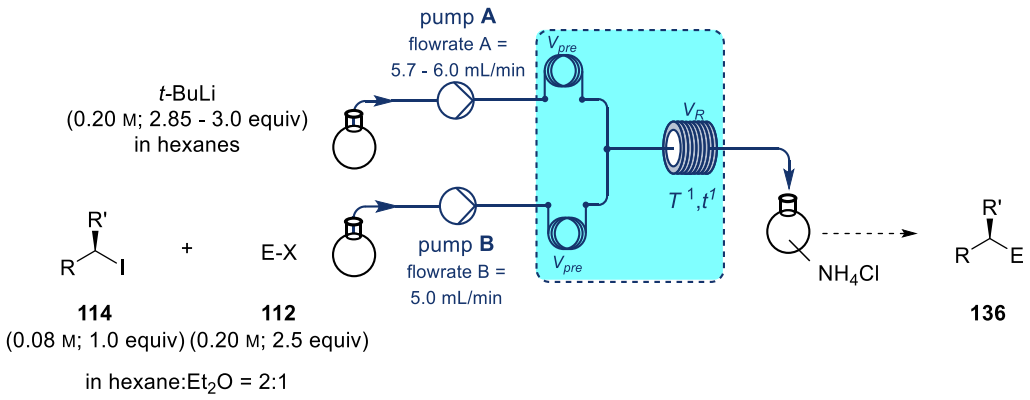
Scheme 117: Procedure for the preparation of (*R*)-**136a** from (*R*)-**114a** and **112k**.

The secondary alkyl iodide (*R*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) was dissolved in dry diethyl ether (0.6 mL) and transferred into a dry and Ar-flushed Schlenk-finger. Then, *n*-pentane (0.8 mL) was added and pentan-3-one (**112k**, 27 µL, 21.5 mg, 0.25 mmol, 2.5 equiv). The Schlenk flask was put into a dry ice/acetone bath at −78 °C and stirred for 1 min at this temperature. Subsequently, *t*-BuLi (2.1 M in pentane, 120 µL, 2.5 mmol, 2.5 equiv) was added dropwise over 10 s at −78 °C. The reaction tube was immediately quenched with sat. aq. NH_4Cl solution, diluted with water (2 mL) and diethyl ether (2 mL)

before warming to ambient temperature over 10 min. The phases were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**136a** (15.1 mg, 0.060 mmol, 60%, 93% *ee*) as colorless oil.

3.1.7 General remarks on flow and subsequent batch quenching reactions (TP8)

Tetradecane ($nC_{14}H_{30}$) was used as internal standard. All flasks were heat gun dried (650 °C) under vacuum and backfilled with argon after cooling. Syringes, which were used to transfer reagents and solvents, were purged with argon three times prior to use. Batch quenching reactions were carried out with magnetic stirring. Flow reactions were performed on the commercially available flow system (Vapourtec E-series Integrated Flow Chemistry System with 3rd Pump Kit. It is of major importance for this procedure, that the Vaportec E-series system is running on peristaltic pumps rather than HPLC or syringe pumps, and therefore significantly facilitates the continuous pumping of highly reactive organometallic species such as *t*-BuLi).[400] Hexane solutions of *t*-BuLi and hexane:Et_2O solutions of the corresponding reagents were kept in flasks with rubber septa under an argon atmosphere during the reactions. All reactions were performed in coiled tube reactors. Coiled reactors were made from PFA or PTFE Teflon (I.D. = 0.8 mm or 0.25 mm, O.D. = 1.6 mm) tubing and T-pieces (I.D. = 0.5 mm) were used as mixers. Prior to performing reactions, the systems were dried by flushing with dry hexane (flow rate of all pumps: 1.00 mL/min; run-time: 30 min).



Scheme 118: Vapourtec E-series Integrated Flow Chemistry System for the iodine-lithium exchange of chiral alkyl substrates with *t*-BuLi in the presence of various electrophiles.

A solution of alkyl iodide (**114**, 0.08 M, 1.00 equiv) and electrophile (**112**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*-BuLi (ca. 0.20 M in hexane, 2.85–3.00 equiv) were prepared. The

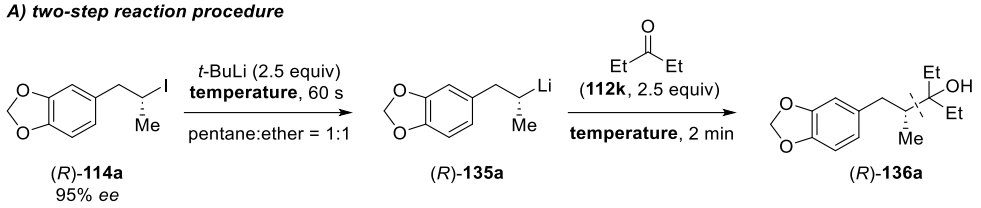
[400] P. R. D. Murray, D. L. Brown. J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process. Res. Dev*. **2013**, *17*, 1192-1208.

solution of *t*-BuLi was pumped by pump A (flow rate A: 5.7–6.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The solution of the alkyl iodide **114** was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = –20 to 25 °C). The stream was subsequently, upon reaching steady state, injected into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted three times with Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel to afford products of type **136**.

3.2 Optimization of the Reaction Conditions

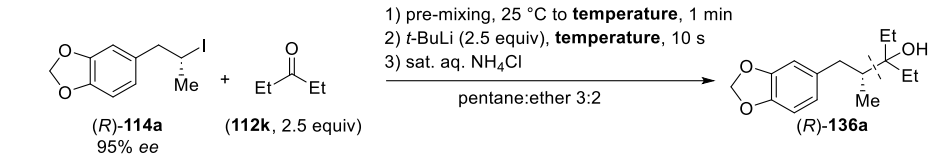
Table 20: Optimization of the reaction conditions for the in situ quench procedure.

A) two-step reaction procedure



Entry	Temperature [°C]	Yield of (*R*)-**136a**[a]	*ee* of (*R*)-**136a**[b]
1	−100	67%	92%
2	−78	61%	53%
3	−40	54%	0%

B) in situ quench (ISQ) procedure



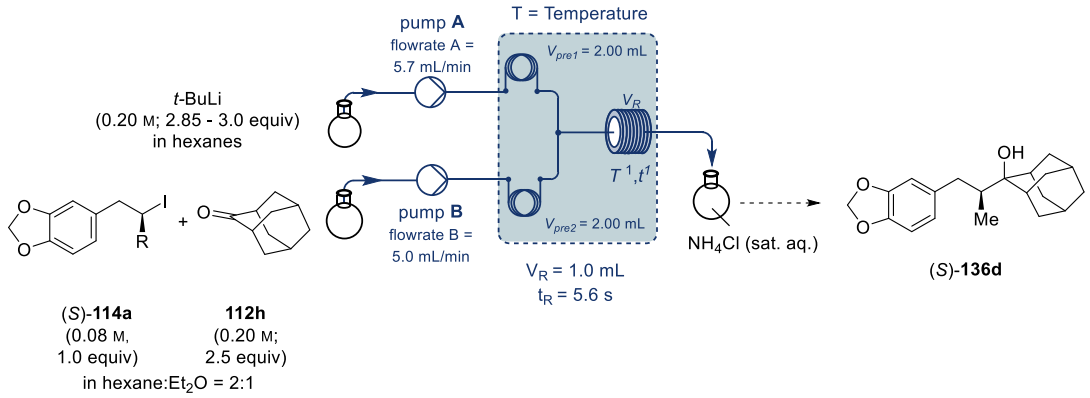
Entry	Temperature [°C]	Yield of (*R*)-**136a**[a]	*ee* of (*R*)-**136a**[b]
4	**−78**	**60%**[c]	**93%**
5	−60	52%	92%
6	−40	54%	90%
7	−20	44%	86%
8	0	41%	69%
9[d]	−78	28%	92%
10[e]	−78	48%	93%
11[f]	−78	31%	93%

[a] The yield was determined by GC-analysis; [b] The enantiomeric excess (% *ee*) was determined by chiral HPLC-analysis; [c] Yield of isolated analytically pure product; [d] 1.0 equiv of electrophile was used; [e] 2.0 equiv of electrophile was used; [f] 3.0 equiv of electrophile was used.

Low yields were attributed to low conversion of the iodide (entry 11) or to competitive reaction of excess *t*-BuLi on the electrophile (entries 9 and 10). In cases of incomplete conversion of the iodide (see chapter B.2. compounds **136x-y** and **136aa**), the amount of *t*-BuLi and electrophile was raised to 3.5 equiv.

If a mixture of secondary alkyl iodide with electrophile was insoluble in pentane/ether at −78 °C, the reaction was performed at −40 °C.

Table 21: Temperature screening for the in situ quench procedure in continuous flow.



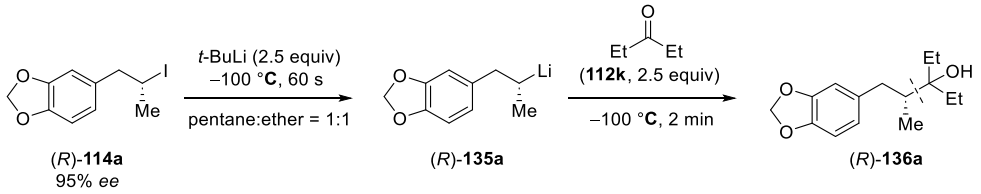
Entry	Temperature [°C]	Yield of (*S*)-**136d**[a]	*ee* of (*S*)-**136d**[b]
1	−40	-	-
2	−30	-	-
3	−20	59%[c]	94%

[a] The yield was determined by GC-analysis; [b] The enantiomeric excess (% *ee*) was determined by chiral HPLC-analysis; [c] Yield of isolated analytically pure product.

Performing the reaction at lower temperatures than −20 °C led to clogging of the tubes due to insoluble mixtures of the iodide and electrophile.

If remaining starting material was observed (see chapter B.2. compounds **136e** and **136ae**), the amount of *t*-BuLi was changed to 3.0 equiv instead of 2.85 equiv. Thus, the flow rate was changed to 6.0 mL/min.

Procedure for the two-step reaction:

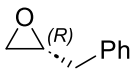


Scheme 119: Procedure for the sequential I/Li-exchange electrophile quench sequence.

A dry and Ar-flushed Schlenk-tube was charged with *n*-pentane/diethyl ether (1.2 mL/0.8 mL) and cooled to −100 °C. *t*-BuLi (2.5 equiv) was added at −100 °C. A solution of the secondary alkyl iodide (*R*)-**114a** (0.1 mmol, 1.0 equiv) in diethyl ether (0.4 mL) was added dropwise over a period of 60 s. Subsequently, the electrophile **112k** (2.5 equiv) was added dropwise and the reaction mixture was stirred for 2 min at −100 °C. After quenching with sat. aq. NH_4Cl product (*R*)-**136a** was obtained.

3.3 Synthesis of Starting Materials

(*R*)-2-benzyloxirane (*R*-138a):



The epoxide (*R*)-**138a** was prepared according to **TP3** using phenylmagnesium chloride (0.5 M, 48 mL, 24 mmol, 1.2 equiv), CuI (152.4 mg, 4 mol%) and (*R*)-epichlorohydrin (*R*-**137**, 1.6 mL, 1.85 g, 20 mmol, 1.0 equiv). After quenching of the alcohol, the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting yellow oil was dissolved in a 1:1 mixture of Et_2O (5 mL) and water (5 mL), treated with KOH (2.47 g, 44 mmol, 2.2 equiv) and heated to 60 °C. After 1 h, a second charge of KOH (561 mg, 10 mmol, 0.5 equiv) was added. When TLC indicated consumption of the starting material, the mixture was extracted with Et_2O (3×20 mL). The combined organic layers were dried with $MgSO_4$, filtered and carefully concentrated.

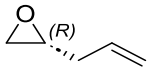
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.35–7.29 (m, 2H), 7.26–7.21 (m, 2H), 3.15 (tdd, *J* = 5.5, 3.9, 2.7 Hz, 1H), 2.92 (dd, *J* = 14.5, 5.7 Hz, 1H), 2.86–2.77 (m, 2H), 2.55 (dd, *J* = 5.0, 2.6 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 137.3, 129.1, 128.7, 126.8, 52.6, 47.0, 38.9.

$[\alpha]_D^{20}$: + 17.0 (c = 1.86., EtOH); Lit: **$[\alpha]_D$**: +17.5 (c = 1.94, EtOH);

The data is in accordance with literature values.[401]

(*R*)-2-allyloxirane (*R*-138b):



The epoxide (*R*)-**138b** was prepared according to **TP3** using vinylmagnesium chloride (0.5 M, 48 mL, 24 mmol, 1.2 equiv), CuI (152.4 mg, 4 mol%) and (*R*)-epichlorohydrin (*R*-**137**, 1.6 mL, 1.85 g, 20 mmol, 1.0 equiv). The combined organic layers were dried with $MgSO_4$, filtered and carefully concentrated. The resulting oil was treated with KOH (2.47 g, 44 mmol, 2.2 equiv) and heated to 60 °C. When TLC indicated consumption of the starting material, the mixture was extracted with Et_2O (3×20 mL). The combined organic layers were dried with $MgSO_4$, filtered and distilled off (300 mbar, 75 °C).

[401] M. Amatore, T. D. Beeson, S. P. Brown, D. W. C. Macmillan, *Angew. Chem. Int. Ed.* **2009**, *48*, 5121–5124.

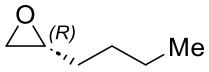
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.89–5.76 (m, 1H), 5.20–5.06 (m, 2H), 3.03–2.95 (m, 1H), 2.76 (dd, *J* = 5.0, 3.9 Hz, 1H), 2.50 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.38–2.24 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 133.1, 117.7, 51.3, 46.7, 36.6.

$[\alpha]_D^{20}$: −5.0 (c = 1.3., $CHCl_3$); Lit: **$[\alpha]_D$**: (*S*)-enantiomer +5.2 (c = 1.4, $CHCl_3$).

The data is in accordance with literature values.[402]

(*R*)-2-butyloxirane (*R*-138c):



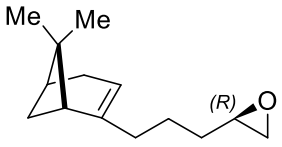
The epoxide (*R*)-**138c** was prepared according to **TP3** using propylmagnesium chloride (0.5 M, 48 mL, 24 mmol, 1.2 equiv), CuI (152.4 mg, 4 mol%) and (*R*)-epichlorohydrin (*R*-**137**, 1.6 mL, 1.85 g, 20 mmol, 1.0 equiv). The combined organic layers were dried with $MgSO_4$, filtered and carefully concentrated. The resulting oil was treated with KOH (2.47 g, 44 mmol, 2.2 equiv) and heated to 60 °C. When TLC indicated consumption of the starting material, the mixture was extracted with Et_2O (3×20 mL). The combined organic layers were dried with $MgSO_4$, filtered and distilled off (300 mbar, 115 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 2.90 (tdd, *J* = 5.6, 3.9, 2.7 Hz, 1H), 2.75 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.46 (dd, *J* = 5.1, 2.8 Hz, 1H), 1.53 (tdd, *J* = 6.9, 5.5, 1.7 Hz, 2H), 1.49–1.31 (m, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 52.55, 47.29, 32.33, 28.24, 22.67, 14.14.
$[\alpha]_D^{20}$: +10.5 (c = 1.05, $CHCl_3$); Lit: $[\alpha]_D^{20}$: +9.1 (c = 1.00, $CHCl_3$).

The data is in accordance with literature values.[403]

(*R*)-2-(3-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)propyl)oxirane (*R*,*R*,*S*-138d):



[402] P. Gupta, P. Kumar, *Tetrahedron: Asymmetry* **2007**, *18*, 1688–1692.
[403] A. Berkessel, E. Ertürk, *Adv. Synth. Catal.* **2006**, *348*, 2619–2625.

According to a modified literature procedure,[404] a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (340 mg, 14.0 mmol, 1.4 equiv). Dry THF (5 mL) was added as well as a corn of I_2 for activation. A solution of (1*R*)-nopol bromide[405] (2.75 g, 12.0 mmol, 1.2 equiv) in 5 mL of dry THF was added dropwise at 0 °C. After addition, the mixture was stirred at room temperature for 3 h. The concentration of the Grignard reagent was determined by titration with I_2 in THF.

The epoxide (*R*,*R*,*S*)-**138d** was afterwards prepared according to **TP3** using (1*R*)-nopolmagnesium bromide (ca. 0.5 M, 20 mL, 10 mmol, 1.2 equiv), CuI (61 mg, 4 mol%) and (*R*)-epichlorohydrin (*R*-**137**, 627 µL, 740 mg, 8 mmol, 1.0 equiv). After quenching of the alcohol, the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting yellow oil was dissolved in a 1:1 mixture of Et_2O (5 mL) and water (5 mL), treated with KOH (953 mg, 17 mmol, 2.2 equiv) and heated to 60 °C. When TLC indicated consumption of the starting material, the mixture was extracted with Et_2O (3×20 mL). The combined organic layers were dried with $MgSO_4$, filtered and carefully concentrated.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.23–5.14 (m, 1H), 2.95–2.86 (m, 1H), 2.75 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.35 (dt, *J* = 8.5, 5.6 Hz, 1H), 2.29–2.12 (m, 2H), 2.10–2.05 (m, 1H), 2.03–1.91 (m, 3H), 1.61–1.39 (m, 4H), 1.26 (s, 3H), 1.13 (d, *J* = 8.5 Hz, 1H), 0.82 (s, 3H).

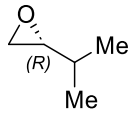
^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.1, 116.3, 52.5, 47.4, 45.8, 41.0, 38.1, 36.7, 32.4, 31.8, 31.4, 26.5, 23.7, 21.4.
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3041, 3026, 2984, 2914, 2879, 2833, 1481, 1467, 1456, 1433, 1410, 1381, 1364, 1346, 1331, 1262, 1219, 1204, 1182, 1128, 1099, 1080, 957, 944, 935, 920, 886, 866, 832, 794, 777, 758, 736.

MS (70 eV, EI): m/z (%): 145 (46), 131 (24), 117 (56), 105 (38), 91 (100).

HRMS (EI) for $C_{14}H_{22}O$: calc. $[M]^{+\bullet}$: 206.1671, found: 206.1664.

$[\alpha]_D^{20}$: −24.8 (c = 1.48, $CHCl_3$).

(*R*)-2-isopropyloxirane (*R*-138e):



[404] G. S. Silverman, P. E. Rakita, *Handbook of Grignard Reagents* **1996**, CRC Press, Florida.
[405] B. Akgun, D. G. Hall, *Angew. Chem. Int. Ed.* **2016**, *55*, 3909-3913.

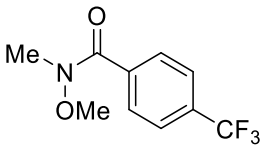
The chiral epoxide (*R*)-**138e** was prepared according to a literature procedure.[406]

^{1}H-NMR ($CDCl_3$, 400 MHz): 2.74–2.66 (m, 2H), 2.50 (dd, *J* = 4.8, 3.0 Hz, 1H), 1.47 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 57.8, 46.3, 30.9, 19.2, 18.3.
$[\alpha]_D^{20}$: −6.1 (c = 1.00, $CHCl_3$), Lit: $[\alpha]_D^{20}$: −6.2 (c = 1.05, $CHCl_3$).

The data is in accordance with literature values.[406]

***N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (112o):**

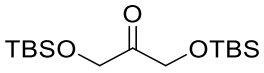


The Weinreb amide **112o** was prepared according to a literature procedure.[407]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.79 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 3.53 (s, 3H), 3.38 (s, 3H).

The data is in accordance with literature values.[407]

2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-138-one (112p):



The ketone **112p** was prepared according to a literature procedure.[408]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.41 (s, 4H), 0.92 (s, 18H), 0.09 (s, 12H).

The data is in accordance with literature values.[408]

[406] H. Hattori, J. Roesslein, P. Caspers, K. Zerbe, H. Miyatake-Ondazabal, D. Ritz, G. Rueedi, K. Gademann, *Angew. Chem. Int. Ed.* **2018**, *57*, 11020–11024.
[407] H. J. A. Dale, C. Nottingham, C. Poree, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2021**, *143*, 2097–2107.
[408] K. Ravindar, M. S. Reddy, P. Deslongchamps, *Org. Lett.* 13, 3178–3181.

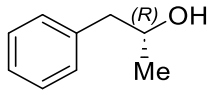
3.3.1 Stereodefined secondary alkyl alcohols

3.3.2 Preparation of literature known stereodefined secondary alkyl alcohols

The alcohols (*R*)- and (*S*)-**139a**, (*R*)- and (*S*)-**139b**, (*S*)-**139c**, and (*R*)- and (*S*)-**139g** were prepared according to literature procedures.[409]

3.3.3 Preparation of new stereodefined secondary alkyl alcohols

(*R*)-1-phenylpropan-2-ol (*R*-139d):



The alcohol (*R*)-**139d** was prepared according to **TP5** from (*R*)-propylene oxide (700 µL, 580 mg, 10.0 mmol, 1.0 equiv) in THF (20 mL), CuI (76 mg, 4 mol%) and phenylmagnesium chloride in THF (24.0 mL, 12.0 mmol, 0.5 M, 1.2 equiv). The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:9 to afford (*R*)-**139d** (1.02 g, 7.5 mmol, 75%) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.36–7.29 (m, 2H), 7.23 (dd, *J* = 7.3, 5.7 Hz, 2H), 4.03 (dqd, *J* = 8.0, 6.2, 4.8 Hz, 1H), 2.80 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.70 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.55 (s, 1H), 1.25 (d, *J* = 6.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 138.5, 129.4, 128.6, 126.5, 68.9, 45.8, 22.8.

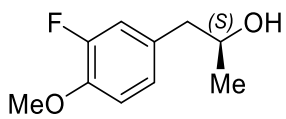
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3349, 3063, 3028, 2969, 2929, 1600, 1496, 1453, 1374, 1310, 1209, 1197, 1180, 1156, 1116, 1078, 1040, 1031, 939, 911, 838, 740, 698.

MS (70 eV, EI): m/z (%):117 (21), 91 (100).

HRMS (EI) for $C_9H_{11}O$: calc. $[M-H]^{+\bullet}$: 135.0810; found: 135.0802.

$[\alpha]_D^{20}$: −36.3 (c = 1.91, $CHCl_3$)

(*S*)-1-(3-fluoro-4-methoxyphenyl)propan-2-ol (*S*-139e):



[409] A. Kremsmair, H. R. Wilke, M. M. Simon, Q. Schmidt, K. Karaghiosoff, P. Knochel, *Chem. Sci.* **2022**, *13*, 44–49.

The alcohol (*S*)-**139e** was prepared according to **TP5** from (*S*)-propylene oxide (1.17 mL, 970 mg, 16.7 mmol, 1.0 equiv) in THF (34 mL), CuI (127 mg, 4 mol%) and the corresponding arylmagnesium reagent in THF (40 mL, 20.0 mmol, 0.5 M, 1.2 equiv). The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:4 to afford (*S*)-**139e** (2.06 g, 11.2 mmol, 67%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.00–6.93 (m, 1H), 6.91 (dd, *J* = 4.3, 2.0 Hz, 2H), 4.04–3.92 (m, 1H), 3.88 (s, 3H), 2.72 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.62 (dd, *J* = 13.7, 8.0 Hz, 1H), 1.48 (s, 1H), 1.23 (d, *J* = 6.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.4 (d, *J* = 245.7 Hz), 146.4 (d, *J* = 10.6 Hz), 131.7 (d, *J* = 6.0 Hz), 125.1 (d, *J* = 3.5 Hz), 117.1 (d, *J* = 17.8 Hz), 113.6 (d, *J* = 2.3 Hz), 68.9, 56.5, 44.8 (d, *J* = 1.4 Hz), 22.9.

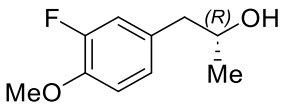
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3357, 2967, 2932, 2840, 1624, 1584, 1516, 1463, 1456, 1443, 1430, 1373, 1312, 1272, 1223, 1183, 1125, 1079, 1052, 1027, 956, 929, 874, 805, 761, 752.

MS (70 eV, EI): m/z (%): 141 (8), 140 (100), 139 (91), 125 (67), 109 (17), 96 (15), 77 (17), 45 (9).

HRMS (EI) for $C_{10}H_{13}FO_2$: calc. $[M]^{+\bullet}$: 184.0900; found: 184.0892.

$[\alpha]_D^{20}$: +18.4 (c = 1.06, $CHCl_3$).

(*R*)-1-(3-fluoro-4-methoxyphenyl)propan-2-ol (*R*-139e):



The alcohol (*R*)-**139e** was prepared according to **TP5** from (*R*)-propylene oxide (1.17 mL, 970 mg, 16.7 mmol, 1.0 equiv) in THF (34 mL), CuI (127 mg, 4 mol%) and the corresponding arylmagnesium reagent in THF (40 mL, 20.0 mmol, 0.5 M, 1.2 equiv). The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:4 to afford (*R*)-**139e** (1.99 g, 10.8 mmol, 65%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.00–6.86 (m, 3H), 3.98 (q, *J* = 5.9 Hz, 1H), 3.87 (s, 3H), 2.72 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.62 (dd, *J* = 13.7, 8.0 Hz, 1H), 1.48 (s, 1H), 1.23 (d, *J* = 6.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.4 (d, *J* = 245.7 Hz), 146.4 (d, *J* = 10.7 Hz), 131.7 (d, *J* = 6.1 Hz), 125.1 (d, *J* = 3.5 Hz), 117.1 (d, *J* = 17.9 Hz), 113.6 (d, *J* = 2.2 Hz), 68.9, 56.5, 44.8 (d, *J* = 1.4 Hz), 22.9.

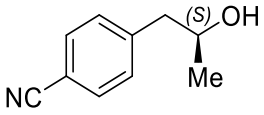
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3367, 2966, 2933, 2840, 1624, 1584, 1517, 1463, 1456, 1443, 1430, 1373, 1313, 1273, 1223, 1183, 1125, 1078, 1053, 1027, 956, 929, 874, 805, 761, 751.

MS (70 eV, EI): m/z (%):141 (8), 140 (100), 139 (92), 125 (66), 109 (17), 96 (15), 77 (18), 45 (9).

HRMS (EI) for $C_{10}H_{13}FO_2$: calc. $[M]^{+\bullet}$: 184.0900; found: 184.0894.

$[\alpha]_D^{20}$: −21.0 (c = 0.98, $CHCl_3$).

(*S*)-4-(2-hydroxypropyl)benzonitrile (*S*-139f):



A solution of 4-iodobenzonitrile (4.58 g, 20 mmol, 1.0 equiv) in THF (10 mL) was cooled to −50 °C before dropwise addition of *i*-PrMgCl·LiCl (1.2 M, 20 mL 24 mmol, 1.2 equiv).[410] The reaction mixture was stirred at −50 °C for 10 min and subsequently charged with CuI (152 mg, 0.8 mmol, 4 mol% equiv). Then, (*S*)-propylene oxide (1.4 mL, 1.16 g, 20.0 mmol, 1.0 equiv) in THF (40 mL). The reaction was let warm to ambient temperature overnight and quenched with sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:9 to afford (*S*)-**139f** (1.45 g, 9.0 mmol, 45%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.64–7.57 (m, 2H), 7.37–7.30 (m, 2H), 4.06 (m, 1H), 2.88–2.73 (m, 2H), 1.42 (s, 1H), 1.26 (d, *J* = 6.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.5, 132.3, 130.4, 119.1, 110.4, 68.6, 45.7, 23.4.

IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3364, 2957, 2925, 2870, 1610, 1514, 1455, 1428, 1413, 1375, 1334, 1316, 1291, 1260, 1202, 1189, 1168, 1154, 1124, 1120, 1055, 1014, 939, 931, 838, 825, 771, 743, 702, 699, 692.

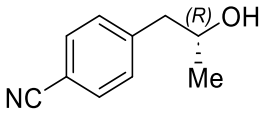
MS (70 eV, EI): m/z (%): 117 (100), 90 (22), 45 (10)

HRMS (EI) for $C_{10}H_{11}ON$: calc. $[M-Me]^{+\bullet}$: 146.0606, found: 146.0600.

$[\alpha]_D^{20}$: −11.8 (c = 1.32, $CHCl_3$).

[410] B. Heinz, D. Djukanovic, M. A. Ganiek, B. Martin, B. Schenkel, P. Knochel, *Org. Lett.* **2020**, *22*, 493–496.

(*R*)-4-(2-hydroxypropyl)benzonitrile (*R*-139f):



A solution of 4-iodobenzonitrile (4.58 g, 20 mmol, 1.0 equiv) in THF (10 mL) was cooled to −50 °C before dropwise addition of *i*-PrMgCl·LiCl (1.2 M, 20 mL 24 mmol, 1.2 equiv).[411] The reaction mixture was stirred at −50 °C for 10 min and subsequently charged with CuI (152 mg, 0.8 mmol, 4 mol% equiv). Then, (*R*)-propylene oxide (1.4 mL, 1.16 g, 20.0 mmol, 1.0 equiv) in THF (40 mL). The reaction was let warm to ambient temperature overnight and quenched with sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:9 to afford (*R*)-**139f** (2.17 g, 13.4 mmol, 67%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.63–7.56 (m, 2H), 7.36–7.30 (m, 2H), 4.05 (p, J = 6.2 Hz, 1H), 2.87–2.72 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.5, 132.3, 130.4, 119.1, 110.4, 68.6, 45.7, 23.4.

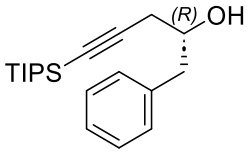
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3318, 2960, 2930, 2873, 2225, 1608, 1586, 1512, 1447, 1375, 1368, 1286, 1251, 1228, 1205, 1190, 1168, 1117, 1105, 1065, 1014, 838, 699.

MS (70 eV, EI): m/z (%): 117 (100), 90 (22), 45 (10).

HRMS (EI) for $C_{10}H_{11}ON$: calc. $[M-H]^{+\bullet}$: 160.0762, found: 160.00756.

$[\alpha]_D^{20}$: +11.6 (c = 1.18, $CHCl_3$).

(*R*)-1-phenyl-5-(triisopropylsilyl)pent-4-yn-2-ol (*R*-139h):



The alcohol (*R*)-**139h** was prepared according to a modified literature procedure.[412] A solution of (triisopropylsilyl)acetylene (6.3 mL, 5.11 g, 28 mmol, 1.4 equiv) in THF (28 mL) was cooled to −78 °C. Then, *n*-BuLi (1.6 M, 25 mL, 40 mmol, 2.0 equiv) was added and the mixture was allowed to

[411] B. Heinz, D. Djukanovic, M. A. Ganiek, B. Martin, B. Schenkel, P. Knochel, *Org. Lett.* **2020**, *22*, 493–496.
[412] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802–6806.

warm to −30 °C and stirred at this temperature for 15 minutes. The reaction mixture was cooled down to −78 °C again and a solution of (*R*)-**138a** in THF (20 mmol, ca. 0.5 M, 40 mL) was added dropwise. $BF_3 \cdot Et_2O$ (2.98 g, 21 mmol, 1.05 equiv) was added and the mixture was allowed to warm to room temperature overnight. A solution of sat. aq. NH_4Cl was added, the phases were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:4 to afford (*R*)-**139h** (5.13 g, 16.2 mmol, 81%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.37–7.28 (m, 2H), 7.27–7.20 (m, 3H), 3.98 (dq, *J* = 7.3, 5.7 Hz, 1H), 2.96 (dd, *J* = 13.5, 5.6 Hz, 1H), 2.85 (dd, *J* = 13.5, 7.3 Hz, 1H), 2.55–2.40 (m, 2H), 1.99–1.85 (m, 1H), 1.09 (d, *J* = 3.5 Hz, 18H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 138.1, 129.6, 128.7, 126.7, 104.6, 84.1, 71.2, 42.6, 28.1, 18.8, 11.4.

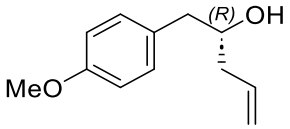
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3374, 3029, 2942, 2891, 2864, 2173, 1602, 1497, 1463, 1456, 1383, 1366, 1292, 1243, 1164, 1073, 1049, 1018, 996, 918, 882, 742, 699, 675, 663.

MS (70 eV, EI): m/z (%): 255 (38), 131 (36), 103 (40), 91 (100).

HRMS (EI) for $C_{20}H_{32}OSi$: calc. $[M]^{+\bullet}$: 316.2222, found: 316.2215.

$[\alpha]_D^{20}$: −17.8 (c = 1.2, $CHCl_3$).

(*R*)-1-(4-methoxyphenyl)pent-4-en-2-ol (*R*-139i):



The alcohol (*R*)-**139i** was prepared according to **TP5** from (*R*)-**138b** (672 mg, 8.0 mmol, 1.0 equiv) dissolved in THF (16 mL), CuI (61 mg, 4 mol%) and the corresponding aryl magnesium reagent in THF (19.2 mL, 9.6 mmol, 0.5 M, 1.2 equiv). The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:2 to afford (*R*)-**139i** (1.21 g, 6.3 mmol, 79%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.17–7.11 (m, 2H), 6.90–6.84 (m, 2H), 5.95–5.80 (m, 1H), 5.21–5.10 (m, 2H), 3.80 (s, 4H), 2.77 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.66 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.39–2.28 (m, 1H), 2.21 (dtt, *J* = 14.1, 7.7, 1.2 Hz, 1H), 1.71 (d, *J* = 3.1 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 158.4, 134.9, 130.5, 130.4, 118.2, 114.1, 71.9, 55.4, 42.5, 41.2.

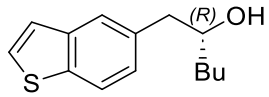
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3412, 3075, 3002, 2933, 2911, 2836, 1640, 1612, 1584, 1511, 1464, 1456, 1441, 1420, 1354, 1318, 1300, 1243, 1177, 1108, 1033, 997, 914, 880, 830, 806, 753.

MS (70 eV, EI): m/z (%): 159 (22), 144 (17), 121 (100), 91 (29), 77 (17).

HRMS (EI) for $C_{12}H_{16}O_2$: calc. $[M]^{+\bullet}$: 192.1150, found: 1141.

$[\alpha]_D^{20}$: −41.1 (c = 0.86, $CHCl_3$).

(*R*)-1-(benzo[*b*]thiophen-5-yl)hexan-2-ol (*R*-139j):



The alcohol (*R*)-**139j** was prepared according to **TP5** from (*R*)-**138c** (801 mg, 8.0 mmol, 1.0 equiv) dissolved in THF (16 mL), CuI (61 mg, 4 mol%) and the corresponding aryl magnesium reagent in THF (19.2 mL, 9.6 mmol, 0.5 M, 1.2 equiv). The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:2 to afford (*R*)-**139j** (1.31 g, 5.6 mmol, 79%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.83 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.30 (d, *J* = 5.4 Hz, 1H), 7.22 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.91–3.83 (m, 1H), 2.97 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.76 (dd, *J* = 13.6, 8.5 Hz, 1H), 1.56–1.46 (m, 4H), 1.44–1.28 (m, 3H), 0.92 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.2, 138.1, 134.8, 126.9, 126.1, 124.3, 123.8, 122.7, 73.0, 44.1, 36.7, 28.1, 22.9, 14.3.

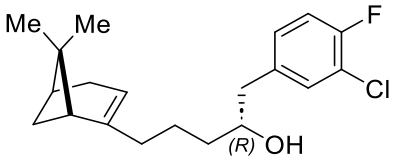
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3421, 2962, 2952, 2922, 2906, 2871, 2858, 1465, 1435, 1420, 1402, 1349, 1333, 1321, 1262, 1223, 1144, 1126, 1114, 1067, 1049, 1035, 1012, 980, 902, 895, 882, 858, 832, 807, 768, 762, 753, 704, 691, 667.

MS (70 eV, EI): m/z (%): 216 (20), 173 (50), 160 (16), 147 (100), 129 (18).

HRMS (EI) for $C_{14}H_{18}OS$: calc. $[M]^{+\bullet}$: 234.1078, found: 234.1068.

$[\alpha]_D^{20}$: −8.2 (c = 1.15, $CHCl_3$).

(*R*)-1-(3-chloro-4-fluorophenyl)-5-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)pentan-2-ol (*R,R,S*-139k):



The alcohol (*R,R,S*)-7**k** was prepared according to **TP5** from (*R,R,S*)-**138d** (1.45 g, 7.0 mmol, 1.0 equiv) dissolved in THF (16 mL), CuI (61 mg, 4 mol%) and the corresponding aryl magnesium reagent in THF (18.0 mL, 9.0 mmol, 0.5 M, 1.2 equiv). The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:3 to afford (*R,R,S*)-**139k** (1.89 g, 5.6 mmol, 80%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.26 (dd, *J* = 5.4, 1.8 Hz, 1H), 7.07 (dd, *J* = 6.8, 1.3 Hz, 2H), 5.25–5.12 (m, 1H), 3.85–3.71 (m, 1H), 2.75 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.62 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.34 (dt, *J* = 8.5, 5.6 Hz, 1H), 2.28–2.13 (m, 2H), 2.10–2.03 (m, 1H), 2.02–1.92 (m, 3H), 1.62–1.35 (m, 4H), 1.26 (s, 3H), 1.10 (d, *J* = 8.4 Hz, 1H), 0.80 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 157.0 (d, *J* = 247.2 Hz), 148.1, 135.9 (d, *J* = 4.0 Hz), 131.5, 129.2 (d, *J* = 6.9 Hz), 120.9 (d, *J* = 17.6 Hz), 116.6 (d, *J* = 20.8 Hz), 116.3, 72.5, 45.8, 43.1, 41.0, 38.1, 36.8, 36.7, 31.8, 31.4, 26.5, 23.3, 21.3.

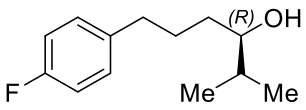
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3383, 2976, 2916, 2872, 2834, 1501, 1457, 1407, 1382, 1365, 1350, 1331, 1264, 1248, 1220, 1204, 1182, 1152, 1121, 1100, 1075, 1061, 1026, 886, 816, 796, 770, 708, 690.

MS (70 eV, EI): m/z (%): 197 (21), 175 (41), 143 (72), 131 (54), 119 (38), 105 (32), 91 (100).

HRMS (EI) for $C_{20}H_{26}ClFO$: calc. $[M]^{+\bullet}$: 336.1656, found: 336.1652.

$[\alpha]_D^{20}$: −20.8 (c = 1.2, $CHCl_3$).

(*R*)-6-(4-fluorophenyl)-2-methylhexan-3-ol (*R*-139l):



According to a modified literature procedure,[413] a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (340 mg, 14.0 mmol, 1.4 equiv). Dry THF (5 mL) was added as well as a corn of I_2 for activation. A solution of 1-(2-

[413] G. S. Silverman, P. E. Rakita, *Handbook of Grignard Reagents* **1996**, CRC Press, Florida.

bromoethyl)-4-fluorobenzene (1.68 mL, 2.43 g, 12.0 mmol, 1.2 equiv) in 5 mL of dry THF was added dropwise at 0 °C. After addition, the mixture was stirred at room temperature for 2 h. The concentration of the Grignard reagent was determined by titration with I_2 in THF.[414]

Then, CuI (76 mg, 4 mol%) and (*R*)-**138e** (ca. 860 mg, ca. 0.5 M, 10.0 mmol, 1.0 equiv) was added dropwise to the diluted (ca. 0.5 M) Grignard reagent at 0 °C and allowed to warm to room temperature overnight. Thereafter, the mixture was quenched with sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**139l** (1.56 g, 7.4 mmol, 74%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.17–7.09 (m, 2H), 7.00–6.92 (m, 2H), 3.43–3.34 (m, 1H), 2.68–2.53 (m, 2H), 1.87–1.73 (m, 1H), 1.69–1.56 (m, 2H), 1.56–1.35 (m, 2H), 1.30 (d, *J* = 5.2 Hz, 1H), 0.90 (dd, *J* = 6.8, 3.5 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 161.3 (d, *J* = 243.0 Hz), 138.2 (d, *J* = 3.2 Hz), 129.8 (d, *J* = 7.7 Hz), 115.1 (d, *J* = 21.0 Hz), 76.7, 35.2, 33.7, 28.2, 19.0, 17.2.

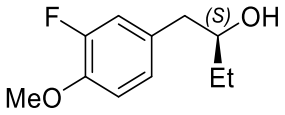
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3361, 2958, 2934, 2891, 2872, 2866, 1601, 1509, 1462, 1385, 1368, 1220, 1157, 1106, 1096, 1057, 1016, 976, 830, 822, 760, 702.

MS (70 eV, EI): m/z (%): 149 (33), 135 (13), 122 (100).

HRMS (EI) for $C_{13}H_{19}FO$: calc. $[M]^{+\bullet}$: 210.1420, found: 210.1410.

$[\alpha]_D^{20}$: −16.7 (c = 1.63, $CHCl_3$).

(*S*)-1-(3-fluoro-4-methoxyphenyl)butan-2-ol (*S*-139m):



The alcohol (*S*)-**139m** was prepared according to **TP5** from (*S*)-butylene oxide (700 µL, 577 mg, 8.0 mmol, 1.0 equiv) dissolved in THF (16 mL), CuI (61 mg, 4 mol%) and the corresponding aryl magnesium reagent in THF (19.2 mL, 9.6 mmol, 0.5 M, 1.2 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**139m** (1.35 g, 6.8 mmol, 71%) as a colorless oil.

[414] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890–891.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.01–6.84 (m, 3H), 3.87 (s, 3H), 3.70 (tt, *J* = 7.5, 4.6 Hz, 1H), 2.75 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.57 (dd, *J* = 13.8, 8.3 Hz, 1H), 1.61–1.42 (m, 3H), 0.99 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.4 (d, *J* = 245.6 Hz), 146.3 (d, *J* = 10.7 Hz), 131.8 (d, *J* = 6.1 Hz), 125.1 (d, *J* = 3.5 Hz), 117.1 (d, *J* = 17.9 Hz), 113.6, 74.0, 56.4, 42.6, 29.7, 10.2.

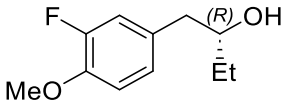
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3377, 3008, 3004, 2934, 2877, 2840, 1624, 1584, 1516, 1463, 1443, 1429, 1379, 1311, 1271, 1222, 1182, 1149, 1125, 1056, 1025, 977, 956, 875, 846, 805, 778, 760, 741

MS (70 eV, EI): m/z (%): 165 (20), 140 (100), 125 (62), 109 (28), 77 (12).

HRMS (EI) for $C_{11}H_{15}FO_2$: calc. $[M]^{+\bullet}$: 198.1056, found: 198.1047.

$[\alpha]_D^{20}$: +21.5 (c = 0.78, $CHCl_3$).

(*R*)-1-(3-fluoro-4-methoxyphenyl)butan-2-ol (*R*-139m):



The alcohol (*R*)-**139m** was prepared according to **TP5** from (*R*)-butylene oxide (700 µL, 577 mg, 8.0 mmol, 1.0 equiv) dissolved in THF (16 mL), CuI (61 mg, 4 mol%) and the corresponding aryl magnesium reagent in THF (19.2 mL, 9.6 mmol, 0.5 M, 1.2 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**139m** (1.01 g, 5.1 mmol, 85%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.99–6.86 (m, 3H), 3.86 (s, 3H), 3.69 (m, 1H), 2.74 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.56 (dd, *J* = 13.7, 8.3 Hz, 1H), 1.62–1.42 (m, 3H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 245.4 Hz), 146.2 (d, *J* = 10.7 Hz), 131.8 (d, *J* = 6.0 Hz), 125.1 (d, *J* = 3.4 Hz), 117.1 (d, *J* = 17.9 Hz), 113.5 (d, *J* = 2.2 Hz), 74.0, 56.4, 42.6, 42.6, 29.6, 10.1.

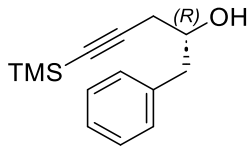
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3381, 2964, 2936, 2878, 2841, 1625, 1585, 1516, 1463, 1454, 1443, 1430, 1311, 1272, 1223, 1183, 1125, 1056, 1026, 977, 956, 876, 805, 760, 743.

MS (70 eV, EI): m/z (%): 140 (100), 125 (65), 109 (25), 97 (13), 77 (24).

HRMS (EI) for $C_{10}H_{15}FO_2$: calc. $[M]^+$: 198.1056, found: 198.1050.

$[\alpha]_D^{20}$: −21.7 (c = 0.78, $CHCl_3$).

(*R*)-1-phenyl-5-(trimethylsilyl)pent-4-yn-2-ol (*R*-139n):



The alcohol (*R*)-**139n** was prepared according to a modified literature procedure.[415] A solution of (trimethylsilyl)acetylene (4.0 mL, 2.75 g, 28 mmol, 1.4 equiv) in THF (28 mL) was cooled to −78 °C. Then, *n*-BuLi (1.6 M, 25 mL, 40 mmol, 2.0 equiv) was added and the mixture was allowed to warm to −30 °C and stirred at this temperature for 15 minutes. The reaction mixture was cooled down to −78 °C again and a solution of (*R*)-**138a** in THF (20 mmol, ca. 0.5 M, 40 mL) was added dropwise. $BF_3{\cdot}Et_2O$ (2.98 g, 21 mmol, 1.05 equiv) was added and the mixture was allowed to warm to room temperature overnight. A solution of sat. aq. NH_4Cl was added, the phases were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography on silica gel with ethyl acetate/*i*-hex = 1:4 to afford (*R*)-**139n** (3.57 g, 15.4 mmol, 77%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.37–7.31 (m, 2H), 7.28–7.23 (m, 3H), 3.99 (dq, *J* = 7.1, 5.7 Hz, 1H), 2.93 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.84 (dd, *J* = 13.6, 7.3 Hz, 1H), 2.51–2.38 (m, 2H), 0.20 (s, 9H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 138.0, 129.5, 128.7, 126.7, 103.1, 88.1, 71.0, 42.6, 28.1, 0.2.

IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3402, 3029, 2958, 2900, 2175, 1603, 1497, 1454, 1418, 1355, 1249, 1077, 1049, 1022, 837, 758, 742, 698.

MS (70 eV, EI): m/z (%): 193 (42), 121 (19), 103 (27), 97 (20), 91 (100), 73 (99).

HRMS (EI) for $C_{14}H_{19}OSi$: calc. $[M-H]^{+\bullet}$: 231.1198, found: 231.1198.

$[\alpha]_D^{20}$: −16.0 (c = 1.49, $CHCl_3$).

[415] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802–6806.

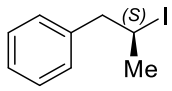
3.3.4 Stereodefined secondary alkyl iodides

3.3.5 Preparation of literature known stereodefined secondary alkyl iodides

The iodides (*R*)- and (*S*)-**114a**, (*R*)- and (*S*)-**114b**, (*S*)-**114c**, and (*R*)- and (*S*)-**114g** were prepared according to literature procedures. A. Kremsmair, H. R. Wilke, M. M. Simon, Q. Schmidt, K. Karaghiosoff, P. Knochel, *Chem. Sci.* **2022**, *13*, 44–49.

3.3.6 Preparation of new stereodefined secondary alkyl iodides

(*S*)-(2-iodopropyl)benzene (*S*-114d):



The iodide (*S*)-**114d** was prepared according to **TP6** from the alcohol (*R*)-**139d** (681 mg, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:1000 to afford (*S*)-**114d** (1.02 g, 4.15 mmol, 83%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.35–7.27 (m, 3H), 7.21–7.16 (m, 2H), 4.35 (h, *J* = 7.0 Hz, 1H), 3.30 (dd, *J* = 14.1, 7.2 Hz, 1H), 3.07 (dd, *J* = 14.1, 7.6 Hz, 1H), 1.90 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 139.8, 129.1, 128.6, 127.0, 49.6, 28.6, 28.2.

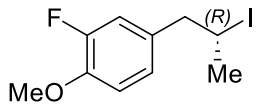
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3062, 3027, 2964, 2918, 2861, 1601, 1585, 1495, 1452, 1376, 1297, 1281, 1227, 1200, 1145, 1134, 1112, 1080, 1065, 1048, 1030, 1002, 988, 916, 896, 880, 860, 816, 800, 742, 696.

MS (70 eV, EI): m/z (%): 119 (47), 91 (100).

HRMS (EI) for $C_9H_{11}I$: calc. $[M]^{+\bullet}$: 245.9905, found: 245.9902.

$[\alpha]_D^{20}$: +42.5 (c = 1.37, $CHCl_3$).

(*R*)-2-fluoro-4-(2-iodopropyl)-1-methoxybenzene (*R*-114e):



The iodide (*R*)-**114e** was prepared according to **TP6** from the alcohol (*S*)-**139e** (921 mg, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:250 to afford (*R*)-**114e** (1.16 g, 3.95 mmol, 79%, 95% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.96–6.85 (m, 3H), 4.27 (h, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 3.18 (dd, *J* = 14.3, 7.5 Hz, 1H), 2.98 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.89 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 245.8 Hz), 146.6 (d, *J* = 10.6 Hz), 132.8 (d, *J* = 6.0 Hz), 124.8 (d, *J* = 3.6 Hz), 116.7 (d, *J* = 18.2 Hz), 113.3 (d, *J* = 2.2 Hz), 56.4, 48.5 (d, *J* = 1.1 Hz), 28.5, 28.1.

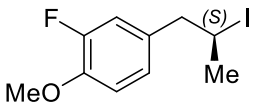
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3000, 2962, 2935, 2912, 2862, 2836, 2166, 1622, 1584, 1514, 1462, 1441, 1432, 1376, 1315, 1271, 1223, 1183, 1124, 1100, 1061, 1026, 990, 951, 898, 879, 856, 807, 760, 743, 727, 696.

MS (70 eV, EI): m/z (%):168 (9), 167 (87), 140 (9), 139 (100), 135 (7), 109 (9), 77 (6).

HRMS (EI) for $C_{10}H_{12}FIO$: calc. $[M]^{+\bullet}$: 293.9917, found: 293.9911.

$[\alpha]_D^{20}$: −31.9 (c = 1.00, $CHCl_3$).

(*S*)-2-fluoro-4-(2-iodopropyl)-1-methoxybenzene (*S*-114e):



The iodide (*S*)-**114e** was prepared according to **TP6** from the alcohol (*R*)-**139e** (921 mg, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:250 to afford (*S*)-**114e** (1.07 g, 3.65 mmol, 73%, 98% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.95–6.86 (m, 3H), 4.27 (h, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 3.18 (dd, *J* = 14.3, 7.5 Hz, 1H), 2.98 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.90 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 245.7 Hz), 146.6 (d, *J* = 10.6 Hz), 132.8 (d, *J* = 5.9 Hz), 124.8 (d, *J* = 3.6 Hz), 116.7 (d, *J* = 18.1 Hz), 113.3 (d, *J* = 2.2 Hz), 56.4, 48.5 (d, *J* = 1.2 Hz), 28.5, 28.1.

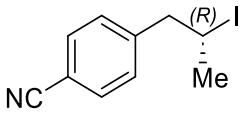
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2962, 2930, 2905, 2891, 2835, 2166, 1623, 1584, 1514, 1462, 1441, 1433, 1375, 1314, 1271, 1223, 1183, 1124, 1100, 1061, 1026, 990, 951, 898, 879, 856, 806, 760, 745, 700, 695.

MS (70 eV, EI): m/z (%):168 (9), 167 (89), 140 (8), 139 (100), 135 (7), 109 (8), 77 (6).

HRMS (EI) for $C_{10}H_{12}FIO$: calc. $[M]^{+\bullet}$: 293.9917, found: 293.9912.

$[\alpha]_D^{20}$: +37.9 (c = 0.96, $CHCl_3$).

(*R*)-4-(2-iodopropyl)benzonitrile (*R*-114f):



The iodide (*R*)-**114f** was prepared according to **TP6** from the alcohol (*S*)-**139f** (806 mg, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:100 to afford (*R*)-**114f** (718 mg, 2.65 mmol, 53%, 90% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.66–7.58 (m, 2H), 7.34–7.27 (m, 2H), 4.36–4.23 (m, 1H), 3.25 (dd, *J* = 14.3, 8.1 Hz, 1H), 3.14 (dd, *J* = 14.3, 6.5 Hz, 1H), 1.94 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 145.0, 132.4, 129.9, 119.0, 111.0, 49.1, 28.5, 26.6.

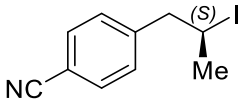
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2964, 2916, 2859, 2226, 1607, 1504, 1444, 1412, 1376, 1297, 1283, 1226, 1205, 1198, 1178, 1150, 1136, 1117, 1100, 1088, 1064, 1058, 1020, 990, 895, 871, 843, 814, 745, 740, 694.

MS (70 eV, EI): m/z (%): 144 (10), 116 (100), 89 (12).

HRMS (EI) for $C_{10}H_{10}NI$: calc. $[M+H]^{+\bullet}$: 271.9936, found: 271.9930.

$[\alpha]_D^{20}$: −41.1 (c = 0.94, $CHCl_3$).

(*S*)-4-(2-iodopropyl)benzonitrile (*S*-114f):



The iodide (*S*)-**114f** was prepared according to **TP6** from the alcohol (*R*)-**139f** (806 mg, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:100 to afford (*S*)-**114f** (759 mg, 2.8 mmol, 56%, 98% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.66–7.58 (m, 2H), 7.34–7.27 (m, 2H), 4.30 (m, 1H), 3.25 (dd, *J* = 14.3, 8.2 Hz, 1H), 3.14 (dd, *J* = 14.3, 6.5 Hz, 1H), 1.94 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 145.0, 132.4, 129.9, 119.0, 111.0, 49.1, 28.5, 26.6.

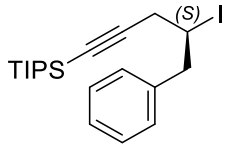
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2976, 2962, 2916, 2858, 2226, 1607, 1504, 1444, 1412, 1376, 1296, 1283, 1226, 1204, 1198, 1178, 1150, 1136, 1117, 1099, 1088, 1064, 1058, 1020, 990, 895, 871, 843, 814, 740, 695.

MS (70 eV, EI): m/z (%): 144 (17), 116 (100), 89 (8).

HRMS (EI) for $C_{10}H_{10}NI$: calc. $[M+H]^{+\bullet}$: 271.9936, found: 271.9931.

$[\alpha]_D^{20}$: +45.9 (c = 0.97, $CHCl_3$).

(*S*)-(4-iodo-5-phenylpent-1-yn-1-yl)triisopropylsilane (*S*-114h):



The iodide (*S*)-**114h** was prepared according to **TP6** from the alcohol (*R*)-**139h** (1.586 g, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:1000 to afford (*S*)-**114h** (1.45 g, 3.4 mmol, 68%) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.35–7.27 (m, 3H), 7.24 (dd, *J* = 8.0, 1.7 Hz, 2H), 4.30 (tt, *J* = 7.3, 5.7 Hz, 1H), 3.39 (dd, *J* = 14.1, 7.3 Hz, 1H), 3.27 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.85 (dd, *J* = 5.7, 1.8 Hz, 2H), 1.12 (d, *J* = 3.6 Hz, 19H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 139.3, 129.3, 128.7, 127.1, 105.5, 84.6, 45.7, 31.2, 31.0, 18.8, 11.4.

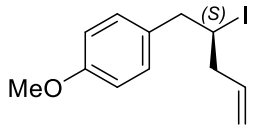
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3028, 2941, 2926, 2890, 2864, 2176, 2169, 1602, 1496, 1462, 1455, 1442, 1418, 1383, 1366, 1346, 1303, 1254, 1222, 1168, 1124, 1074, 1062, 1029, 1019, 995, 956, 918, 882, 849, 744, 698, 677, 665.

MS (70 eV, EI): m/z (%): 383 (35), 255 (100), 109 (30), 91 (100), 75 (20).

HRMS (EI) for $C_{20}H_{31}ISi$: calc. $[M]^{+\bullet}$: 426.1240, found: 426.1232.

$[\alpha]_D^{20}$: +2.9 (c = 1.82, $CHCl_3$).

(*S*)-1-(2-iodopent-4-en-1-yl)-4-methoxybenzene (*S*-114i):



The iodide (*S*)-**114i** was prepared according to **TP6** from the alcohol (*R*)-**139i** (961 mg, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:100 to afford (*S*)-**114i** (861 mg, 2.85 mmol, 57%, 92% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.15 – 7.08 (m, 2H), 6.88 – 6.83 (m, 2H), 5.86 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.24 (qd, *J* = 7.5, 5.2 Hz, 1H), 3.80 (s, 3H), 3.19 (dd, *J* = 14.4, 7.7 Hz, 1H), 3.11 (dd, *J* = 14.4, 7.0 Hz, 1H), 2.67 – 2.51 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 158.6, 136.5, 131.9, 130.2, 118.1, 113.9, 55.4, 45.9, 43.5, 36.9.

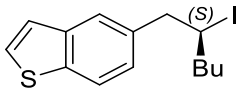
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3076, 3000, 2952, 2834, 1640, 1610, 1584, 1510, 1464, 1439, 1433, 1301, 1244, 1176, 1130, 1107, 1034, 1003, 989, 916, 831, 809, 753, 712, 697.

MS (70 eV, EI): m/z (%): 260 (16), 134 (100), 121 (47), 91 (21).

HRMS (EI) for $C_{12}H_{15}IO$: calc. $[M]^{+\bullet}$: 302.0168, found: 302.0160.

$[\alpha]_D^{20}$: +6.4 (c =1.3, $CHCl_3$).

(*S*)-5-(2-iodohexyl)benzo[*b*]thiophene (*S*-114j):



The iodide (*S*)-**114j** was prepared according to **TP6** from the alcohol (*R*)-**139j** (1.17 g, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:1000 to afford (*S*)-**114j** (877 mg, 2.55 mmol, 52%, 92% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.82 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 1.7 Hz, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.31 (dd, *J* = 5.4, 0.8 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 4.39–4.29 (m, 1H), 3.41 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.29 (dd, *J* = 14.3, 7.0 Hz, 1H), 1.90–1.78 (m, 1H), 1.77–1.68 (m, 1H), 1.66–1.55 (m, 1H), 1.46–1.21 (m, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.0, 138.3, 136.2, 127.0, 125.6, 124.0, 123.8, 122.5, 47.6, 39.5, 39.4, 32.0, 22.0, 14.1.

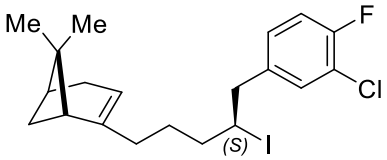
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2954, 2925, 2869, 2856, 2838, 2831, 1463, 1455, 1436, 1421, 1378, 1326, 1299, 1261, 1240, 1226, 1160, 1139, 1089, 1050, 1001, 936, 922, 894, 831, 806, 767, 753, 730, 702, 689, 670.

MS (70 eV, EI): m/z (%): 216 (11), 173 (33), 147 (100), 129 (15).

HRMS (EI) for $C_{14}H_{17}IS$: calc. $[M]^{+\bullet}$: 344.0096, found: 344.0086

$[\alpha]_D^{20}$: +2.3 (c = 1.3, $CHCl_3$).

(1*R*,5*S*)-2-((*S*)-5-(3-chloro-4-fluorophenyl)-4-iodopentyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (*R,S,S*-114k):



The iodide (*R,S,S*)-**114k** was prepared according to **TP6** from the alcohol (*R,S,R*)-**139k** (1.68 g, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with hexane to afford (*R,S,S*)-**114k** (1.09 g, 2.45 mmol, 49%, dr = 95:5, 98% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.22 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.11–7.01 (m, 2H), 5.18–5.12 (m, 1H), 4.23–4.12 (m, 1H), 3.19 (dd, *J* = 14.4, 8.1 Hz, 1H), 3.10 (dd, *J* = 14.5, 6.6 Hz, 1H), 2.37–2.30 (m, 1H), 2.28–2.11 (m, 2H), 2.10–2.04 (m, 1H), 2.01–1.89 (m, 3H), 1.88–1.56 (m, 3H), 1.52–1.40 (m, 1H), 1.26 (s, 3H), 1.07 (d, *J* = 8.5 Hz, 1H), 0.80 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 157.2 (d, *J* = 247.9 Hz), 147.7, 137.0 (d, *J* = 4.0 Hz), 131.1, 128.8 (d, *J* = 7.1 Hz), 120.9 (d, *J* = 17.7 Hz), 116.7, 116.6 (d, *J* = 3.6 Hz), 46.4, 45.8, 40.9, 39.4, 38.1, 37.7, 35.9, 31.8, 31.4, 27.3, 26.5, 21.36.

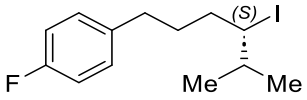
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2983, 2914, 2832, 1597, 1499, 1467, 1453, 1434, 1407, 1381, 1364, 1330, 1302, 1265, 1248, 1218, 1203, 1181, 1128, 1099, 1082, 1061, 957, 944, 914, 902, 886, 818, 800, 772, 750, 708, 688.

MS (70 eV, EI): m/z (%): 319 (27), 197 (48), 145 (46), 127 (62), 105 (31), 91 (100).

HRMS (EI) for $C_{20}H_{25}ClFI$: calc. $[M]^{+\bullet}$: 446.0673, found: 446.0668.

$[\alpha]_D^{20}$: −25.3 (c = 1.73, $CHCl_3$).

(*S*)-1-fluoro-4-(4-iodo-5-methylhexyl)benzene (*S*-114l):



The iodide (*S*)-**114l** was prepared according to **TP6** from the alcohol (*R*)-**139l** (1.05 g, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with hexane to afford (*S*)-**114l** (816 mg, 2.55 mmol, 51%, 86% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.16–7.09 (m, 2H), 7.00–6.93 (m, 2H), 4.16 (dt, *J* = 9.6, 3.7 Hz, 1H), 2.69–2.54 (m, 2H), 2.03–1.83 (m, 2H), 1.76–1.56 (m, 2H), 1.28–1.18 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 161.4 (d, *J* = 243.3 Hz), 137.6 (d, *J* = 3.2 Hz), 129.8 (d, *J* = 7.8 Hz), 115.2 (d, *J* = 21.0 Hz), 51.9, 38.0, 35.0, 34.3, 32.0, 23.2, 20.1.

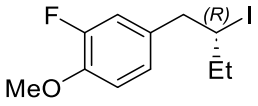
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2962, 2931, 2870, 1601, 1509, 1459, 1416, 1386, 1368, 1316, 1220, 1194, 1156, 1123, 1093, 1055, 1016, 922, 864, 843, 821, 780, 760, 737, 701.

MS (70 eV, EI): m/z (%): 193 (60), 123 (23), 109 (100), 43 (16).

HRMS (EI) for $C_{13}H_{18}FI$: calc. $[M]^{+\bullet}$: 320.0437, found: 320.0448.

$[\alpha]_D^{20}$: +26.7 (c = 1.32, $CHCl_3$).

(*R*)-2-fluoro-4-(2-iodobutyl)-1-methoxybenzene (*R*-114m):



The iodide (*R*)-**114m** was prepared according to **TP6** from the alcohol (*S*)-**139m** (991 mg, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:250 to afford (*R*)-**114m** (1.03 g, 3.35 mmol, 67%, 94% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.96–6.85 (m, 3H), 4.23–4.14 (m, 1H), 3.88 (s, 3H), 3.19 (dd, *J* = 14.4, 7.9 Hz, 1H), 3.08 (dd, *J* = 14.4, 6.8 Hz, 1H), 1.76 (p, *J* = 7.0 Hz, 2H), 1.05 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 245.7 Hz), 146.5 (d, *J* = 10.7 Hz), 133.0 (d, *J* = 6.1 Hz), 124.8 (d, *J* = 3.5 Hz), 116.7 (d, *J* = 18.1 Hz), 113.3 (d, *J* = 2.2 Hz), 56.4, 46.2 (d, *J* = 1.3 Hz), 40.9, 32.7, 14.4.

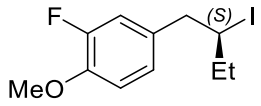
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3003, 2963, 2932, 2908, 2874, 2837, 1622, 1585, 1515, 1460, 1454, 1441, 1433, 1380, 1310, 1271, 1223, 1183, 1124, 1094, 1077, 1027, 954, 907, 872, 806, 783, 760, 741, 712, 695.

MS (70 eV, EI): m/z (%): 181 (12), 139 (100), 109 (5), 77 (3).

HRMS (EI) for $C_{11}H_{14}FIO$: calc. $[M]^{+\bullet}$: 308.0073, found: 308.0066.

$[\alpha]_D^{20}$: −18.0 (c = 1.16, $CHCl_3$).

(*S*)-2-fluoro-4-(2-iodobutyl)-1-methoxybenzene (*S*-114m):



The iodide (*S*)-**114m** was prepared according to **TP6** from the alcohol (*R*)-**139m** (991 mg, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:250 to afford (*S*)-**114m** (1.02 g, 3.35 mmol, 66%, 98% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.97–6.82 (m, 3H), 4.18 (dtd, *J* = 7.9, 6.7, 5.9 Hz, 1H), 3.88 (s, 3H), 3.19 (dd, *J* = 14.4, 7.9 Hz, 1H), 3.08 (dd, *J* = 14.5, 6.8 Hz, 1H), 1.82–1.72 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 245.8 Hz), 146.5 (d, *J* = 10.6 Hz), 133.0 (d, *J* = 6.0 Hz), 124.8 (d, *J* = 3.5 Hz), 116.7 (d, *J* = 18.0 Hz), 113.3 (d, *J* = 2.2 Hz), 56.4, 46.2 (d, *J* = 1.3 Hz), 40.9, 32.7, 14.4.

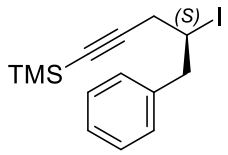
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3005, 2965, 2934, 2875, 2838, 1623, 1586, 1516, 1461, 1454, 1442, 1433, 1381, 1311, 1272, 1224, 1184, 1124, 1094, 1077, 1027, 954, 908, 872, 806, 784, 760, 741, 712.

MS (70 eV, EI): m/z (%): 181 (8), 139 (100), 109 (6), 105 (5), 77 (5).

HRMS (EI) for $C_{11}H_{14}FIO$: calc. $[M]^{+\bullet}$: 308.0073, found: 308.0071.

$[\alpha]_D^{20}$: +17.7 (c = 1.18, $CHCl_3$).

(*S*)-(4-iodo-5-phenylpent-1-yn-1-yl)trimethylsilane (*S*-114n):



The iodide (*S*)-**114n** was prepared according to **TP6** from the alcohol (*R*)-**139n** (1.16 g, 5.0 mmol, 1.0 equiv). The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:1000 to to afford (*S*)-**114n** (1.35 g, 3.95 mmol, 79%) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.36–7.27 (m, 3H), 7.25–7.20 (m, 2H), 4.32–4.24 (m, 1H), 3.35 (dd, *J* = 14.2, 7.0 Hz, 1H), 3.23 (dd, *J* = 14.2, 7.5 Hz, 1H), 2.89–2.75 (m, 2H), 0.21 (s, 9H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 139.2, 129.3, 128.7, 127.1, 104.3, 88.5, 45.7, 31.3, 30.7, 0.1.

IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3064, 3028, 2959, 2898, 2838, 2177, 1603, 1496, 1454, 1434, 1417, 1304, 1249, 1222, 1169, 1156, 1124, 1076, 1029, 1021, 996, 957, 917, 890, 837, 758, 744, 697, 654.

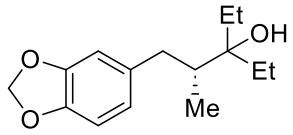
MS (70 eV, EI): m/z (%): 215 (21), 109 (25), 91 (55), 73 (100).

HRMS (EI) for $C_{14}H_{19}ISi$: calc. $[M]^{+\bullet}$: 342.0301, found: 342.0288.

$[\alpha]_D^{20}$: +5.5 (c = 1.01, $CHCl_3$).

3.4 Prepared New Chiral Products

(*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-3-ethyl-2-methylpentan-3-ol (*R*-136a):



The alcohol (*R*)-**136a** was prepared according to **TP7** from the iodide (*R*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) and pentan-3-one (**112k**, 27 µL, 21.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**136a** (15.1 mg, 0.060 mmol, 60%, 93% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.73 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 1.6 Hz, 1H), 6.61 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.92 (s, 2H), 2.92 (dd, *J* = 13.2, 2.9 Hz, 1H), 2.10 (dd, *J* = 13.2, 11.2 Hz, 1H), 1.80 (m, 1H), 1.67–1.49 (m, 4H), 1.14 (s, 1H), 0.91 (td, *J* = 7.5, 3.0 Hz, 6H), 0.77 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.6, 145.6, 136.1, 122.1, 109.6, 108.1, 100.9, 76.2, 41.9, 37.0, 28.3, 28.2, 13.2, 7.7, 7.6.

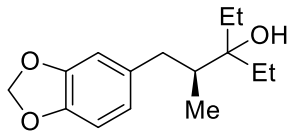
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2967, 2937, 2893, 2887, 2880, 2358, 2215, 2187, 2170, 2146, 1502, 1490, 1457, 1446, 1441, 1358, 1245, 1209, 1187, 1123, 1113, 1096, 1076, 1039, 939, 929, 860, 809, 779.

MS (70 eV, EI): m/z (%): 232 (11), 203 (24), 173 (11), 135 (100), 87 (10).

HRMS (EI) for $C_{15}H_{22}O_3$: calc. $[M]^{+\bullet}$: 250.1569, found: 250.1565.

$[\alpha]_D^{20}$: +12.3 (c = 0.92, $CHCl_3$).

(*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-3-ethyl-2-methylpentan-3-ol (*S*-136a):



The alcohol (*S*)-**136a** was prepared according to **TP7** from the iodide (*S*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) and pentan-3-one (**112k**, 27 µL, 21.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica with diethyl ether/pentane = 1:4 to afford (*S*)-**136a** (17.0 mg, 0.068 mmol, 68%, 90% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.73 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.61 (dd, *J* = 7.8, 1.7 Hz, 1H), 5.92 (s, 2H), 2.92 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.10 (dd, *J* = 13.2, 11.3 Hz, 1H), 1.85–1.75 (m, 1H), 1.68–1.50 (m, 4H), 1.12 (s, 1H), 0.91 (td, *J* = 7.5, 3.0 Hz, 6H), 0.77 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 147.6, 145.6, 136.1, 122.1, 109.6, 108.1, 100.9, 76.2, 41.9, 37.0, 28.3, 28.2, 13.2, 7.8, 7.6.

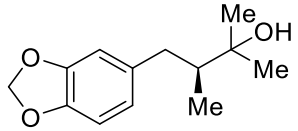
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2968, 2945, 2938, 2930, 2924, 2881, 2217, 2179, 2156, 2129, 1502, 1490, 1460, 1456, 1447, 1440, 1364, 1245, 1208, 1187, 1127, 1094, 1039, 940, 929, 817, 806, 765, 722.

MS (70 eV, EI): m/z (%): 232 (15), 203 (41), 173 (20), 135 (100), 77 (7).

HRMS (EI) for $C_{15}H_{22}O_3$: calc. $[M]^{+\bullet}$: 250.1569, found: 250.1563.

$[\alpha]_D^{20}$: −11.8 (c = 0.88, $CHCl_3$).

(*S*)-4-(benzo[*d*][1,3]dioxol-5-yl)-2,3-dimethylbutan-2-ol (*S*-136b):



The alcohol (*S*)-**136b** was prepared according to **TP7** from the iodide (*S*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) and acetone (**112l**, 18 µL, 14.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136b** (10.0 mg, 0.045 mmol, 45%, 91% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.73 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.7 Hz, 1H), 6.61 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.92 (s, 2H), 3.00 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.06 (dd, *J* = 13.3, 11.1 Hz, 1H), 1.72–1.64 (m, 1H), 1.28 (s, 1H), 1.24 (d, *J* = 5.1 Hz, 6H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.6, 145.7, 135.8, 122.0, 109.6, 108.2, 100.9, 73.4, 46.9, 37.9, 27.9, 26.2, 14.3.

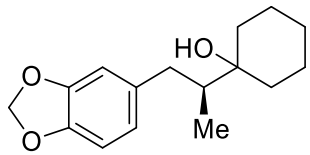
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3380, 2966, 2925, 1503, 1490, 1462, 1441, 1377, 1372, 1246, 1189, 1144, 1098, 1040, 942, 931, 808, 778.

MS (70 eV, EI): m/z (%): 222 (6), 204 (13), 189 (22), 159 (24), 135 (100), 122 (9), 77 (18), 59 (14).

HRMS (EI) for $C_{13}H_{18}O_3$: calc. $[M]^{+\bullet}$: 222.1256, found: 222.1250.

$[\alpha]_D^{20}$: + 29.6 (c = 0.92, $CHCl_3$).

(*S*)-1-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)cyclohexan-1-ol (*S*-136c):



The alcohol (*S*)-**136c** was prepared according to **TP7** from the iodide (*S*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) and cyclohexanone (**112m**, 26 µL, 24.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136c** (16.0 mg, 0.061 mmol, 61%, 92% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.72 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 1.6 Hz, 1H), 6.60 (dd, *J* = 7.8, 1.7 Hz, 1H), 5.92 (s, 2H), 3.00 (dd, *J* = 13.2, 3.0 Hz, 1H), 2.08 (dd, *J* = 13.3, 11.1 Hz, 1H), 1.74–1.42 (m, 11H), 1.25 (s, 1H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.6, 145.6, 136.2, 122.1, 109.6, 108.1, 100.8, 73.5, 45.8, 36.9, 35.1, 33.9, 26.0, 22.1, 22.0, 13.2.

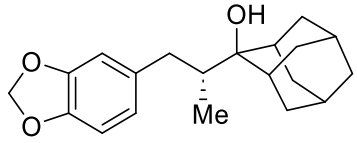
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3463, 2929, 2860, 1698, 1503, 1489, 1441, 1381, 1351, 1310, 1244, 1210, 1187, 1160, 1117, 1038, 957, 939, 928, 904, 871, 846, 835, 806, 780, 731, 714.

MS (70 eV, EI): m/z (%): 135 (100), 109 (11), 77 (16).

HRMS (EI) for $C_{16}H_{22}O_3$: calc. $[M]^{+\bullet}$: 262.1569, found: 262.1563.

$[\alpha]_D^{20}$: +11.6 (c = 1.07, $CHCl_3$).

(1*R*,3*S*,5*R*,7*R*)-2-((*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)adamantan-2-ol (*R*-136d):



The alcohol (*R*)-**136d** was prepared according to **TP7** from the iodide (*R*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) and adamantanone (**112h**, 45.0 mg, 0.3 mmol, 3.0 equiv) at −40 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**136d** (22.6 mg, 0.072 mmol, 72%, 94% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.73 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 1.7 Hz, 1H), 6.60 (dd, *J* = 7.8, 1.7 Hz, 1H), 5.92 (t, *J* = 1.3 Hz, 2H), 2.85 (dd, *J* = 13.3, 2.8 Hz, 1H), 2.35–2.23 (m, 1H), 2.20–2.11 (m, 4H), 1.99 (dd, *J* = 12.8, 3.2 Hz, 1H), 1.92 (q, *J* = 2.9 Hz, 1H), 1.85–1.74 (m, 4H), 1.73–1.56 (m, 5H), 1.43 (s, 1H), 0.74 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.5, 145.5, 136.3, 122.2, 109.7, 108.1, 100.8, 76.1, 38.4, 38.0, 35.7, 34.9, 34.2, 34.1, 33.8, 33.3, 33.2, 27.1, 27.1, 11.3.

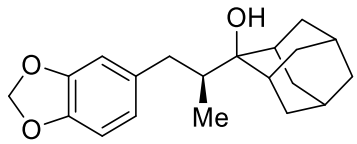
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3533, 3445, 2977, 2914, 2903, 2853, 1503, 1490, 1472, 1452, 1437, 1396, 1376, 1358, 1350, 1329, 1317, 1306, 1244, 1222, 1202, 1186, 1166, 1143, 1135, 1108, 1099, 1082, 1060, 1034, 976, 927, 878, 860, 840, 807, 774, 724, 670.

MS (70 eV, EI): m/z (%): 296 (83), 281 (74), 151 (64), 135 (100), 105 (18), 91 (25), 77 (30).

HRMS (EI) for $C_{20}H_{26}O_3$: calc. $[M]^{+\bullet}$: 314.1882, found: 314.1876.

$[\alpha]_D^{20}$: +28.9 (c = 1.54, $CHCl_3$).

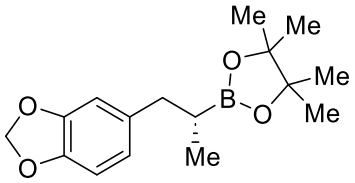
(1*R*,3*S*,5*R*,7*R*)-2-((*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)adamantan-2-ol (*S*-136d):



A solution of alkyl iodide (*S*-**114a**, 0.08 M, 1.00 equiv) and adamantanone (**112h**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*-BuLi (ca. 0.20 M in hexane, 2.85 equiv) were prepared. The solution of *t*-BuLi was pumped by pump A (flow rate A: 5.7 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The solution of the alkyl iodide was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = –20 to 25 °C). The stream was subsequently upon reaching steady state injected for 10 min 30 s into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed

under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136d** (720 mg, 2.3 mmol, 55%, 94% *ee*) as white solid.

(*R*)-2-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*R*-136e):



The boronate (*R*)-**136e** was prepared according to **TP7** from the iodide (*R*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) and methoxy boronic acid pinacol ester (**112n**, 41 µL, 39.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 to afford (*R*)-**136e** (24.1 mg, 0.083 mmol, 83%, 92% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.72–6.68 (m, 2H), 6.64 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.90 (s, 2H), 2.72 (dd, *J* = 13.6, 7.5 Hz, 1H), 2.46 (dd, *J* = 13.6, 8.2 Hz, 1H), 1.35–1.24 (m, 1H), 1.20 (d, *J* = 3.2 Hz, 12H), 0.95 (d, *J* = 7.4 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.4, 145.5, 136.4, 121.8, 109.5, 107.9, 100.7, 83.2, 38.8, 24.9, 24.9, 15.2.

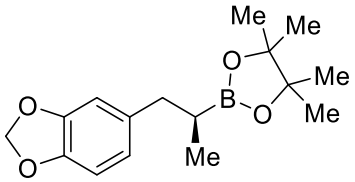
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3373, 2969, 2926, 2883, 1502, 1488, 1440, 1391, 1372, 1346, 1328, 1290, 1243, 1187, 1169, 1148, 1121, 1098, 1075, 1035, 937, 927, 864, 852, 838, 803, 777, 771, 757, 672.

MS (70 eV, EI): m/z (%): 290 (23), 162 (14), 135 (100), 84 (7).

HRMS (EI) for $C_{16}H_{23}BO_4$: calc. $[M]^+$: 290.1689, found: 290.1681.

$[\alpha]_D^{20}$: −6.7 (c = 1.04, $CHCl_3$).

(*S*)-2-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*S*-136e):



The boronate (*S*)-**136e** was prepared according to **TP7** from the iodide (*S*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) and methoxy boronic acid pinacol ester (**112n**, 41 µL, 39.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 to afford (*S*)-**136e** (23.2 mg, 0.080 mmol, 80%, 91% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.72–6.67 (m, 2H), 6.64 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.90 (s, 2H), 2.72 (dd, *J* = 13.6, 7.5 Hz, 1H), 2.46 (dd, *J* = 13.6, 8.3 Hz, 1H), 1.34–1.26 (m, 1H), 1.20 (d, *J* = 3.2 Hz, 12H), 0.95 (d, *J* = 7.4 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.4, 145.5, 136.4, 121.8, 109.5, 107.9, 100.7, 83.2, 38.9, 24.9, 24.9, 15.2.

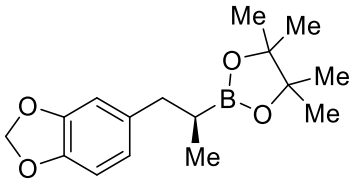
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3373, 2969, 2926, 2883, 1502, 1488, 1440, 1391, 1372, 1346, 1328, 1290, 1243, 1187, 1169, 1148, 1121, 1098, 1075, 1035, 937, 927, 864, 852, 838, 803, 777, 771, 757, 672.

MS (70 eV, EI): m/z (%): 290 (24), 162 (17), 135 (100), 43 (11).

HRMS (EI) for $C_{16}H_{23}BO_4$: calc. $[M]^+$: 290.1689, found: 290.1686.

$[\alpha]_D^{20}$: +3.33 (c = 0.69, $CHCl_3$).

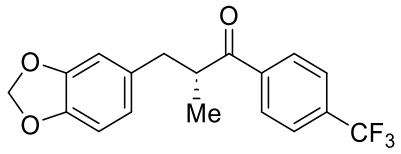
(*S*)-2-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*S*-136e):



A solution of alkyl iodide (*S*-**114a**, 0.08 M, 1.00 equiv) and methoxy boronic acid pinacol ester (**112n**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*-BuLi (ca. 0.20 M in hexane, 3.0 equiv) were prepared. The solution of *t*-BuLi was pumped by pump A (flow rate A: 6.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = 0 to 25 °C. The solution of the alkyl iodide was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = 0 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = 0 to 25 °C). The stream was subsequently upon reaching steady state injected for 1 min 24 s into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted three times with Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude product was purified by flash

column chromatography on silica gel to afford afford (*S*)-**136e** (76 mg, 0.47 mmol, 54%, 88% *ee*) as white solid.

(*R*)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-one (*R*-136f):



The ketone (*R*)-**136f** was prepared according to **TP7** from the iodide (*R*)-**114a** (29.0 mg, 0.1 mmol, 1.0 equiv) and the weinreb amide **112o** (70.0 mg, 0.3 mmol, 3.0 equiv) at −40 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 to afford (*R*)-**136f** (18.8 mg, 0.056 mmol, 56%, 94% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 8.02–7.95 (m, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 6.73–6.59 (m, 3H), 5.90 (q, *J* = 1.4 Hz, 2H), 3.68 (h, *J* = 7.0 Hz, 1H), 3.07 (dd, *J* = 13.8, 6.8 Hz, 1H), 2.64 (dd, *J* = 13.8, 7.3 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 202.9, 146.8 (d, *J* = 158.1 Hz), 139.3, 134.2 (d, *J* = 32.6 Hz), 133.3, 128.6, 125.7 (q, *J* = 3.7 Hz), 123.6 (d, *J* = 272.6 Hz), 122.0, 109.4, 108.2, 100.9, 43.5, 39.1, 17.4.

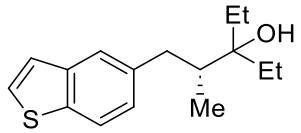
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2969, 2932, 1744, 1686, 1504, 1489, 1458, 1442, 1410, 1322, 1247, 1227, 1167, 1125, 1066, 1039, 1017, 976, 940, 929, 853, 810, 795, 780, 773, 766, 725, 715, 698.

MS (70 eV, EI): m/z (%): 145 (17), 135 (100), 77 (11).

HRMS (EI) for $C_{18}H_{15}F_3O_3$: calc. $[M]^{+\bullet}$: 336.0973, found: 336.0961.

$[\alpha]_D^{20}$: +48.8 (c = 0.84, $CHCl_3$).

(*R*)-1-(benzo[*b*]thiophen-5-yl)-3-ethyl-2-methylpentan-3-ol (*R*-136g):



The alcohol (*R*)-**136g** was prepared according to **TP7** from the iodide (*R*)-**114b** (30.0 mg, 0.1 mmol, 1.0 equiv) and pentan-3-one (**112k**, 27 µL, 21.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**136g** (16.5 mg, 0.063 mmol, 63%, 91% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.79 (d, *J* = 8.2 Hz, 1H), 7.63–7.60 (m, 1H), 7.42 (d, *J* = 5.4 Hz, 1H), 7.28 (dd, *J* = 5.5, 0.8 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.13 (dd, *J* = 13.2, 2.9 Hz, 1H), 2.30 (dd, *J* = 13.2, 11.3 Hz, 1H), 1.97–1.89 (m, 1H), 1.72–1.56 (m, 4H), 1.17 (s, 1H), 0.95 (m, 6H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.0, 138.4, 137.4, 126.6, 126.1, 124.0, 123.7, 122.3, 76.3, 42.1, 37.2, 28.4, 28.2, 13.3, 7.8, 7.7.

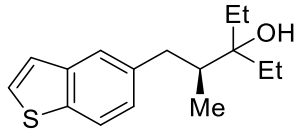
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2959, 2955, 2921, 2873, 2869, 2852, 1699, 1695, 1683, 1456, 1436, 1420, 1375, 1326, 1260, 1231, 1160, 1147, 1140, 1100, 1089, 1061, 1050, 988, 949, 940, 891, 831, 806, 767, 753, 703, 689, 668.

MS (70 eV, EI): m/z (%): 207 (4), 174 (6), 147 (100), 121 (5).

HRMS (EI) for $C_{16}H_{20}S$: calc. $[M\text{-}H_2O]^{+\bullet}$: 244.1280, found: 244.1283.

$[\alpha]_D^{20}$: −35.3 (c = 0.76, $CHCl_3$).

(*S*)-1-(benzo[*b*]thiophen-5-yl)-3-ethyl-2-methylpentan-3-ol (*S*-136g):



The alcohol (*S*)-**136g** was prepared according to **TP7** from the iodide (*S*)-**114b** (30.0 mg, 0.1 mmol, 1.0 equiv) and pentan-3-one (**112k**, 27 µL, 21.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136g** (17.6 mg, 0.067 mmol, 67%, 96% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.79 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.42 (d, *J* = 5.4 Hz, 1H), 7.28 (dd, *J* = 5.4, 0.8 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.13 (dd, *J* = 13.1, 2.8 Hz, 1H), 2.30 (dd, *J* = 13.2, 11.3 Hz, 1H), 1.93 (m, 1H), 1.73–1.57 (m, 4H), 1.18 (s, 1H), 0.95 (m, 6H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.0, 138.4, 137.3, 126.6, 126.1, 124.0, 123.7, 122.3, 76.3, 42.0, 37.2, 28.4, 28.2, 13.3, 7.8, 7.7.

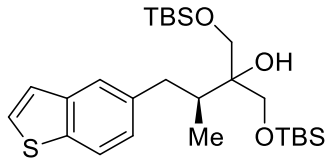
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3486, 2967, 2938, 2880, 1460, 1437, 1421, 1379, 1260, 1159, 1145, 1125, 1090, 1050, 940, 893, 833, 810, 754, 720, 692.

MS (70 eV, EI): m/z (%): 244 (10), 215 (29), 173 (10), 147 (100), 134 (6).

HRMS (EI) for $C_{16}H_{22}OS$: calc. $[M]^{+\bullet}$: 262.1391, found: 262.1389.

$[\alpha]_D^{20}$: +43.4 (c = 0.78, $CHCl_3$).

(*S*)-6-(1-(benzo[*b*]thiophen-5-yl)propan-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (*S*-136h):



The alcohol (*S*)-**136h** was prepared according to **TP7** from the iodide (*S*)-**114b** (30.0 mg, 0.1 mmol, 1.0 equiv) and ketone **112p** (95.6 mg, 0.3 mmol, 3.0 equiv) at −40 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136h** (35.6 mg, 0.072 mmol, 72%, 98% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.78 (d, *J* = 8.2 Hz, 1H), 7.63–7.60 (m, 1H), 7.41 (d, *J* = 5.5 Hz, 1H), 7.27 (dd, *J* = 5.4, 0.8 Hz, 1H), 7.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.71 (dd, *J* = 11.5, 9.6 Hz, 2H), 3.59 (d, *J* = 9.5 Hz, 2H), 3.19 (dd, *J* = 13.3, 3.0 Hz, 1H), 2.64 (s, 1H), 2.42 (dd, *J* = 13.3, 11.5 Hz, 1H), 2.02 (m, 1H), 0.93 (d, *J* = 4.6 Hz, 18H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.11–0.08 (m, 12H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.0, 138.4, 137.3, 126.5, 126.1, 124.1, 123.8, 122.2, 75.3, 64.1, 63.9, 39.3, 37.1, 26.0, 18.4, 13.1, -5.3, -5.3, -5.4, -5.4.

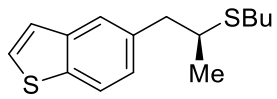
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3555, 2953, 2927, 2903, 2894, 2856, 1736, 1683, 1669, 1471, 1463, 1437, 1389, 1361, 1328, 1291, 1251, 1144, 1087, 1063, 1027, 1005, 939, 913, 890, 888, 834, 814, 774, 753, 732, 725, 722, 715, 698, 690, 667.

MS (70 eV, EI): m/z (%): 331 (24), 261 (21), 213 (100), 199 (21), 147 (74), 105 (13), 89 (27), 73 (39).

HRMS (EI) for $C_{24}H_{39}O_2SSi_2$: calc. $[M-C_2H_7O]^+$: 447.2209, found: 447.2204.

$[\alpha]_D^{20}$: −18.4 (c = 0.78, $CHCl_3$).

(*S*)-5-(2-(butylthio)propyl)benzo[*b*]thiophene (*S*-136i):



The sulfide (*S*)-**136i** was prepared according to **TP7** from the iodide (*S*)-**114b** (30.0 mg, 0.1 mmol, 1.0 equiv) and dibutyl disulfide (**112q**, 48 µL, 44.6 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:100 to afford (*S*)-**136i** (16.7 mg, 0.063 mmol, 63%, 93% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.80 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.43 (d, *J* = 5.5 Hz, 1H), 7.30 (dd, *J* = 5.5, 0.8 Hz, 1H), 7.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.12 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.09–2.99 (m, 1H), 2.77 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.60–2.53 (m, 2H), 1.63–1.52 (m, 2H), 1.48–1.35 (m, 2H), 1.24 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.0, 137.9, 135.9, 126.7, 126.0, 124.1, 123.8, 122.3, 43.8, 41.7, 32.0, 30.6, 22.3, 20.8, 13.8.

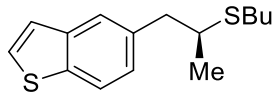
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2956, 2924, 2870, 2861, 1454, 1436, 1421, 1373, 1364, 1327, 1274, 1261, 1221, 1183, 1160, 1145, 1089, 1065, 1050, 1012, 891, 832, 808, 769, 753, 725, 689, 668.

MS (70 eV, EI): m/z (%): 147 (50), 117 (53), 75 (100).

HRMS (EI) for $C_{15}H_{20}S_2$: calc. $[M]^{+\bullet}$: 264.1006, found: 264.0997.

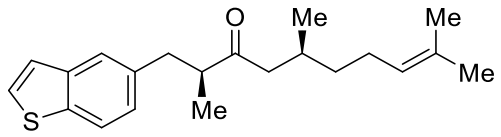
$[\alpha]_D^{20}$: +6.8 (c = 1.99, $CHCl_3$).

(*S*)-5-(2-(butylthio)propyl)benzo[*b*]thiophene (*S*-136i):



A solution of alkyl iodide (*S*-**114b**, 0.08 M, 1.00 equiv) and dibutyl disulfide (**112q**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*-BuLi (ca. 0.20 M in hexane, 2.85 equiv) were prepared. The solution of *t*-BuLi was pumped by pump A (flow rate A: 5.7 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The solution of the alkyl iodide was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = –20 to 25 °C). The stream was subsequently upon reaching steady state injected for 3 min 12 s into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel with diethyl ether/pentane = 1:100 to afford (*S*)-**136i** (209 mg, 0.8 mmol, 63%, 86% *ee*) as white solid.

(1*S*,2'*S*)-1-(benzo[*b*]thiophen-5-yl)-2,5,9-trimethyldec-8-en-3-one (2*S*,5*S*-136j):



The ketone (2*S*,5*S*)-**136j** was prepared according to **TP7** from the iodide (*S*)-**114b** (30.0 mg, 0.1 mmol, 1.0 equiv) and (*S*)-citronellal (**112r**, 45 µL, 38.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude alcohol was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 (ca. 0.05 mmol, 50% yield). Both diastertereoisomers of the alcohol were then dissolved in DCM (0.8 mL) and oxidized using Dess-Martin-Periodinane[416] (31.8 mg, 0.075 mmol) and stirred at ambient temperature for 10 min before quenching with sat. aq. NH_4Cl. The reaction mixture was extracted with Et_2O (3 x 20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (2*S*,5*S*)-**136j** (15.8 mg, 0.048 mmol, 48%, dr = 92:8, 96% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.78 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 1.7 Hz, 1H), 7.42 (d, *J* = 5.4 Hz, 1H), 7.27 (s, 1H), 7.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 5.07–4.98 (m, 1H), 3.10 (dd, *J* = 13.5, 7.1 Hz, 1H), 2.86 (h, *J* = 7.0 Hz, 1H), 2.65 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.33–2.16 (m, 2H), 2.03–1.72 (m, 4H), 1.66 (d, *J* = 1.6 Hz, 3H), 1.55 (s, 3H), 1.24–1.14 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 214.2, 140.0, 137.8, 136.1, 131.5, 126.7, 125.8, 124.5, 124.0, 123.8, 122.5, 49.7, 48.8, 38.9, 37.0, 28.6, 25.9, 25.6, 19.9, 17.8, 16.6.

IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2960, 2926, 2872, 2857, 1716, 1457, 1438, 1422, 1408, 1376, 1267, 1249, 1146, 1116, 1102, 1051, 1034, 1019, 892, 874, 831, 812, 768, 754, 731, 702, 691.

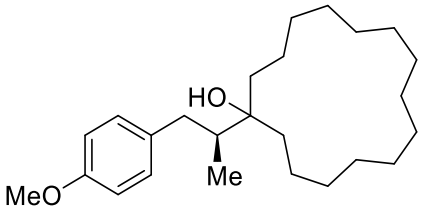
MS (70 eV, EI): m/z (%): 175 (12), 147 (100).

HRMS (EI) for $C_{21}H_{28}OS$: calc. $[M]^{+\bullet}$: 328.1861, found: 328.1852.

$[\alpha]_D^{20}$: +10.6 (c = 0.94, $CHCl_3$).

[416] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.

(*S*)-1-(1-(4-methoxyphenyl)propan-2-yl)cyclopentadecan-1-ol (*S*-136k):



The alcohol (*S*)-**136k** was prepared according to **TP7** from the iodide (*S*)-**114c** (27.6 mg, 0.1 mmol, 1.0 equiv) and cyclopentadecanone (**112s**, 67.3 mg, 0.3 mmol, 3.0 equiv) at −40 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136k** (19.9 mg, 0.053 mmol, 53%, 92% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.11–7.03 (m, 2H), 6.86–6.80 (m, 2H), 3.79 (s, 3H), 2.97 (dd, *J* = 13.3, 3.0 Hz, 1H), 2.17 (dd, *J* = 13.4, 11.2 Hz, 1H), 1.75–1.67 (m, 1H), 1.67–1.57 (m, 2H), 1.56–1.49 (m, 2H), 1.46–1.26 (m, 24H), 1.10 (s, 1H), 0.78 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 157.8, 134.3, 130.2, 113.7, 76.4, 55.4, 42.7, 37.0, 36.8, 36.0, 28.1, 28.0, 27.0, 26.9, 26.9, 26.8, 26.7, 26.1, 22.2, 22.1, 12.8.

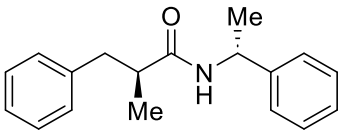
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3401, 3244, 3067, 2927, 2925, 2854, 1705, 1652, 1643, 1637, 1611, 1511, 1458, 1456, 1441, 1429, 1421, 1419, 1362, 1361, 1299, 1245, 1223, 1220, 1175, 1091, 1036, 819, 816, 814, 812, 807, 799, 771, 710.

MS (70 eV, EI): m/z (%): 281 (4), 234 (5), 207 (12), 121 (100), 91 (4).

HRMS (EI) for $C_{25}H_{40}O$: calc. $[M-H_2O]^{+\bullet}$: 356.3074, found: 356.3075.

$[\alpha]_D^{20}$: −7.5 (c = 1.17, $CHCl_3$).

(*S*)-2-methyl-3-phenyl-*N*-((*R*)-1-phenylethyl)propanamide (2'*S*,3*R*-136l):



The amide (2'*S*,3*R*)-**136l** was prepared according to **TP7** from the iodide (*S*)-**114d** (24.6 mg, 0.1 mmol, 1.0 equiv) and (*R*)-(+)-1-phenylethyl isocyanate (*R*-**112t**, 35 µL, 36.8 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (2'*S*,3*R*)-**136l** (19.3 mg, 0.072 mmol, 72%, dr = 98:2, 96% *ee*) as white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.33–7.27 (m, 4H), 7.25–7.16 (m, 6H), 5.32 (d, *J* = 8.0 Hz, 1H), 5.02 (p, *J* = 7.1 Hz, 1H), 2.94 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.71 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.46–2.36 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 174.5, 143.3, 140.1, 129.1, 128.7, 128.6, 127.4, 126.5, 126.3, 48.5, 44.2, 40.9, 21.5, 17.9.

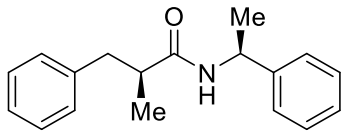
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3306, 2976, 2932, 1639, 1537, 1494, 1446, 1382, 1366, 1245, 1207, 1177, 1130, 1094, 1081, 1031, 1015, 946, 914, 742, 697.

MS (70 eV, EI): m/z (%): 176 (13), 120 (18), 105 (34), 91 (100), 77 (20).

HRMS (EI) for $C_{18}H_{21}NO$: calc. $[M]^{+\bullet}$: 267.1623, found: 267.1618.

$[\alpha]_D^{20}$: −3.9 (c = 0.94, $CHCl_3$).

(*S*)-2-methyl-3-phenyl-*N*-((*S*)-1-phenylethyl)propanamide (2'*S*,3*S*-136l):



A solution of alkyl iodide (*S*-**114d**, 0.08 M, 1.00 equiv) and (*S*)-(−)-1-phenylethyl isocyanate (*S*-**112t**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*-BuLi (ca. 0.20 M in hexane, 2.85 equiv) were prepared. The solution of *t*-BuLi was pumped by pump A (flow rate A: 5.7 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The solution of the alkyl iodide was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = –20 to 25 °C). The stream was subsequently upon reaching steady state injected for 3 min 30 s into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (2'*S*,3*S*)-**136l** (217 mg, 0.81 mmol, 58%, dr = 98:2, 96% *ee*) as white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.25–7.16 (m, 6H), 7.14–7.08 (m, 2H), 7.03–6.98 (m, 2H), 5.46–5.34 (m, 1H), 5.10–5.00 (m, 1H), 2.94 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.67 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.49–2.36 (m, 1H), 1.41 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 174.6, 143.0, 139.9, 129.1, 128.6, 128.6, 127.2, 126.4, 126.3, 48.4, 44.2, 40.6, 21.6, 18.1.

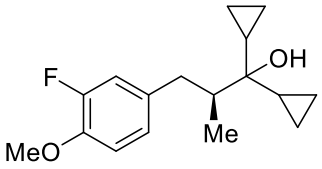
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3305, 2975, 2932, 2922, 1639, 1606, 1537, 1494, 1444, 1382, 1366, 1245, 1207, 1177, 1130, 1081, 1031, 1015, 946, 914, 742, 697.

MS (70 eV, EI): m/z (%): 176 (13), 120 (17), 105 (32), 91 (100), 77 (20).

HRMS (EI) for $C_{18}H_{21}NO$: calc. $[M]^{+\bullet}$: 267.1623, found: 267.1617.

$[\alpha]_D^{20}$: −4.2 (c = 0.98, $CHCl_3$).

(*S*)-1,1-dicyclopropyl-3-(3-fluoro-4-methoxyphenyl)-2-methylpropan-1-ol (*S*-136m):



The alcohol (*S*)-**136m** was prepared according to **TP7** from the iodide (*S*)-**114e** (29.4 mg, 0.1 mmol, 1.0 equiv) and dicyclopropyl ketone (**112u**, 28 µL, 27.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136m** (21.7 mg, 0.078 mmol, 78%, 94% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.95–6.87 (m, 3H), 3.87 (s, 3H), 3.18 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.24 (dd, *J* = 13.3, 11.4 Hz, 1H), 1.90–1.85 (m, 1H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 2H), 0.50–0.39 (m, 7H), 0.35–0.26 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 244.7 Hz), 145.6 (d, *J* = 10.7 Hz), 135.6 (d, *J* = 5.9 Hz), 124.7 (d, *J* = 3.4 Hz), 116.8 (d, *J* = 17.6 Hz), 113.3 (d, *J* = 2.1 Hz), 72.7, 56.5, 47.8, 37.3 (d, *J* = 1.4 Hz), 16.9, 15.8, 14.2, 1.7, 1.4, -0.9, -1.0.

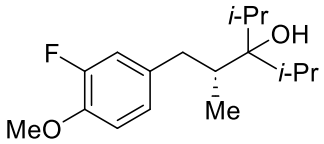
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2960, 2958, 2931, 2903, 1517, 1463, 1443, 1429, 1375, 1311, 1304, 1276, 1275, 1224, 1181, 1127, 1027, 993, 977, 955, 913, 807, 762, 668.

MS (70 eV, EI): m/z (%): 139 (100), 111 (96), 69 (86).

HRMS (EI) for $C_{17}H_{23}FO_2$: calc. $[M]^{+\bullet}$: 278.1682, found: 278.1677.

$[\alpha]_D^{20}$: −17.8 (c = 0.54, $CHCl_3$).

(*R*)-1-(3-fluoro-4-methoxyphenyl)-3-isopropyl-2,4-dimethylpentan-3-ol (*R*-136n):



The alcohol (*R*)-**136n** was prepared according to **TP7** from the iodide (*R*)-**114e** (29.4 mg, 0.1 mmol, 1.0 equiv) and diisopropyl ketone (**112v**, 35 µL, 28.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 to afford (*R*)-**136n** (18.6 mg, 0.066 mmol, 66%, 90% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.95–6.83 (m, 3H), 3.87 (s, 3H), 3.07 (dd, *J* = 13.1, 2.5 Hz, 1H), 2.23–2.11 (m, 3H), 2.04 (m, 1H), 1.18 (s, 1H), 1.06–0.98 (m, 12H), 0.85 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 244.9 Hz), 145.6 (d, *J* = 10.7 Hz), 135.9 (d, *J* = 5.9 Hz), 124.7 (d, *J* = 3.5 Hz), 116.7 (d, *J* = 17.6 Hz), 113.3 (d, *J* = 2.2 Hz), 78.2, 56.5, 41.7, 37.9, 33.1, 33.0, 18.9, 18.8, 18.7, 18.6, 14.9.

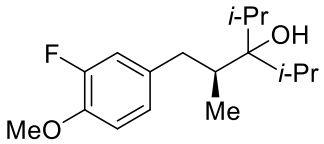
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2964, 2879, 1515, 1464, 1443, 1429, 1382, 1310, 1275, 1224, 1126, 1031, 988, 949, 808, 762.

MS (70 eV, EI): m/z (%): 221 (12), 140 (9), 139 (100), 115 (4), 71 (8).

HRMS (EI) for $C_{14}H_{20}FO_2$: calc. $[M-(i\text{-Pr})]^{+\bullet}$: 239.1447, found: 239.1440.

$[\alpha]_D^{20}$: +62.5 (c = 0.80, $CHCl_3$).

(*S*)-1-(3-fluoro-4-methoxyphenyl)-3-isopropyl-2,4-dimethylpentan-3-ol (*S*-136n):



The alcohol (*S*)-**136n** was prepared according to **TP7** from the iodide (*S*)-**114e** (29.4 mg, 0.1 mmol, 1.0 equiv) and diisopropyl ketone (**112v**, 35 µL, 28.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 to afford (*S*)-**136n** (18.1 mg, 0.064 mmol, 64%, 96% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.94–6.83 (m, 3H), 3.87 (s, 3H), 3.07 (dd, *J* = 13.1, 2.5 Hz, 1H), 2.22–2.11 (m, 3H), 2.04 (m, 1H), 1.18 (s, 1H), 1.06–0.97 (m, 12H), 0.85 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 244.9 Hz), 145.6 (d, *J* = 10.7 Hz), 135.9 (d, *J* = 5.9 Hz), 124.7 (d, *J* = 3.4 Hz), 116.7 (d, *J* = 17.6 Hz), 113.3 (d, *J* = 2.2 Hz), 78.2, 56.5, 41.7, 37.9, 33.1, 33.0, 18.9, 18.8, 18.7, 18.6, 14.9.

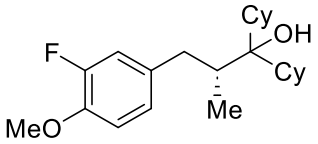
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3613, 2960, 2931, 2915, 2911, 2889, 2862, 2836, 2248, 2220, 2194, 2190, 2167, 2122, 2115, 2084, 1521, 1515, 1453, 1445, 1383, 1278, 1275, 1224, 1127, 1029, 945, 808, 723, 690.

MS (70 eV, EI): m/z (%): 221 (11), 139 (100), 115 (5), 71 (8).

HRMS (EI) for $C_{14}H_{20}FO_2$: calc. $[M-(i\text{-Pr})]^{+\bullet}$: 239.1447, found: 239.1440.

$[\alpha]_D^{20}$: −67.8 (c = 0.72, $CHCl_3$).

(*R*)-1,1-dicyclohexyl-3-(3-fluoro-4-methoxyphenyl)-2-methylpropan-1-ol (*R*-136o):



The alcohol (*R*)-**136o** was prepared according to **TP7** from the iodide (*R*)-**114e** (29.4 mg, 0.1 mmol, 1.0 equiv) and dicyclohexyl ketone (**112w**, 28.5 mg, 0.25 mmol, 2.5 equiv) at −40 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 to afford (*R*)-**136o** (25.0 mg, 0.069 mmol, 69%, 94% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.95–6.81 (m, 3H), 3.87 (s, 3H), 3.04 (dd, *J* = 13.0, 2.4 Hz, 1H), 2.21–2.04 (m, 2H), 1.85–1.67 (m, 12H), 1.27–1.17 (m, 11H), 0.81 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 245.0 Hz), 145.6 (d, *J* = 10.8 Hz), 136.0 (d, *J* = 5.9 Hz), 124.7 (d, *J* = 3.3 Hz), 116.7 (d, *J* = 17.6 Hz), 113.4 (d, *J* = 2.2 Hz), 78.2, 56.5, 44.6, 44.3, 40.9, 37.7, 28.7, 28.6, 28.6, 28.5, 27.6, 27.6, 27.5,f 27.5, 26.9, 26.9, 14.7.

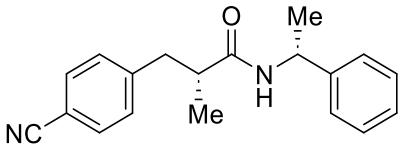
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2924, 2851, 1585, 1516, 1463, 1445, 1429, 1379, 1366, 1310, 1275, 1224, 1184, 1127, 1066, 1031, 981, 954, 893, 876, 819, 805, 759.

MS (70 eV, EI): m/z (%): 279 (17), 195 (23), 139 (100), 95 (10).

HRMS (EI) for $C_{23}H_{36}FO_2$: calc. $[M+H]^+$: 363.2694, found: 363.2694.

$[\alpha]_D^{20}$: +4.3 (c = 0.83, $CHCl_3$).

(*R*)-3-(4-cyanophenyl)-2-methyl-*N*-((*R*)-1-phenylethyl)propanamide (2'*R*,3*R*-136p):



The amide (2'*R*,3*R*)-**136p** was prepared according to **TP7** from the iodide (*R*)-**114f** (27.1 mg, 0.1 mmol, 1.0 equiv) and (*R*)-(+)-1-phenylethyl isocyanate (*R*-**112t**, 35 µL, 36.8 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:3 to afford (2'*R*,3*R*)-**136p** (21.9 mg, 0.075 mmol, 75%, dr = 94:6, 96% *ee*) as white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.44–7.38 (m, 2H), 7.27 (d, *J* = 3.8 Hz, 2H), 7.19–7.13 (m, 2H), 7.02–6.95 (m, 2H), 5.38 (d, *J* = 8.2 Hz, 1H), 5.03 (p, *J* = 7.2 Hz, 1H), 2.98 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.69 (dd, *J* = 13.3, 5.4 Hz, 1H), 2.44–2.32 (m, 1H), 1.41 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 173.7, 145.5, 142.9, 132.3, 129.9, 128.7, 127.6, 126.1, 119.1, 110.3, 48.5, 44.1, 40.6, 21.6, 18.4.

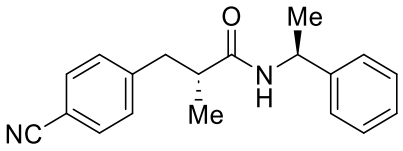
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3265, 2972, 2960, 2930, 2872, 2853, 2226, 1638, 1608, 1540, 1505, 1496, 1470, 1452, 1418, 1375, 1365, 1246, 1108, 1024, 850, 823, 743, 716, 692.

MS (70 eV, EI): m/z (%): 293 (16), 176 (52), 116 (44), 105 (100).

HRMS (EI) for $C_{19}H_{20}N_2O$: calc. $[M+H]^{+\bullet}$: 293.1654, found: 293.1650.

$[\alpha]_D^{20}$: −52.8 (c = 0.62, $CHCl_3$).

(*R*)-3-(4-cyanophenyl)-2-methyl-*N*-((*S*)-1-phenylethyl)propanamide (2'*R*,3*S*-136p):



The amide (2'*R*,3*S*)-**136p** was prepared according to **TP7** from the iodide (*R*)-**114f** (27.1 mg, 0.1 mmol, 1.0 equiv) and (*S*)-(−)-1-phenylethyl isocyanate (*S*-**112t**, 35 µL, 36.8 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:3 to afford (2'*R*,3*S*)-**136p** (24.0 mg, 0.082 mmol, 82%, dr = 8:92, 96% *ee*) as white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.59–7.52 (m, 2H), 7.36–7.24 (m, 6H), 7.21 (dd, *J* = 7.0, 1.8 Hz, 2H), 5.40 (d, *J* = 8.0 Hz, 1H), 5.03 (p, *J* = 7.1 Hz, 1H), 3.04 (dd, *J* = 13.4, 9.0 Hz, 1H), 2.74 (dd, *J* = 13.4, 5.8 Hz, 1H), 2.48–2.31 (m, 1H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 173.7, 145.7, 142.9, 132.3, 130.0, 128.9, 127.6, 126.2, 119.1, 110.4, 48.6, 43.7, 40.5, 21.6, 18.1.

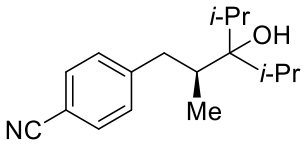
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3345, 3324, 2978, 2966, 2953, 2930, 2226, 1646, 1606, 1527, 1506, 1494, 1449, 1410, 1376, 1366, 1306, 1299, 1282, 1238, 1227, 1212, 1193, 1180, 1131, 1107, 1013, 942, 868, 848, 818, 756, 697.

MS (70 eV, EI): m/z (%): 292 (59), 176 (32), 116 (28), 105 (100).

HRMS (EI) for $C_{19}H_{20}N_2O$: calc. $[M]^{+\bullet}$: 292.1576, found: 292.1569.

$[\alpha]_D^{20}$: −56.0 (c = 0.67, $CHCl_3$).

(*S*)-4-(3-hydroxy-3-isopropyl-2,4-dimethylpentyl)benzonitrile (*S*-136q):



The alcohol (*S*)-**136q** was prepared according to **TP7** from the iodide (*S*)-**114f** (27.1 mg, 0.1 mmol, 1.0 equiv) and diisopropyl ketone (**112v**, 35 µL, 28.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 to afford (*S*)-**136q** (12.7 mg, 0.049 mmol, 49%, 95% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.60–7.54 (m, 2H), 7.31–7.26 (m, 2H), 3.23 (dd, *J* = 13.0, 2.6 Hz, 1H), 2.32 (dd, *J* = 13.0, 11.1 Hz, 1H), 2.20 – 2.06 (m, 3H), 1.20 (s, 1H), 1.08–1.02 (m, 9H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.9, 132.2, 130.0, 119.4, 109.6, 78.1, 41.6, 39.2, 33.2, 33.1, 19.0, 18.8, 18.5, 15.1, 1.2.

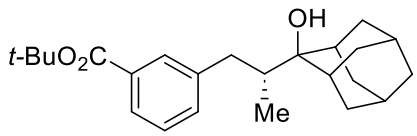
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3534, 2965, 2926, 2880, 2856, 2228, 1672, 1607, 1503, 1468, 1454, 1414, 1382, 1266, 1178, 1160, 1128, 1094, 990, 950, 842, 815.

MS (70 eV, EI): m/z (%): 216 (11), 198 (14), 172 (59), 157 (40), 146 (27), 142 (80), 130 (39), 116 (100), 89 (21), 71 (47).

HRMS (EI) for $C_{17}H_{25}NO$: calc. $[M]^{+\bullet}$: 260.2009, found: 260.2013.

$[\alpha]_D^{20}$: −22.7 (c = 0.93, $CHCl_3$).

***tert*-butyl 3-((*R*)-2-((1*R*,3*S*,5*R*,7*R*)-2-hydroxyadamantan-2-yl)propyl)benzoate (*R*-136r):**



The alcohol (*R*)-**136r** was prepared according to **TP7** from the iodide (*R*)-**114g** (34.6 mg, 0.1 mmol, 1.0 equiv) and adamantanone (**112h**, 45.0 mg, 0.3 mmol, 3.0 equiv) at −40 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**136r** (19.6 mg, 0.053 mmol, 53%, 95% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.82–7.78 (m, 2H), 7.34–7.31 (m, 2H), 2.97 (dd, *J* = 12.9, 2.7 Hz, 1H), 2.43–2.32 (m, 1H), 2.26 (dd, *J* = 13.0, 11.2 Hz, 1H), 2.17 (t, *J* = 3.0 Hz, 3H), 2.02 (d, *J* = 3.1 Hz, 1H), 1.95–1.92 (m, 1H), 1.88–1.77 (m, 5H), 1.74–1.70 (m, 2H), 1.60 (s, 9H), 1.34 (s, 1H), 1.10 (d, *J* = 1.7 Hz, 1H), 1.08 (d, *J* = 1.4 Hz, 1H), 0.72 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.2, 142.8, 133.7, 132.1, 130.3, 128.2, 126.9, 81.1, 76.2, 38.4, 37.8, 35.8, 35.0, 34.2, 34.1, 33.9, 33.4, 33.3, 28.4, 27.1, 27.1, 11.3.

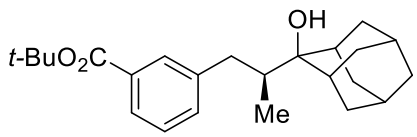
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3521, 2969, 2965, 2960, 2910, 2858, 1739, 1710, 1675, 1604, 1476, 1455, 1419, 1392, 1365, 1331, 1304, 1292, 1257, 1219, 1160, 1111, 1098, 1091, 1071, 1058, 1044, 1032, 991, 980, 937, 927, 913, 850, 811, 804, 760, 747, 718, 692.

MS (70 eV, EI): m/z (%): 293 (11), 207 (6), 203 (6), 164 (14), 151 (100), 135 (15), 91 (18), 81 (10), 71 (13), 57 (49).

HRMS (EI) for $C_{24}H_{35}O_3$: calc. $[M+H]^{+\bullet}$: 371.2581, found: 371.2565.

$[\alpha]_D^{20}$: +9.70 (c = 0.93, $CHCl_3$).

***tert*-butyl 3-((*S*)-2-((1*R*,3*S*,5*R*,7*R*)-2-hydroxyadamantan-2-yl)propyl)benzoate (*S*-136r):**



The alcohol (*S*)-**136r** was prepared according to **TP7** from the iodide (*S*)-**114g** (34.6 mg, 0.1 mmol, 1.0 equiv) and adamantanone (**112h**, 45.0 mg, 0.3 mmol, 3.0 equiv) at −40 °C. The crude product was

purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136r** (18.9 mg, 0.051 mmol, 51%, 95% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.83–7.78 (m, 2H), 7.34–7.30 (m, 2H), 2.97 (dd, *J* = 13.0, 2.6 Hz, 1H), 2.43–2.33 (m, 1H), 2.26 (dd, *J* = 13.0, 11.2 Hz, 1H), 2.20–2.13 (m, 3H), 2.03 (dd, *J* = 13.2, 3.1 Hz, 1H), 1.93 (p, *J* = 2.6 Hz, 1H), 1.88–1.77 (m, 3H), 1.73–1.62 (m, 4H), 1.60 (s, 9H), 1.35 (d, *J* = 1.3 Hz, 1H), 1.09 (dd, *J* = 6.4, 1.5 Hz, 2H), 0.72 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.2, 142.8, 133.7, 132.1, 130.3, 128.2, 126.9, 81.1, 76.2, 38.4, 37.8, 35.8, 35.0, 34.2, 34.1, 33.9, 33.4, 33.3, 28.3, 27.1, 27.1, 11.3.

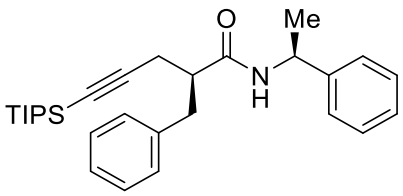
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3419, 3226, 3005, 2952, 2946, 2913, 2874, 2858, 1745, 1706, 1660, 1637, 1608, 1477, 1471, 1456, 1436, 1423, 1421, 1392, 1364, 1362, 1304, 1292, 1258, 1220, 1161, 1111, 1097, 1093, 1091, 1071, 1065, 1058, 1032, 991, 981, 927, 851, 849, 809, 804, 798, 760, 747, 719.

MS (70 eV, EI): m/z (%): 297 (7), 164 (11), 151 (100), 135 (10), 97 (6), 91 (11), 57 (31).

HRMS (EI) for $C_{24}H_{35}O_3$: calc. $[M+H]^{+\bullet}$: 371.2581, found: 371.2584.

$[\alpha]_D^{20}$: −9.3 (c = 1.26, $CHCl_3$).

(*S*)-2-benzyl-*N*-((*S*)-1-phenylethyl)-5-(triisopropylsilyl)pent-4-ynamide (2'*S*,3*S*-136s):



The amide (2'*S*,3*S*)-**136s** was prepared according to **TP7** from the iodide (*S*)-**114h** (42.6 mg, 0.1 mmol, 1.0 equiv) and (*S*)-(−)-1-phenylethyl isocyanate (*S*-**112t**, 35 µL, 36.8 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (2'*S*,3*S*)-**136s** (34.5 mg, 0.077 mmol, 77%, dr = 94:6, 96% *ee*) as white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.40–7.29 (m, 9H), 7.26–7.24 (m, 1H), 5.61 (d, *J* = 7.8 Hz, 1H), 5.07 (p, *J* = 7.0 Hz, 1H), 3.17 (dd, *J* = 13.4, 5.4 Hz, 1H), 2.99 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.63 (dd, *J* = 6.5, 2.3 Hz, 2H), 2.61–2.55 (m, 1H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.19–1.06 (m, 21H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 172.4, 143.0, 139.5, 129.2, 128.7, 128.7, 127.4, 126.7, 126.2, 106.2, 83.1, 49.4, 48.8, 38.2, 22.8, 21.6, 18.8, 11.4.

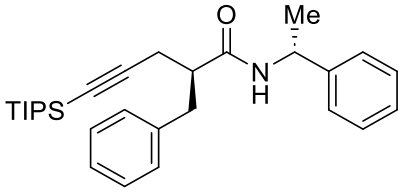
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3290, 2974, 2942, 2892, 2865, 2174, 2168, 1642, 1540, 1506, 1496, 1463, 1455, 1382, 1350, 1280, 1241, 1210, 1183, 1152, 1119, 1075, 1046, 1029, 1018, 996, 919, 883, 744, 698, 676, 661.

MS (70 eV, EI): m/z (%): 105 (100), 91 (32), 78 (17).

HRMS (EI) for $C_{29}H_{41}NOSi$: calc. $[M]^{+\bullet}$: 447.2957, found: 447.2950

$[\alpha]_D^{20}$: +23.6 (c = 1.76, $CHCl_3$).

(*S*)-2-benzyl-*N*-((*R*)-1-phenylethyl)-5-(triisopropylsilyl)pent-4-ynamide (2'*S*,3*R*-136s):



The amide (2'*S*,3*R*)-**136s** was prepared according to **TP7** from the iodide (*S*)-**114h** (42.6 mg, 0.1 mmol, 1.0 equiv) and (*R*)-(−)-1-phenylethyl isocyanate (*R*-**112t**, 35 µL, 36.8 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (2'*S*,3*R*)-**136s** (31.8 mg, 0.071 mmol, 71%, dr = 4:96, 96% *ee*) as white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.25–7.19 (m, 6H), 7.14–7.11 (m, 2H), 6.99–6.96 (m, 2H), 5.64 (d, *J* = 7.8 Hz, 1H), 5.04 (p, *J* = 7.1 Hz, 1H), 2.98 (dd, *J* = 13.4, 5.4 Hz, 1H), 2.92 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.65–2.58 (m, 1H), 2.55–2.47 (m, 2H), 1.41 (d, *J* = 6.9 Hz, 3H), 1.10–1.03 (m, 21H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 172.5, 142.9, 139.3, 129.2, 128.7, 128.6, 127.2, 126.5, 126.2, 106.2, 83.0, 49.6, 48.7, 38.2, 23.2, 21.7, 18.8, 11.4.

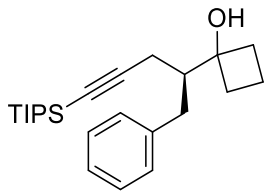
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3288, 3064, 3029, 2942, 2892, 2864, 2169, 1638, 1605, 1586, 1543, 1496, 1462, 1454, 1427, 1382, 1367, 1291, 1240, 1211, 1128, 1075, 1062, 1048, 1030, 1017, 995, 918, 882, 760, 744, 697, 676, 660.

MS (70 eV, EI): m/z (%): 404 (19), 300 (12), 105 (100), 91 (27), 79 (15).

HRMS (EI) for $C_{29}H_{41}NOSi$: calc. $[M]^{+\bullet}$: 447.2957, found: 447.2957

$[\alpha]_D^{20}$: +26.4 (c = 1.61, $CHCl_3$).

(*S*)-1-(1-phenyl-5-(triisopropylsilyl)pent-4-yn-2-yl)cyclobutan-1-ol (*S*-136t):



The alcohol (*S*)-**136t** was prepared according to **TP7** from the iodide (*S*)-**114h** (42.6 mg, 0.1 mmol, 1.0 equiv) and cyclobutanone (**112x**, 19 µL, 17.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:6 to afford (*S*)-**136t** (22.2 mg, 0.060 mmol, 60%, 90% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.17 (m, 6H), 3.07 (s, 1H), 2.95–2.81 (m, 2H), 2.44 (dd, *J* = 17.4, 4.5 Hz, 1H), 2.25–2.01 (m, 5H), 2.00–1.89 (m, 2H), 1.68–1.54 (m, 1H), 1.10 (d, *J* = 3.4 Hz, 21H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 141.1, 129.3, 128.5, 126.2, 107.5, 85.0, 79.6, 46.9, 35.1, 34.8, 33.2, 18.8, 17.6, 12.9, 11.4.

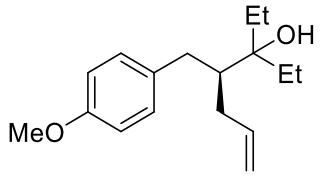
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3563, 3490, 3074, 2966, 2935, 2882, 2835, 1637, 1611, 1584, 1511, 1462, 1442, 1418, 1380, 1300, 1244, 1177, 1125, 1106, 1037, 995, 976, 911, 841, 831, 816, 809, 763.

MS (70 eV, EI): m/z (%): 137 (12), (129 (17), 103 (39), 91 (76), 75 (100).

HRMS (EI) for $C_{21}H_{31}OSi$: calc. $[M-i\text{-}Pr]^{+\bullet}$: 327.2144, found: 327.2132.

$[\alpha]_D^{20}$: +26.3 (c = 3.8, $CHCl_3$).

(*S*)-3-ethyl-4-(4-methoxybenzyl)hept-6-en-3-ol (*S*-136u):



The alcohol (*S*)-**136u** was prepared according to **TP7** from the iodide (*S*)-**114i** (30.2 mg, 0.1 mmol, 1.0 equiv) and pentan-3-one (**112k**, 27 µL, 21.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica with diethyl ether/pentane = 1:9 to afford (*S*)-**136u** (20.5 mg, 0.078 mmol, 78%, 92% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.14–7.08 (m, 2H), 6.85–6.80 (m, 2H), 5.87–5.74 (m, 1H), 5.03–4.89 (m, 2H), 3.79 (s, 3H), 2.85 (dd, *J* = 14.0, 4.1 Hz, 1H), 2.42 (dd, *J* = 14.0, 9.7 Hz, 1H), 2.24–

2.17 (m, 1H), 2.11–2.03 (m, 1H), 1.98–1.91 (m, 1H), 1.66–1.54 (m, 4H), 1.33 (s, 1H), 0.90 (dt, *J* = 8.4, 7.5 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 157.9, 139.0, 134.0, 130.2, 115.9, 113.9, 55.4, 46.5, 34.4, 33.6, 28.9, 28.6, 7.8.

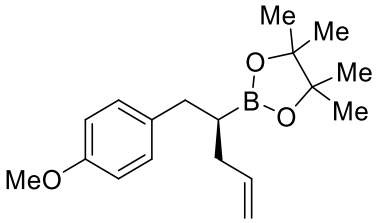
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3564, 3493, 3073, 2967, 2934, 2882, 2836, 1637, 1612, 1584, 1511, 1462, 1442, 1418, 1380, 1300, 1244, 1177, 1125, 1106, 1037, 995, 976, 911, 842, 831, 816, 809, 762.

MS (70 eV, EI): m/z (%): 203 (59), 121 (100), 87 (60), 45 (31).

HRMS (EI) for $C_{17}H_{26}O_2$: calc. $[M]^{+\bullet}$: 262.1933, found: 262.1925.

$[\alpha]_D^{20}$: −43.7 (c = 0.7, $CHCl_3$).

(*S*)-2-(1-(4-methoxyphenyl)pent-4-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*S*-136v):



The boronate (*S*)-**136v** was prepared according to **TP7** from the iodide (*S*)-**114i** (30.2 mg, 0.1 mmol, 1.0 equiv) and methoxy boronic acid pinacol ester (**112n**, 41 µL, 39.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:6 to afford (*S*)-**136v** (22.1 mg, 0.073 mmol, 73%, 90% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.14–7.09 (m, 2H), 6.82–6.77 (m, 2H), 5.82 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H), 5.07–4.93 (m, 2H), 3.77 (s, 3H), 2.72–2.58 (m, 2H), 2.20–2.12 (m, 2H), 1.48–1.37 (m, 1H), 1.15 (d, *J* = 11.3 Hz, 12H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 157.8, 138.4, 134.3, 129.9, 115.3, 113.6, 83.2, 55.4, 36.0, 35.3, 24.9, 24.9.

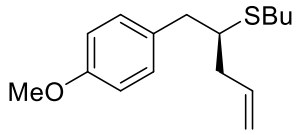
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2977, 2930, 2835, 1640, 1612, 1584, 1512, 1480, 1465, 1443, 1407, 1380, 1372, 1321, 1301, 1269, 1243, 1214, 1176, 1166, 1142, 1108, 1037, 992, 967, 910, 854, 835, 806, 760, 752, 712, 691, 670.

MS (70 eV, EI): m/z (%): 260 (52), 174 (11), 121 (100).

HRMS (EI) for $C_{18}H_{27}O_3B$: calc. $[M]^{+\bullet}$: 302.2053, found: 302.2051.

$[\alpha]_D^{20}$: +8.4 (c = 2.82, $CHCl_3$).

(*S*)-butyl(1-(4-methoxyphenyl)pent-4-en-2-yl)sulfane (*S*-136w):



The sulfide (*S*)-**136w** was prepared according to **TP7** from the iodide (*S*)-**114i** (30.2 mg, 0.1 mmol, 1.0 equiv) and dibutyl disulfide (**112q**, 48 µL, 44.6 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:100 to afford (*S*)-**136w** (15.1 mg, 0.057 mmol, 57%, 91% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.14–7.09 (m, 2H), 6.87–6.81 (m, 2H), 5.89 (ddt, *J* = 17.2, 10.6, 7.0 Hz, 1H), 5.11–5.05 (m, 2H), 3.79 (s, 3H), 2.87 (dq, *J* = 7.5, 5.9 Hz, 1H), 2.79 (dd, *J* = 7.0, 4.6 Hz, 2H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.39–2.21 (m, 2H), 1.54–1.47 (m, 2H), 1.41–1.33 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 158.1, 135.6, 131.6, 130.3, 117.1, 113.7, 55.3, 46.9, 40.4, 38.3, 31.8, 30.6, 22.1, 13.7.

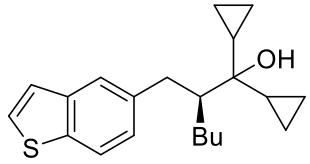
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3076, 2956, 2929, 2872, 2860, 2835, 1640, 1611, 1584, 1511, 1464, 1439, 1378, 1300, 1245, 1200, 1176, 1117, 1107, 1036, 1004, 991, 968, 913, 831, 815, 809, 753, 721, 695.

MS (70 eV, EI): m/z (%): 143 (39), 121 (100), 101 (18), 91 (23), 87 (49), 44 (14).

HRMS (EI) for $C_{13}H_{19}OS$: calc. $[M-C_3H_5]^{+\bullet}$: 223.1147, found: 223.1157.

$[\alpha]_D^{20}$: −6.5 (c = 1.24, $CHCl_3$).

(*S*)-2-(benzo[*b*]thiophen-5-ylmethyl)-1,1-dicyclopropylhexan-1-ol (*S*-136x):



The alcohol (*S*)-**136x** was prepared according to **TP7** from the iodide (*S*)-**114j** (34.4 mg, 0.1 mmol, 1.0 equiv) and dicyclopropyl ketone (**112u**, 39 µL, 38.6 mg, 0.35 mmol, 3.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136x** (16.4 mg, 0.05 mmol, 50%, 92% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.77 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.40 (d, *J* = 5.4 Hz, 1H), 7.27 (d, *J* = 5.6 Hz, 1H), 7.24 (d, *J* = 1.6 Hz, 1H), 3.28 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.64 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.02–1.92 (m, 1H), 1.83–1.71 (m, 1H), 1.45–1.31 (m, 1H), 1.24–1.07 (m, 3H), 1.00–0.87 (m, 2H), 0.83 (s, 1H), 0.79–0.71 (m, 3H), 0.52–0.36 (m, 6H), 0.33–0.22 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.0, 139.2, 137.2, 126.4, 126.1, 123.8, 123.8, 122.2, 73.5, 52.8, 37.3, 31.6, 30.5, 23.2, 17.5, 16.5, 14.1, 2.0, 1.5, -0.5, -0.8.

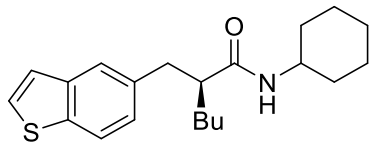
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3589, 3084, 3007, 2954, 2926, 2868, 2858, 1464, 1458, 1436, 1421, 1377, 1326, 1306, 1262, 1222, 1180, 1160, 1146, 1115, 1089, 1050, 1022, 985, 945, 926, 913, 892, 867, 832, 805, 769, 753, 729, 704, 691.

MS (70 eV, EI): m/z (%): 225 (11), 197 (11), 147 (100), 111 (47), 69 (23).

HRMS (EI) for $C_{21}H_{26}S$: calc. $[M-H_2O]^{+\bullet}$: 310.1755, found: 310.1748.

$[\alpha]_D^{20}$: −6.9 (c = 0.72, $CHCl_3$).

(*S*)-2-(benzo[*b*]thiophen-5-ylmethyl)-*N*-cyclohexylhexanamide (*S*-136y):



The alcohol (*S*)-**136y** was prepared according to **TP7** from the iodide (*S*)-**114j** (34.4 mg, 0.1 mmol, 1.0 equiv) and cyclohexyl isocyanate (**112y**, 45 µL, 43.8 mg, 0.35 mmol, 3.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:2 to afford (*S*)-**136y** (21.0 mg, 0.061 mmol, 61%, 92% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.76 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.40 (d, *J* = 5.4 Hz, 1H), 7.25 (d, *J* = 5.6 Hz, 1H), 7.15 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.98 (d, *J* = 8.4 Hz, 1H), 3.76–3.62 (m, 1H), 3.01 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.81 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.26–2.10 (m, 1H), 1.86–1.68 (m, 3H), 1.64–1.56 (m, 1H), 1.54–1.41 (m, 3H), 1.40–1.13 (m, 6H), 1.11–0.93 (m, 2H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.73–0.63 (m, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 173.9, 140.0, 137.7, 136.4, 126.6, 125.7, 123.9, 123.7, 122.3, 51.3, 47.8, 39.5, 33.3, 33.0, 32.7, 30.0, 25.6, 24.9, 24.8, 22.9, 14.2.

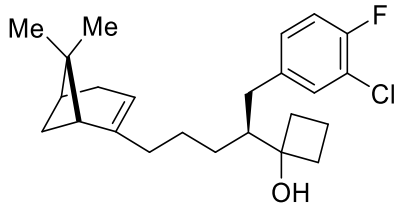
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3291, 2931, 2872, 2853, 1631, 1540, 1506, 1466, 1446, 1438, 1421, 1390, 1346, 1308, 1250, 1237, 1092, 1051, 892, 831, 813, 768, 756, 690.

MS (70 eV, EI): m/z (%): 286 (15), 187 (22), 160 (10), 147 (100).

HRMS (EI) for $C_{21}H_{29}NOS$: calc. $[M]^{+\bullet}$: 343.1970, found: 343.1963.

$[\alpha]_D^{20}$: +33.1 (c = 1.05, $CHCl_3$).

1-((*S*)-1-(3-chloro-4-fluorophenyl)-5-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)pentan-2-yl)cyclobutan-1-ol (*R*,*S*,*S*-136z):



The alcohol (*R*,*S*,*S*)-**136z** was prepared according to **TP7** from the iodide (*S*)-**114k** (42.6 mg, 0.1 mmol, 1.0 equiv) and cyclobutanone (**112x**, 19 µL, 17.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:9 to afford (*R*,*S*,*S*)-**136z** (23.1 mg, 0.059 mmol, 59%, dr = 92:8, 98% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.22 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.08–6.99 (m, 2H), 5.12–5.04 (m, 1H), 2.75 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.43 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.35–2.27 (m, 1H), 2.24–1.69 (m, 10H), 1.67–1.58 (m, 1H), 1.50 (s, 1H), 1.45–1.36 (m, 1H), 1.24 (s, 8H), 1.05 (d, *J* = 8.4 Hz, 1H), 0.75 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 156.6 (d, *J* = 246.3 Hz), 148.1, 139.4 (d, *J* = 4.0 Hz), 131.0, 128.8 (d, *J* = 6.8 Hz), 120.5 (d, *J* = 17.5 Hz), 116.3 (d, *J* = 20.7 Hz), 116.1, 79.8, 48.6, 45.7, 41.0, 38.0, 37.3, 36.0, 35.7, 35.0, 31.8, 31.4, 29.2, 26.4, 26.3, 21.3, 13.3.

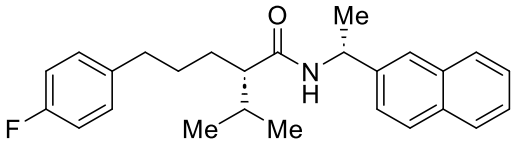
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3419, 2983, 2924, 2876, 2833, 1733, 1710, 1500, 1459, 1449, 1435, 1420, 1406, 1381, 1364, 1331, 1264, 1247, 1221, 1204, 1166, 1126, 1094, 1060, 957, 943, 900, 887, 815, 792, 773, 751, 703, 688.

MS (70 eV, EI): m/z (%): 162 (16), 145 (30), 131 (26), 119 (49), 105 (42), 91 (100).

HRMS (EI) for $C_{24}H_{32}ClFO$: calc. $[M]^{+\bullet}$: 390.2126, found: 390.2137.

$[\alpha]_D^{20}$: −14.3 (c = 1.3, $CHCl_3$).

(*S*)-5-(4-fluorophenyl)-2-isopropyl-*N*-((*R*)-1-(naphthalen-2-yl)ethyl)pentanamide (2'*S*,3*R*-136aa):



The amide (2'*S*,3*R*)-**136aa** was prepared according to **TP7** from the iodide (*S*)-**114l** (32.0 mg, 0.1 mmol, 1.0 equiv) and (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (**112z**, 62 µL, 69 mg, 0.35 mmol, 3.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (2'*S*,3*R*)-**136aa** (18.4 mg, 0.047 mmol, 47%, dr = 91:9, 95% *ee*) as white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = δ 8.20–8.05 (m, 1H), 7.92–7.76 (m, 2H), 7.56–7.42 (m, 4H), 7.07–6.99 (m, 2H), 6.97–6.83 (m, 2H), 5.98 (p, *J* = 7.0 Hz, 1H), 5.55 (d, *J* = 8.3 Hz, 1H), 2.55 (t, *J* = 7.4 Hz, 2H), 1.87–1.70 (m, 1H), 1.71–1.60 (m, 5H), 1.62–1.42 (m, 2H), 1.39–1.26 (m, 1H), 0.85 (dd, *J* = 6.6, 3.5 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 174.1, 161.3 (d, *J* = 243.1 Hz), 138.3, 138.0 (d, *J* = 3.2 Hz), 134.0, 131.3, 129.7 (d, *J* = 7.7 Hz), 128.8, 128.6, 126.6, 126.1, 125.3, 123.9, 122.8, 115.1 (d, *J* = 21.0 Hz), 55.3, 44.4, 35.3, 31.0, 30.0, 29.9, 21.2, 20.6, 20.5.

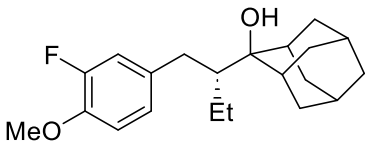
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3289, 3050, 2956, 2926, 2857, 1684, 1633, 1600, 1537, 1509, 1458, 1416, 1397, 1385, 1374, 1304, 1260, 1221, 1172, 1157, 1123, 1096, 1016, 848, 832, 821, 799, 777, 720, 701.

MS (70 eV, EI): m/z (%): 391 (13), 170 (24), 155 (100), 109 (14).

HRMS (EI) for $C_{26}H_{30}FNO$: calc. $[M]^{+\bullet}$: 391.2311, found: 391.2314

$[\alpha]_D^{20}$: +5.7 (c = 1.05, $CHCl_3$).

(1*R*,3*S*,5*R*,7*R*)-2-((*R*)-1-(3-fluoro-4-methoxyphenyl)butan-2-yl)adamantan-2-ol (*R*-136ab):



The alcohol (*R*)-**136ab** was prepared according to **TP7** from the iodide (*R*)-**114m** (30.8 mg, 0.1 mmol, 1.0 equiv) and adamantanone (**112h**, 45.0 mg, 0.3 mmol, 3.0 equiv) at −40 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**136ab** (27.9 mg, 0.084 mmol, 84%, 92% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.96–6.82 (m, 3H), 3.86 (s, 3H), 2.82 (dd, *J* = 14.1, 3.8 Hz, 1H), 2.39 (dd, *J* = 14.1, 9.2 Hz, 1H), 2.23–2.11 (m, 3H), 2.08–1.96 (m, 2H), 1.88–1.77 (m, 4H), 1.73–1.56 (m, 6H), 1.55–1.42 (m, 1H), 1.37–1.20 (m, 2H), 0.81 (t, *J* = 7.5 Hz, 3H).

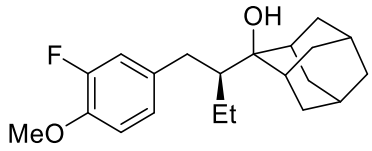
^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 244.9 Hz), 145.5 (d, *J* = 10.8 Hz), 136.0 (d, *J* = 5.9 Hz), 124.8 (d, *J* = 3.4 Hz), 116.8 (d, *J* = 17.6 Hz), 113.3 (d, *J* = 2.1 Hz), 77.4, 56.4, 43.8, 38.3, 35.0, 34.7, 34.3, 34.2, 33.3, 33.2, 33.2, 27.1, 27.0, 20.5, 13.2.
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2905, 2857, 1624, 1584, 1515, 1462, 1454, 1442, 1428, 1377, 1363, 1352, 1308, 1271, 1224, 1201, 1182, 1125, 1099, 1067, 1059, 1030, 1015, 987, 956, 930, 914, 870, 838, 803, 791, 775, 760.

MS (70 eV, EI): m/z (%): 285 (62), 151 (100), 139 (41), 107 (7), 91 (25).

HRMS (EI) for $C_{21}H_{27}FO$: calc. $[M-H_2O]^{+\bullet}$: 314.2046, found: 314.2042.

$[\alpha]_D^{20}$: −9.10 (c = 0.76, $CHCl_3$).

(1*R*,3*S*,5*R*,7*R*)-2-((*S*)-1-(3-fluoro-4-methoxyphenyl)butan-2-yl)adamantan-2-ol (*S*-136ab):



The alcohol (*S*)-**136ab** was prepared according to **TP7** from the iodide (*S*)-**114m** (30.8 mg, 0.1 mmol, 1.0 equiv) and adamantanone (**112h**, 45.0 mg, 0.3 mmol, 3.0 equiv) at −40 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136ab** (26.9 mg, 0.081 mmol, 81%, 90% *ee*) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.96–6.83 (m, 3H), 3.87 (s, 3H), 2.83 (dd, *J* = 14.1, 3.8 Hz, 1H), 2.39 (dd, *J* = 14.0, 9.2 Hz, 1H), 2.22–2.12 (m, 3H), 2.08–1.98 (m, 2H), 1.87–1.76 (m, 4H), 1.73–1.58 (m, 6H), 1.55–1.42 (m, 1H), 1.37–1.20 (m, 2H), 0.81 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 244.7 Hz), 145.5 (d, *J* = 10.7 Hz), 136.0 (d, *J* = 5.9 Hz), 124.8 (d, *J* = 3.3 Hz), 116.8 (d, *J* = 17.6 Hz), 113.3 (d, *J* = 2.2 Hz), 77.4, 56.5, 43.8, 38.4, 35.0, 34.8, 34.3, 34.2, 33.3, 33.3, 33.2, 27.2, 27.0, 20.5, 13.2.

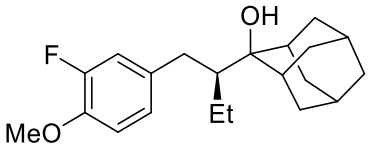
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3482, 2907, 2856, 1732, 1720, 1702, 1676, 1624, 1584, 1517, 1454, 1444, 1378, 1353, 1310, 1273, 1225, 1182, 1126, 1100, 1059, 1031, 1020, 998, 988, 956, 932, 874, 803, 793, 774, 760, 722, 696.

MS (70 eV, EI): m/z (%): 314 (9), 285 (29), 182 (6), 151 (100), 139 (28).

HRMS (EI) for $C_{21}H_{29}FO_2$: calc. $[M]^{+\bullet}$: 332.2119, found: 332.2111.

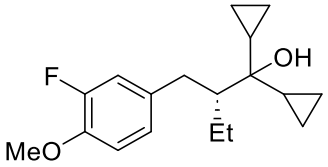
$[\alpha]_D^{20}$: +11.6 (c = 0.86, $CHCl_3$).

(1*R*,3*S*,5*R*,7*R*)-2-((*S*)-1-(3-fluoro-4-methoxyphenyl)butan-2-yl)adamantan-2-ol (*S*-136ab):



A solution of alkyl iodide (*S*-**114m**, 0.08 M, 1.00 equiv) and adamantanone (**112h**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*-BuLi (ca. 0.20 M in hexane, 2.85 equiv) were prepared. The solution of *t*-BuLi was pumped by pump A (flow rate A: 5.7 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The solution of the alkyl iodide was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = –20 to 25 °C). The stream was subsequently upon reaching steady state injected for 4 min 42 s into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136ab** (352 mg, 1.1 mmol, 61%, 93% *ee*) as white solid.

(*R*)-1,1-dicyclopropyl-2-(3-fluoro-4-methoxybenzyl)butan-1-ol (*R*-136ac):



The alcohol (*R*)-**136ac** was prepared according to **TP7** from the iodide (*R*)-**114m** (30.8 mg, 0.1 mmol, 1.0 equiv) and dicyclopropyl ketone (**112u**, 28 µL, 27.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*R*)-**136ac** (18.1 mg, 0.062 mmol, 62%, 93% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.02–6.90 (m, 2H), 6.85 (t, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 3.09 (dd, *J* = 14.1, 4.2 Hz, 1H), 2.45 (dd, *J* = 14.2, 8.4 Hz, 1H), 1.87–1.72 (m, 2H), 1.43–1.27 (m, 1H), 0.96–0.76 (m, 6H), 0.52–0.36 (m, 6H), 0.31–0.20 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 244.7 Hz), 145.5 (d, *J* = 10.8 Hz), 136.4 (d, *J* = 6.0 Hz), 124.5 (d, *J* = 3.3 Hz), 116.6 (d, *J* = 17.7 Hz), 113.3 (d, *J* = 2.1 Hz), 73.3, 56.4, 54.4, 35.9, 23.4, 17.3, 16.6, 14.1, 1.9, 1.6, -0.6, -0.8.

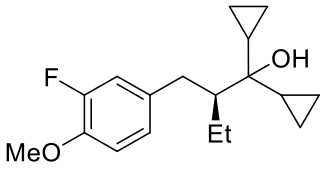
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3594, 3083, 3006, 2957, 2930, 2873, 2843, 2840, 1624, 1584, 1515, 1463, 1442, 1427, 1378, 1270, 1224, 1182, 1146, 1126, 1055, 1027, 986, 956, 926, 912, 876, 848, 832, 828, 823, 804, 786, 782, 779, 772, 761.

MS (70 eV, EI): m/z (%): 245 (4), 139 (100), 111 (30), 91 (12), 69 (24).

HRMS (EI) for $C_{18}H_{25}FO_2$: calc. $[M]^{+\bullet}$: 292.1839, found: 292.1832.

$[\alpha]_D^{20}$: +33.1 (c = 1.00, $CHCl_3$).

(*S*)-1,1-dicyclopropyl-2-(3-fluoro-4-methoxybenzyl)butan-1-ol (*S*-136ac):



The alcohol (*S*)-**136ac** was prepared according to **TP7** from the iodide (*S*)-**114m** (30.8 mg, 0.1 mmol, 1.0 equiv) and dicyclopropyl ketone (**112u**, 28 µL, 27.5 mg, 0.25 mmol, 2.5 equiv) at −78 °C. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136ac** (19.0 mg, 0.062 mmol, 62%, 90% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.01–6.82 (m, 3H), 3.86 (s, 3H), 3.09 (dd, *J* = 14.1, 4.3 Hz, 1H), 2.45 (dd, *J* = 14.1, 8.4 Hz, 1H), 1.82–1.73 (m, 2H), 1.40–1.30 (m, 1H), 0.93–0.78 (m, 6H), 0.50–0.36 (m, 6H), 0.26 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.3 (d, *J* = 244.7 Hz), 145.5 (d, *J* = 10.7 Hz), 136.4 (d, *J* = 5.9 Hz), 124.5 (d, *J* = 3.3 Hz), 116.7 (d, *J* = 17.8 Hz), 113.3 (d, *J* = 2.3 Hz), 73.3, 56.4, 54.4, 35.9, 23.4, 17.3, 16.6, 14.1, 2.0, 1.6, -0.6, -0.8.

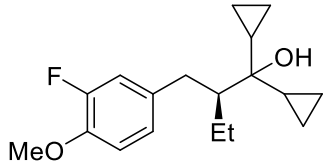
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3608, 3601, 3086, 3007, 2958, 2931, 2874, 2362, 1733, 1719, 1702, 1624, 1584, 1517, 1464, 1444, 1428, 1379, 1272, 1225, 1183, 1126, 1055, 1028, 987, 956, 928, 913, 876, 804, 761.

MS (70 eV, EI): m/z (%): 245 (7), 165 (7), 152 (9), 139 (98), 111 (74), 105 (11), 77 (20), 69 (100).

HRMS (EI) for $C_{18}H_{25}FO_2$: calc. $[M]^{+\bullet}$: 292.1839, found: 292.1836.

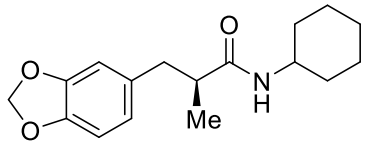
$[\alpha]_D^{20}$: −32.0 (c = 1.00, $CHCl_3$).

(*S*)-1,1-dicyclopropyl-2-(3-fluoro-4-methoxybenzyl)butan-1-ol (*S*-136ac):



A solution of alkyl iodide (*S*-**114m**, 0.08 M, 1.00 equiv) and dicyclopropyl ketone (**112u**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*BuLi (ca. 0.20 M in hexane, 2.85 equiv) were prepared. The solution of *t*-BuLi was pumped by pump A (flow rate A: 5.7 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The solution of the alkyl iodide was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = –20 to 25 °C). The stream was subsequently upon reaching steady state injected for 4 min 42 s into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136ac** (293 mg, 1.0 mmol, 56%, 94% *ee*) as white solid.

(*S*)-3-(benzo[*d*][1,3]dioxol-5-yl)-*N*-cyclohexyl-2-methylpropanamide (*S*-136ad):



A solution of alkyl iodide (*S*-**114a**, 0.08 M, 1.00 equiv) and cyclohexyl isocyanate (**112y**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*-BuLi (ca. 0.20 M in hexane, 2.85 equiv) were prepared. The solution of *t*-BuLi was pumped by pump A (flow rate A: 5.7 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The solution of the alkyl iodide was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = –20 to 25 °C). The stream was subsequently upon reaching steady state injected for 2 min 30 s into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted

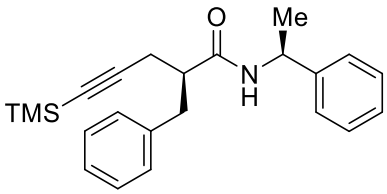
Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (*S*)-**136ad** (204 mg, 0.71 mmol, 71%, 96% *ee*) as white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.71 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.61 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.95–5.87 (m, 2H), 5.03 (d, *J* = 8.3 Hz, 1H), 3.78–3.62 (m, 1H), 2.84 (dd, *J* = 13.5, 8.7 Hz, 1H), 2.58 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.34–2.22 (m, 1H), 1.90–1.77 (m, 1H), 1.73–1.54 (m, 4H), 1.44–1.21 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.13–0.81 (m, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 174.5, 147.6, 146.0, 133.9, 122.0, 109.5, 108.3, 100.9, 47.9, 44.5, 40.5, 33.2, 25.6, 24.9, 24.9, 17.8.

The analytical data was in accordance with literature values.[417]

(*S*)-2-benzyl-*N*-((*S*)-1-phenylethyl)-5-(trimethylsilyl)pent-4-ynamide (2'*S*,3*S*-136ae):



A solution of alkyl iodide (*S*-**114n**, 0.08 M, 1.00 equiv) and electrophile (*S*-**112t**, 0.20 M, 2.50 equiv) in hexane:Et_2O (2:1) and a solution of *t*-BuLi (ca. 0.20 M in hexane, 3.00 equiv) were prepared. The solution of *t*-BuLi was pumped by pump A (flow rate A: 6.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Red as tubing for the peristaltic pump) into a precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The solution of the alkyl iodide was pumped by pump B (flow rate B: 5.0 mL/min, using the 50-1300 V3 Tube Assy Acid Type Blue as tubing for the peristaltic pump) into a second precooling loop (V_{pre} = 2.0 mL) at T^1 = –20 to 25 °C. The precooled solutions were mixed in a T-shaped mixer and passed within a residence time of (t^1 = 5.5 to 5.6 s) through a coil reactor (V_R = 1.0 mL) at the corresponding temperature (T^1 = –20 to 25 °C). The stream was subsequently upon reaching steady state injected for 120 s into a flask charged with sat. aq. NH_4Cl. The aqueous phase was extracted Et_2O (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel with diethyl ether/pentane = 1:4 to afford (2'*S*,3*S*)-**136ae** (194 mg, 0.53 mmol, 67%, dr = 96:4, 96% *ee*) as white solid.

[417] A. Kremsmair, H. R. Wilke, M. M. Simon, Q. Schmidt, K. Karaghiosoff, P. Knochel, *Chem. Sci.* **2022**, *13*, 44–49.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.25–7.19 (m, 6H), 7.12 (dd, *J* = 7.4, 2.0 Hz, 2H), 7.03–6.98 (m, 2H), 5.70 (d, *J* = 8.0 Hz, 1H), 5.08 (p, *J* = 7.1 Hz, 1H), 2.95 (dd, *J* = 13.4, 8.3 Hz, 1H), 2.83 (dd, *J* = 13.4, 5.3 Hz, 1H), 2.63–2.39 (m, 3H), 1.44 (d, *J* = 6.9 Hz, 3H), 0.15 (s, 9H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 172.3, 142.9, 139.2, 129.2, 128.7, 128.6, 127.3, 126.6, 126.2, 104.7, 87.1, 49.4, 48.6, 38.2, 23.2, 21.8, 0.2.

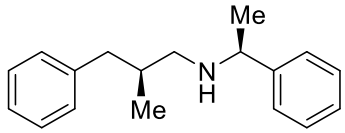
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3262, 3067, 3030, 2964, 2928, 2899, 2180, 1638, 1546, 1506, 1494, 1452, 1420, 1381, 1341, 1318, 1247, 1207, 1194, 1180, 1132, 1122, 1054, 1033, 1022, 1012, 997, 890, 840, 782, 759, 740, 696.

MS (70 eV, EI): m/z (%): 363 (32), 272 (19), 252 (91), 168 (20), 148 (40), 105 (100), 91 (25), 73 (21).

HRMS (EI) for $C_{23}H_{29}NOSi$: calc. $[M]^{+\bullet}$: 363.2018, found: 363.2011

$[\alpha]_D^{20}$: +25.9 (c = 1.51, $CHCl_3$).

(*S*)-2-methyl-3-phenyl-*N*-((*S*)-1-phenylethyl)propan-1-amine (2'*S*,3*S*-140):



The secondary amine (2'*S*,3*S*)-**140** was prepared from the amide (2'*S*,3*S*)-**136l** according to a modified literature procedure.[418] Thus, (1'*S*,2*S*)-**136l** (133 mg, 0.5 mmol, 1.0 equiv) was dissolved in THF (2.5 mL). The mixture was cooled to 0 °C and $LiAlH_4$ (1.0 M in THF, 1.5 mL, 3.0 equiv) was added dropwise. The mixture was heated at 50 °C overnight and after completion, diluted with Et_2O (15 mL). The reaction was carefully quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 30 mL). The crude product was washed with Brine and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:2 to afford (2'*S*,3*S*)-**140** (102.6 mg, 0.405 mmol, 81%, dr = 98:2, 96% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.36–7.28 (m, 4H), 7.28–7.21 (m, 3H), 7.20–7.10 (m, 3H), 3.73 (q, *J* = 6.6 Hz, 1H), 2.80 (dd, *J* = 13.4, 5.5 Hz, 1H), 2.45–2.34 (m, 2H), 2.30 (dd, *J* = 13.4, 8.6 Hz, 1H), 1.97–1.81 (m, 1H), 1.50 (d, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).

[418] B. M. Trost, A. Maruniak, *Angew. Chem. Int. Ed.* **2013**, *52*, 6262–6264.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 146.1, 141.2, 129.3, 128.5, 128.3, 126.9, 126.8, 125.8, 58.5, 54.1, 41.5, 35.7, 24.5, 18.2.

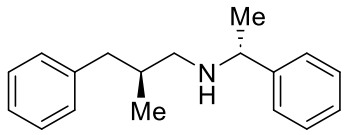
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3568, 3064, 3027, 2963, 2925, 1748, 1711, 1654, 1636, 1603, 1495, 1452, 1438, 1419, 1360, 1220, 1128, 1091, 1030, 911, 763, 742, 701.

MS (70 eV, EI): 238 (14), 134 (35), 105 (100), 91 (22).

HRMS (EI) for $C_{18}H_{23}N$: calc. $[M]^{+\bullet}$: 253.1830, found: 253.1826.

$[\alpha]_D^{20}$: −33 (c = 1.01, $CHCl_3$).

(*S*)-2-methyl-3-phenyl-*N*-((*R*)-1-phenylethyl)propan-1-amine (2'*S*,3*R*-140):



The secondary amine (2'*S*,3*R*)-**140** was prepared from the amide (2'*S*,3*R*)-**136l** according to a modified literature procedure.[419] Thus, (2'*S*,3*R*)-**136l** (53.5 mg, 0.2 mmol, 1.0 equiv) was dissolved in THF (1.0 mL). The mixture was cooled to 0 °C and $LiAlH_4$ (1.0 M in THF, 0.6 mL, 3.0 equiv) was added dropwise. The mixture was heated at 50 °C overnight and after completion, diluted with Et_2O (5 mL). The reaction was carefully quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 10 mL). The crude product was washed with Brine and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel with diethyl ether/pentane = 1:2 to afford (2'*S*,3*R*)-**140** (39 mg, 0.154 mmol, 77%, dr = 2:98, 96% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.35–7.26 (m, 4H), 7.26–7.20 (m, 3H), 7.18–7.13 (m, 1H), 7.12–7.08 (m, 2H), 3.69 (q, *J* = 6.6 Hz, 1H), 2.64 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.48 (dd, *J* = 11.6, 5.5 Hz, 1H), 2.35 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.24 (dd, *J* = 11.5, 7.4 Hz, 1H), 1.96–1.79 (m, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.26–1.17 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 146.2, 141.2, 129.3, 128.5, 128.3, 126.9, 126.7, 125.8, 58.6, 54.1, 41.8, 35.7, 24.7, 18.2.

IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3367, 3062, 3026, 2959, 2924, 1713, 1684, 1654, 1636, 1603, 1494, 1452, 1362, 1304, 1220, 1127, 1089, 1074, 1029, 911, 761, 741, 698.

[419] B. M. Trost, A. Maruniak, *Angew. Chem. Int. Ed.* **2013**, *52*, 6262–6264.

MS (70 eV, EI): 238 (15), 134 (46), 105 (100), 91 (23).

HRMS (EI) for $C_{18}H_{23}N$: calc. $[M]^{+\bullet}$: 253.1830, found: 253.1825.

$[\alpha]_D^{20}$: +30.9 (c = 0.95, $CHCl_3$).

3.5 Single Crystal X-Ray Diffraction Studies

Single crystals of compound (*S*)-**136d**, suitable for X-ray diffraction, were obtained by slow evaporation of an etheral solution of (*S*)-**136d**. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[420] Absorption correction using the multiscan method[421] was applied. The structures were solved with SHELXS-97,[422] refined with SHELXL-97[423] and finally checked using PLATON.[424] Details for data collection and structure refinement are summarized in Table 22.

CCDC-**2210094** contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[420] Program package 'CrysAlisPro 1.171.40.84a (Rigaku OD, 2020)'.
[421] Program package 'CrysAlisPro 1.171.40.84a (Rigaku OD, 2020)'.
[422] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[423] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[424] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 22: Details for X-ray data collection and structure refinement for compound (*S*)-**136d**.

	(*S*)-**136d**
Empirical formula	$C_{20}H_{26}O_3$
Formula mass	314.41
T[K]	123(2)
Crystal size [mm]	0.40 × 0.40 × 0.10
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*1
a [Å]	9.0348(3)
b [Å]	9.1064(4)
c [Å]	11.2425(4)
α [°]	100.035(3)
β [°]	104.789(3)
γ [°]	111.434(4)
V [Å^3]	794.85(6)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.314
μ [mm^{-1}]	0.086
F(000)	340
Θ range [°]	1.96 – 25.24
Index ranges	$-12 \leq h \leq 12$
	$-12 \leq k \leq 12$
	$-14 \leq l \leq 14$
Reflns. collected	13967
Reflns. obsd.	7043
Reflns. unique	7816 (R_{int} = 0.0218)
R_1, wR_2 (2σ data)	0.0489, 0.1200
R_1, wR_2 (all data)	0.0554, 0.1263
GOOF on F^2	1.020
Peak/hole [e Å^{-3}]	0.434 / -0.188

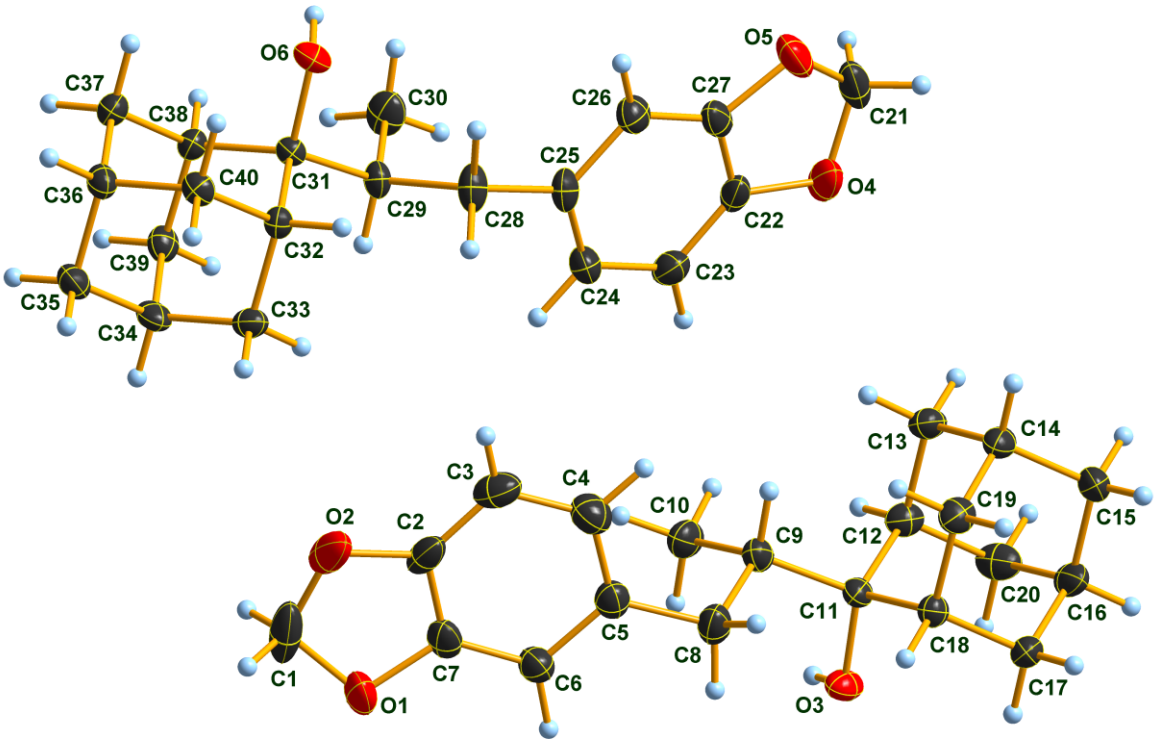


Figure 25: Molecular structure of compound (*S*)-**136d** in the crystal. View of the two crystallographically independent molecules. DIAMOND[425] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 23: Selected bond lengths (Å) of compound (*S*)-**136d**.

O6 – C31	1.452(3)	C25 – C24	1.383(4)
C32 – C40	1.531(3)	C25 – C26	1.410(4)
C32 – C31	1.543(3)	C25 – C28	1.506(4)
C32 – C33	1.543(3)	C14 – C19	1.529(4)
O3 – C11	1.434(3)	C14 – C15	1.539(4)
C31 – C38	1.543(3)	C16 – C20	1.522(5)
C31 – C29	1.558(3)	C16 – C17	1.527(4)
C9 – C10	1.531(4)	C16 – C15	1.529(4)
C9 – C8	1.539(4)	C12 – C20	1.532(4)
C9 – C11	1.552(4)	C27 – C26	1.366(4)
C18 – C17	1.525(4)	O1 – C7	1.382(4)
C18 – C19	1.537(4)	O1 – C1	1.428(5)
C18 – C11	1.554(3)	C6 – C7	1.380(4)
C37 – C36	1.533(4)	C6 – C5	1.407(4)
C37 – C38	1.534(4)	C23 – C24	1.404(4)
C39 – C34	1.534(4)	C4 – C5	1.399(4)
C39 – C38	1.536(4)	C4 – C3	1.400(5)

[425] DIAMOND, Crystal Impact GbR., Version 3.2i.

C35 – C34	1.533(4)	C7 – C2	1.381(5)
C35 – C36	1.540(4)	C5 – C8	1.509(4)
C29 – C30	1.520(4)	O2 – C2	1.375(4)
C29 – C28	1.551(4)	O2 – C1	1.428(6)
C11 – C12	1.556(4)	C2 – C3	1.357(5)
O4 – C22	1.385(3)	C36 – C40	1.530(4)
O4 – C21	1.435(4)	C13 – C14	1.534(4)
C22 – C23	1.366(4)	C13 – C12	1.536(4)
C22 – C27	1.383(5)	O5 – C27	1.380(4)
C34 – C33	1.532(4)	O5 – C21	1.427(5)

Table 24: Selected bond angles (°) of compound (*S*)-**136d**.

C40 – C32 – C31	111.4(2)	C20 – C16 – C17	108.5(2)
C40 – C32 – C33	108.1(2)	C20 – C16 – C15	109.7(2)
C31 – C32 – C33	109.4(2)	C17 – C16 – C15	110.1(3)
O6 – C31 – C32	106.4(2)	C18 – C17 – C16	110.0(2)
O6 – C31 – C38	108.3(2)	C20 – C12 – C13	108.8(2)
C32 – C31 – C38	107.6(2)	C20 – C12 – C11	109.9(2)
O6 – C31 – C29	108.1(2)	C13 – C12 – C11	110.4(2)
C32 – C31 – C29	112.3(2)	C26 – C27 – O5	127.7(3)
C38 – C31 – C29	113.8(2)	C26 – C27 – C22	122.2(3)
C10 – C9 – C8	110.1(2)	O5 – C27 – C22	110.0(3)
C10 – C9 – C11	112.2(2)	C14 – C19 – C18	109.8(2)
C8 – C9 – C11	111.1(2)	C7 – O1 – C1	104.8(3)
C17 – C18 – C19	108.5(2)	C27 – C26 – C25	117.9(3)
C17 – C18 – C11	110.4(2)	C7 – C6 – C5	116.6(3)
C19 – C18 – C11	110.2(2)	C22 – C23 – C24	116.9(3)
C36 – C37 – C38	109.8(2)	C36 – C40 – C32	109.9(2)
C34 – C39 – C38	109.0(2)	C5 – C4 – C3	122.9(3)
C34 – C35 – C36	108.9(2)	C6 – C7 – C2	123.1(3)
C30 – C29 – C28	113.2(2)	C6 – C7 – O1	127.0(3)
C30 – C29 – C31	112.4(2)	C2 – C7 – O1	109.8(3)
C28 – C29 – C31	110.6(2)	C4 – C5 – C6	119.2(3)
O3 – C11 – C9	108.9(2)	C4 – C5 – C8	121.5(3)
O3 – C11 – C18	104.9(2)	C6 – C5 – C8	119.3(3)
C9 – C11 – C18	114.0(2)	C16 – C15 – C14	109.1(2)
O3 – C11 – C12	110.8(2)	C16 – C20 – C12	110.2(2)
C9 – C11 – C12	111.1(2)	C2 – O2 – C1	104.9(3)
C18 – C11 – C12	107.0(2)	C25 – C24 – C23	122.4(3)

C22 – O4 – C21	104.6(2)	C25 – C28 – C29	115.7(2)
C23 – C22 – C27	121.4(3)	C5 – C8 – C9	114.5(2)
C23 – C22 – O4	129.0(3)	O5 – C21 – O4	108.3(2)
C27 – C22 – O4	109.6(3)	C3 – C2 – O2	128.3(3)
C33 – C34 – C35	109.5(2)	C3 – C2 – C7	121.6(3)
C33 – C34 – C39	110.2(2)	O2 – C2 – C7	110.0(3)
C35 – C34 – C39	109.3(2)	C2 – C3 – C4	116.6(3)
C40 – C36 – C37	109.0(2)	O2 – C1 – O1	108.6(3)
C40 – C36 – C35	109.6(2)	C39 – C38 – C31	110.4(2)
C37 – C36 – C35	109.4(2)	C24 – C25 – C26	119.2(3)
C14 – C13 – C12	109.4(2)	C24 – C25 – C28	121.5(3)
C34 – C33 – C32	109.6(2)	C26 – C25 – C28	119.3(3)
C27 – O5 – C21	104.7(2)	C19 – C14 – C13	110.5(2)
C37 – C38 – C39	108.7(2)	C19 – C14 – C15	108.9(2)
C37 – C38 – C31	110.6(2)	C13 – C14 – C15	108.8(2)

Table 25: Selected torsion angles (°) of compound (*S*)-**136d**.

C40 – C32 – C31 – O6	57.5(2)	C18 – C11 – C12 – C13	-60.9(3)
C33 – C32 – C31 – O6	177.0(2)	C21 – O5 – C27 – C26	-171.3(3)
C40 – C32 – C31 – C38	-58.4(2)	C21 – O5 – C27 – C22	10.9(3)
C33 – C32 – C31 – C38	61.1(2)	C23 – C22 – C27 – C26	-0.9(4)
C40 – C32 – C31 – C29	175.6(2)	O4 – C22 – C27 – C26	-179.1(3)
C33 – C32 – C31 – C29	-64.9(2)	C23 – C22 – C27 – O5	177.1(3)
O6 – C31 – C29 – C30	-66.3(3)	O4 – C22 – C27 – O5	-1.1(3)
C32 – C31 – C29 – C30	176.6(2)	C13 – C14 – C19 – C18	58.3(3)
C38 – C31 – C29 – C30	54.1(3)	C15 – C14 – C19 – C18	-61.2(3)
O6 – C31 – C29 – C28	61.4(3)	C17 – C18 – C19 – C14	60.8(3)
C32 – C31 – C29 – C28	-55.7(3)	C11 – C18 – C19 – C14	-60.2(3)
C38 – C31 – C29 – C28	-178.3(2)	O5 – C27 – C26 – C25	-176.6(3)
C10 – C9 – C11 – O3	-62.7(3)	C22 – C27 – C26 – C25	0.9(4)
C8 – C9 – C11 – O3	61.1(3)	C24 – C25 – C26 – C27	-0.3(4)
C10 – C9 – C11 – C18	-179.4(2)	C28 – C25 – C26 – C27	179.4(3)
C8 – C9 – C11 – C18	-55.6(3)	C27 – C22 – C23 – C24	0.2(4)
C10 – C9 – C11 – C12	59.6(3)	O4 – C22 – C23 – C24	178.0(3)
C8 – C9 – C11 – C12	-176.6(2)	C37 – C36 – C40 – C32	-58.9(3)
C17 – C18 – C11 – O3	58.3(3)	C35 – C36 – C40 – C32	60.8(3)
C19 – C18 – C11 – O3	178.2(2)	C31 – C32 – C40 – C36	59.6(3)
C17 – C18 – C11 – C9	177.4(2)	C33 – C32 – C40 – C36	-60.6(3)
C19 – C18 – C11 – C9	-62.7(3)	C5 – C6 – C7 – C2	-1.1(4)

C17 – C18 – C11 – C12	-59.4(3)	C5 – C6 – C7 – O1	-176.1(3)
C19 – C18 – C11 – C12	60.5(3)	C1 – O1 – C7 – C6	-176.8(3)
C21 – O4 – C22 – C23	172.9(3)	C1 – O1 – C7 – C2	7.6(3)
C21 – O4 – C22 – C27	-9.1(3)	C3 – C4 – C5 – C6	1.3(5)
C36 – C35 – C34 – C33	59.9(3)	C3 – C4 – C5 – C8	-178.3(3)
C36 – C35 – C34 – C39	-60.9(3)	C7 – C6 – C5 – C4	-0.7(4)
C38 – C39 – C34 – C33	-58.5(3)	C7 – C6 – C5 – C8	178.9(3)
C38 – C39 – C34 – C35	61.8(3)	C20 – C16 – C15 – C14	60.0(3)
C38 – C37 – C36 – C40	59.8(3)	C17 – C16 – C15 – C14	-59.3(3)
C38 – C37 – C36 – C35	-60.0(3)	C19 – C14 – C15 – C16	59.9(3)
C34 – C35 – C36 – C40	-59.6(3)	C13 – C14 – C15 – C16	-60.7(3)
C34 – C35 – C36 – C37	59.8(3)	C17 – C16 – C20 – C12	60.5(3)
C35 – C34 – C33 – C32	-61.1(3)	C15 – C16 – C20 – C12	-59.8(3)
C39 – C34 – C33 – C32	59.1(3)	C13 – C12 – C20 – C16	59.6(3)
C40 – C32 – C33 – C34	60.8(3)	C11 – C12 – C20 – C16	-61.4(3)
C31 – C32 – C33 – C34	-60.7(3)	C26 – C25 – C24 – C23	-0.4(4)
C36 – C37 – C38 – C39	60.5(3)	C28 – C25 – C24 – C23	180.0(3)
C36 – C37 – C38 – C31	-60.9(3)	C22 – C23 – C24 – C25	0.4(4)
C34 – C39 – C38 – C37	-61.1(3)	C24 – C25 – C28 – C29	-63.8(4)
C34 – C39 – C38 – C31	60.3(3)	C26 – C25 – C28 – C29	116.6(3)
O6 – C31 – C38 – C37	-55.9(3)	C30 – C29 – C28 – C25	-38.0(4)
C32 – C31 – C38 – C37	58.8(3)	C31 – C29 – C28 – C25	-165.2(2)
C29 – C31 – C38 – C37	-176.1(2)	C4 – C5 – C8 – C9	-65.1(4)
O6 – C31 – C38 – C39	-176.2(2)	C6 – C5 – C8 – C9	115.3(3)
C32 – C31 – C38 – C39	-61.5(3)	C10 – C9 – C8 – C5	-47.9(3)
C29 – C31 – C38 – C39	63.5(3)	C11 – C9 – C8 – C5	-172.9(2)
C12 – C13 – C14 – C19	-58.3(3)	C27 – O5 – C21 – O4	-16.5(3)
C12 – C13 – C14 – C15	61.2(3)	C22 – O4 – C21 – O5	15.9(3)
C19 – C18 – C17 – C16	-59.7(3)	C1 – O2 – C2 – C3	174.1(3)
C11 – C18 – C17 – C16	61.2(3)	C1 – O2 – C2 – C7	-8.8(3)
C20 – C16 – C17 – C18	-60.3(3)	C6 – C7 – C2 – C3	2.3(5)
C15 – C16 – C17 – C18	59.8(3)	O1 – C7 – C2 – C3	178.1(3)
C14 – C13 – C12 – C20	-60.4(3)	C6 – C7 – C2 – O2	-175.0(3)
C14 – C13 – C12 – C11	60.4(3)	O1 – C7 – C2 – O2	0.8(4)
O3 – C11 – C12 – C20	-54.5(3)	O2 – C2 – C3 – C4	175.2(3)
C9 – C11 – C12 – C20	-175.7(2)	C7 – C2 – C3 – C4	-1.6(5)
C18 – C11 – C12 – C20	59.2(3)	C5 – C4 – C3 – C2	-0.2(5)
O3 – C11 – C12 – C13	-174.6(2)	C2 – O2 – C1 – O1	13.5(4)
C9 – C11 – C12 – C13	64.2(3)	C7 – O1 – C1 – O2	-13.1(3)

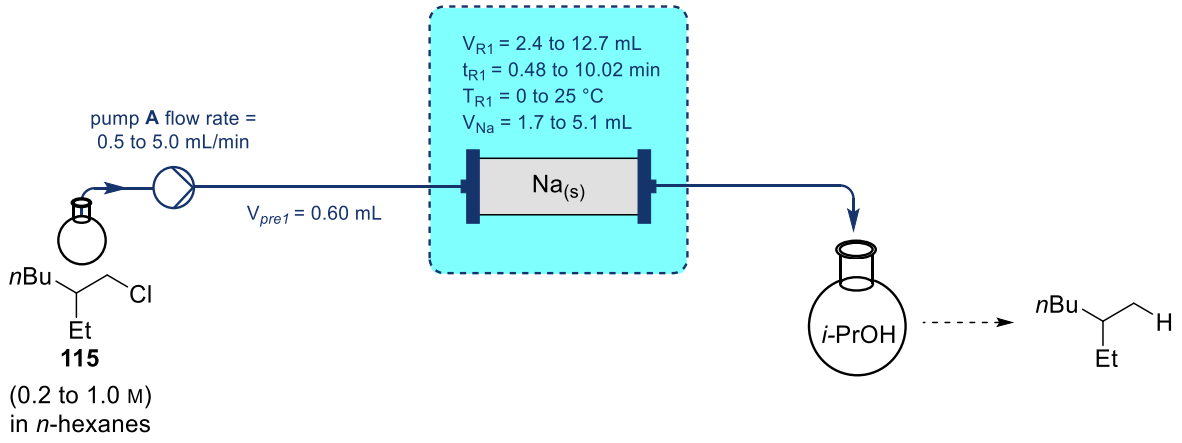
4. (2-Ethylhexyl)sodium: A Hexane-Soluble Reagent for Br/Na-Exchanges and Directed Metalations in Continuous Flow

4.1 General Remarks on Flow and Subsequent Batch Quenching Reactions

Tetradecane (*n*-$C_{14}H_{30}$), tridecane (*n*-$C_{13}H_{28}$), dodecane (*n*-$C_{12}H_{26}$) or undecane (*n*-$C_{11}H_{24}$) were used as internal standards. All flasks were heat gun dried (650 °C) under vacuum and backfilled with argon after cooling. Syringes, which were used to transfer reagents and solvents, were purged with argon three times prior to use. Batch quenching reactions were carried out with magnetic stirring. Flow reactions were performed on commercially available flow systems. A Vapourtec E-series Integrated Flow Chemistry System with 3rd Pump Kit, Organometallic Kit, Collection Valve Kit and Cryogenic Reaction Kit was used. Hexane solutions of the 3-(chloromethyl)heptane and THF solutions of the remaining reactants were kept in flasks with rubber septa under an argon atmosphere during the reactions. All reactions were performed in coiled tube reactors. Coiled reactors were made from PFA or PTFE Teflon (I.D. = 0.8 mm or 0.25 mm, O.D. = 1.6 mm) tubing and T-pieces (I.D. = 0.5 mm) were used as mixers. Prior to performing reactions, the system was dried by flushing with dry THF (flow rate: 1.00 mL/min; run-time: 10 to 30 min) or by first flushing six times with MeOH followed by dry *n*-hexane (flow rate: 1.00 mL/min; run-time: 10 to 30 min).

4.2 Optimizations of the Sodium Packed-Bed Reactor and Subsequent Reactions

4.2.1 Screening of the conditions for the generation of (2-ethylhexyl)sodium using a packed-bed sodium reactor.



Scheme 120: Set-up for the optimization screening for the preparation of (2-ethylhexyl)sodium using a packed-bed sodium reactor.

Solutions of 3-(chloromethyl)heptane **115** (0.2 to 1.0 M) and tetradecane in *n*-hexane were prepared. The solution was pumped with flow rates from 0.5 to 5 mL/min through packed-bed sodium reactors (V_{R1} = 2.4 to 12.7 mL, V_{Na} = 1.7 to 5.1 mL) at various temperatures (T_{R1} = 0 to 25 °C). After passing the reactor (t_{R1} = 0.48 to 10.02 min), the reaction mixture was added to a solution of *i*-PrOH (1.1 M) in *n*-hexane. Conversion of **115** was monitored by GC-analysis.

Table 26: Optimization screening for the preparation of (2-ethylhexyl)sodium using a packed-bed sodium reactor.

Entry	c (**115**) [M]	V_{R1} [mL]	V (Na) [mL]	Flow rate [ml/min]	T [°C]	Conversion [%]
1	0.2	2.4	1.7	0.5	0	47
2	0.2	2.4	1.7	0.5	25 [a]	100
3	0.2	2.4	1.7	1.0	25 [a]	96
4	0.2	2.4	1.7	2.0	25 [a]	92
5	0.2	2.4	1.7	5.0	25 [a]	70
6	0.5	2.4	1.7	0.5	0	48
7	0.5	2.4	1.7	1.0	0	39
8	0.5	2.4	1.7	2.0	0	30
9	0.5	2.4	1.7	5.0	0	15
10	0.5	2.4	1.7	0.5	25 [a]	98
11	0.5	2.4	1.7	1.0	25 [a]	93
12	0.5	2.4	1.7	2.0	25 [a]	66
13	0.5	2.4	1.7	5.0	25 [a]	58
14	1.0	2.4	1.7	0.5	0	Clogging
15	1.0	2.4	1.7	0.5	25 [a]	100 [b]
16	1.0	2.4	1.7	1.0	25 [a]	81 [b]
17	1.0	2.4	1.7	2.0	25 [a]	90 [b]
18	0.2	7.5	3.4	0.5	25	100
19	0.2	7.5	3.4	1.0	25	100
20	0.2	7.5	3.4	2.0	25	100
21	0.5	7.5	3.4	0.5	25	99
22	0.5	7.5	3.4	0.5	5	82
23	0.5	7.5	3.4	1.0	5	89
24	0.5	7.5	3.4	2.0	5	62

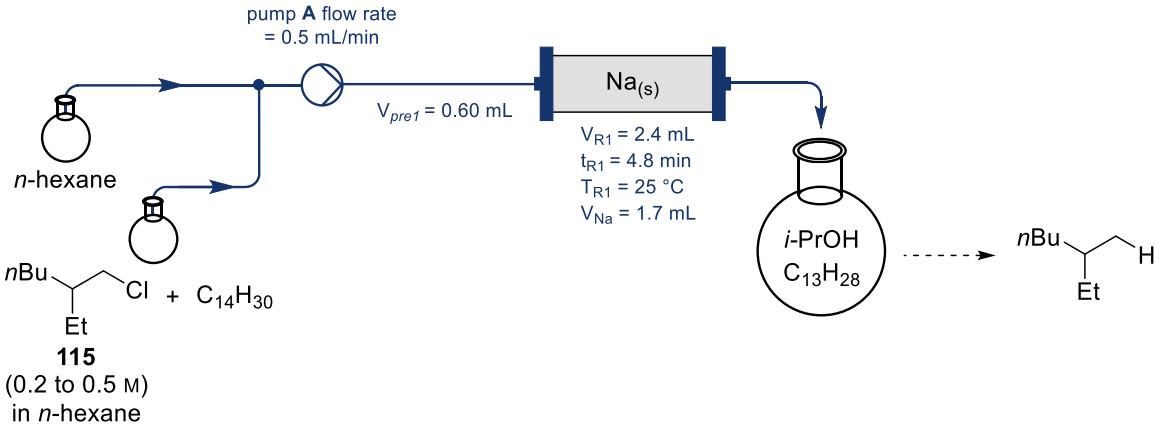
Entry	c (**115**) [M]	V_{R1} [mL]	V (Na) [mL]	Flow rate [ml/min]	T [°C]	Conversion [%]
25	0.5	7.5	3.4	5.0	5	33
26	0.5	12.7	5.1	0.5	5	100
27	0.5	12.7	5.1	1.0	5	100
28	0.5	12.7	5.1	2.0	5	100
29	0.5	12.7	5.1	5.0	5	77
30	0.5	12.7	5.1	0.5	25	100
31	0.2	12.7	5.1	2.0	25	100

[a] Without external *i*-PrOH bath (inefficient heat transfer). [b] Temperature of the packed-bed reactor increased significantly due to inefficient heat removal.

In addition to the results shown in table 26, it was observed that charging the entire volume of the packed-bed reactor with sodium led to clogging. Moreover, the particle size of the sodium is important. Especially, small particles led to fast clogging of the reactor, which is why the sodium dispersion was stirred for 4 h at 300 to 400 rpm (for an appropriate sodium particle size see figure 21).

Without any activation, the conversion of **115** remained unsatisfactory. Mechanical activation by pre-stirring the sodium in a round bottom flask did not result in high conversion rates. Best results were obtained by chemically activating the sodium by pumping a *i*-PrOH solution (0.1 M in *n*-hexane; runtime: 2 min; flow rate: 5.0 mL/min) through the packed-bed reactor. Even though, the longest column gave satisfactory results (Table 26 entry 26 -31), the medium sized column was used to reduce the amount of sodium used and to decrease the retention time of the generated alkylsodium reagent **36**.

4.2.2 Solubility studies of (2-ethylhexyl)sodium



Scheme 121: Set-up for the solubility studies of (2-ethylhexyl)sodium (**36**).

A solution of 3-(chloromethyl)heptane (**115**, 0.2 M or 0.5 M) and tetradecane in *n*-hexane was prepared. After pumping *n*-hexane for 1 min, the solution of **115** was pumped through an activated sodium packed-bed reactor by pump A (flow rate: 0.5 mL/min) and injected for 20 s into 0.5 mL of a stock solution of *i*-PrOH (1.1 M) and tridecane in *n*-hexane. After 16 min, pump A was switched back from pumping the solution of **115** to pumping *n*-hexane. For the first 10 min a sample was taken every 20 s starting at minute 3. Starting from minute 10, an aliquot of 20 s was taken each minute until minute 32.

For comprehensibility, the highest value of the data set of the ratio of tetra- to tridecane (grey) and the hydrolysis product (orange) in figure 26 and 27 is normalized deliberately to 100%. Figure 26 shows that steady state is reached 9.0 minutes after switching from pumping *n*-hexane to pumping the solution of **115** at minute 1.0, as can be seen by the constant maximum level of the grey and orange curves. After switching back to pumping *n*-hexane at minute 16 (red line), the steady state is maintained for additional 4 min until minute 20. Furthermore, the blue curve shows a conversion of just 83% during steady state, which indicates a lack of activation. The conversion is increased before and after steady state, which can be explained by the lower concentration of 3-(chloromethyl)heptane (**115**). The ratio of tetra- to tridecane and the hydrolysis product correlate with each other, indicating a high solubility of (2-ethylhexyl)sodium (**36**). If the sodium species would precipitate in the sodium packed-bed reactor tailing of the hydrolysis product would be expected upon pumping *n*-hexane since additional solvent should dissolve the precipitated alkylsodium species over time. Therefore, figure 26 displays the solubility of (2-ethylhexyl)sodium (36) using a 0.2 M solution of **115**.

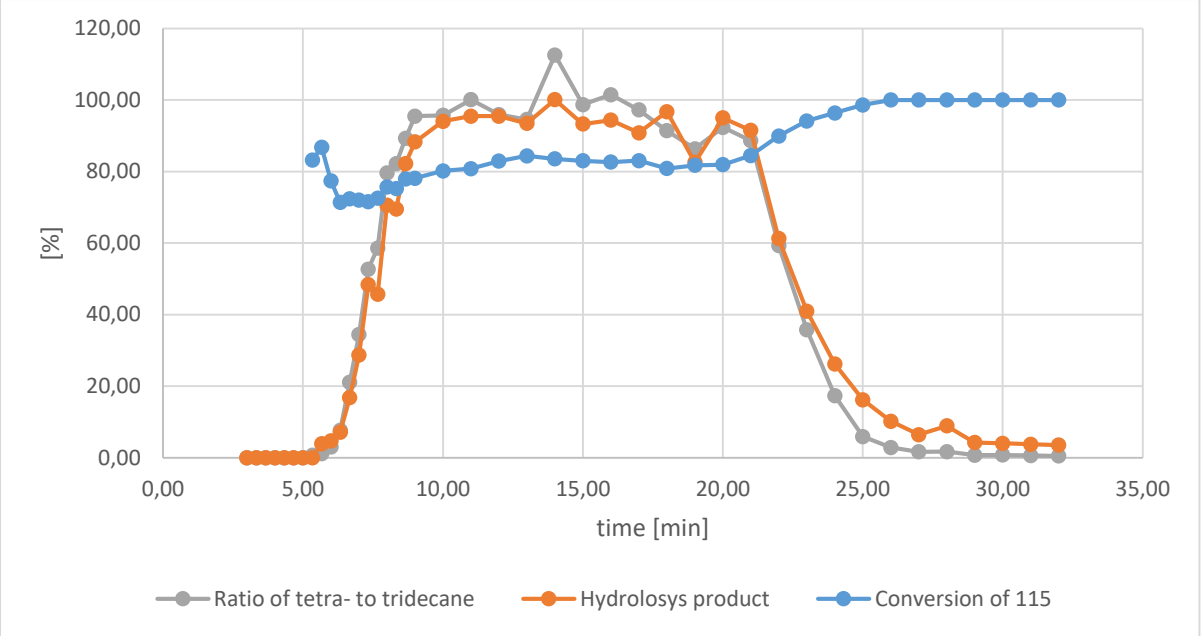


Figure 26: Solubility study of (2-ethylhexyl)sodium (**36**) using a 0.2 M solution of 3-(chloromethyl)heptane (**115**).

The same observation was made using a 0.5 M solution of **115**. The same correlation of the ratio of tetra- to tridecane (grey) with the hydrolysis product (orange) can be observed in figure 27 starting at minute 12. The lower values of the hydrolysis product compared to the ratio of tetra- to tridecane until minute 12 are in agreement with the lower values for the conversion of **115** (blue). At minute 12, the conversion reaches a peak level of about 96%.

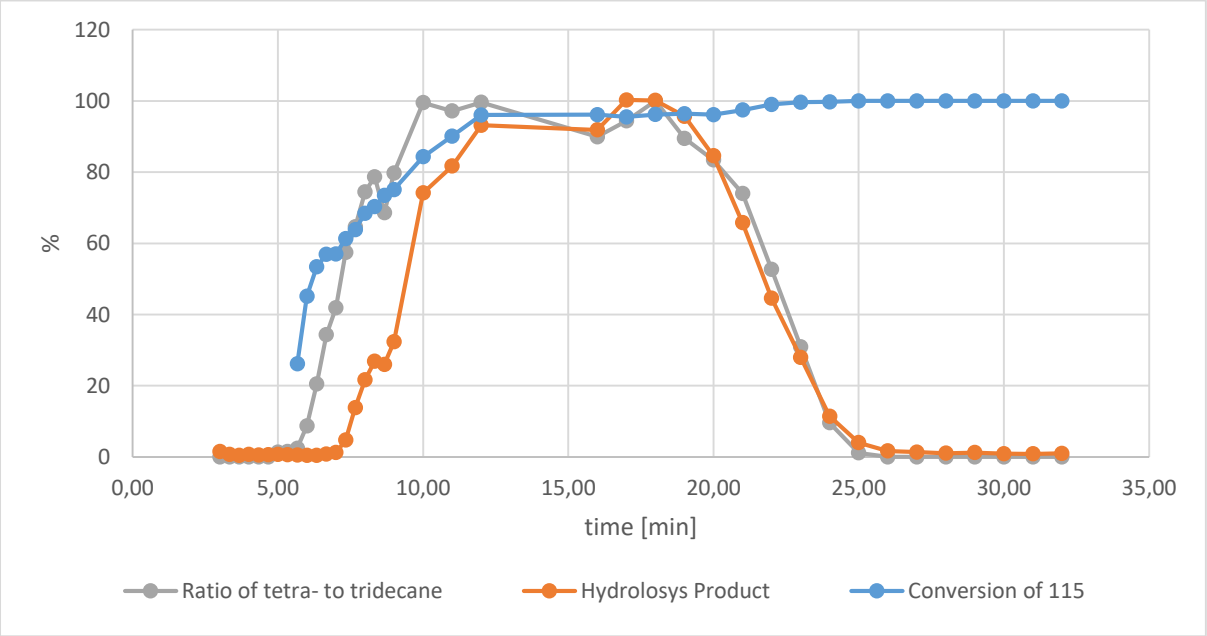
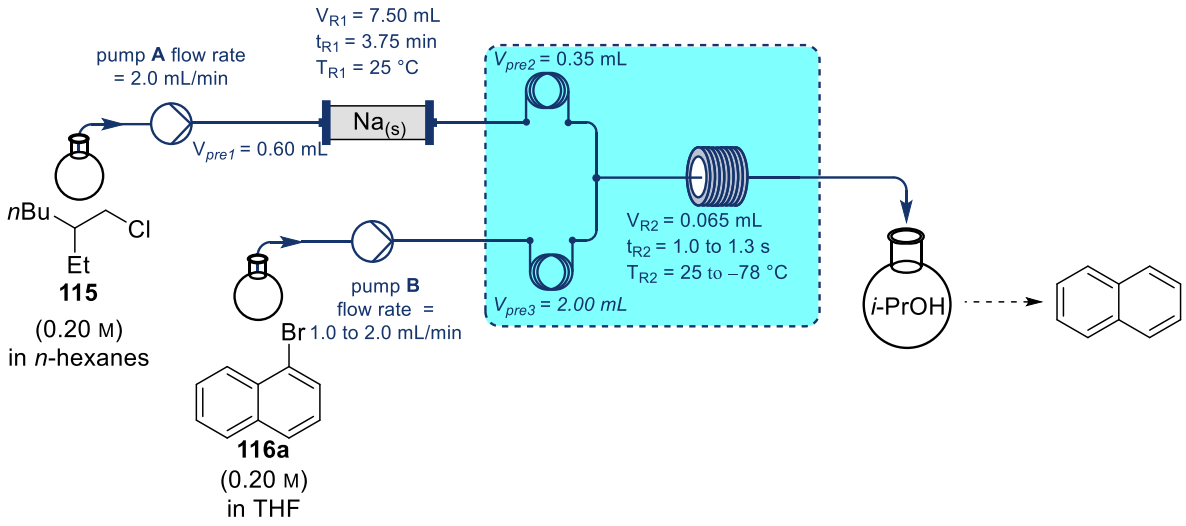


Figure 27: Solubility study of (2-ethylhexyl)sodium (**36**) using a 0.5 M solution of 3-(chloromethyl)heptane (**115**).

4.2.3 Optimization screening for the Br/Na-exchange



Scheme 122: Set-up for the screening of the on-demand generation of (2-ethylhexyl)sodium (**36**) and subsequent in-line Br/Na-exchange.

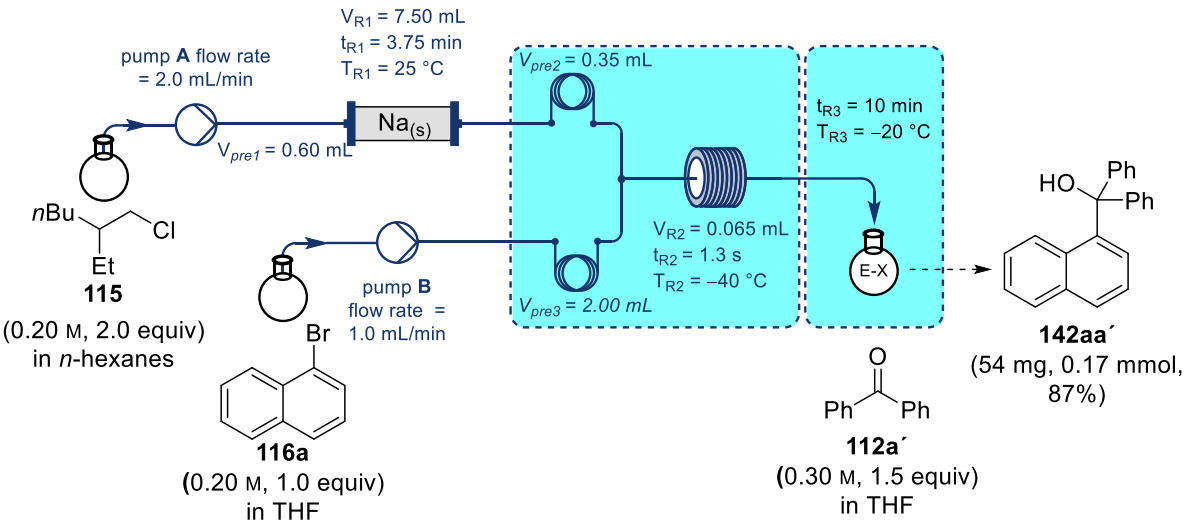
Solutions of 1-bromonaphthalene (**116a**, 0.2 M) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL), which was cooled to the corresponding temperature (T_{R2} = 25 to –78 °C). The solution of **116a** was pumped by pump B (flow rate: 1.0 to 2.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), which was cooled to the corresponding temperature (T_{R2} = 25 to –78 °C). The precooled solutions were mixed with an overall flow rate of 3.0 to 4.0 mL/min in a T-shaped mixer. The combined stream passed a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.0 to 1.3 s), subsequently upon reaching the steady state, it was injected into a vial charged with a solution of *i*-PrOH (1.1 M) in *n*-hexane. Conversion of **116a** and formation of naphthalene was monitored by GC.

Table 27: Optimization screening for the Br/Na-exchange using (2-ethylhexyl)sodium (**36**) and 1-bromonaphthalene (**116a**).

Entry	Flow rate B [ml/min]	V_{R2} [ml]	t_{R2} [s]	T_{R2} [°C]	Conversion [%]	Normalized GC-Yield [a] [%]
1	2.0	0.065	1.0	25	56	53
2	1.8	0.065	1.0	25	67	59
3	1.5	0.065	1.1	25	64	71
4	1.2	0.065	1.2	25	82	82
5	1.0	0.065	1.3	25	93	93
6	2.0	0.065	1.0	0	79	62
7	1.8	0.065	1.0	0	69	68
8	1.5	0.065	1.1	0	83	73
9	1.2	0.065	1.2	0	78	66
10	1.0	0.065	1.3	0	84	81
11	2.0	0.065	1.0	−40	65	64
12	1.8	0.065	1.0	−40	70	70
13	1.5	0.065	1.1	−40	76	78
14	1.2	0.065	1.2	−40	90	95
15	1.0	0.065	1.3	−40	92	100
16	2.0	0.065	1.0	−78	72	49
17	1.8	0.065	1.0	−78	66	80
18	1.5	0.065	1.1	−78	74	70
19	1.2	0.065	1.2	−78	81	77

[a] The largest integrated area under the curve corresponding to naphthalene was normalized to 100% GC-yield the other integrals are adjusted accordingly.

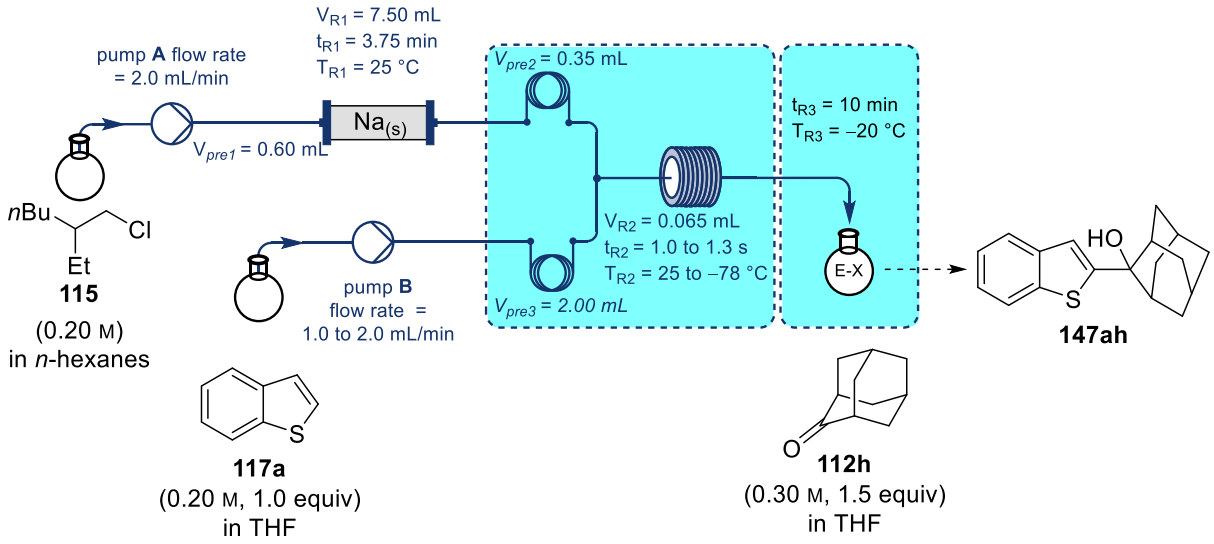
4.2.4 Typical procedure 9 (TP9): On-demand synthesis of (2-ethylhexyl)sodium and its use in Br/Na-exchange reactions.



Scheme 123: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), in-line Br/Na-exchange and subsequent batch quench with electrophiles.

Solutions of 1-bromonaphthalene (**116a**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), which was cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with benzophenone (**112a´**, 55 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 98:2) afforded the title compound **142aa´** as a white solid (54 mg, 0.17 mmol, 87% yield).

4.2.5 Optimization screening for the metalation of benzothiophene



Scheme 124: Set-up for the optimization of the on-demand generation of (2-ethylhexyl)sodium (**36**), in-line sodiation and subsequent batch quench with adamantanone.

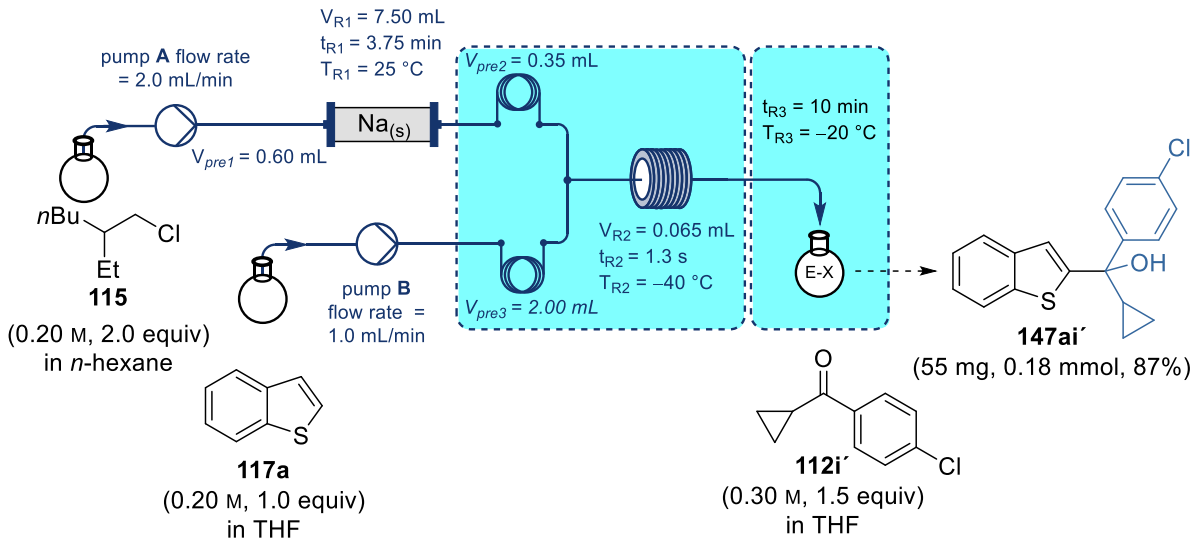
Solutions of benzothiophene (**117a**, 0.2 M) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL), which was cooled to the corresponding temperature (T_{R2} = –40 to –78 °C). The solution of **117a** was pumped by pump B (flow rate: 1.0 to 2.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to the corresponding temperature (T_{R2} = –40 to –78 °C). The precooled solutions were mixed with an overall flow rate of 3.0 to 4.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 to 2.0 mL, t_{R2} = 1.0 to 40 s). Subsequently upon reaching the steady state it was injected into a flask charged with adamantanone (**112h**, 45 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C. Conversion of **117a** and formation of **147ah** was monitored by GC-analysis.

Table 28: Optimization screening for the directed sodiation of benzothiophene (**117a**) using (2-ethylhexyl)sodium (**36**).

Entry	Flow rate B [ml/min]	V_{R2} [ml]	t_{R2} [s]	T_{R2} [°C]	Conversion [%]	Normalized GC-Yield (**147ah**) [a] [%]
1	2.0	0.065	1.0	−40	69	64
2	1.8	0.065	1.0	−40	76	76
3	1.5	0.065	1.1	−40	80	75
4	1.2	0.065	1.2	−40	100	100
5	1.0	0.065	1.3	−40	100	94
6	2.0	2.0	30.0	−40	67	69
7	1.8	2.0	31.6	−40	73	74
8	1.5	2.0	34.3	−40	92	94
9	1.2	2.0	37.5	−40	96	96
10	1.0	2.0	40.0	−40	100	88

[a] The largest integrated area under the curve corresponding to **147ah** was normalized to 100% GC-yield the other integrals are adjusted accordingly.

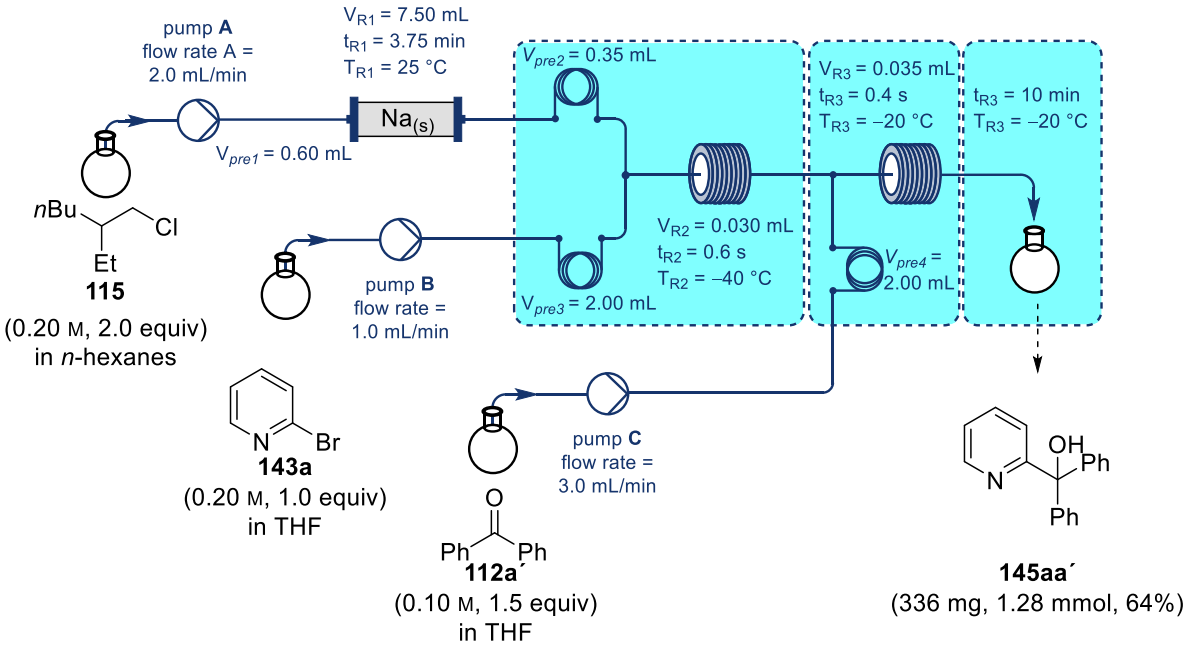
4.2.6 Typical procedure 10 (TP10): On-demand synthesis of (2-ethylhexyl)sodium and its use in metalation reactions.



Scheme 125: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), in-line sodiations and subsequent batch quench with electrophiles.

Solutions of benzothiophene (**117a**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL), which was cooled to –40 °C. The solution of **117a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), which was cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with (4-chlorophenyl)(cyclopropyl)methanone (**112i´**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 9:1) afforded the title compound **147ai´** as a slightly brownish oil (55 mg, 0.18 mmol, 87% yield).

4.2.7 On-demand synthesis of (2-ethylhexyl)sodium and its use in a Br/Na-exchange reactions followed by an in-line quench



Scheme 126: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), in-line Br/Na-exchange using 2-bromopyridine (**143a**) and subsequent in-line quench with benzophenone (**112a´**) electrophiles.

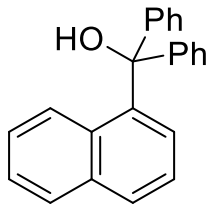
Solutions of 2-bromopyridine (**143a**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane and benzophenone (**112a´**, 0.1 M, 1.5 equiv) in THF were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), which was cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor (V_{R2} = 0.030 mL, t_{R2} = 0.6 s). Pump C (flow rate: 3.0 mL/min) pumped the solution of benzophenone **112a´**, through a precooling loop (V_{pre4} = 2.00 mL), which was cooled to –20 °C. The two streams were mixed in another T-shaped mixer, the combined reaction mixture passed a metal needle (V_{R3} = 0.035 mL) and was, subsequently upon reaching the steady state, injected into an argon filled flask cooled to –20 °C for 10 or 17.5 min. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×70 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 90:10) afforded the title compound **145aa´** as colorless crystals (10 min runtime: 336 mg, 1.28 mmol, 64% yield; 17.5 min runtime: 592 mg, 2.27 mmol, 65% yield).

4.2.8 Typical procedure 11 (TP11): Batch preparation of neopentyl chloride followed by Br/Na-exchange and aldehyde quench.

According to the procedure of Asako, Takai and co-workers[2] sodium dispersion (30 wt% in toluene, particle size <0.1 mm, 1.05 mmol, 4.2 equiv) was added into a flame dried round bottom flask charged with a stirring bar, the toluene was removed *in vacuo* n-hexane (2.0 mL) was added. Neopentyl chloride was added (53 mg, 0.50 mmol, 2.0 equiv) at 0 °C. The mixture was stirred at 0 °C for 20 min before **116a** (52 mg, 0.25 mmol, 1.0 equiv) was added at 0 °C and the mixture was again stirred at this temperature for 30 min. **112b´** (30 mg, 0.30 mmol, 1.2 equiv) was added at 0 °C the mixture was allowed to warm to 25 °C and stirred for 30 min before it was quenched with NH_4Cl. The aqueous layer was extracted three times with EtOAc (3×70 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5) afforded the title compound **142ab´** as colorless crystals (36 mg, 0.16 mmol, 63% yield).

4.3 Preparation of Products

Naphthalen-1-yldiphenylmethanol (142aa´)



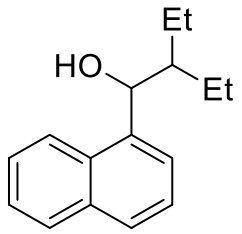
According to **TP9**, solutions of 1-bromonaphthalene (**116a**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with benzophenone (**112a´**, 55 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 98:2) afforded the title compound **142aa´** as colorless crystals (54 mg, 0.17 mmol, 87% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.12 (d, *J* = 8.7 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.26 (m, 12H), 6.88 (dd, J = 7.3, 0.9 Hz, 1H), 3.35 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.1 (2C), 142.2, 135.1, 131.4, 129.5, 129.0, 128.3, 128.2 (5C), 127.9 (4C), 127.3 (2C), 125.7, 125.5, 124.4, 83.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3560, 1490, 1446, 1396, 1329, 1174, 1165, 1157, 1151, 1143, 1032, 1018, 1004, 992, 929, 900, 864, 807, 790, 782, 760, 748, 701, 683, 663.
MS (EI, 70 eV): *m/z* (%) = 310 (18), 233 (16), 231 (11), 215 (32), 205 (24), 204 (11), 202 (12), 183 (14), 155 (15), 155 (23), 128 (20, 127 (16), 105 (100), 77 (54).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{23}H_{18}O$]: 310.1358; found 310.1352.

m.p. (°C): 129.8 – 135.5.

2-Ethyl-1-(naphthalen-1-yl)butan-1-ol (142ab´)



According to **TP9**, solutions of 1-bromonaphthalene (**116a**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with 2-ethylbutanal (**112b´**, 30 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 9:1) afforded the title compound **142ab´** as a colorless oil (31 mg, 0.14 mmol, 70% yield).

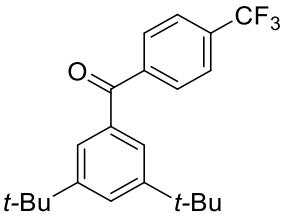
According to **TP11**, sodium dispersion (30 wt% in toluene, particle size <0.1 mm, 1.05 mmol, 4.2 equiv) was added into a flame dried round bottom flask charged with a stirring bar, the toluene was removed *in vacuo* n-hexane (2.0 mL) was added. Neopentyl chloride was added (53 mg, 0.50 mmol,

2.0 equiv) at 0 °C. The mixture was stirred at 0 °C for 20 min before **116a** (52 mg, 0.25 mmol, 1.0 equiv) was added at 0 °C and the mixture was again stirred at this temperature for 30 min. **112b´** (30 mg, 0.30 mmol, 1.2 equiv) was added at 0 °C the mixture was allowed to warm to 25 °C and stirred for 30 min before it was quenched with NH4Cl. The aqueous layer was extracted three times with EtOAc (3×70 mL) and the combined organic layers were dried over anhydrous MgSO4 and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5) afforded in our hands the title compound **142ab´** as colorless oil (36 mg, 0.16 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 – 8.05 (m, 1H), 7.92 – 7.83 (m, 1H), 7.83 – 7.74 (m, 1H), 7.65 (m, 1H), 7.55 – 7.42 (m, 3H), 5.50 (dd, *J* = 5.6, 3.1 Hz, 1H), 1.82 (dd, *J* = 7.8, 3.7 Hz, 2H), 1.63 – 1.29 (m, 4H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.9, 133.9, 130.7, 129.1, 127.9, 125.9, 125.5, 125.4, 124.2, 123.4, 72.5, 46.7, 22.9, 20.4, 11.8, 11.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3414, 3335, 3048, 2958, 2931, 2872, 1596, 1510, 1458, 1394, 1378, 1344, 1308, 1305, 1260, 1227, 1166, 1123, 1107, 1079, 1036, 1021, 999, 954, 944, 912, 863, 858, 799, 776, 747, 731.
MS (EI, 70 eV): *m/z* (%) = 158 (12), 157 (100), 129 (79), 128 (35).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{20}O$]: 228.1514; found 228.1508.

(3,5-Di-tert-butylphenyl)(4-(trifluoromethyl)phenyl)methanone (142bo)



According to **TP9**, solutions of 1-bromo-3,5-di-*tert*-butylbenzene (**116b**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (**112o**, 70 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.*

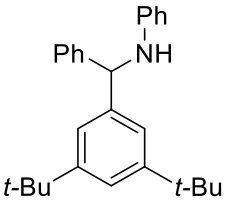
NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99.5:0.5 → 99:1) afforded the title compound **142bo** as colorless crystals (53 mg, 0.15 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.70 (t, *J* = 1.8 Hz, 1H), 7.63 (d, *J* = 1.8 Hz, 2H), 1.35 (s, 18H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.4, 151.4 (2C), 141.3, 136.4, 133.7 (q, *J* = 32.8 Hz), 130.4 (2C), 127.4, 125.4 (q, *J* = 3.8 Hz, 2C), 124.6 (2C), 123.9 (q, *J* = 271.8 Hz), 35.2 (2C), 31.5 (6C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2907, 2870, 1653, 1595, 1476, 1466, 1450, 1404, 1397, 1364, 1322, 1314, 1281, 1246, 1161, 1139, 1118, 1107, 1065, 1015, 988, 963, 899, 893, 857, 839, 776, 764, 753, 726, 705, 679.
MS (EI, 70 eV): *m/z* (%) = 348 (23), 347 (100), 173 (47), 145 (16).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{22}H_{25}F_3O$]: 362.1858; found 362.1853.

m.p. (°C): 86.3 – 89.9.

***N*-((3,5-Di-tert-butylphenyl)(phenyl)methyl)aniline (142bc´)**



According to **TP9**, solutions of 1-bromo-3,5-di-*tert*-butylbenzene (**116b**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with *N*,1-diphenylmethanimine (**112c´**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the

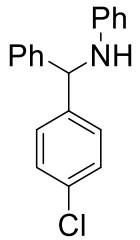
solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99.5:0.5 → 99:1) afforded the title compound **142bc´** as a colorless solid (48 mg, 0.13 mmol, 65% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.43 (d, *J* = 7.3 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.29 – 7.23 (m, 1H), 7.20 – 7.09 (m, 4H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 2H), 5.50 (s, 1H), 4.29 (s, 1H), 1.30 (s, 18H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.2 (2C), 147.7, 143.1, 142.5, 129.2 (2C), 128.7 (2C), 127.3 (2C), 127.1, 122.1 (2C), 121.5, 117.5, 113.6 (2C), 63.8, 35.0 (2C), 31.6 (6C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3411, 2960, 2951, 2928, 2923, 2902, 2863, 1599, 1501, 1491, 1476, 1464, 1454, 1424, 1390, 1360, 1327, 1316, 1269, 1262, 1244, 1202, 1181, 1159, 1154, 1130, 1105, 1073, 1034, 1026, 990, 923, 896, 871, 863, 759, 748, 718, 700, 691.
MS (EI, 70 eV): *m/z* (%) = 280 (13), 279 (58), 263 (36), 191 (13), 182 (42), 180 (18), 179 (27), 178 (29), 174 (10), 167 (10), 165 (35), 152 (11), 129 (12), 128 (14), 115 (15), 104 (13), 93 (100), 92 (71), 91 (18), 77 (25), 65 (32), 57 (16), 41 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{27}H_{33}N$]: 371.2613; found 371.2611.

m.p. (°C): 115.1 – 122.7.

***N*-((4-Chlorophenyl)(phenyl)methyl)aniline (142cc´)**



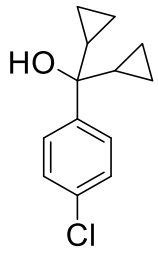
According to **TP9**, solutions of 1-bromo-4-chlorobenzene (**116c**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with *N*,1-diphenylmethanimine (**112c´**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the

solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 99:1) afforded the title compound **142cc´** as a colorless oil (36 mg, 0.12 mmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41 – 7.23 (m, 9H), 7.17 – 7.11 (m, 2H), 6.73 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.59 – 6.49 (m, 2H), 5.48 (d, *J* = 2.3 Hz, 1H), 4.20 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.2, 142.7, 141.4, 133.2, 129.3 (2C), 129.0 (4C), 128.8 (2C), 127.8, 127.6 (2C), 118.0, 113.6 (2C), 62.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} =3412, 3050, 3026, 1600, 1577, 1500, 1487, 1451, 1426, 1405, 1338, 1312, 1265, 1240, 1180, 1154, 1116, 1089, 1077, 1065, 1029, 1014, 1005, 992, 871, 845, 835, 819, 797, 749, 719, 698, 692, 673, 668.
MS (EI, 70 eV): *m/z* (%) = 203 (10), 201 (29), 166 (31), 166 (13), 165 (100), 164 (15), 163 (13), 92 (11), 77 (25), 65 (16).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{19}H_{16}NCl$]: 293.0971; found 293.0966.

(4-Chlorophenyl)dicyclopropylmethanol (142cu)



According to **TP9**, solutions of 1-bromo-4-chlorobenzene (**116c**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with dicyclopropylmethanone (**112u**, 33 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 98:2 → 9:1) afforded the title compound **142cu** as a colorless oil (37 mg, 0.17 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.55 – 7.47 (m, 2H), 7.32 – 7.27 (m, 2H), 1.46 (s, 1H), 1.21 – 1.10 (m, 2H), 0.61 – 0.49 (m, 4H), 0.43 – 0.30 (m, 4H).

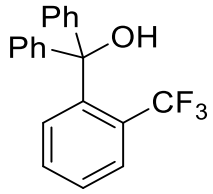
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.9, 132.6, 128.0 (2C), 127.4 (2C), 73.7, 20.7 (2C), 2.2 (2C), 0.3 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3591, 3581, 3470, 3415, 3085, 3007, 2926, 1594, 1488, 1461, 1425, 1399, 1376, 1313, 1193, 1156, 1091, 1051, 1025, 1013, 994, 967, 943, 912, 871, 851, 816, 779, 722, 714.

MS (EI, 70 eV): *m/z* (%) = 196 (29), 195 (10), 194 (85), 183 (31), 182 (11), 181 (86), 179 (11), 159 (55), 152 (19), 144 (18), 141 (17), 141 (28), 139 (100), 128 (15), 125 (19), 115 (17), 111 (29), 91 (12), 77 (11), 75 (13), 69 (50), 44 (31), 43 (10), 41 (38).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{13}H_{15}ClO$]: 222.0811; found 222.0799.

Diphenyl(2-(trifluoromethyl)phenyl)methanol (142da´)



According to **TP9**, solutions of 1-bromo-2-(trifluoromethyl)benzene (**116d**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with benzophenone (**112a´**, 55 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 98:2) afforded the title compound **142da´** as colorless crystals (59 mg, 0.18 mmol, 90% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (d, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.37 – 7.27 (m, 7H), 7.18 – 7.10 (m, 4H), 6.86 (d, *J* = 7.8 Hz, 1H), 3.33 – 3.30 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.5, 145.2 (q, *J* = 1.6 Hz), 132.5 (2C), 130.6, 129.4 (q, *J* =31.9 Hz), 128.6 (q, *J* = 6.7 Hz), 128.2 (4C), 128.1 (q, *J* = 22.3 Hz), 127.8 (4C), 127.8, 127.6 (2C), 124.8 (q, *J* = 274.5 Hz) 83.3.

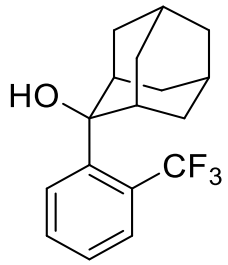
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3638, 3055, 1657, 1598, 1584, 1577, 1490, 1446, 1440, 1317, 1303, 1274, 1213, 1187, 1173, 1156, 1142, 1124, 1102, 1088, 1081, 1061, 1035, 1020, 1001, 986, 976, 960, 941, 919, 907, 894, 876, 872, 853, 841, 833, 809, 782, 763, 751, 697, 659, 654.

MS (EI, 70 eV): *m/z* (%) = 328 (16), 231 (52), 212 (15), 211 (100), 184 (15), 183 (98), 183 (44), 173 (13), 165 (13), 155 (56), 154 (44), 145 (19), 105 (74), 77 (32).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{20}H_{15}F_3O$]: 328.1075; found 328.1067.

m.p. (°C): 117.7 – 118.8.

2-(2-(Trifluoromethyl)phenyl)adamantan-2-ol (142dh)



According to **TP9**, solutions of 1-bromo-2-(trifluoromethyl)benzene (**116d**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with adamantanone (**112h**, 45 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 98:2) afforded the title compound **142dh** as colorless crystals (45 mg, 0.15 mmol, 76% yield).

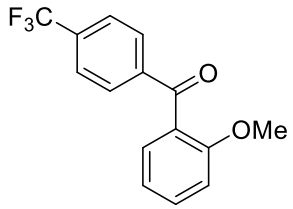
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 (dd, *J* = 8.0, 3.4 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 2.71 (s, 2H), 2.45 (d, *J* = 12.3 Hz, 2H), 2.29 (q, *J* = 4.1 Hz, 1H), 1.87 (s, 1H), 1.82 – 1.60 (m, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.8 (q, *J* = 1.5 Hz), 131.9 (q, *J* = 1.5 Hz), 129.4, 129.1 (q, *J* = 7.4 Hz), 127.63 (q, *J* = 29.1 Hz), 127.5, 125.5 (q, *J* = 274 Hz), 37.6, 35.7 (q, *J* = 2.6 Hz), 35.0 (2C), 33.4 (2C), 27.2 (2C), 26.4 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3425, 2913, 2876, 2855, 1451, 1443, 1362, 1297, 1284, 1266, 1251, 1185, 1173, 1154, 1124, 1111, 1103, 1097, 1085, 1062, 1051, 1044, 1040, 1030, 1008, 996, 970, 963, 956, 935, 910, 774, 766, 757, 692, 674, 652.
MS (EI, 70 eV): *m/z* (%) = 278 (28), 276 (17), 256 (11), 200 (14), 173 (100), 155 (27), 151 (11), 145 (19), 133 (13), 131 (22), 123 (10), 93 (15), 91 (11), 81 (25), 80 (14), 79 (20).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{17}H_{19}F_3O$]: 296.1388; found 296.1381.

m.p. (°C): 67.8 – 69.3.

(2-Methoxyphenyl)(4-(trifluoromethyl)phenyl)methanone (142eo)



According to **TP9**, solutions of 1-bromo-2-methoxybenzene (**116e**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116e** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with N-methoxy-N-methyl-4-(trifluoromethyl)benzamide (**112o**, 70 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical

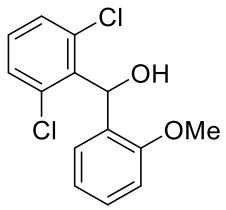
purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **142eo** as colorless crystals (40 mg, 0.14 mmol, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.89 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.47 (m, 1H), 7.42 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.07 (td, *J* = 7.5, 0.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 3.71 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 195.6, 157.7, 141.0, 134.1 (q, *J* = 32.4 Hz), 132.9, 130.1, 130.0 (2C), 128.0, 125.4 (q, *J* = 3.8 Hz, 2C), 123.9 (q, *J* = 272.5 Hz), 120.9, 111.6, 55.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2849, 2839, 1673, 1600, 1584, 1510, 1486, 1466, 1454, 1432, 1410, 1325, 1314, 1293, 1262, 1245, 1159, 1149, 1130, 1109, 1063, 1047, 1022, 1017, 983, 942, 925, 862, 772, 754, 709, 701.
MS (EI, 70 eV): *m/z* (%) = 280 (18), 263 (25), 262 (22), 235 (14), 211 (28), 173 (18), 145 (32), 135 (100), 121 (13), 79 (10), 77 (14).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{11}F_3O_2$]: 280.0711; found 280.0706.

m.p. (°C): 77.7 – 83.1.

(2,6-Dichlorophenyl)(2-methoxyphenyl)methanol (142ei)



According to **TP9**, solutions of 1-bromo-2-methoxybenzene (**116e**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116e** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with 2,6-dichlorobenzaldehyde (**112i**, 70 mg, 0.4 mmol, 2.0 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent,

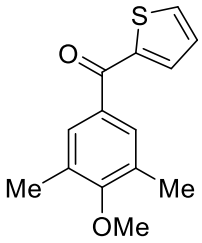
flash column chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **142ei** as colorless crystals (45 mg, 0.16 mmol, 79% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 3.29 (m, 2H), 7.28 – 7.24 (m, 2H), 7.16 (dd, *J* = 8.5, 7.6 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 7.4 Hz, 1H), 3.78 (s, 3H), 3.47 (d, *J* = 7.5 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.0, 137.0, 135.7, 129.4 (2C), 129.1, 128.9, 128.8 (2C), 127.9, 120.2, 110.8, 69.9, 55.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3568, 3478, 2935, 2833, 1600, 1586, 1578, 1562, 1488, 1463, 1456, 1434, 1389, 1308, 1285, 1251, 1236, 1221, 1200, 1181, 1170, 1159, 1149, 1116, 1084, 1075, 1047, 1032, 1026, 1006, 964, 938, 929, 870, 864, 856, 851, 823, 815, 791, 775, 751, 730, 663, 657.
MS (EI, 70 eV): *m/z* (%) = 284 (10), 282 (14), 281 (29), 265 (10), 225 (20), 215 (14), 209 (11), 208 (13), 207 (100), 191 (21), 175 (24), 173 (37), 165 (14), 158 (11), 152 (11), 137 (16), 135 (20), 109 (32), 108 (16), 107 (16), 105 (17), 44 (19).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{12}Cl_2O_2$]: 282.0214; found 282.0210.

m.p. (°C): 133.1 – 137.8.

(4-Methoxy-3,5-dimethylphenyl)(thiophen-2-yl)methanone (142fd´)



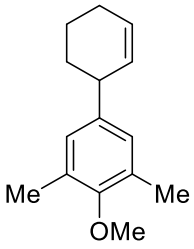
According to **TP9**, solutions of 5-bromo-2-methoxy-1,3-dimethylbenzene (**116f**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116f** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with *N*-methoxy-*N*-methylthiophene-2-carboxamide (**112d´**, 51 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$

and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **142fd´** as a colorless oil (33 mg, 0.13 mmol, 67% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.70 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.65 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.56 (s, 2H), 7.16 (dd, *J* = 4.9, 3.8 Hz, 1H), 3.79 (s, 3H), 2.35 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 187.8, 160.8, 144.0, 134.6, 133.9, 133.8, 131.3, 130.4 (2C), 128.0 (2C), 59.9, 16.4 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2858, 2827, 1629, 1593, 1513, 1480, 1459, 1451, 1434, 1410, 1379, 1352, 1317, 1244, 1212, 1172, 1116, 1081, 1055, 1004, 960, 950, 896, 862, 825, 794, 770, 764, 743, 719, 698, 664.
MS (EI, 70 eV): *m/z* (%) = 281 (27), 247 (13), 246 (82), 231 (42), 225 (31), 215 (36), 209 (10), 209 (16), 208 (15), 207 (100), 203 (17), 191 (20), 164 (10), 163 (100), 111 (31), 105 (10), 91 (13), 73 (10), 44 (14).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{14}O_2S$]: 246.0715; found 246.0709.

4'-Methoxy-3',5'-dimethyl-1,2,3,4-tetrahydro-1,1'-biphenyl (142fe´)



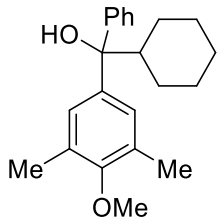
According to **TP9**, solutions of 5-bromo-2-methoxy-1,3-dimethylbenzene (**116f**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116f** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with 3-bromocyclohex-1-ene (**112e´**, 48 mg, 0.3 mmol, 1.5 equiv) and CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol, 0.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column

chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 98:2) afforded the title compound **142fe´** as a colorless oil (36 mg, 0.17 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.85 (s, 2H), 5.92 – 5.81 (m, 1H), 5.72 – 5.65 (m, 1H), 3.71 (s, 3H), 3.35 – 3.23 (m, 1H), 2.27 (s, 6H), 2.12 –2.04 (m, 2H), 2.01 – 1.94 (m, 1H), 1.79 – 1.69 (m, 1H), 1.67 – 1.47 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.1, 141.9, 130.6 (2C), 130.5, 128.1, 128.0 (2C), 59.7, 41.2, 32.7, 25.0, 21.3, 16.1 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2924, 2853, 1716, 1651, 1598, 1482, 1455, 1375, 1306, 1220, 1215, 1154, 1147, 1010, 865, 862.
MS (EI, 70 eV): *m/z* (%) = 216 (79), 215 (28), 213 (27), 202 (25), 201 (69), 185 (25), 178 (85), 174 (23), 173 (58), 163 (100), 162 (21), 159 (32), 157 (21), 149 (38), 141 (21), 136 (33), 135 (69), 129 (25), 128 (32), 119 (19), 115 (36), 105 (53), 103 (19), 91 (61), 81 (35), 79 (34), 77 (40), 57 (24), 42 (20), 41 (68).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{20}O$]: 216.1514.; found 216.1503.

Cyclohexyl(4-methoxy-3,5-dimethylphenyl)(phenyl)methanol (142ff´)



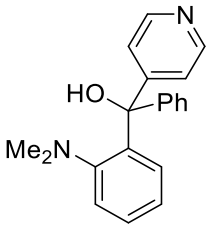
According to **TP9**, solutions of 5-bromo-2-methoxy-1,3-dimethylbenzene (**116f**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116f** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with cyclohexyl(phenyl)methanone (**112f´**, 56 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel,

isohexane:EtOAc = 98:2 → 97:3) afforded the title compound **142ff´** as a colorless oil (62 mg, 0.19 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.51 7.47 (m, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.21 – 7.14 (m, 1H), 7.11 (s, 2H), 3.67 (s, 3H), 2.45 – 2.34 (m, 1H), 2.25 (s, 6H), 2.06 (s, 1H), 1.81 1.61 (m, 4H), 1.51 (d, *J* = 12.3 Hz, 1H), 1.38 – 1.24 (m, 2H), 1.19 – 1.01 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.4, 146.8, 141.6, 130.3 (2C), 128.1 (2C), 126.3, 126.2 (2C), 125.8 (2C), 80.2, 59.7, 45.8, 27.3 (2C), 26.8 (2C), 26.7, 16.6 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3486, 2928, 2850, 2824, 1598, 1484, 1445, 1416, 1373, 1353, 1334, 1306, 1300, 1276, 1221, 1190, 1157, 1146, 1127, 1080, 1069, 1012, 977, 943, 909, 896, 868, 852, 825, 803, 765, 757, 728, 699, 676, 665, 656.
MS (EI, 70 eV): *m/z* (%) = 242 (17), 241 (32), 241 (100), 241 (70), 105 (69).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{22}H_{28}O_2$]: 324.2089; found 324.2087.

(2-(Dimethylamino)phenyl)(phenyl)(pyridin-4-yl)methanol (142gg´)



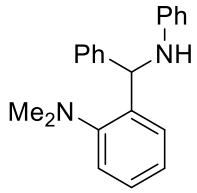
According to **TP9**, solutions of 2-bromo-*N*,*N*-dimethylaniline (**116g**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116g** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with phenyl(pyridin-4-yl)methanone (**112g´**, 55 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 85:15) afforded the title compound **142gg´** as colorless crystals (52 mg, 0.17 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.03 (s, 1H), 8.58 – 8.46 (m, 2H), 7.36 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.32 – 7.18 (m, 8H), 7.05 (td, *J* = 7.5, 1.5 Hz, 1H), 6.65 (dd, *J* = 7.8, 1.6 Hz, 1H), 2.36 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.5, 152.1, 149.6 (2C), 146.2, 141.3, 130.3, 128.9, 128.1 (2C), 128.1 (2C), 127.5, 125.6, 123.9, 123.3 (2C), 82.4, 45.8 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 3021, 2982, 2947, 2863, 2832, 2789, 1734, 1591, 1577, 1553, 1483, 1459, 1446, 1432, 1405, 1373, 1323, 1283, 1266, 1242, 1220, 1198, 1174, 1147, 1098, 1068, 1055, 1037, 1001, 993, 939, 931, 922, 903, 816, 766, 755, 733, 700, 667.
MS (EI, 70 eV): *m/z* (%) = 304 (17), 227 (53), 226 (85), 212 (16), 211 (100), 210 (30), 209 (30), 208 (58), 195 (24), 194 (18), 193 (38), 184 (17), 167 (27), 165 (16), 152 (16), 136 (66), 120 (55), 118 (20), 106 (22), 96 (19), 91 (97), 78 (23), 77 (48).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{20}H_{20}N_2O$]: 304.1576; found 304.1567.

m.p. (°C): 109.8 – 111.5.

***N,N*-Dimethyl-2-(phenyl(phenylamino)methyl)aniline (142gc´)**



According to **TP9**, solutions of 2-bromo-*N*,*N*-dimethylaniline (**116g**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116g** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with *N*,1-diphenylmethanimine (**112c´**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 98:2) afforded the title compound **142gc´** as a colorless crystals (48 mg, 0.16 mmol, 79% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30 – 7.25 (m, 2H), 7.22 – 7.08 (m, 6H), 7.04 – 6.98 (m, 2H), 6.98 – 6.93 (m, 1H), 6.56 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.51 – 6.44 (m, 2H), 6.08 (s, 1H), 4.33 (s, 1H), 2.53 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.5, 147.7, 143.6, 138.4, 129.2 (2C), 128.9, 128.5 (2C), 128.2, 127.6 (2C), 126.9, 124.5, 120.8, 117.3, 113.3 (2C), 56.3, 45.7 (2C).

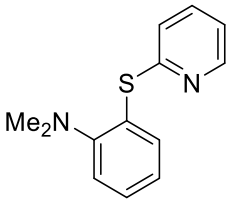
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3414, 3022, 2973, 2940, 2926, 2855, 2825, 2785, 1600, 1583, 1504, 1488, 1477, 1459, 1447, 1429, 1406, 1351, 1313, 1299, 1266, 1237, 1197, 1183, 1178, 1164, 1153, 1119, 1107, 1098, 1083, 1078, 1064, 1045, 1027, 991, 985, 944, 888, 866, 847, 814, 770, 757, 749, 742, 730, 692.

MS (EI, 70 eV): *m/z* (%) = 302 (42), 287 (13), 211 (21), 210 (100), 209 (39), 208 (28), 194 (26), 180 (10), 165 (16), 132 (13), 118 (15), 91 (44), 77 (15), 44 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{21}H_{22}N_2$]: 302.1783; found 302.1775.

m.p. (°C): 128.7 – 129.8.

***N*,*N*-Dimethyl-2-(pyridin-2-ylthio)aniline (142gh´)**



According to **TP9**, solutions of 2-bromo-*N*,*N*-dimethylaniline (**116g**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **116g** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with aldrithiol (**112h´**, 66 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **142gh´** as a colorless oil (41 mg, 0.18 mmol, 89% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.45 – 8.42 (m, 1H), 7.50 – 7.40 (m, 2H), 7.36 – 7.30 (m, 1H), 7.13 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.03 – 6.96 (m, 2H), 6.86 (dt, *J* = 8.2, 1.0 Hz, 1H), 2.80 (s, 6H).

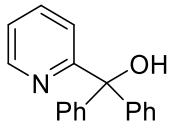
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.3, 155.3, 149.6, 136.7, 136.6, 130.0, 125.6, 123.3, 122.1, 120.0, 119.8, 44.6 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 3041, 2936, 2827, 2779, 1582, 1572, 1558, 1478, 1445, 1427, 1415, 1316, 1278, 1266, 1188, 1158, 1143, 1117, 1095, 1085, 1057, 1041, 984, 944, 874, 754, 738, 721, 670.

MS (EI, 70 eV): *m/z* (%) = 197 (25), 186 (22), 150 (49), 136 (29), 109 (17), 93 (100), 91 (18), 80 (13).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{13}H_{14}N_2S$]: 230.0878; found 230.0874.

Diphenyl(pyridin-2-yl)methanol (145aa´)



According to **TP9**, solutions of 2-bromopyridine (**143a**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with benzophenone (**112a´**, 55 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **145aa´** as colorless crystals (45 mg, 0.17 mmol, 86% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.60 (dt, *J* = 4.8, 1.4 Hz, 1H), 7.64 (td, *J* = 7.7, 1.8 Hz, 1H), 7.35 – 7.21 (m, 11H), 7.12 (dt, *J* = 8.0, 1.1 Hz, 1H), 6.30 (s, 1H).

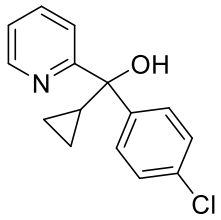
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.3, 147.9, 146.2 (2C), 136.6, 128.3 (4C), 128.1 (4C), 127.5 (2C), 123.1, 122.5, 81.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3341, 3334, 3070, 3054, 3029, 3017, 2923, 2896, 2852, 1591, 1571, 1487, 1466, 1445, 1437, 1379, 1294, 1255, 1210, 1201, 1178, 1167, 1155, 1103, 1088, 1077, 1038, 1026, 998, 987, 971, 940, 930, 913, 896, 852, 784, 766, 761, 756, 715, 697, 655.
MS (EI, 70 eV): *m/z* (%) = 262 (11), 261 (54), 260 (24), 244 (15), 243 (100), 242 (24), 241 (34), 240 (11), 207 (23), 184 (56), 167 (14), 165 (17), 156 (10), 120 (13), 106 (17), 105 (30), 78 (17), 77 (16).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{18}H_{15}NO$]: 261.1154; found 261.1150.

m.p. (°C): 104.6 – 108.2.

(4-Chlorophenyl)(cyclopropyl)(pyridin-2-yl)methanol (145ai´)



According to **TP9**, solutions of 2-bromopyridine (**143a**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with (4-chlorophenyl)(cyclopropyl)methanone (**112i´**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **145ai´** as a colorless oil (42 mg, 0.16 mmol, 81% yield).

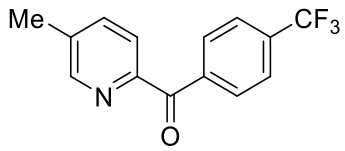
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.43 (d, *J* = 4.9 Hz, 1H), 7.59 (td, *J* = 7.7, 1.8 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.23 – 7.16 (m, 3H), 7.16 – 7.12 (m, 1H), 5.70 (s, 1H), 1.60 – 1.47 (m, 1H), 0.60 – 0.49 (m, 2H), 0.44 – 0.36 (m, 1H), 0.34 – 0.26 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.8, 147.1, 145.3, 137.1, 133.1, 128.7 (2C), 128.3 (2C), 122.4, 121.2, 75.0, 20.5, 1.9, 0.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3433, 3340, 3085, 3007, 1591, 1570, 1488, 1468, 1432, 1397, 1355, 1302, 1294, 1210, 1192, 1151, 1090, 1047, 1014, 994, 965, 958, 884, 872, 824, 785, 771, 748, 733, 719, 683.

MS (EI, 70 eV): *m/z* (%) = 260 (12), 259 (12), 258 (37), 244 (20), 240 (22), 230 (28), 220 (13), 218 (40), 204 (12), 190 (10), 167 (13), 148 (14), 141 (21), 139 (10), 139 (64), 134 (63), 132 (19), 125 (11), 111 (12), 106 (45), 93 (20), 79 (37), 78 (100).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{14}ClNO$]: 259.0765; found 259.0768.

(5-Methylpyridin-2-yl)(4-(trifluoromethyl)phenyl)methanone (145bo)



According to **TP9**, solutions of 2-bromo-5-methylpyridine (**143b**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (**112o**, 70 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 7:3) afforded the title compound **145bo** as colorless crystals (44 mg, 0.17 mmol, 83% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.56 – 8.52 (m, 1H), 8.17 (d, *J* = 8.1 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.76 – 7.72 (m, 3H), 2.47 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 192.8, 151.8, 149.3, 139.8 (q, *J* = 1.3 Hz, 2C), 137.8, 137.5, 133.9 (q, *J* = 32.6 Hz), 131.3, 125.2 (q, *J* = 3.8 Hz, 2C), 124.7, 123.9 (q, *J* = 271.9 Hz), 18.9.

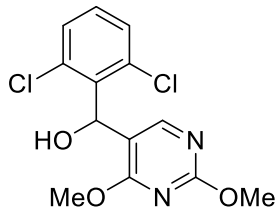
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2852, 1668, 1643, 1582, 1567, 1510, 1407, 1383, 1325, 1312, 1307, 1292, 1245, 1220, 1188, 1158, 1108, 1063, 1028, 1016, 975, 968, 935, 858, 849, 836, 814, 805, 779, 773, 746, 702, 683, 652.

MS (EI, 70 eV): *m/z* (%) = 265 (43), 264 (69), 238 (16), 237 (100), 236 (51), 207 (11), 196 (17), 173 (51), 170 (13), 146 (74), 92 (14), 65 (16), 57 (12), 45 (10), 44 (37), 43 (11).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{10}F_3NO$]: 265.0714; found 265.0709.

m.p. (°C): 61.4 – 64.5.

(2,6-Dichlorophenyl)(2,4-dimethoxypyrimidin-5-yl)methanol (145ci)



According to **TP9**, solutions of 5-bromo-2,4-dimethoxypyrimidine (**143c**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with 2,6-dichlorobenzaldehyde (**112i**, 70 mg, 0.4 mmol, 2.0 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 7:3 → 1:1) afforded the title compound **145ci** as colorless crystals (54 mg, 0.17 mmol, 86% yield).

According to **TP11**, sodium dispersion (30 wt% in toluene, particle size <0.1 mm, 1.05 mmol, 4.2 equiv) was added into a flame dried round bottom flask charged with a stirring bar, the toluene was removed *in vacuo* n-hexane (2.0 mL) was added. Neopentyl chloride was added (53 mg, 0.50 mmol, 2.0 equiv) at 0 °C. The mixture was stirred at 0 °C for 20 min before **143c** (55 mg, 0.25 mmol, 1.0 equiv) was added at 0 °C and the mixture was again stirred at this temperature for 30 min. **112i** (53 mg, 0.30 mmol, 1.2 equiv) was added at 0 °C the mixture was allowed to warm to 25 °C and stirred for 30 min before it was quenched with NH4Cl. In our hands no product **145ci** was detected on GCMS.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.23 (s, 1H), 7.35 – 7.29 (m, 2H), 7.19 (dd, *J* = 8.6, 7.4 Hz, 1H), 6.63 – 6.55 (m, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.31 (d, *J* = 8.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.4, 165.0, 156.8, 135.4, 135.3 (2C), 129.7, 129.5 (2C), 114.0, 67.4, 55.0, 54.1.

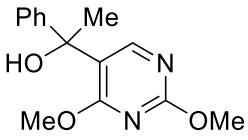
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3267, 3005, 2953, 1598, 1558, 1480, 1462, 1433, 1399, 1382, 1354, 1285, 1263, 1225, 1193, 1175, 1163, 1091, 1081, 1072, 1042, 1015, 833, 792, 787, 780, 764, 728, 690, 675, 655.

MS (EI, 70 eV): *m/z* (%) = 225 (16), 209 (10), 207 (44), 191 (13), 175 (18), 173 (28), 169 (100), 167 (16), 141 (43), 109 (12), 85 (20), 84 (11), 75 (18), 73 (19).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{13}H_{12}Cl_2N_2O_3$]: 314.0225; found 314.0223.

m.p. (°C): 140.6-145.6.

1-(2,4-Dimethoxypyrimidin-5-yl)-1-phenylethan-1-ol (145ce)



According to **TP9**, solutions of 5-bromo-2,4-dimethoxypyrimidine (**143c**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with acetophenone (**112e**, 36 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 1:1 → 4:6) afforded the title compound **145ce** as a colorless oil (50 mg, 0.19 mmol, 96% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.31 (s, 1H), 7.33 – 7.20 (m, 5H), 4.00 (s, 3H), 3.86 (s, 3H), 3.71 (s, 1H), 1.85 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.4, 164.8, 155.4, 147.3, 128.3 (2C), 127.2, 125.0 (2C), 120.5, 74.0, 55.0, 54.3, 29.3.

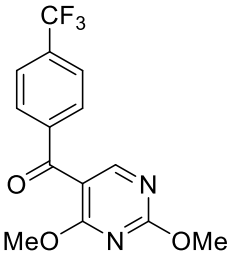
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2954, 1591, 1560, 1467, 1455, 1381, 1320, 1288, 1277,

1237, 1221, 1197, 1119, 1103, 1085, 1059, 1037, 1026, 1011, 964, 938, 922, 908, 832, 801, 765, 739, 697.

MS (EI, 70 eV): *m/z* (%) = 246 (15). 245 (100), 242 (10). 183 (28), 167 (22), 105 (11), 77 (10), 43 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{16}N_2O_3$]: 260.1161; found 260.1155.

2,4-Dimethoxy-5-(pyridin-2-ylthio)pyrimidine (145co)



According to **TP9**, solutions of 5-bromo-2,4-dimethoxypyrimidine (**143c**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (**112o**, 70 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 8:2 → 7:3) afforded the title compound **145co** as colorless crystals (49 mg, 0.16 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.53 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 4.09 (s, 3H), 3.95 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 191.3, 169.3, 166.8, 162.0 (2C), 140.8, 134.4 (q, *J* = 32.7 Hz), 129.7 (2C), 125.6 (q, *J* = 3.7 Hz), 121.0 (q, *J* = 273.1 Hz), 113.9, 55.7, 54.6.

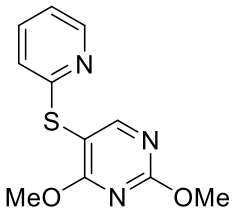
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2923, 2851, 1661, 1585, 1555, 1510, 1471, 1462, 1398, 1389, 1320, 1310, 1294, 1266, 1251, 1242, 1189, 1162, 1148, 1127, 1102, 1061, 1005, 985, 960, 935, 918, 860, 841, 800, 780, 771, 767, 740, 713, 702, 666.

MS (EI, 70 eV): *m/z* (%) = 313 (11), 312 (88), 311 (22), 282 (25), 173 (35), 167 (100), 145 (49), 44 (14), 42 (26).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{11}F_3N_2O_3$]: 312.0722; found 312.0716.

m.p. (°C): 98.2 – 99.9.

2,4-Dimethoxy-5-(pyridin-2-ylthio)pyrimidine (145ch´)



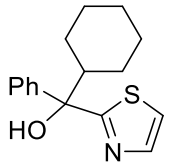
According to **TP9**, solutions of 5-bromo-2,4-dimethoxypyrimidine (**143c**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with aldrithiol (**112h´**, 66 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 1:1 → 4:6) afforded the title compound **145ch´** as colorless crystals (45 mg, 0.18 mmol, 90% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.44 (s, 1H), 8.40 – 8.33 (m, 1H), 7.49 (td, *J* = 7.8, 1.9 Hz, 1H), 7.04 – 6.98 (m, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 4.05 (s, 3H), 3.98 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 171.1, 166.4, 165.3, 158.9, 149.8, 136.7, 120.7, 120.3, 104.9, 55.4, 54.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 1573, 1552, 1479, 1471, 1452, 1414, 1376, 1312, 1284, 1267, 1245, 1198, 1177, 1146, 1120, 1100, 1086, 1040, 1004, 989, 985, 956, 795, 755, 731, 719.
MS (EI, 70 eV): *m/z* (%) = 248 (52), 218 (100), 207 (27), 191 (17), 177 (37), 163 (11), 161 (15), 149 (14), 99 (14), 78 (46), 73 (11), 70 (10).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{11}H_{11}N_3O_2S$]: 249.0572; found 249.0566.

m.p. (°C): 94.0 – 98.9.

Cyclohexyl(phenyl)(thiazol-2-yl)methanol (145df´)



According to **TP9**, solutions of 2-bromothiazole (**143d**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with cyclohexyl(phenyl)methanone (**112f´**, 56 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **145df´** as a white solid (36 mg, 0.13 mmol, 66% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 – 7.67 (m, 3H), 7.34 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.26 – 7.20 (m, 2H), 3.66 (s, 1H), 2.49 (tt, *J* = 11.6, 3.2 Hz, 1H), 1.80 – 1.62 (m, 3H), 1.45 – 1.37 (m, 2H), 1.35 – 1.04 (m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 178.0, 143.9, 141.8, 128.4 (2C), 127.2, 125.6 (2C), 119.4, 81.5, 48.7, 27.1, 26.7, 26.6, 26.5, 26.4.

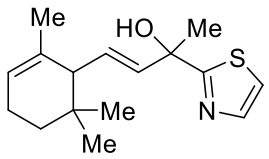
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2852, 1501, 1493, 1446, 1431, 1178, 1167, 1153, 1100, 1081, 1071, 1057, 1034, 994, 966, 841, 770, 760, 717, 696, 623.

MS (EI, 70 eV): *m/z* (%) = 199 (100), 105 (18).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{19}NOS$]: 273.1187; found 273.1182.

m.p. (°C): 105.8 – 108.8.

(*E*)-2-(Thiazol-2-yl)-4-(2,6,6-trimethylcyclohex-2-en-1-yl)but-3-en-2-ol (145dj´)



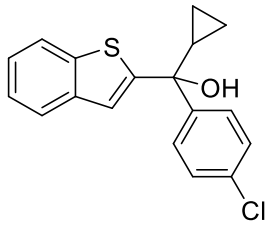
According to **TP9**, solutions of 2-bromothiazole (**143d**, 0.2 M, 1.0 equiv) in THF, 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **143d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s), subsequently upon reaching the steady state, it was injected into a flask charged with a racemic mixture of α-ionone (**112j´**, 58 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) at –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **145dj´** as a colorless oil (28 mg, 0.10 mmol, 50% yield, *dr* : 1:1).

Mixture of the two diastereoisomers:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.70 (d, *J* = 3.3 Hz, 1H), 7.27 (s, 1H), 5.86 (s, 1H), 5.82 (s, 1H), 5.63 (d, *J* = 9.4, 1H), 5.59 (d, *J* = 9.4, 1H), 5.42 – 5.37 (m, 1H), 3.17 (s, 1H), 2.14 (d, *J* = 9.4 Hz, 1H), 2.04 – 1.93 (m, 2H), 1.76 (s, 3H), 1.57 (q, *J* = 1.9 Hz, 3H), 1.53 (q, *J* = 2.0 Hz, 3H), 1.45 – 1.35 (m, 2H), 1.20 – 1.12 (m, 2H), 0.88 (s, 3H), 0.87 (s, 3H), 0.81 (s, 3H), 0.78 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 177.9, 177.8, 142.3, 136.5, 136.4, 133.8, 133.8, 131.0, 131.0, 121.5, 121.4, 119.4, 74.9, 74.9, 53.8, 32.4, 32.3, 31.7, 31.6, 29.9, 29.8, 27.7, 27.6, 27.1, 27.1, 23.2, 23.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3413, 3378, 3346, 3343, 3337, 3333, 2962, 2929, 2869, 1698, 1694, 1689, 1683, 1651, 1499, 1448, 1417, 1386, 1367, 1265, 1237, 1181, 1133, 1056, 1037, 977, 907, 732, 702.
MS (EI, 70 eV): *m/z* (%) = 203 (12), 202 (100), 188 (48), 187 (18), 186 (11), 178 (26), 176 (12), 174 (12), 173 (18), 162 (11), 150 (54), 141 (12), 138 (12), 137 (83), 136 (93), 129 (20), 128 (14), 121 (19), 115 (11), 112 (12), 111 (33), 93 (18), 91 (37), 86 (33), 79 (18), 77 (21).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{16}H_{21}NS$]: 259.1395; found 259.1390.

Benzo[*b*]thiophen-2-yl(4-chlorophenyl)(cyclopropyl)methanol (147ai´)



According to **TP10**, solutions of benzothiophene (**117a**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with (4-chlorophenyl)(cyclopropyl)methanone (**112i´**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 9:1) afforded the title compound **147ai´** as a slightly brownish oil (55 mg, 0.18 mmol, 87% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.78 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.37 – 7.27 (m, 4H), 7.24 (s, 1H), 2.20 (s, 1H), 1.73 (tt, *J* = 8.1, 5.5 Hz, 1H), 0.79 – 0.63 (m, 2H), 0.65 – 0.51 (m, 2H).

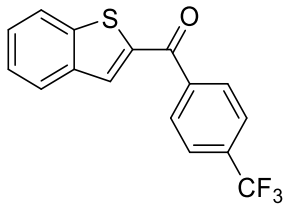
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.8, 144.3, 139.9, 139.3, 133.5, 128.2 (2C), 127.9 (2C), 124.6, 124.5, 123.8, 122.5, 121.8, 75.6, 22.7, 2.7, 1.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3570, 3560, 3556, 3515, 3463, 3448, 3419, 3057, 3007, 2923, 2919, 1708, 1703, 1592, 1573, 1487, 1469, 1457, 1434, 1397, 1376, 1365, 1329, 1305, 1249, 1168, 1150, 1128, 1101, 1091, 1066, 1052, 1025, 1013, 963, 947, 936, 926, 878, 859, 829, 791, 744, 726, 712.

MS (EI, 70 eV): *m/z* (%) = 314 (11), 288 (32), 287 (15), 286 (89), 275 (13), 273 (35), 245 (13), 210 (11), 161 (32), 160 (11), 147 (55), 141 (33), 139 (11), 139 (100), 134 (11), 89 (11).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{18}H_{15}ClOS$]: 314.0532; found 314.0527.

Benzo[*b*]thiophen-2-yl(4-(trifluoromethyl)phenyl)methanone (147ao)

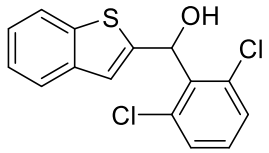


According to **TP10**, solutions of benzothiophene (**117a**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (**112o**, 70 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99.5:0.5 → 99:1) afforded the title compound **147ao** as colorless crystals (52 mg, 0.17 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01 (d, *J* = 8.0 Hz, 2H), 7.91 (dd, *J* = 13.4, 8.1 Hz, 2H), 7.86 – 7.76 (m, 3H), 7.52 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.44 (t, *J* = 7.0 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 188.7, 143.1, 142.5, 141.0, 139.1, 134.0 (q, *J* = 32.8 Hz), 133.0, 129.6 (2C), 128.0, 126.4, 125.7 (q, *J* = 3.8 Hz, 2C), 125.4, 123.8 (q, *J* = 272.7 Hz), 123.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2919, 1629, 1614, 1592, 1577, 1574, 1555, 1510, 1503, 1494, 1458, 1454, 1428, 1405, 1323, 1310, 1289, 1246, 1190, 1181, 1158, 1134, 1130, 1107, 1062, 1015, 974, 944, 913, 882, 867, 855, 844, 837, 767, 745, 728, 725, 708, 700, 691, 678.
MS (EI, 70 eV): *m/z* (%) = 306 (53), 173 (12), 162 (10), 161 (100), 145 (21), 133 (14), 89 (16).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_9F_3OS$]: 306.0326; found 306.0320.
m.p. (°C): 164.8 – 172.6.

Benzo[*b*]thiophen-2-yl(2,6-dichlorophenyl)methanol (147ai)



According to **TP10**, solutions of benzothiophene (**117a**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with 2,6-dichlorobenzaldehyde (**112i**, 70 mg, 0.4 mmol, 2.0 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 95:5) afforded the title compound **147ai** as a slightly brownish oil (45 mg, 0.15 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (d, *J* = 6.9 Hz, 1H), 7.68 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.24 (m, 3H), 6.92 (s, 1H), 6.85 (dd, *J* = 11.3, 1.7 Hz, 1H), 3.92 (d, *J* = 11.3 Hz, 1H).

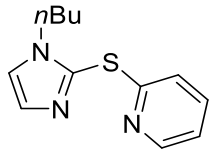
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 146.6, 139.9, 139.8, 136.6, 135.1 (2C), 130.1, 129.6 (2C), 124.5, 124.3, 123.6, 122.5, 120.6, 70.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3549, 3415, 3358, 3056, 2923, 1579, 1561, 1457, 1434, 1397, 1328, 1302, 1249, 1237, 1201, 1178, 1149, 1132, 1107, 1087, 1072, 1019, 1008, 972, 936, 906, 858, 840, 820, 776, 755, 743, 725, 704, 678.

MS (EI, 70 eV): *m/z* (%) = 310 (12), 308 (18), 255 (11), 221 (10), 175 (15), 173 (23), 135 (100), 134 (36), 91 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{10}Cl_2OS$]: 307.9829; found 307.9823.

2-((1-Butyl-1*H*-imidazol-2-yl)thio)pyridine (147bh´)



According to **TP10**, solutions of 1-butyl-1*H*-imidazole (**117b**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with aldrithiol (**112h´**, 66 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 50:50 → 20:80) afforded the title compound **147bh´** as a yellow oil (37 mg, 0.16 mmol, 79% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.39 (m, 1H), 7.48 (m, 1.9 Hz, 1H), 7.28 (d, *J* = 1.3 Hz, 1H), 7.17 (d, *J* = 1.3 Hz, 1H), 7.02 (m, 1H), 6.83 (dt, *J* = 8.0, 1.1 Hz, 1H), 4.04 (t, *J* = 7.3 Hz, 2H), 1.72 – 1.60 (m, 2H), 1.29 – 1.23 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

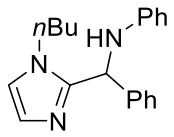
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.5, 149.8, 137.2, 135.6, 131.0, 123.0, 121.2, 120.6, 47.2, 33.1, 19.8, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3103, 3043, 2956, 2930, 2871, 1572, 1560, 1501, 1494, 1447, 1428, 1416, 1392, 1378, 1341, 1273, 1148, 1116, 1085, 1065, 1044, 985, 968, 914, 756, 720, 691.

MS (EI, 70 eV): *m/z* (%) = 233 (10), 205 (10), 204 (100), 200 (10), 191 (24), 190 (12), 176 (46), 158 (23), 155 (64), 134 (17), 133 (11), 123 (47), 122 (22), 119 (46), 118 (11), 113 (10), 111 (34), 96 (11), 84 (11), 81 (17), 78 (80).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{12}H_{15}N_3S$]: 233.0987; found: 233.0988.

***N*-((1-Butyl-1*H*-imidazol-2-yl)(phenyl)methyl)aniline (147bc´)**



According to **TP10**, solutions of 1-butyl-1*H*-imidazole (**117b**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with *N*,1-diphenylmethanimine (**112c´**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 8:2 → 7:3) afforded the title compound **147bc´** as a colorless oil (42 mg, 0.14 mmol, 69% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.21 – 7.12 (m, 2H), 7.07 (d, *J* = 1.3 Hz, 1H), 6.88 (s, 1H), 6.78 – 6.64 (m, 3H), 5.65 (s, 1H), 5.32 (s, 1H), 4.02 – 3.76 (m, 2H), 1.70 – 1.44 (m, 2H), 1.35 – 1.23 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

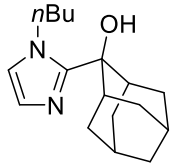
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.5, 146.7, 140.5, 129.2 (2C), 128.9 (2C), 127.8, 127.7, 127.6 (2C), 119.9, 117.9, 113.6 (2C), 55.2, 45.8, 32.8, 19.9, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3388, 3352, 3105, 3025, 2957, 2930, 2871, 1600, 1573, 1567, 1535, 1503, 1486, 1460, 1454, 1422, 1378, 1371, 1315, 1272, 1180, 1154, 1137, 1114, 1095, 1077, 1062, 1046, 1028, 992, 935, 869, 841, 827, 744, 690.

MS (EI, 70 eV): *m/z* (%) = 214 (15), 213 (100), 207 (34), 180 (17), 169 (11), 157 (85), 156 (18), 130 (17), 77 (21).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{20}H_{23}N_3$]: 305.1892; found: 305.1886.

2-(1-butyl-1H-imidazol-2-yl)adamantan-2-ol (147bh)

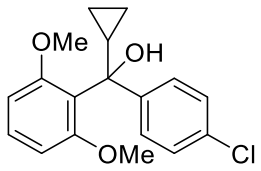


According to **TP10**, solutions of 1-butyl-1*H*-imidazole (**117b**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with adamantanone (**112h**, 45 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 8:2 → 7:3) afforded the title compound **147bh** as a yellow oil (30 mg, 0.11 mmol, 55% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.86 (m, 2H), 4.21 – 4.06 (m, 2H), 2.46 – 2.28 (m, 5H), 2.13 – 2.04 (m, 2H), 1.84 (s, 1H), 1.79 – 1.60 (m, 9H), 1.43 – 1.31 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 150.3, 126.1, 120.9, 75.3, 47.2, 37.9, 36.9 (2C), 35.1 (2C), 33.6, 32.9 (2C), 27.2, 27.0, 20.2, 13.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3333, 3322, 2955, 2934, 2910, 2896, 2885, 2864, 2848, 1483, 1478, 1467, 1453, 1412, 1390, 1377, 1368, 1357, 1349, 1336, 1296, 1291, 1270, 1260, 1188, 1182, 1109, 1103, 1078, 1048, 1042, 1012, 996, 970, 939, 926, 907, 853, 753, 748, 731, 654.
MS (EI, 70 eV): *m/z* (%) = 275 (19), 274 (85), 273 (15), 257 (45), 246 (18), 245 (34), 232 (25), 231 (20), 227 (30), 217 (20), 203 (13), 191 (21), 179 (18), 151 (39), 151 (14), 123 (100), 123 (15), 96 (20), 95 (25), 91 (18), 82 (37), 79 (25), 69 (51), 68 (14), 55 (12), 40 (30).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{17}H_{26}N_2O$]: 274.2045; found: 274.2040.

(4-Chlorophenyl)(cyclopropyl)(2,6-dimethoxyphenyl)methanol (147ci´)



According to **TP10**, solutions of 1,3-dimethoxybenzene (**117c**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with (4-chlorophenyl)(cyclopropyl)methanone (**112i´**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 95:5) afforded the title compound **147ci´** as colorless crystals (55 mg, 0.17 mmol, 86% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.43 (d, *J* = 8.5 Hz, 2H), 7.25 – 7.17 (m, 3H), 6.61 (d, *J* = 8.3 Hz, 2H), 6.05 (s, 1H), 3.61 (s, 6H), 1.91 (tt, *J* = 8.3, 6.0 Hz, 1H), 0.80 – 0.70 (m, 1H), 0.61 – 0.49 (m, 2H), 0.48 – 0.36 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 158.2 (2C), 148.7, 131.6, 128.5, 127.7 (2C), 127.5 (2C), 123.9, 106.7 (2C), 77.8, 56.4 (2C), 20.2, 2.2, 1.2.

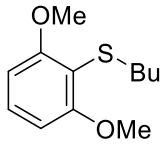
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3460, 3007, 2982, 2950, 2918, 2870, 2847, 1592, 1584, 1567, 1490, 1470, 1454, 1442, 1432, 1412, 1397, 1376, 1356, 1278, 1245, 1204, 1189, 1171, 1139, 1098, 1093, 1085, 1048, 1020, 1012, 982, 962, 951, 897, 866, 843, 828, 775, 742, 731, 722, 704.

MS (EI, 70 eV): *m/z* (%) = 290 (25), 166 (10), 165 (100), 139 (18), 137 (11).

HRMS (EI-orbitrap): *m/z:* [M – C_2H_4] calc. for [$C_{16}H_{15}ClO_3$]: 290.0710; found: 290.0705.

m.p. (°C): 125.6 – 130.3.

Butyl(2,6-dimethoxyphenyl)sulfane (147cq)

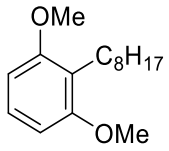


According to **TP10**, solutions of 1,3-dimethoxybenzene (**117c**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with 1,2-dibutyldisulfane (**112q**, 54 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 95:5) afforded the title compound **147cq** as a slightly yellow oil (40 mg, 0.18 mmol, 88% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.23 (t, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 3.88 (s, 6H), 2.80 (dd, *J* = 7.9, 6.7 Hz, 2H), 1.51 – 1.43 (m, 2H), 1.43 – 1.32 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.2 (2C), 129.4, 110.6, 104.1 (2C), 56.3 (2C), 33.8, 31.8, 22.0, 13.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2870, 2835, 1578, 1556, 1467, 1429, 1377, 1291, 1267, 1245, 1186, 1171, 1102, 1059, 1032, 915, 770, 755, 747, 715.
MS (EI, 70 eV): *m/z* (%) = 226 (37), 183 (10), 170 (100), 168 (30), 167 (13), 155 (21), 127 (16), 124 (11).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{12}H_{18}O_2S$]: 226.1028; found 226.1020.

1,3-Dimethoxy-2-octylbenzene (147ck´)



According to **TP10**, solutions of 1,3-dimethoxybenzene (**117c**, 0.2 M, 1.0 equiv) in THF and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) cooled to –40 °C. The solution of **117c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL) cooled to –40 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL, t_{R2} = 1.3 s). Subsequently upon reaching the steady state, it was injected into a flask charged with 1-iodooctane (**112k´**, 72 mg, 0.3 mmol, 1.5 equiv) in THF (1.0 mL) cooled to –20 °C for 60 s. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5) afforded the title compound **147ck´** as a colorless oil (23 mg, 0.09 mmol, 46% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.11 (t, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 2H), 3.81 (s, 6H), 2.67 – 2.57 (m, 2H), 1.51 – 1.42 (m, 2H), 1.35 – 1.24 (m, 10H), 0.91 – 0.85 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 158.4 (2C), 126.5, 119.8, 103.8 (2C), 55.8 (2C), 32.1, 30.0, 29.7, 29.5, 29.4, 23.0, 22.9, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2923, 2853, 2834, 1593, 1573, 1566, 1562, 1472, 1455, 1434, 1377, 1328, 1275, 1254, 1187, 1171, 1156, 1127, 1090, 1043, 773, 722, 697, 686.
MS (EI, 70 eV): *m/z* (%) = 250 (12), 151 (100), 123 (13), 91 (13).

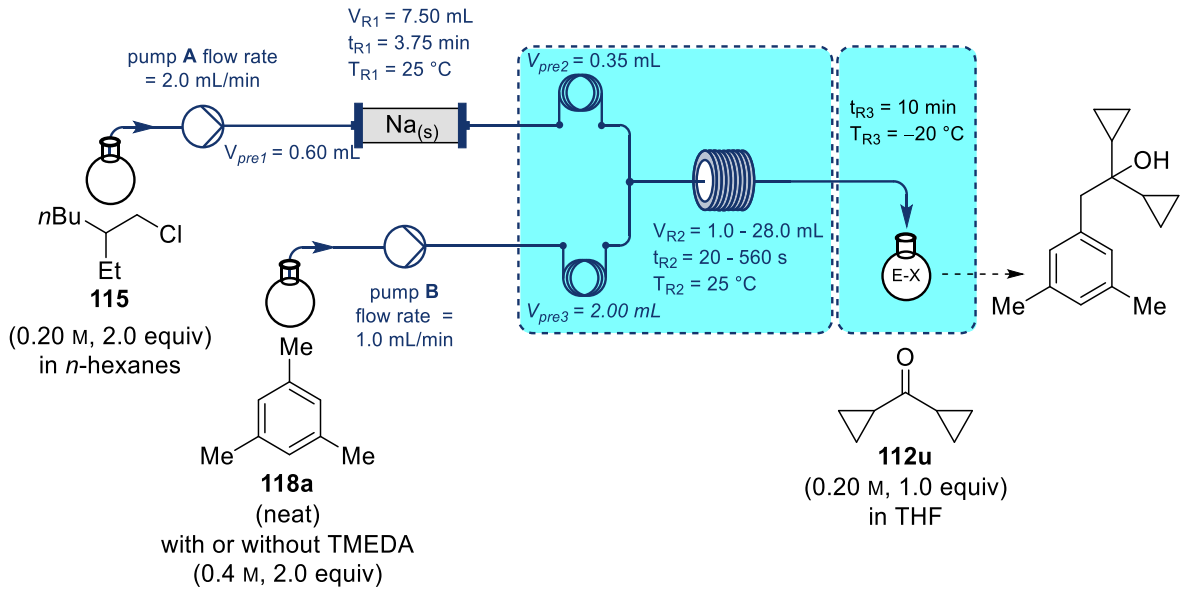
HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{26}O_2$]: 250.1933; found 250.1926.

5. Continuous Flow Preparation of Benzylic Sodium Organometallics

5.1 Screenings

Ketones were used as electrophiles in most metalation screenings, since sodiation of alkylsubstituted arenes proceeded in the presence of epoxides. Therefore, monitoring of the metalation time is complicated using epoxide electrophiles. Screenings at lower temperatures in continuous flow were not feasible due to significantly increased precipitation and therefore clogging.

5.1.1 Time screening for the sodiation of methyl substituted arenes in continuous flow



Scheme 127: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), in-line benzylic sodiation of mesitylene (**118a**) and subsequent batch quench with dicyclopropylketone (**112u**) as electrophile.

Solutions of mesitylene (**118a**) with and without TMEDA (0.4 M, 2.0 equiv) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor (V_{R2} = 1.0 – 28.0 mL, t_{R2} = 20 s – 560 s) and were, subsequently upon reaching the steady state, injected for 1 min into a flask charged with dicyclopropylketone (**112u**, 0.20 mmol, 1.0 equiv). Formation of the product was monitored by GC.

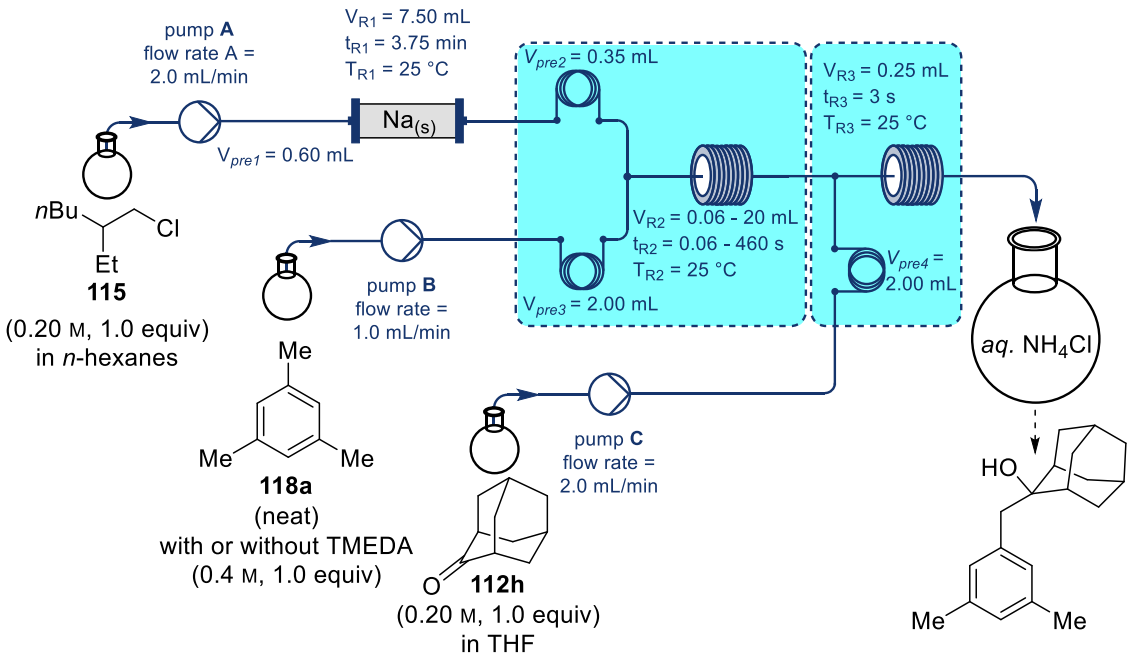
Table 29: Time screening for the sodiation of mesitylene (118a) in continuous flow

Entry	Reactorsize [mL]	t [s]	Additive	Normalized GC-Yield [%][a]
1	1	20	TMEDA	86
2	5	100	TMEDA	92
3	13	260	TMEDA	98
4	23	460	TMEDA	100
5	28	560	TMEDA	95
6	5	100	-	12
7	13	260	-	11
8	23	460	-	9
9	28	560	-	5

[a]The largest integrated area under the curve corresponding to dicyclopropylketone was normalized to 100% GC-yield the other integrals were adjusted accordingly.

Using TMEDA as additive a plateau value is reached at a reaction time between 100 and 260 s (entry 2 and 3). The low GC-yields obtained without additive (entry 6 - 9) are explained by high the degree of precipitation in the tube reactors. TMEDA is crucial to solubilize the benzylsodium species (**119a**). Even though a plateau level was reached earlier, we used the conditions resulting in the absolute highest product formation (entry 4)

5.1.2 Time screening for the sodiation of methyl substituted arenes in continuous flow followed by in-line quench



Scheme 128: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), in-line benzylic sodiation of mesitylene (**118a**) and subsequent in-line quench with adamantanone (**112h**) as electrophile.

Solutions of mesitylene (**118a**) with and without TMEDA (0.4 M, 1.0 equiv), 3-(chloromethyl)heptane (**115**, 0.2 M, 1.0 equiv) in *n*-hexane and adamantone (**112h**, 0.2 M, 1.0 equiv) in THF were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor (V_{R2} = 0.06 – 20.00 mL, t_{R2} = 0.6 s – 400 s). Pump C (flow rate: 2.0 mL/min) pumped the solution of adamantone **112h**, through a precooling loop (V_{pre4} = 2.00 mL), which at 25 °C. The two streams were mixed in another T-shaped mixer, the combined reaction mixture passed through a tube reactor (V_{R3} = 0.25 mL) and was, subsequently upon reaching the steady state, injected into a flask charged with sat. *aq.* NH_4Cl at 25 °C. Formation of the product was monitored by GC.

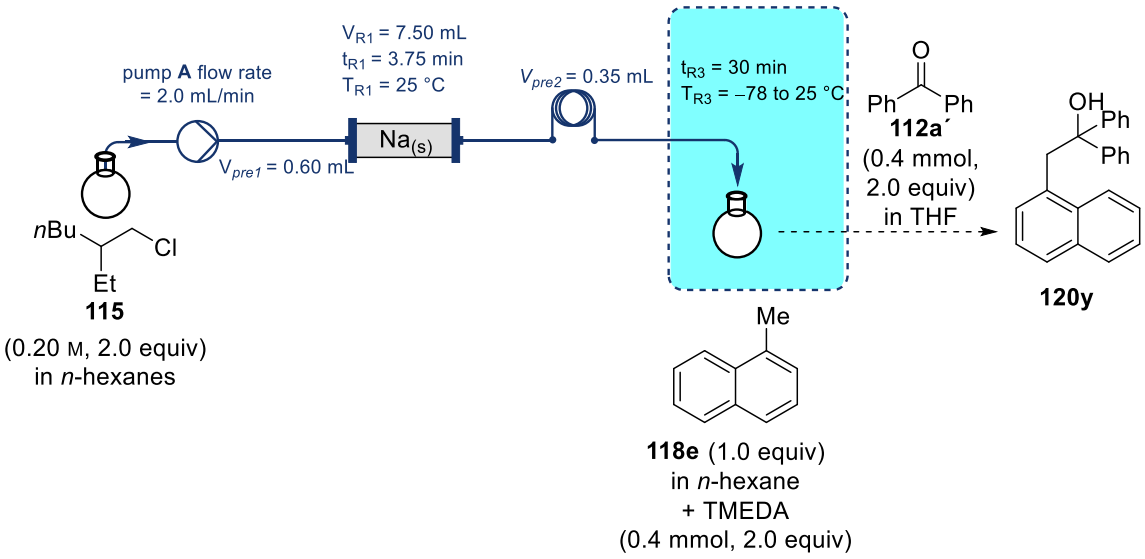
Table 30: Time screening for the sodiation of mesitylene (118a) in continuous flow followed by an in-line quench

Entry	Reactorsize [mL]	t [s]	Additive	Normalized GC-Yield [%][a]
1	0.06	1.2	TMEDA	26
2	0.25	5	TMEDA	70
3	0.5	10	TMEDA	82
4	1	20	TMEDA	90
5	2	40	TMEDA	88
6	5	100	TMEDA	96
7	10	200	TMEDA	95
8	20	400	TMEDA	100
9	0.06	1.2	-	16
10	0.25	5	-	16
11	0.5	10	-	16
12	1	20	-	21
13	2	40	-	18
14	5	100	-	17
15	10	200	-	12
16	20	400	-	7

[a]The largest integrated area under the curve corresponding to product was normalized to 100% GC-yield the other integrals were adjusted accordingly.

Using TMEDA as additive a plateau value is reached at a reaction time of around 100 s (entry 6). The low GC-yields obtained without additive (entry 9 – 16) are explained by high the degree of precipitation in the tube reactors. TMEDA is crucial to solubilize the benzylsodium species (**119a**).

5.1.3 Temperature screening for the sodiation of alkylsubstituted arenes in batch



Scheme 129: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), benzylic sodiation of 1-methylnaphtalene (**118e**) and subsequent batch quench with benzophenone (**112a´**) as electrophile.

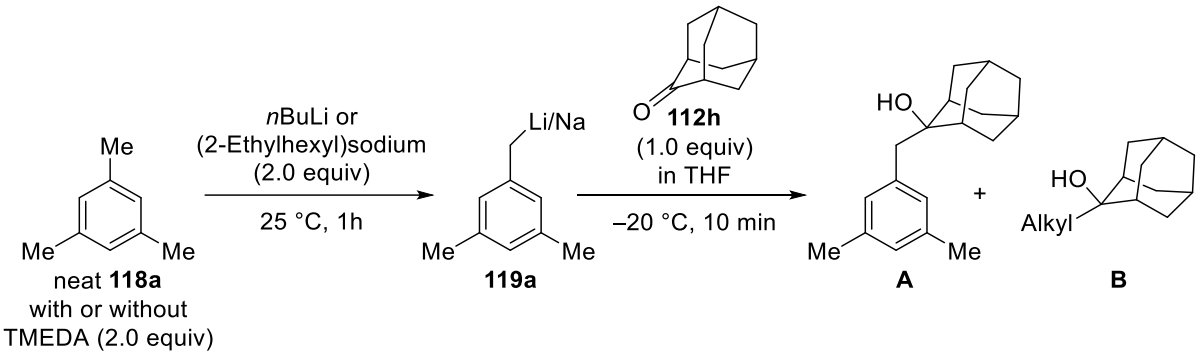
A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. It was injected for 1 min into a flask charged with 1-methylnaphtalene (**118e**, 28 mg, 0.20 mmol, 1.0 equiv) and TMEDA (0.40 mmol, 2.0 equiv) in *n*-hexane (1.0 mL) at the corresponding temperature (–78 to 25 °C). The mixture was stirred at the same temperature for 30 min before benzophenone (**112a´**, 73 mg, 0.40 mmol, 2.0 equiv) was added. Conversion of 1-methylnaphtalene (**118e**) was monitored by GC.

Table 31: Temperature screening for the sodiation of 1-methylnaphtalene (118e) in batch

Entry	T [°C]	Conversion (**118e**) [%]
1	–78	13
2	–40	50
3	0	85
4	25	100[a]

[a] Product was isolated in 81% yield in case of entry 4.

5.1.4 Comparison between the metalation with *n*BuLi and (2-Ethylhexyl)sodium (36)



Scheme 130: Benzylic metalation of mesitylene (**118a**) using either (2-ethylhexyl)sodium (**36**) or *n*BuLi with or without the presence of TMEDA, and subsequent quench with adamantanone (**112h**) as electrophile.

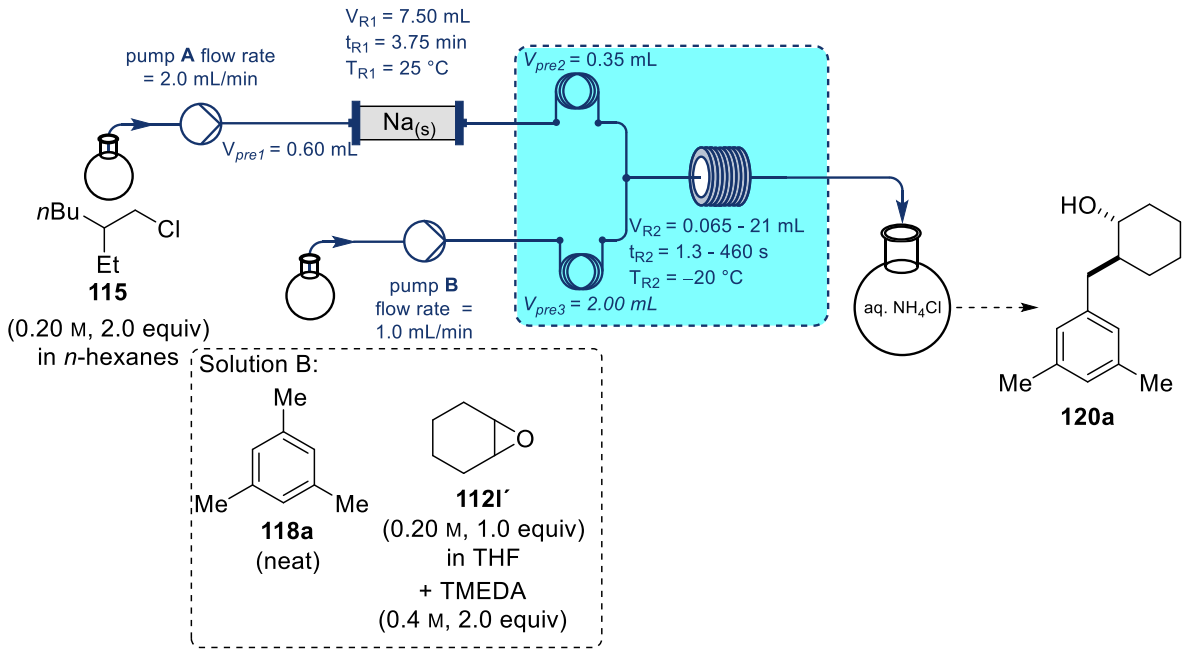
*n*BuLi (0.80 mmol, 2.0 equiv) or (2-Ethylhexyl)sodium (0.80 mmol, 2.0 equiv) in *n*-hexane was added to a mixture of either neat mesitylene (**118a**, 1.0 mL) or a solution of TMEDA (0.80 mmol, 2.0 equiv) in mesitylene (**118a**, 1.0 mL) at 25 °C. The mixture was stirred at the same temperature for 1 h. The mixture was cooled to –20 °C and adamantone (**112h**, 120 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added and stirred at –20 °C for 10 min before sat. *aq.* NH_4Cl was added. Formation of the products **A** and **B** were monitored by GC and GCMS.

Table 32: Comparison between the metalation with *n*BuLi and (2-Ethylhexyl)sodium (36).

Entry	Base	Additive	Ratio **A**/**B**
1	*n*BuLi	-	**A** was not detected
2	*n*BuLi	TMEDA	>95/5 (75%)[a]
3	(2-Ethylhexyl)sodium	-	89/11
4	(2-Ethylhexyl)sodium	TMEDA	>95/5

[a]Isolated yield of product **A**.

5.1.5 Time screening for the continous flow preparation of *trans*-2-(3,5-dimethylbenzyl)cyclohexan-1-ol (10a) under Barbiertype conditions



Scheme 131: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), followed by an in-line benzylic sodiation of mesitylene (**118a**) in the presence of cyclohexeneoxide (**112l´**) as electrophile.

A Solution **A** of 3-(chloromethyl)heptane (**115**, 0.2 M) in *n*-hexane and a solution **B** cyclohexeneoxide (**112l´** 0.2 M) and TMEDA (0.4 M) in a 1:1 mixture of mesitylene (**118a**) and THF were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL), which was cooled to –20 °C. Solution **B** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), which was cooled to –20 °C. The precooled solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor and a metal needle (V_{R2} = 0.065 mL to 21 mL, t_{R2} = 1.3 s to 420 s), subsequently upon reaching the steady state, it was injected into a vial charged with a sat. *aq.* NH_4Cl-solution. Formation of product **120a** was monitored by GC.

Table 33: Time screening for the continous flow preparation of 2-(3,5-dimethylbenzylcyclohexan-1-ol (120a) under Barbiertype conditions

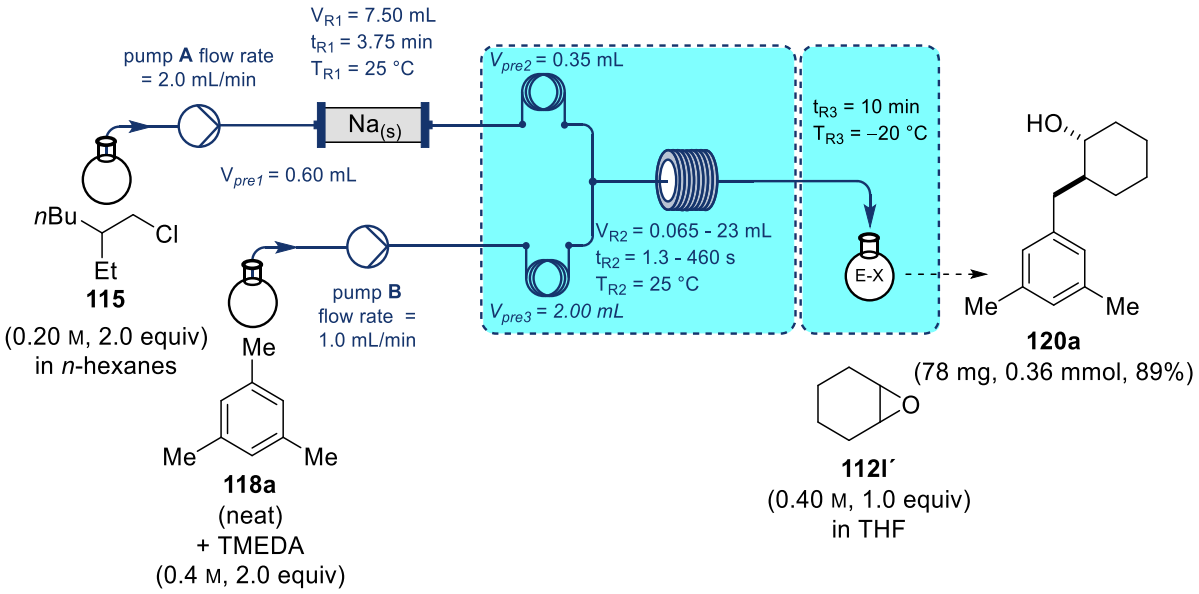
Entry	Reactorsize [mL]	t [s]	Normalized GC-Yield [%][a]
1	21	420	98
2	19	380	97
3	17	340	107
4	15	300	100
5	10	200	99
6	5	100	98
7	2	40	90
8	1	20	71
9	0.5	10	40
10	0.25	5	22
11	0.065	1.3	13

[a]The largest integrated area under the curve corresponding to the product **120a** was normalized to 100% GC-yield the other integrals were adjusted accordingly.

No significant increase in yield was observable by prolonging the reaction time longer than 100 s (entry 6). The high yield in entry 3 might be considered as an outlier.

5.2 Typical Procedures

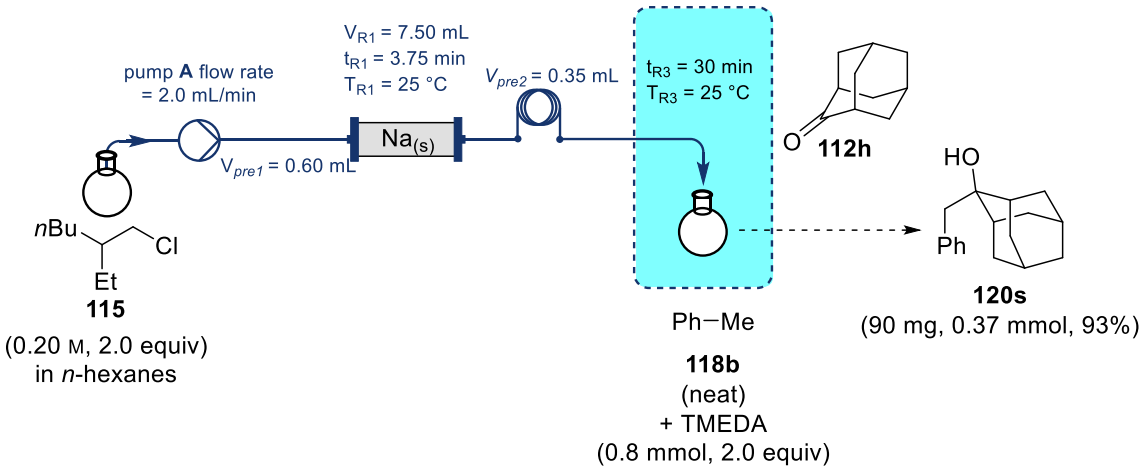
5.2.1 Typical procedure 12 (TP12): On-demand synthesis of (2-ethylhexyl)sodium and its use in-line benzylic sodiations.



Scheme 132: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), in-line benzylic sodiations and subsequent batch quench with electrophiles.

Solutions of TMEDA (0.4 M, 2.0 equiv) in mesitylene (**118a**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 0.065 mL to 23.0 mL, t_{R2} = 1.3 s to 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with cyclohexene oxide (**112l´**, 55 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 99:1 → 98:2) afforded the title compound **120a** as a white solid (78 mg, 0.36 mmol, 89% yield).

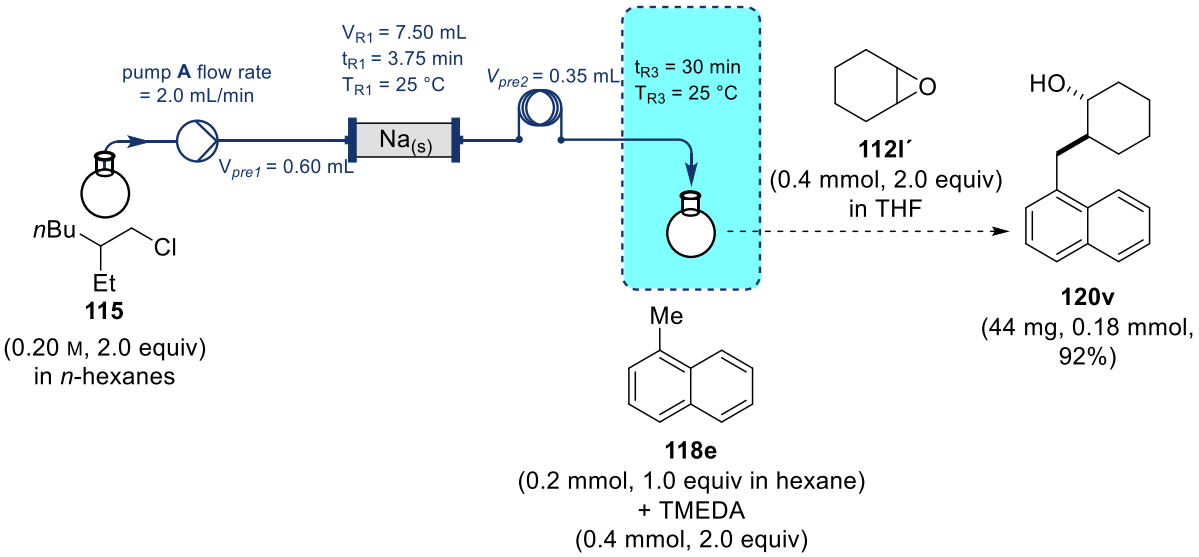
5.2.2 Typical procedure 13 (TP13): On-demand synthesis of (2-ethylhexyl)sodium and its use in batch sodiations.



Scheme 133: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), followed by benzylic batch sodiation of neat **118b** and subsequent electrophile quench with **112h**.

A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in toluene (**118b**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of adamantanone (**112h**, 60 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 80:20) afforded the title compound **120s** as a white solid (90 mg, 0.37 mmol, 93% yield).

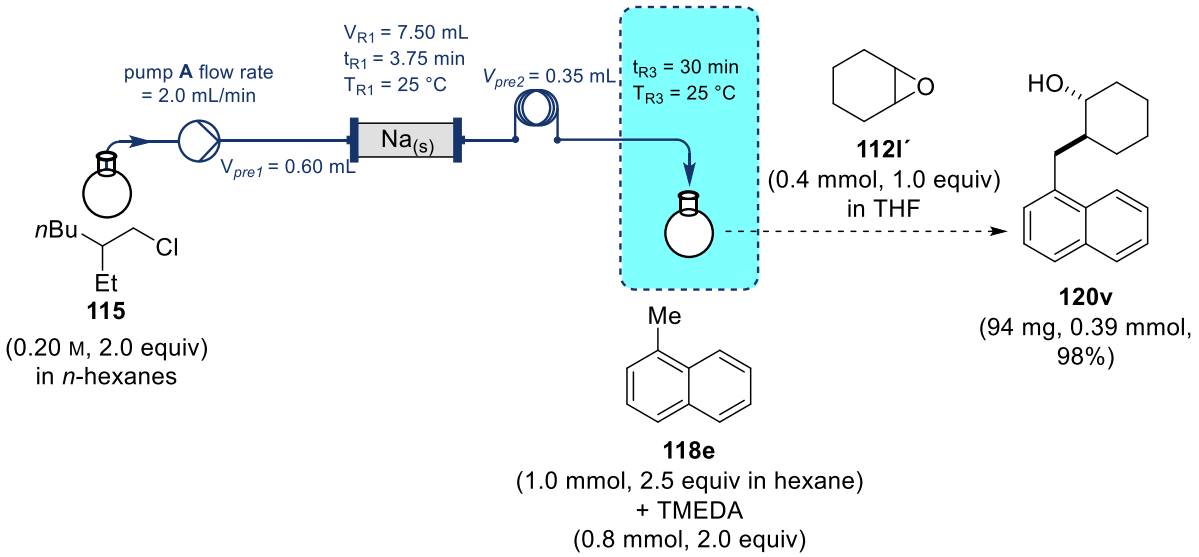
5.2.3 Typical procedure 14 (TP14): On-demand synthesis of (2-ethylhexyl)sodium and its use in batch sodiations.



Scheme 134: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), followed by benzylic batch sodiation of **118e** and subsequent electrophile quench with **5a**.

A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 1 min into a flask charged with a solution of TMEDA (0.40 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 28 mg, 0.20 mmol, 1.0 equiv) in hexane (1.0 ml) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 2.0 equiv) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 85:15) afforded the title compound **120v** as a colorless solid (44 mg, 0.18 mmol, 92% yield).

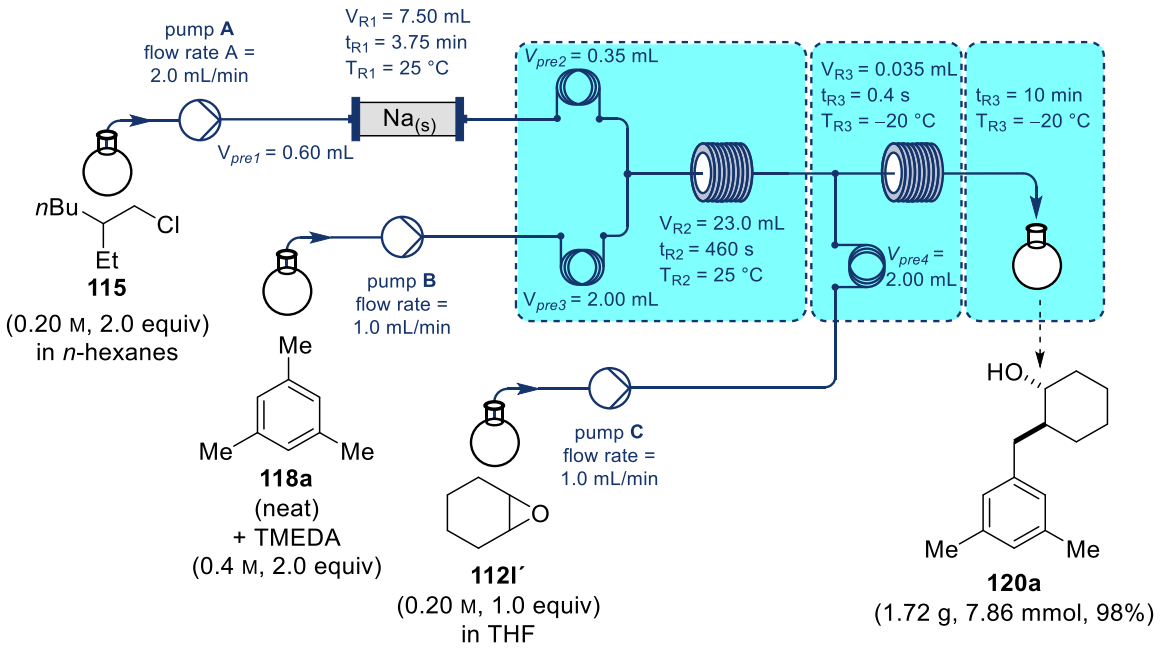
5.2.4 Typical procedure 15 (TP15): On-demand synthesis of (2-ethylhexyl)sodium and its use in batch sodiations using excess of alkyl substituted arenes.



Scheme 135: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), followed by benzylic batch sodiation of **118e** and subsequent electrophile quench with **112l´**.

A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 142 mg, 1.00 mmol, 2.5 equiv) in hexane (1.0 ml) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 2.0 equiv) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 85:15) afforded the title compound **120v** as a colorless solid (94 mg, 0.39 mmol, 98% yield).

5.2.5 On-demand synthesis of (2-ethylhexyl)sodium and its use in a lateral metalation reaction followed by an in-line quench.

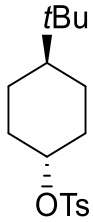


Scheme 136: Set-up for the on-demand generation of (2-ethylhexyl)sodium (**36**), in-line benzylic sodiation of mesitylene (**118a**) and subsequent in-line quench cyclohexene oxide (**112l´**) as electrophile.

Solutions of TMEDA (0.4 M, 2.0 equiv) in mesitylene (**118a**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane and cyclohexene oxide (**112l´**, 0.2 M, 1.0 equiv) in THF were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor (V_{R2} = 0.030 mL, t_{R2} = 0.6 s). Pump C (flow rate: 1.0 mL/min) pumped the solution of cyclohexene oxide **112l´**, through a precooling loop (V_{pre4} = 2.00 mL), which was cooled to –20 °C. The two streams were mixed in another T-shaped mixer, the combined reaction mixture passed a metal needle (V_{R3} = 0.035 mL) and was, subsequently upon reaching the steady state, injected into an argon filled flask cooled to –20 °C for 40 min. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C and stirred at this temperature for 30 min before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×70 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 90:10) afforded the title compound **120a** as colorless crystals (1.72 g, 7.86 mmol, 98% yield).

5.3 Preparation of Starting Materials

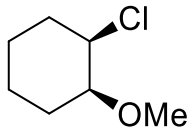
trans-4-(tert-butyl)cyclohexyl 4-methylbenzenesulfonate (153n)



According to the literature[426] 4-toluenesulfonylchloride (11.44 g, 60 mmol, 2.0 equiv) was added portionwise to a solution of *trans*-4-(tert-butyl)cyclohexan-1-ol (4.69 g, 30 mmol, 1.0 equiv), triethylamine (9.2 mL, 60 mmol, 2 equiv), DMAP (0.73 g, 6 mmol, 0.20 mmol) and DCM (300 mL) at 0 °C. The reaction mixture was stirred overnight at 25 °C. Afterwards the mixture was quenched with H_2O (200 mL). The aqueous layer was extracted with DCM (3×150 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, *n*-pentane:EtOAc = 98:2) afforded the title compound **153n** as colorless crystals (2.93 g, 9.43 mmol, 31% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.82 – 7.76 (m, 2H), 7.36 – 7.29 (m, 2H), 4.38 – 4.30 (m, 1H), 2.44 (s, 3H), 2.01 – 1.92 (m, 2H), 1.80 – 1.72 (m, 2H), 1.49 – 1.35 (m, 2H), 1.08 – 0.87 (m, 3H), 0.80 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.5, 134.9, 129.9 (2C), 127.7 (2C), 82.8, 46.7, 33.0 (2C), 32.3, 27.6 (3C), 25.7 (2C), 21.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2948, 2865, 1381, 1366, 1361, 1345, 1327, 1306, 1186, 1179, 1170, 1097, 1043, 1004, 948, 930, 923, 901, 878, 858, 844, 819, 805, 800, 757, 666.
m.p. (°C): 89 – 90.

(1*R*,2*S*)-1-chloro-2-methoxycyclohexane (153d)



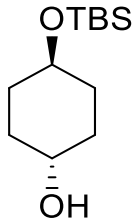
According to the literature[427] *trans*-2-methoxycyclohexan-1-ol (6.50 g, 50.0 mmol, 1.0 equiv) was added dropwise to a solution of NCS (13.4 g, 100 mmol, 2.0 equiv), PPh_3 (19.7 g, 75.0 mmol, 1.5 equiv)

[426] Y. Wang, X. Hu, C. A. Morales-Rivera, G.-X. Li, X. Huang, G. He, P. Liu, G. Chen, *J. Am. Chem. Soc.* **2018**, *140*, 9678-9684.
[427] E. A. Jaseer, A. B. Naidu, S. S. Kumar, R, K. Rao, K. G. Thakur, G. Sekar *Chem. Commun.* **2007**, 867 – 869.

and THF (150 mL) at 0 °C. The reaction mixture was stirred over night at 25 °C. Afterwards the mixture was quenched with H_2O (250 mL). The aqueous layer was extracted three times with EtOAc (3×150 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, pentane was added to precipitate triphenylphosphine oxide the precipitate was removed by filtration. Flash column chromatographical purification (silica gel, *n*-pentane:EtOAc = 98:2) afforded the title compound **153d** as a yellow oil (1.50 g, 10.1 mmol, 20% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.40 – 4.32 (m, 1H), 3.40 (s, 3H), 3.35 (dt, *J* = 9.0, 3.2 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.88 – 1.58 (m, 5H), 1.46 – 1.35 (m, 1H), 1.35 – 1.21 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 79.8, 61.3, 56.3, 32.3, 26.8, 22.6, 21.4.
Spectral data is in accordance with the literature.[428]

***trans*-4-((tert-butyldimethylsilyl)oxy)cyclohexan-1-ol**



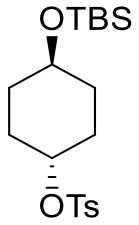
According to the literature,[429] TBSCl (3.17 g, 21 mmol, 1.05 equiv) was dissolved in DMF (10 mL) and the resulting solution was added dropwise to a mixture of *trans*-cyclohexane-1,4-diol (2.32 g, 20 mmol, 1.0 equiv) and imidazole (3.40 g, 50 mmol, 2.5 equiv) in DMF (7.5 mL) and THF (10 mL) at 0 °C. After stirring for 1 h at the same temperature brine (100 mL) was added and the aqueous layer was extracted with EtOAc (3x100 mL) the organic layer was dried over $MgSO_4$. Flash column chromatographical purification (silica gel, *n*-pentane:EtOAc = 4:1) afforded the title compound as a colorless oil (2.50 g, 11 mmol, 54% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.79 – 3.51 (m, 2H), 1.98 – 1.90 (m, 2H), 1.89 – 1.80 (m, 2H), 1.44 – 1.22 (m, 5H), 0.88 (s, 9H), 0.05 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 70.2, 69.7, 32.9 (2C), 32.8 (2C), 26.0 (3C), 18.3, -4.6. (2C).
MS (EI, 70 eV): *m/z* (%) = 173 (79), 171 (16), 98 (13), 97 (100), 97 (100), 97 (17) 97 (17), 81 (47), 75 (47), 75 (47), 75 (34), 75 (34), 73 (25).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{12}H_{26}O_2Si$]: 230.1702; found 230.1698.

[428] C. N. Barry, S. J. Baumrucker, R. C. Andrews, S. A. Evans Jr. *J. org. Chem.* **1982**, *47*, 3890 – 3983.
[429] Z. L. Song, B. M. Wang, Y. Q. Tu, C. A. Fan, S. Y. Zhang, *Org. Lett.* **2003**, *5*, 2319 – 2321.

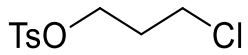
***trans*-4-((tert-butyldimethylsilyl)oxy)cyclohexyl 4-methylbenzenesulfonate (153m)**



TsCl (3.81 g, 20 mmol, 2.0 equiv) was added portionwise to a mixture of *trans*-4-((tert-butyldimethylsilyl)oxy)cyclohexan-1-ol (2.30 g, 10 mmol, 1.0 equiv), Et_3N (5.6 mL, 40 mmol, 4.0 equiv) in DCM (30 mL) at 0 °C the mixture was allowed to slowly warm to 25 °C and stirred over night at the same temperature. Brine (100 mL) was added and the aqueous layer was extracted with EtOAc (3x250 mL) the organic layer was dried over $MgSO_4$. Flash column chromatographical purification (silica gel, *n*-pentane:EtOAc = 99:1) afforded the title compound **153m** as a colorless solid (3.08 g, 8.0 mmol, 80% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 – 7.74 (m, 2H), 7.36 – 7.29 (m, 2H), 4.62 – 4.49 (m, 1H), 3.83 – 3.66 (m, 1H), 2.44 (s, 3H), 1.96 – 1.84 (m, 2H), 1.83 – 1.72 (m, 2H), 1.59 – 1.47 (m, 2H), 1.41 – 1.30 (m, 2H), 0.84 (s, 9H), 0.01 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.6, 134.7, 129.9 (2C), 127.8 (2C), 80.7, 67.7, 30.8 (2C), 28.0 (2C), 25.9 (3C), 21.8, 18.2, -4.7 (2C).

3-chloropropyl 4-methylbenzenesulfonate (153o)



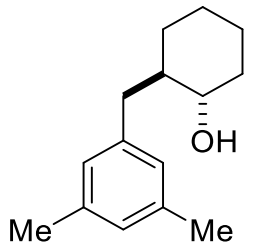
Et_3N (11.2 mL, 80 mmol, 4.0 equiv) was added dropwise to a mixture of 3-chloropropan-1-ol (1.89 g, 20 mmol, 1.0 equiv) and TsCl (7.63 g, 40 mmol, 2.0 equiv) in DCM (60 mL) at 0 °C. The mixture was allowed to warm to 25 °C and stirred over night at the same temperature. Brine (100 mL) was added and the aqueous layer was extracted with EtOAc (3x250 mL) the organic layer was dried over $MgSO_4$. Flash column chromatographical purification (silica gel, *n*-pentane:EtOAc = 99:1) afforded the title compound **153o** as a colorless oil (4.13 g, 16.6 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.82 – 7.73 (m, 2H), 7.39 – 7.30 (m, 2H), 4.17 (t, *J* = 5.9 Hz, 2H), 3.55 (t, *J* = 6.2 Hz, 2H), 2.44 (s, 3H), 2.13 – 2.04 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.1, 132.7, 130.0 (2C), 127.9 (2C), 66.9, 40.4, 31.7, 21.7.
MS (EI, 70 eV): *m/z* (%) = 173 (51), 172 (100), 155 (60), 119 (24), 108 (26), 107 (12), 91 (86), 65 (10).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{10}H_{13}ClO_3S$]: 248.0274; found 248.0269.

5.4 Preparation of Products

trans-2-(3,5-dimethylbenzyl)cyclohexan-1-ol (120a)



According to **TP12**, solutions of TMEDA (0.4 M, 2.0 equiv) in mesitylene (**118a**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 90:10) afforded the title compound **120a** as a colorless solid (78 mg, 0.36 mmol, 89% yield).

In-line scale-up reaction

Solutions of TMEDA (0.40 M, 2.0 equiv) in mesitylene (**118a**) and 3-(chloromethyl)heptane (**115**, 0.20 M, 2.0 equiv) in *n*-hexane and cyclohexene oxide (**112l´**, 0.07 M, 1.0 equiv) in THF were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor (V_{R2} = 0.030 mL, t_{R2} = 0.6 s). Pump C (flow rate: 3.0 mL/min) pumped the solution of **112l´**, through a precooling loop (V_{pre4} = 2.00 mL), which was cooled to –20 °C. The two streams were mixed in another T-shaped mixer, the combined reaction mixture passed a metal needle (V_{R3} = 0.035 mL) and was, subsequently upon reaching the steady state, injected into an argon filled flask cooled to –20 °C for 40 min. The reaction mixture was stirred at –20 °C for 10 min and allowed to warm to 25 °C and stirred at this temperature for 30 min before sat. *aq.* NH_4Cl solution was

added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×70 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 90:10) afforded the title compound **120a** as colorless crystals (1.72 g, 7.86 mmol, 98% yield).

Barbier-type reaction

Solutions of TMEDA (0.4 M, 2.0 equiv) and cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 1.0 equiv) in a mesitylene (**118a**, 1.0 mL) THF (1.0 mL) mixture and a second solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with the first solution of cyclohexene oxide (**112l´**) and mesitylene (**118a**) at –20 °C. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 90:10) afforded the title compound **120a** as a colorless solid (72 mg, 0.33 mmol, 82% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.83 (s, 1H), 6.81 (s, 2H), 3.37 – 3.24 (m, 1H), 3.07 (dd, *J* = 13.2, 4.2 Hz, 1H), 2.29 (s, 7H), 2.02 – 1.91 (m, 1H), 1.79 – 1.62 (m, 2H), 1.62 – 1.54 (m, 1H), 1.54 – 1.40 (m, 2H), 1.33 – 1.19 (m, 2H), 1.16 – 1.02 (m, 1H), 0.91 (qd, *J* = 12.8, 3.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.8, 137.7 (2C), 127.5, 127.3 (2C), 74.8, 47.2, 39.1, 35.9, 30.3, 25.6, 25.0, 21.4 (2C).

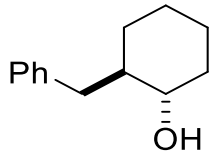
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3338, 2920, 2854, 1605, 1461, 1447, 1070, 1058, 1034, 845, 706.

MS (EI, 70 eV): *m/z* (%) = 131 (13), 129 (10), 128 (11), 121 (10), 120 (100), 119 (42), 117 (19), 115 (24), 105 (76), 91 (42), 79 (18), 77 (14).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{22}O$]: 218.1671; found 218.1663.

m.p. (°C): 88.3 – 90.4.

***trans*-2-benzylcyclohexan-1-ol (120b)**



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in toluene (**118b**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 80:20) afforded the title compound **120b** as a colorless solid (62 mg, 0.33 mmol, 81% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.26 (m, 2H), 7.22 – 7.18 (m, 3H), 3.35 – 3.27 (m, 1H), 3.19 (dd, *J* = 13.3, 3.9 Hz, 1H), 2.36 (dd, *J* = 13.3, 9.2 Hz, 1H), 2.02 – 1.97 (m, 1H), 1.80 – 1.46 (m, 5H), 1.36 – 1.18 (m, 2H), 1.17 – 1.01 (m, 1H), 0.97 0.87 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.9, 129.5 (2C), 128.3 (2C), 125.8, 74.6, 47.1, 39.1, 35.9, 30.1, 25.5, 25.0.

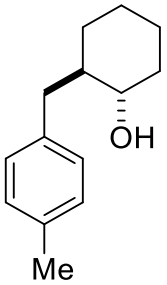
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3338, 3025, 2922, 2853, 1603, 1494, 1447, 1077, 1061, 1032, 1027, 853, 743, 699.

MS (EI, 70 eV): *m/z* (%) = 172 (60), 143 (10), 130 (14), 129 (36), 128 (19), 117 (23), 115 (33), 104 (56), 92 (55), 91 (100), 81 (37), 80 (18), 79 (26), 77 (11), 65 (11).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{13}H_{16}$]: 172.1252; found 172.1246.

m.p. (°C): 78.0 – 80.2.

***trans*-2-(4-methylbenzyl)cyclohexan-1-ol (120c)**



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in *p*-xylene (**118c**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 80:20) afforded the title compound **120c** as a white solid (65 mg, 0.32 mmol, 80% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.10 (s, 4H), 3.36 – 3.25 (m, 1H), 3.14 (dd, *J* = 13.4, 4.0 Hz, 1H), 2.34 (s, 4H), 2.06 – 1.92 (m, 1H), 1.82 – 1.55 (m, 4H), 1.55 – 1.44 (m, 1H), 1.37 – 1.18 (m, 2H), 1.18 – 1.04 (m, 1H), 0.98 – 0.82 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.7, 135.3, 129.4 (2C), 129.0 (2C), 74.6, 47.2, 38.6, 35.9, 30.1, 25.5, 25.0, 21.1.

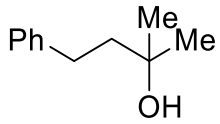
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3342, 2921, 2854, 1514, 1447, 1067, 1058, 1029, 1021, 807, 778.

MS (EI, 70 eV): *m/z* (%) = 187 (14), 186 (100), 171 (34), 157 (13), 144 (18), 143 (34), 157 (13), 144 (18), 143 (34), 131 (12), 129 (34), 128 (14), 118 (69), 117 (30), 115 (20), 106 (41), 105 (86), 103 (12), 91 (66), 81 (12), 80 (10), 79 (30), 77 (13).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{20}O$]: 204.1514; found 204.1509.

m.p. (°C): 99.3 – 101.2.

2-methyl-4-phenylbutan-2-ol (120d)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in toluene (**118b**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with 2,2-dimethyloxirane (**112m´**, 29 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 80:20) afforded the title compound **120d** as a colorless oil (41 mg, 0.25 mmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 2.78 – 2.66 (m, 2H), 1.86 – 1.74 (m, 2H), 1.46 (s, 1H), 1.31 (s, 6H).

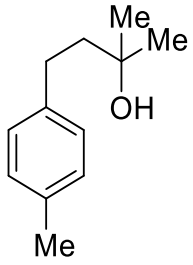
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.6, 128.5 (2C), 128.4 (2C), 125.8, 71.0, 45.9, 30.9, 29.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3366, 2968, 2967, 2931, 1494, 1454, 1376, 1365, 1210, 1150, 1124, 926, 913, 738, 696.

MS (EI, 70 eV): *m/z* (%) = 146 (37), 132 (10), 131 (100), 129 (10), 91 (78), 59 (10).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{11}H_{14}$]: 146.1096; found 146.1090.

2-methyl-4-(p-tolyl)butan-2-ol (120e)



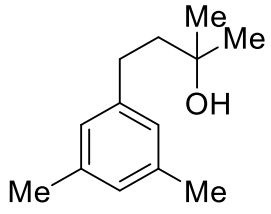
According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in *p*-xylene (**118c**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with 2,2-dimethyloxirane (**112m´**, 29 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 80:20) afforded the title compound **120e** as a colorless oil (70 mg, 0.39 mmol, 98% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.12 (s, 4H), 2.73 – 2.59 (m, 2H), 2.34 (s, 3H), 1.84 – 1.72 (m, 2H), 1.46 (s, 1H), 1.30 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.5, 135.3, 129.2 (2C), 128.3 (2C), 71.0, 46.0, 30.4, 29.4 (2C), 21.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3364, 2968, 2926, 1515, 1468, 1455, 1377, 1364, 1210, 1150, 1128, 1100, 925, 909, 808.
MS (EI, 70 eV): *m/z* (%) = 160 (32), 146 (12), 145 (100), 117 (16), 115 (11), 105 (57), 91 (11).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{12}H_{16}$]: 160.1252; found 160.1245.

m.p. (°C): 50.4 – 52.3.

4-(3,5-dimethylphenyl)-2-methylbutan-2-ol (120f)



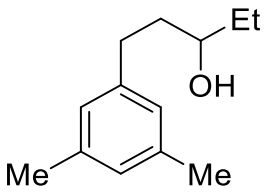
According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in mesitylene (**118a**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow

rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged 2,2-dimethyloxirane (**112m´**, 29 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 85:15) afforded the title compound **120f** as a colorless oil (74 mg, 0.38 mmol, 96% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.87 (s, 3H), 2.77 – 2.52 (m, 2H), 2.33 (s, 6H), 1.92 – 1.71 (m, 2H), 1.54 (s, 1H), 1.32 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.6, 138.0 (2C), 127.5, 126.3 (2C), 71.0, 46.0, 30.7, 29.4 (2C), 21.4 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3374, 3014, 2969, 2942, 2920, 2864, 1606, 1468, 1376, 1364, 1210, 1149, 1120, 922, 910, 844, 699.
MS (EI, 70 eV): *m/z* (%) = 174 (40), 160 (13), 159 (100), 144 (10), 131 (13), 119 (69), 117 (14), 115 (10), 91 (18),

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{13}H_{18}$]: 174.1409; found 174.1402.

1-(3,5-dimethylphenyl)pentan-3-ol (120g)



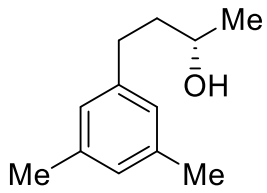
According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in mesitylene (**118a**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with 2-ethyloxirane (**112n´**, 29 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by

another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 85:15) afforded the title compound **120g** as a colorless oil (73 mg, 0.38 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.86 (s, 3H), 3.65 – 3.51 (m, 1H), 2.81 – 2.69 (m, 1H), 2.69 – 2.57 (m, 1H), 2.32 (s, 6H), 1.87 – 1.67 (m, 2H), 1.65 – 1.42 (m, 3H), 0.98 (t, *J* = 7.5 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.3, 138.0 (2C), 127.6, 126.4 (2C), 72.9, 38.8, 32.1, 30.4, 21.4 (2C), 10.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3343, 3012, 2961, 2959, 2933, 2929, 2918, 2874, 2859, 1606, 1456, 1119, 1035, 948, 843, 702.
MS (EI, 70 eV): *m/z* (%) = 145 (32), 133 (12), 131 (15), 120 (78), 120 (10), 119 (100), 117 (58), 115 (56), 115 (56), 105 (84), 103 (19), 91 (93), 79 (15), 78 (14), 77 (27).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{13}H_{20}O$]: 192.1514; found 192.1507.

(*S*)-4-(3,5-dimethylphenyl)butan-2-ol (120h)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in mesitylene (**118a**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with (*S*)-2-methyloxirane (**112o´**, 23 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 85:15) afforded the title compound **120h** as a colorless oil (64 mg, 0.36 mmol, 90% yield, ee > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.85 (s, 3H), 3.91 – 3.77 (m, 1H), 2.75 – 2.56 (m, 2H), 2.32 (s, 6H), 1.86 – 1.70 (m, 2H), 1.58 (s, 1H), 1.25 (d, *J* = 6.2 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.1, 138.0 (2C), 127.6, 126.3 (2C), 67.7, 41.0, 32.1, 23.7, 21.4 (2C).

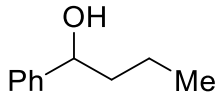
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3340, 3014, 2965, 2919, 2861, 1606, 1460, 1374, 1128, 1072, 840, 702.

MS (EI, 70 eV): *m/z* (%) = 145 (59), 120 (100), 119 (37), 117 (26), 115 (18), 105 (91), 91 (27).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{12}H_{18}O$]: 178.1358; found 178.1351.

Chiral HPLC: >99% *ee*, OD-H column, heptane:*i*-PrOH = 99.3:0.7, 1.0 mL/min, 30 °C.

1-phenylbutan-1-ol (120i)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in benzene (**118d**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 5.0 mL, t_{R2} = 100 s). Subsequently upon reaching the steady state, it was injected into a flask charged with butyraldehyde (**112p´**, 29 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 99:1 → 95:5) afforded the title compound **120i** as a colorless oil (44 mg, 0.29 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35 (d, *J* = 4.4 Hz, 4H), 7.31 – 7.24 (m, 1H), 4.68 (dd, *J* = 7.6, 5.8 Hz, 1H), 1.86 – 1.74 (m, 2H), 1.74 – 1.62 (m, 1H), 1.51 – 1.39 (m, 1H), 1.37 – 1.22 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H).

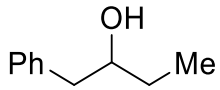
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.1, 128.6 (2C), 127.6, 126.0 (2C), 74.6, 41.4, 19.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3360, 2958, 2932, 2872, 1454, 1028, 762, 700.

MS (EI, 70 eV): *m/z* (%) = 107 (91), 79 (100), 77 (25).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{10}H_{14}O$]: 150.1045; found 150.1038.

1-phenylbutan-2-ol (120j)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in toluene (**118b**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with propionaldehyde (**112q´**, 23 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 90:10 → 80:20) afforded the title compound **120j** as a colorless oil (44 mg, 0.29 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.36 – 7.29 (m, 2H), 7.26 – 7.20 (m, 3H), 3.83 – 3.69 (m, 1H), 2.84 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.65 (dd, *J* = 13.6, 8.4 Hz, 1H), 1.68 – 1.41 (m, 3H), 1.00 (t, *J* = 7.4 Hz, 3H).

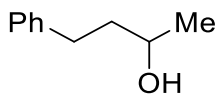
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 138.8, 129.6 (2C), 128.7 (2C), 126.6, 74.2, 43.7, 29.7, 10.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3378, 2956, 2932, 2871, 1495, 1454, 1123, 1080, 1026, 1015, 745, 738, 699.

MS (EI, 70 eV): *m/z* (%) = 103 (13), 92 (95), 91 (100).

HRMS (EI-orbitrap): *m/z:* [M – H] calc. for [$C_{10}H_{13}O$]: 149.0966; found 149.0961.

4-phenylbutan-2-ol (120k)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in toluene (**118b**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with

an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with 2-methyloxirane (**112r´**, 23 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 90:10 → 80:20) afforded the title compound **120k** as a colorless oil (40 mg, 0.27 mmol, 67% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 3.84 (h, *J* = 6.2 Hz, 1H), 2.82 – 2.61 (m, 2H), 1.82 – 1.74 (m, 2H), 1.48 (s, 1H), 1.24 (d, *J* = 6.2 Hz, 3H).

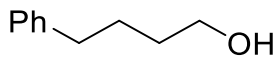
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.2, 128.5 (4C), 125.9, 67.6, 41.0, 32.3, 23.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3350, 3027, 2966, 2928, 2860, 1496, 1454, 1374, 1128, 1082, 1055, 954, 746, 698.

MS (EI, 70 eV): *m/z* (%) = 132 (26), 117 (100), 115 (18), 92 (17), 91 (55).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{10}H_{14}O$]: 150.1045; found 150.1038.

4-phenylbutan-1-ol (120l)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in toluene (**118b**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118b** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with oxetane (**112s´**, 23 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 80:20) afforded the title compound **120l** as a colorless oil (50 mg, 0.33 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 1.88 (s, 1H), 1.78 – 1.66 (m, 2H), 1.66 – 1.54 (m, 2H).

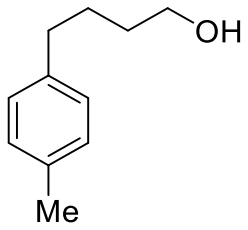
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.4, 128.5 (2C), 128.4 (2C), 125.8, 62.7, 35.7, 32.3, 27.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3324, 3025, 2934, 2858, 1603, 1495, 1452, 1058, 1029, 982, 936, 745, 696.

MS (EI, 70 eV): *m/z* (%) = 132 (23), 117 (30), 115 (15), 104 (100), 91 (75), 78 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{10}H_{14}O$]: 150.1045; found 150.1039.

4-(p-tolyl)butan-1-ol (120m)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in *p*-xylene (**118c**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118c** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with oxetane (**112s´**, 23 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 80:20) afforded the title compound **120m** as a colorless oil (51 mg, 0.31 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.10 (s, 4H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.62 (t, *J* = 7.4 Hz, 2H), 2.33 (s, 3H), 1.76 – 1.49 (m, 5H).

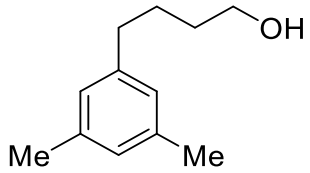
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.3, 135.3, 129.1 (2C), 128.4 (2C), 62.9, 35.3, 32.4, 27.8, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3327, 2933, 2931, 2928, 2858, 1515, 1453, 1058, 1032, 1021, 805.

MS (EI, 70 eV): *m/z* (%) = 164 (20), 146 (19), 131 (43), 129 (14), 128 (11), 119 (10), 118 (100), 117 (47), 115 (22), 105 (83), 103 (16), 91 (26), 79 (15), 77 (10), 45 (11), 44 (91, 43 (15), 42 (24).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{11}H_{16}O$]: 164.1201; found 164.1194.

4-(3,5-dimethylphenyl)butan-1-ol (120n)

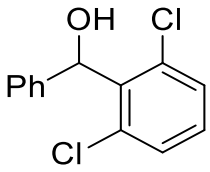


According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in mesitylene (**118a**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118a** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 23.0 mL, t_{R2} = 460 s). Subsequently upon reaching the steady state, it was injected into a flask charged with oxetane (**112s´**, 23 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 80:20) afforded the title compound **120n** as a colorless oil (48 mg, 0.27 mmol, 67% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.84 (s, 1H), 6.82 (s, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.30 (s, 6H), 1.74 – 1.55 (m, 4H), 1.43 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.4, 137.9 (2C), 127.5, 126.4 (2C), 63.0, 35.6, 32.6, 27.7, 21.4 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3326, 3014, 2934, 2920, 2859, 1606, 1460, 1376, 1062, 1037, 985, 843, 701.
MS (EI, 70 eV): *m/z* (%) = 178 (10), 160 (43), 145 (52), 132 (45), 120 (11), 119 (100), 117 (37), 115 (16), 107 (13), 105 (27), 91 (33).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{12}H_{18}O$]: 178.1358; found 178.1351.

(2,6-dichlorophenyl)(phenyl)methanol (120o)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in benzene (**118d**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 5.0 mL, t_{R2} = 100 s). Subsequently upon reaching the steady state, it was injected into a flask charged with 2,6-dichlorobenzaldehyde (**112i**, 70 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 99:1 → 95:5) afforded the title compound **120o** as a colorless oil (76 mg, 0.30 mmol, 75% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.38 – 7.27 (m, 7H), 7.22 (dd, *J* = 8.6, 7.5 Hz, 1H), 6.66 (d, *J* = 10.9 Hz, 1H), 3.43 (d, *J* = 10.9 Hz, 1H).

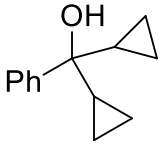
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.6, 137.9, 135.3, 129.6 (2C), 129.5 (2C), 128.4 (2C), 127.4, 125.5 (2C), 72.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3566, 3428, 1579, 1562, 1494, 1449, 1436, 1178, 1089, 1037, 1023, 829, 827, 779, 767, 737, 697.

MS (EI, 70 eV): *m/z* (%) = 254 (19), 252 (30), 251 (10), 199 (27), 176 (10), 175 (12), 175 (63), 173 (100), 165 (10), 163 (10), 152 (15), 146 (11), 79 (14), 78 (22), 77 (10).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{13}H_{10}Cl_2O$]: 252.0109; found 252.0101.

dicyclopropyl(phenyl)methanol (120p)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in benzene (**118d**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was

pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 5.0 mL, t_{R2} = 100 s). Subsequently upon reaching the steady state, it was injected into a flask charged with dicyclopropylmethanone (**112u**, 44 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 95:5) afforded the title compound **120p** as a colorless oil (69 mg, 0.37 mmol, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.66 – 7.54 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.21 (m, 1H), 1.47 (s, 1H), 1.25 – 1.15 (m, 2H), 0.69 – 0.47 (m, 4H), 0.46 – 0.26 (m, 4H).

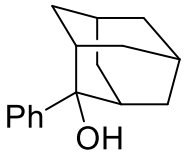
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.3, 127.9 (2C), 126.8, 125.9 (2C), 73.9, 20.8 (2C), 2.1 (2C), 0.3 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3583, 3471, 3086, 3008, 1492, 1446, 1317, 1154, 1025, 995, 970, 916, 870, 851, 823, 780, 753, 699, 680.

MS (EI, 70 eV): *m/z* (%) = 160 (53), 159 (39), 155 (14), 147 (53), 146 (10), 145 (100), 142 (13), 141 (23), 131 (17), 129 (19), 128 (24), 127 (10), 118 (31), 117 (33), 115 (31), 105 (99), 91 (22), 90 (12), 77 (26).

HRMS (EI-orbitrap): *m/z:* [M – H] calc. for [$C_{13}H_{15}O$]: 187.1123; found 187.1115.

2-phenyladamantan-2-ol (120q)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in benzene (**118d**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 5.0 mL, t_{R2} = 100 s). Subsequently upon reaching the steady state, it was injected into a flask charged with adamantanone (**112h**, 60 mg, 0.40 mmol, 1.0 equiv) in

THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 95:5) afforded the title compound **120q** as a colorless solid (87 mg, 0.38 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.60 – 7.48 (m, 2H), 7.43 – 7.33 (m, 2H), 7.32 – 7.24 (m, 1H), 2.58 (s, 2H), 2.47 – 2.35 (m, 2H), 1.91 (p, *J* = 3.1 Hz, 1H), 1.79 – 1.65 (m, 9H), 1.52 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.5, 128.9 (2C), 127.5, 125.6 (2C), 75.8, 37.8, 35.8 (2C), 35.0 (2C), 33.1 (2C), 27.6, 27.1.

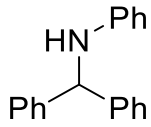
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3354, 2909, 2854, 1449, 1102, 1043, 1005, 998, 969, 937, 914, 767, 697.

MS (EI, 70 eV): *m/z* (%) = 228 (24), 211 (16), 210 (100), 185 (22), 168 (11) 167 (15), 155 (10), 151 (14), 150 (19), 129 (10), 128 (10), 117 (10), 115 (14), 105 (79), 92 (11), 91 (21), 80 (11), 79 (28), 77 (26).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{20}O$]: 228.1514; found 228.1504.

m.p. (°C): 79.7 – 81.6.

N-benzhydrylaniline (120r)



According to **TP12,** solutions of TMEDA (0.4 M, 2.0 equiv) in benzene (**118d**) and 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane were prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. The solution of **118d** was pumped by pump B (flow rate: 1.0 mL/min) through a precooling loop (V_{pre3} = 2.00 mL), at 25 °C. The solutions were mixed with an overall flow rate of 3.0 mL/min in a T-shaped mixer. The combined stream passed through a tube reactor connected to a metal needle (V_{R2} = 5.0 mL, t_{R2} = 100 s). Subsequently upon reaching the steady state, it was injected into a flask charged with *N*,1-diphenylmethanimine (**112c´**, 72 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) at –20 °C for 2 min. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added to quench the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column

chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 95:5) afforded the title compound **120r** as a yellow resin (96 mg, 0.37 mmol, 93% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.34 (m, 8H), 7.34 – 7.28 (m, 2H), 7.20 – 7.14 (m, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.63 – 6.57 (m, 2H), 5.56 (s, 1H), 4.28 (s, 1H).

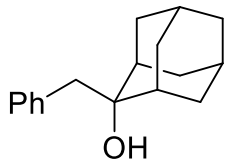
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.5, 143.0 (2C), 129.2 (2C), 128.9 (4C), 127.6 (4C), 127.5 (2C), 117.8, 113.6 (2C), 63.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3410, 3058, 3053, 3026, 1600, 1586, 1501, 1451, 1426, 1314, 1267, 1028, 747, 699.

MS (EI, 70 eV): *m/z* (%) = 168 (13), 167 (100), 165 (39), 152 (23).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{19}H_{17}N$]: 259.1361; found 259.1356.

2-benzyladamantan-2-ol (120s)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in toluene (**118b**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of adamantanone (**112h**, 60 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 80:20) afforded the title compound **120s** as a colorless solid (90 mg, 0.37 mmol, 93% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.29 (m, 2H), 7.29 – 7.22 (m, 3H), 3.02 (s, 2H), 2.25 – 2.05 (m, 4H), 1.99 – 1.90 (m, 1H), 1.87 – 1.76 (m, 3H), 1.76 – 1.65 (m, 4H), 1.59 – 1.49 (m, 2H), 1.41 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.4, 130.8 (2C), 128.4 (2C), 126.6, 74.8, 44.0, 38.6, 37.0 (2C), 34.8 (2C), 33.1 (2C), 27.7, 27.5.

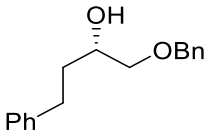
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3544, 3499, 3027, 2898, 2852, 1602, 1493, 1451, 1352, 1282, 1196, 1184, 1157, 1149, 1114, 1100, 1082, 1022, 1006, 987, 962, 930, 891, 879, 868, 778, 760, 700, 667.

MS (EI, 70 eV): *m/z* (%) = 225 (18), 224 (100), 223 (24), 181 (18), 167 (42), 166 (12), 165 (26), 155 (10), 153 (17), 152 (10), 151 (98), 150 (15), 142 (14), 141 (27), 133 (14), 129 (35), 128 (28), 117 (11), 115 (23), 105 (15), 91 (85), 79 (24), 77 (12).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{17}H_{20}$]: 224.1565; found 224.1562.

m.p. (°C): 61.7 – 63.4.

(*S*)-1-(benzyloxy)-4-phenylbutan-2-ol (120t)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in toluene (**118b**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (*S*)-2-((benzyloxy)methyl)oxirane (**112t´**, 66 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 85:15) afforded the title compound **120t** as a colorless oil (85 mg, 0.33 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41 – 7.26 (m, 7H), 7.21 (d, *J* = 7.4 Hz, 3H), 4.56 (s, 2H), 3.85 (t, *J* = 7.6 Hz, 1H), 3.52 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.37 (dd, *J* = 9.4, 7.7 Hz, 1H), 2.89 – 2.77 (m, 1H), 2.75 – 2.63 (m, 1H), 2.45 (s, 1H), 1.88 – 1.64 (m, 2H).

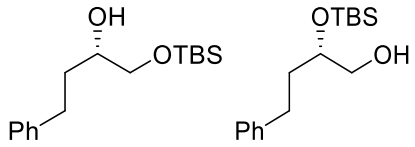
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.0, 138.0, 128.6 (4C), 128.5 (2C), 127.9, 127.9 (2C), 126.0, 74.7, 73.5, 69.8, 34.9, 31.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3442, 3062, 3027, 2922, 2859, 1603, 1495, 1453, 1365, 1310, 1258, 1207, 1155, 1118, 1088, 1075, 1028, 1002, 942, 908, 737, 696.

MS (EI, 70 eV): *m/z* (%) = 105 (39), 92 (23), 91 (100).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{20}O$]: 256.1463; found 256.1473.

(*S*)-1-((tert-butyldimethylsilyl)oxy)-4-phenylbutan-2-ol and (*S*)-2-((tert-butyldimethylsilyl)oxy)-4-phenylbutan-1-ol (120u)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in toluene (**118b**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (*S*)-tert-butyldimethyl(oxiran-2-ylmethoxy)silane (**112u´**, 75 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 97:3 → 90:10) afforded the title compounds as colorless oils (*S*)-1-((tert-butyldimethylsilyl)oxy)-4-phenylbutan-2-ol (86 mg, 0.31 mmol, 76% yield) and (*S*)-2-((tert-butyldimethylsilyl)oxy)-4-phenylbutan-1-ol (20 mg, 0.07 mmol, 18%). Combined yield: 106 mg, 0.38 mmol, 94%.

(*S*)-1-((tert-butyldimethylsilyl)oxy)-4-phenylbutan-2-ol

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.27 (m, 2H), 7.20 (dd, *J* = 14.3, 7.1 Hz, 3H), 3.72 – 3.58 (m, 2H), 3.43 (dd, *J* = 9.7, 7.2 Hz, 1H), 2.84 (ddd, *J* = 15.2, 9.6, 5.6 Hz, 1H), 2.70 (ddd, *J* = 13.8, 9.5, 7.1 Hz, 1H), 2.48 (s, 1H), 1.83 – 1.64 (m, 2H), 0.91 (s, 9H), 0.08 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.2, 128.6 (2C), 128.5 (2C), 126.0, 71.2, 67.3, 34.6, 32.0, 26.0, 18.4 (3C), -5.2, -5.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2929, 2884, 2857, 1255, 1113, 1044, 835, 776, 698.
MS (EI, 70 eV): *m/z* (%) = 131 (100), 91 (24), 75 (40), 73 (19).

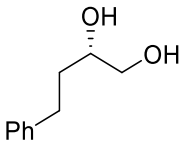
HRMS (EI-orbitrap): *m/z:* [M – CH_3 and – H_2O] calc. for [$C_{15}H_{23}OSi$]: 247.1518; found 247.1474.

(*S*)-2-((tert-butyldimethylsilyl)oxy)-4-phenylbutan-1-ol

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 3.85 – 3.73 (m, 1H), 3.62 (dt, *J* = 11.2, 4.3 Hz, 1H), 3.53 (dt, *J* = 10.8, 5.2 Hz, 1H), 2.72 – 2.56 (m, 2H), 1.95 – 1.78 (m, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.2, 128.5 (2C), 128.4 (2C), 126.0, 72.5, 66.3, 35.9, 31.8, 26.0, 18.2 (3C), -4.3, -4.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3399, 3028, 2953, 2929, 2884, 2857, 2359, 2343, 2332, 1496, 1472, 1462, 1456, 1388, 1374, 1361, 1255, 1113, 1044, 1004, 986, 979, 835, 811, 776, 748, 698, 668.
MS (EI, 70 eV): *m/z* (%) = 131 (100), 91 (24), 75 (40), 73 (19).

HRMS (EI-orbitrap): *m/z:* [M – CH_2OH] calc. for [$C_{15}H_{25}OSi$]: 249.1675; found 249.1705.

(S)-4-phenylbutane-1,2-diol (152u)



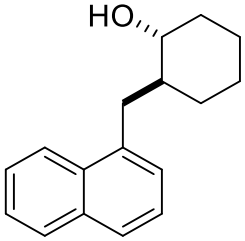
According to the literature[430] TBAF (1.0 M in THF, 2.0 mL) was added to a regioisomeric mixture of **120u** and **120u´** (90 mg, 0.32 mmol, 1.0 equiv), the mixture was stirred for 2.5 h at 25 °C. EtOAc (20 mL) was added to the mixture and the organic layer was washed with Brine (2x20 mL). The organic layer was dried over $MgSO_4$. The crude mixture was purified by flash column chramotography (silica gel, pentane:EtOAc = 88:12 → 85:15) to afforded the title compound **152u** as a colorless oil (50 mg, 0.30 mmol, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.23 (m, 2H), 7.20 (d, *J* = 7.3 Hz, 3H), 3.78 – 3.67 (m, 1H), 3.63 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.45 (dd, *J* = 11.1, 7.6 Hz, 1H), 3.01 – 2.62 (m, 4H), 1.84 – 1.64 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.8, 128.6 (2C), 128.5 (2C), 126.1, 71.7, 66.9, 34.7, 31.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3334, 2927, 2862, 1496, 1454, 1098, 1067, 1038, 1032, 748, 698.
MS (EI, 70 eV): *m/z* (%) = 130 (15), 117 (51), 115 (13), 104 (16), 92 (11), 91 (100).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{10}H_{12}O$]: 148.0888; found 148.0882.

[430] M. Akehi, M. Kawamoto, T. Mandai, *Tetrahedron*. **2015**, *71*, 6488 6498.

***trans*-2-(naphthalen-1-ylmethyl)cyclohexan-1-ol (120v)**



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 1 min into a flask charged with a solution of TMEDA (0.40 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 28 mg, 0.20 mmol, 1.0 equiv) in hexane (1.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 2.0 equiv) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 80:20) afforded the title compound **120v** as a colorless solid (44 mg, 0.18 mmol, 92% yield).

According to **TP15**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 142 mg, 1.00 mmol, 2.5 equiv) in hexane (1.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 85:15) afforded the title compound **120v** as a colorless solid (94 mg, 0.39 mmol, 98% yield).

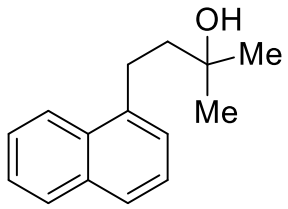
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.44 (m, 2H), 7.43 – 7.36 (m, 1H), 7.31 (d, *J* = 6.6 Hz, 1H), 3.91 (dd, *J* = 13.5, 3.4 Hz, 1H), 3.52 – 3.38 (m, 1H), 2.62 – 2.51 (m, 1H), 2.11 – 1.96 (m, 1H), 1.80 – 1.59 (m, 4H), 1.59 – 1.49 (m, 1H), 1.38 – 1.22 (m, 2H), 1.06 – 0.92 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 134.1, 132.3, 128.8, 127.6, 126.8, 125.8, 125.5, 125.4, 124.6, 75.5, 46.4, 36.6, 36.1, 30.7, 25.5, 25.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3375, 3306, 2935, 2918, 2894, 2882, 2854, 1509, 1449, 1442, 1393, 1360, 1126, 1064, 1047, 1026, 1014, 930, 875, 798, 776, 766.
MS (EI, 70 eV): *m/z* (%) = 240 (13), 179 (10), 165 (36), 153 (16), 152 (10), 143 (12), 142 (100), 141 (76), 115 (25).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{17}H_{20}O$]: 240.1514; found 240.1508.

m.p. (°C): 83.8 – 85.6.

2-methyl-4-(naphthalen-1-yl)butan-2-ol (120w)



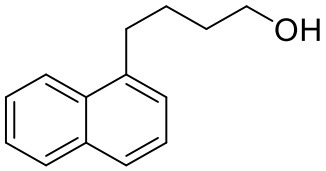
According to **TP14**, A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 56 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of 2,2-dicyclopropylmethanone (**112u**, 88 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 80:20) afforded the title compound **120w** as a colorless oil (75 mg, 0.35 mmol, 87% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.09 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.46 (m, 2H), 7.45 – 7.39 (m, 1H), 7.37 (d, *J* = 6.3 Hz, 1H), 3.26 – 3.11 (m, 2H), 1.98 – 1.85 (m, 2H), 1.52 (s, 1H), 1.39 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 138.8, 134.0, 131.9, 128.9, 126.7, 125.9, 125.9, 125.8, 125.6, 123.8, 71.2, 45.0, 29.4 (2C), 27.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3385, 2968, 1597, 1510, 1467, 1396, 1376, 1364, 1279, 1217, 1165, 1150, 1121, 927, 911, 801, 781.
MS (EI, 70 eV): *m/z* (%) = 196 (29), 182 (15), 181 (100), 166 (23), 165 (17), 153 (36), 152 (11), 141 (68), 128 (10), 115 (23).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{18}O$]: 214.1358; found 214.1351.

4-(naphthalen-1-yl)butan-1-ol (120x)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 1 min into a flask charged with a solution of TMEDA (0.40 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 28 mg, 0.20 mmol, 1.0 equiv) in hexane (1.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of oxetane (**112s´**, 23 mg, 0.40 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 75:25) afforded the title compound **120x** as a colorless oil (27 mg, 0.14 mmol, 68% yield).

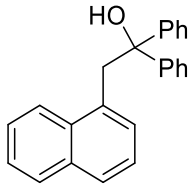
According to **TP15**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 142 mg, 1.00 mmol, 2.5 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of oxetane (**112s´**, 23 mg, 0.40 mmol, 2.0 equiv) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After

removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 75:25) afforded the title compound **120x** as a colorless solid (55 mg, 0.27 mmol, 69% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 8.4, 1.4 Hz, 1H), 7.93 – 7.82 (m, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.45 (m, 2H), 7.45 – 7.37 (m, 1H), 7.34 (d, *J* = 6.8 Hz, 1H), 3.68 (t, *J* = 6.5 Hz, 2H), 3.17 – 3.05 (m, 2H), 1.90 – 1.79 (m, 2H), 1.75 – 1.65 (m, 2H), 1.48 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 138.5, 134.0, 131.9, 128.9, 126.7, 126.1, 125.8, 125.6, 125.5, 123.9, 62.9, 32.9, 32.8, 27.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3327, 3045, 2934, 2863, 1596, 1510, 1462, 1395, 1354, 1261, 1166, 1056, 1029, 1011, 978, 796, 788, 774, 732.
MS (EI, 70 eV): *m/z* (%) = 200 (25), 167 (11), 154 (30), 153 (18), 142 (12), 141 (100), 115 (32).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{16}O$]: 200.1201; found 200.1195.

2-(naphthalen-1-yl)-1,1-diphenylethan-1-ol (120y)



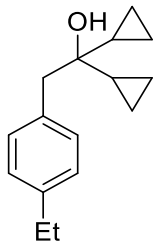
According to **TP15**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 142 mg, 1.00 mmol, 2.5 equiv) in hexane (1.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of benzophenone (**112a´**, 73 mg, 0.40 mmol, 2.0 equiv) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 99:1 → 95:5) afforded the title compound **120y** as a colorless oil (105 mg, 0.32 mmol, 81% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.08 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.93 – 7.83 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.43 (m, 6H), 7.40 – 7.34 (m, 4H), 7.34 – 7.27 (m, 3H), 7.01 – 6.89 (m, 1H), 4.22 (s, 2H), 2.43 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 146.9 (2C), 133.9, 133.7, 132.0, 129.4, 128.7, 128.2 (4C), 127.6, 127.1 (2C), 126.4, 126.0 (4C), 125.5, 125.1, 124.6, 78.9, 43.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3560, 3056, 1597, 1510, 1493, 1447, 1397, 1341, 1265, 1165, 1057, 1032, 1020, 1002, 944, 799, 781, 772, 756, 736, 698, 662.
MS (EI, 70 eV): *m/z* (%) = 184 (15), 183 (62), 183 (100), 183 (42), 142 (64), 141 (18), 115 (10), 105 (88), 77, (35).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{24}H_{20}O$]: 324.1514; found 324.1506.

1,1-dicyclopropyl-2-(4-ethylphenyl)ethan-1-ol (120z)



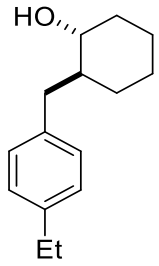
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 1 min into a flask charged with a solution of TMEDA (0.40 mmol, 2.0 equiv) and 4-ethyltoluene (**118f**, 24 mg, 0.20 mmol, 1.0 equiv) in hexane (1.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of 2,2-dicyclopropylmethanone (**112u**, 44 mg, 0.40 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 98:2 → 95:5) afforded the title compound **120z** as a colorless oil (43 mg, 0.19 mmol, 93% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.22 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 2.85 (s, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H), 0.92 (s, 1H), 0.84 – 0.71 (m, 2H), 0.45 – 0.31 (m, 6H), 0.31 – 0.19 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.3, 134.8, 130.9 (2C), 127.5 (2C), 71.1, 48.3, 28.6, 18.5 (2C), 15.8, 1.2 (2C), -0.3 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3588, 3484, 3086, 3049, 3008, 2962, 2925, 2871, 2855, 2360, 2342, 1514, 1463, 1458, 1437, 1420, 1376, 1320, 1247, 1181, 1122, 1045, 1022, 996, 929, 914, 821.

MS (EI, 70 eV): *m/z* (%) = 212 (16). 197 (20), 184 (12), 183 (82), 171 (51), 169 (36), 168 (19), 167 (23), 165 (22), 156 (12), 155 (92), 154 (23), 153 (51), 152 (25), 143 (33), 142 (20), 132 (12), 131 (100), 129 (31), 128 (48), 119 (13), 117 (20), 115 (38), 91 (45), 78 (11).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{16}H_{20}$]: 212.1565; found 212.1559.

***trans*-2-(4-ethylbenzyl)cyclohexan-1-ol (120aa)**



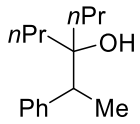
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 1 min into a flask charged with a solution of TMEDA (0.40 mmol, 2.0 equiv) and 4-ethyltoluene (**118f**, 24 mg, 0.20 mmol, 1.0 equiv) in hexane (1.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of 2,2-cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 80:20) afforded the title compound **120aa** as colorless solid (41 mg, 0.19 mmol, 94% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.11 (s, 4H), 3.36 – 3.23 (m, 1H), 3.12 (dd, *J* = 13.3, 4.1 Hz, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.34 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.76 – 1.43 (m, 5H), 1.33 – 1.18 (m, 5H), 1.09 (qt, *J* = 12.6, 3.5 Hz, 1H), 0.98 – 0.84 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.8, 138.0, 129.5 (2C), 127.8 (2C), 74.8, 47.2, 38.8, 35.9, 30.2, 28.6, 25.6, 25.0, 15.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3350, 2963, 2926, 2855, 2360, 2342, 1740, 1735, 1456, 1448, 1031.
MS (EI, 70 eV): *m/z* (%) = 201 (11), 200 (71), 172 (14), 171 (100), 143 (20), 132 (34), 129 (54), 128 (12), 120 (27), 119 (85), 117 (58), 115 (22), 105 (61), 91 (67), 71 (11), 79 (18).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{22}O$]: 218.1671; found 218.1664.

m.p. (°C): 63.6 – 65.5.

4-(1-phenylethyl)heptan-4-ol (120ab)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in ethylbenzene (**118g**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of heptan-4-one (**112v´**, 46 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 98:2 → 95:5) afforded the title compound **120ab** as a colorless oil (54 mg, 0.25 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.30 (m, 2H), 7.30 – 7.21 (m, 3H), 2.88 (q, *J* = 7.2 Hz, 1H), 1.61 – 1.47 (m, 2H), 1.39 – 1.26 (m, 8H), 1.25 – 1.15 (m, 1H), 1.10 (s, 1H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H).

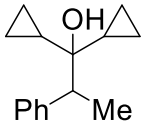
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.8, 129.3 (2C), 128.2 (2C), 126.5, 75.8, 46.3, 39.9, 38.1, 17.1, 16.8, 15.5, 14.9, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3478, 3027, 2957, 2934, 2873, 1494, 1453, 1378, 1343, 1287, 1132, 1097, 1008, 997, 981, 952, 908, 846, 775, 723, 702.

MS (EI, 70 eV): *m/z* (%) = 177 (30), 117 (14), 115 (100), 106 (18), 105 (23), 97 (15), 91 (46), 79 (11), 77 (11), 73 (16), 55 (24).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{15}H_{22}$]: 202.1722; found 202.1715.

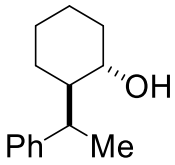
1,1-dicyclopropyl-2-phenylpropan-1-ol (120ac)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in ethylbenzene (**118g**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of dicyclopropylmethanone (**112u**, 44 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 98:2) afforded the title compound **120ac** as a colorless oil (48 mg, 0.22 mmol, 55% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.38 – 7.32 (m, 2H), 7.31 – 7.26 (m, 2H), 7.25 – 7.19 (m, 1H), 3.01 (q, *J* = 7.3 Hz, 1H), 1.47 (d, *J* = 7.3 Hz, 3H), 0.95 – 0.86 (m, 1H), 0.85 (s, 1H), 0.73 – 0.64 (m, 1H), 0.41 – 0.16 (m, 8H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.5, 129.6 (2C), 127.8 (2C), 126.4, 72.3, 51.2, 17.2, 16.4, 15.9, 1.7, 1.1, -0.4, -0.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3585, 3085, 3025, 3007, 2936, 1494, 1452, 1373, 1288, 1181, 1021, 990, 969, 928, 913, 764, 702.
MS (EI, 70 eV): *m/z* (%) = 183 (12), 155 (17), 153 (11), 142 (10), 141 (29), 129 (19), 128 (20), 115 (18), 111 (100), 105 (35), 103 (14), 91 (27), 79 (20), 77 (21), 69 (98).
HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{15}H_{18}$]: 198.1409; found 198.1402.

***t*rans-(1-phenylethyl)cyclohexan-1-ol (120ad) mixture of diastereoisomeres**



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**)

by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in ethylbenzene (**118g**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 80:20) afforded the title compound **120ad** as a colorless oil (58 mg, 0.28 mmol, 71% yield, d.r. = 2:1).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30 – 7.20 (m, 4H), 7.19 – 7.14 (m, 1H), 3.48 – 3.41 (m, 1H), 3.12 – 3.04 (m, 1H), 1.91 – 1.84 (m, 1H), 1.83 – 1.76 (m, 1H), 1.63 – 1.36 (m, 4H) 1.31 (d, *J* = 7.4 Hz, 3H), 1.27 – 1.19 (m, 1H), 1.15 – 0.97 (m, 2H), 0.74 – 0.63 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.7, 128.9 (2C), 127.8 (2C), 126.0, 71.6, 49.3, 37.8, 36.3, 25.7, 25.0, 24.7, 18.5.

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30 – 7.20 (m, 4H), 7.19 – 7.14 (m, 1H), 3.48 – 3.41 (m, 1H), 3.35 – 3.28 (m, 1H), 2.00 – 1.93 (m, 1H), 1.70 – 1.65 (m, 1H), 1.63 – 1.36 (m, 4H), 1.27 – 1.19 (m, 5H), 1.15 – 0.97 (m, 2H),

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 146.5, 128.2 (2C), 128.0 (2C), 125.9, 72.3, 51.5, 38.3, 35.5, 25.5, 25.0, 24.6, 13.8.

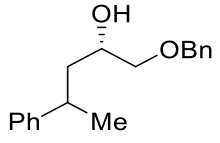
Mixture:

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3343, 3028, 2962, 2929, 2856, 1494, 1451, 1378, 1053, 1024, 975, 843, 769, 748, 702.

MS (EI, 70 eV): *m/z* (%) = 186 (54), 171 (28), 157 (14), 144 (22), 143 (26), 129 (33), 128 (13), 118 (29), 117 (26), 115 (25), 106 (49), 105 (100), 104 (10), 103 (19), 91 (96), 81 (26), 79 (39), 78 (11), 77 (22).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{14}H_{18}$]: 186.1409; found 186.1401.

(2*S*)-1-(benzyloxy)-4-phenylpentan-2-ol (120ae) mixture of diastereoisomeres



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in ethylbenzene (**118g**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (S)-2-((benzyloxy)methyl)oxirane (**112t´**, 66 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 80:20) afforded the title compound **120ae** as a colorless oil (66 mg, 0.24 mmol, 61% yield d.r. = 1.15:1).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 – 7.28 (m, 7H), 7.25 – 7.18 (m, 3H), 4.49 (s, 2H) 3.60 – 3.54 (m, 1H), 3.40 – 3.31 (m, 1H), 3.30 – 3.24 (m, 1H), 3.12 – 3.00 (m, 1H), 2.41 – 2.27 (m, 1H), 1.89 – 1.56 (m, 2H), 1. 30 (d, *J* = 7.0 Hz, 3H)

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 – 7.28 (m, 7H), 7.25 – 7.18 (m, 3H), 4.55 (s, 2H), 3.90 – 3.80 (m, 1H), 3.52 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.40 – 3.31 (m, 1H), 2.99 – 2.88 (m, 1H), 2.41 – 2.27 (m, 1H), 1.89 – 1.56 (m, 2H), 1.29 (d, *J* = 6.9 Hz, 3H).

Mixture:

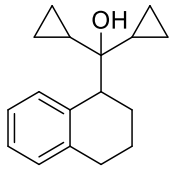
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.5, 146.6, 138.0, 138.0, 128.6 (2C), 128.6 (2C), 128.5 (2C), 128.5 (2C), 127.9, 127.9 (2C), 127.9, 127.8 (2C), 127.3 (2C), 127.0 (2C), 126.2, 126.2, 75.1, 74.6, 73.4, 73.4, 68.5, 68.5, 41.6, 41.6, 36.2, 36.0, 23.3, 21.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3441, 3028, 2927, 2866, 1494, 1453, 1365, 1308, 1205, 1087, 1076, 1028, 1012, 952, 907, 850, 763, 737, 698.

MS (EI, 70 eV): *m/z* (%) = 119 (70), 106 (20), 105 (53), 105 (53), 105 (85), 105 (92), 105 (49), 105 (49), 92 (18), 91 (100), 79 (12), 77 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{18}H_{22}O_2$]: 270.1620; found 270.1614.

dicyclopropyl(1,2,3,4-tetrahydronaphthalen-1-yl)methanol (120af)

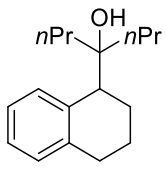


According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and tetralin (**118h**, 53 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of dicyclopropylmethanone (**112u**, 88 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 98:2) afforded the title compound **120af** as a colorless oil (50 mg, 0.21 mmol, 52% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 – 7.50 (m, 1H), 7.12 (dd, *J* = 9.3, 7.0 Hz, 3H), 3.16 (dd, *J* = 7.5, 5.7 Hz, 1H), 2.83 – 2.65 (m, 2H), 2.16 – 1.98 (m, 3H), 1.62 – 1.49 (m, 1H), 1.02 (s, 1H), 0.88 (tt, *J* = 8.3, 5.6 Hz, 1H), 0.75 (tt, *J* = 8.5, 5.6 Hz, 1H), 0.60 – 0.50 (m, 1H), 0.50 – 0.33 (m, 4H), 0.32 – 0.19 (m, 2H), 0.17 – 0.05 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.4, 137.4, 131.6, 128.7, 125.8, 125.0, 74.2, 48.6, 30.5, 25.2, 22.1, 17.4, 16.2, 3.3, 1.8, -0.2, -1.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3083, 3009, 2931, 2891, 2862, 1489, 1450, 1436, 1427, 1377, 1308, 1286, 1263, 1208, 1178, 1160, 1122, 1080, 1020, 986, 939, 926, 913, 890, 831, 762, 745.
MS (EI, 70 eV): *m/z* (%) = 131 (24), 129 (20), 128 (17), 115 (21), 111 (100), 91 (25), 69 (76).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{17}H_{22}O$]: 242.1671; found 242.1664.

4-(1,2,3,4-tetrahydronaphthalen-1-yl)heptan-4-ol (120ag)



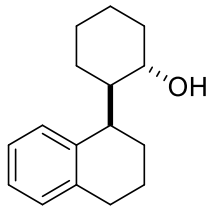
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and tetralin (**118h**, 53 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture

was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of heptan-4-one (**112v´**, 92 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **120ag** as a colorless oil (53 mg, 0.22 mmol, 54% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 – 7.27 (m, 1H), 7.18 – 7.07 (m, 3H), 3.05 – 2.96 (m, 1H), 2.83 – 2.66 (m, 2H), 2.21 – 2.07 (m, 1H), 1.93 – 1.76 (m, 2H), 1.61 – 1.25 (m, 9H), 1.10 (s, 1H), 0.95 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.5, 137.0, 131.2, 129.2, 126.1, 125.0, 77.5, 44.4, 40.3, 37.8, 29.7, 25.0, 21.2, 16.9, 16.8, 14.9, 14.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2931, 2871, 1490, 1455, 1378, 1294, 1152, 1136, 994, 976, 740.
MS (EI, 70 eV): *m/z* (%) = 199 (12), 185 (18), 157 (38), 141 (14), 132 (33), 131 (43), 130 (19), 130 (11), 129 (100), 128 (53), 117 (12), 115 (18), 115 (31), 104 (36), 91 (30), 55 (13).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{17}H_{24}$]: 228.1878; found 228.1871.

***trans*-2-(1,2,3,4-tetrahydronaphthalen-1-yl)cyclohexan-1-ol (120ah) mixture of diastereoisomers**



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and tetralin (**118h**, 53 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 79 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the

solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 85:15) afforded the title compound **120ah** as a colorless oil (52 mg, 0.33 mmol, 56% yield, d.r. = 1.2:1).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31 (d, *J* = 7.6 Hz, 1H), 7.17 – 7.04 (m, 3H), 3.72 – 3.56 (m, 1H), 3.13 – 3.03 (m, 1H), 2.86 – 2.64 (m, 2H), 2.03 – 1.84 (m, 4H), 1.84 – 1.74 (m, 1H), 1.73 – 1.57 (m, 4H), 1.29 – 1.18 (m, 4H), 1.16 – 1.04 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.6, 138.2, 129.5, 128.9, 125.8, 125.7, 73.1, 51.0, 39.8, 36.3, 30.4, 30.0, 26.5, 26.3, 24.9, 22.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3371, 2926, 2856, 1491, 1449, 1052, 1037, 1013, 767, 740.
MS (EI, 70 eV): *m/z* (%) = 212 (22), 132 (18), 131 (100), 130 (33), 129 (22), 128 (14), 91 (16), 57 (13).

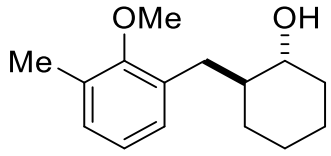
HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{22}O$]: 230.1671; found 230.1674.

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26 (d, *J* = 7.7 Hz, 1H), 7.17 – 7.03 (m, 3H), 3.61 (td, *J* = 10.1, 4.2 Hz, 1H), 3.47 – 3.38 (m, 1H), 2.70 (dd, *J* = 7.7, 4.5 Hz, 2H), 2.11 – 2.03 (m, 1H), 2.01 – 1.89 (m, 4H), 1.73 – 1.57 (m, 4H), 1.29 – 1.18 (m, 4H), 1.07 – 0.93 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.6, 139.0, 129.1, 127.2, 125.9, 125.1, 71.6, 50.1, 36.7, 36.7, 30.6, 26.1, 25.4, 25.1, 23.7, 22.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3355, 2928, 2856, 1492, 1450, 1062, 1034, 762, 739.
MS (EI, 70 eV): *m/z* (%) = 213 (18), 212 (91), 207 (23), 184 (20), 183 (11), 170 (10), 169 (19), 165 (10), 155 (12), 145 (10), 144 (49), 143 (16), 142 (15), 141 (25), 132 (51), 130 (100), 129 (74), 128 (74), 128 (57), 127 (14), 117 (17), 116 (27), 115 (34), 103 (21), 97 (15), 91 (63), 83 (14), 77 (14), 71 (17), 67 (11), 57 (30), 55 (21), 44 (67), 43 (23), 43 (43), 41 (32).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{22}O$]: 230.1671; found 230.1669.

***trans*-2-(2-methoxy-3-methylbenzyl)cyclohexan-1-ol (120ai)**



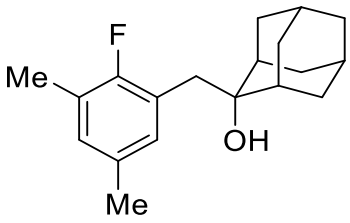
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently

upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-methoxy-1,3-dimethylbenzene (**118i**, 54 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 79 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 80:20) afforded the title compound **120ai** as a colorless oil (62 mg, 0.26 mmol, 66% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.05 (d, *J* = 6.9 Hz, 1H), 7.01 – 6.92 (m, 2H), 3.75 (s, 3H), 3.18 (s, 1H), 3.13 – 3.03 (m, 1H), 2.86 – 2.72 (m, 2H), 2.31 (s, 3H), 1.95 (d, *J* = 12.7 Hz, 1H), 1.73 – 1.62 (m, 2H), 1.62 – 1.48 (m, 2H), 1.34 – 1.19 (m, 1H), 1.18 – 0.94 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.9, 132.6, 130.9, 129.6, 129.5, 124.0, 73.4, 60.6, 46.7, 35.0, 32.7, 30.5, 25.8, 25.1, 16.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3414, 2925, 2855, 1469, 1448, 1422, 1259, 1213, 1167, 1086, 1068, 1059, 1031, 1013, 810, 767.
MS (EI, 70 eV): *m/z* (%) = 216 (20), 201 (13), 185 (10), 137 (10), 136 (100), 133 (15), 122 (14), 121 (79), 115 (10), 105 (88), 103 (10), 91 (25), 79 (18).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{22}O_2$]: 234.1620; found: 234.1612.

2-(2-fluoro-3,5-dimethylbenzyl)adamantan-2-o (120aj)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-fluoro-1,3,5-trimethylbenzene (**118j**, 55 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at –40 °C. Before a solution of adamantanone (**112h**, 120 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C

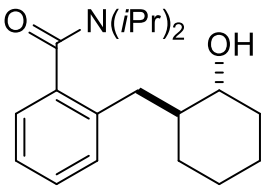
for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 95:5) afforded the title compound **120aj** as a colorless solid (76 mg, 0.26 mmol, 66% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.91 – 6.81 (m, 2H), 3.02 – 2.94 (m, 2H), 2.25 (s, 3H), 2.24 – 2.15 (m, 5H), 2.16 – 2.07 (m, 2H), 1.95 – 1.85 (m, 1H), 1.84 – 1.74 (m, 3H), 1.74 – 1.65 (m, 4H), 1.56 – 1.47 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 158.65 (d, *J* = 240.8 Hz), 132.61 (d, *J* = 4.1 Hz), 130.86 (d, *J* = 4.7 Hz), 130.52 (d, *J* = 4.8 Hz), 124.46 (d, *J* = 19.2 Hz), 123.55 (d, *J* = 17.2 Hz), 75.1, 38.5, 37.5 (2C), 37.5, 34.7, 34.7, 33.2 (2C), 27.6, 27.5, 20.7, 14.9 (d, *J* = 4.3 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2903, 2857, 1484, 1474, 1456, 1442, 1215, 1202, 1141, 1124, 1100, 1062, 1043, 1022, 1008, 993, 928, 859, 756.
MS (EI, 70 eV): *m/z* (%) = 270 (31), 175 (17), 152 (10), 151 (98), 138 (100), 137 (41), 133 (16), 123 (33), 115 (15), 105 (14), 91 (49), 79 (18).

HRMS (EI-orbitrap): *m/z:* [M – H] calc. for [$C_{19}H_{24}FO$]: 287.1811; found 287.1803.

m.p. (°C): 66.3 – 68.7.

***trans*-2-((2-hydroxycyclohexyl)methyl)-N,N-diisopropylbenzamide (120ak) mixture of diastereoisomers**



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and *N*,*N*-diisopropyl-2-methylbenzamide (**118k**, 88 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at –40 °C. Before a solution of cyclohexene oxide (**112l´**, 79 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the

solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 80:20) afforded the title compound **120ak** as a colorless solid (109 mg, 0.34 mmol, 86% yield, d.r. 2.6:1).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.36 – 7.33 (m, 2H), 7.26 – 7.20 (m, 1H), 7.14 – 7.08 (m, 1H), 4.38 (d, *J* = 5.6 Hz, 1H), 3.82 (hept, *J* = 6.7 Hz, 1H), 3.67 – 3.53 (m, 1H), 3.41 – 3.27 (m, 1H), 2.86 – 2.77 (m, 1H), 2.47 (dd, *J* = 13.6, 4.6 Hz, 1H), 2.07 – 1.86 (m, 2H), 1.84 – 1.70 (m, 3H), 1.68 (d, *J* = 6.8 Hz, 3H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.38 – 1.23 (m, 3H), 1.19 (t, *J* = 6.6 Hz, 6H), 1.14 (d, *J* = 6.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 172.3, 139.0, 136.5, 130.4, 128.6, 125.7, 124.7, 75.9, 51.2, 49.0, 46.1, 38.8, 35.4, 33.1, 26.0, 25.3, 21.1, 20.7, 20.5 (2C).

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.39 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.16 (dt, *J* = 7.4, 1.2 Hz, 1H), 3.73 (d, *J* = 4.9 Hz, 1H), 3.67 – 3.53 (m, 1H), 3.25 – 3.15 (m, 1H), 3.00 (dd, *J* = 13.7, 3.8 Hz, 1H), 2.76 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.07 – 1.86 (m, 2H), 1.84 – 1.70 (m, 3H), 1.68 (d, *J* = 6.8 Hz, 3H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.38 – 1.23 (m, 3H), 1.19 (t, *J* = 6.6 Hz, 6H), 1.14 (d, *J* = 6.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 172.0, 138.7, 136.0, 131.2, 127.9, 126.1, 125.0, 72.0, 51.1, 47.1, 46.1, 35.5, 34.8, 30.7, 26.1, 25.2, 20.9, 20.7, 20.5 (2C).

Mixture:

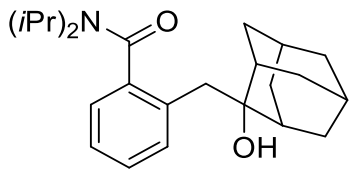
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3400, 2968, 2927, 2855, 1611, 1597, 1492, 1446, 1438, 1370, 1338, 1212, 1203, 1186, 1161, 1136, 1123, 1101, 1082, 1067, 1031, 920, 771, 745, 732.

MS (EI, 70 eV): *m/z* (%) = 298 (16), 288 (17), 274 (24), 218 (20), 217 (16), 204 (100), 199 (36), 198 (27), 189 (20), 181 (78), 179 (22), 176 (25), 171 (39), 170 (23), 169 (23), 166 (26), 165 (18), 162 (18), 157 (28), 145 (39), 143 (20), 141 (30),135 (24), 131 (46), 129 (76), 128 (26), 119 (82), 117 (40), 116 (23), 115 (47), 103 (18), 91 (52), 86 (74), 79 (15), 77 (16).

HRMS (EI-orbitrap): *m/z:* [M – H] calc. for [$C_{20}H_{30}NO_2$]: 316.2277; found 316.2271.

m.p. (°C): 121.7 – 125.0.

2-((2-hydroxyadamantan-2-yl)methyl)-N,N-diisopropylbenzamide (120al)



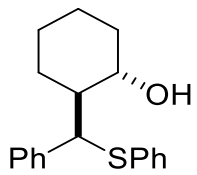
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) *N*,*N*-diisopropyl-2-methylbenzamide (**118k**, 88 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at –40 °C. Before a solution of adamantanone (**112h**, 120 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 80:20) afforded the title compound **120al** as a colorless solid (120 mg, 0.32 mmol, 81% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.26 (m, 1H), 7.23 – 7.14 (m, 2H), 7.11 (dd, *J* = 7.6, 1.5 Hz, 1H), 4.79 (s, 1H), 3.70 (hept, *J* = 6.7 Hz, 1H), 3.58 – 3.43 (m, 2H), 2.46 (d, *J* = 9.1 Hz, 1H), 2.35 (d, *J* = 13.8 Hz, 1H), 2.20 (d, *J* = 12.0 Hz, 2H), 1.96 – 1.85 (m, 3H), 1.85 – 1.68 (m, 5H), 1.62 – 1.52 (m, 7H), 1.51 – 1.42 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 172.6, 138.1, 136.0, 130.9, 128.4, 126.0, 124.9, 73.4, 51.2, 46.2, 42.1, 40.7, 38.7, 35.0, 34.6, 34.3, 33.8, 32.7, 27.8, 27.6, 21.3, 20.7, 20.5, 20.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3325, 2964, 2904, 2855, 1721, 1610, 1596, 1492, 1472, 1453, 1441, 1379, 1371, 1344, 1322, 1307, 1213, 1203, 1161, 1128, 1100, 1057, 1040, 1031, 997, 776, 761, 735, 701.
MS (EI, 70 eV): *m/z* (%) = 350 (10), 308 (23), 252 (18), 251 (100), 233 (14), 223 (29), 195 (14), 181 (19), 167 (17), 165 (22), 157 (15), 152 (10), 141 (31), 129 (15), 128 (13), 115 (14), 91 (16), 86 (17).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{24}H_{35}NO$]: 351.2562; found 351.2556.

m.p. (°C): 138.5 – 143.5.

***trans*-2-(phenyl(phenylthio)methyl)cyclohexan-1-ol (120am) mixture of diastereoisomers**



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently

upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and benzyl(phenyl)sulfane (**118l**, 80 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 79 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 90:10) afforded the title compound **120am** as a colorless oil (107 mg, 0.36 mmol, 90% yield, d.r. = 1.8:1).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.49 – 7.43 (m, 2H), 7.38 – 7.08 (m, 8H), 4.98 (d, *J* = 4.2 Hz, 1H), 3.16 (td, *J* = 10.2, 4.4 Hz, 1H), 2.13 – 1.90 (m, 3H), 1.88 – 1.61 (m, 3H), 1.39 – 0.87 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.2, 135.5, 130.7 (2C), 129.6 (2C), 128.8 (2C), 128.0 (2C), 127.1, 126.5, 70.0, 53.0, 48.9, 36.3, 26.1, 25.5, 24.7.

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.56 – 7.52 (m, 2H), 7.38 – 7.08 (m, 8H), 4.95 (d, *J* = 3.2 Hz, 1H), 3.93 – 3.85 (m, 1H), 2.13 – 1.90 (m, 3H), 1.88 – 1.61 (m, 3H), 1.39 – 0.87 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.6, 136.6, 129.8 (2C), 128.8 (2C), 128.7 (2C), 128.3 (2C), 126.9, 126.1, 73.0, 54.4, 52.9, 32.5, 25.9, 25.7, 24.8.

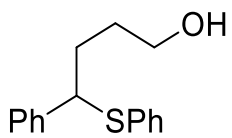
Mixture:

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3372, 2929, 2856, 1583, 1494, 1480, 1449, 1439, 1088, 1064, 1040, 1025, 852, 764, 750, 736, 702, 690.

MS (EI, 70 eV): *m/z* (%) = 199 (15), 197 (11), 190 (13), 189 (100), 188 (20), 172 (13), 171 (91), 143 (17), 129 (58), 117 (17), 115 (21), 110 (14), 97 (13), 91 (71), 84 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{19}H_{22}OS$]: 298.1391; found 298.1384.

4-phenyl-4-(phenylthio)butan-1-ol (120an)



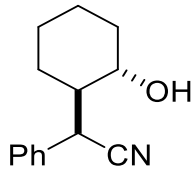
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently

upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and benzyl(phenyl)sulfane (**118l**, 80 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of oxetane (**112s´**, 46 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 75:25) afforded the title compound **120an** as a colorless oil (65 mg, 0.25 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.18 (m, 10H), 4.24 – 4.12 (m, 1H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.17 – 1.95 (m, 2H), 1.72 – 1.51 (m, 2H), 1.48 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm =142.0, 134.9, 132.5 (2C), 128.8 (2C), 128.5 (2C), 127.9 (2C), 127.3, 127.2, 62.5, 53.5, 32.6, 30.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3341, 3059, 3028, 2942, 2868, 1583, 1493, 1480, 1452, 1438, 1086, 1066, 1055, 1025, 923, 747, 720, 693.
MS (EI, 70 eV): *m/z* (%) = 149 (12), 132 (11), 131 (100), 129 (12), 110 (19), 91 (22).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{18}OS$]: 258.1078; found 226.1072.

***trans*-2-((2-hydroxycyclohexyl)-2-phenylacetonitrile (120ao) mixture of diastereoisomeres**



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) 2-phenylacetonitrile (**118m**, 47 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 79 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10

→ 80:20) afforded the title compound **120ao** as a colorless oil (53 mg, 0.25 mmol, 62% yield, d.r. 4.2:1).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 – 7.29 (m, 5H), 4.72 (d, *J* = 3.4 Hz, 1H), 3.70 – 3.62 (m, 1H), 2.13 – 1.98 (m, 2H), 1.79 – 1.70 (m, 1H), 1.70 – 1.59 (m, 2H), 1.54 1.46 (m, 1H), 1.40 1.17 (m. 3H), 1.12 – 0.95 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 134.7, 128.9 (2C), 127.1 (2C), 127.9, 119.3, 72.1, 50.2, 38.5, 36.1, 25.4, 25.1, 24.5.

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 – 7.29 (m, 5H), 4.59 (d, *J* = 3.7 Hz, 1H), 3.13 – 3.04 (m, 1H), 1.97 – 1.86 (m, 2H), 1.79 – 1.70 (m, 1H), 1.70 – 1.59 (m, 2H), 1.40 1.17 (m. 3H), 1.12 – 0.95 (m, 1H), 0.94 – 0.83 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 132.2, 129.3 (2C), 128.6 (2C), 128.1, 121.6, 70.1, 48.7, 37.6, 36.1, 26.1, 25.2, 24.6.

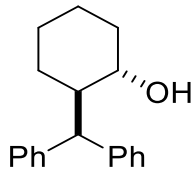
Mixture:

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3426, 2931, 2858, 1494, 1452, 1354, 1344, 1067, 1045, 1031, 914, 754, 700, 678.

MS (EI, 70 eV): *m/z* (%) = 197 (18), 130 (17), 117 (100), 116 (11), 81 (26).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{17}NO$]: 215.1310; found 215.1295.

***trans*-2-benzhydrylcyclohexan-1-ol (120ap)**



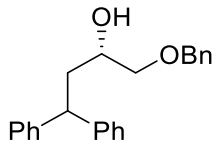
According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in diphenylmethane (**118n**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of cyclohexene oxide (**112l´**, 39 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction

mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 85:15) afforded the title compound **120ap** as a colorless oil (103 mg, 0.39 mmol, 97% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 (d, *J* = 7.3 Hz, 2H), 7.33 – 7.26 (m, 6H), 7.24 – 7.16 (m, 2H), 4.21 (d, *J* = 8.0 Hz, 1H), 3.45 (td, *J* = 8.7, 4.0 Hz, 1H), 2.39 – 2.27 (m, 1H), 1.97 – 1.88 (m, 1H), 1.82 – 1.64 (m, 2H), 1.65 – 1.52 (m, 1H), 1.45 – 1.18 (m, 4H), 1.03 – 0.88 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.3, 143.3, 129.2 (2C), 128.8 (2C), 128.4 (2C), 128.3 (2C), 126.5, 126.3, 72.7, 53.8, 47.5, 34.4, 27.8, 24.7, 24.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3340, 3060, 3026, 2930, 2857, 1599, 1495, 1449, 1355, 1266, 1064, 1041, 1032, 1023, 1002, 970, 785, 764, 753, 745, 731, 700, 674.
MS (EI, 70 eV): *m/z* (%) = 248 (16), 206 (10), 205 (10), 192 (10), 168 (14), 167 (100), 165 (44), 152 (23).

HRMS (EI-orbitrap): *m/z:* [M – H_2O] calc. for [$C_{19}H_{20}$]: 248.1565; found 248.1559.

(*S*)-1-(benzyloxy)-4,4-diphenylbutan-2-ol (120aq)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in diphenylmethane (**118n**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (*S*)-2-((benzyloxy)methyl)oxirane (**112t´**, 66 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 85:15) afforded the title compound **120aq** as a colorless oil (110 mg, 0.33 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35 – 7.21 (m, 13H), 7.19 – 7.12 (m, 2H), 4.48 (s, 2H), 4.25 (t, *J* = 8.0 Hz, 1H), 3.65 (t, *J* = 9.9 Hz, 1H), 3.45 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.33 (dd, *J* = 9.4, 7.4 Hz, 1H), 2.43 – 2.30 (m, 1H), 2.20 – 2.08 (m, 2H).

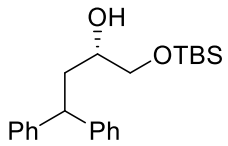
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.1, 144.1, 138.0, 128.6 (2C), 128.6 (4C), 128.3 (2C), 127.9, 127.9 (2C), 127.8 (2C), 126.4, 126.3, 74.7, 73.4, 68.3, 46.9, 39.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3434, 3061, 3027, 2922, 2856, 1599, 1494, 1451, 1364, 1306, 1259, 1203, 1075, 1029, 1001, 945, 907, 871, 787, 749, 737, 695.

MS (EI, 70 eV): *m/z* (%) = 241 (10), 223 (15), 181 (73), 168 (13), 167 (100), 166 (11), 165 (27), 152 (12), 103 (20), 91 (38).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{23}H_{24}O_2$]: 332.1766; found 332.1765.

(*S*)-1-((tert-butyldimethylsilyl)oxy)-4,4-diphenylbutan-2-ol (120ar) mixture of regioisomers



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in diphenylmethane (**118n**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (S)-tert-butyldimethyl(oxiran-2-ylmethoxy)silane (**112u´**, 75 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 97:3 → 90:10) afforded the title compound **120ar** as a colorless oil (137 mg, 0.38 mmol, 96% yield, r.r. = 4.0:1.0).

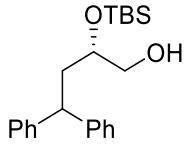
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.26 (m, 8H), 7.24 – 7.16 (m, 2H), 4.29 (dd, *J* = 9.0, 6.9 Hz, 1H), 3.61 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.58 – 3.49 (m, 1H), 3.45 (dd, *J* = 9.5, 7.0 Hz, 1H), 2.39 (s, 1H), 2.21 – 2.12 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.3, 144.3, 128.7 (2C), 128.6 (2C), 128.3 (2C), 127.8 (2C), 126.4, 126.3, 69.6, 67.5, 47.1, 38.8, 26.0 (3C), 18.4, -5.2, -5.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3419, 2953, 2928, 2885, 2856, 1494, 1472, 1462, 1451, 1253, 1109, 1074, 1041, 968, 948, 834, 811, 776, 755, 745, 699.
MS (EI, 70 eV): *m/z* (%) = 207 (56), 181 (10), 180 (12), 168 (14), 167 (100), 166 (11), 165 (30), 152 (12), 129 (83), 105 (11), 91 (64), 75 (43), 73 (15).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{22}H_{32}O_2Si$]: 356.2172; found 356.2156.

(*S*)-2-((tert-butyldimethylsilyl)oxy)-4,4-diphenylbutan-1-ol (120ar´)

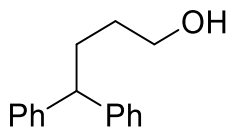


^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31 – 7.20 (m, 8H), 7.20 – 7.14 (m, 2H), 4.05 (t, *J* = 7.9 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.57 (d, *J* = 11.1 Hz, 1H), 3.53 – 3.43 (m, 1H), 2.33 (ddd, *J* = 14.2, 8.0, 6.3 Hz, 1H), 2.28 – 2.18 (m, 1H), 1.84 (dd, *J* = 7.2, 5.3 Hz, 1H), 0.91 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.9, 144.3, 128.7 (2C), 128.7 (2C), 128.0 (2C), 127.9 (2C), 126.4 (2C), 71.2, 66.3, 47.4, 40.1, 26.0 (3C), 18.2, -4.3, -4.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3411, 3062, 3027, 2953, 2928, 2885, 2856, 1600, 1494, 1472, 1462, 1451, 1388, 1361, 1253, 1109, 1074, 1041, 1004, 968, 948, 865, 834, 811, 776, 755, 745, 699, 670.
MS (EI, 70 eV): *m/z* (%) = 207 (39), 196 (10), 195 (68), 177 (27), 168 (13), 167 (100), 166 (12), 165 (30), 152 (15), 129 (40), 91 (54), 75 (69), 73 (13).

HRMS (EI-orbitrap): *m/z:* [M – C_4H_9] calc. for [$C_{18}H_{23}O_2$]: 299.1467; found 299.1460.

4,4-diphenylbutan-1-ol (120as)



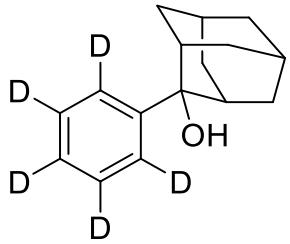
According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in diphenylmethane (**118n**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of oxetane (**112s´**, 23 mg, 0.40 mmol, 1.0 equiv)

in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 80:20) afforded the title compound **120as** as a colorless oil (68 mg, 0.30 mmol, 75% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.26 (m, 8H), 7.26 – 7.17 (m, 2H), 3.95 (t, *J* = 7.9 Hz, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 2.24 – 2.09 (m, 2H), 1.66 – 1.47 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.0 (2C), 128.5 (4C), 127.9(4C), 126.3 (2C), 62.9, 51.2, 31.9, 31.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3331, 3025, 2938, 2866, 1600, 1494, 1450, 1052, 1031, 761, 747, 734, 697.
MS (EI, 70 eV): *m/z* (%) = 180 (14), 168 (14), 167 (100), 165 (59), 152 (27), 130 (15).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{18}O$]: 226.1358; found 226.1353.

2-(phenyl-d_5)adamantan-2-ol (120at)



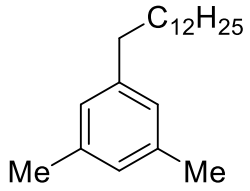
According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (1 min) into a flask charged with TMEDA (0.40 mmol, 2.0 equiv) in benzene-d_6 (**118o**, 0.5 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of adamantanone (**112h**, 30 mg, 0.20 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5) afforded the title compound **120at** as a colorless solid (44 mg, 0.19 mmol, 94% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 2.57 (s, 2H), 2.41 (d, *J* = 12.0 Hz, 2H), 1.91 (s, 1H), 1.79 – 1.65 (m, 9H), 1.54 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.3, 128.3 (t, *J* = 24.3 Hz, 2C), 126.9 (t, *J* = 24.6 Hz), 125.1 (t, *J* =23.8 Hz, 2C), 75.8, 37.8, 35.7 (2C), 35.0 (2C), 33.1 (2C), 27.5, 27.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 2902, 2853, 2361, 1450, 1102, 1043, 1003, 997, 934, 913.
MS (EI, 70 eV): *m/z* (%) = 233 (25), 216 (17), 215 (100), 190 (22), 151 (13), 150 (17), 112 (20), 110 (88), 91 (11), 84 (18), 82 (16), 80 (11), 79 (13).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{15}D_5O$]: 233.1828; found 233.1822.

m.p. (°C): 78.5 – 80.4.

1,3-dimethyl-5-tridecylbenzene (154a)

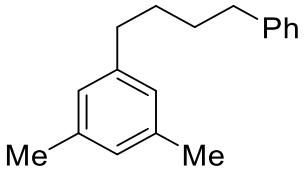


According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in mesitylene (**118a**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of 1-chlorododecane (**153a**, 82 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane) afforded the title compound **154a** as a colorless oil (101 mg, 0.35 mmol, 88% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.84 (s, 1H), 6.83 (s, 2H), 2.59 – 2.51 (m, 2H), 2.32 (s, 6H), 1.61 (p, *J* = 7.4 Hz, 2H), 1.31 (d, *J* = 17.4 Hz, 20H), 0.91 (t, *J* = 6.8 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.1, 137.8 (2C), 127.3, 126.4 (2C), 36.0, 32.1, 31.8, 29.9, 29.9 (2C), 29.8, 29.8, 29.7, 29.6, 29.5, 22.9, 21.4 (2C), 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3015, 2955, 2922, 2853, 2361, 1607, 1466, 1377, 842, 722, 702.
MS (EI, 70 eV): *m/z* (%) = 288 (14), 133 (10), 120 (100), 119 (44), 105 (31).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{21}H_{36}$]: 288.2817; found 288.2813.

1,3-dimethyl-5-(4-phenylbutyl)benzene (154b)

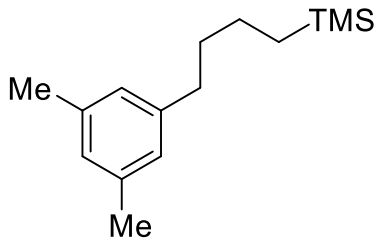


According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in mesitylene (**118a**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (3-chloropropyl)benzene (**153b**, 62 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 99:1 → 98:2) afforded the title compound **154b** as a colorless oil (88 mg, 0.37 mmol, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 – 7.34 (m, 2H), 7.31 – 7.25 (m, 3H), 6.94 6.88 (m, 3H), 2.74 (t, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.39 (s, 6H), 1.83 – 1.68 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.8, 142.6, 137.8 (2C), 128.6 (2C), 128.4 (2C), 127.4, 126.4, 125.8 (2C), 36.0, 35.8, 31.4, 31.3, 21.4 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 3017, 3015, 2933, 2930, 2923, 2916, 2855, 1606, 1496, 1462, 1460, 1453, 844, 747, 698.
MS (EI, 70 eV): *m/z* (%) = 238 (36), 195 (18), 133 (16), 120 (100), 119 (51), 117 (12), 115 (12), 105 (60), 91 (33).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{18}H_{22}$]: 238.1722; found 238.1716.

(4-(3,5-dimethylphenyl)butyl)trimethylsilane (154c)

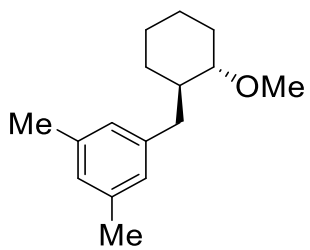


According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in mesitylene (**118a**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (3-chloropropyl)trimethylsilane (**153c**, 60 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154c** as a colorless oil (79 mg, 0.34 mmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.85 (d, *J* = 5.8 Hz, 3H), 2.61 – 2.54 (m, 2H), 2.34 (s, 6H), 1.66 (dt, *J* = 15.3, 7.6 Hz, 2H), 1.45 – 1.34 (m, 2H), 0.61 – 0.54 (m, 2H), 0.03 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.0, 137.8 (2C), 127.3, 127.1, 126.4 (2C), 35.7, 23.9, 21.4 (2C), 16.6, -1.5 (3C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2921, 2855, 1607, 1460, 1258, 1247, 858, 833, 757, 746, 701, 690.
MS (EI, 70 eV): *m/z* (%) = 219 (10), 217 (13), 157 (15), 145 (10), 121 (10), 120 (100), 119 (42), 117 (10), 105 (33), 91 (12), 73 (37).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{26}Si$]: 234.1804; found 234.1796.

1-(((1*R*,2*S*)-2-methoxycyclohexyl)methyl)-3,5-dimethylbenzene (154d)

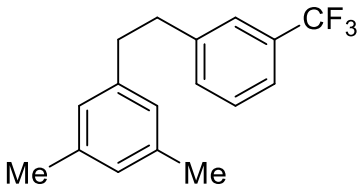


According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in mesitylene (**118a**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (1*R*,2*S*)-1-chloro-2-methoxycyclohexane (**153d**, 59 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 99:1) afforded the title compound **154d** as a colorless oil (46 mg, 0.20 mmol, 49% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.82 (s, 1H), 6.79 (s, 2H), 3.41 (s, 3H), 3.16 – 3.08 (m, 1H), 2.86 – 2.75 (m, 1H), 2.29 (s, 6H), 2.25 – 2.11 (m, 2H), 1.80 – 1.71 (m, 1H), 1.70 – 1.63 (m, 1H), 1.60 – 1.51 (m, 2H), 1.26 – 1.02 (m, 3H), 0.99 – 0.84 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.1, 137.5 (2C), 127.5, 127.3 (2C), 83.2, 56.2, 45.2, 38.6, 30.5, 30.2, 25.5, 24.8, 21.4 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2856, 2818, 1606, 1461, 1448, 1373, 1194, 1181, 1111, 1098, 846, 707.
MS (EI, 70 eV): *m/z* (%) = 200 (19), 185 (24), 157 (15), 143 (20), 132 (22), 120 (100), 119 (37), 117 (17), 115 (10), 113 (13), 105 (70), 91 (16).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{24}O$]: 232.1827; found: 232.1822.

1,3-dimethyl-5-(3-(trifluoromethyl)phenethyl)benzene (154e)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in mesitylene (**118a**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of 1-(chloromethyl)-3-(trifluoromethyl)benzene (**153e**, 78 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –

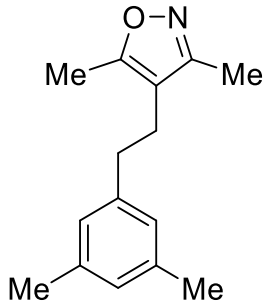
20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane) afforded the title compound **154e** as a colorless oil (76 mg, 0.27 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.52 – 7.36 (m, 4H), 6.90 (s, 1H), 6.84 (s, 2H), 3.03 – 2.93 (m, 2H), 2.92 – 2.84 (m, 2H), 2.33 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.9, 141.2, 138.1 (2C), 132.0 (q, *J* = 1.5 Hz), 130.7 (q, *J* = 31.9 Hz), 128.8, 127.9, 126.4 (2C), 125.3 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 272.4 Hz), 122.9 (q, *J* = 3.8 Hz), 38.0, 37.8, 21.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3016, 2921, 2863, 1607, 1450, 1347, 1327, 1198, 1162, 1122, 1094, 1075, 898, 844, 799, 701.
MS (EI, 70 eV): *m/z* (%) = 120 (10), 119 (100), 91 (14).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{17}H_{17}F_3$]: 278.1282; found 278.1276.

4-(3,5-dimethylphenethyl)-3,5-dimethylisoxazole (154f)



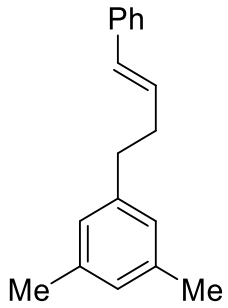
According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in mesitylene (**118a**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of 4-(chloromethyl)-3,5-dimethylisoxazole (**153f**, 58 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent,

flash column chromatographical purification (silica gel, pentane:EtOAc = 97:3 → 90:10) afforded the title compound **154f** as a colorless oil (52 mg, 0.23 mmol, 57% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.85 (s, 1H), 6.71 (s, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.28 (s, 6H), 2.12 (s, 3H), 2.09 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 165.2, 159.8, 140.8, 138.1 (2C), 127.9, 126.5 (2C), 112.9, 36.1, 24.5, 21.3 (2C), 10.7, 10.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3011, 2916, 2859, 1639, 1451, 1424, 1261, 1194, 890, 842, 699.
MS (EI, 70 eV): *m/z* (%) = 229 (26), 214 (44), 221 (13), 186 (39), 145 (11), 119 (100), 117 (11) 115 (10), 110 (14), 91 (24), 68 (23).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{19}NO$]: 229.1467; found 229.1461.

(*E*)-1,3-dimethyl-5-(4-phenylbut-3-en-1-yl)benzene (154g)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in mesitylene (**118a**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (*E*)-(3-chloroprop-1-en-1-yl)benzene (**153g**, 61 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane) afforded the title compound **154g** as a colorless oil (52 mg, 0.22 mmol, 55% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 – 7.29 (m, 4H), 7.25 – 7.19 (m, 1H), 6.88 (s, 3H), 6.46 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.30 (dt, *J* = 15.8, 6.7 Hz, 1H), 2.74 (dd, *J* = 9.4, 6.5 Hz, 2H), 2.61 – 2.51 (m, 2H), 2.34 (s, 6H).

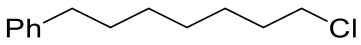
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.9, 138.0 (2C), 137.9, 130.4, 130.3, 128.6 (2C), 127.7, 127.0, 126.4 (2C), 126.1 (2C), 35.9, 35.2, 21.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3431, 3299, 3028, 2923, 2874, 2855, 1718, 1700, 1684, 1603, 1493, 1451, 1267, 1179, 1076, 1065, 1030, 755, 700.

MS (EI, 70 eV): *m/z* (%) = 145 (18), 119 (79), 118 (10), 117 (100), 115 (56), 91 (27).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{18}H_{20}$]: 236.1565; found 236.1558.

(7-chloroheptyl)benzene (154h)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and toluene (**118b**, 37 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of 1,6-dichlorohexane (**153h**, 124 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154h** as colorless oil (73 mg, 0.35 mmol, 87% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.26 (m, 2H), 7.22 – 7.14 (m, 3H), 3.54 (t, *J* = 6.7 Hz, 2H), 2.69 – 2.53 (m, 2H), 1.85 – 1.72 (m, 2H), 1.65 (d, *J* = 14.9 Hz, 2H), 1.49 – 1.32 (m, 6H).

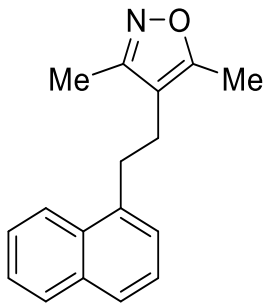
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.9, 128.5 (2C), 128.4 (2C), 125.7, 45.3, 36.0, 32.7, 31.5, 29.2, 28.9, 26.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3026, 2928, 2855, 1604, 1496, 1463, 1453, 1308, 1030, 746, 726, 698.

MS (EI, 70 eV): *m/z* (%) = 210 (20), 92 (68), 91 (100).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{13}H_{19}Cl$]: 210.1175; found 210.1170.

3,5-dimethyl-4-(2-(naphthalen-1-yl)ethyl)isoxazole (154i)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 1 min into a flask charged with a solution of TMEDA (0.40 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 28 mg, 0.20 mmol, 1.0 equiv) in hexane (1.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of 4-(chloromethyl)-3,5-dimethylisoxazole (**153f**, 58 mg, 0.40 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 90:10) afforded the title compound **154i** as a colorless solid (35 mg, 0.14 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01 (d, *J* = 8.3 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.47 (m, 2H), 7.35 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.11 (d, *J* = 6.9 Hz, 1H), 3.21 (t, *J* = 7.3 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.08 (s, 3H), 1.90 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 165.4, 159.7, 136.6, 134.0, 131.7, 129.1, 127.2, 126.8, 126.1, 125.7, 125.6, 123.3, 113.0, 33.3, 23.4, 10.6, 10.2.

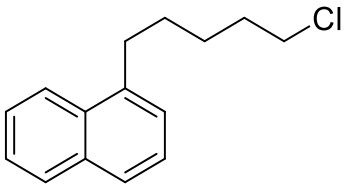
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 2942, 2927, 2871, 1638, 1452, 1437, 1423, 1393, 1262, 1193, 886, 807, 790, 775, 758, 749, 733, 682.

MS (EI, 70 eV): *m/z* (%) = 208 (16), 142 (12), 141 (100), 115 (26).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{17}H_{17}NO$]: 251.1310; found 251.1304.

m.p. (°C): 92.6 – 94.8.

1-(5-chloropentyl)naphthalene (154j)

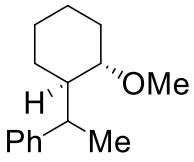


According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 1–methylnaphtalene (**118e**, 57 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of 1-bromo-4-chlorobutane (**153i**, 137 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154j** as a colorless oil (68 mg, 0.29 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 8.5 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.44 – 7.38 (m, 1H), 7.33 (d, *J* = 5.8 Hz, 1H), 3.56 (t, *J* = 6.7 Hz, 2H), 3.10 (d, *J* = 15.5 Hz, 2H), 1.91 – 1.75 (m, 4H), 1.65 – 1.55 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 138.5, 134.0, 132.0, 128.9, 126.7, 126.1, 125.9, 125.7, 125.6, 123.9, 45.2, 33.1, 32.7, 30.2, 27.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3045, 2934, 2859, 1596, 1510, 1463, 1444, 1432, 1395, 1304, 1255, 1166, 797, 776, 730.
MS (EI, 70 eV): *m/z* (%) = 232 (20), 142 (11), 142 (12), 141 (100), 115 (18).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{17}Cl$]: 232.1019; found 232.1013.

(1-((1*R*,2*S*)-2-methoxycyclohexyl)ethyl)benzene (154k) mixture of diastereoisomeres



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in ethylbenzene (**118g**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of (1*R*,2*S*)-1-chloro-2-methoxycyclohexane (**153d**, 59 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 99:1) afforded the title compound **154k** as a slightly yellow oil (59 mg, 0.27 mmol, 68% yield, d.r. = 2.1:1.0).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.27 (m, 2H), 7.25 7.16 (m, 3H), 3.53 – 3.46 (m, 1H), 3.38 (s, 3H), 2.63 (td, *J* = 9.9, 4.1 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.87 – 1.80 (m, 1H), 1.74 1.49 (m, 3H), 1.30 (d, *J* = 7.5 Hz, 3H), 1.21 – 0.96 (m, 3H), 0.79 – 0.65 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.9, 129.0 (2C), 127.7 (2C), 125.9, 80.1, 55.2, 49.2, 37.5, 30.1, 25.7, 24.8, 24.3, 18.9.

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.27 (m, 2H), 7.25 7.16 (m, 3H), 3.44 – 3.39 (m, 1H), 3.39 (s, 3H), 3.02 – 2.95 (m, 1H), 2.17 – 2.07 (m, 1H), 1.74 1.49 (m, 4H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.21 – 0.96 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 146.6, 128.1 (2C), 128.0 (2C), 125.6, 80.6, 56.0, 49.2, 37.4, 30.3, 25.3, 24.6, 24.2, 13.6.

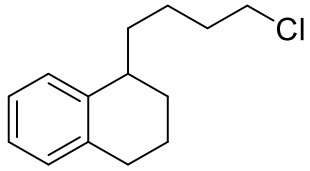
Mixture:

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2965, 2928, 2858, 2819, 1494, 1451, 1375, 1190, 1131, 1100, 958, 906, 769, 702.

MS (EI, 70 eV): *m/z* (%) =187 (15), 186 (100), 171 (49), 157 (25), 144 (42), 143 (49), 131 (11), 130 (15), 129 (57), 128 (16), 118 (48), 117 (27), 115 (22), 113 (26), 112 (15), 106 (30), 105 (67), 103 (14), 91 (45), 81 (40), 79 (27), 77 (13).

HRMS (EI-orbitrap): *m/z:* [M – CH_3OH] calc. for [$C_{14}H_{18}$]: 186.1409; found 186.1402.

1-(4-chlorobutyl)-1,2,3,4-tetrahydronaphthalene (154l)

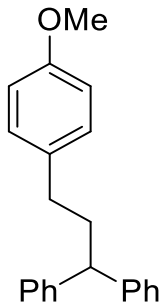


According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and tetralin (**118h**, 53 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of 1-bromo-4-chlorobutane (**153i**, 137 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154l** as a colorless oil (50 mg, 0.22 mmol, 56% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.22 – 7.03 (m, 4H), 3.57 (td, *J* = 6.7, 1.2 Hz, 2H), 2.85 – 2.68 (m, 3H), 1.90 – 1.78 (m, 4H), 1.77 – 1.68 (m, 3H), 1.65 – 1.50 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.3, 137.2, 129.2, 128.6, 125.6, 125.6, 45.2, 37.6, 36.3, 33.0, 29.8, 27.4, 24.8, 19.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 2860, 1490, 1450, 759, 742.
MS (EI, 70 eV): *m/z* (%) = 132 (10), 131 (100), 129 (41), 128 (33), 116 (12), 115 (37), 91 (27).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{14}H_{19}Cl$]: 222.1175; found 222.1170.

(3-(4-methoxyphenyl)propane-1,1-diyl)dibenzene (154m)



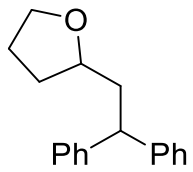
According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**)

by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in diphenylmethane (**118n**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of 1-(2-chloroethyl)-4-methoxybenzene (**153j**, 68 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154m** as a colorless oil (85 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 – 7.30 (m, 4H), 7.30 – 7.26 (m, 4H), 7.23 – 7.18 (m, 2H), 7.10 – 7.06 (m, 2H), 6.87 – 6.83 (m, 2H), 3.94 (t, *J* = 7.7 Hz, 1H), 3.81 (s, 3H), 2.55 (dd, *J* = 9.2, 6.4 Hz, 2H), 2.43 – 2.32 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.8, 145.0 (2C), 134.2, 129.5 (2C), 128.6 (4C), 128.0 (4C), 126.3 (2C), 113.8 (2C), 55.4, 50.7, 37.6, 33.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 3026, 2932, 1612, 1600, 1512, 1494, 1464, 1449, 1300, 1245, 1178, 1033, 830, 747, 700.
MS (EI, 70 eV): *m/z* (%) = 302 (15), 168 (18), 168 (13), 167 (92), 166 (11), 165 (57), 152 (33), 135 (100), 122 (13), 121 (47), 105 (15), 91 (14), 77 (10).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{22}H_{22}O$]: 302.1671; found 302.1665.

2-(2,2-diphenylethyl)tetrahydrofuran (154n)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in diphenylmethane (**118n**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of 2-(chloromethyl)tetrahydrofuran (**153k**, 48 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching

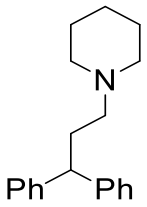
the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154n** as a colorless solid (48 mg, 0.19 mmol, 48% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.29 – 7.25 (m, 8H), 7.20 – 7.15 (m, 2H), 4.15 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.74 – 3.59 (m, 2H), 2.35 – 2.25 (m, 1H), 2.24 – 2.15 (m, 1H), 1.91 (dd, *J* = 37.0, 19.6 Hz, 2H), 1.85 – 1.74 (m, 1H), 1.54 – 1.41 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.2, 144.6, 128.6 (2C), 128.6 (2C), 128.2 (2C), 127.9 (2C), 126.3, 126.2, 77.0, 67.6, 48.3, 41.8, 31.6, 25.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 3061, 3026, 3001, 2969, 2936, 2865, 2365, 2359, 2343, 2336, 1600, 1494, 1450, 1362, 1114, 1082, 1059, 1031, 1016, 786, 752, 739, 700.
MS (EI, 70 eV): *m/z* (%) = 205 (16), 178 (12), 168 (19), 168 (14), 167 (100), 165 (60), 152 (28), 115 (17).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{18}H_{20}O$]: 252.1514; found 252.1507.

m.p. (°C): 57.0 – 59.6.

fenpiprane (150)



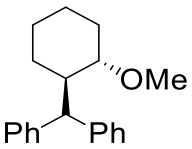
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and diphenylmethane (**118n**, 67 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. The reaction mixture was cooled to –20 °C and a solution of 1-(2-chloroethyl)piperidine (**153l**, 118 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel,

pentane:EtOAc = 50:50 → 30:70) afforded the title compound **150** as a colorless oil (57 mg, 0.20 mmol, 51% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31 – 7.22 (m, 8H), 7.19 – 7.12 (m, 2H), 4.00 – 3.90 (m, 1H), 2.46 – 2.20 (m, 8H), 1.57 (q, *J* = 5.6 Hz, 4H), 1.42 (q, *J* = 5.9 Hz, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.1 (2C), 128.5 (4C), 128.0 (4C), 126.2 (2C), 57.9, 54.8 (2C), 49.5, 32.9, 26.1 (2C), 24.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3026, 2933, 2852, 2801, 2767, 1494, 1450, 1118, 762, 748, 700.
MS (EI, 70 eV): *m/z* (%) = 180 (13), 179 (13), 178 (22), 165 (41), 152 (13), 115 (10), 98 (100), 96 (10).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{20}H_{25}N$]: 279.1987; found 279.1983.

(((1*R*,2*S*)-2-methoxycyclohexyl)methylene)dibenzene (154o)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and diphenylmethane (**118n**, 67 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –20 °C and a solution of (1*R*,2*S*)-1-chloro-2-methoxycyclohexane (**153d**, 118 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154o** as a slightly yellow solid (85 mg, 0.30 mmol, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.23 (m, 8H), 7.22 – 7.12 (m, 2H), 4.38 (d, *J* = 7.8 Hz, 1H), 3.24 (s, 3H), 2.87 (td, *J* = 7.1, 3.4 Hz, 1H), 2.55 – 2.42 (m, 1H), 1.97 – 1.85 (m, 1H), 1.85 – 1.74 (m, 1H), 1.71 – 1.50 (m, 2H), 1.46 – 1.35 (m, 1H), 1.33 – 1.19 (m, 2H), 1.13 – 1.01 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.2, 143.2, 129.6 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 126.2, 125.9, 79.0, 55.7, 50.9, 44.0, 27.9, 25.3, 23.5, 22.8.

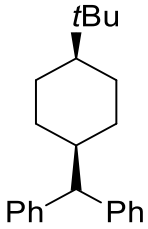
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3086, 3026, 2970, 2932, 2858, 2820, 2359, 2343, 2326, 1740, 1736, 1719, 1601, 1495, 1450, 1375, 1227, 1217, 1198, 1191, 1159, 1123, 1097, 1032, 754, 745, 730, 703.

MS (EI, 70 eV): *m/z* (%) = 179 (10), 178 (11), 167 (46), 166 (13), 166 (13), 165 (100), 164 (10), 152 (38), 115 (22), 91 (12), 81 (10), 79 (10).

HRMS (EI-orbitrap): *m/z:* [M – $HOCH_3$] calc. for [$C_{19}H_{20}$]: 248.1565; found 248.1559.

m.p. (°C): 95.4 – 98.9.

***cis*-4-(tert-butyl)cyclohexyl)methylene)dibenzene (154p)**



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and diphenylmethane (**118n**, 67 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. The reaction mixture was cooled to –20 °C and a solution of *cis*-4-(tert-butyl)cyclohexyl 4-methylbenzenesulfonate (**153m**, 248 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154p** as a colorless solid (67 mg, 0.22 mmol, 55% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.30 (m, 4H), 7.29 – 7.23 (m, 4H), 7.14 (t, *J* = 7.3 Hz, 2H), 4.05 (d, *J* = 12.3 Hz, 1H), 2.57 (d, *J* = 10.1 Hz, 1H), 1.63 – 1.51 (m, 2H), 1.48 – 1.33 (m, 4H), 1.31 – 1.20 (m, 2H), 1.09 – 0.97 (m, 1H), 0.88 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.8 (2C), 128.6 (4C), 128.2 (4C), 126.1 (2C), 51.6, 48.3, 36.2, 32.8, 28.5 (2C), 27.7 (3C), 21.5 (2C).

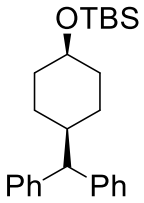
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3026, 2962, 2954, 2928, 2858, 1597, 1584, 1491, 1474, 1466, 1449, 1390, 1373, 1360, 1177, 1074, 1031, 911, 854, 750, 741, 692.

MS (EI, 70 eV): *m/z* (%) = 168 (57), 168 (14), 167 (100), 165 (38), 152 (18), 83 (17).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{23}H_{30}$]: 306.2348; found 306.2341.

m.p. (°C): 120.5 – 133.8.

***cis*-4-benzhydrylcyclohexyl)oxy)(tert-butyl)dimethylsilane (154q)**



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in diphenylmethane (**118n**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of *trans*-4-((tert-butyldimethylsilyl)oxy)cyclohexyl 4-methylbenzenesulfonate (**153n**, 154 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154q** as a colorless oil (83 mg, 0.22 mmol, 55% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.32 (m, 4H), 7.31 – 7.26 (m, 4H), 7.19 – 7.13 (m, 2H), 3.95 (tt, *J* = 4.7, 2.1 Hz, 1H), 3.65 (d, *J* = 11.2 Hz, 1H), 2.27 – 2.10 (m, 1H), 1.71 – 1.59 (m, 2H), 1.51 – 1.31 (m, 6H), 0.93 (s, 9H), 0.05 (s, 6H).

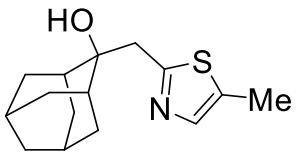
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.6 (2C), 128.5 (4C), 128.2 (4C), 126.1 (2C), 67.2, 58.4, 40.4, 33.3 (2C), 26.0 (3C), 25.9 (2C), 18.3, -4.7 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 3062, 3027, 2928, 2884, 2856, 1597, 1494, 1472, 1462, 1450, 1406, 1376, 1360, 1251, 1198, 1180, 1156, 1110, 1087, 1049, 1022, 1006, 939, 912, 886, 833, 807, 773, 752, 744, 702, 676.

MS (EI, 70 eV): *m/z* (%) = 323 (37), 247 (14), 169 (17), 168 (14), 167 (100), 165 (30), 152 (17), 143 (19), 75 (42).

HRMS (EI-orbitrap): *m/z:* [M – CH_3] calc. for [$C_{24}H_{33}OSi$] 365.2301; found 365.2290.

2-((5-methylthiazol-2-yl)methyl)adamantan-2-ol (156a)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2,4-dimethylthiazole (**155a**, 45 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at –40 °C. Before a solution solution of adamantanone (**112h**, 120 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 80:20) afforded the title compound **156a** as a colorless solid (75 mg, 0.28 mmol, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.70 (d, *J* = 1.0 Hz, 1H), 4.55 (s, 1H), 3.29 (s, 2H), 2.41 (d, *J* = 1.0 Hz, 3H), 2.28 (d, *J* = 9.9 Hz, 2H), 1.94 – 1.77 (m, 4H), 1.75 – 1.60 (m, 6H), 1.49 (d, *J* = 12.6 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.8, 152.7, 112.3, 75.3, 40.5, 38.4, 37.0 (2C), 34.7 (2C), 32.9 (2C), 27.4, 27.4, 17.2.

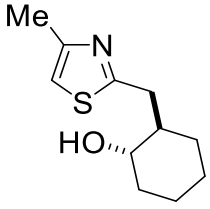
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3376, 3092, 2949, 2936, 2914, 2902, 2889, 2854, 1532, 1524, 1473, 1455, 1442, 1418, 1370, 1356, 1352, 1328, 1311, 1304, 1162, 1154, 1129, 1109, 1098, 1064, 1050, 1041, 1026, 1014, 1000, 994, 974, 929, 891, 864, 855, 773, 747, 668.

MS (EI, 70 eV): *m/z* (%) = 151 (18), 113 (100).

HRMS (EI-orbitrap): *m/z:* [M – H] calc. for [$C_{15}H_{20}NOS$]: 262.1266; found 262.1263.

m.p. (°C): 112.9 – 115.7.

***trans*-2-((4-methylthiazol-2-yl)methyl)cyclohexan-1-ol (156b)**



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2,4-dimethylthiazole (**155a**, 45 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at 25 °C. Before the mixture was cooled to –40 °C and a solution of cyclohexene oxide (**112l´**, 79 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 10 min followed by another 1 h at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 30:70 → 10:90) afforded the title compound **156b** as a colorless oil (36 mg, 0.17 mmol, 43% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.68 (s, 1H), 4.06 (s, 1H), 3.33 – 3.16 (m, 2H), 2.95 (dd, *J* = 14.9, 6.2 Hz, 1H), 2.38 (d, *J* = 0.9 Hz, 3H), 2.02 – 1.95 (m, 1H), 1.76 – 1.66 (m, 3H), 1.65 – 1.58 (m, 1H), 1.33 – 1.03 (m, 4H).

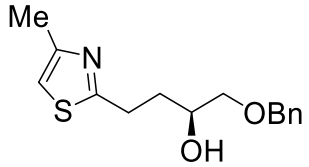
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 169.5, 152.2, 112.7, 74.5, 45.8, 37.4, 35.5, 31.5, 25.7, 24.9, 17.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3324, 2924, 2854, 1531, 1462, 1446, 1304, 1132, 1093, 1070, 1060, 1032, 730.

MS (EI, 70 eV): *m/z* (%) = 211 (25), 192 (13), 183 (27), 182 (20), 168 (20), 140 (64), 138 (10), 127 (19), 126 (100), 115 (20), 114 (31), 112 (25), 73 (19), 72 (50), 71 (45), 68 (11), 67 (13), 55 (12), 53 (13), 45 (32), 44 (24), 43 (65), 42 (11), 41 (32).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{11}H_{17}NOS$]: 211.1031; found 211.1031.

(*S*)-1-(benzyloxy)-4-(4-methylthiazol-2-yl)butan-2-ol (156c)



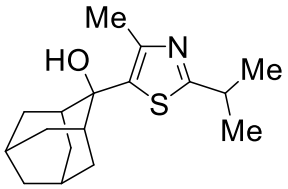
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2,4-dimethylthiazole (**155a**, 45 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at 25 °C. Before the mixture was cooled to –40°C and a solution of

(S)-2-((benzyloxy)methyl)oxirane (**112t´**, 131 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 30:70 → 10:90) afforded the title compound **156c** as a colorless oil (54 mg, 0.19 mmol, 49% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.38 – 7.26 (m, 5H), 6.70 (d, *J* = 1.0 Hz, 1H), 4.54 (s, 2H), 3.94 – 3.84 (m, 1H), 3.61 (s, 1H), 3.51 – 3.47 (m, 1H), 3.46 – 3.38 (m, 1H), 3.16 – 3.09 (m, 2H), 2.39 (d, *J* = 0.9 Hz, 3H), 2.03 – 1.83 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 170.2, 152.2, 138.0, 128.5 (2C), 127.8 (3C), 112.6, 74.4, 73.5, 69.6, 33.0, 29.7, 17.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3339, 2921, 2857, 1531, 1452, 1445, 1364, 1303, 1203, 1088, 1075, 1028, 968, 734, 697.
MS (EI, 70 eV): *m/z* (%) = 171 (10), 168 (11), 156 (75), 127 (10), 126 (72), 111 (33), 91 (100), 72 (14), 71 (17), 65 (14), 45 (12), 43 (14).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{19}NO_2S$]: 277.1136; found 277.1129.

2-(2-isopropyl-4-methylthiazol-5-yl)adamantan-2-ol (158a)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-isopropyl-4-methylthiazole (**155b**, 56 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at –40 °C. Before a solution of adamantanone (**112h**, 120 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 10 min followed by another 1 h at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent,

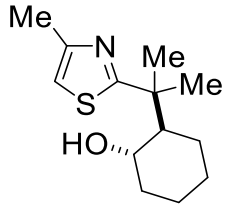
flash column chromatographical purification (silica gel, pentane:EtOAc = 80:20 → 70:30) afforded the title compound **158a** as a colorless solid (85 mg, 0.29 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.17 (hept, *J* = 6.9 Hz, 1H), 2.47 (s, 3H), 2.42 (s, 2H), 2.36 (d, *J* = 13.0 Hz, 2H), 1.88 (d, *J* = 8.5 Hz, 3H), 1.85 – 1.74 (m, 4H), 1.71 (s, 2H), 1.64 (d, *J* = 12.2 Hz, 2H), 1.34 (s, 3H), 1.33 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 173.9, 147.6, 136.9, 75.6, 38.6 (2C), 37.7, 35.3 (2C), 33.2, 33.0 (2C), 27.2, 26.7, 23.3 (2C), 18.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3404, 2961, 2950, 2925, 2900, 2890, 2854, 1521, 1470, 1447, 1385, 1376, 1362, 1350, 1334, 1308, 1285, 1218, 1196, 1104, 1076, 1044, 1027, 1006, 962, 932, 898, 879, 841, 831, 672.
MS (EI, 70 eV): *m/z* (%) = 291 (42), 281 (12), 274 (27), 273 (22), 233 (15), 207 (29), 170 (39), 168 (100), 161 (86), 142 (15), 142 (35), 140 (14), 119 (14),117 (15), 93 (14), 91 (21), 79 (16), 77 (16), 72 (44), 69 (13), 57 (32), 55 (20), 52 (30), 48 (22), 48 21), 48 (72).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{17}H_{25}NOS$]: 291.1657; found 291.1653.

m.p. (°C): 115.8 – 117.6.

***trans*-2-(2-(4-methylthiazol-2-yl)propan-2-yl)cyclohexan-1-ol (160a)**



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-isopropyl-4-methylthiazole (**155b**, 56 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at –40 °C. Before a solution cyclohexene oxide (**112l´**, 79 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 10 min followed by another 1 h at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 80:20 → 70:30) afforded the title compound **160a** as a colorless solid (91 mg, 0.38 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.72 (s, 1H), 3.72 (s, 1H), 3.31 – 3.17 (m, 1H), 2.40 (s, 3H), 1.95 – 1.78 (m, 3H), 1.69 (d, *J* = 9.0 Hz, 2H), 1.48 (s, 3H), 1.45 (s, 3H), 1.33 – 1.14 (m, 3H), 1.03 – 0.91 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 182.2, 151.7, 112.3, 73.7, 53.9, 42.9, 36.4, 30.6, 27.0, 26.4, 25.5, 25.2, 17.2.

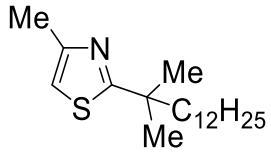
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3276, 2940, 2919, 2851, 1530, 1458, 1447, 1385, 1366, 1351, 1342, 1326, 1300, 1289, 1193, 1121, 1097, 1067, 1034, 1008, 998, 863, 724, 687.

MS (EI, 70 eV): *m/z* (%) = 161 (28), 154 (32), 142 (12), 141 (83), 140 (100), 126 (17), 81 (11), 72 (25), 61 (11), 59 (12), 57 (15), 55 (14), 45 (10), 43 (12), 43 (66), 41 (20).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{13}H_{21}NOS$]: 239.1344; found 239.1354.

m.p. (°C): 93.5 – 95.8.

4-methyl-2-(2-methyltetradecan-2-yl)thiazole (160b)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-isopropyl-4-methylthiazole (**155b**, 56 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at –40 °C. Before a solution of 1-chlorododecane (**153a**, 164 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 10 min followed by another 16 h at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 97:3) afforded the title compound **160b** as a colorless oil (109 mg, 0.35 mmol, 88% yield).

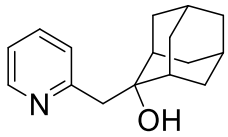
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.69 (q, *J* = 1.0 Hz, 1H), 2.42 (d, *J* = 1.1 Hz, 3H), 1.73 – 1.64 (m, 2H), 1.39 (s, 6H), 1.29 – 1.15 (m, 20H), 0.90 – 0.84 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 180.3, 152.1, 111.9, 44.4, 40.7, 32.1, 30.3, 29.8, 29.8 (2C), 29.8, 29.7, 29.5, 28.7 (2C), 24.7, 22.8, 17.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2922, 2853, 1530, 1478, 1458, 1384, 1375, 1363, 1304, 1259, 1210, 1140, 1121, 1050, 960, 862, 725, 702, 668.
MS (EI, 70 eV): *m/z* (%) = 281 (28), 225 (35), 209 (18), 207 (69), 191 (14), 141 (100), 140 (61), 126 (25).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{19}H_{35}NS$]: 309.2490; found 309.2488.

2-(pyridin-2-ylmethyl)adamantan-2-ol (163a)



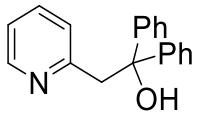
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-picoline (**161a**, 37 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at 25 °C. Before the mixture was cooled to –40°C and a solution of adamantanone (**112h**, 120 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq*. NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 85:15 → 75:25) afforded the title compound **163a** as a colorless crystals (83 mg, 0.34 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.50 – 8.45 (m, 1H), 7.60 (td, *J* = 7.7, 1.9 Hz, 1H), 7.17 – 7.10 (m, 2H), 6.06 (s, 1H), 3.13 (s, 2H), 2.31 (dd, *J* = 12.5, 3.1 Hz, 2H), 1.95 – 1.88 (m, 2H), 1.86 – 1.81 (m, 1H), 1.80 – 1.75 (m, 1H), 1.71 – 1.65 (m, 4H), 1.58 – 1.53 (m, 2H), 1.48 – 1.41 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.8, 148.5, 136.9, 124.6, 121.5, 75.6, 43.7, 38.6, 37.4 (2C), 34.8 (2C), 32.9 (2C), 27.6, 27.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3258, 2942, 2912, 2896, 2890, 2854, 1592, 1567, 1476, 1466, 1453, 1432, 1421, 1356, 1337, 1184, 1098, 1063, 1051, 1027, 1013, 1003, 992, 932, 886, 868, 761, 750, 704, 680, 664.
MS (EI, 70 eV): *m/z* (%) = 224 (22), 93 (100).

HRMS (EI-orbitrap): *m/z:* [M–H] calc. for [$C_{16}H_{20}NO$]: 242.1545; found 242.1538.

m.p. (°C): 84.3 87.1.

1,1-diphenyl-2-(pyridin-2-yl)ethan-1-ol (163b)



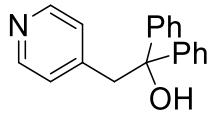
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-picoline (**161a**, 37 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at 25 °C. Before the mixture was cooled to –40°C and a solution of benzophenone (**112a´**, 145 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 80:20 → 60:40) afforded the title compound **163b** as a colorless crystals (110 mg, 0.39 mmol, 99% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.41 – 8.29 (m, 1H), 7.74 (s, 1H), 7.54 – 7.44 (m, 5H), 7.29 – 7.19 (m, 4H), 7.18 – 7.11 (m, 2H), 7.08 – 6.99 (m, 2H), 3.71 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.4, 148.0, 147.4 (2C), 137.0, 128.0 (4C), 126.6 (2C), 126.3 (4C), 124.7, 121.6, 78.5, 47.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3212, 1594, 1568, 1491, 1479, 1445, 1437, 1416, 1248, 1221, 1196, 1104, 1054, 1032, 1010, 998, 908, 891, 791, 764, 749, 709, 697.
MS (EI, 70 eV): *m/z* (%) = 257 (20), 256 (100), 254 (14), 105 (10).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{19}H_{17}NO$]: 275.1310; found 275.1306.

m.p. (°C): 149.4 – 152.0.

1,1-diphenyl-2-(pyridin-4-yl)ethan-1-ol (163c)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA

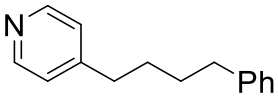
(0.80 mmol, 2.0 equiv) and 4-picoline (**161b**, 37 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at 25 °C. Before the mixture was cooled to –40°C and a solution of benzophenone (**112a´**, 145 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 80:20 → 40:60) afforded the title compound **163c** as a colorless crystals (95 mg, 0.35 mmol, 86% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.24 – 8.14 (m, 2H), 7.42 – 7.34 (m, 4H), 7.33 – 7.26 (m, 4H), 7.26 – 7.21 (m, 2H), 6.85 – 6.77 (m, 2H), 3.58 (s, 2H), 3.23 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.9 (2C), 146.3 (2C), 146.1, 128.3 (4C), 127.3 (2C), 126.3 (4C), 126.3 (2C), 78.1, 47.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3144, 3059, 1605, 1493, 1446, 1418, 1212, 1051, 1003, 905, 814, 776, 753, 730, 710, 696.
MS (EI, 70 eV): *m/z* (%) = 257 (17), 256 (16), 207 (22), 183 (13), 182 (100), 180 (14), 170 (10), 169 (79), 168 (45), 167 (69), 166 (10), 105 (10), 91 (15).

HRMS (EI-orbitrap): *m/z:* [M–H_2O] calc. for [$C_{19}H_{15}N$]: 257.1204; found 257.1201.

m.p. (°C): 159.0 – 160.5.

4-(4-phenylbutyl)pyridine (163d)



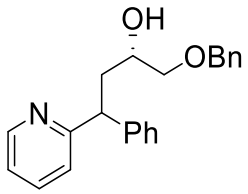
According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 4-picoline (**161b**, 37 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at 25 °C. Before the mixture was cooled to –40°C and a solution of (3-chloropropyl)benzene (**153b**, 123 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel,

pentane:EtOAc = 90:10 → 60:40) afforded the title compound **163d** as a colorless oil (42 mg, 0.20 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.60 – 8.45 (m, 2H), 7.37 – 7.29 (m, 2H), 7.28 – 7.18 (m, 3H), 7.16 – 7.10 (m, 2H), 2.80 – 2.56 (m, 4H), 1.83 – 1.59 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.5, 149.7 (2C), 142.3, 128.5 (4C), 125.9, 124.0 (2C), 35.8, 35.2, 31.0, 29.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 3025, 2934, 2858, 1601, 1558, 1496, 1453, 1414, 1219, 1030, 992, 839, 800, 774, 746, 698.
MS (EI, 70 eV): *m/z* (%) = 182 (12), 120 (13), 106 (100), 92 (10), 91 (100), 65 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{17}N$]: 211.1361; found 211.1354.

(2*S*)-1-(benzyloxy)-4-phenyl-4-(pyridin-2-yl)butan-2-ol (163e) mixture of diastereoisomers



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-benzylpyridine (**161c**, 68 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at 25 °C. Before the mixture was cooled to –40°C and a solution of (S)-2-((benzyloxy)methyl)oxirane (**112t´**, 131 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 90:10 → 40:60) afforded the title compound (**163e**) as a slightly yellow oil (82 mg, 0.25 mmol, 62% yield; d.r. = 1.4:1.0).

Major:
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.60 – 8.50 (m, 1H), 7.60 – 7.50 (m, 1H), 7.37 – 7.24 (m, 9H), 7.23 – 7.06 (m, 3H), 4.53 – 4.47 (m, 3H), 3.71 – 3.63 (m, 1H), 3.53 – 3.46 (m, 1H), 3.45 – 3.39 (m, 1H), 2.53 – 2.43 (m, 1H), 2.18 – 2.09 (m, 1H), 2.08 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.0, 148.8, 143.6, 138.2, 136.9, 128.6 (2C), 128.5 (2C), 128.2 (2C), 127.9 (2C), 127.8, 126.6, 123.9, 121.6, 74.8, 73.4, 67.9, 49.4, 38.5.

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.60 – 8.50 (m, 1H), 7.60 – 7.50 (m, 1H), 7.37 – 7.24 (m, 9H), 7.23 – 7.06 (m, 3H), 4.52 (s, 2H), 4.40 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.71 – 3.63 (m, 1H), 3.53 – 3.46 (m, 1H), 3.45 – 3.39 (m, 1H), 2.40 – 2.26 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.8, 148.7, 143.7, 138.2, 136.7, 128.7 (2C), 128.5 (2C), 128.5 (2C), 127.9 (2C), 127.8, 126.7, 123.5, 121.5, 75.1, 73.5, 69.0, 50.1, 38.8.

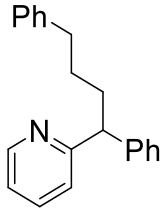
Mixture:

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3396, 3062, 3028, 2915, 2858, 1589, 1569, 1495, 1472, 1452, 1433, 1363, 1308, 1251, 1205, 1149, 1121, 1088, 1074, 1052, 1028, 995, 909, 876, 802, 744, 733, 697.

MS (EI, 70 eV): *m/z* (%) = 213 (12), 212 (77), 194 (16), 183 (11), 182 (79), 180 (15), 169 (66), 169 (13), 168 (100), 168 (11), 167 (78), 166 (10), 91 (24).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{22}H_{23}NO_2$]: 333.1729; found 333.1673.

2-(1,4-diphenylbutyl)pyridine (163f)



According to **TP14**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-benzylpyridine (**161c**, 68 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at 25 °C. Before the mixture was cooled to –40°C and a solution of (3-chloropropyl)benzene (**153b**, 123 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 85:15) afforded the title compound **163f** as a colorless oil (90 mg, 0.31 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.63 – 8.57 (m, 1H), 7.57 (td, *J* = 7.7, 1.9 Hz, 1H), 7.39 – 7.25 (m, 6H), 7.24 – 7.13 (m, 5H), 7.12 – 7.08 (m, 1H), 4.11 (t, *J* = 7.8 Hz, 1H), 2.76 – 2.62 (m, 2H), 2.41 – 2.27 (m, 1H), 2.23 – 2.10 (m, 1H), 1.68 – 1.59 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.0, 149.4, 143.8, 142.5, 136.5, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.1 (2C), 126.5, 125.8, 122.8, 121.4, 53.8, 36.0, 34.8, 29.9.

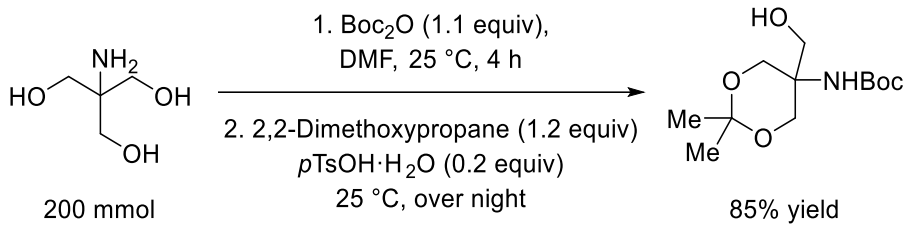
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 3025, 2934, 2858, 1601, 1588, 1568, 1494, 1471, 1452, 1432, 1148, 1073, 1050, 1030, 993, 910, 790, 745, 697.

MS (EI, 70 eV): *m/z* (%) = 183 (14), 182 (100), 170 (10), 169 (79), 168 (47), 167 (70), 166 (10), 91 (12).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{21}H_{21}N$]: 287.1674; found 287.1677.

5.5 Synthesis of Fingolimod (148)

tert-butyl (5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate

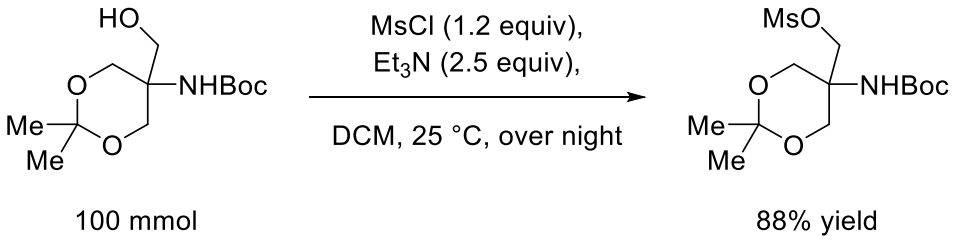


Scheme 137: Sequential Boc_2O and acetal protection of 2-amino-2-(hydroxymethyl)propane-1,3-diol.

According to the literature,[431] Boc_2O (48.02 g, 220 mmol, 1.1 equiv) was added to a mixture of 2-amino-2-(hydroxymethyl)propane-1,3-diol (24.33 g, 200 mmol, 1.0 equiv) in DMF (180 mL) at 25 °C. The mixture was stirred at this temperature for 4 h. 2,2-Dimethoxypropane (25.00 g, 240 mmol, 1.2 equiv) and *p*-TsOH·H_2O (1.90 g, 10 mmol, 0.2 equiv) were added at 25 °C and the mixture was stirred over night at the same temperature. Et_2O (500 mL) was added, the mixture was washed with $NaHCO_3$ (3x200 mL) and brine (200 mL), the organic layer was dried over $MgSO_4$. Evaporation of the solvent led to the title compound as a colorless solid (44. 65 g, 171 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.34 (s, 1H), 4.29 (s, 1H), 3.90 – 3.76 (m, 4H), 3.72 (d, *J* = 6.6 Hz, 2H), 1.53 (s, 3H), 1.45 (s, 9H), 1.44 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.6, 98.9, 80.6, 64.6 (2C), 53.5, 28.5 (3C), 27.6 (2C), 20.2.

(5-((_tert_-butoxycarbonyl)amino)-2,2-dimethyl-1,3-dioxan-5-yl)methyl methanesulfonate



Scheme 138: Introduction of a mesilate group on (5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate.

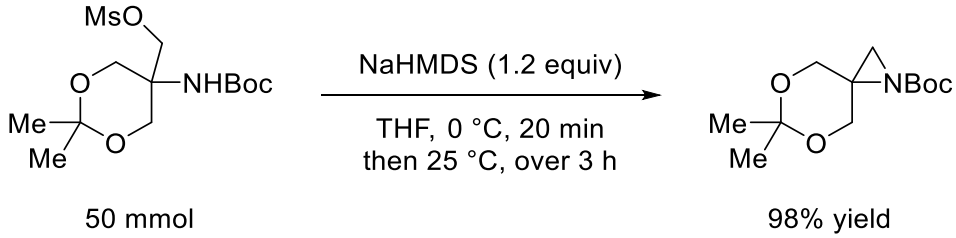
According to the literature,[431] NEt_3 (25.3 g, 250 mmol, 2.5 equiv) was added at 0 °C to a solution of tert-butyl (5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (26.1 g, 100 mmol, 1.0 equiv) in DCM (100 mL). MsCl was added dropwise at the same temperature, the reaction mixture was allowed to slowly warm up to 25 °C and stirred over night at this temperature. MTBE (200 mL) was added to the mixture the organic layer was washed with H_2O (2x300 mL), citric acid (10 wt%, 2x200 mL) and

[431] J. Doubský, S. Rádl, J. Cinibulk, Robert Klvaňa, *Org. Process. Res. Dev.* **2022**, *26*, 859.

$NaHCO_3$ (200 mL) and dried over $MgSO_4$. Evaporation of solvents gave the title compound as a slightly yellow oil (29.9 g, 88.1 mmol, 88% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.73 (s, 1H), 4.58 (s, 2H), 4.02 (d, *J* = 11.9 Hz, 2H), 3.88 (d, *J* = 12.0 Hz, 2H), 3.04 (s, 3H), 1.48 (s, 3H), 1.43 (s, 9H), 1.41 (s, 3H).

tert-butyl 6,6-dimethyl-5,7-dioxa-1-azaspiro[2.5]octane-1-carboxylate (166)

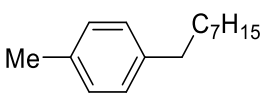


Scheme 139: NaHMDS mediated formation of an aziridine ring.

According to the literature,[432] NaHMDS (1.0 m, 60 mL, 60 mmol, 1.2 equiv) was added dropwise to a solution of (5-((tert-butoxycarbonyl)amino)-2,2-dimethyl-1,3-dioxan-5-yl)methyl methanesulfonate (16.97 g, 50 mmol, 1.0 equiv) in THF (250 mL) at –10 °C the mixture was stirred at the same temperature for 20 min. Afterwards the mixture was stirred for 3 h at 25 °C. The mixture was quenched with sat. *aq.* NH_4Cl (100 mL), H_2O (100 mL) was added, the mixture was diluted with MTBE (200 mL). The aqueous layer was extracted with MTBE (2x100 mL), the combined organic layers were washed with citric acid (10 wt%, 500 mL) and sat *aq.* $NaHCO_3$ (400 mL). The organic layers were dried over $MgSO_4$. Evaporation of solvents gave the title compound **166** as a beige solid (11.93 g, 49.05 mmol, 98% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.96 (d, *J* = 12.5 Hz, 2H), 3.65 (d, *J* = 12.6 Hz, 2H), 2.21 (s, 2H), 1.52 (s, 3H), 1.47 (s, 12H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.5, 98.7, 81.9, 64.0 (2C), 40.3, 35.5, 28.0 (3C), 24.7, 22.8.

1-methyl-4-octylbenzene (154s)



A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady

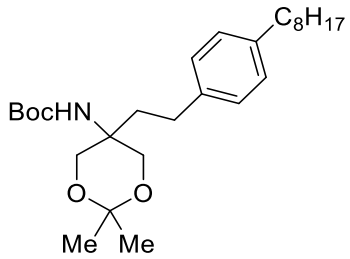
[432] J. Doubský, S. Rádl, J. Cinibulk, Robert Klvaňa, *Org. Process. Res.* **2022**, *26*, 859.

state, it was injected (40 min) into a flask charged with TMEDA (16.00 mmol, 2.0 equiv) in xylene (**118c**, 20.0 mL) and the resulting mixture was stirred at 25 °C for 1 h. The reaction flask was cooled to –20 °C and a solution of 1-chloroheptane (**153p**, 1.08 g, 8.00 mmol, 1.0 equiv) in THF (20.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min before it was allowed to warm to 25 °C over night. Sat. *aq*. NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. Removing the solvent afforded the title compound **154s** as a yellow oil (1.60 mg, 7.84 mmol, 98% yield) without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.11 – 7.02 (m, 4H), 2.60 – 2.51 (m, 2H), 2.32 (s, 3H), 1.67 – 1.50 (m, 2H), 1.37 – 1.21 (m, 10H), 0.92 – 0.83 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.0, 135.1, 129.0 (2C), 128.4 (2C), 35.7, 32.0, 31.8, 29.6, 29.5, 29.4, 22.8, 21.1, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3358, 3020, 2956, 2923, 2854, 1516, 1464, 1458, 1378, 1118, 1022, 806, 723.
MS (EI, 70 eV): *m/z* (%) = 204 (27), 106 (21), 105 (100), 91 (16).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{15}H_{24}$]: 204.1878; found 204.1872.

***tert*-butyl (2,2-dimethyl-5-(4-octylphenethyl)-1,3-dioxan-5-yl)carbamate (165)**



A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 0.8 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (4 min) into a flask charged with TMEDA (1.60 mmol, 0.8 equiv) and 1-methyl-4-octylbenzene (**154s**, 2.00 mmol, 1.0 equiv) in hexane (2.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction mixture was cooled to –78 °C and MgCl·LiCl (0.5 M in THF, 1.2 mL, 0.60 mmol, 0.3 equiv) was added the mixture was stirred for 10 min at the same temperature.
In a second flask a mixture of tert-butyl 6,6-dimethyl-5,7-dioxa-1-azaspiro[2.5]octane-1-carboxylate (**166**, 97 mg, 0.40 mmol, 0.2 equiv) and CuBr·SMe_2 (16 mg, 0.08 mmol, 4 mol%) in THF (4.0 mL) was prepared and stirred for 10 min at 25 °C before it was cooled to –78 °C and the gas space was evacuated and refilled with argon for three times.

The mixture of electrophile **166** was transferred to the first flask filled with the organometallic reagent at –78 °C and the combined mixture was stirred at that temperature for 30 min before it was allowed to warm to 25 °c and stirred overnight.

Sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 95:5 → 90:10) afforded the title compound **165** as a beige solid (107 mg, 0.24 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.08 (s, 4H), 4.98 (s, 1H), 3.90 (d, *J* = 11.6 Hz, 2H), 3.68 (d, *J* = 11.9 Hz, 2H), 2.60 – 2.46 (m, 4H), 2.02 – 1.91 (m, 2H), 1.62 – 1.53 (m, 2H), 1.48 (s, 9H), 1.44 (s, 3H), 1.42 (s, 3H), 1.28 (m, 10H), 0.90 – 0.85 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.0, 140.7, 139.2, 128.6 (2C), 128.3 (2C), 98.5, 79.4, 66.5 (2C), 51.8, 35.7, 33.8, 32.0, 31.7, 29.6, 29.5, 29.4, 28.8, 28.6 (3C), 27.6, 22.8, 19.8, 14.3.

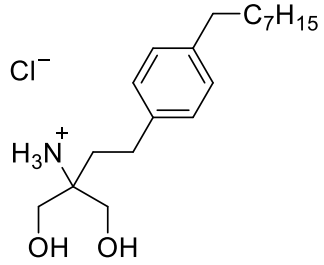
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3347, 2977, 2955, 2924, 2853, 1698, 1520, 1515, 1464, 1453, 1389, 1374, 1367, 1362, 1304, 1251, 1216, 1198, 1170, 1133, 1121, 1078, 1069, 1041, 1008, 1002, 940, 908, 827, 788, 731.

MS (EI, 70 eV): *m/z* (%) = 333 (12), 316 (14), 275 (23), 272 (11), 258 (25), 255 (14), 244 (10), 242 (11), 217 (21), 216 (100), 203 (19), 190 (17), 134 (15), 117 (27), 117 (11), 105 (23), 104 (13), 91 (11), 57 (75), 43 (12), 43 (15), 41 (17).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{27}H_{45}NO_4$]: 447.3349; found 447.3347.

m.p. (°C): 68.0 – 70.2.

Fingolimod Hydrochloride (148)



Aq. HCl (37%, 0.2 ml, ca. 2.4 mmol, 8.4 equiv) was added to a solution of *tert*-butyl (2,2-dimethyl-5-(4-octylphenethyl)-1,3-dioxan-5-yl)carbamate (**165**, 128 mg, 0.29 mmol, 1.0 equiv) in EtOH (5.5 mL). The mixture was heated to reflux for 2 d. Evaporation under reduced pressure led to the title compound **148** as slightly beige crystals (88 mg, 0.26 mmol, 89% yield).

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm 7.82 (s, 3H), 7.10 (s, 4H), 5.38 (t, *J* = 5.0 Hz, 2H), 3.51 (d, *J* = 5.1 Hz, 4H), 2.60 – 2.51 (m, 4H), 1.80 – 1.71 (m, 2H), 1.58 – 1.46 (m, 2H), 1.31 – 1.18 (m, 10H), 0.89 – 0.81 (m, 3H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ / ppm = 139.8, 138.8, 128.3 (2C), 128.0 (2C), 61.0, 60.2, 34.8, 33.3, 31.3, 31.1, 28.8, 28.7 (3C), 27.9, 22.1, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3354, 3261, 3034, 2952, 2920, 2872, 2851, 1600, 1515, 1469, 1456, 1439, 1417, 1242, 1117, 1067, 1045, 1030, 1020, 1002, 864, 824, 772, 764, 722.

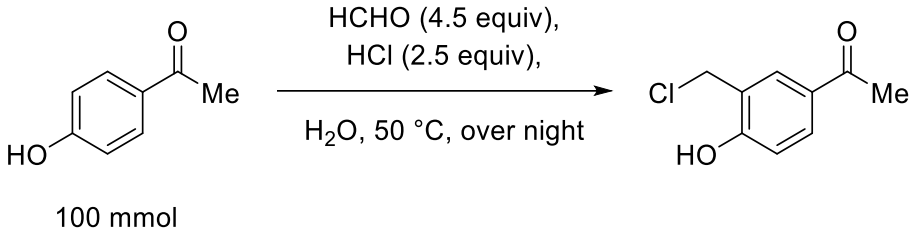
HRMS (FTMS-ESI): *m/z:* [M–Cl$^-$] calc. for [$C_{19}H_{34}NO_2^+$]: 308.25841; found 308.25845.

[M–H$^+$] calc. for [$C_{19}H_{33}ClNO_2^-$]: 342.22053; found 342.22131.

m.p. (°C): 228.3 – 233.5.

5.6 Synthesis of Salmeterol-d_7 (149)

1-(3-(chloromethyl)-4-hydroxyphenyl)ethan-1-one



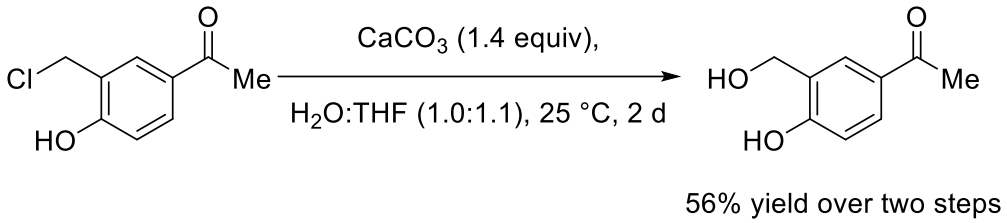
Scheme 140: Preparation of 1-(3-(chloromethyl)-4-hydroxyphenyl)ethan-1-one.

According to the literature[433], 4-Hydroxyacetophenone (13.62 g, 100 mmol, 1.0 equiv) was added *aq.* formaldehyde (37%, 33.5 mL, 450 mmol, 4.5 equiv) subsequently an aqueous solution of HCl (37%, 100 mL, 1223 mmol, 12.2 equiv) was added. The mixture was stirred over night at 50 °C. Filtration gave the crude title compound as a dark red solid which was used without further purification in the following step.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.80 (s, 1H), 4.70 (s, 2H), 2.57 (s, 3H).

1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethan-1-one

[433] N. Gisch, F. Pertenbreiter, J. Balzarini, C. Meier *J. Med. Chem.* **2008**, *51*, 8115 – 8123.

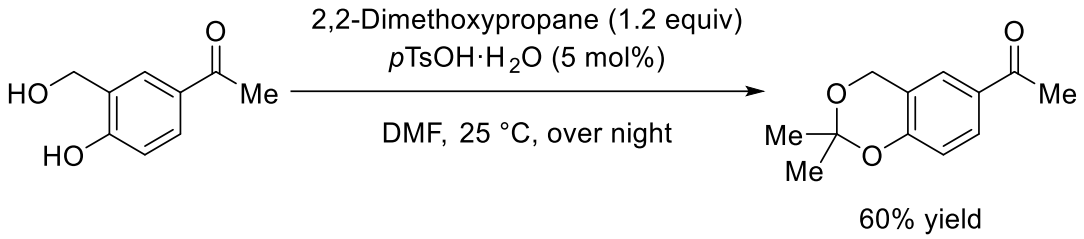


Scheme 141: Dechlorinative hydorxylation of 1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethan-1-one.

According to the literature[434], the crude 1-(3-(chloromethyl)-4-hydroxyphenyl)ethan-1-one was used without further purification and dissolved in THF (200 mL), and H_2O (175 mL). $CaCO_3$ (14.0 g, 140.0 mmol, 1.4 equiv) was added and the mixture was stirred for 2 d at 25 °C. The pH-value of the mixture was adjusted to pH = 6 by addition of aq. HCl (37%). The reaction mixture was extracted with EtOAc (3x200 mL). The combined organic layers were dried over $MgSO_4$. Flash column chromatographical purification (silica gel, DCM:MeOH = 19:1) afforded the title compound as a slightly pink solid (9.38 g, 56.4 mmol, 56% yield over two steps).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 2.0 Hz, 1H), 7.84 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 4.96 (s, 2H), 2.54 (s, 3H) 2.32 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 197.0, 161.0, 130.9, 129.8, 128.4, 124.2, 116.8, 65.0, 26.5.

1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethan-1-one



Scheme 142: Acetal protection of 1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethan-1-one.

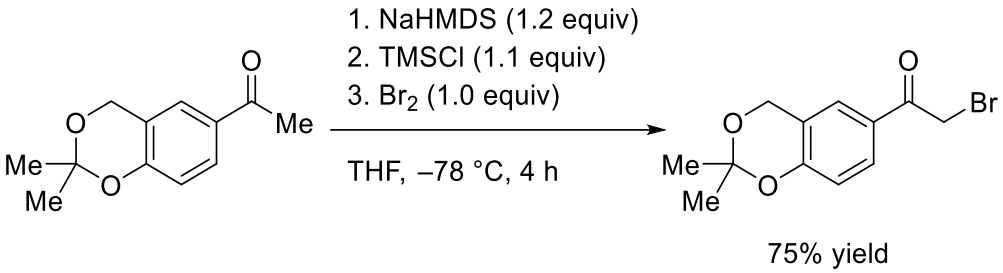
*p*TsOH·H_2O (0.52 g, 2.8 mmol, 5 mol%) was added to a mixture of 1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethan-1-one (9.38 g, 56.4, 1.00 equiv) and 2,2-dimethoxypropane (7.00 g, 67.2 mmol, 1.2 equiv) in DMF (60 mL). The mixture was stirred over night at 25 °C. The solution was diluted with Et_2O (400 mL) and washed with $NaHCO_3$ (3x200 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Solvents were removed *in vacuo* to give the title compound as a slightly orange solid (6.92 g, 33.6 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.79 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.67 – 7.63 (m, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 4.89 (s, 2H), 2.55 (s, 3H), 1.56 (s, 6H).

[434] N. Gisch, F. Pertenbreiter, J. Balzarini, C. Meier *J. Med. Chem.* **2008**, *51*, 8115 – 8123.

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 197.0, 155.8, 130.0, 129.2, 125.8, 119.3, 117.2, 100.7, 60.9, 26.5, 24.9 (2C).

2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethan-1-one



Scheme 143: Bromination of the methyl ketone.

NaHMDS (1.0 M in THF, 20 mmol, 20 mL, 1.2 equiv) was added dropwise to a solution of 1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)ethan-1-one (3.40 g, 16.5 mmol, 1.0 equiv) in THF (120 mL) at –78 °C. The mixture was stirred for 40 min at the same temperature before TMSCl (1.98 g, 18.2 mmol, 1.1 equiv) was added and the mixture was stirred for another 2 h at –78 °C. Br_2 (2.64 g, 16.5 mmol, 1.0 equiv) was added dropwise at –78 °C and stirring was continued for 1 h. The mixture was allowed to warm up to 25 °C and sat. aq. $Na_2S_2O_3$ (100 mL) was added. The aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Flash column chromatographical purification (silica gel, pentane:EtOAc = 9:1) afforded the title compound as a colorless oil (3.52 g, 12.3 mmol, 75% yield).

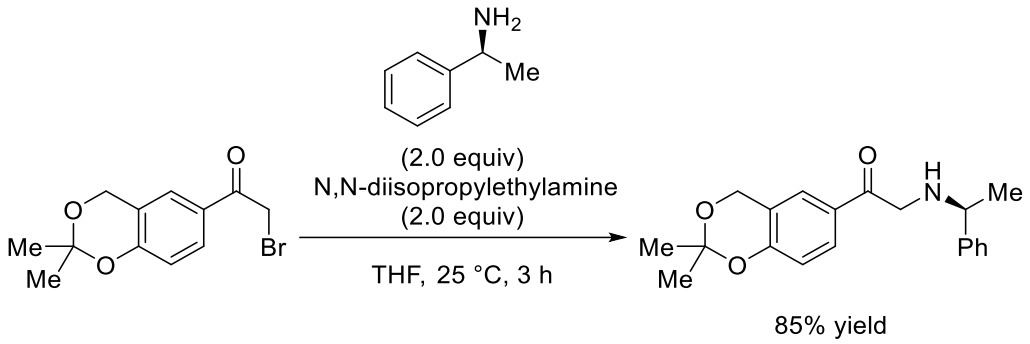
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.82 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.72 – 7.61 (m, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 4.89 (s, 2H), 4.38 (s, 2H), 1.57 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 190.1, 156.5, 129.8, 126.7, 126.6, 119.7, 117.5, 101.0, 60.8, 30.7, 25.0 (2C).

MS (EI, 70 eV): *m/z* (%) = 229 (15), 228 (15), 227 (14), 226 (15), 191 (16), 147 (24), 134 (10), 133 (100), 91 (14).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{12}H_{13}BrO3$]: 284.0048; found 284.0044.

(S)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-((1-phenylethyl)amino)ethan-1-one



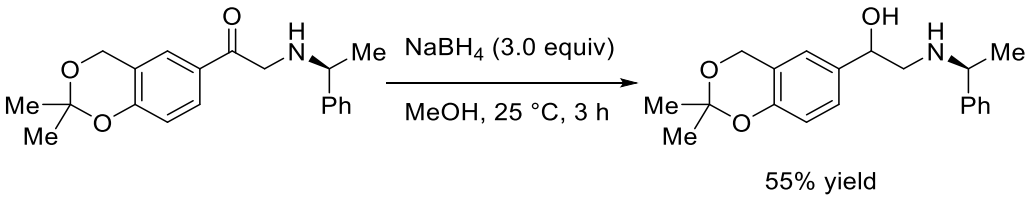
Scheme 144: Amination of the bromomethyl ketone using (S)-1-phenylethan-1-amine.

(S)-1-phenylethan-1-amine (2.9 g, 24.0 mmol, 2.0 equiv) was added at 0 °C to a solution of 2-bromo-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)ethan-1-one (3.4 g, 12.0 mmol, 1.0 equiv), *N*,*N*-diisopropyletylamine (3.1 g, 24.0 mmol, 2.0 equiv) and THF (26 mL). The mixture was stirred for 3 h at 25 °C. Solids were removed *via* filtration, solvents of the filtrate were removed *in vacuo* and the crude product was purified by flash column chromatograph (silica gel, pentane:EtOAc = 1:1) to give the title compound as a yellow oil (3.3 g, 10.1 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.68 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 4.84 (s, 2H), 3.91 (d, *J* = 1.7 Hz, 2H), 3.82 (q, *J* = 6.6 Hz, 1H), 1.54 (s, 6H), 1.43 (d, *J* = 6.6 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.3, 156.0, 144.9, 128.8 (2C), 128.4, 128.1, 127.4, 126.9 (2C), 125.3, 119.4, 117.3, 100.7, 60.8, 58.4, 53.3, 24.9, 24.9, 24.7.
MS (EI, 70 eV): *m/z* (%) = 134 (30), 133 (21), 120 (22), 105 (100), 77 (15).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{20}H_{23}NO_3$]: 325.1678; found 325.1662.

1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-(((S)-1-phenylethyl)amino)ethan-1-ol



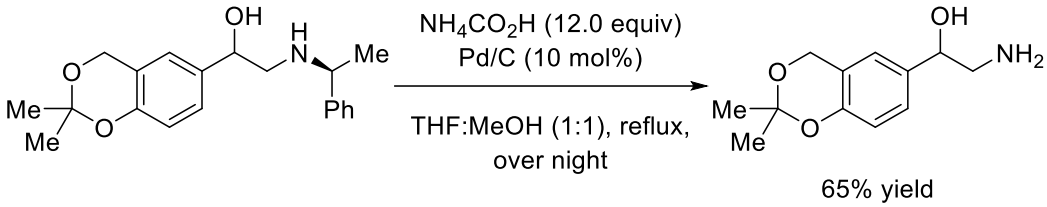
Scheme 145: $NaBH_4$ reduction towards the secondary alcohol.

$NaBH_4$ (1.13 g, 30.0 mmol, 3.0 equiv) was added to a mixture of (S)-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)-2-((1-phenylethyl)amino)ethan-1-one (3.31 g, 10.0 mmol, 1.0 equiv) in MeOH (40 mL) at 0 °C.The mixture was stirred for 1 h at this temperature before it was allowed to

warm up to 25 °C and stir for another 2 h at 25 °C. The mixture was filtered and the solid residue was washed with MeOH and H_2O to give the title compound as a colorless solid (1.81 g, 5.5 mmol, 55% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 (m, 4H), 7.24 (m, 1H), 7.06 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.94 (d, *J* = 2.1 Hz, 1H), 6.74 (dd, *J* = 8.5, 3.4 Hz, 1H), 4.80 (m, 2H), 4.56 (dd, *J* = 9.1, 3.4 Hz, 1H), 3.83 (q, *J* = 6.6 Hz, 1H), 2.74 (dd, *J* = 12.2, 3.6 Hz, 1H), 2.63 (dd, *J* = 12.2, 9.0 Hz, 1H), 1.53 (s, 6H), 1.45 (d, *J* = 6.6 Hz, 3H).

2-amino-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethan-1-ol (167)



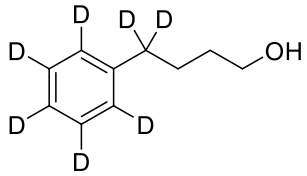
Scheme 146: Hydrogenative removal of the benzylic protecting group.

Pd/C (10 wt%, 0.53 g 0.5 mmol, 10 mol%) was added to a mixture of 1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)-2-(((S)-1-phenylethyl)amino)ethan-1-ol (1.81 g, 5.5 mmol, 1.0 equiv), ammonium formate (4.16 g, 66 mmol, 12.0 equiv) in a solvent mixture of THF (10 mL) and MeOH (10 mL). The mixture was heated to reflux, after 4 h another 30 mL of THF were added and the mixture was stirred overnight under reflux. The mixture was filtrated and the solid residues were washed with THF and MeOH. Solvent of the filtrate was removed *in vacuo* and the crude product was purified *via* flash column chromatograph (silica gel, DCM:MeOH = 9:1) to give the title compound **167** as a slightly brown solid (0.80 g, 3.6 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.12 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.84 (s, 2H), 4.55 (dd, *J* = 8.0, 3.9 Hz, 1H), 2.98 (dd, *J* = 12.8, 3.8 Hz, 1H), 2.78 (dd, *J* = 12.7, 7.9 Hz, 1H), 1.72 (s, 2H), 1.53 (d, *J* = 1.9 Hz, 6H).
^{1}H NMR (400 MHz, DMSO): δ / ppm = 7.10 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 4.80 (s, 2H), 4.43 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.97 (s, 2H), 2.69 (dd, *J* = 12.8, 4.1 Hz, 1H), 2.60 (dd, *J* = 12.8, 8.1 Hz, 1H), 1.45 (s, 6H).

^{13}C-NMR (100 MHz, DMSO): δ / ppm = 149.7, 135.7, 125.7, 122.6, 119.0, 116.0, 99.1, 73.0, 60.2, 49.2, 24.6, 24.5.

4-(phenyl-d_5)butan-4,4-d_2-1-ol (120au)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in toluene-d_8 (**118p**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 2 h. The reaction flask was cooled to –20 °C and a solution of oxetane (**112s´**, 23 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. Removal of the solvent afforded the title compound **120au** as a colorless oil (47 mg, 0.30 mmol, 75% yield) without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.65 (t, *J* = 6.4 Hz, 2H), 1.75 – 1.66 (m, 2H), 1.66 – 1.51 (m, 3H).

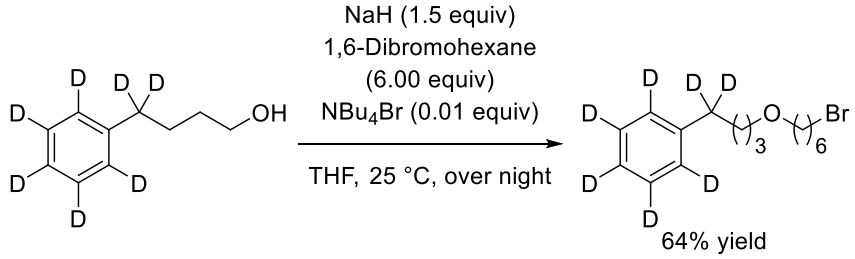
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.2, 128.1 (t, *J* = 23.7 Hz, 2C),127.9 (t, *J* = 24.2 Hz, 2C), 125.3 (t, *J* = 24.4 Hz), 62.8, 34.87 (p, *J* = 19.2 Hz), 32.3, 27.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3327, 2932, 2862, 2273, 1455, 1433, 1384, 1328, 1057, 1034, 1010, 948, 821.

MS (EI, 70 eV): *m/z* (%) = 138 (13), 137 (12), 123 (25), 122 (16), 110 (100), 109 (63), 108 (16), 98 (94), 97 (33), 96 (13), 83 (11), 70 (13).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{10}H_7D_7O$]: 157.1484; found 157.1478.

1-(4-((6-bromohexyl)oxy)butyl-1,1-d_2)benzene-2,3,4,5,6-d_5



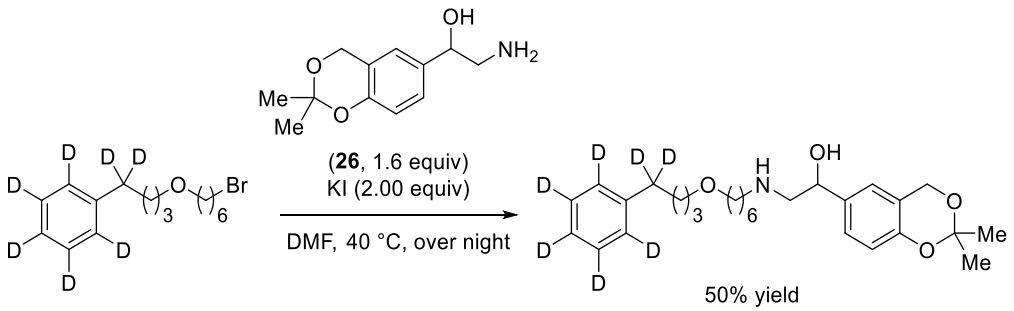
Scheme 147: Preparation of 1-(4-((6-bromohexyl)oxy)butyl-1,1-d_2)benzene-2,3,4,5,6-d_5 via ether formation.

NaH (40 mg, 0.68 mmol, 1.50 equiv) was added to a solution of 4-(phenyl-d_5)butan-4,4-d_2-1-ol (**120au**, 70 mg, 0.45 mmol, 1.00 equiv) in THF (5.0 mL) at 25 °C, after stirring for 20 min NBu_4Br (2 mg, 0.005 mmol, 0.01 equiv) and 1,6-dibromohexane (659 mg, 2.7 mmol, 6.00 equiv) were added. The mixture was stirred over night at 25 °C. H_2O (20 mL) was added and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Flash column chromatographical purification (silica gel, pentane → pentane:EtOAc = 9:1) afforded the title compound as a colorless oil (92 mg, 0.29 mmol, 64% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.47 – 3.36 (m, 6H), 1.87 (p, *J* = 6.9 Hz, 2H), 1.71 – 1.54 (m, 6H), 1.49 – 1.35 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.3, 128.0 (q, *J* = 23.6 Hz, 4C), 125.9 – 124.7 (m), 70.9, 70.8, 35.0 (p, *J* = 19.3 Hz), 34.0, 32.9, 29.7, 29.5, 28.1, 28.0, 25.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 2858, 1458, 1436, 1372, 1259, 1242, 1229, 1117.
MS (EI, 70 eV): *m/z* (%) = 138 (23), 137 (15), 111 (13), 110 (100), 109 (33), 98 (27), 97 (21), 96 (14), 83 (19), 55 (17), 43 (14), 41 (10).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{16}H_{18}D_7BrO$]: 319.1528; found .319.1498.

1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)((6-(4-(phenyl-d_5)butoxy-4,4-d_2)hexyl)amino)ethan-1-ol



Scheme 148: Formation of the acetal protected salemeterol precursor via alkylation of **26**.

According to the literature,[435] KI (62 mg, 0.37 mmol, 1.0 equiv) and 2-amino-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)ethan-1-ol (**167**, 134 mg, 0.6 mmol, 1.6 equiv) was added to a mixture of 1-(4-((6-bromohexyl)oxy)butyl-1,1-d_2)benzene-2,3,4,5,6-d_5 (121 mg, 0.37 mmol, 1.0 equiv) in DMF (2 mL). The reaction mixture was heated to 40 °C and stirred over night. KI (62 mg, 0.37 mmol, 1.0 equiv) was added another time and again the mixture was stirred over night at 40 °C. The mixture was allowed to cool to 25 °C EtOAc was added (20 mL), the organic layer was washed with brine (3x30 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Flash column chromatographical

[435] L. Jiang, C. Lin, Y. Qiu, X. Quan, J. Zhu, H. Shi, *J. Chem. Res.* **2016**, *40*, 564 – 566.

purification (silica gel, pentane:EtOAc:MeOH = 10:5:0.5 → EtOAc:MeOH = 19:1) afforded the title compound as a slightly brown resin (85 mg, 0.18 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.15 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.62 (s, 2H), 5.13 (td, *J* = 10.1, 9.6, 2.9 Hz, 1H), 4.77 (s, 2H), 3.38 (t, *J* = 6.2 Hz, 2H), 3.34 (t, *J* = 6.5 Hz, 2H), 3.09 – 2.83 (m, 4H), 1.79 1.69 (m, 2H), 1.66 – 1.48 (m, 12H), 1.37 1.29 (m, 4H).

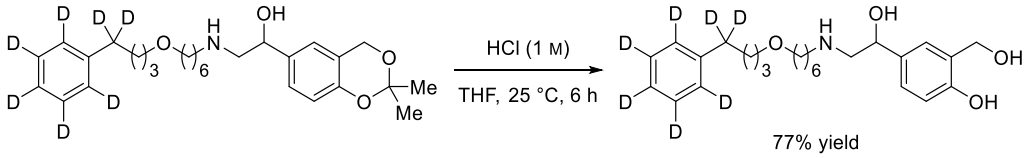
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.1, 142.3, 132.6, 128.1 (t, *J* = 23.1 Hz, 2C), 127.8 (t, *J* = 23.7 Hz, 2C), 125.8, 125.2 (t, *J* = 24.0 Hz), 122.4, 119.6, 117.3, 99.7, 70.8, 70.7, 69.4, 60.9, 55.6, 48.7, 35.0 (quintet, *J* = 19.2 Hz), 29.6, 29.4, 28.0, 26.8, 26.8, 25.9, 24.9, 24.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3332, 2994, 2937, 2859, 2798, 2248, 1620, 1594, 1500, 1454, 1384, 1374, 1356, 1263, 1202, 1144, 1117, 1063, 957, 908, 871, 823, 796, 727, 696.

MS (EI, 70 eV): *m/z* (%) = 270 (19), 269 (100), 135 (16), 112 (21), 98 (29), 97 (19), 96 (12), 55 (11), 44 (24).

HRMS (EI-orbitrap): *m/z:* [M + H^+] calc. for [$C_{28}H_{35}D_7NO_4^+$]: 463.3548; found: 463.3580.

Salmeterol-d_7 (149)



Scheme 149: Formation of salmeterol via acidic acetal deprotection.

According to the literature,[436] HCl (1.0 M, 0.5 mL) was added to a mixture of 1-(2,2-dimethyl-4H-benzo[*d*][1,3]dioxin-6-yl)-((6-(4-(phenyl-d_5)butoxy-4,4-d_2)hexyl)amino)ethan-1-ol (80 mg, 0.17 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was stirred for 6 h at 25 °C. The mixture was extracted with EtOAc (3x30 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The title compound **149** was obtained as a colorless solid (55 mg, 0.13 mmol, 77% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.98 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 5.13 (bs, 4H), 4.61 (s, 2H), 4.48 (t, *J* = 6.3 Hz, 1H), 3.40 (t, *J* = 6.2 Hz, 2H), 3.36 (t, *J* = 6.6 Hz, 2H), 2.70 – 2.59 (m, 2H), 2.59 – 2.46 (m, 2H), 1.68 – 1.57 (m, 4H), 1.56 – 1.48 (m, 2H), 1.47 – 1.38 (m, 2H), 1.33 – 1.22 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.8, 142.3, 133.5, 128.1 (t, *J* = 22.6 Hz, 2C), 127.9 (t, *J* = 23.8 Hz, 2C), 126.5, 126.3, 125.9, 125.3 (t, *J* = 23.5 Hz), 116.4, 71.4, 71.0, 70.9, 63.0, 56.6, 49.4, 35.0 (quintet, *J* = 19.8 Hz), 29.7, 29.4, 29.4, 28.0, 27.2, 26.1.

[436] L. Jiang, C. Lin, Y. Qiu, X. Quan, J. Zhu, H. Shi, *J. Chem. Res.* **2016**, *40*, 564 – 566.

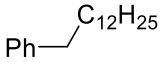
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3292, 2927, 2895, 2860, 1612, 1508, 1456, 1447, 1375, 1263, 1148, 1113, 1038, 825.

HRMS (FTMS-ESI): *m/z:* [M+H$^+$] calc. for [$C_{25}H_{31}D_7NO_4^+$]: 423.32347; found 423.32346.

[M–H$^+$] calc. for [$C_{25}H_{29}D_7NO_4^-$]: 421.30892; found 421.30862.

5.7 Synthesis of the SLAB 4-Tridecylbenzenesulfonic Acid (151)

tridecylbenzene (154t)



According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (12 min) into a flask charged with TMEDA (4.80 mmol, 1.7 equiv) in toluene (**118b**, 6.0 mL) and the resulting mixture was stirred at 25 °C for 2 h. The reaction flask was cooled to –20 °C and a solution of 1-chlorododecane (**153a**, 573 mg, 2.80 mmol, 1.0 equiv) in THF (7.0 mL) was added The reaction mixture was stirred at –20 °C for 10 min before it was allowed to warm to 25 °C and stirred overnight. Sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. Removal of the solvent afforded the title compound **154t** as a colorless oil (721 mg, 2.77 mmol, 99% yield) without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.38 – 7.31 (m, 2H), 7.25 (d, *J* = 7.3 Hz, 3H), 2.72 – 2.63 (m, 2H), 1.74 – 1.63 (m, 2H), 1.42 – 1.31 (m, 20H), 0.96 (t, *J* = 6.9 Hz, 3H).

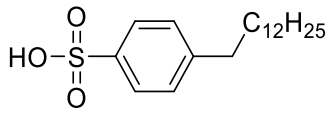
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.1, 128.5 (2C), 128.4 (2C), 125.7, 36.2, 32.1, 31.7, 29.9, 29.9 (2C), 29.8, 29.8, 29.7, 29.5, 29.5, 22.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2922, 2853, 1496, 1466, 1454, 744, 722, 696.

MS (EI, 70 eV): *m/z* (%) = 133 (12), 105 (10), 92 (93), 91 (100).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{19}H_{32}$]: 260.2504; found 260.2499.

4-tridecylbenzenesulfonic acid (151)



According to the literature[437], a solution of tridecylbenzene (**154t**, 500 mg, 1.92 mmol, 1.0 equiv) in $CHCl_3$ (5.0 mL) was prepared. Chlorosulfonic acid (**168**, 0.15 mL, 2.31 mmol, 1.2 equiv) was added at 0 °C and the mixture was stirred at the same temperatura for 3 h. Solvents were removed *in vacuo* and the obtained crude was dried over night under high vacuum. The residues were washed with small amounts of toluene and the solid residue was dried under vacuum to give the title compound **151** as grey solid (520 mg, 1.52 mmol, 80%).

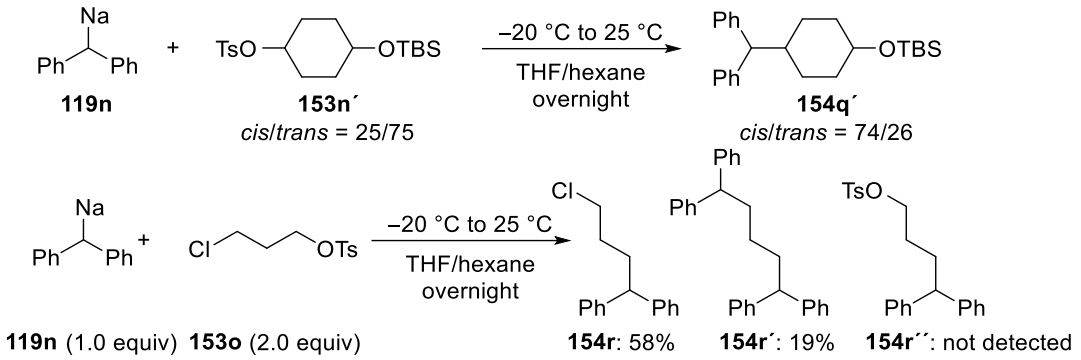
^{1}H-NMR (400 MHz, MeOD): δ / ppm = 7.73 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.62 (p, *J* = 6.4 Hz, 2H), 1.30 (m, 20H), 0.90 (t, *J* = 6.5 Hz, 3H).
^{13}C-NMR (100 MHz, MeOD): δ / ppm = 147.0, 143.1, 129.4 (2C), 127.0 (2C), 36.6, 33.1, 32.5, 30.8, 30.7 (3C), 30.7, 30.6, 30.5, 30.3, 23.7, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3389, 2956, 2922, 2872, 2852, 1716, 1126, 1035, 1008, 694.
MS (EI, 70 eV): *m/z* (%) = 340 (24), 292 (14), 172 (22), 139 (10), 123 (26), 92 (27), 91 (44), 71 (10), 61 (14), 57 (18), 55 (11), 45 (14), 43 (22), 43 (100), 41 (14).

HRMS (EI-orbitrap): *m/z:* [M] calc. for [$C_{19}H_{32}O_3S$]: 340.2072; found 340.2066.

m.p. (°C): 59.2 – 62.2.

[437] P. K. Bhowmik, A. Chang, J. Kim, E. J. Dizon, R. C. G. Principe, H. Han, *Crystals*, **2019**, *9*, 77.

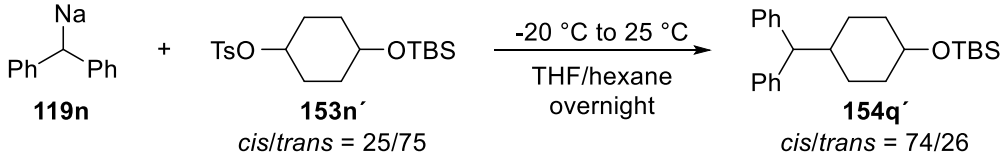
5.8 Stereo- amd Chemoselectivity studies on the Wurtz-type Coupling of Benzhydrylsodium (119n)



Scheme 150: Stereo- amd chemoselectivity studies on the Wurtz-type coupling of benzhydrylsodium (**119n**).

To exclude the possibility that the inversion of the stereochemistry during the reaction towards **154q** is due to an energetically favorable formation of the *cis*-product, the sequence was repeated using a mixture of *cis* and *trans* (25/75) electrophile **153n´**. As expected the stereochemistry was indeed inverted and the product **154q´** was obtained as a diastereomeric mixture (*cis*/*trans* = 74/26). Furthermore, we treated **119n** (1.0 equiv) with 3-chloropropyl tosylate (**153o**, 2.0 equiv). Substitution of the tosylate was the major pathway producing the alkylchloride **154r** in 58% yield. Whereas the twofold substitution took place to smaller degree (**154r´**, 19%). The chlorine-substituted product **154r´´** was not detected.

((4-benzhydrylcyclohexyl)oxy)(tert-butyl)dimethylsilane (154q´)



Scheme 151: Reaction of benzhydrylsodium (**119n**) with the none steropure **153**.

According to **TP13**, a solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected (2 min) into a flask charged with TMEDA (0.80 mmol, 2.0 equiv) in diphenylmethane (**118n**, 1.0 mL) and the resulting mixture was stirred at 25 °C for 30 min. The reaction flask was cooled to –20 °C and a solution of 4-((tert-butyldimethylsilyl)oxy)cyclohexyl 4-methylbenzenesulfonate (**153n**, 154 mg, 0.40 mmol, 1.0 equiv, *cis*/*trans* : 25/75) in THF (1.0 mL) was added. The reaction mixture was stirred at –20 °C for 10 min followed by another 30 min at 25 °C,

before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compound **154q´** as a colorless oil (*cis*/*trans* : 74/26)[438].

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.32 (m, 4H), 7.31 – 7.26 (m, 4H), 7.19 – 7.13 (m, 2H), 3.95 (tt, *J* = 4.7, 2.1 Hz, 1H), 3.65 (d, *J* = 11.2 Hz, 1H), 2.27 – 2.10 (m, 1H), 1.71 – 1.59 (m, 2H), 1.51 – 1.31 (m, 6H), 0.93 (s, 9H), 0.05 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.6 (2C), 128.5 (4C), 128.2 (4C), 126.1 (2C), 67.2, 58.4, 40.4, 33.3 (2C), 26.0 (3C), 25.9 (2C), 18.3, -4.7 (2C).

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.32 (m, 4H), 7.31 – 7.26 (m, 4H), 7.19 – 7.13 (m, 2H), 3.65 – 3.52 (m, 1H), 3.45 (d, *J* = 10.7 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.86 – 1.82 (m, 2H), 1.51 – 1.31 (m, 6H), 0.91 (s, 9H), 0.07 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.5 (2C), 128.6 (4C), 128.1 (4C), 126.2 (2C), 72.0, 59.3, 40.5, 35.9 (2C), 26.0 (3C), 26.1 (2C), 18.4, -4.43 (2C).

Mixture:

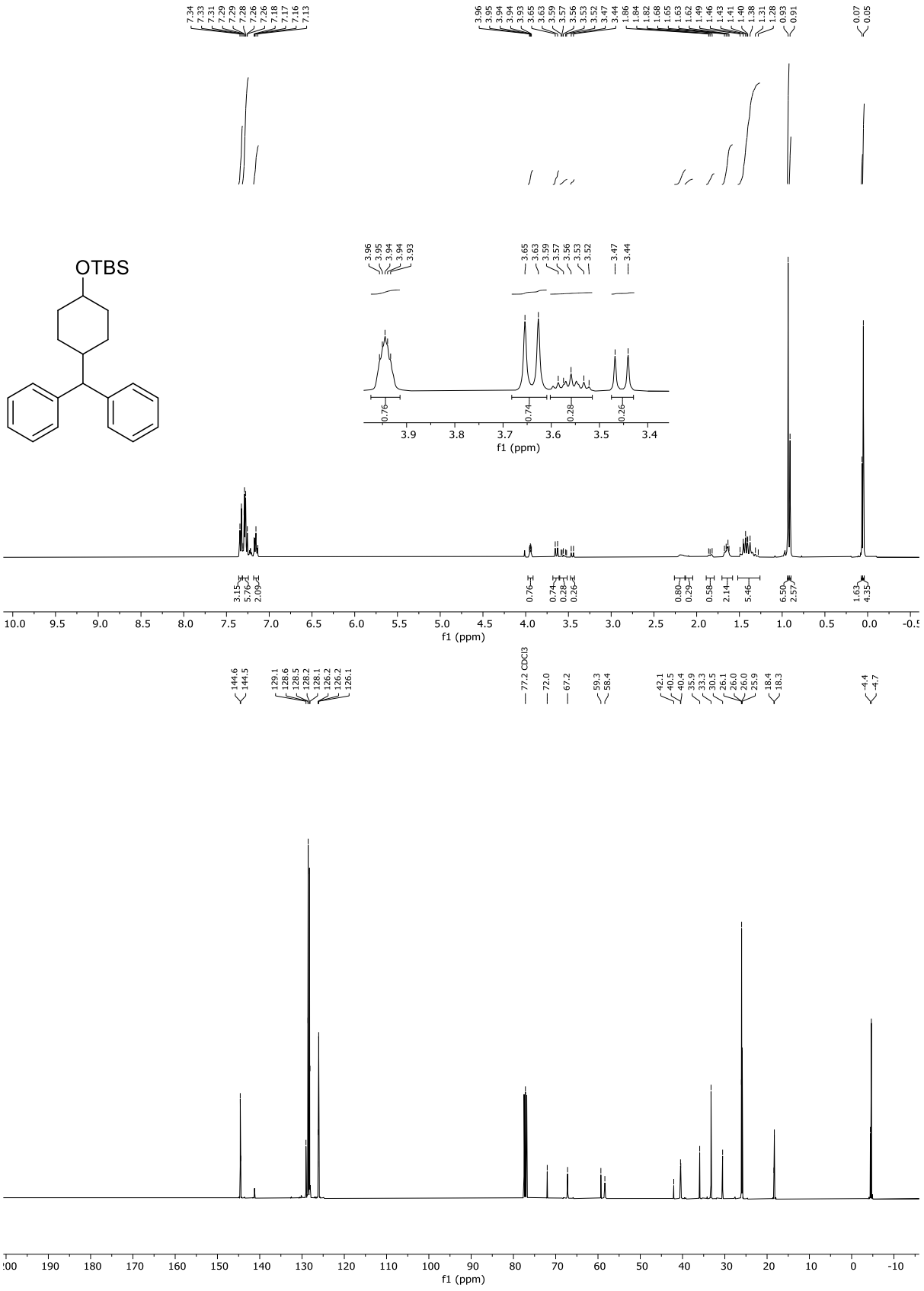
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3027, 2928, 2884, 2856, 1598, 1494, 1472, 1462, 1450, 1376, 1360, 1250, 1181, 1155, 1090, 1049, 1022, 1005, 964, 939, 912, 886, 863, 832, 772, 752, 743, 700, 675.

MS (EI, 70 eV): *m/z* (%) = 324 (10), 323 (41), 247, (17), 169 (22), 168 (13), 167 (100), 165 (34), 152 (20), 143 (25), 117 (12), 75 (39).

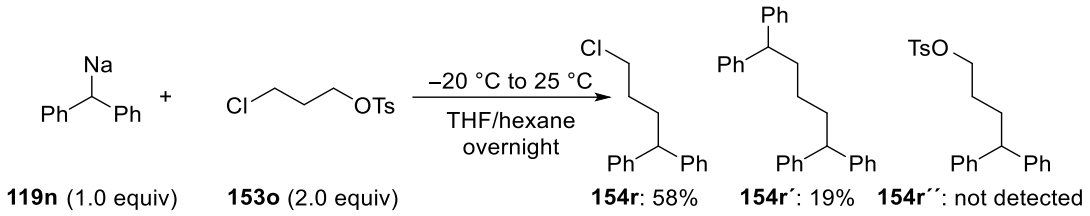
HRMS (EI-orbitrap): *m/z:* [M – CH_3] calc. for [$C_{24}H_{33}OSi$]: 365.2301; found 365.2295.

[438] Ratio was determined by ^{1}H-NMR.

((4-benzhydrylcyclohexyl)oxy)(tert-butyl)dimethylsilane (154q´)



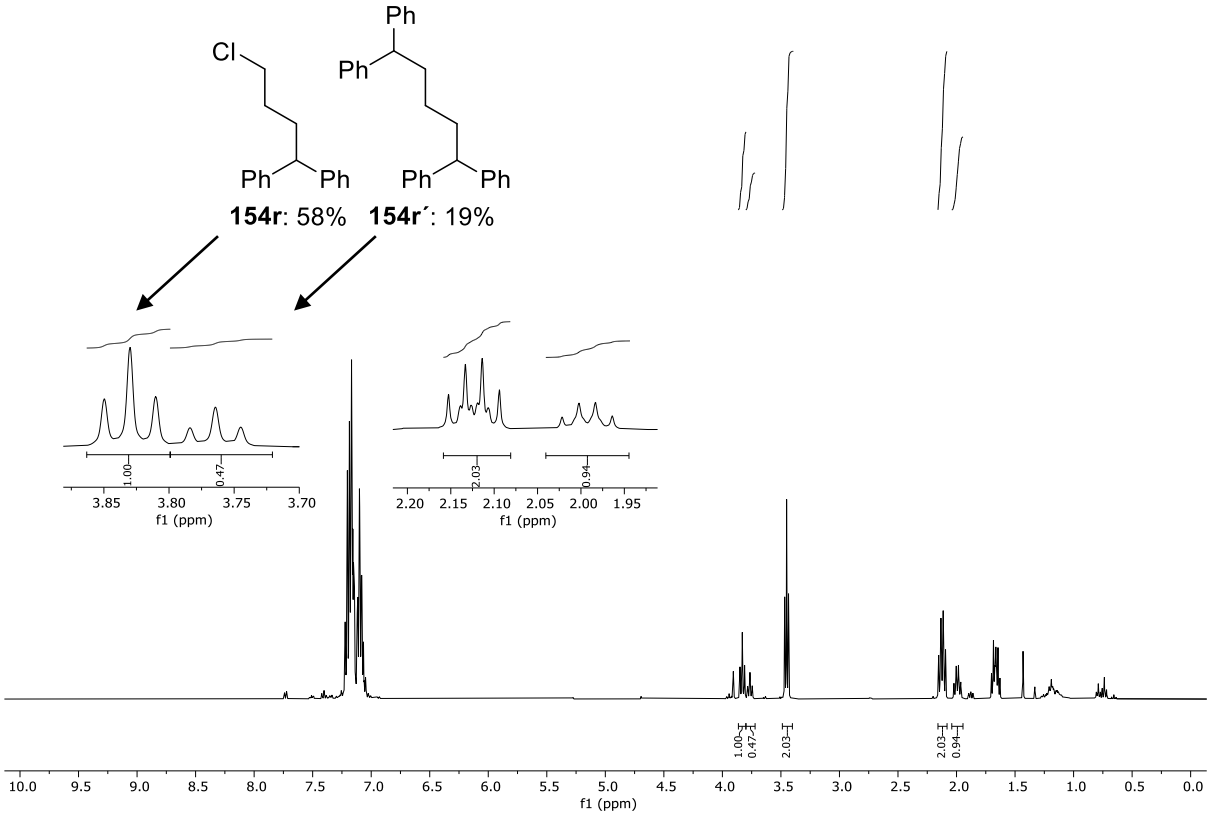
(4-chlorobutane-1,1-diyl)dibenzene (154r)



Scheme 152: Reaction of benzhydrylsodium (**119n**) with the chloropropy tosylate **153o.**

According to **TP14**, A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and diphenylmethane (**118n**, 67 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 30 min at 25 °C. Before it was cooled to –40 °C and a solution of 3-chloropropyl 4-methylbenzenesulfonate (**153o**, 199 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at –40 °C for 1 h followed by another 1 h at 25 °C, before sat. *aq.* NH_4Cl solution was added for quenching the reaction mixture. The aqueous layer was extracted three times with EtOAc (3×30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash column chromatographical purification (silica gel, pentane:EtOAc = 100:0 → 98:2) afforded the title compounds as a mixture of **154r**:**154r´** = 1.0:0.3[439] (total yield: 84 mg, **154r**: 0.23 mmol, 58% yield; **154r´:** 0.08 mmol, 19 % yield corresponding to a total conversion of **118n** of 96%. **154r´´** was not detected).

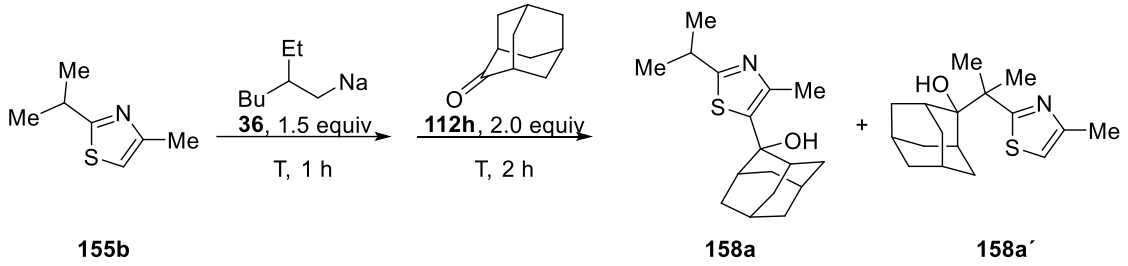
[439] Ratio was determined by ^{1}H-NMR.


Cl
Ph
Ph
Ph
Ph
Ph
Ph
154r: 58%
154r´: 19%
1.00
0.47
3.85
3.80
3.75
3.70
f1 (ppm)
2.03
0.94
2.20
2.15
2.10
2.05
2.00
1.95
f1 (ppm)
1.00
0.47
2.03
2.03
0.94
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

5.9 Temperature Influence on the Metalation Site of 2-Isopropyl-4-Methylthiazole (155b)

A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-isopropyl-4-methylthiazole (**155b**, 56 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at the corresponding temperature (T = –40 to 25 °C). Before a solution of adamantanone (**112h**, 120 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at the corresponding temperature for 2 h before an aliquot was taken and analysed by GC.

Table 34: Temperature screening for the sodiation of 2-isopropyl-4-methylthiazole (155b).



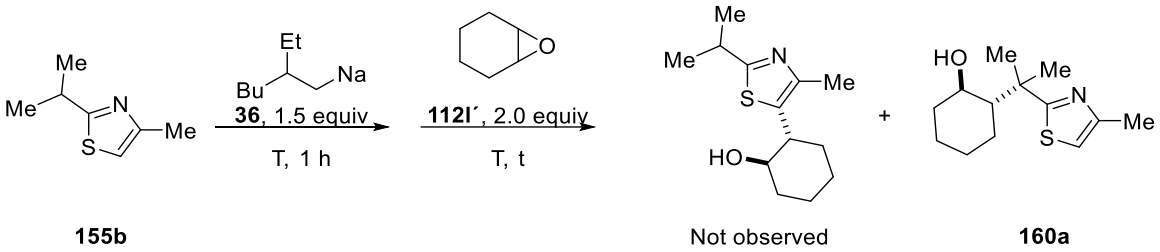
155b **158a** **158a´**

Entry	T [°C]	Conversion (**155b**) [%]	Ratio **158a**/**158a´**[a]
1	–40	93	99/1
2	–20	92	90/10
3	0	87	70/30
4	25	88	42/58

[a] Ratio was determined comparing the integrated area under the curve after GC-analysis.

A solution of 3-(chloromethyl)heptane (**115**, 0.2 M, 2.0 equiv) in *n*-hexane was prepared. The solution of **115** was pumped through the activated sodium packed-bed reactor (see **TP1**) by pump A (flow rate: 2.0 mL/min) into the precooling loop (V_{pre2} = 0.35 mL) at 25 °C. Subsequently upon reaching the steady state, it was injected for 2 min into a flask charged with a solution of TMEDA (0.80 mmol, 2.0 equiv) and 2-isopropyl-4-methylthiazole (**155b**, 56 mg, 0.40 mmol, 1.0 equiv) in hexane (2.0 mL) the mixture was stirred for 1 h at the corresponding temperature (T = –40 to 25 °C). Before a solution of cyclohexene oxide (**112l´**, 79 mg, 0.80 mmol, 2.0 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at the corresponding temperature for 2 h before an aliquot was taken and analysed by GC. A second aliquot was taken and analysed after stirring for 20 h at the corresponding temperature.

Table 35: Temperature screening for the sodiation of 2-isopropyl-4-methylthiazole (155b).



155b Not observed **160a**

Entry	T [°C]	t [h]	Conversion (**155b**) [%]	Normalized GC-Yield **160a**[a]
1	–40	2	22	11
2	–20	2	38	41
3	0	2	78	87
4	25	2	93	47
5	–40	20	49	18
6	–20	20	98	71
7	0	20	90	100
8	25	20	94	46

[a]The largest integrated area under the curve corresponding to the product **160a** was normalized to 100% GC-yield the other integrals were adjusted accordingly.

5.10 Single Crystal X-ray Diffraction Studies

trans-2-(naphthalen-1-ylmethyl)cyclohexan-1-ol (120v)

Single crystals of compound **120v**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. The X-ray intensity data were measured on a 'D8 Venture' system equipped with a 'Bruker D8 Venture TXS' 'rotating-anode X-ray tube' ('Mo Kα', λ = 0.71073 Å) and a 'multilayer mirror optics' monochromator.
Data collection[440], data reduction[441] and cell refinement[442] were performed with the Bruker specific software. Absorption correction using the multiscan method was applied. The structures were solved with SHELXS-97,[443] refined with SHELXL-97[444] and finally checked using PLATON.[445] Details for data collection and structure refinement are summarized in Table 36.
CCDC-2158223 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[440] Program package 'Bruker Instrument Service v3.0.21'.
[441] Program package 'SAINT V8.18C (Bruker AXS Inc., 2011)'.
[442] Program package 'APEX2 v2012.4-3 (Bruker AXS)'.
[443] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany
[444] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany
[445] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands

Table 36: Details for X-ray data collection and structure refinement for compound **120v**.

	120v
Empirical formula	$C_{17}H_{20}O$
Formula mass	240.33
T[K]	173(2)
Crystal size [mm]	0.16 × 0.04 × 0.02
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	11.7544(8)
b [Å]	5.1712(4)
c [Å]	22.3353(15)
α [°]	90.0
β [°]	99.832(2)
γ [°]	90.0
V [Å^3]	1337.70(16)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.193
μ [mm^{-1}]	0.072
F(000)	520
Θ range [°]	3.52 – 25.24
Index ranges	$-15 \leq h \leq 15$
	$-6 \leq k \leq 6$
	$-28 \leq l \leq 28$
Reflns. collected	37157
Reflns. obsd.	2523
Reflns. unique	3062 (R_{int} = 0.0598)
R_1, wR_2 (2σ data)	0.0509, 0.1078
R_1, wR_2 (all data)	0.0651, 0.1142
GOOF on F^2	1.093
Peak/hole [e Å^{-3}]	0.216 / -0.228

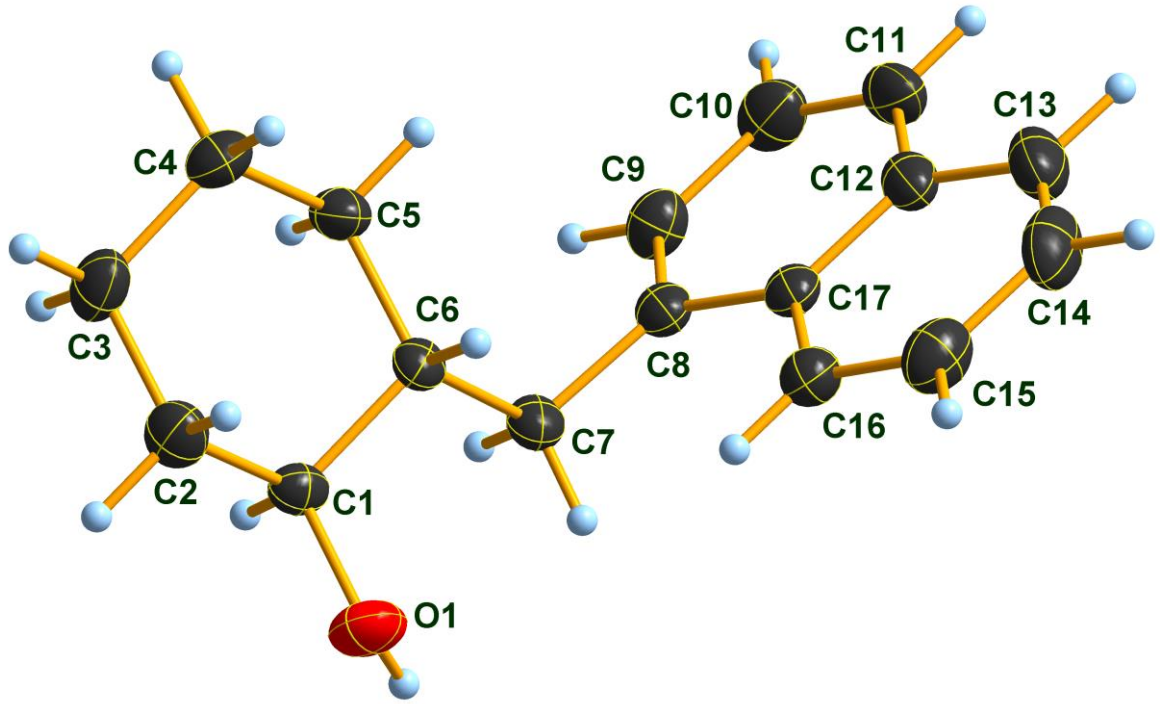


Figure 28: Molecular structure of compound **120v** in the crystal. DIAMOND[446] representation; thermal ellipsoids are drawn at 50 % probability level. The hydrogen atom of the OH group is disordered over two positions; only the more strongly occupied position is shown.

Table 37: Selected bond lengths (Å) of compound **120v**.

O1 – C1	1.431(2)	C16 – C15	1.367(2)
C1 – C2	1.519(2)	C8 – C9	1.370(2)
C1 – C6	1.529(2)	C2 – C3	1.522(2)
C6 – C5	1.530(2)	C11 – C10	1.351(2)
C6 – C7	1.540(2)	C11 – C12	1.418(2)
C5 – C4	1.521(2)	C13 – C14	1.354(3)
C4 – C3	1.520(2)	C13 – C12	1.414(2)
C17 – C16	1.422(2)	C9 – C10	1.407(2)
C17 – C12	1.427(2)	C15 – C14	1.409(2)
C17 – C8	1.429(2)	C7 – C8	1.509(2)

Table 38: Selected bond angles (°) of compound **120v**.

O1 – C1 – C2	109.2(1)	C9 – C8 – C17	119.0(1)
O1 – C1 – C6	111.7(1)	C9 – C8 – C7	119.8(1)
C2 – C1 – C6	112.5(1)	C17 – C8 – C7	121.2(1)

[446] DIAMOND, Crystal Impact GbR., Version 3.2i.

C1 – C6 – C5	110.3(1)	C1 – C2 – C3	111.3(1)
C1 – C6 – C7	110.6(1)	C10 – C11 – C12	120.8(1)
C5 – C6 – C7	111.9(1)	C14 – C13 – C12	121.2(2)
C4 – C5 – C6	112.6(1)	C13 – C12 – C11	121.7(1)
C3 – C4 – C5	110.8(1)	C13 – C12 – C17	119.1(1)
C16 – C17 – C12	118.0(1)	C11 – C12 – C17	119.1(1)
C16 – C17 – C8	123.0(1)	C8 – C9 – C10	121.8(2)
C12 – C17 – C8	119.0(1)	C11 – C10 – C9	120.3(2)
C8 – C7 – C6	114.6(1)	C4 – C3 – C2	111.1(1)
C15 – C16 – C17	121.1(1)	C16 – C15 – C14	120.3(2)
C13 – C14 – C15	120.3(2)		

Table 39: Selected torsion angles (°) of compound **120v**.

O1 – C1 – C6 – C5	-176.3(1)	C6 – C1 – C2 – C3	55.0(2)
C2 – C1 – C6 – C5	-53.1(2)	C14 – C13 – C12 – C11	-179.7(2)
O1 – C1 – C6 – C7	59.4(2)	C14 – C13 – C12 – C17	-0.3(2)
C2 – C1 – C6 – C7	-177.5(1)	C10 – C11 – C12 – C13	178.3(2)
C1 – C6 – C5 – C4	53.6(2)	C10 – C11 – C12 – C17	-1.1(2)
C7 – C6 – C5 – C4	177.1(1)	C16 – C17 – C12 – C13	0.3(2)
C6 – C5 – C4 – C3	-55.6(2)	C8 – C17 – C12 – C13	-179.0(1)
C1 – C6 – C7 – C8	-177.7(1)	C16 – C17 – C12 – C11	179.8(1)
C5 – C6 – C7 – C8	59.0(2)	C8 – C17 – C12 – C11	0.5(2)
C12 – C17 – C16 – C15	-0.1(2)	C17 – C8 – C9 – C10	-1.5(2)
C8 – C17 – C16 – C15	179.2(1)	C7 – C8 – C9 – C10	178.8(1)
C16 – C17 – C8 – C9	-178.5(1)	C12 – C11 – C10 – C9	0.5(2)
C12 – C17 – C8 – C9	0.8(2)	C8 – C9 – C10 – C11	0.8(2)
C16 – C17 – C8 – C7	1.2(2)	C5 – C4 – C3 – C2	56.1(2)
C12 – C17 – C8 – C7	-179.5(1)	C1 – C2 – C3 – C4	-56.0(2)
C6 – C7 – C8 – C9	-102.2(2)	C17 – C16 – C15 – C14	-0.2(2)
C6 – C7 – C8 – C17	78.1(2)	C12 – C13 – C14 – C15	0.0(3)
O1 – C1 – C2 – C3	179.6(1)	C16 – C15 – C14 – C13	0.2(2)

(((1*R*,2*S*)-2-methoxycyclohexyl)methylene)dibenzene (154o)

Single crystals of compound **154o**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[447] Absorption correction using the multiscan method[448] was applied. The structures were solved with SHELXS-97,[449] refined with SHELXL-97[450] and finally checked using PLATON.[451] Details for data collection and structure refinement are summarized in Table 40.

CCDC-2158222 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[447] Program package 'CrysAlisPro 1.171.40.84a (Rigaku OD, 2020)'.
[448] Program package 'CrysAlisPro 1.171.40.84a (Rigaku OD, 2020)'.
[449] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[450] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[451] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 40: Details for X-ray data collection and structure refinement for compound **154o**.

	154o
Empirical formula	$C_{20}H_{24}O$
Formula mass	280.39
T[K]	123(2)
Crystal size [mm]	0.40 × 0.30 × 0.25
Crystal description	colorless block
Crystal system	Orthorhombic
Space group	*P*212121
a [Å]	5.9937(2)
b [Å]	14.6073(6)
c [Å]	18.3043(7)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	1602.57(10)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.162
μ [mm^{-1}]	0.069
F(000)	608
Θ range [°]	2.23 – 25.24
Index ranges	$-7 \leq h \leq 7$
	$-19 \leq k \leq 19$
	$-24 \leq l \leq 24$
Reflns. collected	27266
Reflns. obsd.	3446
Reflns. unique	3947 (R_{int} = 0.0451)
R_1, wR_2 (2σ data)	0.0443, 0.0979
R_1, wR_2 (all data)	0.0537, 0.1029
GOOF on F^2	1.040
Peak/hole [e Å^{-3}]	0.307 / -0.152

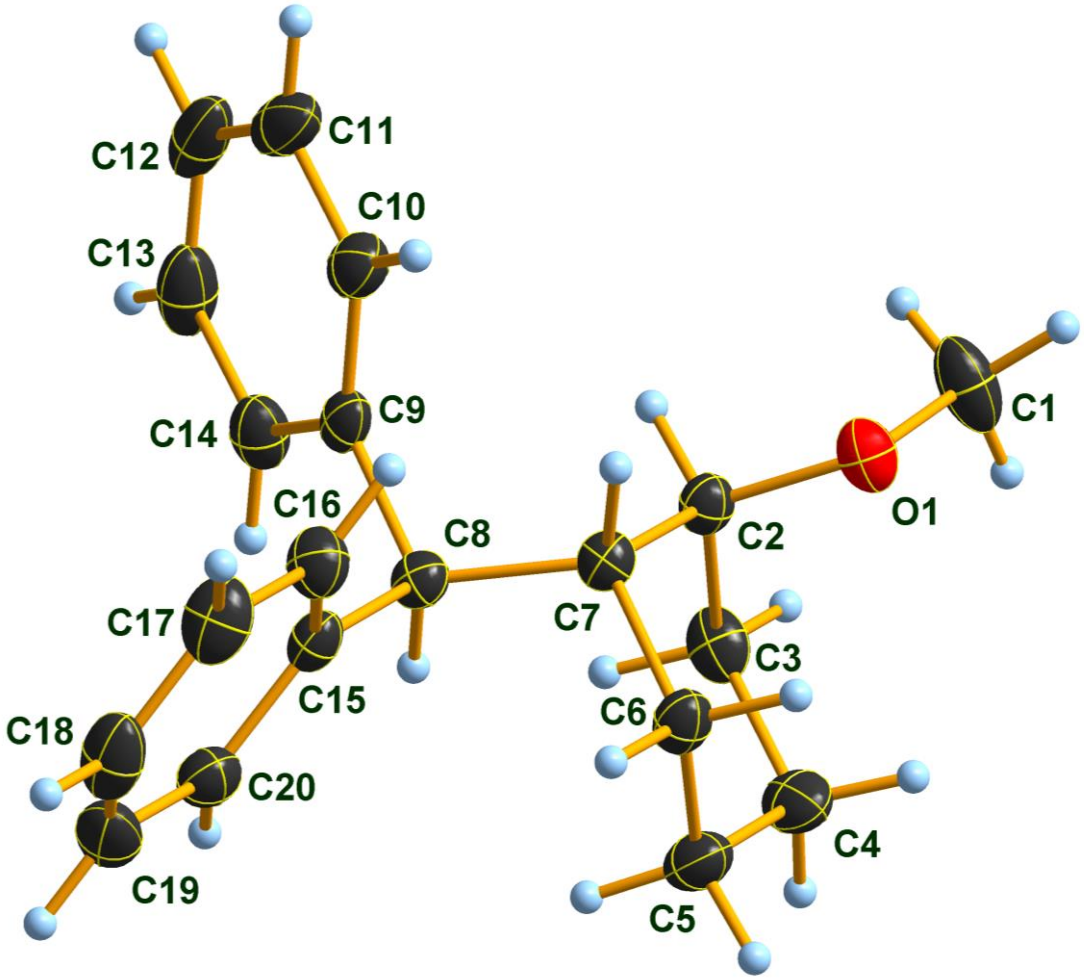


Figure 29: Molecular structure of compound **154o** in the crystal. DIAMOND[452] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 41: Selected bond lengths (Å) of compound **154o**.

O1 – C1	1.427(3)	C16 – C17	1.394(3)
O1 – C2	1.435(2)	C10 – C11	1.391(3)
C6 – C5	1.526(3)	C20 – C19	1.391(3)
C6 – C7	1.541(3)	C19 – C18	1.373(4)
C2 – C3	1.530(3)	C18 – C17	1.389(4)
C2 – C7	1.538(3)	C11 – C12	1.382(4)
C8 – C15	1.528(3)	C13 – C12	1.378(4)
C8 – C9	1.530(3)	C13 – C14	1.397(3)
C8 – C7	1.549(3)	C15 – C16	1.394(3)
C9 – C10	1.392(3)	C15 – C20	1.394(3)
C9 – C14	1.394(3)	C3 – C4	1.527(3)

[452] DIAMOND, Crystal Impact GbR., Version 3.2i.

C5 – C4	1.532(3)		

Table 42: Selected bond angles (°) of compound **154o**.

C1 – O1 – C2	112.3(2)	C17 – C16 – C15	120.8(2)
C5 – C6 – C7	112.7(2)	C11 – C10 – C9	120.6(2)
O1 – C2 – C3	111.8(2)	C19 – C20 – C15	121.0(2)
O1 – C2 – C7	106.7(2)	C3 – C4 – C5	110.4(2)
C3 – C2 – C7	111.0(2)	C18 – C19 – C20	120.4(2)
C15 – C8 – C9	110.8(2)	C19 – C18 – C17	119.7(2)
C15 – C8 – C7	112.9(2)	C12 – C11 – C10	120.3(2)
C9 – C8 – C7	113.0(2)	C12 – C13 – C14	120.2(2)
C10 – C9 – C14	118.6(2)	C18 – C17 – C16	120.1(2)
C10 – C9 – C8	122.2(2)	C9 – C14 – C13	120.4(2)
C14 – C9 – C8	119.2(2)	C13 – C12 – C11	119.8(2)
C6 – C5 – C4	110.8(2)	C2 – C7 – C6	109.8(2)
C16 – C15 – C20	118.1(2)	C2 – C7 – C8	110.6(2)
C16 – C15 – C8	122.4(2)	C6 – C7 – C8	113.0(2)
C20 – C15 – C8	119.5(2)	C4 – C3 – C2	111.3(2)

Table 43: Selected torsion angles (°) of compound **154o**.

C1 – O1 – C2 – C3	64.2(2)	O1 – C2 – C3 – C4	61.2(2)
C1 – O1 – C2 – C7	-174.2(2)	C7 – C2 – C3 – C4	-57.8(2)
C15 – C8 – C9 – C10	74.8(2)	C20 – C15 – C16 – C17	0.1(3)
C7 – C8 – C9 – C10	-53.0(2)	C8 – C15 – C16 – C17	178.5(2)
C15 – C8 – C9 – C14	-104.2(2)	C14 – C9 – C10 – C11	0.2(3)
C7 – C8 – C9 – C14	128.0(2)	C8 – C9 – C10 – C11	-178.8(2)
C7 – C6 – C5 – C4	55.3(2)	C16 – C15 – C20 – C19	-0.1(3)
C9 – C8 – C15 – C16	-75.5(2)	C8 – C15 – C20 – C19	-178.7(2)
C7 – C8 – C15 – C16	52.3(2)	C2 – C3 – C4 – C5	57.5(2)
C9 – C8 – C15 – C20	102.9(2)	C6 – C5 – C4 – C3	-55.7(2)
C7 – C8 – C15 – C20	-129.3(2)	C15 – C20 – C19 – C18	0.1(3)
O1 – C2 – C7 – C6	-66.8(2)	C20 – C19 – C18 – C17	0.1(3)
C3 – C2 – C7 – C6	55.2(2)	C9 – C10 – C11 – C12	0.1(3)
O1 – C2 – C7 – C8	167.8(2)	C19 – C18 – C17 – C16	-0.1(4)
C3 – C2 – C7 – C8	-70.2(2)	C15 – C16 – C17 – C18	0.1(3)
C5 – C6 – C7 – C2	-54.7(2)	C10 – C9 – C14 – C13	-0.5(3)
C5 – C6 – C7 – C8	69.3(2)	C8 – C9 – C14 – C13	178.6(2)

C15 – C8 – C7 – C2	178.3(2)	C12 – C13 – C14 – C9	0.4(3)
C9 – C8 – C7 – C2	-55.1(2)	C14 – C13 – C12 – C11	-0.1(3)
C15 – C8 – C7 – C6	54.7(2)	C10 – C11 – C12 – C13	-0.2(3)
C9 – C8 – C7 – C6	-178.6(2)		

***cis*-4-(tert-butyl)cyclohexyl)methylene)dibenzene (154p)**

Single crystals of compound **154p**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[453] Absorption correction using the multiscan method[454] was applied. The structures were solved with SHELXS-97,[455] refined with SHELXL-97[456] and finally checked using PLATON.[457] Details for data collection and structure refinement are summarized in Table 44.

CCDC-2158220 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[453] Program package 'CrysAlisPro 1.171.40.84a (Rigaku OD, 2020'.
[454] Program package 'CrysAlisPro 1.171.40.84a (Rigaku OD, 2020'.
[455] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[456] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[457] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 44: Details for X-ray data collection and structure refinement for compound **154p**.

	154p
Empirical formula	$C_{23}H_{30}$
Formula mass	306.47
T[K]	123(2)
Crystal size [mm]	0.40 × 0.25 × 0.10
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*m*
a [Å]	5.9437(3)
b [Å]	14.9446(7)
c [Å]	10.7329(6)
α [°]	90.0
β [°]	104.224(5)
γ [°]	90.0
V [Å^3]	924.13(8)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.101
μ [mm^{-1}]	0.061
F(000)	336
Θ range [°]	2.39 – 25.24
Index ranges	$-8 \leq h \leq 8$
	$-20 \leq k \leq 20$
	$-14 \leq l \leq 14$
Reflns. collected	16402
Reflns. obsd.	1926
Reflns. unique	2564 (R_{int} = 0.0460)
R_1, wR_2 (2σ data)	0.0493, 0.1194
R_1, wR_2 (all data)	0.0686, 0.1326
GOOF on F^2	1.030
Peak/hole [e Å^{-3}]	0.359 / -0.197

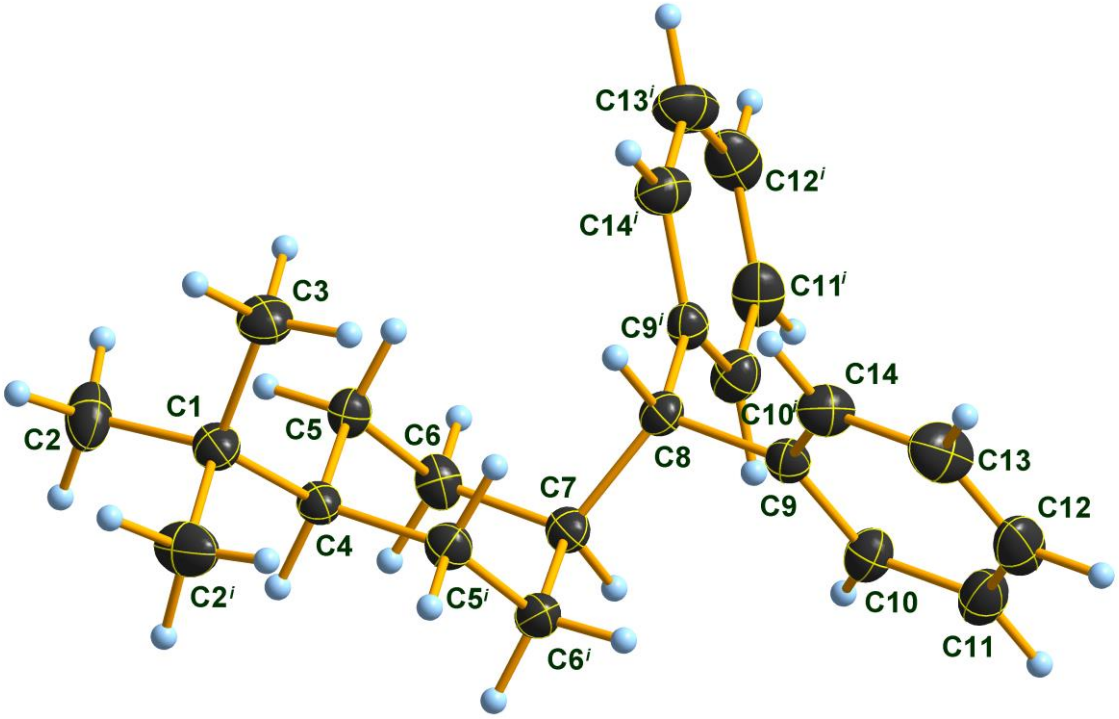


Figure 30: Molecular structure of compound **154p** in the crystal. DIAMOND[458] representation; thermal ellipsoids are drawn at 50 % probability level. Symmetry code: *i*: x, 0.5-y, z.

Table 45: Selected bond lengths (Å) of compound **154p**. Symmetry code: *i*: x, 0.5-y, z.

C1 – C2	1.531(2)	C12 – C13	1.377(2)
C1 – C2^i	1.531(2)	C12 – C11	1.382(2)
C1 – C3	1.533(2)	C8 – C9	1.523(1)
C1 – C4	1.551(2)	C8 – C9^i	1.523(1)
C5 – C6	1.532(2)	C8 – C7	1.556(2)
C5 – C4	1.533(1)	C14 – C9	1.392(2)
C6 – C7	1.533(1)	C14 – C13	1.392(2)
C10 – C11	1.388(2)	C9 – C10	1.395(2)

Table 46: Selected bond angles (°) of compound **154p**. Symmetry code: *i*: x, 0.5-y, z.

C2 – C1 – C2^i	108.0(1)	C13 – C12 – C11	119.6(1)
C2 – C1 – C3	108.7(1)	C9 – C8 – C9^i	112.0(1)
C2^i – C1 – C3	108.7(1)	C9 – C8 – C7	112.1(1)
C2 – C1 – C4	109.7(1)	C9^i – C8 – C7	112.1(1)
C2^i – C1 – C4	109.7(1)	C6^i – C7 – C6	109.3(1)
C3 – C1 – C4	112.0(1)	C6^i – C7 – C8	112.1(1)

[458] DIAMOND, Crystal Impact GbR., Version 3.2i.

C6 – C5 – C4	111.4(1)	C6 – C7 – C8	112.1(1)
$C5^{i}$ – C4 – C5	108.8(1)	C9 – C14 – C13	120.9(1)
$C5^{i}$ – C4 – C1	114.6(1)	C14 – C9 – C10	117.9(1)
C5 – C4 – C1	114.6(1)	C14 – C9 – C8	120.0(1)
C5 – C6 – C7	112.7(1)	C10 – C9 – C8	122.1(1)
C12 – C11 – C10	120.2(1)	C11 – C10 – C9	121.0(1)
C12 – C13 – C14	120.3(1)		

Table 47: Selected torsion angles (°) of compound **154p**. Symmetry code: *i*: x, 0.5-y, z.

C6 – C5 – C4 – $C5^{i}$	57.2(1)	C9 – C8 – C7 – C6	-54.9(2)
C6 – C5 – C4 – C1	-173.2(1)	C13 – C14 – C9 – C10	0.4(2)
C2 – C1 – C4 – $C5^{i}$	-175.8(1)	C13 – C14 – C9 – C8	179.7(1)
C2 – C1 – C4 – $C5^{i}$	-57.4(2)	C9 – C8 – C9 – C14	108.4(1)
C3 – C1 – C4 – $C5^{i}$	63.4(1)	C7 – C8 – C9 – C14	-124.6(1)
C2 – C1 – C4 – C5	57.4(2)	C9 – C8 – C9 – C10	-72.3(2)
C2 – C1 – C4 – C5	175.8(1)	C7 – C8 – C9 – C10	54.7(1)
C3 – C1 – C4 – C5	-63.4(1)	C14 – C9 – C10 – C11	-0.4(2)
C4 – C5 – C6 – C7	-57.1(1)	C8 – C9 – C10 – C11	-179.7(1)
C5 – C6 – C7 – $C6^{i}$	53.6(2)	C13 – C12 – C11 – C10	0.1(2)
C5 – C6 – C7 – C8	-71.2(1)	C9 – C10 – C11 – C12	0.2(2)
C9 – C8 – C7 – $C6^{i}$	54.9(2)	C11 – C12 – C13 – C14	-0.1(2)
C9 – C8 – C7 – $C6^{i}$	-178.2(1)	C9 – C14 – C13 – C12	-0.1(2)
C9 – C8 – C7 – C6	178.2(1)		

2-((5-methylthiazol-2-yl)methyl)adamantan-2-ol (156a)

Single crystals of compound **156a**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[459] Absorption correction using the multiscan method[460] was applied. The structures were solved with SHELXS-97,[461] refined with SHELXL-97[462] and finally checked using PLATON.[463] Details for data collection and structure refinement are summarized in Table 48.

CCDC-2158221 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[459] Program package 'CrysAlisPro 1.171.40.84a (Rigaku OD, 2020'.
[460] Program package 'CrysAlisPro 1.171.40.84a (Rigaku OD, 2020'.
[461] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[462] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[463] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 48: Details for X-ray data collection and structure refinement for compound **156a**.

	156a
Empirical formula	$C_{15}H_{21}NOS$
Formula mass	263.39
T[K]	123(2)
Crystal size [mm]	0.40 × 0.30 × 0.15
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*n*
a [Å]	6.4494(2)
b [Å]	15.6555(7)
c [Å]	13.3328(5)
α [°]	90.0
β [°]	94.321(3)
γ [°]	90.0
V [Å^3]	1342.37(9)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.303
μ [mm^{-1}]	0.229
F(000)	568
Θ range [°]	2.01 – 25.24
Index ranges	$-9 \leq h \leq 9$
	$-22 \leq k \leq 22$
	$-19 \leq l \leq 19$
Reflns. collected	27047
Reflns. obsd.	3282
Reflns. unique	4089 (R_{int} = 0.0435)
R_1, wR_2 (2σ data)	0.0418, 0.1000
R_1, wR_2 (all data)	0.0560, 0.1091
GOOF on F^2	1.055
Peak/hole [e Å^{-3}]	0.360 / -0.173

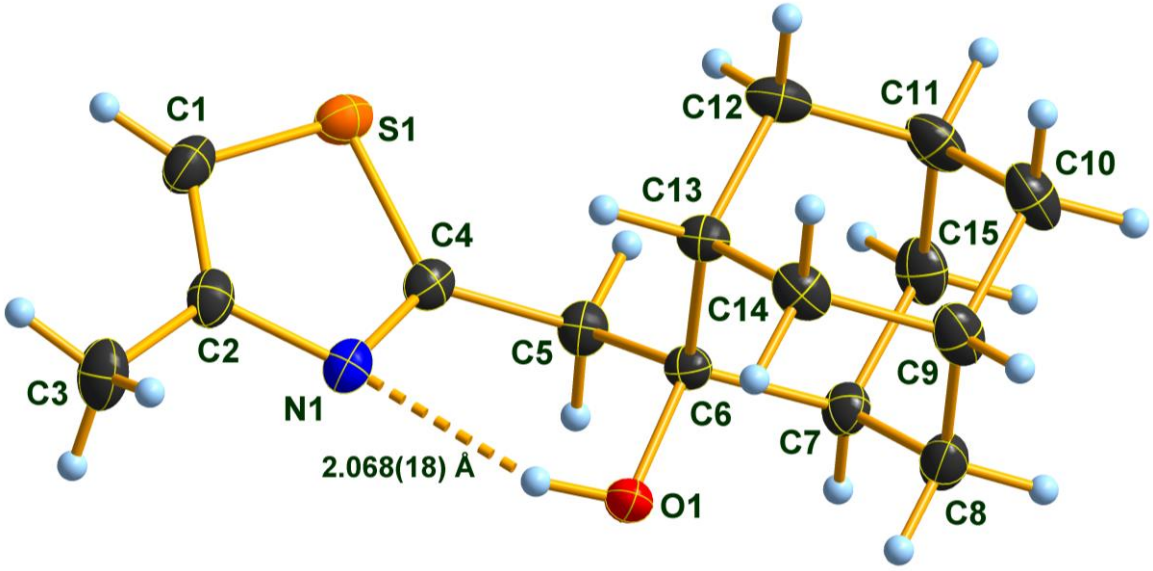


Figure 31: Molecular structure of compound **156a** in the crystal. DIAMOND[464] representation; thermal ellipsoids are drawn at 50 % probability level. Symmetry code: *i*: x, 0.5-y, z.

Table 49: Selected bond lengths (Å) of compound **156a**.

S1 – C1	1.715(2)	C11 – C15	1.533(2)
S1 – C4	1.725(1)	C11 – C12	1.537(2)
C6 – O1	1.444(1)	C11 – C10	1.537(2)
C6 – C7	1.541(2)	C2 – C1	1.363(2)
C6 – C13	1.543(2)	C2 – C3	1.493(2)
C6 – C5	1.545(2)	C7 – C8	1.535(2)
C4 – N1	1.310(2)	C7 – C15	1.541(2)
C4 – C5	1.497(2)	C9 – C8	1.534(2)
C13 – C14	1.537(2)	C9 – C14	1.534(2)
C13 – C12	1.540(2)	C9 – C10	1.536(2)
N1 – C2	1.384(2)		

Table 50: Selected bond angles (°) of compound **156a**.

C1 – S1 – C4	89.7(1)	C2 – C1 – S1	110.4(1)
O1 – C6 – C7	106.7(1)	C9 – C14 – C13	109.9(1)
O1 – C6 – C13	110.1(1)	C15 – C11 – C12	109.7(1)
C7 – C6 – C13	108.4(1)	C15 – C11 – C10	109.2(1)
O1 – C6 – C5	107.5(1)	C12 – C11 – C10	109.3(1)
C7 – C6 – C5	110.7(1)	C11 – C12 – C13	109.8(1)
C13 – C6 – C5	113.3(1)	C11 – C15 – C7	109.9(1)

[464] DIAMOND, Crystal Impact GbR., Version 3.2i.

N1 – C4 – C5	123.4(1)	C9 – C10 – C11	109.2(1)
N1 – C4 – S1	114.1(1)	C8 – C7 – C15	108.4(1)
C5 – C4 – S1	122.5(1)	C8 – C7 – C6	109.7(1)
C14 – C13 – C12	108.6(1)	C15 – C7 – C6	110.6(1)
C14 – C13 – C6	109.4(1)	C8 – C9 – C14	109.2(1)
C12 – C13 – C6	110.5(1)	C8 – C9 – C10	109.6(1)
C4 – N1 – C2	111.4(1)	C14 – C9 – C10	109.6(1)
C1 – C2 – N1	114.5(1)	C9 – C8 – C7	109.8(1)
C1 – C2 – C3	126.5(1)	C4 – C5 – C6	112.6(1)
N1 – C2 – C3	119.1(1)		

Table 51: Selected torsion angles (°) of compound **156a**.

C1 – S1 – C4 – N1	-0.3(1)	S1 – C4 – C5 – C6	127.8(1)
C1 – S1 – C4 – C5	-179.9(1)	O1 – C6 – C5 – C4	65.0(1)
O1 – C6 – C13 – C14	56.0(1)	C7 – C6 – C5 – C4	-178.8(1)
C7 – C6 – C13 – C14	-60.4(1)	C13 – C6 – C5 – C4	-56.9(1)
C5 – C6 – C13 – C14	176.4(1)	N1 – C2 – C1 – S1	-0.7(2)
O1 – C6 – C13 – C12	175.5(1)	C3 – C2 – C1 – S1	179.3(1)
C7 – C6 – C13 – C12	59.1(1)	C4 – S1 – C1 – C2	0.6(1)
C5 – C6 – C13 – C12	-64.1(1)	C8 – C9 – C14 – C13	-59.7(1)
C5 – C4 – N1 – C2	179.6(1)	C10 – C9 – C14 – C13	60.4(1)
S1 – C4 – N1 – C2	0.0(1)	C12 – C13 – C14 – C9	-60.0(1)
C4 – N1 – C2 – C1	0.5(2)	C6 – C13 – C14 – C9	60.6(1)
C4 – N1 – C2 – C3	-179.6(1)	C15 – C11 – C12 – C13	59.0(1)
O1 – C6 – C7 – C8	-58.1(1)	C10 – C11 – C12 – C13	-60.7(1)
C13 – C6 – C7 – C8	60.5(1)	C14 – C13 – C12 – C11	60.2(1)
C5 – C6 – C7 – C8	-174.7(1)	C6 – C13 – C12 – C11	-59.7(1)
O1 – C6 – C7 – C15	-177.5(1)	C12 – C11 – C15 – C7	-58.9(1)
C13 – C6 – C7 – C15	-59.0(1)	C10 – C11 – C15 – C7	60.8(1)
C5 – C6 – C7 – C15	65.8(1)	C8 – C7 – C15 – C11	-60.7(1)
C14 – C9 – C8 – C7	59.5(1)	C6 – C7 – C15 – C11	59.6(1)
C10 – C9 – C8 – C7	-60.5(1)	C8 – C9 – C10 – C11	59.8(2)
C15 – C7 – C8 – C9	60.3(1)	C14 – C9 – C10 – C11	-59.9(2)
C6 – C7 – C8 – C9	-60.5(1)	C15 – C11 – C10 – C9	-59.9(1)
N1 – C4 – C5 – C6	-51.7(2)	C12 – C11 – C10 – C9	60.1(2)

6. Continuous Flow Sodiation of Substituted Acrylonitriles, Alkenyl Sulfides and Acrylates

6.1 Typical Procedures and Screening of Reaction Conditions

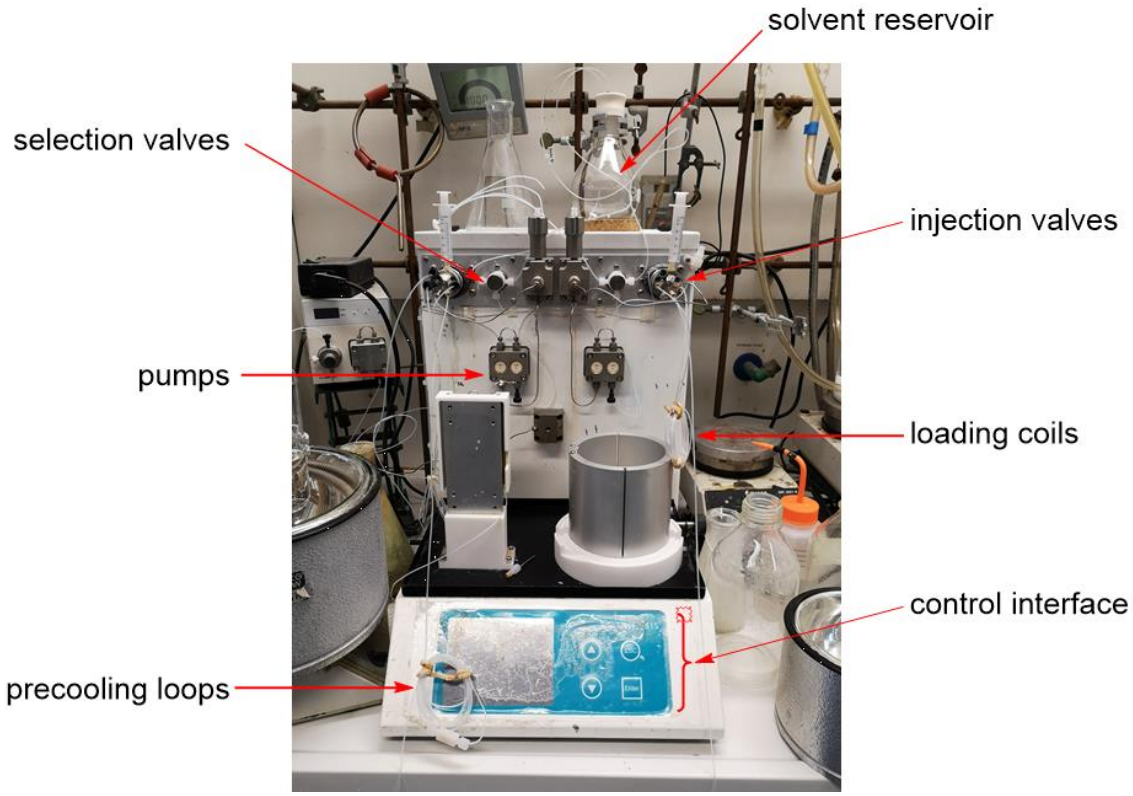
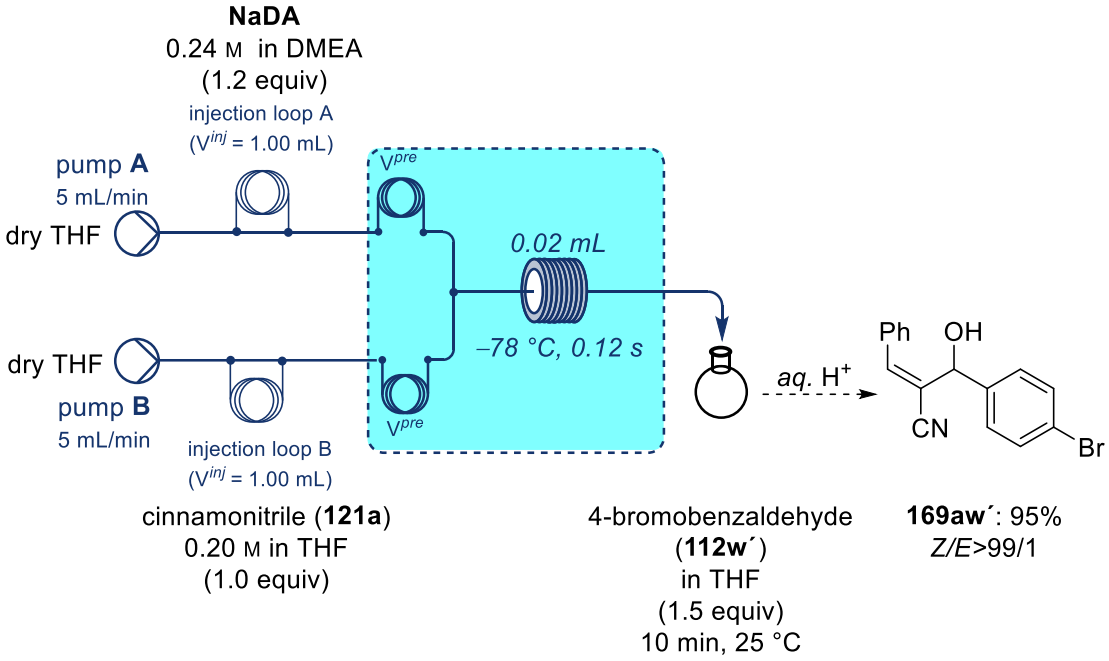


Figure 32: Picture of the standard continuous flow reaction set-up.

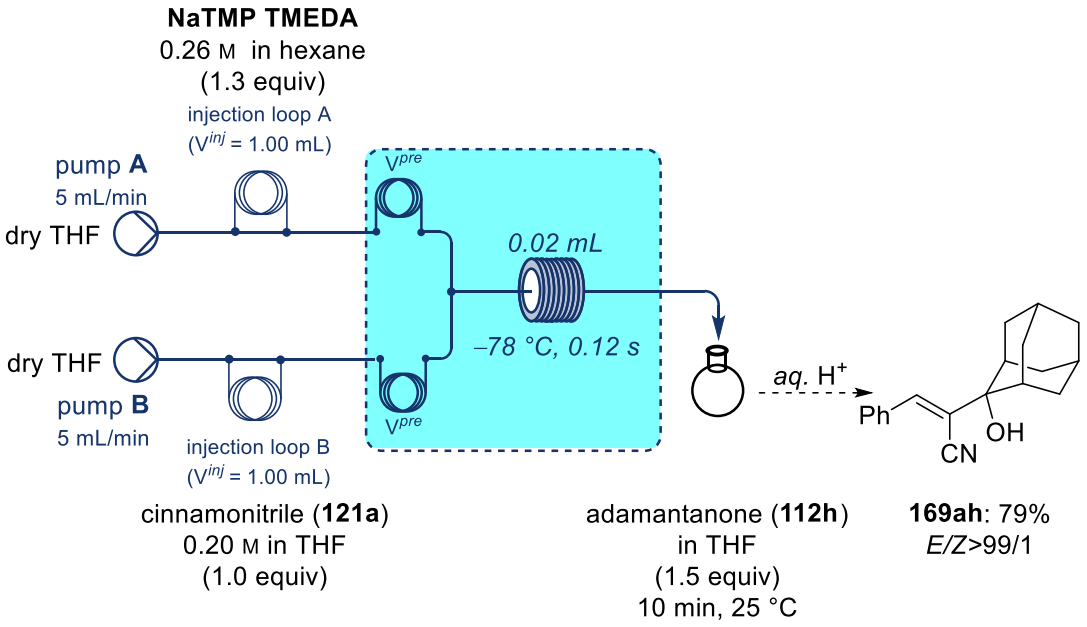
6.1.1 Typical procedure 16 (TP16) using a Uniqsis flow setup (Scheme 153): Sodiation of (substituted) acrylonitriles and alkenes using NaDA and subsequent batch quench with various electrophiles leading to functionalized acrylonitriles and alkenes.



Scheme 153: Uniqsis flow setup for the sodiation of cinnamonitrile (**121a**) using a microflow reactor and subsequent batch quench of the intermediate organosodium **2a** with 4-bromobenzaldehyde (**112w´**) leading to secondary alcohol **169aw´**.

A NaDa solution (0.24 M, 1.2 equiv) in DMEA and a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 1.0 equiv) in THF were prepared. Injection loop A (V^{inj} =1.0 mL) was loaded with the NaDA solution and injection loop B (V^{inj} =1.0 mL) was loaded with the solution of cinnamonitrile (**121a**). The solutions were simultaneously injected into separate streams of THF (flow-rates: 5 mL·min^{-1}), which each passed a pre-cooling loop (V^{pre} = 1.0 mL, T^1 = –78 °C, residence time: 12 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (V^R = 0.02 mL; residence time: t^1 = 0.12 s, T^1 = –78 °C) and was subsequently injected in a flask containing a stirred, solution of 4-bromobenzaldehyde (**112w´**, 56 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was further stirred for 10 minutes at 25 °C and quenched with a *sat. aq.* NH_4Cl solution. The aqueous phase was extracted with EtOAc and the organic phases were dried and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169aw´** as colorless crystals (64 mg, 0.19 mmol, 95% yield; *Z/E* > 99/1).

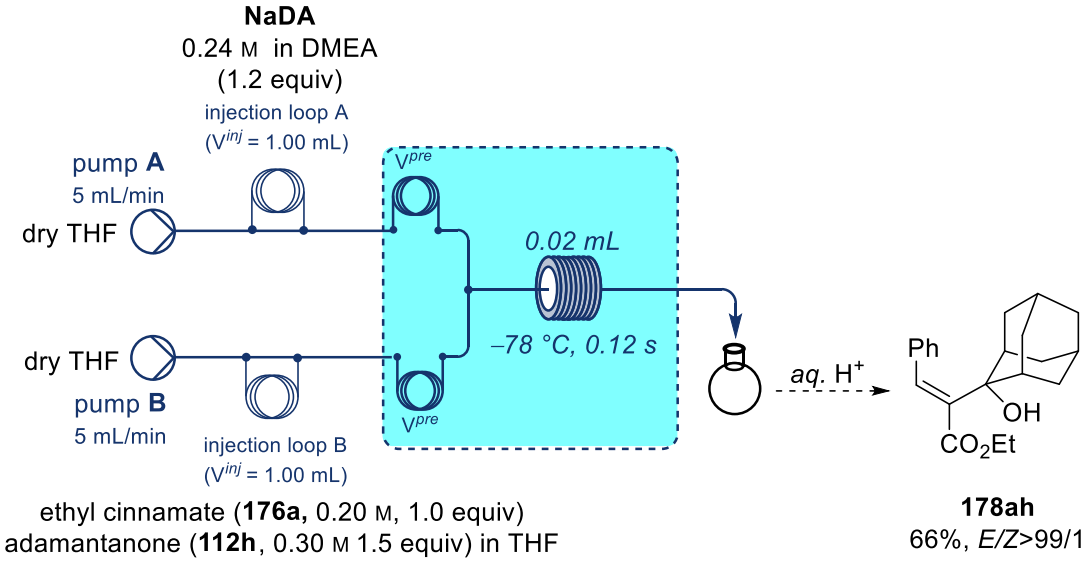
6.1.2 Typical procedure 17 (TP17) using a Uniqsis flow setup (Scheme 154): Sodiation of (substituted) acrylonitriles and alkenes using NaTMP and subsequent batch quench with various electrophiles leading to functionalized acrylonitriles and alkenes.



Scheme 154: Uniqsis flow setup for the sodiation of cinnamonitrile (**121a**) using a microflow reactor and subsequent batch quench of the intermediate organosodium **2a** with 2-adamantanone (**112h**) leading to tertiary alcohol **169ah**.

A NaTMP solution (0.26 M, 1.2 equiv) in hexane and a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 1.0 equiv; *E/Z* > 99/1) in THF were prepared. Injection loop A (V^{inj} =1.0 mL) was loaded with the NaTMP solution and injection loop B (V^{inj} =1.0 mL) was loaded with the solution of cinnamonitrile (**121a**). The solutions were simultaneously injected into separate streams of THF (flow-rates: 5 mL·min^{-1}), which each passed a pre-cooling loop (V^{pre} = 1.0 mL, T^1 = –78 °C, residence time: 12 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (V^R = 0.02 mL; residence time: t^1 = 0.12 s, T^1 = –78 °C) and was subsequently injected in a flask containing a stirred, solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was further stirred for 10 minutes at 25 °C and quenched with a *sat. aq.* NH_4Cl solution. The aqueous phase was extracted with EtOAc and the organic phases were dried and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ah** as colorless oil (44 mg, 0.16 mmol, 79% yield; *E/Z* > 99/1).

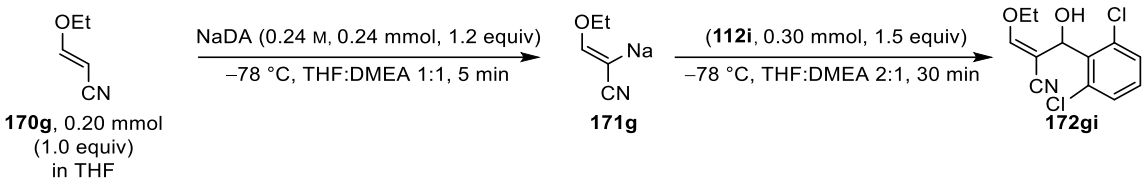
6.1.3 Typical procedure 18 (TP18) using a Uniqsis flow setup (Scheme 155): Sodiation of (substituted) acrylonitriles and alkenes using NaDA and under Barbier-type condtitions with various electrophiles leading to functionalized acrylonitriles and alkenes.



Scheme 155: Uniqsis flow setup for the sodiation of ethyl cinnamate (**176a**) using a microflow reactor under Barbier-type conditions with adamantanone (**112h**) leading to tertiary alcohol **178ah**.

A solution of ethyl cinnamate (**176a**, 0.20 M, 35 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* > 99/1) and adamantanone (**112h**, 45 mg, 0.30 mmol, 1.5 equiv) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. Injection loop A (V^{inj} =1.0 mL) was loaded with the NaDA solution and injection loop B (V^{inj} =1.0 mL) was loaded with the solution of ethyl cinnamate (**176a**) and adamantanone (**112h**). The solutions were simultaneously injected into separate streams of THF (flow-rates: 5 mL·min^{-1}), which each passed a pre-cooling loop (V^{pre} = 1.0 mL, T^1 = –78 °C, residence time: 12 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (V^R = 0.02 mL; residence time: t^1 = 0.12 s, T^1 = –78 °C) and was subsequently injected in a flask containing a stirrbar. The reaction was stirred for 30 min at −78 °C and quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel) afforded the title compound **178ah** as white solid (43 mg, 0.13 mmol, 66% yield; *E*/*Z* > 99/1).

6.1.4 Typical procedure 19 (TP19) using batch conditions: Sodiation of (substituted) acrylonitriles and alkenes using NaDA and under batch condtitions with various electrophiles leading to functionalized acrylonitriles and alkenes.



Scheme 156: Sodiation of cinnamonitrile (**121a**) under batch conditions subsequent quench with 4-chlorobenzaldehyde (**112x´**) leading to tertiary alcohol **172gi**.

To a solution of (*E*)-ethoxyacrylonitrile (**170g**, 0.20 M, 0.20 mmol, 1.0 equiv; *E*/*Z* > 99/1) in THF (total volume: 1 mL) at −78 °C was added a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv). The mixture was stirred for 5 min at −78 °C. After 5 min a solution of 2,6-dichlorobenzaldehyde (**112i**, 53 mg, 0.30 mmol, 1.5 equiv) in THF (1.0 mL) was added at the same temperature. After stirring for 30 min at −78 °C the mixture was quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel) afforded the title compound **172gi** as a colorless solid (38 mg, 0.14 mmol, 72% yield; *Z*/*E* > 99/1).

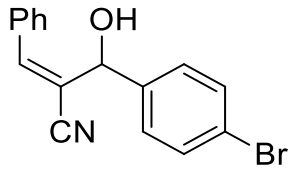
Table 52: Screening of flow conditions for the preparation of **172gi**.

Entry	T [°C]	Combined flow-rate [mL/min]	Reactor volume [mL]	Residence time [s]	Conversion [%]	GC yield[a] [%]
1	0	2	0.02	0.6	100	19
2	0	2	1	30	100	37
3	0	10	0.02	0.12	100	29
4	0	10	1	6	100	30
5	0	10	4	24	100	39
6	-40	2	0.02	0.6	100	17
7	-40	2	1	30	100	14
8	-40	2	4	120	100	12
9	-40	10	0.02	0.12	100	74
10	-40	10	1	6	100	65
11	-40	10	4	24	100	44
12	-78	2	0.02	0.6	100	60
13	-78	2	1	30	100	26
14	-78	2	4	120	100	25
15	-78	10	0.02	0.12	100	95[b]
16	-78	10	1	6	100	50
17	-78	10	4	24	100	54

a) GC-yield normalized to isolated yield. b) isolated yield.

6.2 Preparation of the Products

(*Z*)-2-((4-Bromophenyl)(hydroxy)methyl)-3-phenylacrylonitrile (169aw´)



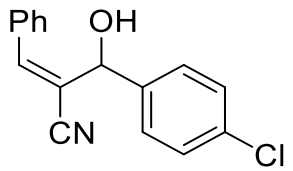
According to the **TP16**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 4-bromobenzaldehyde (**112w´**, 56 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169aw´** as colorless crystals (64 mg, 0.19 mmol, 95% yield; *Z/E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.57 – 7.53 (m, 2H), 7.48 (d, *J* = 0.8 Hz, 1H), 7.45 – 7.41 (m, 3H), 7.38 – 7.32 (m, 4H), 5.75 (s, 1H), 2.37 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 146.2, 138.9, 133.1, 132.3 (2C), 130.4, 129.3 (2C), 129.2 (2C), 128.1 (2C), 123.1, 118.2, 118.1, 69.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3480, 2213, 1616, 1591, 1574, 1488, 1447, 1399, 1391, 1361, 1292, 1283, 1248, 1218, 1194, 1159, 1136, 1108, 1074, 1030, 1012, 977, 946, 934, 906, 866, 847, 827, 778, 759, 699, 657.
MS (EI, 70 eV): *m/z* (%) = 315 (11), 313 (11), 187 (28) 185 (50), 183 (31), 157 (10), 140 (11), 130 (100), 129 (33), 105 (13), 102 (24), 78 (30), 77 (61), 76 (12), 75 (11), 51 (16), 43 (32).

HRMS (EI): *m/z* calc. for [$C_{16}H_{12}ONBr$]: 313.0102; found: 313.0087.

m.p. (°C): 134.3 – 136.3.

(*Z*)-2-((4-Chlorophenyl)(hydroxy)methyl)-3-phenylacrylonitrile (169ax´)



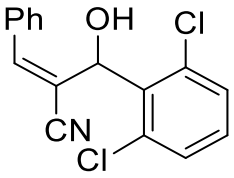
According to the **TP16**, a solution of cinnamonitrile (**121a**, 0.18 M, 23 mg, 0.18 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.21 M in DMEA, 0.21 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 4-chlorobenzaldehyde (**112x´**, 42 mg, 0.30 mmol, 1.7 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ax´** as colorless crystals (45 mg, 0.17 mmol, 92% yield; *Z/E* > 99/1).

^{1}H-MR (400 MHz, $CDCl_3$): δ / ppm = 7.49 (s, 1H), 7.46 – 7.42 (m, 3H), 7.41 (d, *J* = 4.1 Hz, 3H), 7.33 (dt, *J* = 7.9, 3.5 Hz, 2H), 5.77 (s, 1H), 4.68 (s, 1H), 2.42 – 2.23 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 146.2, 138.3, 130.4, 129.4 (2C), 129.3 (2C), 129.2 (2C), 128.8 (2C), 128.4, 127.8, 118.2, 69.1, 29.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3398, 2922, 2852, 2219, 1616, 1596, 1575, 1490, 1464, 1456, 1447, 1404, 1091, 1042, 1013, 836, 799, 777, 755, 728, 697.
MS (EI, 70 eV): *m/z* (%) = 253 (16), 251 (50), 217 (17), 216 (100), 214 (27), 189 (32), 141 (13), 139 (36), 130 (26), 77 (17).

HRMS (EI): *m/z* calc. for [$C_{16}H_{12}NOCl$]: 269.0607; found: 251.0498 [M – H_2O]

m.p. (°C): 124.2 – 128.3.

2-((4-Chlorophenyl)(hydroxy)methyl)-3-phenylacrylonitrile (169ai)



According to the **TP16**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 2,6-dichlorobenzaldehyde (**112i**, 52 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical

purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ai** as a colorless solid (45 mg, 0.15 mmol, 74% yield; *Z/E* = 89/11).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*Z*)-2-((4-Chlorophenyl)(hydroxy)methyl)-3-phenylacrylonitrile: δ / ppm = 7.50 – 7.48 (m, 2H), 7.48 – 7.47 (m, 1H), 7.41 – 7.38 (m, 3H), 7.30 – 7.26 (m, 2H), 7.18 (dd, *J* = 8.7, 7.3 Hz, 1H), 6.27 – 6.20 (m, 1H), 3.83 (s, 1H).

(*E*)-2-((4-Chlorophenyl)(hydroxy)methyl)-3-phenylacrylonitrile: δ / ppm = 7.79 – 7.76 (m, 2H), 7.51 – 7.38 (m, 7H), 6.31 (d, *J* = 2.2 Hz, 1H), 2.69 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*Z*)-2-((4-Chlorophenyl)(hydroxy)methyl)-3-phenylacrylonitrile: δ / ppm = 148.8, 135.0 (2C), 134.3, 133.3, 130.3 (2C), 129.6 (2C), 129.5 (2C), 128.9 (2C), 118.7, 116.2, 68.5.

(*E*)-2-((4-Chlorophenyl)(hydroxy)methyl)-3-phenylacrylonitrile: δ / ppm = 143.3, 135.4, 134.3, 133.1, 130.7 (3C), 129.8 (2C), 129.2 (2C), 129.0 (2C), 116.8, 112.0, 77.1.

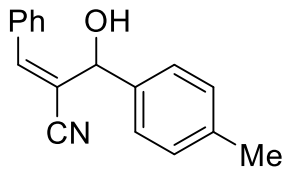
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3492, 3437, 3066, 2923, 2854, 2211, 1792, 1683, 1601, 1579, 1561, 1492, 1446, 1437, 1305, 1228, 1202, 1184, 1148, 1093, 1077, 1033, 983, 943, 890, 826, 793, 782, 767, 756, 720, 696.

MS (EI, 70 eV): *m/z* (%) = 285 (12), 281 (15), 250 (26), 227 (10), 226 (10), 225 (76), 214 (19), 209 (34), 208 (10), 207 (7 8), 191 (16), 177 (10), 175 (69), 174 (10), 173 (100), 130 (11), 102 (11), 78 (12), 75 (12).

HRMS (EI): *m/z* calc. for [$C_{16}H_{11}Cl_2NO$]: 303.0218; found: 303.0218.

m.p. (°C): 86.0 – 88.1.

(*Z*)-4-Hydroxy-3-phenyl-4-(*p*-tolyl)but-2-enenitrile (169aj)



According to the **TP16**, a solution cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 4-methylbenzaldehyde (**112j**, 36 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over

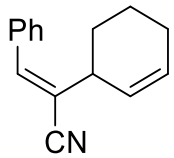
anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169aj** as pale yellow crystals (46 mg, 0.19 mmol, 93% yield; *Z*/*E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.37 (m, 6H), 7.35 – 7.31 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.73 (d, *J* = 5.2 Hz, 1H), 2.38 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.5, 138.9, 137.1, 133.3, 130.1, 129.9 (2C), 129.4 (2C), 129.0 (2C), 126.3 (2C), 118.8, 118.5, 69.6, 21.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3498, 3026, 2918, 2855, 2214, 1613, 1574, 1513, 1491, 1446, 1390, 1358, 1320, 1304, 1246, 1213, 1192, 1181, 1159, 1134, 1122, 1078, 1040, 1021, 1000, 950, 931, 896, 866, 843, 826, 796, 755, 739, 697, 666.
MS (EI, 70 eV): *m/z* (%) = 283 (10), 282 (14), 281 (73), 267 (13), 265 (24), 249 (15), 248 (75), 234 (29), 232 (14), 231 (100), 230 (79), 227 (10), 225 (37), 221 (10), 220 (33), 217 (11), 216 (75).

HRMS (EI): *m/z* calc. for [$C_{17}H_{15}NO$]: 249.3130; found: 248.1071 (M – H).

m.p. (°C): 116.2 – 118.8.

2-(Cyclohex-2-en-1-yl)-3-phenylacrylonitrile (169ae´)



According to the **TP16**, a solution cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.26 M in DMEA, 0.26 mmol, 1.3 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohexene (**112e´**, 48 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (20 µL, 0.02 mmol, 0.1 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ae´** as a colorless oil (46 mg, 0.19 mmol, 93% yield; *E/Z* = 90/10).

^{1}H-NMR (400 MHz, $CDCl_3$):
(*E*)-2-(Cyclohex-2-en-1-yl)-3-phenylacrylonitrile: δ / ppm = 7.44 – 7.36 (m, 3H), 7.31 – 7.27 (m, 2H), 7.24 (s, 1H), 5.97 (ddt, *J* = 10.0, 5.0, 2.6 Hz, 1H), 5.59 – 5.48 (m, 1H), 3.56 (ddp, *J* = 10.3, 5.4, 2.6 Hz, 1H), 2.19 – 1.98 (m, 2H), 1.96 – 1.86 (m, 2H), 1.82 – 1.73 (m, 1H), 1.63 – 1.51 (m, 1H).

(*Z*)-2-(Cyclohex-2-en-1-yl)-3-phenylacrylonitrile: δ / ppm = 7.76 – 7.72 (m, 2H), 7.44 – 7.33 (m, 2H), 6.96 (s, 1H), 6.03 – 6.00 (m, 1H), 5.62 (dq, *J* = 10.0, 2.5 Hz, 1H), 3.18 (d, *J* = 7.3 Hz, 1H), 2.20 (s, 1H), 2.19 – 1.98 (m, 2H), 1.96 – 1.86 (m, 2H), 1.82 (d, *J* = 2.2 Hz, 1H), 1.63 – 1.51 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-2-(Cyclohex-2-en-1-yl)-3-phenylacrylonitril:e δ / ppm = 143.9, 134.2, 131.4, 129.4, 129.1 (2C), 128.9 (2C), 126.5, 121.1, 119.7, 35.6, 28.5, 24.6, 21.3.

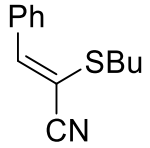
(*Z*)-2-(Cyclohex-2-en-1-yl)-3-phenylacrylonitril:e δ / ppm = 143.2, 134.2, 131.5, 130.0, 128.8 (2C), 128.4 (2C), 126.3, 121.1, 119.7, 41.7, 29.8, 25.0, 20.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2929, 2926, 2880, 2857, 2839, 2835, 2210, 1616, 1490, 1456, 1446, 1436, 1431, 1302, 1132, 1075, 1048, 1029, 1000, 979, 927, 907, 889, 886, 873, 844, 778, 752, 724, 696, 676, 672, 668, 661, 655.

MS (EI, 70 eV): *m/z* (%) = 209 (28), 208 (85), 195 (12), 194 (74), 192 (31), 191 (18.22), 181 (34), 180 (14), 168 (11), 167 (85), 166 (100), 165 (19), 154 (19), 153 (24), 152 (20), 141 (26), 140 (19), 130 (19), 128 (14), 115 (27).

HRMS (EI): *m/z* calc. for [$C_{15}H_{15}N$]: 209.1204; found: 209.1198.

2-(Butylthio)-3-phenylacrylonitrile (169aq)



According to the **TP16**, a solution cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfide (**112q**, 54 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169aq** as a pale yellow oil (46 mg, 0.19 mmol, 93% yield; *Z*/*E* = 54/46).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*Z*)-2-(Butylthio)-3-phenylacrylonitrile: δ / ppm = 7.73 (dd, *J* = 6.5, 3.0 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.45 – 7.38 (m, 3H), 7.32 (s, 1H), 2.97 – 2.89 (m, 2H), 1.66 (tt, *J* = 15.0, 7.9 Hz, 2H), 1.45 (dp, *J* = 14.4, 7.3 Hz, 2H), 0.93 (td, *J* = 7.3, 5.5 Hz, 3H).

(*E*)-2-(Butylthio)-3-phenylacrylonitrile: δ / ppm = 7.73 (dd, *J* = 6.5, 3.0 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.45 – 7.38 (m, 3H), 7.25 (s, 1H), 3.06 – 3.01 (m, 2H), 1.66 (tt, *J* = 15.0, 7.9 Hz, 2H), 1.45 (dp, *J* = 14.4, 7.3 Hz, 2H), 0.93 (td, *J* = 7.3, 5.5 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*Z*)-2-(Butylthio)-3-phenylacrylonitrile: δ / ppm = 146.1, 133.5, 129.9, 129.1 (2C), 128.8 (2C), 116.5, 109.5, 33.4, 31.7, 21.8, 13.7.

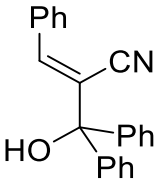
(*E*)-2-(Butylthio)-3-phenylacrylonitrile: δ / ppm = 142.7, 134.2, 130.7, 130.5 (2C), 128.7 (2C), 115.8, 105.5, 34.2, 32.0, 21.8, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2927, 2871, 2858, 2359, 2210, 1464, 1456, 1445, 1289, 1274, 919, 754, 689.

MS (EI, 70 eV): *m/z* (%) = 217 (43), 161 (24), 160 (13), 134 (100).

HRMS (EI): *m/z* calc. for [$C_{13}H_{15}NS$]: 217.0925; found: 217.0920.

(*E*)-2-(Hydroxydiphenylmethyl)-3-phenylacrylonitrile (169aa´)



According to the **TP16**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of benzophenone (**112a´**, 55 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169aa´** as colorless crystals (51 mg, 0.16 mmol, 82% yield; *E/Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.78 – 7.75 (m, 2H), 7.48 – 7.36 (m, 13H), 7.12 (s, 1H), 2.91 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.3, 143.2, 133.1, 130.7 (2C), 129.4 (2C), 129.0 (2C), 128.6 (4C), 128.6 (2C), 127.8 (4C), 118.5, 118.2, 81.3.

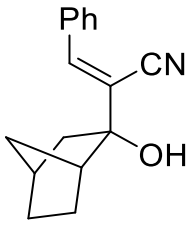
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3371, 2921, 2852, 2224, 1614, 1492, 1449, 1375, 1346, 1203, 1185, 1168, 1156, 1119, 1101, 1087, 1071, 1047, 1030, 1025, 1002, 950, 925, 911, 885, 770, 753, 733, 700, 688, 680, 660.

MS (EI, 70 eV): *m/z* (%) = 299 (10), 281 816), 227 (14), 226 (13), 225 (100), 209 (40), 208 (11), 207 (80), 206 (13), 191 (17), 183 (12), 151 (10), 105 (58), 78 (11), 77 (20).

HRMS (EI): *m/z* calc. for [$C_{22}H_{17}NO$]: 311.1310 found: 311.1305.

m.p. (°C): 152.1 – 158.0.

(*E*)-2-(2-Hydroxybicyclo[2.2.1]heptan-2-yl)-3-phenylacrylonitrile (169ag)



According to the **TP16**, a solution of cinnamonitrile (**121a**, 0.18 M, 23 mg, 0.18 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.21 M in DMEA, 0.21 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of norcamphor (**112g**, 33 mg, 0.30 mmol, 1.7 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ag** as a colorless solid (39 mg, 0.16 mmol, 82% yield; *E/Z* > 99/1, *d.r.* > 99/1).

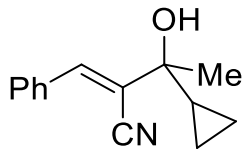
According to the **TP17**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaTMP (0.26 M in hexane, 0.26 mmol, 1.3 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of norcamphor (**112g**, 33 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ag** as a colorless solid (34 mg, 0.14 mmol, 71% yield; *E/Z* > 99/1, *d.r.* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.80 – 7.73 (m, 2H), 7.47 – 7.37 (m, 3H), 7.25 (s, 1H), 2.58 (dd, *J* = 3.8, 1.5 Hz, 1H), 2.37 (t, *J* = 4.9 Hz, 1H), 2.31 – 2.26 (m 1H), 2.13 – 2.06 (m 1H), 1.93 (s, 1H), 1.72 – 1.61 (m, 2H), 1.57 – 1.45 (m, 2H), 1.45 – 1.42 (m, 1H), 1.41 – 1.40 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.5, 133.5, 130.4, 129.2 (2C), 129.0 (2C), 120.0, 118.6, 80.5, 47.1, 45.6, 39.0, 37.5, 28.7, 22.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3432, 2952, 2870, 2212, 1608, 1599, 1575, 1495, 1476, 1448, 1374, 1366, 1339, 1326, 1309, 1292, 1271, 1254, 1211, 1185, 1165, 1126, 1077, 1046, 1030, 1013, 969, 956, 927, 890, 871, 843, 806, 755, 734, 690, 666.
MS (EI, 70 eV): *m/z* (%) = 221 (31), 220 (15), 194 (15), 193 (100), 192 (87), 191 (34), 190 (25), 178 (66), 177 (10), 170 (11), 166 (16), 165 (72), 152 (13), 143 (10), 115 (14), 91 (19), 77 (14).

HRMS (EI): *m/z* calc. for [$C_{16}H_{17}NO$]: 239.1310 found: 239.1315.

m.p. (°C): 74.5 – 77.3.

(*E*)-2-Benzylidene-3-cyclopropyl-3-hydroxybutanenitrile (169ay´)



According to the **TP16**, a solution of cinnamonitrile (**121a**, 0.18 M, 23 mg, 0.18 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.21 M in DMEA, 0.21 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclopropylmethylketone (**112y´**, 25 mg, 0.30 mmol, 1.7 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ay´** as a yellow oil (30 mg, 0.14 mmol, 78% yield; *E/Z* > 99/1).

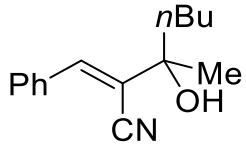
According to the **TP17**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaTMP (0.26 M in hexane, 0.26 mmol, 1.3 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of methylcyclopropyl ketone (**112y´**, 25 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous

phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ay´** as a yellow oil (29 mg, 0.14 mmol, 68% yield; *E*/*Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.78 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.46 – 7.38 (m, 4H), 1.65 (s, 1H), 1.52 (s, 3H), 1.36 – 1.27 (m, 1H), 0.66 – 0.48 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.1, 133.6, 130.3, 129.2 (2C), 128.9 (2C), 119.1, 118.3, 72.9, 26.9, 21.1, 2.2, 1.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3451, 2974, 2924, 2853, 2212, 1494, 1447, 1374, 1219, 1194, 1155, 1079, 1049, 1037, 1023, 1000, 961, 931, 903, 874, 757, 690.
MS (EI, 70 eV): *m/z* (%) = 195 (21), 194 (50), 193 (13), 184 (41), 180 (70), 168 (20), 167 (21), 166 (97), 165 (19), 156 (12), 155 (33), 154 (100), 153 (50), 152 (35), 141 (17), 140 (20), 139 (16), 128 (15), 127 (26), 126 (15), 115 (22), 91 (16), 77 (11).

HRMS (EI): *m/z* calc. for [$C_{14}H_{15}NO$]: 213.1154; found: 213.1148

(*E*)-2-Benzylidene-3-hydroxy-3-methylheptanenitrile (169az´)



According to the **TP16**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of hexan-2-one (**112z´**, 30 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169az´** as a colorless oil (40 mg, 0.17 mmol, 87% yield; *E*/*Z* > 99/1).

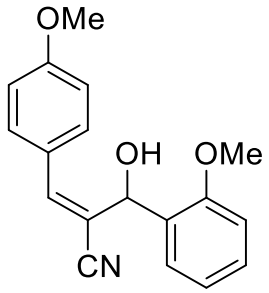
According to the **TP17**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaTMP (0.26 M in hexane, 0.26 mmol, 1.3 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in

a flask containing a stirred solution of hexan-2-one (**112z´**, 30 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169az´** as a white solid (38 mg, 0.17 mmol, 83% yield; *E*/*Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.47 – 7.39 (m, 3H), 7.37 (s, 1H), 1.94 – 1.82 (m, 1H), 1.79 (dd, *J* = 11.0, 5.1 Hz, 1H), 1.74 (s, 1H), 1.56 (s, 3H), 1.41 – 1.29 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.5, 133.5, 130.3, 129.1 (2C), 129.0 (2C), 118.7,118.1, 74.8, 41.2, 28.4, 258, 23.0, 14.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3466, 2957, 2931, 2862, 2210, 1722, 1619, 1495, 1466, 1448, 1376, 1342, 1289, 1260, 1232, 1165, 1128, 1096, 1074, 1045, 1035, 945, 929, 886, 775, 746, 731, 690, 666, 656.
MS (EI, 70 eV): *m/z* (%) = 172 (39), 169 (14), 168 (47), 167 (21), 155 (11), 154 (100), 153 (11), 130 (17).

HRMS (EI): *m/z* calc. for [$C_{15}H_{19}NO$]: 229.1467; found: 229.1457.

2-(Hydroxy(2-methoxyphenyl)methyl)-3-(4-methoxyphenyl)acrylonitrile (172aa´´)



According to the **TP16**, a solution of 3-(4-methoxyphenyl)acrylonitrile (**170a**, 0.20 M, 32 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 76/24) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, – 78 °C) and was subsequently injected in a flask containing a stirred solution of 2-methoxybenzaldehyde (**112a´´**, 41 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the

solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **172aa´´** as colorless crystals (57 mg, 0.19 mmol, 97% yield; *Z/E* = 89/11).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*Z*)-2-(Hydroxy(2-methoxyphenyl)methyl)-3-(4-methoxyphenyl)acrylonitrile: δ / ppm = 7.79 – 7.72 (m, 2H), 7.45 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.16 (s, 1H), 6.94 – 6.90 (m, 3H), 5.69 – 5.62 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.13 – 3.08 (m, 1H).

(*E*)-2-(Hydroxy(2-methoxyphenyl)methyl)-3-(4-methoxyphenyl)acrylonitrile: δ / ppm = 7.41 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.05 (d, *J* = 0.9 Hz, 1H), 7.01 (dd, *J* = 2.7, 0.9 Hz, 1H), 6.97- 6.89 (m, 3H), 5.93 (d, *J* = 5.4 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.39 – 3.27 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*Z*)-2-(Hydroxy(2-methoxyphenyl)methyl)-3-(4-methoxyphenyl)acrylonitrile: δ / ppm = 161.4, 156.8, 142.5, 131.1 (2C), 129.9, 128.2, 127.9, 126.2, 121.3, 118.1, 114.4 (3C), 111.1, 72.2, 55.7, 55.5.

(*E*)-2-(Hydroxy(2-methoxyphenyl)methyl)-3-(4-methoxyphenyl)acrylonitrile: δ / ppm = 161.1, 157.1, 145.8, 131.7 (2C), 130.1, 128.1, 127.6, 126.4, 121.4, 115.4, 114.3, 111.1, 111.1 (2C), 67.2, 55.7, 55.5.

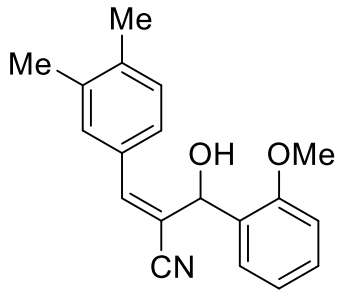
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3431, 3005, 2959, 2932, 2928, 2838, 2359, 2210, 1602, 1570, 1512, 1490, 1463, 1439, 1424, 1404, 1399, 1388, 1306, 1288, 1256, 1179, 1162, 1136, 1110, 1046, 1028, 832, 791, 756.

MS (EI, 70 eV): *m/z* (%) = 277 (18), 262 (13), 253 (10).

HRMS (EI): *m/z* calc. for [$C_{18}H_{17}NO_3$]: 295.1208 found: 295.1203.

m.p. (°C): 101.8 –106.1.

3-(3,4-Dimethylphenyl)-2-(hydroxy(2-methoxyphenyl)methyl)acrylonitrile (172ba´´)



According to the **TP16**, a solution of 3-(3,4-dimethylphenyl)acrylonitrile (**170b**, 0.20 M, 31 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 79/21) in THF (total volume: 1 mL) and a solution of NaDA (0.22 M in DMEA, 0.22 mmol, 1.10 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, – 78 °C) and was subsequently injected in a flask containing a stirred solution of 2-methoxybenzaldehyde

(**112a´´**, 41 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **172ba´´** as colorless crystals (49 mg, 0.17 mmol, 84% yield; *Z*/*E* = 90/10).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*Z*)-3-(3,4-Dimethylphenyl)-2-(hydroxy(2-methoxyphenyl)methyl)acrylonitrile: δ / ppm = 7.44 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.16 – 7.13 (m, 3H), 7.01 (td, *J* = 7.6, 1.1 Hz, 1H), 6.94 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.96 (s, 1H), 3.83 (s, 3H), 3.30 (s, 1H), 2.29 (s, 3H), 2.25 (s, 3H).

(*E*)-3-(3,4-Dimethylphenyl)-2-(hydroxy(2-methoxyphenyl)methyl)acrylonitrile: δ / ppm = 7.57 – 7.50 (m, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 7.32 (d, *J* = 1.7 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.19 – 7.16 (m, 2H), 7.14 – 7.11 (m, 1H), 6.92 – 6.87 (m, 1H), 5.66 (s, 1H) 4.69 (s, 1H), 3.86 (d, *J* = 4.7 Hz, 3H), 2.29 (s, 3H), 2.25 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*Z*)-3-(3,4-Dimethylphenyl)-2-(hydroxy(2-methoxyphenyl)methyl)acrylonitrile: δ / ppm = 156.9, 146.1, 139.1, 137.1, 131.3, 130.9, 130.1, 130.0, 128.2, 127.6, 127.2, 121.3, 119.3, 116.8, 111.0, 66.8, 55.5, 19.9 (2C).

(*E*)-3-(3,4-Dimethylphenyl)-2-(hydroxy(2-methoxyphenyl)methyl)acrylonitrile: δ / ppm = 156.7, 143.0, 139.7, 137.2, 131.1, 130.5, 130.2, 129.9, 129.1, 128.9, 128.1, 127.9, 126.7, 120.8, 110.3, 72.1, 55.6, 19.9, 19.8.

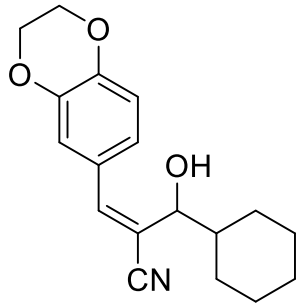
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3456, 2973, 2919, 2846, 2208, 1602, 1590, 1565, 1489, 1469, 1458, 1440, 1411, 1382, 1353, 1342, 1296, 1282, 1244, 1195, 1180, 1161, 1127, 1116, 1047, 1030, 910, 877, 853, 821, 789, 751, 724, 710, 674.

MS (EI, 70 eV): *m/z* (%) = 293 (30), 278 (21), 170 (14), 159 (10), 158 (59), 157 (12), 137 (71), 136 (13), 135 (100), 121 (13), 119 (10), 107 (35), 91 (12), 77 (31).

HRMS (EI): *m/z* calc. for [$C_{19}H_{19}NO_2$]: 293.1416; found: 293.1400.

m.p. (°C): 122.0 – 123.7.

(*Z*)-2-(Cyclohexyl(hydroxy)methyl)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile (172cd)

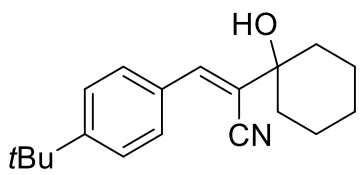


According to the **TP16**, a solution of 3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile (**170c**, 0.19 M, 36 mg, 0.19 mmol, 1.0 equiv; *E*/*Z* = 83/17) in THF (total volume: 1 mL) and a solution of NaDA (0.22 M in DMEA, 0.22 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexanecarbaldehyde (**112d**, 34 mg, 0.30 mmol, 1.6 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 4:1) afforded the title compound **172cd** as a colorless oil (42 mg, 0.15 mmol, 74% yield; *Z*/*E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.23 (s, 1H), 6.94 – 6.90 (m, 1H), 6.89 – 6.85 (m, 2H), 4.31 – 4.26 (m, 4H), 2.10 (d, *J* = 12.8 Hz, 1H), 1.99 (s, 1H), 1.82 – 1.75 (m, 1H), 1.72 – 1.64 (m, 3H), 1.34 – 1.21 (m, 3H), 1.18 – 1.10 (m, 1H), 1.09 – 0.98 (m, 1H), 0.87 (qd, *J* = 13.0, 12.5, 3.9 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 146.1, 145.1, 143.6, 126.8, 123.2, 118.9, 118.4, 117.7, 117.0, 71.8, 64.6, 64.3, 42.7, 29.2, 29.0, 26.2, 25.8, 25.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3443, 2924, 2851, 2212, 1606, 1578, 1504, 1450, 1433, 1312, 1285, 1256, 1243, 1212, 1187, 1160, 1127, 1065, 1050, 1018, 964, 919, 887, 850, 816, 784, 730, 677.
MS (EI, 70 eV): *m/z* (%) = 217 (18), 216 (100), 198 (12), 188 (16), 55 (13), 42 (12).

HRMS (EI): *m/z* calc. for [$C_{18}H_{21}O_3N$]: 299.1521 found: 299.1515.

(*E*)-3-(4-(*Tert*-butyl)phenyl)-2-(1-hydroxycyclohexyl)acrylonitrile (172dm)



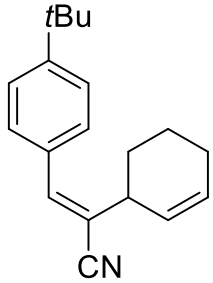
According to the **TP16**, a solution of 3-(4-(*tert*-butyl)phenyl)-2-(cyclohexyl(hydroxy) methyl)acrylonitrile (**170d**, 0.18 M, 33 mg, 0.18 mmol, 1.0 equiv; *E*/*Z* = 79/21) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.1 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexanone (**112m**, 29 mg, 0.30 mmol, 1.7 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **172dm** as a colorless solid (34 mg, 0.5 mmol, 67% yield; *E*/*Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 – 7.69 (m, 2H), 7.46 – 7.41 (m, 2H), 7.38 (s, 1H), 1.99 – 1.87 (m, 2H), 1.76 – 1.62 (m, 8H), 1.33 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 153.8, 141.0, 130.8, 129.0 (2C), 125.9 (2C), 119.4, 118.5, 73.4, 36.7 (2C), 35.0, 31.3 (3C), 25.0, 21.7 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3451, 2961, 2930, 2854, 2211, 1708, 1607, 1507, 1460, 1446, 1430, 1412, 1384, 1367, 1352, 1317, 1290, 1266, 1260, 1221, 1200, 1172, 1131, 1107, 1077, 1056, 1039, 1015, 991, 955, 935, 926, 916, 901, 844, 828, 802, 664.
MS (EI, 70 eV): *m/z* (%) = 283 (32), 268 (43), 240 (18), 226 (45), 184 (21), 171 (17), 170 (100), 154 (11), 147 (29), 115 (13), 57 (68), 55 (13), 43 (13), 41 (31).

HRMS (EI): *m/z* calc. for [$C_{19}H_{25}NO$]: 283.1936; found: 283.1931.

m.p. (°C): 89.6 – 93.2.

(*E*)-3-(4-(*Tert*-butyl)phenyl)-2-(cyclohex-2-en-1-yl)acrylonitrile (172de´)



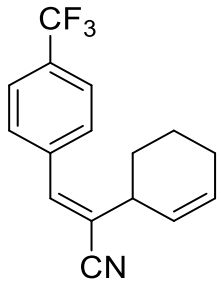
According to the **TP16**, a solution of 3-(4-(*tert*-butyl)phenyl)acrylonitrile (**170d**, 0.18 M, 33 mg, 0.18 mmol 1.0 equiv; *E*/*Z* = 79/21) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.1 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –

78 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohexene (**112e´**, 46 mg, 0.30 mmol, 1.7 equiv) and CuCN·2LiCl (20 µL, 0.02 mmol, 0.1 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 49:1) afforded the title compound **172de´** as a yellow oil (27 mg, 0.10 mmol, 57% yield; *E/Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.41 (m, 2H), 7.27 – 7.23 (m, 2H), 7.20 (s, 1H), 5.96 (ddt, *J* = 9.8, 4.9, 2.6 Hz, 1H), 5.54 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.67 – 3.54 (m, 1H), 2.20 – 2.04 (m, 2H), 1.98 – 1.87 (m, 2H), 1.83 – 1.76 (m, 1H), 1.66 – 1.58 (m, 1H), 1.33 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.9, 143.8, 131.4, 131.3, 129.1 (2C), 126.7, 125.9 (2C), 120.2, 119.9, 35.6, 35.0, 31.3 (3C), 28.5, 24.6, 21.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2960, 2931, 2863, 2836, 2210, 1607, 1506, 1475, 1461, 1447, 1432, 1412, 1395, 1363, 1301, 1289, 1270, 1201, 1132, 1108, 1016, 980, 932, 924, 898, 874, 858, 846, 824, 723, 664.
MS (EI, 70 eV): *m/z* (%) = 250 (51), 209 (38), 208 (100), 194 (40), 192 (24), 191 (12), 182 (15), 181 (20), 180 (52) 167 (25), 166 (82), 165 (22), 154 (17), 153 (12), 152 (14), 141 (12), 115 (28), 104, (13), 91 (15), 79 (12).

HRMS (EI): *m/z* calc. for [$C_{19}H_{23}N$]: 265.1830; found: 265.1826.

(*E*)-2-(Cyclohex-2-en-1-yl)-3-(4-(trifluoromethyl)phenyl)acrylonitrile (172ee´)



According to the **TP16**, a solution of 3-(4-(trifluoromethyl)phenyl)acrylonitrile (**170e**, 0.20 M, 39 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 78/22) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, – 78 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohexene (**112e´**, 48 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (20 µL, 1.0 M, 0.02 mmol, 0.1 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over

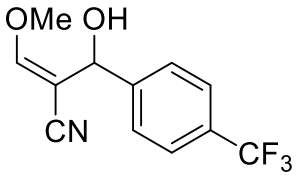
anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound **172ee´** as white crystals (33 mg, 0.13 mmol, 66% yield; *E/Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.67 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.26 (s, 1H), 5.99 (ddt, *J* = 9.9, 5.0, 2.6 Hz, 1H), 5.53 – 5.47 (m, 1H), 3.50 – 3.44 (m, 1H), 2.18 – 1.99 (m, 2H), 1.95 – 1.86 (m, 2H), 1.81 – 1.73 (m, 1H), 1.62 – 1.50 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.1, 137.5, 132.0, 131.2 (q, *J* = 32.8 Hz), 129.3 (2C), 125.9 (q, *J* = 3.8 Hz, 2C), 125.9, 123.9 (q, *J* =272.5 Hz), 123.5, 119.0, 35.8, 28.4, 24.5, 21.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2922, 2856, 2210, 1614, 1456, 1446, 1408, 1344, 1322, 1278, 1255, 1170, 1127, 1108, 1080, 1066, 1014, 976, 960, 934, 900, 873, 848, 830, 763, 728, 667, 656.
MS (EI, 70 eV): *m/z* (%) = 277 (18), 276 (51), 262 (22), 248 (56), 235 (97), 234 (51), 221 (26), 209 (23), 208 (61), 204 (21), 202 (20), 183 (20), 180 (51), 173 (29), 166 (100), 165 (21), 159 (53), 154 (46), 153 (22), 152 (20), 145 (29), 140 (15), 80 (15), 79 (52), 78 (27), 77 (33).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}NF_3$]: 277.1078; found: 277.1082.

m.p. (°C): 74.9 – 78.2.

(*Z*)-4-Hydroxy-3-methoxy-4-(4-(trifluoromethyl)phenyl)but-2-enenitrile (172fb´´)



According to the **TP16**, a solution 3-methoxyacrylonitrile (**170f**, 0.20 M, 17 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 83:17) in THF (total volume: 1 mL) and a solution of NaDA (0.21 M in DMEA, 0.21 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 $mL \cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of (4-trifluoromethyl)benzaldehyde (**112b´´**, 52 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 3:1) afforded the title compound **172fb´´** as a pale orange solid (36 mg, 0.14 mmol, 93% yield; *Z/E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.63 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 0.8 Hz, 1H), 5.80 (s, 1H), 3.92 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.3, 144.7 (d, *J* = 1.4 Hz), 130.5 (q, *J* = 32.4 Hz, 2C), 126.2, 125.8 (q, *J* = 3.8 Hz, 2C), 124.2 (q, *J* = 272.2 Hz), 116.9, 97.5, 66.5, 62.7.

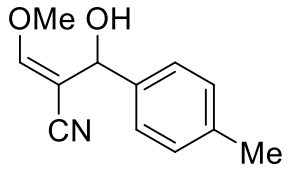
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3391, 2952, 2922, 2852, 2224, 1712, 1632, 1457, 1446, 1411, 1319, 1259, 1206, 1161, 1148, 1118, 1110, 1064, 1052, 1015, 973, 961, 917, 869, 853, 788, 771, 724, 700.

MS (EI, 70 eV): *m/z* (%) = 257 (12), 256 (65), 240 (13), 238 (22), 236 (16), 228 (26), 227 (13), 226 (25), 225 (34), 224 (94), 223 (17), 223 (20), 222 (42), 214 (73), 210 (11), 208 (68), 207 (34), 206 (88), 203 (12), 200 (17), 198 (30), 197 (100), 196 (99), 195 (66), 194 (25), 188 (52), 187 (10), 186 (15), 185 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{10}F_3NO_2$]: 257.0664; found 256.0579 (M – H).

m.p. (°C): 100.1 – 102.5.

(*Z*)-2-(Hydroxy(*p*-tolyl)methyl)-3-methoxyacrylonitrile (172fj)



According to the **TP16**, a solution of 3-methoxyacrylonitrile (**170f**, 0.20 M, 17 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 83:17) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 4-methylbenzaldehyde (**112j**, 36 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 7:3) afforded the title compound **172fj** as white crystals (40 mg, 0.20 mmol, 98% yield; *Z*/*E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.82 (d, *J* = 0.8 Hz, 1H), 5.69 (s, 1H), 3.89 (s, 3H), 2.35 (s, 3H), 2.20 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.7, 138.3, 138.1, 129.5 (2C), 125.8 (2C), 117.4, 98.2, 67.1, 62.4, 21.3.

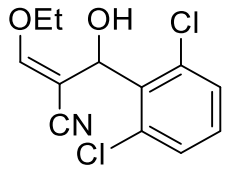
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3401, 2939, 2922, 2904, 2850, 2224, 1636, 1612, 1512, 1450, 1407, 1319, 1294, 1257, 1238, 1195, 1175, 1148, 1111, 1063, 1022, 978, 972, 951, 916, 859, 840, 792, 767, 680.

MS (EI, 70 eV): *m/z* (%) = 203 (15), 171 (10), 156 (43), 121 (39), 120 (21), 115 (17), 111 (14), 97 (19), 92 (18), 91 (46), 85 (15), 83 (19), 77 (15), 71 (17), 70 (11), 65 (16), 61 (13), 57 (47), 56 (14), 55 (28), 45 (17), 44 (28), 43 (100), 42 (13), 41 (27).

HRMS (EI): *m/z* calc. for [$C_{12}H_{13}NO_2$]: 203.0946; found: 203.0944.

m.p. (°C): 129.7 – 132.3.

(*Z*)-2-((2,6-Dichlorophenyl)(hydroxy)methyl)-3-ethoxyacrylonitrile (172gi)



According to the **TP16**, a solution of 3-ethoxyacrylonitrile (**170g**, 0.20 M, 19 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 68:32) in THF (total volume: 1 mL) and a solution of NaDA (0.22 M in DMEA, 0.22 mmol, 1.1 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 2,6-dichlorobenzaldehyde (**112i**, 52 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 7:3) afforded the title compound **172gi** as a colorless solid (52 mg, 0.19 mmol, 95% yield; *Z*/*E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.15 (m, 1H), 6.87 (d, *J* = 1.8 Hz, 1H), 6.24 (d, *J* = 1.5 Hz, 1H), 4.03 (dq, *J* = 10.1, 7.1 Hz, 1H), 3.94 (dq, *J* = 10.1, 7.1 Hz, 1H), 3.41 (s, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.0, 135.6, 135.1, 129.7 (2C), 129.2 (2C), 117.8, 95.8, 71.6, 66.2, 15.1.

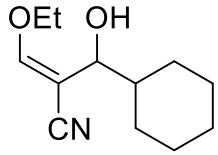
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3376, 2956, 2921, 2852, 2223, 1627, 1581, 1563, 1539, 1453, 1437, 1399, 1376, 1302, 1222, 1196, 1179, 1149, 1111, 1088, 1076, 1061, 1023, 967, 910, 874, 856, 819, 771, 761, 724, 712, 699, 688.

MS (EI, 70 eV): *m/z* (%) = 190 (15), 173 (11), 61 (19), 57 (11), 45 (15), 44 (32), 43 (100), 41 (13).

HRMS (EI): *m/z* calc. for [$C_{12}H_{11}Cl_2NO_2$]: 271.0167; found: 271.0172.

m.p. (°C): 85.0 – 87.3.

(*Z*)-4-Cyclohexyl-3-ethoxy-4-hydroxybut-2-enenitrile (172gd)

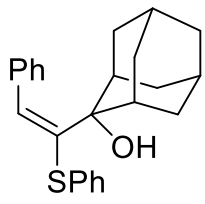


According to the **TP16**, a solution 3-ethoxyacrylonitrile (**170g**, 0.20 M, 19 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 68:32) in THF (total volume: 1 mL) and a solution of NaDA (0.21 M in DMEA, 0.21 mmol, 1.1 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexanecarbaldehyde (**112d**, 34 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 4:1) afforded the title compound **172gd** as a colorless liquid (38 mg, 0.18 mmol, 91% yield; *Z*/*E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.90 (s, 1H), 4.26 (d, *J* = 8.5 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.01 (d, *J* = 12.9 Hz, 1H), 1.93 (s, 1H), 1.73 (dd, *J* = 29.6, 13.0 Hz, 2H), 1.64 (t, *J* = 15.2 Hz, 2H), 1.58 – 1.52 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.27 – 1.21 (m, 2H), 1.19 – 1.12 (m, 1H), 0.98 (dq, *J* = 37.4, 12.3 Hz, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.3, 118.2, 96.4, 71.2, 70.0, 42.6, 29.1, 28.7, 26.4, 25.9, 25.7, 15.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3442, 2983, 2923, 2850, 2211, 1633, 1476, 1449, 1391, 1336, 1326, 1302, 1213, 1190, 1171, 1144, 1107, 1086, 1083, 1014, 964, 920, 891, 883, 848, 809, 794, 678.
MS (EI, 70 eV): *m/z* (%) = 162 (10), 134 (29), 126 (39), 117 (12), 107 (11), 106 (16), 98 (100), 81 (48), 79 (29), 77 (11), 70 (11), 67 (20).

HRMS (EI): *m/z* calc. for [$C_{12}H_{19}NO_2$]: 209.1416; found 209.1413.

2-(2-Phenyl-1-(phenylthio)vinyl)adamantan-2-ol (172hh)



According to the **TP16**, a solution phenyl(styryl)sulfane (**170h**, 0.20 M, 43 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 71/29) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound **172hh** as colorless crystals (69 mg, 0.19 mmol, 95% yield; *E*/*Z* = 77/23).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*/*Z*)-2-(2-Phenyl-1-(phenylthio)vinyl)adamantan-2-ol: δ / ppm = 7.65 – 7.60 (m, 2H), 7.57 (d, J = 6.9 Hz, 1H), 7.40 – 6.99 (m, 7H), 6.81 (s, 1H), 2.57 (s, 1H), 2.45 – 2.37 (m, 1H), 2.34 (t, J = 2.9 Hz, 1H), 2.28 (d, J = 13.1 Hz, 1H), 2.23 – 2.14 (m, 1H), 2.00 (d, J = 12.5 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.85 – 1.67 (m, 2H), 1.65 (d, J = 3.3 Hz, 2H), 1.60 – 1.53 (m, 2H), 1.53 – 1.44 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-2-(2-Phenyl-1-(phenylthio)vinyl)adamantan-2-ol: δ / ppm = 139.4, 136.4, 135.9, 135.7, 129.4 (2C), 128.8 (2C), 128.7 (2C), 127.9 (2C), 127.7, 125.7, 79.0, 39.4, 37.9, 35.7, 34.8 (2C), 33.3 (2C), 27.6, 27.0.

(*Z*)-2-(2-Phenyl-1-(phenylthio)vinyl)adamantan-2-ol: δ / ppm = 144.7, 139.3, 137.4, 135.8, 132.0 (2C), 129.5 (2C), 128.6 (2C), 128.0 (2C), 127.3, 127.1, 79.0, 39.1, 37.5, 35.5, 35.0 (2C), 32.9 (2C), 26.8, 26.6.

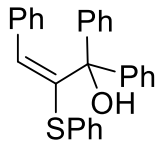
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3524, 2952, 2911, 2898, 2891, 2851, 1492, 1487, 1480, 1469, 1445, 1439, 1380, 1364, 1344, 1327, 1317, 1308, 1303, 1292, 1284, 1267, 1178, 1172, 1162, 1128, 1118, 1112, 1103, 1097, 1083, 1068, 1057, 1041, 1025, 1007, 999, 983, 965, 951, 930, 917, 907, 890, 880, 848, 832, 806, 791, 776, 763, 749, 741, 695, 689, 681, 667, 657.

MS (EI, 70 eV): *m/z* (%) = 362 (32), 253 (13), 213 (17), 212 (100), 211 (29), 179 (12), 178 (11), 167 (15), 151 (25), 121 (11), 91 (21), 79 (12), 77 (11), 41 (10).

HRMS (EI): *m/z* calc. for [$C_{24}H_{26}OS$]: 362.1704; found 362.1697.

m.p. (°C): 101.9 – 106.1.

1,1,3-Triphenyl-2-(phenylthio)prop-2-en-1-ol (172ha´)



According to the **TP16**, a solution phenyl(styryl)sulfane (**170h**, 0.20 M, 43 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 71/29) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of benzophenone (**112a´**, 45 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound **172ha´** as a colorless liquid (67 mg, 0.17 mmol, 85% yield; *E*/*Z* = 68/32).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*/*Z*)-1,1,3-Triphenyl-2-(phenylthio)prop-2-en-1-ol: δ / ppm = 7.56 – 7.43 (m, 6H), 7.40 – 7.18 (m, 9H), 7.18 – 7.06 (m, 1H), 7.06 – 6.95 (m, 2H), 6.81 (ddt, *J* = 6.0, 4.8, 3.8 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 3.60 (d, *J* = 225.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

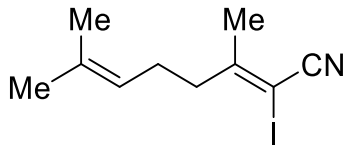
(*E*/*Z*)-1,1,3-Triphenyl-2-(phenylthio)prop-2-en-1-ol: δ / ppm = 146.4, 145.2, 144.5, 140.1, 137.3, 135.4, 133.1, 131.3, 129.6, 129.5, 128.9, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 127.9, 127.9, 127.8, 127.7, 127.0, 125.8, 84.6, 82.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3480, 3057, 3023, 2959, 2923, 2849, 1657, 1616, 1597, 1578, 1559, 1490, 1477, 1445, 1439, 1317, 1309, 1276, 1176, 1155, 1091, 1074, 1048, 1031, 1024, 1015, 999, 987, 941, 919, 909, 883, 853, 809, 788, 754, 736, 696, 661.

MS (EI, 70 eV): *m/z* (%) = 213 (18), 212 (100), 211 (19), 183 (42), 178 (14), 105 (64), 77 (36).

HRMS (EI): *m/z* calc. for [$C_{27}H_{22}OS$]: 394.1391; found 394.1389.

2-(Hydroxyiodomethyl)-3,7-dimethylocta-2,6-dienenitrile (175ac´´)



According to the **TP16**, a solution geranyl nitrile (**173a**, 0.18 M, 27 mg, 0.18 mmol, 1.0 equiv; *E/Z* = 50/50) in THF (total volume: 1 mL) and a solution of NaDA (0.22 M in DMEA, 0.22 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of iodine (**112c´´**, 76 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound **175ac´´** as a brown oil (37 mg, 0.13 mmol, 75% yield; *Z/E* = 68/32).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)-2-(Hydroxyiodomethyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 5.13 – 5.04 (m, 1H), 2.38 (dd, *J* = 8.7, 7.0 Hz, 2H), 2.24 – 2.13 (m, 2H), 2.20 (s, 2H), 2.03 (s, 1H), 1.70 (s, 3H), 1.63 (s, 3H).

(*Z*)-2-(Hydroxyiodomethyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 5.13 – 5.04 (m, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.24 – 2.13 (m, 2H), 2.20 (s, 2H), 2.03 (s, 1H), 1.70 (s, 3H), 1.61 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-2-(Hydroxyiodomethyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 166.4, 134.0, 121.9, 117.8, 53.8, 42.0, 26.6, 25.8, 23.0, 17.9.

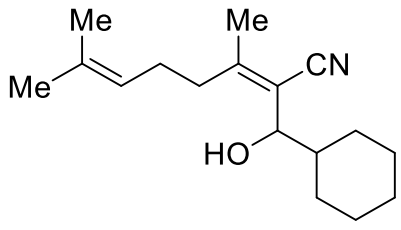
(*Z*)-2-(Hydroxyiodomethyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 166.9, 134.2, 121.7, 117.6, 54.6, 38.7, 29.9, 27.3, 25.6, 17.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3452, 3058, 3026, 2966, 2920, 2855, 2208, 1657, 1597, 1491, 1446, 1376, 1320, 1278, 1157, 1111, 1075, 1024, 1002, 921, 898, 825, 750, 699.

MS (EI, 70 eV): *m/z* (%) = 260 (11), 207 (40), 148 (43), 128 (10), 127 (100), 69 (99), 67 (10).

HRMS (EI): *m/z* calc. for [$C_{10}H_{14}IN$]: 275.0171; found 275.0176.

2-(Cyclohexyl(hydroxy)methyl)-3,7-dimethylocta-2,6-dienenitrile (175ad)



According to the **TP16**, a solution geranyl nitrile (**173a**, 0.18 M, 27 mg, 0.18 mmol, 1.0 equiv; *E/Z* = 50/50) in THF (total volume: 1 mL) and a solution of NaDA (0.22 M in DMEA, 0.22 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer.

The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexanecarbaldehyde (**112d**, 34 mg, 0.30 mmol, 1.7 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound **175ad** as an orange oil (28 mg, 0.11 mmol, 60% yield; *Z*/*E* = 64/36).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)-2-(Cyclohexyl(hydroxy)methyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 5.15 – 5.03 (m, 1H), 4.13 – 4.05 (m, 1H), 2.43 – 2.33 (m, 1H), 2.33 – 2.04 (m, 4H), 2.11 (s, 3H), 1.82 – 1.75 (m, 1H), 1.74 – 1.64 (m, 6H), 1.62 – 1.53 (m, 2H), 1,61 (s, 3H), 1.32 – 1.23 (m, 2H), 1.15 (dd, *J* = 25.3, 6.9 Hz, 1H), 1.07 – 0.93 (m, 1H), 0.90 – 0.77 (m, 1H).

(*Z*)-2-(Cyclohexyl(hydroxy)methyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 5.15 – 5.03 (m, 1H), 4.13 – 4.05 (m, 1H), 2.61 – 2.51 (m, 1H), 2.33 – 2.04 (m, 4H), 1.87 (s, 3H), 1.82 – 1.75 (m, 1H), 1.74 – 1.64 (m, 6H), 1.62 – 1.53 (m, 2H), 1,61 (s, 3H), 1.32 – 1.23 (m, 2H), 1.15 (dd, *J* = 25.3, 6.9 Hz, 1H), 1.07 – 0.93 (m, 1H), 0.90 – 0.77 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-2-(Cyclohexyl(hydroxy)methyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 157.8, 133.9, 122.6, 117.6, 114.6, 72.7, 42.6, 34.2, 29.4, 29.4, 26.4 (2C), 26.0, 25.8, 25.8, 22.0, 17.9.

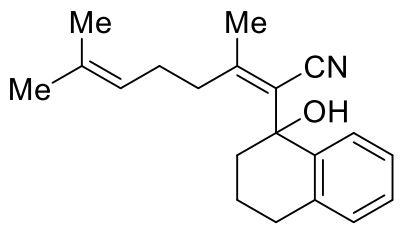
(*Z*)-2-(Cyclohexyl(hydroxy)methyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 157.5, 133.5, 122.5, 117.3, 114.3, 73.1, 42.9, 39.0, 29.3, 28.9, 26.4 (2C), 26.0, 25.8, 23.0, 18.8, 17.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3430, 2924, 2853, 2211, 1658, 1600, 1506, 1492, 1447, 1408, 1377, 1352, 1320, 1305, 1278, 1260, 1225, 1185, 1159, 1110, 1100, 1083, 1026, 1014, 960, 892, 833, 821, 812, 751, 700.

MS (EI, 70 eV): *m/z* (%) = 69 (19), 61 (14), 45 (13), 43 (100), 41 (11).

HRMS (EI): *m/z* calc. for [$C_{17}H_{27}NO$]: 261.2093 found 261.2080.

2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3,7-dimethylocta-2,6-dienenitrile (175ad´´)



According to the **TP16**, a solution geranyl nitrile (**173a**, 0.18 M, 27 mg, 0.18 mmol, 1.0 equiv; *E/Z* = 50/50) in THF (total volume: 1 mL) and a solution of NaDA (0.22 M in DMEA, 0.22 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of α-tetralone (**112d´´**, 44 mg, 0.30 mmol, 1.7 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound **175ad´´** as an orange oil (53 mg, 0.18 mmol, 98% yield; *Z/E* = 53/47).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)-2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 7.33 – 7.27 (m, 1H), 7.24 – 7.17 (m, 2H), 7.14 – 7.09 (m, 1H), 4.75 – 4.71 (m, 1H), 2.90 – 2.71 (m, 2H), 2.57 – 2.41 (m, 1H), 2.26 – 2.16 (m, 3H), 2.14 (s, 3H), 2.06 – 1.95 (m, 3H), 1.95 – 1.82 (m, 2H), 1.61 (s, 3H), 1.47 (s, 3H).

(*Z*)-2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3,7-dimethylocta-2,6-dienenitrile δ / ppm = 7.33 – 7.27 (m, 1H), 7.24 – 7.17 (m, 2H), 7.14 – 7.09 (m, 1H), 5.18 – 5.11 (m, 1H), 2.90 – 2.71 (m, 2H), 2.57 – 2.41 (m, 1H), 2.26 – 2.16 (m, 3H), 2.06 – 1.95 (m, 3H), 1.95 – 1.82 (m, 2H), 1.73 (s, 3H), 1.62 (s, 3H), 1.41 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 157.1, 140.5, 137.1, 132.9, 129.5, 128.4, 127.7, 127.2, 122.9, 120.4, 118.5, 73.3, 38.1, 34.7, 29.7, 25.9, 25.8, 23.6, 19.3, 17.7.

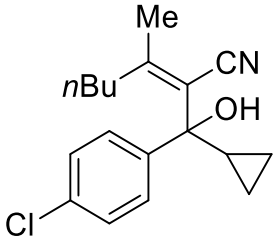
(*Z*)-2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 157.0, 140.1, 137.2, 133.2, 129.5, 128.3, 127.6, 127.2, 122.6, 120.4, 118.1, 72.9, 39.9, 37.3, 29.7, 26.6, 25.6, 19.8, 19.2, 17.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3443, 3020, 2928, 2864, 2209, 1609, 1488, 1449, 1440, 1376, 1327, 1277, 1195, 1182, 1158, 1112, 1090, 1076, 1038, 1020, 978, 955, 943, 931, 906, 876, 848, 824, 782, 758, 732.

MS (EI, 70 eV): *m/z* (%) = 277 (11), 227 (11), 226 (60), 208 (14), 194 (10), 147 (29), 129 (11), 118 (11), 115 (10), 91 (28), 69 (100), 41 (58).

HRMS (EI): *m/z* calc. for [$C_{20}H_{25}NO$]: 295.1936; found 295.1932.

2-((4-Chlorophenyl)(cyclopropyl)(hydroxy)methyl)-3-methylhept-2-enenitrile (175bi´)



According to the **TP16**, a solution 3-methylhept-2-enenitrile (**173b**, 0.20 M, 25 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 65/35) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of (4-chlorophenyl)(cyclopropyl)methanone (**112i´**, 45 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound **175bi´** as a colorless oil (67 mg, 0.17 mmol, 85% yield; *Z*/*E* = 55/45).

(*E*/*Z*)-2-((4-Chlorophenyl)(cyclopropyl)(hydroxy)methyl)-3-methylhept-2-enenitrile:

^{1}H-NMR (400 MHz, $CDCl_3$):

δ / ppm = 7.31 (qd, *J* = 8.7, 2.0 Hz, 4H), 2.54 – 2.33 (m, 1H), 2.12 (s, 2H), 2.06 – 1.98 (m, 1H), 1.94 (d, *J* = 6.4 Hz, 1H), 1.60 (s, 1H), 1.56 – 1.42 (m, 2H), 1.38 (dt, *J* = 14.9, 7.3 Hz, 1H), 1.21 – 1.08 (m, 1H), 0.95 (q, *J* = 8.4, 7.2 Hz, 3H), 0.67 (dt, *J* = 15.5, 7.8 Hz, 2H), 0.57 – 0.47 (m, 1H), 0.42 (d, *J* = 5.2 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*Z*)-2-((4-Chlorophenyl)(cyclopropyl)(hydroxy)methyl)-3-methylhept-2-enenitrile: δ / ppm = 164.2, 144.0, 133.1, 128.2 (2C), 127.3 (2C), 118.6, 118.2, 74.6, 35.2, 29.2, 24.2, 22.9, 22.6, 13.78, 2.3, 2.3.

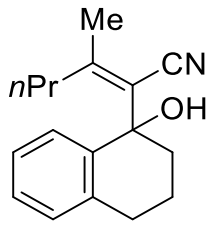
(*E*)-2-((4-Chlorophenyl)(cyclopropyl)(hydroxy)methyl)-3-methylhept-2-enenitrile: δ / ppm = 164.3, 143.3, 133.2, 128.4 (2C), 127.3 (2C), 118.5, 118.2, 74.8, 39.7, 30.2, 24.0, 23.6, 20.5, 14.1, 2.3, 2.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3432, 3009, 2956, 2928, 2871, 2861, 2358, 2338, 2208, 1604, 1489, 1456, 1401, 1186, 1163, 1092, 1014, 986, 869, 832, 827, 824, 807.

MS (EI, 70 eV): *m/z* (%) = 277 (12), 275 (36), 246 (12), 220 (14), 218 (43), 206 (11), 204 (11), 184 (12), 181 (25), 150 (64), 141 (33), 139 (100), 125 (20).

HRMS (EI): *m/z* calc. for [$C_{18}H_{21}ClNO$]: 302.1312; found: 302.1306 [M – H].

2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylhex-2-enenitrile (175cd´´)



According to the **TP16**, a solution (*E*)-3-methylhex-2-enenitrile (**173c**, 0.20 M, 22 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of α-tetralone (**112d´´**, 44 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound **175cd´´** as a colorless oil (34 mg, 0.17 mmol, 67% yield; *Z*/*E* = 58/42).

(*Z*)-2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylhex-2-enenitrile

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 (dd, *J* = 7.2, 2.0, 1H), 7.20 (ddd, *J* = 7.1, 4.3, 1.9, 2H), 7.14 – 7.10 (m, 1H), 2.91 – 2.71 (m, 2H), 2.28 – 2.17 (m, 2H), 2.11 (s, 3H), 2.01 – 1.70 (m, 5H), 1.36 – 1.23 (m, 1H), 1.13 – 0.97 (m, 1H), 0.58 (t, *J* = 7.3, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.5, 140.6, 137.0, 129.5, 128.4, 127.8, 127.2, 120.2, 118.4, 73.0, 38.3, 36.7, 29.8, 23.4, 20.5, 19.3, 14.3.

(*E*)-2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylhex-2-enenitrile

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.29 (m, 1H), 7.23 – 7.18 (m, 2H), 7.13 (dt, *J*=6.0, 3.4, 1H), 2.92 – 2.72 (m, 2H), 2.44 (td, *J*=7.3, 1.9, 2H), 2.30 – 2.15 (m, 2H), 2.05 – 1.81 (m, 3H), 1.58 – 1.48 (m, 2H), 1.41 (s, 3H), 0.98 (t, *J*=7.4, 3H).

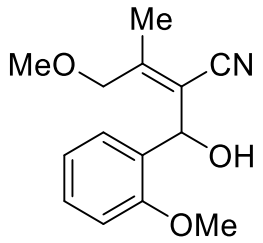
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.5, 140.1, 137.2, 129.6, 128.3, 127.6, 127.3, 120.3, 118.2, 72.9, 41.8, 37.4, 29.7, 21.4, 19.6, 19.2, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3447, 2957, 2932, 2871, 2209, 1706, 1610, 1489, 1450, 1441, 1379, 1363, 1329, 1277, 1260, 1223, 1182, 1162, 1086, 1039, 1020, 979, 945, 905, 827, 783, 758, 732.

MS (EI, 70 eV): *m/z* (%) = 227 (11), 148 (11), 147 (100), 129 (21), 91 (17).

HRMS (EI): *m/z* calc. for [$C_{17}H_{21}NO$]: 255.1623; found: 254.1538 [M – H].

(*Z*)-2-(Hydroxy(2-methoxyphenyl)methyl)-4-methoxy-3-methylbut-2-enenitrile (175da´´)



According to the **TP16**, a solution of 4-methoxy-3-methylbut-2-enenitrile (**173d**, 0.20 M, 35 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* = 80/20) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, – 78 °C) and was subsequently injected in a flask containing a stirred solution of *o*-anisaldehyde (**112a´´**, 41 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 1:1) afforded the title compound **175da´´** as a white solid (29 mg, 0.12 mmol, 58% yield; *Z*/*E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.54 – 7.47 (m, 1H), 7.31 (ddd, *J*=8.2, 7.5, 1.7, 1H), 7.02 (td, *J*=7.5, 1.1, 1H), 6.89 (dd, *J*=8.3, 1.1, 1H), 5.86 (s, 1H), 4.30 (d, *J*=13.2, 1H), 4.05 (d, *J*=13.2, 1H), 3.85 (s, 3H), 3.34 (s, 3H), 2.14 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.3, 153.4, 129.6, 128.4, 127.2, 121.2, 116.8, 116.7, 110.6, 71.4, 65.9, 58.8, 55.4, 20.7.

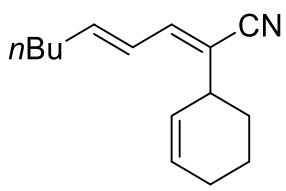
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3416, 3353, 2938, 2843, 2217, 1600, 1590, 1488, 1463, 1449, 1438, 1377, 1290, 1266, 1245, 1190, 1166, 1133, 1114, 1095, 1079, 1042, 1030, 958, 942, 834, 790, 780, 756, 721, 661.

MS (EI, 70 eV): *m/z* (%) = 215 (12), 214 (26), 201 (13), 200 (100), 198 (14), 184 (29), 183 (28), 173 (25), 172 (12), 157 (19), 145 (12), 137 (13), 135 (35), 107 (29), 77 (11).

HRMS (EI): *m/z* calc. for [$C_{14}H_{17}NO_3$]: 247.1208; found: 229.1097 [M – H_2O].

m.p. (°C): 77.3 – 78.2.

2-(Cyclohex-2-en-1-yl)nona-2,4-dienenitrileenenitrile (175ee´)



According to the **TP16**, a solution of (*2E,4E*)-nona-2,4-dienenitrile (**173e**, 0.20 M, 27 mg, 0.20 mmol, 1.0 equiv; 2*E*/2*Z* = 69/31) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexene bromide (**112e´**, 30 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (1.0 M in THF, 20 µL, 0.02 mmol, 0.1 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **175ee´** as a yellow oil (32 mg, 0.15 mmol, 74% yield; 2*Z*/*2E* = 77/23).

^{1}H-NMR (400 MHz, $CDCl_3$):

(2*E*,4*E*)-2-(Cyclohex-2-en-1-yl)nona-2,4-dienenitrileenenitrile: δ = 6.69 (d, *J*=11.2, 1H), 6.35 (ddd, *J*=14.5, 11.2, 1.5, 1H), 6.05 (ddt, *J*=14.4, 11.4, 7.0, 1H), 5.91 (ddt, *J*=10.1, 4.6, 2.9, 1H), 5.46 (dq, *J*=10.1, 2.4, 1H), 3.34 (dh, *J*=7.9, 2.7, 1H), 2.18 (qd, *J*=7.2, 1.4, 2H), 2.04 (ddddd, *J*=12.2, 10.7, 8.7, 5.7, 2.9, 2H), 1.92 – 1.78 (m, 2H), 1.62 (qdd, *J*=14.2, 5.7, 3.7, 2H), 1.47 – 1.26 (m, 4H), 0.90 (td, *J*=7.2, 1.9, 3H).

(2*Z*,4*E*)-2-(Cyclohex-2-en-1-yl)nona-2,4-dienenitrileenenitrile: δ = 6.57 (d, *J*=11.0, 1H), 6.53 – 6.43 (m, 1H), 6.08 – 5.99 (m, 1H), 5.91 (ddt, *J*=10.1, 4.6, 2.9, 1H), 5.53 (dq, *J*=10.2, 2.5, 1H), 2.98 (tq, *J*=5.6, 2.8, 1H), 2.18 (qd, *J*=7.2, 1.4, 2H), 2.04 (ddddd, *J*=12.2, 10.7, 8.7, 5.7, 2.9, 2H), 1.92 – 1.79 (m, 2H), 1.62 (qdd, *J*=14.2, 5.7, 3.7, 2H), 1.46 – 1.29 (m, 4H), 0.90 (td, *J*=7.2, 1.9, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(2*E*,4*E*)-2-(Cyclohex-2-en-1-yl)nona-2,4-dienenitrileenenitrile: δ / ppm = 145.1, 143.6, 130.8, 126.9, 124.2, 120.3, 116.1, 35.3, 33.0, 31.0, 28.5, 24.6, 22.4, 21.4, 14.0.

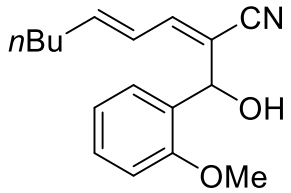
(2*Z*,4*E*)-2-(Cyclohex-2-en-1-yl)nona-2,4-dienenitrileenenitrile: δ / ppm = 144.2, 143.6, 131.0, 127.1, 126.4, 118.2, 115.5, 39.6, 32.8, 31.6, 31.1, 29.8, 24.9, 22.4, 20.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2930, 2871, 2861, 2208, 1712, 1636, 1455, 1448, 1433, 1378, 1362, 1249, 1220, 1183, 1138, 1079, 1046, 973, 903, 724.

MS (EI, 70 eV): *m/z* (%) = 215 (19), 172 (15), 158 (40), 156 (15), 145 (96), 144 (80), 143 (37), 132 (20), 131 (25), 130 (89), 129 (18), 128 (19), 118 (34), 117 (100), 116 (79), 115 (38), 104 (31), 103 (18), 92 (46), 91 (42), 90 (14), 81 (15), 79 (30), 77 (23).

HRMS (EI): *m/z* calc. for [$C_{15}H_{21}N$]: 215.1674; found: 215.1669.

2-(Hydroxy(2-methoxyphenyl)methyl)nona-2,4-dienenitrile (175ea´´)



According to the **TP16**, a solution of (*2E,4E*)-nona-2,4-dienenitrile (**173e**, 0.20 M, 27 mg, 0.20 mmol, 1.0 equiv; 2*E*/2*Z* = 69/31) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of *o*-anisaldehyde (**112a´´**, 41 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **175ea´´** as a off-white solid (45 mg, 0.16 mmol, 82% yield; 2*Z*/*2E* = 76/24).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*2Z,4E*)-2-(Hydroxy(2-methoxyphenyl)methyl)nona-2,4-dienenitrile: δ / ppm = 7.48 (dd, *J*=7.6, 1.7, 1H), 7.31 (ddd, *J*=8.2, 7.4, 1.7, 1H), 7.01 (td, *J*=7.5, 1.1, 1H), 6.90 (dd, *J*=8.2, 1.0, 1H), 6.75 (d, *J*=11.4, 1H), 6.57 (ddt, *J*=14.5, 11.4, 1.5, 1H), 6.11 (dt, *J*=14.5, 7.0, 1H), 5.91 (d, *J*=2.6, 1H), 3.85 (s, 3H), 2.93 (s, 1H), 2.21 (qd, *J*=7.0, 1.4, 2H), 1.48 – 1.27 (m, 4H), 0.92 (t, *J*=7.2, 3H).

(*2E,4E*)-2-(Hydroxy(2-methoxyphenyl)methyl)nona-2,4-dienenitrile: δ / ppm = 7.39 – 7.28 (m, 2H), 7.01 (td, *J*=7.5, 1.1, 1H), 6.91 (dd, *J*=8.3, 1.1, 1H), 6.81 (dt, *J*=11.2, 1.0, 1H), 6.50 (ddt, *J*=15.0, 11.1, 1.5, 1H), 6.11 (dt, *J*=14.6, 7.1, 1H), 5.53 (s, 1H), 3.86 (s, 3H), 3.03 (d, *J*=6.1, 1H), 2.23 – 2.15 (m, 2H), 1.47 – 1.28 (m, 4H), 0.90 (t, *J*=7.2, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*2Z,4E*)-2-(Hydroxy(2-methoxyphenyl)methyl)nona-2,4-dienenitrile: δ / ppm = 156.5, 146.3, 144.5, 129.7, 128.5, 127.2, 124.7, 121.3, 119.2, 114.1, 110.8, 66.1, 55.4, 33.0, 30.9, 22.4, 14.0.

(*2E,4E*)-2-(Hydroxy(2-methoxyphenyl)methyl)nona-2,4-dienenitrile: δ / ppm = 156.6, 145.4, 144.0, 129.7, 128.1, 127.7, 126.6, 121.2, 116.7, 113.8, 110.9, 70.8, 55.5, 32.7, 30.8, 22.3, 13.9.

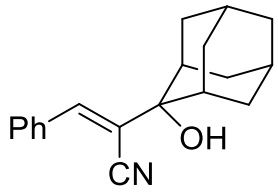
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 2961, 2928, 2856, 2838, 2220, 1633, 1599, 1588, 1488, 1462, 1436, 1407, 1383, 1370, 1324, 1304, 1285, 1251, 1235, 1200, 1188, 1173, 1161, 1148, 1119, 1053, 1046, 1023, 981, 947, 940, 931, 917, 860, 843, 789, 754, 724, 688.

MS (EI, 70 eV): *m/z* (%) = 240 (13), 228 (32), 214 (18).

HRMS (EI): *m/z* calc. for [$C_{17}H_{21}NO_2$]: 271.1572; found: 271.1506.

m.p. (°C): 84.1 – 85.2.

(*E*)-2-(Hydroxyadamantan-2-yl)-3-phenylacrylonitrile (169ah)

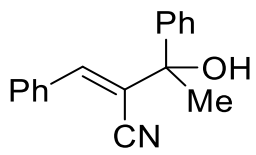


According to the **TP17**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaTMP (0.26 M in hexane, 0.26 mmol, 1.3 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ah** as a colorless oil (44 mg, 0.16 mmol, 79% yield; *E*/*Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.79 (dd, *J* = 7.4, 2.3, 2H), 7.43 (dt, *J* = 4.8, 2.8, 3H), 7.22 (s, 1H), 2.39 (t, *J* = 2.9, 2H), 2.30 (d, *J* = 12.9, 2H), 1.93 – 1.79 (m, 7H), 1.73 (h, *J* = 3.9, 3.0, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.0, 133.6, 130.6, 129.2 (2C), 129.0 (2C), 118.4, 117.8, 75.7, 37.4, 35.7 (2C), 34.6 (2C), 32.7 (2C), 27.1, 26.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3432, 3373, 2932, 2912, 2904, 2852, 2212, 1468, 1448, 1352, 1215, 1144, 1106, 1085, 1078, 1050, 1043, 1018, 1009, 968, 950, 934, 911, 765, 745, 687, 676.
MS (EI, 70 eV): *m/z* (%) = 279 (19), 278 (15), 207 (14), 173 (78), 156 (10), 152 (10), 151 (95), 140 (10), 130 (21), 129 (11), 128 (14), 115 (16), 93 (17), 91 (100), 81 (13), 79 (28), 77 (16).

HRMS (EI): *m/z* calc. for [$C_{19}H_{21}NO$]: 279.1623; found: 279.1620.

(*E*)-2-Benzylidene-3-hydroxy-3-phenylbutanenitrile (169ae)

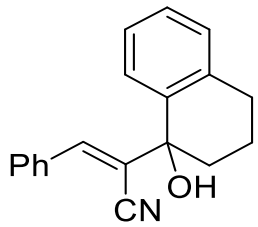


According to the **TP17**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaTMP (0.26 M in hexane, 0.26 mmol, 1.3 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of acetophenone (**112e**, 36 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ae** as a slightly yellow oil (29 mg, 0.12 mmol, 58% yield; *E/Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.70 – 7.56 (m, 2H), 7.41 (d, *J* = 7.6, 2H), 7.31 – 7.20 (m, 6H), 7.13 (s, 1H), 2.25 (s, 1H), 1.84 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.8, 141.6, 133.3, 130.5, 129.2 (2C), 129.0 (2C), 128.9 (2C), 128.4, 125.7 (2C), 119.1, 117.9, 75.8, 28.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3432, 2984, 2211, 1704, 1621, 1494, 1448, 1420, 1362, 1286, 1223, 1163, 1159, 1132, 1107, 1092, 1072, 1029, 926, 915, 902, 758, 737, 692.
MS (EI, 70 eV): *m/z* (%) = 249 (10), 248 (16), 235 (12), 234 (69), 207 (15), 206 (100), 179 (31), 178 (16), 156 (73), 130 (13), 129 (12), 128 (13), 121 (23), 105 (15), 77 (11).

HRMS (EI): *m/z* calc. for [$C_{17}H_{15}NO$]: 249.1154; found: 249.1152.

(*E*)-2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-phenylacrylonitrile (169ad´´)



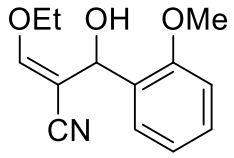
According to the **TP17**, a solution of cinnamonitrile (**121a**, 0.20 M, 26 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaTMP (0.26 M in hexane, 0.26 mmol, 1.3 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of α-tetralone (**112d´´**, 44 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical

purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **169ad´´** as a brown viscose oil (37 mg, 0.13 mmol, 67% yield; *E/Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 – 7.75 (m, 2H), 7.47 – 7.38 (m, 4H), 7.35 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.25 (pd, *J* = 7.3, 1.7 Hz, 2H), 7.18 (dd, *J* = 7.5, 1.6 Hz, 1H), 2.88 (dd, *J* = 7.4, 5.1 Hz, 2H), 2.38 (ddd, *J* = 14.2, 11.1, 3.3 Hz, 1H), 2.22 (s, 1H), 2.13 – 1.82 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.8, 138.0, 137.7, 133.4, 130.4, 129.7, 129.2 (2C), 129.0 (2C), 128.9, 127.7, 127.1, 119.1, 118.0, 75.1, 37.2, 29.5, 19.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3426, 3061, 3027, 2937, 2868, 2212, 1621, 1602, 1576, 1489, 1448, 1360, 1328, 1290, 1278, 1209, 1185, 1161, 1127, 1114, 1104, 1081, 1058, 1040, 1021, 990, 935, 911, 900, 879, 858, 850, 770, 754, 734, 690, 671.
MS (EI, 70 eV): *m/z* (%) = 274 (16), 246 (11), 148 (12), 147 (100), 129 (24), 91 (28).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}NO$]: 275.1310; found: 275.1303.

(*Z*)-3-Ethoxy-2-(hydroxy(2-methoxyphenyl)methyl)acrylonitrile (172ga´´)



According to the **TP17**, a solution of 3-ethoxyacrylonitrile (**170g**, 0.20 M, 19 mg, 0.20 mmol, 1.0 equiv; *E/Z* = 68/32) in THF (total volume: 1 mL) and a solution of NaTMP (0.24 M in hexane, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of *o*-anisaldehyde (**112a´´**, 41 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 7:3) afforded the title compound **172ga´´** as a yellow solid (34 mg, 0.16 mmol, 78% yield; *Z*/*E* > 99/1).

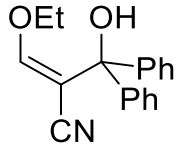
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 (d, *J* = 8.9 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.36 (td, *J* = 7.5, 0.9 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.26 (s, 1H), 6.17 (s, 1H), 4.50 – 4.43 (m, 2H), 4.28 (s, 3H), 1.72 (t, *J* = 7.1 Hz, 3H), 1.66 (d, *J* = 5.9 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 158.6, 157.0, 129.4, 128.9, 127.7, 121.0, 118.2, 111.0, 97.3, 71.3, 65.9, 55.5, 15.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3387, 2935, 2840, 2212, 1637, 1599, 1587, 1488, 1462, 1438, 1392, 1371, 1355, 1325, 1306, 1290, 1242, 1216, 1190, 1171, 1161, 1146, 1108, 1091, 1027, 1013, 949, 940, 920, 892, 855, 790, 768, 756, 732, 688.
MS (EI, 70 eV): *m/z* (%) = 233 (44), 232 (10), 204 (12), 202 (15), 188 (11), 187 (12), 174 (14), 156 (15), 137 (100), 135 (68), 121 (19), 109 (30), 108 (19), 107 (61), 98 (11), 94 (12), 91 (14), 78 (11), 77 (37), 65 (11), 43 (12).

HRMS (EI): *m/z* calc. for [$C_{13}H_{15}NO_3$]: 233.1052; found: 233.1048.

m.p. (°C): 42.9 – 47.0.

(*Z*)-3-Ethoxy-2-(hydroxydiphenylmethyl)acrylonitrile (172ga´)

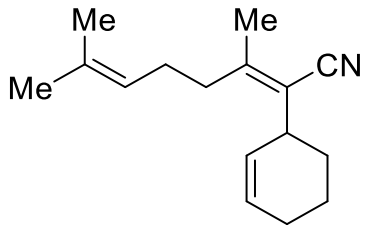


According to the **TP17**, a solution of 3-ethoxyacrylonitrile (**170g**, 0.20 M, 19 mg, 0.20 mmol, 1.0 equiv; *E/Z* = 68/32) in THF (total volume: 1 mL) and a solution of NaTMP (0.24 M in hexane, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of benzophenone (**112a´**, 55 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 7:3) afforded the title compound **172ga´** as a brown viscose oil (36 mg, 0.13 mmol, 65% yield; *Z*/*E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 – 7.28 (m, 10H), 6.62 (s, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.2, 143.8 (2C), 128.5 (4C), 128.3 (2C), 127.3 (4C), 116.4, 98.7, 78.8, 71.1, 15.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3428, 2983, 2211, 1628, 1600, 1492, 1447, 1395, 1370, 1304, 1218, 1183, 1144, 1107, 1088, 1019, 935, 917, 893, 768, 751, 737, 698, 672, 653.
MS (EI, 70 eV): *m/z* (%) = 183 (16), 182 (34), 105 (100), 77 (76), 69 (14), 68 (18).

HRMS (EI): *m/z* calc. for [$C_{18}H_{17}NO_2$]: 279.1259; found: 279.1255.

2-(Cyclohex-2-en-1-yl)-3,7-dimethylocta-2,6-dienenitrile (175ae´)



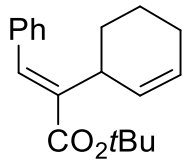
According to the **TP17**, a solution of geranyl nitrile (**173a**, 0.20 M, 30 mg, 0.20 mmol, 1.0 equiv; *E/Z* = 50/50) in THF (total volume: 1 mL) and a solution of NaTMP (0.26 M in hexane, 0.26 mmol, 1.3 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexene bromide (**112e´**, 30 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (1.0 M in THF, 20 µL, 0.02 mmol, 0.1 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane) afforded the title compound **175ae´** as a yellow oil (25 mg, 0.11 mmol, 54% yield; *Z*/*E* = 52/48).

(*E*/*Z*)-2-(Cyclohex-2-en-1-yl)-3,7-dimethylocta-2,6-dienenitrile:

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.88 (ddt, *J* = 10.1, 5.2, 2.8 Hz, 1H), 5.43 (dddd, *J* = 11.2, 8.7, 2.7, 1.3 Hz, 1H), 5.14 – 5.03 (m, 1H), 3.21 (dddt, *J* = 18.0, 8.8, 6.0, 3.0 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.31 – 2.12 (m, 3H), 2.07 (s, 2H), 1.86 (s, 3H), 1.69 (d, *J* = 1.4 Hz, 4H), 1.66 – 1.53 (m, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 154.9, 154.8, 133.4, 133.1, 130.4, 130.3, 127.6, 127.5, 122.7, 122.6, 118.7, 118.4, 115.4, 115.1, 38.8, 36.2, 36.0, 34.0, 28.6, 28.2, 26.6, 26.5, 25.8, 25.8, 24.6, 24.6, 23.0, 21.7, 21.6, 18.4, 17.8 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3022, 2964, 2927, 2860, 2840, 2209, 1624, 1447, 1377, 1109, 978, 901, 886, 871, 823, 764, 722.
MS (EI, 70 eV): *m/z* (%) = 214 (70), 201 (67), 200 (22), 187 (29), 186 (83), 173 (65), 172 (42), 161 (29), 160 (94), 159 (100), 158 (89), 146 (93), 145 (23), 144 (92), 133 (47), 132 (75), 131 (76), 130 (71), 119 (22), 118 (66), 117 (24), 116 (33), 91 (27), 79 (19), 69 (50), 41 (36).

HRMS (EI): *m/z* calc. for [$C_{16}H_{23}N$]: 229.1830; found: 229.1827.

***Tert*-butyl (*E*)-2-(cyclohex-2-en-1-yl)-3-phenylacrylate (178be´)**

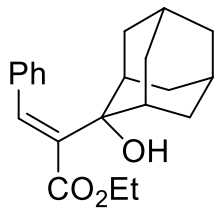


According to the **TP16**, a solution *tert*-butyl cinnamate (**176b**, 0.20 M, 41 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* > 99/1) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexene bromide (**112e´**, 30 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (1.0 M in THF, 20 µL, 0.02 mmol, 0.1 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **178be´** as a yellow oil (23 mg, 0.12 mmol, 61% yield; *E*/*Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.58 (s, 1H), 7.40 – 7.33 (m, 2H), 7.33 – 7.27 (m, 3H), 5.68 (dddd, *J*=10.1, 5.0, 2.7, 0.9, 1H), 5.57 – 5.50 (m, 1H), 3.64 – 3.54 (m, 1H), 2.14 – 1.93 (m, 3H), 1.88 – 1.80 (m, 1H), 1.76 (dddd, *J*=11.0, 5.4, 2.7, 1.3, 1H), 1.62 – 1.55 (m, 1H), 1.52 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.5, 138.7, 138.6, 136.2, 130.5, 129.1 (2C), 128.4 (2C), 128.0, 126.2, 80.9, 36.2, 28.3, 28.3 (3C), 24.8, 22.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2976, 2929, 2861, 2835, 1705, 1626, 1493, 1446, 1391, 1366, 1302, 1243, 1223, 1206, 1161, 1138, 1106, 1075, 1051, 977, 928, 886, 851, 841, 776, 761, 742, 720, 695.
MS (EI, 70 eV): *m/z* (%) = 228 (16), 185 (11), 184 (15), 183 (100), 167 (13), 155 (13), 141 (73), 129 (15), 115 (10).

HRMS (EI): *m/z* calc. for [$C_{19}H_{24}O_2$]: 284.1776; found: 227.1064 [M – *t*Bu].

Ethyl (*E*)-2-(2-hydroxyadamantan-2-yl)-3-phenylacrylate (178ah)



According to **TP18**, a solution of ethyl cinnamate (**176a**, 0.20 M, 35 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* > 99/1) and adamantanone (**112h**, 45 mg, 0.30 mmol, 1.5 equiv) in THF (total volume: 1 mL) and a

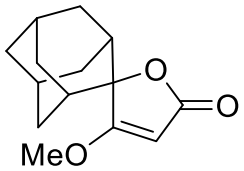
solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flame-dried flask. The reaction was stirred for 30 min at −78 °C and quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **178ah** as a white solid (43 mg, 0.13 mmol, 66% yield; *E/Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 – 7.23 (m, 5H), 6.86 (s, 1H), 4.12 (q, *J*=7.1, 2H), 3.31 (s, 1H), 2.45 – 2.32 (m, 2H), 2.10 (d, *J*=4.1, 2H), 1.96 (d, *J*=12.9, 2H), 1.86 (dp, *J*=6.5, 3.2, 2H), 1.76 (dqd, *J*=13.0, 2.7, 1.3, 2H), 1.71 (d, *J*=3.5, 2H), 1.62 (dtd, *J*=12.8, 3.5, 1.5, 2H), 1.06 (t, *J*=7.2, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 171.2, 139.3, 136.1, 131.1, 128.4 (2C), 128.2 (2C), 128.2, 76.1, 61.2, 37.7, 35.4 (2C), 34.8 (2C), 32.8 (2C), 27.5, 27.2, 13.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3407, 2958, 2917, 2903, 2856, 1708, 1678, 1636, 1468, 1459, 1446, 1410, 1392, 1375, 1352, 1338, 1319, 1296, 1284, 1231, 1208, 1130, 1118, 1110, 1104, 1095, 1072, 1040, 1003, 962, 936, 926, 911, 874, 857, 756, 732, 702, 683.
MS (EI, 70 eV): *m/z* (%) = 280 (73), 279 (38), 253 (74), 252 (59), 251 (71), 235 (29), 225 (73), 224 (100), 223 (41), 204 (30), 179 (41), 167 (35), 162 (78), 159 (29), 143 (28), 141 (38), 131 (59), 129 (33), 128 (25), 121 (31), 115 (33), 103 (32), 93 (28), 91 (72), 79 (44), 77 (25).

HRMS (EI): *m/z* calc. for [$C_{21}H_{26}O_3$]: 326.1882; found: 308.1768 [M – H_2O].

m.p. (°C): 64.6 – 65.7.

3'-Methoxy-5'*H*-spiro[adamantane-2,2'-furan]-5'-one (178ch)



According to **TP18**, a solution of methyl Methyl (*E*)-3-methoxyacrylate (**176c**, 0.20 M, 23 mg, 0.20 mmol, 1.0 equiv; *E/Z* > 99/1) and adamantanone (**112h**, 45 mg, 0.30 mmol, 1.5 equiv) in THF (total volume: 1 mL) and a solution of NaDA (0.24 M in DMEA, 0.24 mmol, 1.2 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.12 s, –78 °C) and was subsequently injected in a flame-dried flask. The reaction was stirred for 30 min at –78 °C and quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash

chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **178ch** as a white solid (27 mg, 0.12 mmol, 58% yield).

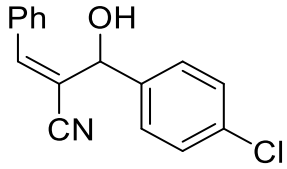
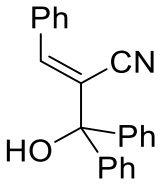
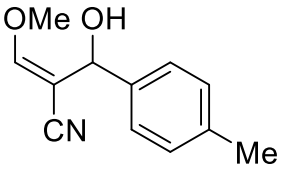
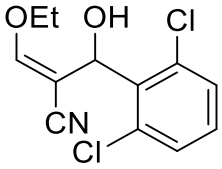
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.99 (s, 1H), 3.87 (s, 3H), 2.41 – 2.24 (m, 4H), 1.89 (dt, *J*=20.0, 3.2, 4H), 1.74 (qd, *J*=4.3, 1.9, 4H), 1.70 – 1.58 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): 187.4, 171.7, 88.2, 88.1, 59.5, 37.9, 36.4 (2C), 34.7 (2C), 33.3 (2C), 26.7, 26.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3111, 2946, 2908, 2895, 2864, 2851, 1754, 1619, 1471, 1455, 1436, 1377, 1346, 1315, 1286, 1254, 1203, 1177, 1113, 1104, 1066, 1050, 1041, 1018, 1009, 1002, 959, 954, 934, 924, 888, 866, 826, 802, 777, 753, 739, 709, 666.
MS (EI, 70 eV): *m/z* (%) = 235 (14), 234 (100), 233 (14), 216 (15), 206 (38), 202 (67), 201 (16), 192 (20), 184 (52), 177 (16), 175 (13), 174 (31), 169 (25), 163 (13), 161 (18), 160 (28), 157 (17), 129 (15), 127 (21), 125 (25), 117 (17), 115 (14), 93 (13), 91 (29), 79 (21).

HRMS (EI): *m/z* calc. for [$C_{14}H_{18}O_3$]: 234.1256; found: 234.1251.

m.p. (°C): 128.6 – 131.4.

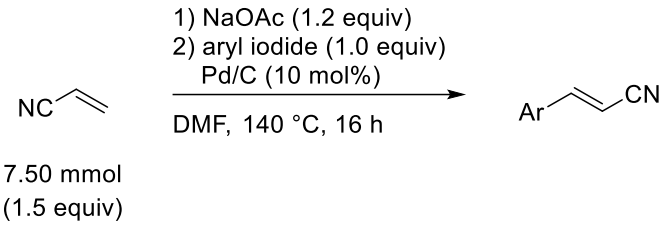
6.3 Additional Experiments under Batch and Barbier-type Conditions:

Table 53: Summarized Barbier-type, batch and sequential flow results: Barbier-type experiments were conducted according to **TP18**, experiments under batch conditions were conducted according to **TP19,** sequential flow condtions according to **TP16**.

Entry	Product	Barbier-type	batch conditions	sequential flow conditions
1	 **169ax´**	only traces of product according to GCMS	only traces of product according to GCMS	92% isolated yield
2	 **169aa´**	only traces of product according to GCMS	only traces of product according to GCMS	82% isolated yield
3	 **172fj**	only traces of product according to GCMS	74% isolated yield Z/E = 9/1	98% isolated yield Z/E = 99/1
4	 **172gi**	26% isolated yield	72% isolated yield	95% isolated yield

6.4 Preparation of the Starting Materials

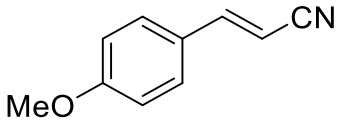
Typical procedure for the synthesis of aryl acrylonitriles



Scheme 157: Typical procedure for the synthesis of aryl acrylonitriles.

A suspension of acrylonitrile (0.40 g, 7.5 mmol, 1.5 equiv) and NaOAc (0.49 g, 6.0 mmol, 1.2 equiv) in dry DMF (15 mL) was prepared. To this suspension a solution of the aryliodine (5.0 mmol, 1.0 equiv) in dry DMF (10 mL) was added as well as 10 weight-% Pd/C (53 mg, 0.05 mmol, 0.01 equiv). The mixture was stirred at 140 °C over night. EtOAc was added to the reaction mixture. The mixture was filtrated and the filtrate was washed with an aqueous LiCl solution (10%, 3 x 30 mL), the combined aqueous layers were extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$. Solvents were removed *in vacuo*. The crude product was purified by column chromatography.[465]

3-(4-Methoxyphenyl)acrylonitrile (170a)



According to the typical procedure for the preparation of aryl acrylonitriles, 1-iodo-4-methoxybenzene (1.16 g, 5.0 mmol, 1.0 equiv) in DMF (10 mL) was added to a mixture of acrylonitrile (0.40 g, 7.5 mmol, 1.5 equiv) and NaOAc (0.49 g, 6.0 mmol, 1.2 equiv) in DMF (15 mL), 10 weight-% Pd/C (53 mg. 0.05 mmol, 0.01 equiv) was added and the mixture was stirred over night at 140 °C. The crude product was purified by column chromatography (isohexane:EtOAc = 9:1) to give the titel compound as colorless solid (0.62 g, 3.9 mmol, 78% yield; *E*/*Z* = 76/24).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)- 3-(4-Methoxyphenyl)acrylonitrile: δ / ppm = 7.40 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 16.6 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.72 (d, *J* = 16.6 Hz, 1H), 3.85 (s, 3H).

[465] P. An, Z. Yu, Q. Lin, *Org. Lett.* **2013**, *15*, 5496.

(*Z*)- 3-(4-Methoxyphenyl)acrylonitrile: δ / ppm = 7.80 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 12.1 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 5.29 (d, *J* = 12.1 Hz, 1H), 3.86 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)- 3-(4-Methoxyphenyl)acrylonitrile: δ / ppm = 150.8, 140.6, 137.5, 130.4, 128.5 (2C), 125.0 (2C), 94.8, 19.9.

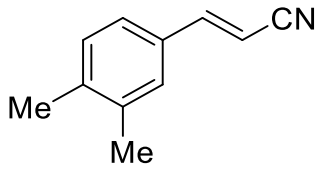
(*Z*)- 3-(4-Methoxyphenyl)acrylonitrile: δ / ppm = 148.8, 131.3 (2C), 130.3, 130.2, 126.6, 118.6 (2C), 93.5, 19.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 3026, 2968, 2953, 2932, 2914, 2846, 2212, 1699, 1614, 1599, 1568, 1509, 1490, 1471, 1458, 1440, 1420, 1309, 1297, 1274, 1249, 1173, 1113, 1022, 1003, 985, 976, 963, 942, 853, 844, 827, 818, 806, 769, 728, 719, 710, 690.

MS (EI, 70 eV): *m/z* (%) = 160 (10), 159 (100), 144 (26), 129 (17), 116 (40), 89 (22).

HRMS (EI): *m/z* calc. for [$C_{10}H_9NO$]: 159.0684; found: 159.0680.

3-(3,4-Dimethylphenyl)acrylonitrile (170b)



According to the typical procedure for the preparation of arylacrylonitriles, 4-iodo-1,2-dimethylbenzene (1.16 g, 5.0 mmol, 1.0 equiv) in DMF (10 mL) was added to a mixture of acrylonitrile (0.40 g, 7.5 mmol, 1.5 equiv) and NaOAc (0.49 g, 6.0 mmol, 1.2 equiv) in DMF (15 mL), 10 weight-% Pd/C (53 mg. 0.05 mmol, 0.01 equiv) was added and the mixture was stirred over night at 140 °C. The crude product was purified by column chromatography (isohexane:EtOAc = 19:1) to give the titel compound as colorless solid (0.51 g, 3.3 mmol, 65% yield; *E*/*Z* = 79/21).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)-3-(3,4-Dimethylphenyl)acrylonitrile: δ / ppm = 7.34 (d, *J* = 16.6 Hz, 1H), 7.23 – 7.16 (m, 3H), 5.82 (d, *J* = 16.6 Hz, 1H), 2.32 – 2.26 (m, 6H).

(*Z*)-3-(3,4-Dimethylphenyl)acrylonitrile: δ / ppm = 7.61 – 7.54 (m, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 12.1 Hz, 1H), 5.36 (d, *J* = 12.1 Hz, 1H), 2.30 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-3-(3,4-Dimethylphenyl)acrylonitrile: δ / ppm = 150.9, 140.8, 137.6, 131.4, 130.5, 128.6, 125.1, 118.7, 94.9, 20.0, 19.9.

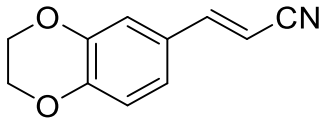
(*Z*)-3-(3,4-Dimethylphenyl)acrylonitrile: δ / ppm = 148.9, 140.5, 137.4, 131.5, 130.4, 130.3, 126.7, 113.9, 93.6, 20.1, 19.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 3018, 2973, 2944, 2920, 2901, 2875, 2856, 2208, 1617, 1603, 1565, 1497, 1479, 1449, 1410, 1386, 1310, 1302, 1296, 1285, 1267, 1239, 1223, 1206, 1124, 1026, 1004, 976, 952, 890, 877, 828, 814, 805, 775, 756, 744, 707.

MS (EI, 70 eV): *m/z* (%) = 158 (12), 157 (100), 156 (59), 143 (10), 142 (97), 140 (10), 129 (38), 128 (16), 115 (49).

HRMS (EI): *m/z* calc. for [$C_{11}H_{11}N$]: 157.0891; found: 157.0886.

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile (170c)



According to the typical procedure for the preparation of arylacrylonitriles, 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine (3.93 g, 15.0 mmol, 1.0 equiv) in DMF (30 mL) was added to a mixture of acrylonitrile (1.19 g, 22.5 mmol, 1.5 equiv.) and NaOAc (1.48 g, 18.0 mmol, 1.2 equiv) in DMF (15 mL), 10 weight-% Pd/C (159 mg, 0.15 mmol, 0.01 equiv) was added and the mixture was stirred over night at 140 °C. The crude product was purified by column chromatography (isohexane:EtOAc = 9:1) to give the titel compound as colorless solid (2.05 g, 11.0 mmol, 73% yield; *E*/*Z* = 83/17).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)- 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile: δ / ppm = 7.27 (d, *J* = 16.5 Hz 1H), 6.99 – 6.93 (m, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 5.69 (d, *J* = 16.6 Hz, 1H), 4.34 – 4.24 (m, 4H).

(*Z*)- 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile: δ / ppm = δ 7.37 (d, *J* = 2.1 Hz, 1H), 7.35 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.99 – 6.93 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.30 (d, *J* = 12.1 Hz, 1H), 4.34 – 4.24 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)- 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile: δ / ppm = 150.1, 146.5, 144.0, 127.4, 121.6, 118.7, 118.1, 116.1, 94.2, 64.7, 64.3.

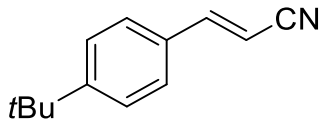
(*Z*)- 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile: δ / ppm = 148.1, 129.0, 123.2, 118.2, 117.8, 117.6, 116.4, 92.8, 64.8, 64.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2875, 2852, 2212, 2190, 1619, 1603, 1576, 1505, 1455, 1450, 1432, 1392, 1313, 1285, 1256, 1239, 1207, 1166, 1156, 1123, 1060, 1037, 1010, 959, 931, 913, 884, 856, 850, 815, 795, 783, 746, 733, 713, 664.

MS (EI, 70 eV): *m/z* (%) = 188.07 (12), 187.06 (100), 172.04 (27), 131.04 (39), 103.04 (33).

HRMS (EI): *m/z* calc. for [$C_{11}H_8NO_2$]: 187.0633; found: 197.0628.

3-(4-(*Tert*-butyl)phenyl)acrylonitrile (170d)



According to the typical procedure for the preparation of arylacrylonitriles, 1-(*tert*-butyl)-4-iodobenzene (3.90 g, 15.0 mmol, 1.0 equiv) in DMF (30 mL) was added to a mixture of acrylonitrile (1.19 g, 22.5 mmol, 1.5 equiv) and NaOAc (1.48 g, 18.0 mmol, 1.2 equiv) in DMF (15 mL), 10 weight-% Pd/C (159 mg. 0.15 mmol, 0.01 equiv) was added and the mixture was stirred over night at 140 °C. The crude product was purified by column chromatography (isohexane:EtOAc = 49:1) to give the titel compound as brownish oil (2.14 g, 10.8 mmol, 72% yield; *E*/*Z* = 79/21).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)-3-(4-(*Tert*-butyl)phenyl)acrylonitrile: δ / ppm = 7.45 – 7.38 (m, 4H), 7.38 (d, *J* = 16.3 Hz, 1H), 5.84 (d, *J* = 16.7 Hz, 1H), 1.33 (s, 9H).

(*Z*)-3-(4-(*Tert*-butyl)phenyl)acrylonitrile: δ / ppm = 7.76 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 12.1 Hz, 1H), 5.39 (d, *J* = 12.1 Hz, 1H), 1.34 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-3-(4-(*Tert*-butyl)phenyl)acrylonitrile: δ / ppm = 155.1, 150.6, 131.0, 127.4 (2C), 126.2 (2C), 118.6, 95.4, 35.1, 31.2 (3C).

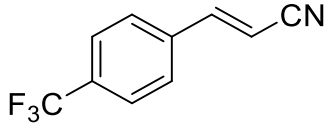
(*Z*)-3-(4-(*Tert*-butyl)phenyl)acrylonitrile: δ / ppm = 154.8, 148.7, 131.1, 129.1 (2C), 126.0 (2C), 117.1, 94.1, 35.1, 31.2 (3C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3055, 2962, 2904, 2868, 2214, 1618, 1605, 1562, 1506, 1475, 1463, 1412, 1395, 1364, 1324, 1295, 1271, 1230, 1217, 1202, 1190, 1121, 1107, 1016, 968, 948, 924, 859, 842, 808, 763, 734, 719, 696.

MS (EI, 70 eV): *m/z* (%) = 185 (15), 171 (13), 170 (100), 155 (44), 154 (13), 142 (24), 115 (12).

HRMS (EI): *m/z* calc. for [$C_{13}H_{15}N$]: 185.1204; found: 185.1199.

3-(4-(Trifluoromethyl)phenyl)acrylonitrile (170e)



According to the typical procedure for the preparation of arylacrylonitriles, 1-iodo-4-(trifluoromethyl)benzene (4.08 g, 15.0 mmol, 1.0 equiv) in DMF (30 mL) was added to a mixture of acrylonitrile (1.19 g, 22.5 mmol, 1.5 equiv) and NaOAc (1.48 g, 18.0 mmol, 1.2 equiv) in DMF (15 mL), 10 weight-% Pd/C (159 mg. 0.15 mmol, 0.01 equiv) was added and the mixture was stirred over night at 140 °C. The crude product was purified by column chromatography (isohexane:EtOAc = 19:1) to give the titel compound as colorless solid (2.31 g, 118 mmol, 78% yield; *E*/*Z* = 78/22).

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)- 3-(4-(Trifluoromethyl)phenyl)acrylonitrile: δ / ppm = 7.68 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 16.7 Hz, 1H), 5.99 (d, *J* = 16.7 Hz, 1H).

(*Z*)- 3-(4-(Trifluoromethyl)phenyl)acrylonitrile: δ / ppm = 7.91 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 12.1 Hz, 1H), 5.61 (d, *J* = 12.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)- 3-(4-(Trifluoromethyl)phenyl)acrylonitrile: δ / ppm = 149.0, 136.8, 132.9 (q, *J* = 32.6 Hz), 127.7 (2C), 126.3 (q, *J* = 3.7 Hz, 2C), 123.7 (d, *J* = 272.4 Hz), 117.5, 99.4.

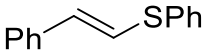
(*Z*)- 3-(4-(Trifluoromethyl)phenyl)acrylonitrile: δ / ppm = 147.2, 136.8, 132.9 (q, *J* = 32.6 Hz), 129.3 (2C), 126.1 (q, *J* = 3.9 Hz, 2C), 123.7 (d, *J* = 272.2 Hz), 116.8, 98.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3055, 3029, 2219, 1622, 1579, 1414, 1320, 1274, 1213, 1194, 1165, 1153, 1107, 1065, 1034, 1015, 978, 970, 954, 859, 851, 837, 812, 760, 733, 657.

MS (EI, 70 eV): *m/z* (%) = 198 (10), 197 (100), 196 (16), 178 (25), 176 (17), 170 (15), 169 (12), 147 (47), 128 (24).

HRMS (EI): *m/z* calc. for [$C_{10}H_6NF_3$]: 197.0452; found: 197.0447.

Phenyl(styryl)sulfane (170h)



Phenylacetylene (1.02 g, 10.0 mmol, 1.0 equiv) and thiophenol (1.2 g, 10.0 mmol, 1.0 equiv) were solved in DMF (5 mL). CuI (0.06 g, 0.30 mmol, 0.03 equiv) was added the mixture was stirred for 2 d. EtOAc (40 mL) was added to the reaction mixture. The mixture was washed with an aqueous LiCl-solution (10%, 3 x 50 mL). The organic layer was dried over $MgSO_4$, solvents were removed *in vacuo* to give the titel compound as orange oil (2.04 g, 9.6 mmol, 96% yield; *E*/*Z* = 71/29).[466]

^{1}H-NMR (400 MHz, $CDCl_3$):

[466] I. P. Beletskaya, I. G. Trostyanskaya, *Synlett*, **2012**, *4*, 535.

(*E*)-Phenyl(styryl)sulfane: δ / ppm = 7.54 (d, *J* = 7.4 Hz, 2H), 7.50 – 7.44 (m, 2H) 7.43– 7.21 (m, 6H), 6.60 (d, *J* = 10.8 Hz, 1H), 6.51 (d, *J* = 10.7 Hz, 1H).

(*Z*)-Phenyl(styryl)sulfane: δ / ppm = 7.57 – 7.21 (m, 10H), 6.89 (d, *J* = 15.5 Hz, 1H), 6.74 (d, *J* = 15.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-Phenyl(styryl)sulfane: δ / ppm = 136.6, 136.4, 130.2 (2C), 129.3 (2C), 128.9 (2C), 128.5 (2C), 127.4, 127.4, 127.3, 126.2.

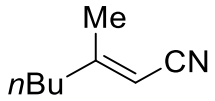
(*Z*)-Phenyl(styryl)sulfane: δ / ppm = 136.6, 135.4, 132.0, 130.0 (2C), 129.3 (2C), 128.8 (2C), 127.7 (2C), 127.1, 126.2, 123.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 3055, 3019, 1597, 1582, 1573, 1569, 1490, 1476, 1439, 1354, 1331, 1156, 1087, 1069, 1024, 999, 944, 908, 858, 846, 772, 738, 729, 700, 686.

MS (EI, 70 eV): *m/z* (%) = 213 (14), 212 (100), 211 (61), 179 (28), 178 (61), 167 (26), 165 (13), 152 (11), 135 (11), 134 (12), 121 (25).

HRMS (EI): *m/z* calc. for [$C_{14}H_{12}S$]: 212.0660; found: 212.0655.

3-Methylhept-2-enenitrile (173b)



KOH (0.56 g, 10.0 mmol, 1.0 equiv) was added in a 100 mL three-necked Schlenk flask, MeCN (20 mL) was added and the mixture was heated to reflux. A solution of hexan-2-one (1.0 g, 10.0 mmol, 1.0 equiv) in MeCN (20 mL) was added dropwise over a period of 20 min. The mixture was stirred at reflux over night. The mixture was poured on ice water (50 mL), and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and solvents were removed *in vacuo* (200 mbar). The crude product was purified by column chromatography (isohexane:EtOAc = 49:1) to give the titel compound as a colorless oil (0.34 g, 2.7 mmol, 27% yield; *E*/*Z* = 65/35).[467]

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)-3-Methylhept-2-enenitrile: δ / ppm = 5.10 (s, 1H), 2.18 (t, *J* = 7.6 Hz, 2H), 2.04 (s, 3H), 1.53 – 1.41 (m, 2H), 1.39 – 1.27 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

[467] S. A. DiBiase, B. A. Lipisko, A. Haag, A. W. Raymond, G. W. Gokel, *J. Org. Chem.* **1979**, *44*, 4640.

(*Z*)-3-Methylhept-2-enenitrile: δ / ppm = 5.10 (s, 1H), 2.44 – 2.37 (t, *J* = 7.6 Hz, 2H), 1.90 (d, *J* = 1.4 Hz, 3H), 1.53 – 1.41 (m, 2H), 1.39 – 1.27 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

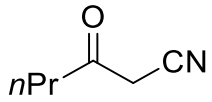
^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-3-Methylhept-2-enenitrile: δ / ppm = 165.8, 117.5, 95.1, 38.5, 29.3, 22.3, 21.1, 13.9.

(*Z*)-3-Methylhept-2-enenitrile: δ / ppm = 165.9, 117.3, 95.6, 36.2, 29.8, 23.0, 22.4, 14.0.

The spectra matched with those reported in the literature.[468]

3-Oxohexanenitrile

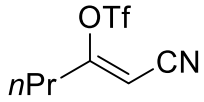


According to the literature[469], to a solution of ethyl butyrate (23.2 g, 26.4 mL, 200 mmol, 1.0 equiv) and acetonitrile (12.3 g, 15.6 mL, 300 mmol, 1.5 equiv) in THF (400 mL) was added NaH (60% dispersion in mineral oil, 12.0 g, 300 mmol, 1.5 equiv) in small portions. The mixture was heated to reflux overnight. HCl was added until pH=7. The aqueous phase was extracted three times with Et_2O (3×100 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:Et_2O = 1:1) afforded the title compound as an orange oil (11.7 g, 106 mmol, 52% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.44 (s, 2H), 2.60 (t, *J*=7.2, 2H), 1.67 (p, *J*=7.4, 2H), 0.95 (t, *J*=7.4, 3H).

The spectra matched with those reported in the literature[470].

(*Z*)-1-Cyanopent-1-en-2-yl 4-methylbenzenesulfonate



According to the literature[471], Et_3N (11.1 g, 110 mmol, 1.1 equiv) was added carefully to a solution of 3-oxohexanenitrile (11.1 g, 100 mmol, 1.0 equiv) in DCM (500 mL) at −78 °C. After stirring for 5 min triflic anhydride (18.5 mL, 110 mmol, 1.1 equiv) was added at the same temperature. The mixture was

[468] T. T. Vasilev, N. A. Kuzmina, O. V. Chakovskaya, N. E. Mysova, A. B. Terentev, *Russ. J. Org. Chem.* **2004**, *40*, 174.
[469] S. Havel, P. Khirsariya, N. Akavaram, K. Paruch, B. Carbain *J. Org. Chem.* **2018**, *83*, 15380.
[470] Y. Chen, S. McN. Sieburth, *Synthesis*, **2002**, *15*, 2191.
[471] Z. Fang, Y. Song, T. Sarkar, E. Hamel, W. E. Fogler, G. E. Agoston, P. E. Fanwick, M. Cushman, *J. Org. Chem.* **2008**, *73*, 4241.

stirred for 30 min at −78 °C before it was allowed to warm to 25 °C and stirred overnight. Water (100 mL) was added. The aqueous phase was extracted three times with Et_2O (3×100 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound as a yellow oil (18.5 g, 76 mmol, 76% yield, *Z/E* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.30 (t, *J*=1.2, 1H), 2.54 (td, *J*=7.5, 1.2, 2H), 1.66 (h, *J*=7.4, 2H), 1.01 (t, *J*=7.4, 3H).

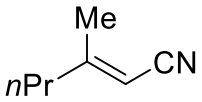
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.4, 118.4 (q, *J*=320.5), 111.9, 92.0, 36.4, 19.5, 13.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974, 2236, 1664, 1423, 1209, 1134, 1103, 1030, 914, 893, 862, 817, 780, 730, 687, 658.

MS (EI, 70 eV): *m/z* (%) = 151 (51), 136 (100), 109 (11), 69 (42), 65 (25).

HRMS (EI): *m/z* calc. for [$C_7H_8F_3NO_3S$]: 243.0177; found: 243.0171.

(*E*)-3-Methylhex-2-enenitrile (173c)



According to the literature[472], to a stirred solution of CuCN (2.51 g, 28.0 mmol, 1.4 equiv) in Et_2O (20 mL) was added MeLi (1.0 M, 28.0 mL, 28 mmol, 1.4 equiv) at −78 °C. The mixture was stirred for 2 h at −78 °C. (*Z*)-1-cyanopent-1-en-2-yl (4.86 g, 20.0 mmol, 1.0 equiv) was added dropwise and the mixture was stirred for 4 h hours at −78 °C, before it was quenched with *sat. aq.* NH_4Cl solution (30 mL). The aqueous phase was extracted three times with Et_2O (3×100 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo* (100 mbar), flash chromatographical purification (silica gel, isohexane) afforded the title compound as a yellow oil (1.97 g, 18.0 mmol, 90% yield, *E/Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.10 (d, *J*=1.2, 1H), 2.17 (dtd, *J*=15.3, 7.6, 1.5, 2H), 2.03 (d, *J*=1.1, 2H), 1.56 – 1.43 (m, 2H), 0.91 (t, *J*=7.4, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 165.4, 117.4, 95.2, 40.7, 21.0, 20.4, 13.6.

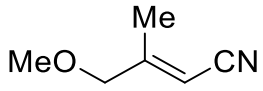
[472] A. Jolit, P. M. Walleser, G. P. A. Yap, M. A. Tius, *Angew. Chem. Int. Ed.*, **2014**, *53*, 6180; *Angew. Chem.* **2014**, *126*, 6294.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2936, 2876, 2218, 1632, 1458, 1443, 1420, 1384, 968, 835, 798.

MS (EI, 70 eV): *m/z* (%) = 110 (18), 94 (16), 81 (76), 80 (71), 68 (100), 67 (14), 56 (10), 41 (20).

HRMS (EI): *m/z* calc. for [$C_7H_{11}N$]: 109.0891; found: 110.0965 [M + H].

4-Methoxy-3-methylbut-2-enenitrile (173d)



NaH (1.8 g, 45.0 mmol, 60% in mineral oil) was added to a three-necked round bottom flask. THF was added to the flask and the suspension was cooled to 0 °C. Diethyl cyanomethyl-phosphonate (7.8 mL, 48 mmol, 1.6 equiv) was added dropwise at 0 °C. After the addition was complete (reaction mixture turned colorless), the mixture was stirred at 0 °C for 1 h. 1-Methoxypropan-2-one (2.64 g, 30.0 mmol, 1.0 equiv) in THF (100 mL) was added dropwise and the reaction mixture was heated to reflux for 3 h. The reaction mixture was cooled to 25 °C and was poured into a separatory funnel containing *sat. aq.* NH_4Cl (150 mL). The aqueous layer was extracted with Et_2O (3x150 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (pentane:Et_2O = 100:0 → 95:5) to give the titel compound as a colorless oil (2.63 g, 23.7 mmol, 79% yield; *E*/*Z* = 80/20).[473]

^{1}H-NMR (400 MHz, $CDCl_3$):

(*E*)-4-Methoxy-3-methylbut-2-enenitrile: δ / ppm = 5.46 (tt, *J*=2.2, 1.1, 1H), 3.93 (dd, *J*=1.9, 0.9, 2H), 3.38 (s, 3H), 2.00 (d, *J*=1.2, 3H).

(*Z*)-4-Methoxy-3-methylbut-2-enenitrile: δ / ppm = 5.27 (h, *J*=1.4, 1H), 4.18 (s, 2H), 3.36 (s, 3H), 1.96 (d, *J*=1.6, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

(*E*)-4-Methoxy-3-methylbut-2-enenitrile: δ / ppm = 160.4, 117.0, 94.8, 74.8, 59.0, 17.9.

(*Z*)-4-Methoxy-3-methylbut-2-enenitrile: δ / ppm = 161.3, 116.0, 97.1, 73.2, 58.6, 20.6.

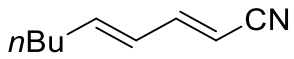
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 2828, 2220, 1730, 1641, 1469, 1452, 1438, 1383, 1265, 1200, 1114, 1074, 990, 955, 920, 808.

[473] P. J. Gilligan, B. K. Folmer, R. A. Hartz, S. Koch, K. K. Nanda, S. Andreuski, L. Fitzgerald, K. Miller, W. J. Marshall, *Bioorg. Med. Chem.*, **2003**, *11*, 4093.

MS (EI, 70 eV): *m/z* (%) = 111 (11), 96 (100), 81 (19), 71 (28), 68 (26), 55 (16).

HRMS (EI): *m/z* calc. for [C_6H_9NO]: 111.0684; found: 111.0679.

(*4E*)-nona-2,4-dienenitrile (173e)



NaH (0.48 g, 12.0 mmol, 1.2 equiv, 60% in mineral oil) was dissolved in THF (10 mL) and cooled to 0 °C. Diethyl(cyanomethyl)phosphonate (2.13 g, 12.0 mmol, 1.2 equiv) was added dropwise. The resulting solution was allowed to warm to 25 °C and stirred for 30 min. After cooling to 0 °C, (*E*)-hept-2-enal (1.12 g, 10.0 mmol, 1.0 equiv) in THF (4 mL) was added dropwise. The resulting solution was stirred for 1.5 h at 25 °C. After quenching with NH_4Cl, the aqueous layer was extracted with Et_2O. The combind organic layers were dried over $MgSO_4$, solvents were removed in vacuo (200 mbar). The crude product was purified by column chromatography (pentane:Et_2O = 100:0 → 95:5) to give the titel compound as a colorless oil (1.08 g, 8.0 mmol, 80% yield, *E*/*Z* = 69/31).[474]

^{1}H-NMR (400 MHz, $CDCl_3$):

(2*E*,4*E*)-nona-2,4-dienenitrile: δ / ppm = 7.04 – 6.91 (m, 1H), 6.17 – 6.09 (m, 2H), 5.23 (d, *J*=15.9, 1H), 2.26 – 2.10 (m, 2H), 1.51 – 1.19 (m, 4H), 0.91 (td, *J*=7.2, 3.9, 3H).

(2*Z*,4*E*)-nona-2,4-dienenitrile: δ / ppm = 6.78 (t, *J*=10.9, 1H), 6.63 – 6.50 (m, 1H), 6.25 – 6.15 (m, 1H), 5.09 (d, *J*=10.7, 1H), 2.19 (dddd, *J*=12.7, 9.7, 6.4, 1.9, 2H), 1.52 – 1.20 (m, 4H), 0.91 (td, *J*=7.2, 3.9, 3H).

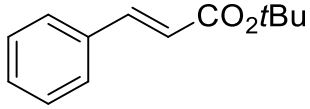
^{13}C-NMR (100 MHz, $CDCl_3$):

(2*E*,4*E*)-nona-2,4-dienenitrile: δ / ppm = 151.1, 146.2, 128.1, 118.6, 96.5, 32.7, 30.7, 22.4, 14.0.

(2*Z*,4*E*)-nona-2,4-dienenitrile: δ / ppm = 150.0, 146.5, 127.0, 116.8, 94.8, 32.8, 30.8, 22.4, 14.0.

The spectra matched with those reported in the literature.[475]

***(E)*-*Tert*-butyl cinnamate (176b)**



[474] J. K. Gawronski, H. M. Walborsky, *J. Org. Chem.* **1986**, *51*, 2863.
[475] C. H. Yoon, K. S. Yoo, S. W. Yi, R. K. Mishra, K. W. Jung, *Org. Lett.* **2004**, *6*, 4037.

According to literature, to a solution of cinnamoyl chloride (3.32 g, 20.0 mmol, 1.0 equiv) in THF (20 mL) KOtBu solution (24 mL, 24.0 mmol, 1.0 M in THF) was added over 10 min at 0 °C. After stirring for 30 min, the reaction mixture was quenched by adding sat. aq. NH_4Cl solution. The aqueous layer was extracted with Et_2O (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. After evaporation of the solvent, the crude product was purified by column chromatography (isohexane) to give the titel compound as a colorless oil (3.27 g, 16.0 mmol, 80% yield, *E/Z* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.59 (d, *J*=16.0, 1H), 7.51 (dq, *J*=5.6, 3.1, 2H), 7.37 (dd, *J*=5.0, 2.0, 3H), 6.37 (d, *J*=16.0, 1H), 1.54 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.5, 143.7, 134.8, 130.1, 129.0 (2C), 128.1 (2C), 120.3, 80.7, 28.3 (3C).

The spectra matched with those reported in the literature.[476]

6.5 Single Crystall X-ray Diffraction Studies

Single crystals of compound **169aj**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[477] Absorption correction using the multiscan method[478] was applied. The structures were solved with SHELXS-97,[479] refined with SHELXL-97[480] and finally checked using PLATON.[481] Details for data collection and structure refinement are summarized in Table 54.

CCDC-1831884 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[476] T. Onozawa, M. Kitajima, N. Kogure, H. Takayama, *J. Org. Chem.* **2018**, *83*, 15312.
[477] Program package CrysAlisPro 1.171.38.46 (Rigaku OD, 2015).
[478] Program package CrysAlisPro 1.171.38.46 (Rigaku OD, 2015).
[479] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[480] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[481] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 54: Details for X-ray data collection and structure refinement for compound **169aj**.

	169aj
Empirical formula	$C_{17}H_{15}NO$
Formula mass	249.30
T[K]	143(2)
Crystal size [mm]	0.49 × 0.12 × 0.07
Crystal description	colorless rod
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	5.4338(5)
b [Å]	15.5658(15)
c [Å]	15.8523(12)
α [°]	90
β [°]	90.515(7)
γ [°]	90
V [Å^3]	1340.8(2)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.235
μ [mm^{-1}]	0.077
F(000)	528
Θ range [°]	4.17 – 25.24
Index ranges	$-6 \leq h \leq 6$
	$-19 \leq k \leq 17$
	$-19 \leq l \leq 18$
Reflns. collected	9448
Reflns. obsd.	1501
Reflns. unique	2726 (R_{int} = 0.0744)
R_1, wR_2 (2σ data)	0.0570, 0.1081
R_1, wR_2 (all data)	0.1207, 0.1329
GOOF on F^2	0.994
Peak/hole [e Å^{-3}]	0.197 / -0.204

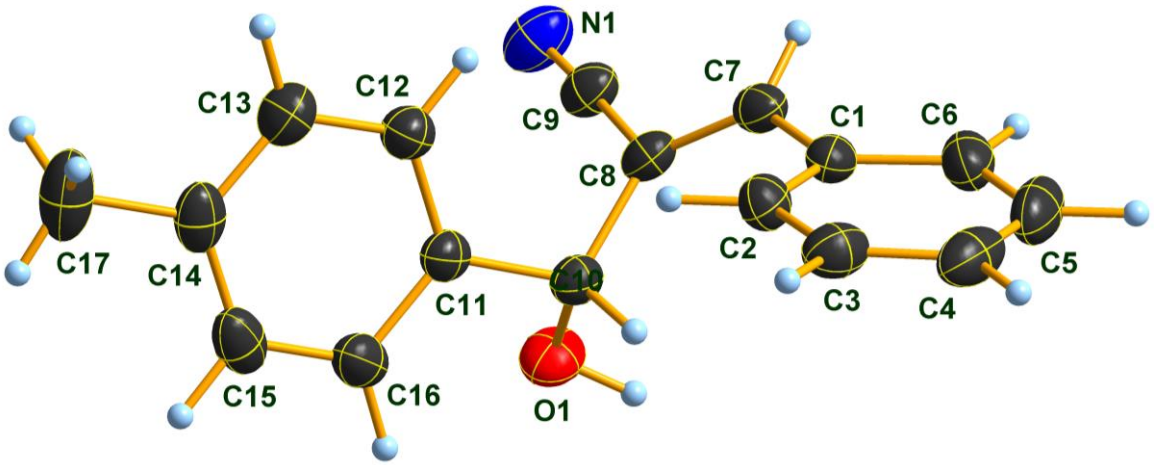


Figure 33: Molecular structure of compound **169aj** in the crystal, DIAMOND[482] representation; thermal ellipsoids are drawn at 50 % probability level.

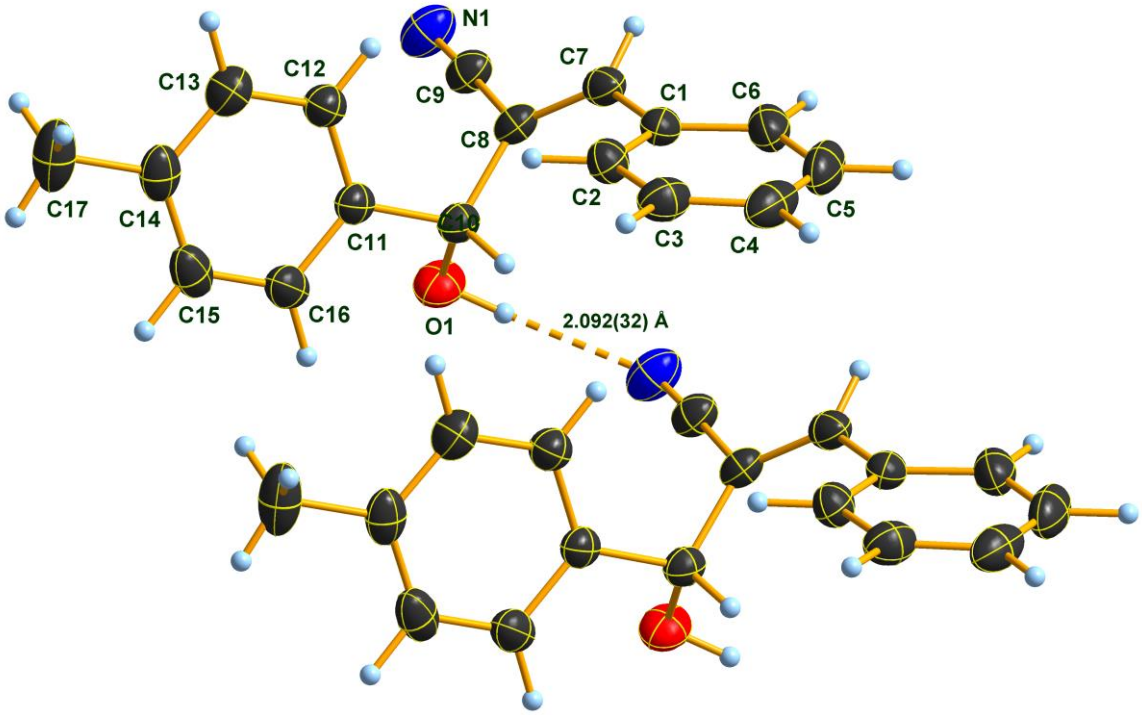


Figure 34: Hydrogen bonding in the crystal of compound **169aj**, DIAMOND[483] representation; thermal ellipsoids are drawn at 50 % probability level. Symmetry code for the second (not labeled) molecule: 1+x, y, z.

[482] DIAMOND, Crystal Impact GbR., Version 3.2i.
[483] DIAMOND, Crystal Impact GbR., Version 3.2i.

Table 55: Selected bond lengths (Å) of compound **169aj**.

O1 – C10	1.434(3)	C14 – C13	1.384(3)
C8 – C7	1.342(3)	C14 – C15	1.386(3)
C8 – C9	1.443(3)	C14 – C17	1.509(3)
C8 – C10	1.521(3)	C12 – C13	1.387(3)
C11 – C12	1.387(3)	C6 – C5	1.382(4)
C11 – C16	1.392(3)	C3 – C4	1.377(4)
C11 – C10	1.512(3)	C5 – C4	1.384(4)
C1 – C6	1.391(3)	N1 – C9	1.148(3)
C1 – C2	1.395(3)	C16 – C15	1.387(3)
C1 – C7	1.466(3)	C2 – C3	1.388(3)

Table 56: Selected bond angles (°) of compound **169aj**.

C7 – C8 – C9	119.5(2)	C15 – C14 – C17	121.4(2)
C7 – C8 – C10	126.9(2)	C13 – C12 – C11	120.7(2)
C9 – C8 – C10	113.6(2)	C5 – C6 – C1	120.5(3)
C12 – C11 – C16	118.3(2)	C14 – C15 – C16	121.6(2)
C12 – C11 – C10	122.3(2)	C4 – C3 – C2	120.5(3)
C16 – C11 – C10	119.4(2)	C6 – C5 – C4	120.3(3)
O1 – C10 – C11	107.7(2)	C14 – C13 – C12	121.4(2)
O1 – C10 – C8	108.3(2)	C3 – C4 – C5	119.6(3)
C11 – C10 – C8	114.2(2)	N1 – C9 – C8	177.5(3)
C6 – C1 – C2	118.9(2)	C8 – C7 – C1	127.1(2)
C6 – C1 – C7	119.4(2)	C3 – C2 – C1	120.1(2)
C2 – C1 – C7	121.7(2)	C13 – C14 – C15	117.6(2)
C15 – C16 – C11	120.3(2)	C13 – C14 – C17	120.9(2)

Table 57: Selected torsion angles (°) of compound **169aj**.

C12 – C11 – C10 – O1	-132.8(2)	C7 – C1 – C2 – C3	179.5(2)
C16 – C11 – C10 – O1	48.3(3)	C16 – C11 – C12 – C13	-1.0(3)
C12 – C11 – C10 – C8	-12.5(3)	C10 – C11 – C12 – C13	-179.9(2)
C16 – C11 – C10 – C8	168.7(2)	C2 – C1 – C6 – C5	2.8(3)
C7 – C8 – C10 – O1	-129.0(2)	C7 – C1 – C6 – C5	-178.6(2)
C9 – C8 – C10 – O1	48.0(2)	C13 – C14 – C15 – C16	-1.7(4)
C7 – C8 – C10 – C11	111.0(3)	C17 – C14 – C15 – C16	177.6(2)
C9 – C8 – C10 – C11	-71.9(2)	C11 – C16 – C15 – C14	0.5(4)
C12 – C11 – C16 – C15	0.9(3)	C1 – C2 – C3 – C4	-0.6(3)

C10 – C11 – C16 – C15	179.8(2)	C1 – C6 – C5 – C4	-1.3(3)
C9 – C8 – C7 – C1	177.4(2)	C15 – C14 – C13 – C12	1.6(4)
C10 – C8 – C7 – C1	-5.7(4)	C17 – C14 – C13 – C12	-177.7(2)
C6 – C1 – C7 – C8	141.0(2)	C11 – C12 – C13 – C14	-0.3(4)
C2 – C1 – C7 – C8	-40.5(3)	C2 – C3 – C4 – C5	2.2(4)
C6 – C1 – C2 – C3	-1.9(3)	C6 – C5 – C4 – C3	-1.3(4)

Single crystals of compound **169aa´**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[484] Absorption correction using the multiscan method[485] was applied. The structures were solved with SHELXS-97,[486] refined with SHELXL-97[487] and finally checked using PLATON.[488] Details for data collection and structure refinement are summarized in Table 58.

CCDC-2027326 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 58: Details for X-ray data collection and structure refinement for compound **169aa´**.

	169aa´
Empirical formula	$C_{22}H_{17}NO$
Formula mass	311.36
T[K]	143(2)
Crystal size [mm]	0.40 × 0.10 × 0.05
Crystal description	colorless rod
Crystal system	orthorhombic
Space group	*P*212121
a [Å]	8.2139(4)

[484] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[485] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[486] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[487] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[488] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

b [Å]	11.0953(6)
c [Å]	18.3781(9)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	1674.90(15)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.235
μ [mm^{-1}]	0.075
F(000)	656
Θ range [°]	3.28 – 25.24
Index ranges	$-9 \leq h \leq 10$
	$-14 \leq k \leq 14$
	$-21 \leq l \leq 24$
Reflns. collected	13597
Reflns. obsd.	3180
Reflns. unique	4144 (R_{int} = 0.0644)
R_1, wR_2 (2σ data)	0.0502, 0.0817
R_1, wR_2 (all data)	0.0763, 0.0922
GOOF on F^2	1.028
Peak/hole [e Å^{-3}]	0.201 / -0.208

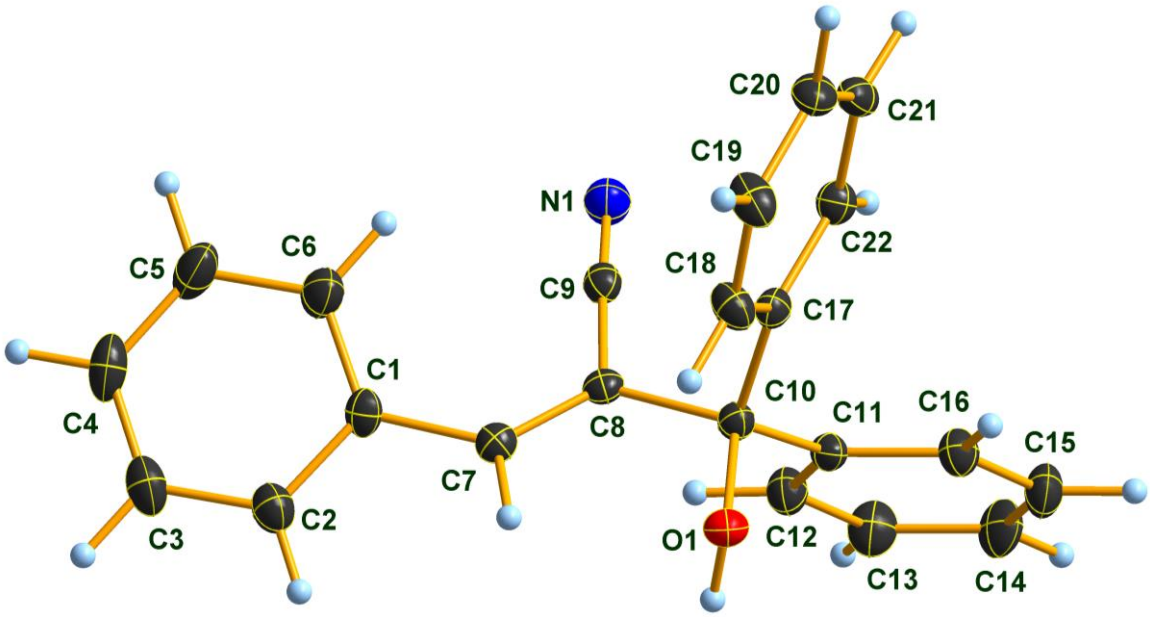


Figure 35: Molecular structure of compound **169aa´** in the crystal. DIAMOND[489] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 59: Selected bond lengths (Å) of compound **169aa´**.

O1 – C10	1.419(3)	C15 – C14	1.382(4)
C7 – C8	1.342(3)	C1 – C6	1.394(4)
C7 – C1	1.467(3)	C1 – C2	1.398(4)
C8 – C9	1.431(4)	C2 – C3	1.383(4)
C8 – C10	1.548(3)	C22 – C21	1.385(3)
N1 – C9	1.149(3)	C3 – C4	1.376(4)
C17 – C22	1.389(3)	C13 – C14	1.377(4)
C17 – C18	1.389(3)	C5 – C4	1.381(4)
C17 – C10	1.524(3)	C5 – C6	1.383(4)
C18 – C19	1.384(4)	C12 – C11	1.383(3)
C16 – C15	1.385(4)	C12 – C13	1.392(4)
C16 – C11	1.396(3)	C20 – C19	1.381(4)
C10 – C11	1.531(3)	C20 – C21	1.385(4)

Table 60: Selected bond angles (°) of compound **169aa´**.

C8 – C7 – C1	130.2(2)	C2 – C1 – C7	118.1(2)
C7 – C8 – C9	122.1(2)	C3 – C2 – C1	121.0(3)

[489] DIAMOND, Crystal Impact GbR., Version 3.2i.

C7 – C8 – C10	123.3(2)	C12 – C11 – C16	118.6(2)
C9 – C8 – C10	114.5(2)	C12 – C11 – C10	121.6(2)
C22 – C17 – C18	118.7(2)	C16 – C11 – C10	119.5(2)
C22 – C17 – C10	122.6(2)	C21 – C22 – C17	120.7(3)
C18 – C17 – C10	118.4(2)	C20 – C21 – C22	120.2(2)
C19 – C18 – C17	120.5(3)	C4 – C3 – C2	119.8(3)
C15 – C16 – C11	120.5(3)	C14 – C13 – C12	119.9(3)
N1 – C9 – C8	176.8(3)	C4 – C5 – C6	120.1(3)
O1 – C10 – C17	106.5(2)	C20 – C19 – C18	120.5(3)
O1 – C10 – C11	109.3(2)	C5 – C6 – C1	120.7(3)
C17 – C10 – C11	114.9(2)	C13 – C14 – C15	120.0(3)
O1 – C10 – C8	109.6(2)	C3 – C4 – C5	120.3(3)
C17 – C10 – C8	104.6(2)	C14 – C15 – C16	120.1(3)
C11 – C10 – C8	111.7(2)	C6 – C1 – C2	118.1(2)
C11 – C12 – C13	120.8(3)	C6 – C1 – C7	123.7(2)
C19 – C20 – C21	119.3(3)		

Table 61: Selected torsion angles (°) of compound **169aa´**.

C1 – C7 – C8 – C9	-3.4(4)	C15 – C16 – C11 – C12	0.5(4)
C1 – C7 – C8 – C10	172.6(2)	C15 – C16 – C11 – C10	174.4(2)
C22 – C17 – C18 – C19	1.3(4)	O1 – C10 – C11 – C12	98.4(3)
C10 – C17 – C18 – C19	-173.2(2)	C17 – C10 – C11 – C12	-141.9(2)
C22 – C17 – C10 – O1	155.3(2)	C8 – C10 – C11 – C12	-23.0(3)
C18 – C17 – C10 – O1	-30.4(3)	O1 – C10 – C11 – C16	-75.4(3)
C22 – C17 – C10 – C11	34.1(3)	C17 – C10 – C11 – C16	44.3(3)
C18 – C17 – C10 – C11	-151.6(2)	C8 – C10 – C11 – C16	163.2(2)
C22 – C17 – C10 – C8	-88.7(3)	C18 – C17 – C22 – C21	-0.4(4)
C18 – C17 – C10 – C8	85.6(3)	C10 – C17 – C22 – C21	173.9(2)
C7 – C8 – C10 – O1	6.1(3)	C19 – C20 – C21 – C22	1.9(4)
C9 – C8 – C10 – O1	-177.6(2)	C17 – C22 – C21 – C20	-1.2(4)
C7 – C8 – C10 – C17	-107.8(3)	C1 – C2 – C3 – C4	-1.1(4)
C9 – C8 – C10 – C17	68.6(3)	C11 – C12 – C13 – C14	0.7(4)
C7 – C8 – C10 – C11	127.3(2)	C21 – C20 – C19 – C18	-1.0(4)
C9 – C8 – C10 – C11	-56.3(3)	C17 – C18 – C19 – C20	-0.6(4)
C11 – C16 – C15 – C14	0.2(4)	C4 – C5 – C6 – C1	0.2(4)
C8 – C7 – C1 – C6	-23.0(4)	C2 – C1 – C6 – C5	-1.8(4)
C8 – C7 – C1 – C2	159.2(3)	C7 – C1 – C6 – C5	-179.5(3)
C6 – C1 – C2 – C3	2.2(4)	C12 – C13 – C14 – C15	0.0(4)
C7 – C1 – C2 – C3	-179.9(3)	C16 – C15 – C14 – C13	-0.4(4)

C13 – C12 – C11 – C16	-0.9(4)	C2 – C3 – C4 – C5	-0.5(4)
C13 – C12 – C11 – C10	-174.8(2)	C6 – C5 – C4 – C3	1.0(5)

Single crystals of compound **169ag**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[490] Absorption correction using the multiscan method[491] was applied. The structures were solved with SHELXS-97,[492] refined with SHELXL-97[493] and finally checked using PLATON.[494] Details for data collection and structure refinement are summarized in Table 62.

CCDC-2027327 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 62: Details for X-ray data collection and structure refinement for compound **169ag**.

	169ag
Empirical formula	$C_{16}H_{17}NO$
Formula mass	239.30
T[K]	123(2)
Crystal size [mm]	0.40 × 0.20 × 0.03
Crystal description	colorless platelet
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	9.2621(3)
b [Å]	12.2356(4)
c [Å]	22.9278(8)
α [°]	90.0
β [°]	90.780(3)
γ [°]	90.0

[490] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[491] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[492] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[493] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[494] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

V [Å^3]	2598.11(15)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.224
μ [mm^{-1}]	0.076
F(000)	1024
Θ range [°]	1.88 – 25.24
Index ranges	$-11 \leq h \leq 11$
	$-15 \leq k \leq 15$
	$-28 \leq l \leq 28$
Reflns. collected	34878
Reflns. obsd.	3828
Reflns. unique	5322 (R_{int} = 0.0521)
R_1, wR_2 (2σ data)	0.0488, 0.0935
R_1, wR_2 (all data)	0.0763, 0.1057
GOOF on F^2	1.020
Peak/hole [e Å^{-3}]	0.315 / -0.341

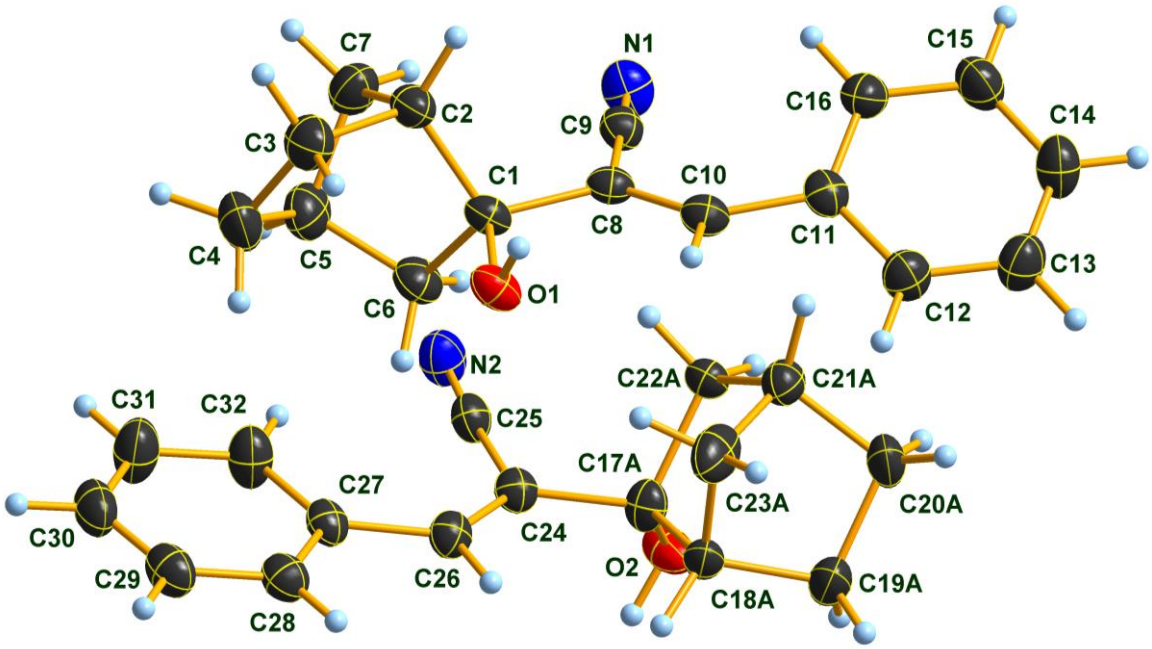


Figure 36: Molecular structure of compound **169ag** in the crystal; view of the two crystallographically independent molecules. In one of the molecules (bottom) the norbornane ring is disordered over two positions.

Only the position with higher occupancy (70 %) has been shown for clarity. DIAMOND[495] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 63: Selected bond lengths (Å) of compound **169ag**.

O1 – C1	1.425(2)	C32 – C31	1.380(3)
C8 – C10	1.340(2)	C3 – C4	1.552(3)
C8 – C9	1.443(2)	C30 – C31	1.378(3)
C8 – C1	1.537(2)	C17A – C18A	1.536(3)
C9 – N1	1.143(2)	C17A – C22A	1.632(3)
O2 – C17A	1.417(2)	C18A – C19A	1.527(4)
C10 – C11	1.469(2)	C18A – C23A	1.534(3)
C24 – C26	1.339(2)	C19A – C20A	1.541(4)
C24 – C25	1.439(2)	C20A – C21A	1.537(4)
C24 – C17A	1.533(2)	C21A – C23A	1.424(3)
C26 – C27	1.473(2)	C21A – C22A	1.538(4)
C12 – C13	1.383(3)	C28 – C29	1.384(2)
C12 – C11	1.394(2)	C15 – C14	1.380(3)
C11 – C16	1.393(2)	C29 – C30	1.374(3)
C27 – C28	1.392(2)	C14 – C13	1.375(3)
C27 – C32	1.393(2)	C16 – C15	1.383(2)
C2 – C3	1.536(2)	C1 – C6	1.556(2)
C2 – C7	1.537(3)	C5 – C6	1.520(3)
C2 – C1	1.554(2)	C5 – C7	1.521(3)
C25 – N2	1.148(2)	C5 – C4	1.537(3)

Table 64: Selected bond angles (°) of compound **169ag**.

C10 – C8 – C9	119.7(2)	C29 – C30 – C31	119.3(2)
C10 – C8 – C1	123.8(2)	C14 – C13 – C12	120.0(2)
C9 – C8 – C1	116.3(1)	C30 – C31 – C32	120.9(2)
N1 – C9 – C8	176.3(2)	C5 – C4 – C3	103.1(1)
C8 – C10 – C11	129.4(2)	O2 – C17A – C24	108.1(1)
C26 – C24 – C25	122.9(2)	O2 – C17A – C18A	120.4(2)
C26 – C24 – C17A	126.1(2)	C24 – C17A – C18A	113.7(2)
C25 – C24 – C17A	111.0(1)	O2 – C17A – C22A	105.6(2)
C24 – C26 – C27	131.4(2)	C24 – C17A – C22A	109.0(2)
C13 – C12 – C11	121.0(2)	C18A – C17A – C22A	99.0(2)
C16 – C11 – C12	118.5(2)	C19A – C18A – C23A	99.4(2)

[495] DIAMOND, Crystal Impact GbR., Version 3.2i.

C16 – C11 – C10	123.6(2)	C19A – C18A – C17A	109.3(2)
C12 – C11 – C10	117.8(2)	C23A – C18A – C17A	101.3(2)
C28 – C27 – C32	117.7(2)	C18A – C19A – C20A	104.5(2)
C28 – C27 – C26	117.2(2)	C21A – C20A – C19A	102.3(2)
C32 – C27 – C26	125.1(2)	C23A – C21A – C20A	102.2(2)
C3 – C2 – C7	99.6(2)	C23A – C21A – C22A	100.6(2)
C3 – C2 – C1	108.0(1)	C20A – C21A – C22A	107.4(2)
C7 – C2 – C1	102.5(1)	C21A – C22A – C17A	104.3(2)
N2 – C25 – C24	175.4(2)	C21A – C23A – C18A	99.0(2)
C15 – C16 – C11	119.9(2)	C29 – C28 – C27	121.3(2)
O1 – C1 – C8	108.0(1)	C14 – C15 – C16	120.9(2)
O1 – C1 – C2	112.9(1)	C5 – C6 – C1	103.7(1)
C8 – C1 – C2	112.7(1)	C30 – C29 – C28	120.2(2)
O1 – C1 – C6	107.7(1)	C13 – C14 – C15	119.7(2)
C8 – C1 – C6	113.2(1)	C31 – C32 – C27	120.7(2)
C2 – C1 – C6	102.2(1)	C5 – C7 – C2	94.9(1)
C6 – C5 – C7	100.7(1)	C2 – C3 – C4	103.1(2)
C6 – C5 – C4	109.5(2)	C7 – C5 – C4	101.9(2)

Table 65: Selected torsion angles (°) of compound **169ag**.

C9 – C8 – C10 – C11	3.8(3)	C1 – C2 – C7 – C5	53.0(2)
C1 – C8 – C10 – C11	179.5(2)	C7 – C2 – C3 – C4	39.3(2)
C25 – C24 – C26 – C27	-1.4(3)	C1 – C2 – C3 – C4	-67.3(2)
C17A – C24 – C26 – C27	176.9(2)	C28 – C29 – C30 – C31	-1.7(3)
C13 – C12 – C11 – C16	-2.0(3)	C15 – C14 – C13 – C12	0.4(3)
C13 – C12 – C11 – C10	177.8(2)	C11 – C12 – C13 – C14	0.8(3)
C8 – C10 – C11 – C16	32.0(3)	C29 – C30 – C31 – C32	1.3(3)
C8 – C10 – C11 – C12	-147.8(2)	C27 – C32 – C31 – C30	0.8(3)
C24 – C26 – C27 – C28	-177.8(2)	C6 – C5 – C4 – C3	74.5(2)
C24 – C26 – C27 – C32	-0.4(3)	C7 – C5 – C4 – C3	-31.5(2)
C12 – C11 – C16 – C15	1.9(3)	C2 – C3 – C4 – C5	-5.1(2)
C10 – C11 – C16 – C15	-177.9(2)	C26 – C24 – C17A – O2	125.5(2)
C10 – C8 – C1 – O1	-6.0(2)	C25 – C24 – C17A – O2	-56.0(2)
C9 – C8 – C1 – O1	169.9(1)	C26 – C24 – C17A – C18A	-10.9(3)
C10 – C8 – C1 – C2	119.5(2)	C25 – C24 – C17A – C18A	167.5(2)
C9 – C8 – C1 – C2	-64.7(2)	C26 – C24 – C17A – C22A	-120.2(2)
C10 – C8 – C1 – C6	-125.1(2)	C25 – C24 – C17A – C22A	58.2(2)
C9 – C8 – C1 – C6	50.7(2)	O2 – C17A – C18A – C19A	43.8(3)
C3 – C2 – C1 – O1	-39.7(2)	C24 – C17A – C18A – C19A	174.3(2)

C7 – C2 – C1 – O1	-144.3(1)	C22A – C17A – C18A – C19A	-70.3(2)
C3 – C2 – C1 – C8	-162.4(1)	O2 – C17A – C18A – C23A	148.0(2)
C7 – C2 – C1 – C8	93.1(2)	C24 – C17A – C18A – C23A	-81.4(2)
C3 – C2 – C1 – C6	75.8(2)	C22A – C17A – C18A – C23A	34.0(2)
C7 – C2 – C1 – C6	-28.8(2)	C23A – C18A – C19A – C20A	-30.8(3)
C32 – C27 – C28 – C29	1.9(3)	C17A – C18A – C19A – C20A	74.8(3)
C26 – C27 – C28 – C29	179.5(2)	C18A – C19A – C20A – C21A	-0.5(3)
C11 – C16 – C15 – C14	-0.7(3)	C19A – C20A – C21A – C23A	34.7(3)
C7 – C5 – C6 – C1	40.9(2)	C19A – C20A – C21A – C22A	-70.7(3)
C4 – C5 – C6 – C1	-65.8(2)	C23A – C21A – C22A – C17A	-33.7(2)
O1 – C1 – C6 – C5	112.1(2)	C20A – C21A – C22A – C17A	72.8(2)
C8 – C1 – C6 – C5	-128.6(2)	O2 – C17A – C22A – C21A	-127.0(2)
C2 – C1 – C6 – C5	-7.1(2)	C24 – C17A – C22A – C21A	117.2(2)
C27 – C28 – C29 – C30	0.1(3)	C18A – C17A – C22A – C21A	-1.8(2)
C16 – C15 – C14 – C13	-0.5(3)	C20A – C21A – C23A – C18A	-54.8(2)
C28 – C27 – C32 – C31	-2.3(3)	C22A – C21A – C23A – C18A	55.8(2)
C26 – C27 – C32 – C31	-179.7(2)	C19A – C18A – C23A – C21A	53.4(2)
C6 – C5 – C7 – C2	-57.6(2)	C17A – C18A – C23A – C21A	-58.6(2)
C4 – C5 – C7 – C2	55.2(2)	C3 – C2 – C7 – C5	-58.0(2)

Single crystals of compound **172ba´´**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[496] Absorption correction using the multiscan method[497] was applied. The structures were solved with SHELXS-97,[498] refined with SHELXL-97[499] and finally checked using PLATON.[500] Details for data collection and structure refinement are summarized in Table 66.

CCDC-2027330 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[496] Program package CrysAlisPro 1.171.39.46e (Rigaku OD, 2018).
[497] Program package CrysAlisPro 1.171.39.46e (Rigaku OD, 2018).
[498] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[499] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[500] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 66: Details for X-ray data collection and structure refinement for compound **172ba´´**.

	172ba´´
Empirical formula	$C_{19}H_{19}NO_2$
Formula mass	293.35
T[K]	143(2)
Crystal size [mm]	0.47 × 0.23 × 0.11
Crystal description	colorless block
Crystal system	Triclinic
Space group	*P*-1
a [Å]	7.0122(4)
b [Å]	8.2204(6)
c [Å]	14.2407(8)
α [°]	104.500(5)
β [°]	94.810(5)
γ [°]	103.432(6)
V [Å^3]	764.15(9)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.275
μ [mm^{-1}]	0.082
F(000)	312
Θ range [°]	3.39 – 25.24
Index ranges	$-9 \leq h \leq 10$
	$-11 \leq k \leq 11$
	$-20 \leq l \leq 20$
Reflns. collected	15402
Reflns. obsd.	3719
Reflns. unique	4648 (R_{int} = 0.0307)
R_1, wR_2 (2σ data)	0.0447, 0.1051
R_1, wR_2 (all data)	0.0583, 0.1151
GOOF on F^2	1.032
Peak/hole [e Å^{-3}]	0.363 / -0.199

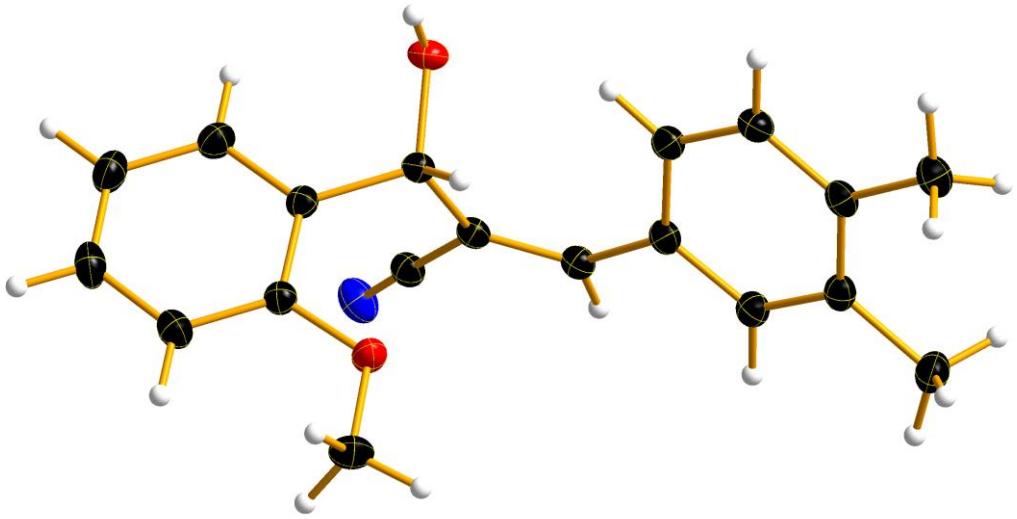


Figure 37: Molecular structure of compound **172ba´´** in the crystal, DIAMOND[501] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 67: Selected bond lengths (Å) of compound **172ba´´**.

O1 – C6	1.366(1)	C10 – C15	1.398(2)
O1 – C17	1.426(1)	C16 – N1	1.147(2)
O2 – C7	1.428(1)	C2 – C3	1.391(2)
C6 – C5	1.387(2)	C14 – C15	1.388(2)
C6 – C1	1.340(1)	C3 – C4	1.380(2)
C1 – C2	1.388(2)	C5 – C4	1.387(2)
C1 – C7	1.512(2)	C9 – C10	1.464(2)
C7 – C8	1.516(2)	C8 – C16	1.440(2)
C13 – C14	1.395(2)	C11 – C12	1.390(2)
C13 – C12	1.403(2)	C11 – C10	1.401(2)
C13 – C19	1.503(2)	C12 – C18	1.503(2)
C9 – C8	1.346(2)		

Table 68: Selected bond angles (°) of compound **172ba´´**.

C6 – O1 – C17	117.2(1)	C15 – C14 – C13	122.2(1)
O1 – C6 – C5	124.3(1)	C14 – C15 – C10	119.5(1)
O1 – C6 – C1	115.1(1)	C4 – C3 – C2	119.3(1)
C5 – C6 – C1	120.6(1)	C6 – C5 – C4	119.4(1)
C2 – C1 – C6	118.7(1)	C3 – C4 – C5	120.9(1)

[501] DIAMOND, Crystal Impact GbR., Version 3.2i.

C2 – C1 – C7	122.2(1)	C16 – C8 – C7	117.5(1)
C6 – C1 – C7	119.1(1)	C12 – C11 – C10	122.4(1)
O2 – C7 – C1	112.7(1)	C11 – C12 – C13	118.9(1)
O2 – C7 – C8	106.9(1)	C11 – C12 – C18	120.4(1)
C1 – C7 – C8	112.2(1)	C13 – C12 – C18	120.7(1)
C14 – C13 – C12	118.7(1)	C15 – C10 – C11	118.2(1)
C14 – C13 – C19	120.3(1)	C15 – C10 – C9	124.1(1)
C12 – C13 – C19	121.0(1)	C11 – C10 – C9	117.6(1)
C8 – C9 – C10	129.3(1)	N1 – C16 – C8	178.0(1)
C9 – C8 – C16	116.0(1)	C1 – C2 – C3	121.0(1)
C9 – C8 – C7	126.6(1)		

Table 69: Selected torsion angles (°) of compound **172ba´´**.

C17 – O1 – C6 – C5	-1.6(2)	C19 – C13 – C12 – C11	-179.6(1)
C17 – O1 – C6 – C1	178.5(1)	C14 – C13 – C12 – C18	178.0(1)
O1 – C6 – C1 – C2	177.9(1)	C19 – C13 – C12 – C18	-1.2(2)
C5 – C6 – C1 – C2	-2.0(2)	C12 – C11 – C10 – C15	2.4(2)
O1 – C6 – C1 – C7	-3.2(1)	C12 – C11 – C10 – C9	179.4(1)
C5 – C6 – C1 – C7	176.9(1)	C8 – C9 – C10 – C15	-28.3(2)
C2 – C1 – C7 – O2	17.2(1)	C8 – C9 – C10 – C11	155.0(1)
C6 – C1 – C7 – O2	-161.6(1)	C6 – C1 – C2 – C3	1.5(2)
C2 – C1 – C7 – C8	-103.5(1)	C7 – C1 – C2 – C3	-177.4(1)
C6 – C1 – C7 – C8	77.7(1)	C12 – C13 – C14 – C15	1.1(2)
C10 – C9 – C8 – C16	178.9(1)	C19 – C13 – C14 – C15	-179.7(1)
C10 – C9 – C8 – C7	-2.5(2)	C13 – C14 – C15 – C10	-0.1(2)
O2 – C7 – C8 – C9	89.7(1)	C11 – C10 – C15 – C14	-1.7(2)
C1 – C7 – C8 – C9	-146.3(1)	C9 – C10 – C15 – C14	-178.4(1)
O2 – C7 – C8 – C16	-91.7(1)	C1 – C2 – C3 – C4	0.2(2)
C1 – C7 – C8 – C16	32.3(1)	O1 – C6 – C5 – C4	-179.1(1)
C10 – C11 – C12 – C13	-1.3(2)	C1 – C6 – C5 – C4	0.9(2)
C10 – C11 – C12 – C18	-179.8(1)	C2 – C3 – C4 – C5	-1.4(2)
C14 – C13 – C12 – C11	-0.4(2)	C6 – C5 – C4 – C3	0.9(2)

Single crystals of compound **172dm**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[502] Absorption correction using the multiscan method[503] was applied. The structures were solved with SHELXS-97,[504] refined with SHELXL-97[505] and finally checked using PLATON.[506] Details for data collection and structure refinement are summarized in Table 70.

CCDC-2027331 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 70: Details for X-ray data collection and structure refinement for compound **172dm**.

	172dm
Empirical formula	$C_{19}H_{25}NO$
Formula mass	283.40
T[K]	143(2)
Crystal size [mm]	0.40 × 0.40 × 0.30
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	15.0865(5)
b [Å]	19.5830(4)
c [Å]	11.8768(3)
α [°]	90.0
β [°]	106.655(2)
γ [°]	90.0
V [Å^3]	3361.66(16)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.120
μ [mm^{-1}]	0.068
F(000)	1232
Θ range [°]	3.31 – 25.24

[502] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[503] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[504] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[505] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[506] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Index ranges	$-21 \leq h \leq 21$
	$-27 \leq k \leq 27$
	$-16 \leq l \leq 16$
Reflns. collected	68256
Reflns. obsd.	7556
Reflns. unique	10231 (R_{int} = 0.0554)
R_1, wR_2 (2σ data)	0.0510, 0.1220
R_1, wR_2 (all data)	0.0733, 0.1380
GOOF on F^2	1.027
Peak/hole [e Å^{-3}]	0.392 / -0.210

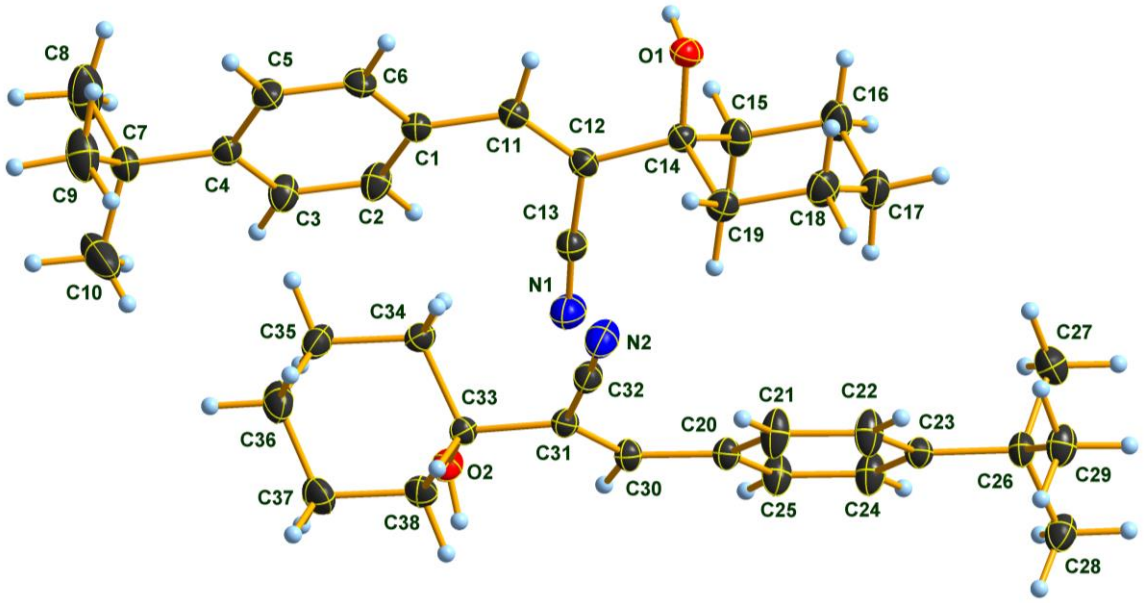


Figure 38: Molecular structure of compound **172dm** in the crystal. DIAMOND[507] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 71: Selected bond lengths (Å) of compound **172dm**.

O1 – C14	1.422(1)	C3 – C2	1.388(2)
C14 – C19	1.533(2)	C36 – C35	1.517(2)
C14 – C12	1.535(2)	C36 – C37	1.525(2)
C14 – C15	1.536(2)	C16 – C17	1.526(2)

[507] DIAMOND, Crystal Impact GbR., Version 3.2i.

C7 – C10	1.522(2)	C16 – C15	1.528(2)
C7 – C8	1.526(2)	C18 – C17	1.522(2)
C7 – C9	1.527(2)	C13 – N1	1.149(2)
C7 – C4	1.529(2)	C22 – C21	1.390(2)
C12 – C11	1.343(2)	C4 – C5	1.391(2)
C12 – C13	1.440(2)	C4 – C3	1.399(2)
O2 – C33	1.419(1)	C1 – C2	1.394(2)
C31 – C30	1.348(2)	C1 – C6	1.396(2)
C31 – C32	1.436(2)	C32 – N2	1.151(2)
C31 – C33	1.536(2)	C6 – C5	1.389(2)
C23 – C22	1.388(2)	C25 – C24	1.389(2)
C23 – C24	1.393(2)	C25 – C20	1.399(2)
C23 – C26	1.530(2)	C20 – C21	1.394(2)
C19 – C18	1.530(2)	C38 – C37	1.526(2)
C30 – C20	1.465(2)	C26 – C27	1.534(2)
C34 – C35	1.527(2)	C26 – C28	1.537(2)
C34 – C33	1.535(2)	C33 – C38	1.534(2)
C26 – C29	1.532(2)	C11 – C1	1.465(2)

Table 72: Selected bond angles (°) of compound **172dm**.

O1 – C14 – C19	106.6(1)	C25 – C24 – C23	121.9(1)
O1 – C14 – C12	109.6(1)	C17 – C16 – C15	110.8(1)
C19 – C14 – C12	109.4(1)	C17 – C18 – C19	110.9(1)
O1 – C14 – C15	110.4(1)	C16 – C15 – C14	111.9(1)
C19 – C14 – C15	110.4(1)	C36 – C35 – C34	111.5(1)
C12 – C14 – C15	110.3(1)	C3 – C2 – C1	120.9(1)
C10 – C7 – C8	109.2(1)	C6 – C5 – C4	121.5(1)
C10 – C7 – C9	107.2(1)	N1 – C13 – C12	175.6(1)
C8 – C7 – C9	109.3(1)	C23 – C22 – C21	122.3(1)
C10 – C7 – C4	111.4(1)	C18 – C17 – C16	110.8(1)
C8 – C7 – C4	108.1(1)	C22 – C21 – C20	121.3(1)
C9 – C7 – C4	111.6(1)	C3 – C4 – C7	121.1(1)
C11 – C12 – C13	122.6(1)	C2 – C1 – C6	117.5(1)
C11 – C12 – C14	123.2(1)	C2 – C1 – C11	124.9(1)
C13 – C12 – C14	114.2(1)	C6 – C1 – C11	117.6(1)
C30 – C31 – C32	122.1(1)	N2 – C32 – C31	176.5(1)
C30 – C31 – C33	123.8(1)	C5 – C6 – C1	121.4(1)
C32 – C31 – C33	114.1(1)	C24 – C25 – C20	121.6(1)
C22 – C23 – C24	116.3(1)	C21 – C20 – C25	116.6(1)

C22 – C23 – C26	122.3(1)	C21 – C20 – C30	125.4(1)
C24 – C23 – C26	121.4(1)	C25 – C20 – C30	118.0(1)
C18 – C19 – C14	111.8(1)	C37 – C38 – C33	112.2(1)
C31 – C30 – C20	130.1(1)	C2 – C3 – C4	121.9(1)
C35 – C34 – C33	112.3(1)	C35 – C36 – C37	110.9(1)
C23 – C26 – C29	112.4(1)	C36 – C37 – C38	110.7(1)
C23 – C26 – C27	108.4(1)	O2 – C33 – C31	110.1(1)
C29 – C26 – C27	108.5(1)	C38 – C33 – C31	109.6(1)
C23 – C26 – C28	110.7(1)	C34 – C33 – C31	109.9(1)
C29 – C26 – C28	107.6(1)	C12 – C11 – C1	130.7(1)
C27 – C26 – C28	109.3(1)	C5 – C4 – C3	116.9(1)
O2 – C33 – C38	110.7(1)	C5 – C4 – C7	122.0(1)
O2 – C33 – C34	106.1(1)	C38 – C33 – C34	110.3(1)

Table 73: Selected torsion angles (°) of compound **172dm**.

O1 – C14 – C12 – C11	-7.0(2)	C2 – C1 – C6 – C5	1.9(2)
C19 – C14 – C12 – C11	109.6(1)	C11 – C1 – C6 – C5	-178.0(1)
C15 – C14 – C12 – C11	-128.8(1)	C24 – C25 – C20 – C21	-1.6(2)
O1 – C14 – C12 – C13	175.4(1)	C24 – C25 – C20 – C30	179.0(1)
C19 – C14 – C12 – C13	-68.1(1)	C31 – C30 – C20 – C21	13.8(2)
C15 – C14 – C12 – C13	53.6(1)	C31 – C30 – C20 – C25	-166.8(1)
O1 – C14 – C19 – C18	-65.7(1)	O2 – C33 – C38 – C37	-63.2(1)
C12 – C14 – C19 – C18	175.8(1)	C34 – C33 – C38 – C37	54.0(1)
C15 – C14 – C19 – C18	54.2(1)	C31 – C33 – C38 – C37	175.2(1)
C32 – C31 – C30 – C20	1.0(2)	C5 – C4 – C3 – C2	1.6(2)
C33 – C31 – C30 – C20	-179.4(1)	C7 – C4 – C3 – C2	179.8(1)
C22 – C23 – C26 – C29	14.0(2)	C35 – C36 – C37 – C38	56.8(2)
C24 – C23 – C26 – C29	-167.6(1)	C33 – C38 – C37 – C36	-56.4(2)
C22 – C23 – C26 – C27	-105.9(1)	C20 – C25 – C24 – C23	1.1(2)
C24 – C23 – C26 – C27	72.5(1)	C22 – C23 – C24 – C25	0.0(2)
C22 – C23 – C26 – C28	134.3(1)	C26 – C23 – C24 – C25	-178.6(1)
C24 – C23 – C26 – C28	-47.3(2)	C14 – C19 – C18 – C17	-56.1(1)
C35 – C34 – C33 – O2	67.0(1)	C17 – C16 – C15 – C14	55.9(2)
C35 – C34 – C33 – C38	-52.9(1)	O1 – C14 – C15 – C16	63.3(1)
C35 – C34 – C33 – C31	-174.0(1)	C19 – C14 – C15 – C16	-54.3(1)
C30 – C31 – C33 – O2	-7.8(2)	C12 – C14 – C15 – C16	-175.3(1)
C32 – C31 – C33 – O2	171.8(1)	C37 – C36 – C35 – C34	-56.2(1)
C30 – C31 – C33 – C38	114.2(1)	C33 – C34 – C35 – C36	54.8(1)
C32 – C31 – C33 – C38	-66.2(1)	C4 – C3 – C2 – C1	0.4(2)

C30 – C31 – C33 – C34	-124.4(1)	C6 – C1 – C2 – C3	-2.2(2)
C32 – C31 – C33 – C34	55.3(1)	C11 – C1 – C2 – C3	177.7(1)
C13 – C12 – C11 – C1	-1.4(2)	C1 – C6 – C5 – C4	0.2(2)
C14 – C12 – C11 – C1	-178.9(1)	C3 – C4 – C5 – C6	-1.9(2)
C10 – C7 – C4 – C5	-151.1(1)	C7 – C4 – C5 – C6	179.9(1)
C8 – C7 – C4 – C5	88.9(2)	C24 – C23 – C22 – C21	-0.4(2)
C9 – C7 – C4 – C5	-31.3(2)	C26 – C23 – C22 – C21	178.1(1)
C10 – C7 – C4 – C3	30.8(2)	C19 – C18 – C17 – C16	57.0(2)
C8 – C7 – C4 – C3	-89.2(2)	C15 – C16 – C17 – C18	-56.9(2)
C9 – C7 – C4 – C3	150.7(1)	C23 – C22 – C21 – C20	-0.2(2)
C12 – C11 – C1 – C2	-19.6(2)	C25 – C20 – C21 – C22	1.2(2)
C12 – C11 – C1 – C6	160.3(1)	C30 – C20 – C21 – C22	-179.5(1)

Single crystals of compound **172ee´**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[508] Absorption correction using the multiscan method[509] was applied. The structures were solved with SHELXS-97,[510] refined with SHELXL-97[511] and finally checked using PLATON.[512] Details for data collection and structure refinement are summarized in Table 74.

CCDC-2027328 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 74: Details for X-ray data collection and structure refinement for compound **172ee´**.

	172ee´
Empirical formula	$C_{16}H_{14}F_3N$
Formula mass	277.28
T[K]	143(2)

[508] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[509] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[510] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[511] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[512] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Crystal size [mm]	0.40 × 0.05 × 0.05
Crystal description	colorless rod
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	5.2514(4)
b [Å]	26.0806(18)
c [Å]	10.2125(8)
α [°]	90.0
β [°]	103.387(8)
γ [°]	90.0
V [Å^3]	1360.70(18)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.354
μ [mm^{-1}]	0.108
F(000)	576
Θ range [°]	3.74 – 25.24
Index ranges	$-8 \leq h \leq 8$
	$-32 \leq k \leq 32$
	$-11 \leq l \leq 12$
Reflns. collected	9402
Reflns. obsd.	1848
Reflns. unique	2673 (R_{int} = 0.0664)
R_1, wR_2 (2σ data)	0.0635, 0.1523
R_1, wR_2 (all data)	0.0939, 0.1748
GOOF on F^2	1.030
Peak/hole [e Å^{-3}]	0.666 / -0.240

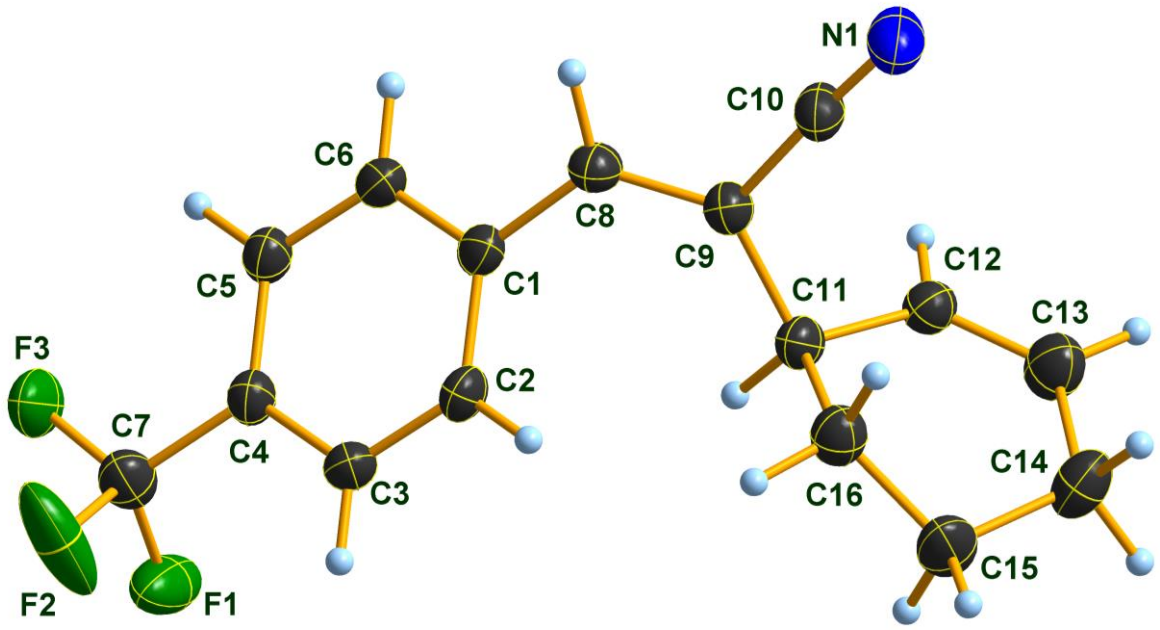


Figure 39: Molecular structure of compound **172ee´** in the crystal. DIAMOND[513] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 75: Selected bond lengths (Å) of compound **172ee´**.

F1 – C7	1.348(3)	C4 – C3	1.392(4)
C5 – C6	1.385(4)	C4 – C7	1.490(4)
C5 – C4	1.389(4)	C3 – C2	1.374(4)
C8 – C9	1.342(4)	F2 – C7	1.320(3)
C8 – C1	1.472(3)	C12 – C13	1.324(4)
C9 – C10	1.446(4)	C12 – C11	1.515(3)
C9 – C11	1.513(3)	C14 – C15	1.504(4)
F3 – C7	1.330(3)	C14 – C13	1.511(4)
C1 – C6	1.393(3)	C16 – C11	1.538(3)
C1 – C2	1.397(3)	N1 – C10	1.150(3)
C16 – C15	1.514(4)		

Table 76: Selected bond angles (°) of compound **172ee´**.

C6 – C5 – C4	119.3(2)	C9 – C11 – C16	111.3(2)
C9 – C8 – C1	127.5(2)	C12 – C11 – C16	110.6(2)
C8 – C9 – C10	117.4(2)	N1 – C10 – C9	176.7(3)

[513] DIAMOND, Crystal Impact GbR., Version 3.2i.

C8 – C9 – C11	128.6(2)	C3 – C2 – C1	120.8(2)
C10 – C9 – C11	114.1(2)	F2 – C7 – F3	107.0(2)
C6 – C1 – C2	118.5(2)	F2 – C7 – F1	106.4(2)
C6 – C1 – C8	119.5(2)	F3 – C7 – F1	104.9(2)
C2 – C1 – C8	121.9(2)	F2 – C7 – C4	112.3(2)
C5 – C6 – C1	121.3(2)	F3 – C7 – C4	113.8(2)
C15 – C16 – C11	112.0(2)	F1 – C7 – C4	111.9(2)
C5 – C4 – C3	120.1(2)	C15 – C14 – C13	111.8(2)
C5 – C4 – C7	121.7(2)	C14 – C15 – C16	112.9(2)
C3 – C4 – C7	118.1(2)	C12 – C13 – C14	122.6(3)
C2 – C3 – C4	120.1(2)	C9 – C11 – C12	109.6(2)
C13 – C12 – C11	125.3(3)		

Table 77: Selected torsion angles (°) of compound **172ee´**.

C1 – C8 – C9 – C10	-175.1(2)	C13 – C12 – C11 – C16	11.1(4)
C1 – C8 – C9 – C11	6.3(5)	C15 – C16 – C11 – C9	-162.6(2)
C9 – C8 – C1 – C6	-145.1(3)	C15 – C16 – C11 – C12	-40.5(3)
C9 – C8 – C1 – C2	39.4(4)	C4 – C3 – C2 – C1	0.6(4)
C4 – C5 – C6 – C1	1.4(4)	C6 – C1 – C2 – C3	-0.3(4)
C2 – C1 – C6 – C5	-0.7(4)	C8 – C1 – C2 – C3	175.3(2)
C8 – C1 – C6 – C5	-176.4(2)	C5 – C4 – C7 – F2	-122.8(3)
C6 – C5 – C4 – C3	-1.1(4)	C3 – C4 – C7 – F2	55.1(3)
C6 – C5 – C4 – C7	176.7(2)	C5 – C4 – C7 – F3	-1.0(4)
C5 – C4 – C3 – C2	0.1(4)	C3 – C4 – C7 – F3	176.8(2)
C7 – C4 – C3 – C2	-177.8(2)	C5 – C4 – C7 – F1	117.6(3)
C8 – C9 – C11 – C12	124.2(3)	C3 – C4 – C7 – F1	-64.5(3)
C10 – C9 – C11 – C12	-54.4(3)	C13 – C14 – C15 – C16	-43.9(4)
C8 – C9 – C11 – C16	-113.1(3)	C11 – C16 – C15 – C14	59.1(3)
C10 – C9 – C11 – C16	68.3(3)	C11 – C12 – C13 – C14	2.6(5)
C13 – C12 – C11 – C9	134.2(3)	C15 – C14 – C13 – C12	13.7(4)

Single crystals of compound **172fb´´**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[514] Absorption correction using the multiscan method[515] was applied. The structures were solved with SHELXS-97,[516] refined with SHELXL-97[517] and finally checked using PLATON.[518] Details for data collection and structure refinement are summarized in Table 78.

CCDC-1831885 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 78: Details for X-ray data collection and structure refinement for compound **172fb´´**.

	172fb´´
Empirical formula	$C_{12}H_{10}F_3NO_2$
Formula mass	257.21
T[K]	143(2)
Crystal size [mm]	0.45 × 0.12 × 0.06
Crystal description	colorless rod
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	12.3101(13)
b [Å]	8.1799(6)
c [Å]	12.7623(11)
α [°]	90
β [°]	112.598(12)
γ [°]	90
V [Å^3]	1186.4(2)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.440
μ [mm^{-1}]	0.129
F(000)	528
Θ range [°]	4.16 – 25.24

[514] Program package CrysAlisPro 1.171.38.46 (Rigaku OD, 2015).
[515] Program package CrysAlisPro 1.171.38.46 (Rigaku OD, 2015).
[516] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[517] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[518] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Index ranges	$-16 \leq h \leq 16$
	$-10 \leq k \leq 10$
	$-16 \leq l \leq 17$
Reflns. collected	10879
Reflns. obsd.	2130
Reflns. unique	2943 (R_{int} = 0.0425)
R_1, wR_2 (2σ data)	0.0491, 0.1053
R_1, wR_2 (all data)	0.0719, 0.1204
GOOF on F^2	1.044
Peak/hole [e Å^{-3}]	0.275 / -0.284

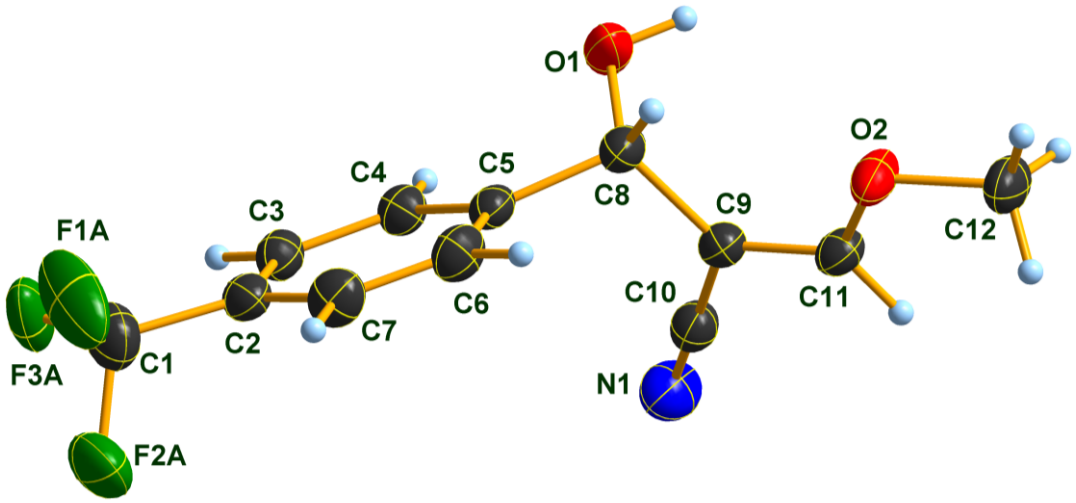


Figure 40: Molecular structure of compound **172fb´´** in the crystal, DIAMOND[519] representation; thermal ellipsoids are drawn at 50 % probability level. The CF_3 group is disordered over two positions; only one position is shown for clarity.

[519] DIAMOND, Crystal Impact GbR., Version 3.2i.

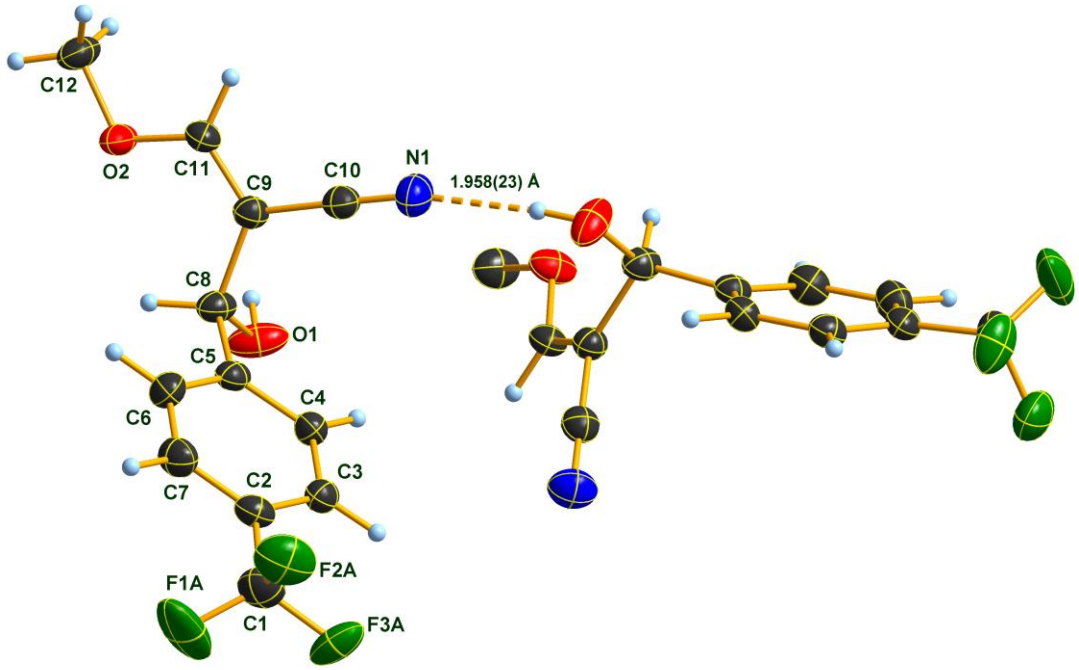


Figure 41: Hydrogen bonding in the crystal of compound **172fb´´**, DIAMOND[520] representation; thermal ellipsoids are drawn at 50 % probability level. Symmetry code for the second (not labeled) molecule: -x, -0.5+y, 0.5-z.

Table 79: Selected bond lengths (Å) of compound **172fb´´**.

C9 – C11	1.340(2)	C6 – C7	1.381(2)
C9 – C10	1.426(2)	C1 – F1A	1.312(4)
C9 – C8	1.519(2)	C1 – F2A	1.356(4)
C8 – O1	1.418(2)	C1 – F3A	1.408(5)
C8 – C5	1.512(2)	C10 – N1	1.146(2)
O2 – C11	1.333(2)	C2 – C3	1.383(2)
O2 – C12	1.440(2)	C2 – C7	1.384(2)
C5 – C6	1.386(2)	C2 – C1	1.494(2)
C5 – C4	1.391(2)	C4 – C3	1.386(2)

Table 80: Selected bond angles (°) of compound **172fb´´**.

C11 – C9 – C10	117.2(1)	C7 – C6 – C5	120.8(2)
C11 – C9 – C8	123.6(1)	C6 – C7 – C2	119.8(2)
C10 – C9 – C8	119.0(1)	F1A – C1 – F2A	102.4(4)
O1 – C8 – C5	107.3(1)	F1A – C1 – F3A	116.8(4)
O1 – C8 – C9	111.3(1)	F2A – C1 – F3A	98.3(3)

[520] DIAMOND, Crystal Impact GbR., Version 3.2i.

C5 – C8 – C9	113.6(1)	F1A – C1 – C2	113.5(2)
C11 – O2 – C12	115.2(1)	F2A – C1 – C2	112.5(2)
C6 – C5 – C4	118.9(2)	F3A – C1 – C2	111.9(2)
C6 – C5 – C8	119.8(1)	C7 – C2 – C1	118.7(2)
C4 – C5 – C8	121.2(2)	C3 – C4 – C5	120.5(2)
N1 – C10 – C9	179.1(2)	O2 – C11 – C9	121.1(1)
C3 – C2 – C7	120.1(2)	C2 – C3 – C4	119.8(2)
C3 – C2 – C1	121.1(2)		

Table 81: Selected torsion angles (°) of compound **172fb´´**.

C11 – C9 – C8 – O1	104.5(2)	C3 – C2 – C1 – F1A	-140.1(4)
C10 – C9 – C8 – O1	-71.0(2)	C7 – C2 – C1 – F1A	37.1(5)
C11 – C9 – C8 – C5	-134.3(2)	C3 – C2 – C1 – F2A	104.1(3)
C10 – C9 – C8 – C5	50.1(2)	C7 – C2 – C1 – F2A	-78.6(3)
O1 – C8 – C5 – C6	-145.4(2)	C3 – C2 – C1 – F3A	-5.3(3)
C9 – C8 – C5 – C6	91.2(2)	C7 – C2 – C1 – F3A	172.0(2)
O1 – C8 – C5 – C4	31.6(2)	C1 – C2 – C7 – C6	-175.5(2)
C9 – C8 – C5 – C4	-91.8(2)	C1 – C2 – C3 – C4	175.2(2)
C6 – C5 – C4 – C3	1.7(2)	C5 – C4 – C3 – C2	0.2(2)
C8 – C5 – C4 – C3	-175.3(1)	C4 – C5 – C6 – C7	-2.0(2)
C12 – O2 – C11 – C9	-173.1(2)	C8 – C5 – C6 – C7	175.1(2)
C10 – C9 – C11 – O2	178.9(2)	C5 – C6 – C7 – C2	0.3(3)
C8 – C9 – C11 – O2	3.3(2)	C3 – C2 – C7 – C6	1.8(3)
C7 – C2 – C3 – C4	-2.0(2)		

Single crystals of compound **172fj**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[521] Absorption correction using the multiscan method[522] was applied. The structures were solved with SHELXS-

[521] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[522] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.

97,[523] refined with SHELXL-97[524] and finally checked using PLATON.[525] Details for data collection and structure refinement are summarized in Table 82.

CCDC-2027324 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 82: Details for X-ray data collection and structure refinement for compound **172fj**.

	172fj
Empirical formula	$C_{12}H_{13}NO_2$
Formula mass	203.23
T[K]	143(2)
Crystal size [mm]	0.20 × 0.15 × 0.03
Crystal description	colorless platelet
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	10.7401(17)
b [Å]	11.8914(16)
c [Å]	9.1036(12)
α [°]	90.0
β [°]	111.337(17)
γ [°]	90.0
V [Å^3]	1083.0(3)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.246
μ [mm^{-1}]	0.085
F(000)	432
Θ range [°]	4.05 – 25.24
Index ranges	$-13 \leq h \leq 13$
	$-14 \leq k \leq 14$
	$-9 \leq l \leq 11$
Reflns. collected	6315

[523] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[524] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[525] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Reflns. obsd.	1355
Reflns. unique	2005 (R_{int} = 0.0648)
R_1, wR_2 (2σ data)	0.0820, 0.1732
R_1, wR_2 (all data)	0.1231, 0.1953
GOOF on F^2	1.053
Peak/hole [e Å^{-3}]	0.349 / -0.259

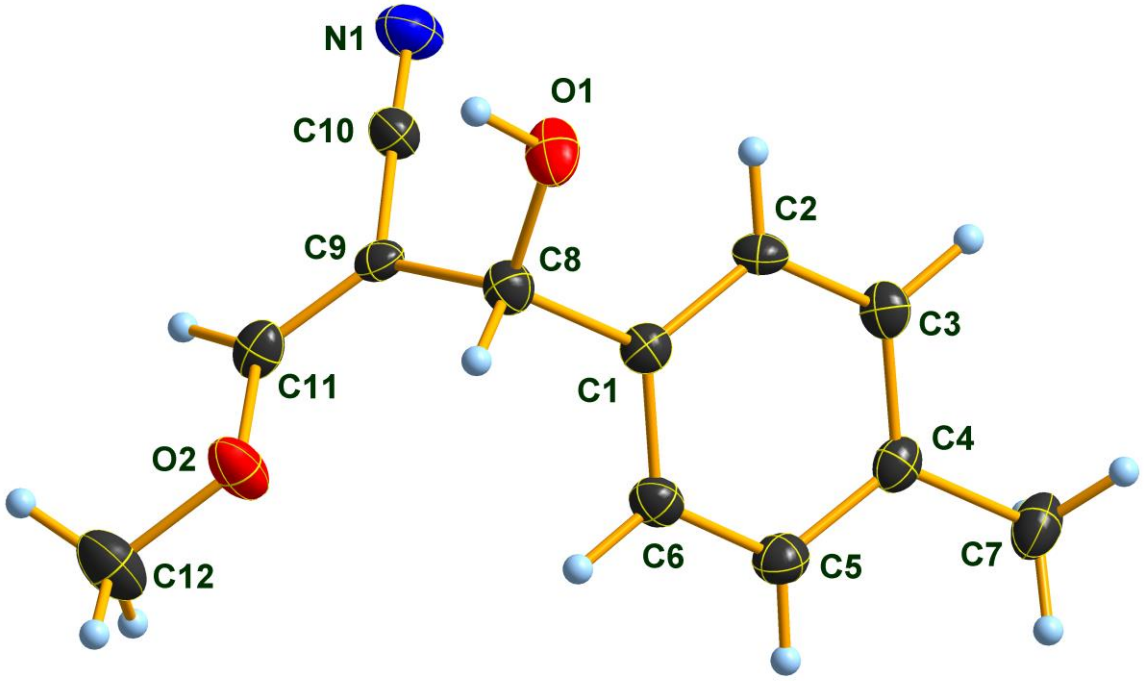


Figure 42: Molecular structure of compound **172fj** in the crystal. DIAMOND[526] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 83: Selected bond lengths (Å) of compound **172fj**.

O1 – C8	1.420(4)	C8 – C9	1.522(5)
O2 – C11	1.335(4)	C4 – C5	1.387(5)
O2 – C12	1.442(5)	C4 – C7	1.513(5)
C1 – C2	1.384(5)	C11 – C9	1.330(5)
C1 – C6	1.391(5)	C10 – C9	1.434(5)
C1 – C8	1.512(5)	C6 – C5	1.388(5)

[526] DIAMOND, Crystal Impact GbR., Version 3.2i.

C2 – C3	1.377(5)	C3 – C4	1.396(5)
N1 – C10	1.137(5)		

Table 84: Selected bond angles (°) of compound **172fj**.

C11 – O2 – C12	116.5(3)	C9 – C11 – O2	120.9(3)
C2 – C1 – C6	118.6(3)	C4 – C5 – C6	120.9(4)
C2 – C1 – C8	121.5(3)	N1 – C10 – C9	178.4(4)
C6 – C1 – C8	119.9(3)	C11 – C9 – C10	118.6(3)
C3 – C2 – C1	121.1(3)	C11 – C9 – C8	124.9(3)
C5 – C6 – C1	120.4(3)	C10 – C9 – C8	116.5(3)
C2 – C3 – C4	120.6(3)	C5 – C4 – C3	118.3(3)
O1 – C8 – C1	107.7(3)	C5 – C4 – C7	121.4(3)
O1 – C8 – C9	111.8(3)	C3 – C4 – C7	120.3(3)
C1 – C8 – C9	110.4(3)		

Table 85: Selected torsion angles (°) of compound **172fj**.

C6 – C1 – C2 – C3	-1.9(5)	C12 – O2 – C11 – C9	-174.6(3)
C8 – C1 – C2 – C3	-179.9(3)	C3 – C4 – C5 – C6	-1.5(5)
C2 – C1 – C6 – C5	0.7(5)	C7 – C4 – C5 – C6	177.0(3)
C8 – C1 – C6 – C5	178.8(3)	C1 – C6 – C5 – C4	1.0(5)
C1 – C2 – C3 – C4	1.4(5)	O2 – C11 – C9 – C10	-178.9(3)
C2 – C1 – C8 – O1	-27.4(4)	O2 – C11 – C9 – C8	3.7(5)
C6 – C1 – C8 – O1	154.7(3)	O1 – C8 – C9 – C11	-136.1(3)
C2 – C1 – C8 – C9	95.0(4)	C1 – C8 – C9 – C11	104.0(4)
C6 – C1 – C8 – C9	-83.0(4)	O1 – C8 – C9 – C10	46.4(4)
C2 – C3 – C4 – C5	0.3(5)	C1 – C8 – C9 – C10	-73.4(4)
C2 – C3 – C4 – C7	-178.2(3)		

Single crystals of compound **172gi**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[527] Absorption

[527] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.

correction using the multiscan method[528] was applied. The structures were solved with SHELXS-97,[529] refined with SHELXL-97[530] and finally checked using PLATON.[531] Details for data collection and structure refinement are summarized in Table 86.

CCDC-2027325 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 86: Details for X-ray data collection and structure refinement for compound **172gi**.

	172gi
Empirical formula	$C_{12}H_{11}Cl_2NO_2$
Formula mass	272.12
T[K]	143(2)
Crystal size [mm]	0.10 × 0.10 × 0.04
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	8.6835(4)
b [Å]	14.3010(7)
c [Å]	20.7726(11)
α [°]	98.709(4)
β [°]	91.623(4)
γ [°]	92.076(4)
V [Å^3]	2546.7(2)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.419
μ [mm^{-1}]	0.498
F(000)	1120
Θ range [°]	3.27 – 25.24
Index ranges	$-10 \leq h \leq 10$
	$-17 \leq k \leq 17$
	$-25 \leq l \leq 25$

[528] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[529] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[530] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[531] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Reflns. collected	20854
Reflns. obsd.	6770
Reflns. unique	10356 (R_{int} = 0.0414)
R_1, wR_2 (2σ data)	0.0523, 0.0937
R_1, wR_2 (all data)	0.0930, 0.1122
GOOF on F^2	1.017
Peak/hole [e Å^{-3}]	0.419 / -0.286

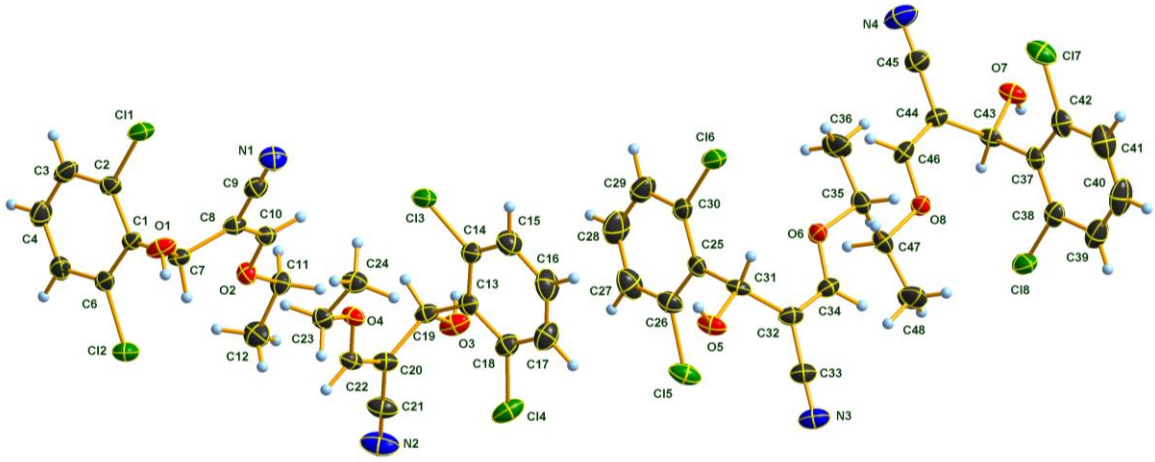


Figure 43: Molecular structure of compound **172gi** in the crystal. DIAMOND[532] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 87: Selected bond lengths (Å) of compound **172gi**.

Cl6 – C30	1.753(3)	C26 – C25	1.387(4)
Cl3 – C14	1.751(3)	C26 – C27	1.390(4)
Cl1 – C2	1.731(3)	C45 – N4	1.137(4)
Cl4 – C18	1.741(3)	C35 – C36	1.491(4)
Cl2 – C6	1.750(3)	C47 – C48	1.500(4)
Cl8 – C38	1.742(3)	C4 – C5	1.375(4)
Cl7 – C42	1.744(3)	C4 – C3	1.387(4)
Cl5 – C26	1.740(3)	C34 – C32	1.335(4)
O5 – C31	1.419(3)	C14 – C15	1.367(4)
O2 – C10	1.331(3)	C30 – C29	1.383(4)
O2 – C11	1.451(3)	C30 – C25	1.398(4)

[532] DIAMOND, Crystal Impact GbR., Version 3.2i.

O4 – C22	1.327(3)	C2 – C3	1.389(4)
O4 – C23	1.455(3)	C6 – C5	1.379(4)
O8 – C46	1.343(3)	C21 – N2	1.142(4)
O8 – C47	1.452(3)	C8 – C9	1.428(4)
O1 – C7	1.423(3)	C17 – C16	1.376(4)
C46 – C44	1.334(4)	C29 – C28	1.379(5)
O3 – C19	1.417(3)	C24 – C23	1.492(4)
C13 – C18	1.397(4)	C27 – C28	1.374(4)
C13 – C14	1.405(4)	C39 – C40	1.365(5)
C13 – C19	1.511(4)	C41 – C40	1.373(5)
O6 – C34	1.337(3)	C15 – C16	1.392(4)
O6 – C35	1.450(3)	C37 – C42	1.396(4)
C20 – C22	1.331(4)	C37 – C38	1.402(4)
C20 – C21	1.427(4)	C37 – C43	1.514(4)
C20 – C19	1.536(4)	C31 – C32	1.521(4)
C11 – C12	1.496(4)	C31 – C25	1.522(4)
C1 – C6	1.403(4)	C18 – C17	1.390(4)
C1 – C2	1.410(4)	C42 – C41	1.383(4)
C1 – C7	1.515(4)	N1 – C9	1.150(4)
C44 – C45	1.433(4)	C38 – C39	1.390(4)
C44 – C43	1.523(4)	C7 – C8	1.534(4)
C10 – C8	1.337(4)	C33 – N3	1.140(3)
O7 – C43	1.426(3)	C33 – C32	1.430(4)

Table 88: Selected bond angles (°) of compound **172gi**.

C10 – O2 – C11	117.7(2)	C25 – C30 – Cl6	120.8(2)
C22 – O4 – C23	118.7(2)	O4 – C22 – C20	118.8(2)
C46 – O8 – C47	117.0(2)	C3 – C2 – C1	122.5(3)
C44 – C46 – O8	119.0(3)	C3 – C2 – Cl1	117.3(2)
C18 – C13 – C14	115.2(3)	C1 – C2 – Cl1	120.2(2)
C18 – C13 – C19	123.0(3)	C5 – C6 – C1	123.4(3)
C14 – C13 – C19	121.8(3)	C5 – C6 – Cl2	116.4(2)
C34 – O6 – C35	116.9(2)	C1 – C6 – Cl2	120.2(2)
C22 – C20 – C21	120.5(3)	N2 – C21 – C20	179.4(4)
C22 – C20 – C19	120.7(3)	O7 – C43 – C37	111.1(2)
C21 – C20 – C19	118.7(2)	O7 – C43 – C44	109.7(2)
O2 – C11 – C12	106.8(2)	C37 – C43 – C44	113.1(2)
C6 – C1 – C2	115.0(3)	C10 – C8 – C9	119.7(3)
C6 – C1 – C7	122.0(2)	C10 – C8 – C7	121.3(3)

C2 – C1 – C7	122.9(3)	C9 – C8 – C7	118.8(2)
C46 – C44 – C45	118.4(3)	C4 – C3 – C2	119.3(3)
C46 – C44 – C43	122.5(2)	C4 – C5 – C6	119.4(3)
C45 – C44 – C43	118.8(2)	N1 – C9 – C8	177.9(3)
O2 – C10 – C8	118.7(3)	C16 – C17 – C18	119.3(3)
C42 – C37 – C38	115.4(3)	C28 – C29 – C30	118.7(3)
C42 – C37 – C43	122.7(3)	C26 – C25 – C30	115.7(3)
C38 – C37 – C43	121.9(3)	C26 – C25 – C31	122.6(2)
O5 – C31 – C32	108.6(2)	C30 – C25 – C31	121.7(3)
O5 – C31 – C25	111.4(2)	C34 – C32 – C33	118.7(3)
C32 – C31 – C25	113.9(2)	C34 – C32 – C31	121.0(2)
C17 – C18 – C13	122.9(3)	C33 – C32 – C31	120.1(2)
C17 – C18 – Cl4	117.2(2)	C28 – C27 – C26	119.0(3)
C13 – C18 – Cl4	120.0(2)	O4 – C23 – C24	106.6(2)
C41 – C42 – C37	123.0(3)	C40 – C39 – C38	119.3(3)
C41 – C42 – Cl7	117.1(3)	C40 – C41 – C42	119.0(3)
C37 – C42 – Cl7	119.9(2)	C39 – C40 – C41	121.0(3)
C39 – C38 – C37	122.3(3)	C27 – C28 – C29	120.8(3)
C39 – C38 – Cl8	117.0(2)	C14 – C15 – C16	119.4(3)
C37 – C38 – Cl8	120.7(2)	C17 – C16 – C15	120.0(3)
O1 – C7 – C1	109.7(2)	C5 – C4 – C3	120.3(3)
O1 – C7 – C8	110.3(2)	C32 – C34 – O6	118.6(3)
C1 – C7 – C8	113.1(2)	O3 – C19 – C13	111.9(2)
N3 – C33 – C32	178.4(3)	O3 – C19 – C20	108.4(2)
C25 – C26 – C27	122.8(3)	C13 – C19 – C20	112.7(2)
C25 – C26 – Cl5	120.9(2)	C15 – C14 – C13	123.2(3)
C27 – C26 – Cl5	116.3(3)	C15 – C14 – Cl3	116.3(2)
N4 – C45 – C44	178.5(4)	C13 – C14 – Cl3	120.5(2)
O6 – C35 – C36	106.9(2)	C29 – C30 – C25	123.0(3)
O8 – C47 – C48	106.6(2)	C29 – C30 – Cl6	116.2(2)

Table 89: Selected torsion angles (°) of compound **172gi**.

C47 – O8 – C46 – C44	-177.9(3)	C45 – C44 – C43 – O7	-1.2(4)
C10 – O2 – C11 – C12	168.9(2)	C46 – C44 – C43 – C37	-62.4(4)
O8 – C46 – C44 – C45	177.1(3)	C45 – C44 – C43 – C37	123.3(3)
O8 – C46 – C44 – C43	2.8(4)	O2 – C10 – C8 – C9	176.1(2)
C11 – O2 – C10 – C8	178.5(3)	O2 – C10 – C8 – C7	1.8(4)
C14 – C13 – C18 – C17	0.2(4)	O1 – C7 – C8 – C10	166.9(3)
C19 – C13 – C18 – C17	178.5(3)	C1 – C7 – C8 – C10	-69.8(3)

C14 – C13 – C18 – Cl4	179.8(2)	O1 – C7 – C8 – C9	-7.5(3)
C19 – C13 – C18 – Cl4	-2.0(4)	C1 – C7 – C8 – C9	115.8(3)
C38 – C37 – C42 – C41	-0.1(4)	C5 – C4 – C3 – C2	-0.1(5)
C43 – C37 – C42 – C41	-178.3(3)	C1 – C2 – C3 – C4	0.2(5)
C38 – C37 – C42 – Cl7	-179.2(2)	Cl1 – C2 – C3 – C4	178.8(2)
C43 – C37 – C42 – Cl7	2.6(4)	C3 – C4 – C5 – C6	0.2(5)
C42 – C37 – C38 – C39	-0.2(4)	C1 – C6 – C5 – C4	-0.4(5)
C43 – C37 – C38 – C39	178.1(3)	Cl2 – C6 – C5 – C4	179.2(2)
C42 – C37 – C38 – Cl8	178.7(2)	C13 – C18 – C17 – C16	0.1(5)
C43 – C37 – C38 – Cl8	-3.1(4)	Cl4 – C18 – C17 – C16	-179.4(2)
C6 – C1 – C7 – O1	-114.4(3)	C25 – C30 – C29 – C28	0.2(5)
C2 – C1 – C7 – O1	63.0(3)	Cl6 – C30 – C29 – C28	-179.7(3)
C6 – C1 – C7 – C8	122.0(3)	C27 – C26 – C25 – C30	-1.7(4)
C2 – C1 – C7 – C8	-60.6(3)	Cl5 – C26 – C25 – C30	178.7(2)
C34 – O6 – C35 – C36	173.7(3)	C27 – C26 – C25 – C31	176.3(3)
C46 – O8 – C47 – C48	-176.1(3)	Cl5 – C26 – C25 – C31	-3.3(4)
C35 – O6 – C34 – C32	175.3(3)	C29 – C30 – C25 – C26	1.2(4)
C18 – C13 – C19 – O3	-60.5(3)	Cl6 – C30 – C25 – C26	-179.0(2)
C14 – C13 – C19 – O3	117.7(3)	C29 – C30 – C25 – C31	-176.8(3)
C18 – C13 – C19 – C20	62.0(3)	Cl6 – C30 – C25 – C31	3.0(4)
C14 – C13 – C19 – C20	-119.9(3)	O5 – C31 – C25 – C26	-61.3(3)
C22 – C20 – C19 – O3	-176.2(3)	C32 – C31 – C25 – C26	61.9(3)
C21 – C20 – C19 – O3	1.6(4)	O5 – C31 – C25 – C30	116.5(3)
C22 – C20 – C19 – C13	59.3(4)	C32 – C31 – C25 – C30	-120.3(3)
C21 – C20 – C19 – C13	-122.9(3)	O6 – C34 – C32 – C33	-177.4(3)
C18 – C13 – C14 – C15	-0.5(4)	O6 – C34 – C32 – C31	-2.1(4)
C19 – C13 – C14 – C15	-178.8(3)	O5 – C31 – C32 – C34	-171.1(3)
C18 – C13 – C14 – Cl3	-178.5(2)	C25 – C31 – C32 – C34	64.2(3)
C19 – C13 – C14 – Cl3	3.2(4)	O5 – C31 – C32 – C33	4.2(4)
C23 – O4 – C22 – C20	-170.4(3)	C25 – C31 – C32 – C33	-120.6(3)
C21 – C20 – C22 – O4	-177.5(3)	C25 – C26 – C27 – C28	0.9(5)
C19 – C20 – C22 – O4	0.3(4)	Cl5 – C26 – C27 – C28	-179.5(3)
C6 – C1 – C2 – C3	-0.4(4)	C22 – O4 – C23 – C24	150.8(2)
C7 – C1 – C2 – C3	-178.0(3)	C37 – C38 – C39 – C40	-0.1(5)
C6 – C1 – C2 – Cl1	-178.9(2)	Cl8 – C38 – C39 – C40	-178.9(2)
C7 – C1 – C2 – Cl1	3.5(4)	C37 – C42 – C41 – C40	0.6(5)
C2 – C1 – C6 – C5	0.5(4)	Cl7 – C42 – C41 – C40	179.7(2)
C7 – C1 – C6 – C5	178.1(3)	C38 – C39 – C40 – C41	0.6(5)
C2 – C1 – C6 – Cl2	-179.1(2)	C42 – C41 – C40 – C39	-0.8(5)
C7 – C1 – C6 – Cl2	-1.5(4)	C26 – C27 – C28 – C29	0.6(5)

C42 – C37 – C43 – O7	58.9(3)	C30 – C29 – C28 – C27	-1.1(5)
C38 – C37 – C43 – O7	-119.3(3)	C13 – C14 – C15 – C16	0.5(5)
C42 – C37 – C43 – C44	-64.9(3)	Cl3 – C14 – C15 – C16	178.6(2)
C38 – C37 – C43 – C44	116.9(3)	C18 – C17 – C16 – C15	-0.2(5)
C46 – C44 – C43 – O7	173.1(3)	C14 – C15 – C16 – C17	-0.1(5)

Single crystals of compound **172hh**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[533] Absorption correction using the multiscan method[534] was applied. The structures were solved with SHELXS-97,[535] refined with SHELXL-97[536] and finally checked using PLATON.[537] Details for data collection and structure refinement are summarized in Table 90.

CCDC-2027329 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 90: Details for X-ray data collection and structure refinement for compound **172hh**.

	172hh
Empirical formula	$C_{24}H_{26}OS$
Formula mass	362.51
T[K]	123(2)
Crystal size [mm]	0.40 × 0.30 × 0.08
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	6.5370(3)
b [Å]	11.1601(6)

[533] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[534] Program package 'CrysAlisPro 1.171.39.46e (Rigaku OD, 2018)'.
[535] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[536] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[537] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

c [Å]	13.1519(9)
α [°]	102.872(5)
β [°]	95.207(5)
γ [°]	91.589(4)
V [Å^3]	930.37(9)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.294
μ [mm^{-1}]	0.184
F(000)	388
Θ range [°]	3.32 – 25.24
Index ranges	$-9 \leq h \leq 9$
	$-15 \leq k \leq 15$
	$-18 \leq l \leq 18$
Reflns. collected	19026
Reflns. obsd.	4569
Reflns. unique	4569 (R_{int} = 0.0356)
R_1, wR_2 (2σ data)	0.0431, 0.1070
R_1, wR_2 (all data)	0.0575, 0.1194
GOOF on F^2	1.036
Peak/hole [e Å^{-3}]	0.489 / -0.258

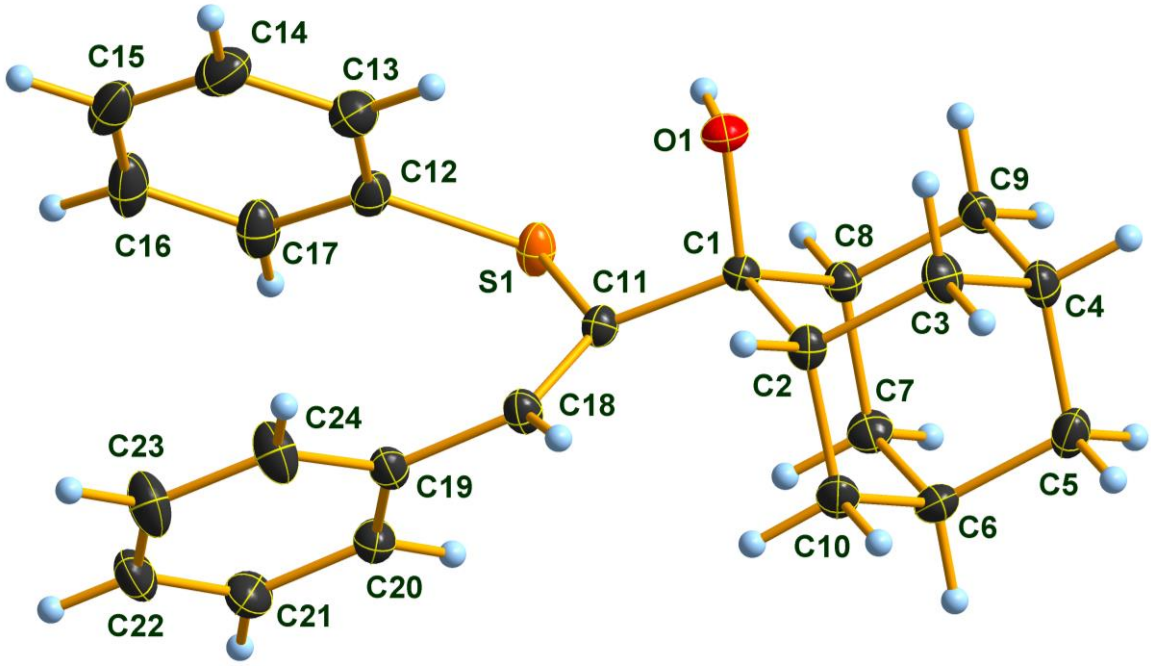


Figure 44: Molecular structure of compound **172hh** in the crystal. DIAMOND[538] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 91: Selected bond lengths (Å) of compound **172hh**.

S1 – C12	1.779(1)	C12 – C13	1.384(2)
S1 – C11	1.789(1)	C12 – C17	1.390(2)
C1 – O1	1.439(1)	C11 – C18	1.340(2)
C1 – C11	1.530(2)	C20 – C21	1.388(2)
C1 – C2	1.543(2)	C20 – C19	1.395(2)
C1 – C8	1.550(2)	C14 – C15	1.385(2)
C2 – C3	1.537(2)	C14 – C13	1.394(2)
C2 – C10	1.539(2)	C16 – C15	1.377(2)
C3 – C4	1.534(2)	C16 – C17	1.392(2)
C4 – C9	1.532(2)	C19 – C24	1.390(2)
C4 – C5	1.534(2)	C19 – C18	1.477(2)
C5 – C6	1.531(2)	C23 – C24	1.388(2)
C10 – C6	1.532(2)	C23 – C22	1.389(2)
C7 – C6	1.534(2)	C21 – C22	1.381(2)
C7 – C8	1.536(2)	C8 – C9	1.532(2)

Table 92: Selected bond angles (°) of compound **172hh**.

[538] DIAMOND, Crystal Impact GbR., Version 3.2i.

C12 – S1 – C11	102.3(1)	C7 – C8 – C1	110.1(1)
O1 – C1 – C11	107.2(1)	C13 – C12 – C17	120.1(1)
O1 – C1 – C2	106.5(1)	C13 – C12 – S1	121.0(1)
C11 – C1 – C2	114.0(1)	C17 – C12 – S1	118.9(1)
O1 – C1 – C8	110.1(1)	C18 – C11 – C1	125.9(1)
C11 – C1 – C8	111.4(1)	C18 – C11 – S1	121.3(1)
C2 – C1 – C8	107.6(1)	C1 – C11 – S1	112.6(1)
C3 – C2 – C10	108.2(1)	C4 – C9 – C8	110.0(1)
C3 – C2 – C1	109.6(1)	C21 – C20 – C19	120.6(1)
C10 – C2 – C1	111.0(1)	C15 – C14 – C13	120.1(1)
C4 – C3 – C2	110.0(1)	C12 – C13 – C14	119.8(1)
C9 – C4 – C5	109.2(1)	C15 – C16 – C17	120.2(1)
C9 – C4 – C3	108.9(1)	C16 – C15 – C14	120.2(1)
C5 – C4 – C3	109.7(1)	C24 – C19 – C20	118.4(1)
C6 – C5 – C4	109.3(1)	C24 – C19 – C18	121.0(1)
C6 – C10 – C2	110.0(1)	C20 – C19 – C18	120.7(1)
C6 – C7 – C8	109.6(1)	C12 – C17 – C16	119.7(1)
C5 – C6 – C10	109.5(1)	C24 – C23 – C22	120.1(1)
C5 – C6 – C7	110.1(1)	C11 – C18 – C19	126.3(1)
C10 – C6 – C7	108.6(1)	C22 – C21 – C20	120.5(1)
C9 – C8 – C7	109.5(1)	C23 – C24 – C19	121.0(1)
C9 – C8 – C1	109.6(1)	C21 – C22 – C23	119.4(1)

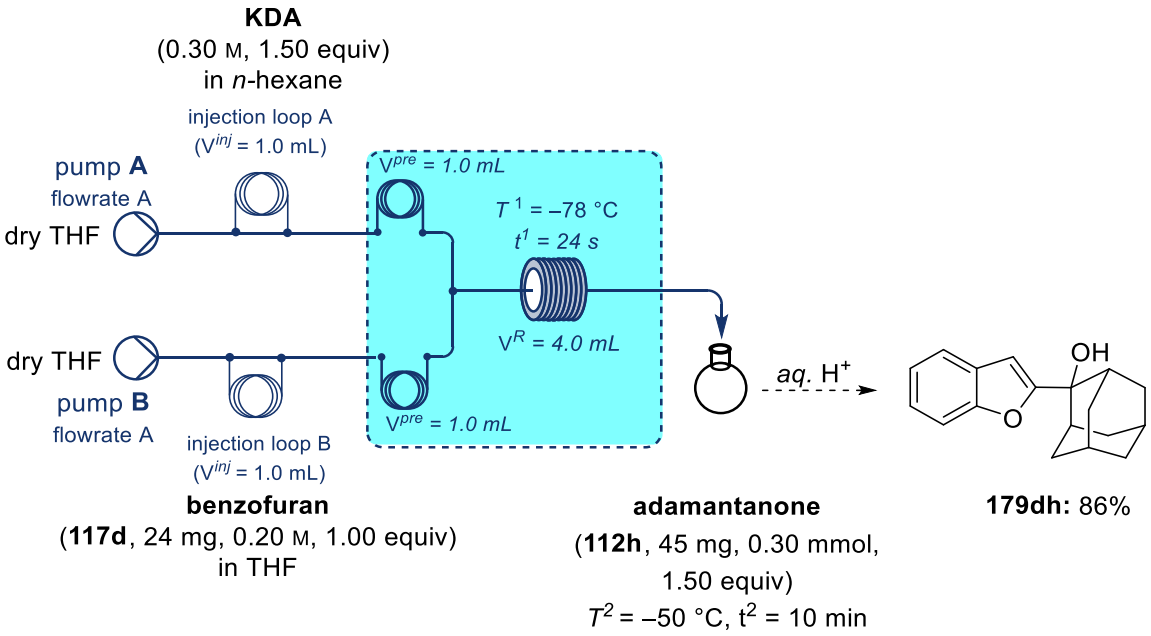
Table 93: Selected torsion angles (°) of compound **172hh**.

O1 – C1 – C2 – C3	-57.2(1)	C2 – C1 – C11 – C18	12.0(2)
C11 – C1 – C2 – C3	-175.2(1)	C8 – C1 – C11 – C18	133.9(1)
C8 – C1 – C2 – C3	60.8(1)	O1 – C1 – C11 – S1	68.8(1)
O1 – C1 – C2 – C10	-176.6(1)	C2 – C1 – C11 – S1	-173.7(1)
C11 – C1 – C2 – C10	65.5(1)	C8 – C1 – C11 – S1	-51.7(1)
C8 – C1 – C2 – C10	-58.5(1)	C12 – S1 – C11 – C18	46.0(1)
C10 – C2 – C3 – C4	60.0(1)	C12 – S1 – C11 – C1	-128.7(1)
C1 – C2 – C3 – C4	-61.1(1)	C5 – C4 – C9 – C8	60.3(1)
C2 – C3 – C4 – C9	59.4(1)	C3 – C4 – C9 – C8	-59.5(1)
C2 – C3 – C4 – C5	-60.1(1)	C7 – C8 – C9 – C4	-59.7(1)
C9 – C4 – C5 – C6	-60.0(1)	C1 – C8 – C9 – C4	61.2(1)
C3 – C4 – C5 – C6	59.3(1)	C17 – C12 – C13 – C14	1.8(2)
C3 – C2 – C10 – C6	-60.4(1)	S1 – C12 – C13 – C14	-179.8(1)
C1 – C2 – C10 – C6	59.8(1)	C15 – C14 – C13 – C12	-1.2(2)
C4 – C5 – C6 – C10	-59.5(1)	C17 – C16 – C15 – C14	0.9(2)
C4 – C5 – C6 – C7	59.9(1)	C13 – C14 – C15 – C16	-0.2(2)
C2 – C10 – C6 – C5	60.8(1)	C21 – C20 – C19 – C24	0.9(2)
C2 – C10 – C6 – C7	-59.5(1)	C21 – C20 – C19 – C18	179.8(1)
C8 – C7 – C6 – C5	-59.2(1)	C13 – C12 – C17 – C16	-1.0(2)
C8 – C7 – C6 – C10	60.8(1)	S1 – C12 – C17 – C16	-179.4(1)
C6 – C7 – C8 – C9	58.7(1)	C15 – C16 – C17 – C12	-0.3(2)
C6 – C7 – C8 – C1	-61.9(1)	C1 – C11 – C18 – C19	-177.2(1)
O1 – C1 – C8 – C9	54.7(1)	S1 – C11 – C18 – C19	8.9(2)
C11 – C1 – C8 – C9	173.4(1)	C24 – C19 – C18 – C11	-124.8(2)
C2 – C1 – C8 – C9	-61.0(1)	C20 – C19 – C18 – C11	56.3(2)
O1 – C1 – C8 – C7	175.2(1)	C19 – C20 – C21 – C22	0.8(2)
C11 – C1 – C8 – C7	-66.1(1)	C22 – C23 – C24 – C19	1.4(2)
C2 – C1 – C8 – C7	59.5(1)	C20 – C19 – C24 – C23	-2.0(2)
C11 – S1 – C12 – C13	52.6(1)	C18 – C19 – C24 – C23	179.1(1)
C11 – S1 – C12 – C17	-129.0(1)	C20 – C21 – C22 – C23	-1.4(2)
O1 – C1 – C11 – C18	-105.6(1)	C24 – C23 – C22 – C21	0.3(2)

7. Preparation of Functionalized Aryl, Heteroaryl, and Benzylic Potassium Organometallics Using Potassium Diisopropylamide in Continuous Flow

7.1 Typical Procedures

7.1.1 Typical procedure 20 (TP20) using a flow setup (Scheme 158): Preparation of tertiary alcohol 4aa starting from benzofuran (117d) and subsequent batch trapping with adamantanone (112h).



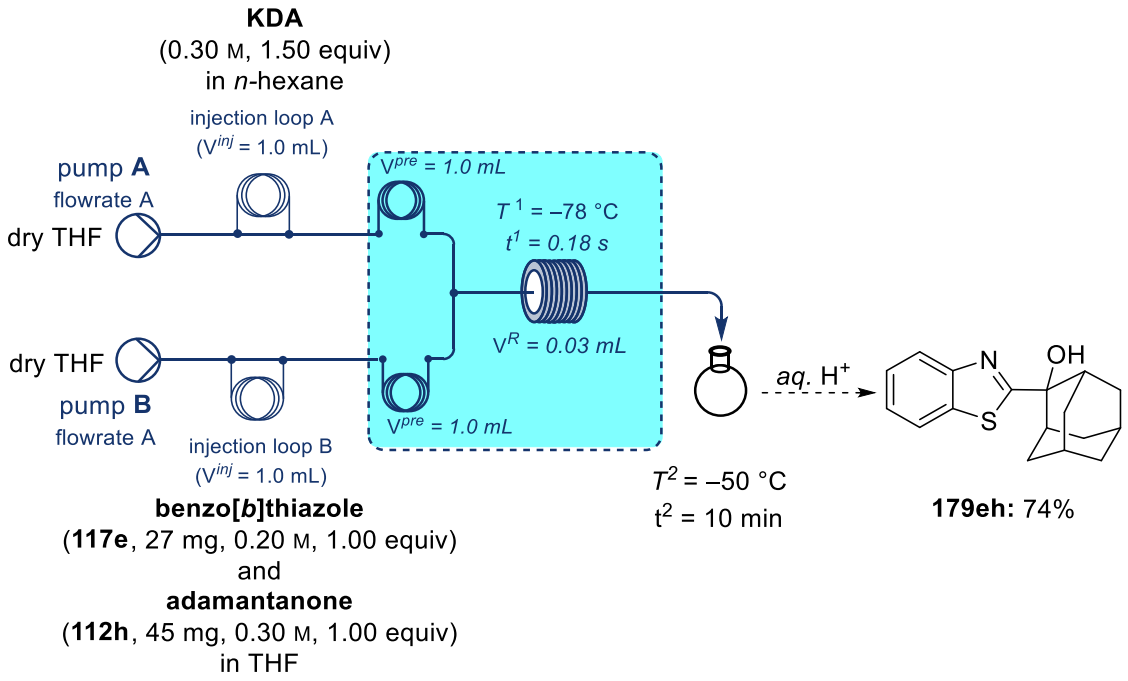
Scheme 158: Flow setup for the deprotonation of (hetero)aromatic substrates with KDA and batch quench with an electrophile (E^+). See text for abbreviations.

A solution of benzofuran (**117d**, 24 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. Injection loop A (V^{inj} =1.00 mL) was loaded with KDA and injection loop B (V^{inj} =1.00 mL) was loaded with the benzofuran solution.

The solutions were simultaneously injected into separate streams of THF, respectively (pump A: THF; pump B: THF, combined flow rates: 10 mL/min), which each passed a pre-cooling loop (V^{pre} = 1.00 mL, T^1 = -78 °C, residence time: 12 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.50 mm). The combined stream passed a PTFE reactor tube (V^R = 4.00 mL; residence time: t^1 = 24.0 s, T^1 = -78 °C) and was subsequently injected in a flask containing a stirred solution of an adamantanone (**112h**, 45

mg, 0.30 M, 1.50 equiv) in THF. The reaction mixture was stirred further for the indicated times and temperatures (T^2 = -50 °C, reaction time: t^2 = 10 min) and quenched with a *sat. aq.* NH_4Cl solution. The aqueous phase was extracted with EtOAc and the organic phases were dried and filtrated. After removal of the solvent *in vacuo*, flash column chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179dh** as white crystals (47 mg, 0.18 mmol, 86% yield).

7.1.2 Typical procedure 21 (TP21) for a Barbier-type reaction using a flow setup (Scheme 159): Preparation of tertiary alcohol 4ba starting from a premixed solution of benzo[b]thiazole (117e) and adamantanone (112h).

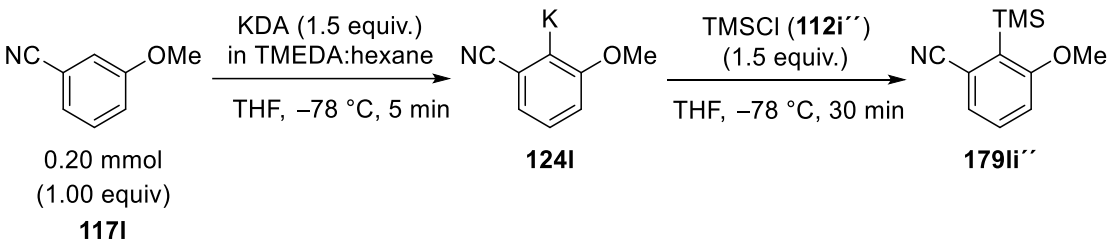


Scheme 159: Flow setup for the deprotonation of (hetero)aromatic substrates with KDA in the presence of an electrophile (E^+). See text for abbreviations.

A KDA solution in *n*-hexane (0.30 M, 1.50 equiv) and a solution of benzo[*b*]thiazole (**117e**, 27 mg, 0.20 M, 1.00 equiv) and 2-adamantanone (**112h**, 45 mg, 0.30 M, 1.50 equiv) in dry THF were prepared. Injection loop A (V^{inj} =1.00 mL) was loaded with KDA and injection loop B (V^{inj} =1.00 mL) was loaded with the solution of benzo[*b*]thiazole (**117e**) and 2-adamantanone (**112h**). The solutions were simultaneously injected into separate streams of THF, respectively (pump A: THF; pump B: THF, combined flow rates: 10 mL/min), which each passed a pre-cooling loop (V^{pre} = 1.00 mL, T^1 = -78 °C, residence time: 12 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.50 mm). The combined stream passed a PTFE reactor tube (V^R = 0.03 mL; residence time: t^1 = 0.18 s, T^1 = -78 °C) and was subsequently injected in a flask. The reaction mixture was stirred for t^2 = 10 min at T^2 = - 50 °C and quenched with a *sat. aq.* NH_4Cl solution. The aqueous phase was extracted with EtOAc and the organic

phases were dried and filtrated. After removal of the solvent *in vacuo*, flash column chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **179eh** as white crystals (42 mg, 0.15 mmol, 74% yield).

7.1.3 Typical procedure 22 (TP22) for metalation using KDA in batch

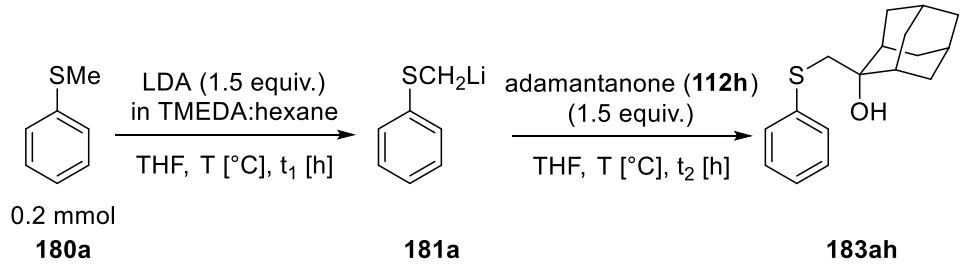


Scheme 160: Batch metalation of 3-methoxybenzonitrile (**117l**) using KDA followed by an TMSCl quench.

A solution of 3-methoxybenzonitrile (**117l**, 27 mg, 0.20 mmol, 1.00 equiv) in THF (1.00 mL) and a solution of KDA (0.30 M in hexane) were prepared. The KDA solution (1.00 mL, 0.30 mmol, 1.50 equiv) was slowly added to **117l** at -78 °C and the mixture was stirred for 5 min. TMSCl (**112i´´**, 45 mg, 0.30 mmol, 1.50 equiv) was added to the reaction mixture and stirring at -78 °C was continued for 30 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179li´´** as colorless crystals (32 mg, 0.16 mmol, 78% yield).

7.2 Reaction Optimization

7.2.1 Screening for attempted lithiation of thioanisole (180a) using LDA under batch conditions:



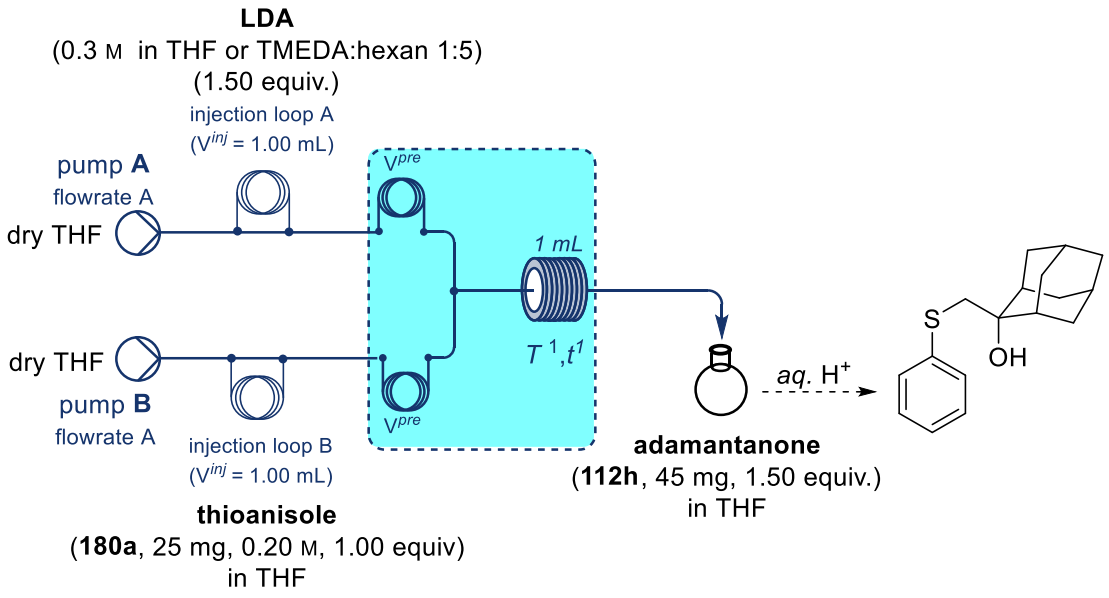
Scheme 161: Attempted metalation of thioanisole **180a** under batch conditions using LDA as base and subsequent quench with adamantanone **112h**.

LDA in TMEDA:hexane (1.0 mL, 0.30 M, 0.3 mmol, 1.50 equiv) was added to thioanisole (**180a**) (25 mg, 0.2 mmol, 1.0 equiv) dissolved in THF (1.0 mL) at the indicated temperature (T) and stirred for the time t_1. Afterwards, adamantanone (**112h**) (45 mg, 0.3 mmol 1.5 equiv) dissolved in THF (1.0 mL) was added to the mixture and stirred at indicated temperature T for the time t_2. After quenching with *sat. aq.* NH_4Cl-solution, yields were determined using GC.

Table 94: Attempts to lithiate **180a** under batch conditions using LDA and subsequent quench using **112h**.

entry	T [°C]	t_1 [h]	t_2 [h]	conversion [%]	GC-yield
1	0	0.5	0.5	18	n.d.
2	–40	0.5	0.5	19	traces
3	–78	0.5	0.5	7	n.d.
4	0	3	10	17	traces
5	–40	3	10	5	n.d.
6	–78	3	10	12	traces

7.2.2 Screening for attempted lithiation of thioanisole (180a) using LDA under continuous flow conditions:



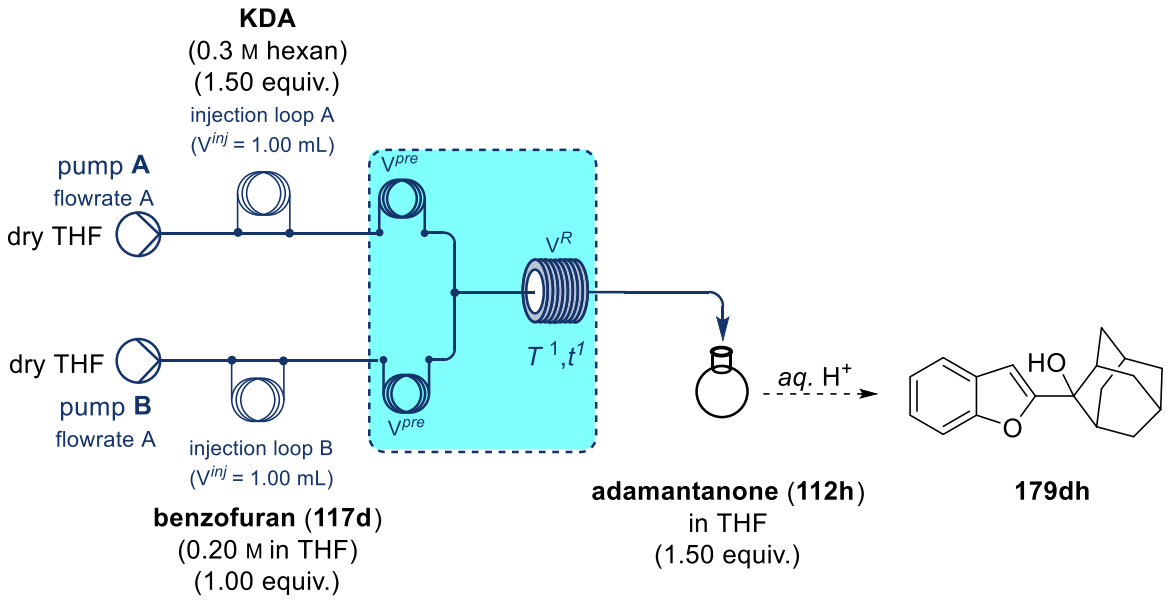
Scheme 162: Flow setup for the metalation of thioanisole **180a** with LDA and batch quench with adamantanone **112h**.

A LDA solution (0.30 M, 1.50 equiv) in TMEDA:hexane (1:5) or THF and a solution of thioanisole **180a** (0.20 M, 1.00 equiv) in THF were prepared. Injection loop A (V^{inj} =1.00 mL) was loaded with the LDA solution and injection loop B (V^{inj} =1.0 mL) was loaded with the solution of 5a. The solutions were simultaneously injected into separate streams of THF (flow rates: 5 mL/min), which each passed a pre-cooling loop (V^{pre} = 1.00 mL, T^1 [°C], residence time: 12 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (V^R = 1.00 mL; residence time: t^1 = 6 s, T^1 [°C]) and was subsequently injected in a flask containing a stirred, solution of adamantanone (**112h**) (1.50 equiv) in THF. The reaction mixture was stirred for 30 min at -40 °C and quenched with a *sat. aq.* NH_4Cl solution. Yields were determined using GC.

Table 95: Attempts to lithiate **180a** under continuous flow conditions using LDA and subsequent batch quench using **112h**.

entry	solvent	T^1 [°C]	conversion [%]	GC-yield
1	TMEDA:hexan	0	15	n.d.
2	TMEDA:hexan	–40	25	n.d.
3	TMEDA:hexan	–78	20	n.d.
4	THF	0	13	n.d.
5	THF	–40	10	n.d.
6	THF	–78	7	traces

7.2.3 Optimization screening of flow conditions for benzofuran (117d) metalation using KDA as example for general flow optimizations:



Scheme 163: Flow setup for the metalation of benzofuran **117d** with KDA and batch quench with adamantanone **112h**.

A KDA solution (0.30 M, 1.50 equiv) in hexane and a solution of the benzofuran **117d** (0.20 M, 1.00 equiv) in THF were prepared. Injection loop A (V^{inj} =1.00 mL) was loaded with the KDA solution and injection loop B (V^{inj} =1.0 mL) was loaded with a solution of substrate **117d**. The solutions were simultaneously injected into separate streams of THF (flow rates: Table 96), which each passed a pre-cooling loop (V^{pre} = 1.0 mL, T^1 [°C], residence time: 12 s or 60 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (V^R = see table 96; residence time: t^1, T^1 [°C]) and was subsequently injected in a flask containing a stirred solution of adamantanone **112h** (1.50 equiv) in THF. The reaction mixture was stirred for 30 min at 0 °C to -78 °C and quenched with a *sat. aq.* NH_4Cl solution. Yields were determined using GC.

Table 96: Optimization screening of flow conditions for benzofuran (**117d**) metalation using KDA.

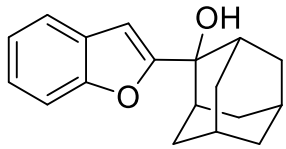
entry	T^1 [°C]	V^R [mL]	flow rate [mL/min]	t^1 [s]	GC-yield[a]
1	0	0.03	1	0.9	21
2	–20	0.03	1	0.9	19
3	–40	0.03	1	0.9	16
4	–78	0.03	1	0.9	28
5	0	0.03	5	0.18	60
6	–20	0.03	5	0.18	29

7	–40	0.03	5	0.18	27
8	–78	0.03	5	0.18	44
9	0	1	1	30	11
10	–20	1	1	30	11
11	–40	1	1	30	26
12	–78	1	1	30	22
13	0	1	5	6	67
14	–20	1	5	6	56
15	–40	1	5	6	39
16	–78	1	5	6	40
17	0	4	1	120	43
18	–20	4	1	120	53
19	–40	4	1	120	48
20	–78	4	1	120	40
21	0	4	5	24	66
22	–20	4	5	24	77
23	–40	4	5	24	46
24	–78	4	5	24	95

[a] GC-yields are normalized to the 95% isolated yield obtained under conditions in entry 24.

7.3 Synthesis of Products

2-(Benzofuran-2-yl)adamantan-2-ol (179dh)



According to **TP20**, a solution of benzofuran (**117d**, 24 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 m in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179dh** as white crystals (47 mg, 0.18 mmol, 86% yield).

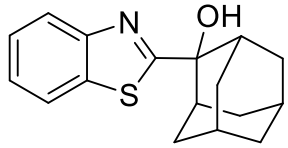
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.57 – 7.52 (m, 1H), 7.46 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.31 – 7.17 (m, 2H), 6.65 (d, *J* = 0.9 Hz, 1H), 2.52 (s, 2H), 2.40 (d, *J* = 12.8 Hz, 2H), 2.12 – 1.59 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.7, 154.2, 128.4, 124.2, 122.8, 121.1, 111.4, 102.7, 74.3, 39.4, 37.8, 35.5 (2C), 35.3 (2C), 32.4, 27.2, 27.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3528, 3424, 2956, 2916, 2904, 2891, 2852, 1469, 1451, 1402, 1360, 1352, 1332, 1286, 1262, 1248, 1233, 1193, 1181, 1167, 1159, 1116, 1102, 1082, 1052, 1044, 1016, 1006, 997, 982, 949, 930, 908, 900, 886, 876, 858, 806, 749, 740, 706, 680.

MS (EI, 70 eV): *m/z* (%) = 269 (11), 268 (61), 267 (24), 252 (19), 251 (100), 241 (12), 240 (68), 165 (10), 160 (11), 147 (51), 145 (20), 144 (11), 133 (12), 131 (22), 115 (11), 91 (28), 89 (11).

HRMS (EI): *m/z* calc. for [$C_{18}H_{20}O_2$]: 268.1463; found 268.1457.

m.p. (°C): 133.4 – 135.5.

2-(Benzo[*d*]thiazol-2-yl)adamantan-2-ol (179eh)



According to **TP20**, a solution of benzo[*b*]thiazole (**117e**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **179eh** as white crystals (54 mg, 0.19 mmol, 95% yield).

According to **TP21**, a solution of benzo[*b*]thiazole (**117e**, 0.20 M, 0.20 mmol) and 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **179eh** as white crystals (42 mg, 0.147 mmol, 74% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 8.1, 1H), 7.84 (d, *J* = 7.9, 1H), 7.48 – 7.40 (m, 1H), 7.35 (t, *J* = 7.6, 1H), 2.55 (t, *J* = 3.0, 3H), 2.43 (dd, *J* = 12.8, 3.1, 2H), 2.06 – 1.98 (m, 2H), 1.94 – 1.91 (m, 1H), 1.88 – 1.69 (m, 7H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 178.0, 152.7, 135.1, 125.9, 125.3, 123.3, 121.8, 77.4, 37.7, 37.6 (2C), 34.9 (2C), 32.9 (2C), 27.3, 27.0.

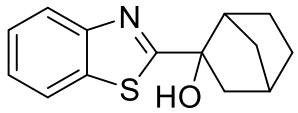
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3372, 3331, 2942, 2921, 2902, 2882, 2854, 1504, 1454, 1437, 1372, 1358, 1350, 1324, 1314, 1279, 1244, 1240, 1233, 1207, 1168, 1152, 1124, 1102, 1084, 1066, 1045, 1034, 1018, 1010, 996, 959, 937, 908, 885, 812, 804, 755, 727, 712, 696, 690.

MS (EI, 70 eV): *m/z* (%) = 162 (26), 149 (23), 136 (100), 135 (12).

HRMS (EI): *m/z* calc. for [$C_{17}H_{19}NOS$]: 285.1187; found 285.1181.

m.p. (°C): 146.4 – 147.6.

2-(Benzo[*d*]thiazol-2-yl)bicyclo[3.1.1]heptan-2-ol (179eg)



According to **TP20**, a solution of benzothiazole (**117e**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of norcamphor (**112g**, 33 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179eg** as slightly yellow solid (38 mg, 0.15 mmol, 77% yield).

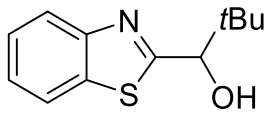
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.98 (dd, *J* = 8.1, 0.8, 1H), 7.87 (dd, *J* = 8.0, 0.9, 1H), 7.46 (ddd, *J* = 8.3, 7.2, 1.3, 1H), 7.36 (ddd, *J* = 8.3, 7.2, 1.2, 1H), 3.15 (s, 1H), 2.62 (ddd, *J* = 13.2, 4.6, 2.8, 1H), 2.56 – 2.52 (m, 1H), 2.43 (tt, *J* = 3.4, 1.6, 1H), 2.20 (ddt, *J* = 13.6, 10.3, 3.5, 1H), 2.06 (dt, *J* = 10.3, 2.0, 1H), 1.74 – 1.65 (m, 1H), 1.61 – 1.39 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 180.4, 152.9, 135.6, 126.1, 125.0, 123.1, 121.8, 81.6, 49.8, 47.3, 38.7, 37.3, 28.6, 22.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3330, 2971, 2949, 2940, 2925, 2868, 1503, 1493, 1455, 1446, 1437, 1416, 1325, 1313, 1294, 1278, 1251, 1238, 1176, 1165, 1152, 1130, 1123, 1079, 1065, 1046, 1022, 972, 953, 937, 885, 809, 756, 730, 710, 698.

MS (EI, 70 eV): *m/z* (%) = 218 (14), 217 (100), 216 (11), 199 (28), 198 (11), 189 (26), 188 (34), 178 (48), 176 (39), 175 (18), 174 (10), 163 (13), 162 (50), 149 (75), 136 (84), 135 (30), 109 (12), 108 (13).

HRMS (EI): *m/z* calc. for [$C_{14}H_{15}NOS$]: 245.0874; found 245.0871.

m.p. (°C): 94.4 – 95.8.

1-(Benzo[*d*]thiazol-2-yl)-2,2-dimethylpropan-1-ol (179ee´´)



According to **TP20**, a solution of benzothiazole (**117e**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of pivaldehyde (**112e´´**, 26 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179ee´´** as slightly yellow solid (33 mg, 0.15 mmol, 75% yield).

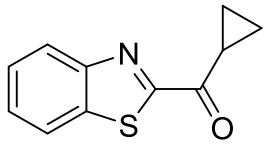
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.99 (dq, *J* = 8.1, 1.1, 1H), 7.88 (dd, *J* = 7.9, 1.4, 1H), 7.47 (ddt, *J* = 8.5, 7.4, 1.4, 1H), 7.42 – 7.33 (m, 1H), 4.73 (d, *J* = 2.0, 1H), 3.39 (s, 1H), 1.07 (d, *J* = 1.4, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 173.7, 152.4, 135.0, 126.1, 125.1, 123.0, 121.7, 80.2, 36.2, 26.0 (3C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3423, 2962, 2869, 1510, 1501, 1476, 1464, 1455, 1437, 1392, 1368, 1360, 1329, 1313, 1284, 1237, 1218, 1188, 1168, 1154, 1126, 1086, 1075, 1061, 1016, 900, 764, 757, 731, 708, 687.

MS (EI, 70 eV): *m/z* (%) = 166 (12), 165 (100), 164 (31), 136 (16), 135 (11), 57 (15).

HRMS (EI): *m/z* calc. for [$C_{12}H_{15}NOS$]: 221.0874; found 221.0878.

m.p. (°C): 104.5 – 106.9.

Benzo[*d*]thiazol-2-yl(cyclopropyl)methanone (179ef´´)



According to **TP20**, a solution of benzothiazole (**117e**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of *N*-methoxy-*N*-methylcyclopropanecarboxamide (**112f´´**, 39 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the

solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179ef´´** as slightly yellow crystals (37 mg, 0.18 mmol, 91% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 (d, *J* = 8.1, 1H), 7.98 (d, *J* = 8.1, 1H), 7.58 (ddd, *J* = 8.3, 7.2, 1.3, 1H), 7.53 (ddd, *J* = 8.2, 7.1, 1.2, 1H), 3.38 (tt, *J* = 8.0, 4.6, 1H), 1.40 – 1.36 (m, 2H), 1.23 (dq, *J* = 7.5, 3.7, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 195.2, 167.2, 153.8, 137.4, 127.7, 127.1, 125.5, 122.6, 17.5, 17.5, 13.5.

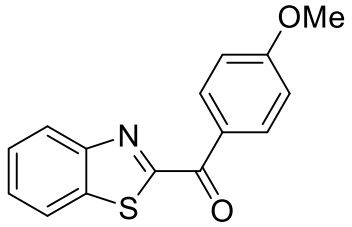
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 3049, 3012, 2924, 2854, 1738, 1668, 1626, 1592, 1550, 1486, 1462, 1456, 1443, 1427, 1414, 1381, 1316, 1277, 1238, 1213, 1184, 1163, 1117, 1094, 1070, 1036, 1013, 951, 879, 831, 806, 760, 726, 708, 694.

MS (EI, 70 eV): *m/z* (%) = 203 (11), 202 (37), 175 (37), 174 (100), 162 (11), 149 (24), 134 (16).

HRMS (EI): *m/z* calc. for [$C_{11}H_9NOS$]: 203.0405; found 203.0396.

m.p. (°C): 80.6 – 81.0.

Benzo[*d*]thiazol-2-yl(4-methoxyphenyl)methanone (179eg´´)



According to **TP20**, a solution of benzothiazole (**117e**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of *N*,*4*-dimethoxy-*N*-methylbenzamide (**112g´´**, 59 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179eg´´** as slightly yellow solid (50 mg, 0.19 mmol, 93% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.68 – 8.63 (m, 2H), 8.23 (d, *J* = 8.2, 1H), 8.01 (d, *J* = 8.0, 1H), 7.62 – 7.49 (m, 2H), 7.07 – 7.02 (m, 2H), 3.92 (d, *J* = 0.6, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 183.5, 168.0, 164.5, 154.0, 137.0, 134.0 (2C), 127.9, 127.5, 126.9, 125.7, 122.3, 114.0 (2C), 55.7.

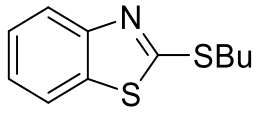
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 1628, 1593, 1569, 1554, 1509, 1490, 1455, 1438, 1425, 1322, 1300, 1273, 1260, 1240, 1177, 1129, 1115, 1065, 1025, 891, 865, 839, 820, 778, 761, 753, 724, 707, 696.

MS (EI, 70 eV): *m/z* (%) = 269 (18), 241 (33), 240 (12), 135 (100).

HRMS (EI): *m/z* calc. for [$C_{15}H_{11}NO_2S$]: 269.0510; found 269.0506.

m.p. (°C): 122.6 – 124.2.

2-(Butylthio)benzo[*d*]thiazole (179eq)



According to **TP20**, a solution of benzothiazole (**117e**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfide (**112q**, 54 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 92:2 → 95:5)) afforded the title compound **179eq** as orange oil (41 mg, 0.18 mmol, 92% yield).

According to **TP21**, a solution of benzothiazole (**117e**, 0.20 M, 0.20 mmol) and *n*-butyl disulfide (**112q**, 54 mg, 0.30 mmol, 1.50 equiv) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, -78 °C) and was subsequently injected in a flask. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 92:2 → 95:5) afforded the title compound **179eq** as yellow oil (21 mg, 0.094 mmol, 47% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.87 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.41 (td, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.29 (td, *J* = 8.3, 7.3, 1.2 Hz, 1H), 3.35 (t, *J* = 7.3 Hz, 2H), 1.87 – 1.75 (m, 2H), 1.51 (h, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

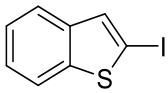
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.6, 153.5, 135.2, 126.1, 124.2, 121.6, 121.0, 33.5, 31.4, 22.1, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2928, 2872, 1456, 1426, 1308, 1275, 1238, 1074, 1018, 992, 753, 725, 704.

MS (EI, 70 eV): *m/z* (%) = 194 (10), 181 (16), 176 (75), 167 (100), 148 (11), 136 (10), 123 (11).

HRMS (EI): *m/z* calc. for [$C_{11}H_{13}NS_2$]: 223.0489; found 223.0484.

2-Iodobenzo[*b*]thiophene (179ac´´)



According to **TP20**, a solution of benzo[*b*]thiophene (**117a**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in cyclohexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of I_2 (**112c´´**, 76 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane) afforded the title compound **179ac´´** as yellow oil (33mg, 0.13 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 7.79 – 7.75 (m, 1H), 7.73 – 7.70 (m, 1H), 7.54 (d, *J* = 0.8 Hz, 1H), 7.33 – 7.26 (m, 2H).

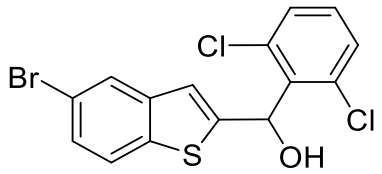
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.5, 140.9, 133.9, 124.6, 124.5, 122.4, 121.4, 78.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2924, 2872, 2855, 2361, 1728, 1463, 1459, 1378, 1286, 1270, 1161, 1122, 1072, 1040, 961, 742.

MS (EI, 70 eV): *m/z* (%) = 133 (100), 132 (17), 131 (10), 122 (11), 121 (13), 104 (18), 84 (10), 71 (45), 70 (17).

HRMS (EI): *m/z* calc. for [C_8H_5S]: 133.0112; found 133.0131 (M – I).

(5-Bromobenzo[*b*]thiophen-2-yl)(2,6-dichlorophenyl)methanol (179fi)



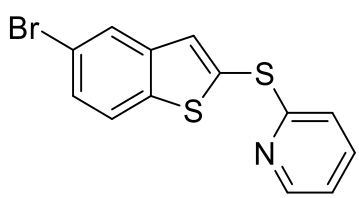
According to **TP20**, a solution of 5-bromobenzo[*b*]thiophene (**117f**, 43 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2,6-dichlorobenzaldehyde (**112i**, 53 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179fi** as yellow oil (77 mg, 0.20 mmol, 98% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 (d, *J* = 1.9 Hz, 1H), 7.60 (dt, *J* = 8.5, 0.7 Hz, 1H), 7.37 – 7.32 (m, 3H), 7.23 (dd, *J* = 7.1, 1.6 Hz, 1H), 6.81 – 6.76 (m, 2H), 3.81 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.9, 141.4, 138.5, 136.4, 135.1 (2C), 130.3, 129.6 (2C), 127.3, 126.3, 123.8, 119.7, 118.5, 70.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 1580, 1562, 1434, 1412, 1397, 1248, 1237, 1177, 1148, 1115, 1087, 1067, 1055, 1013, 971, 893, 873, 841, 795, 776, 756, 729, 718, 704.

MS (EI, 70 eV): *m/z* (%) = 388 (16), 215 (28), 214 (31), 213 (30), 212 (30), 175 (39), 173 (61), 134 (100).

HRMS (EI): *m/z* calc. for [$C_{15}H_9BrCl_2OS$]: 385.8935; found 385.8930.

2-((5-Bromobenzo[*b*]thiophen-2-yl)thio)pyridine (179fh´)



According to **TP20**, a solution of 5-bromobenzo[*b*]thiophene (**117f**, 43 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The

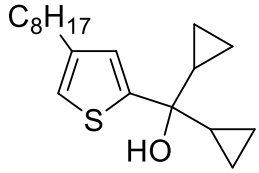
combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 1,2-di(pyridin-2-yl)disulfane (**112h´**, 66 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179fh´** as yellow oil (60 mg, 0.19 mmol, 93% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.44 (m, 1H), 7.93 (d, *J* = 1.9 Hz, 1H), 7.65 (dt, *J* = 8.6, 0.7 Hz, 1H), 7.54 (d, *J* = 0.7 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.47 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.08 – 7.03 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.1, 149.8, 142.0, 141.2, 137.2, 133.2, 132.3, 128.6, 126.6, 123.6, 121.2, 120.8, 118.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3044, 2919, 1572, 1559, 1544, 1494, 1446, 1428, 1416, 1401, 1307, 1280, 1272, 1242, 1169, 1148, 1115, 1085, 1068, 1060, 1044, 985, 970, 877, 831, 796, 754, 719, 687, 678.

MS (EI, 70 eV): *m/z* (%) = 323 (32), 322 (100), 321 (30), 320 (96), 241 (33), 164 (11), 120 (23).

HRMS (EI): *m/z* calc. for [$C_{13}H_7BrNS_2$]: 319.9203; found 319.9175 (M – H).

Dicyclopropyl(4-octylthiophen-2-yl)methanol (179gu)



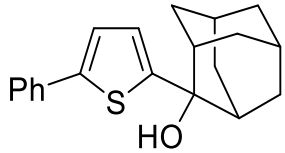
According to **TP20**, a solution of 3-octylthiophene (**117g**, 39 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (**112u**, 33 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179gu** as slightly yellow oil (40 mg, 0.13 mmol, 65% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.92 (d, *J* = 1.5 Hz, 1H), 6.79 (d, *J* = 1.3 Hz, 1H), 2.58 – 2.53 (m, 2H), 1.63 – 1.57 (m, 2H), 1.34 – 1.24 (m, 13H), 0.90 – 0.86 (m, 3H), 0.59 – 0.45 (m, 8H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.0, 142.7, 124.9, 118.7, 72.8, 32.0, 30.8, 30.5, 29.6, 29.6, 29.4, 22.8, 21.4 (2C), 14.3, 1.7 (2C), 1.0 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3009, 2955, 2924, 2870, 2854, 1465, 1378, 1299, 1183, 1157, 1133, 1109, 1052, 1024, 987, 919, 913, 839, 735.

MS (EI, 70 eV): *m/z* (%) = 278 (43), 266 (10), 265 (62), 237 (23), 224 (10), 223 (84), 193 (12), 180 (100), 175 (12), 165 (44), 139 (12), 138 (11), 137 (10), 125 (16), 111 (10), 97 (30), 91 (11), 69 (11).

HRMS (EI): *m/z* calc. for [$C_{19}H_{30}OS$]: 306.2017; found 306.2014.

2-(5-Phenylthiophen-2-yl)adamantan-2-ol (179hh)



According to **TP20**, a solution of 2-phenylthiophene (**117h**, 32 mg, 0.17 M, 0.17 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.26 M in hexane, 0.26 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179hh** as deep blue oil (42 mg, 0.14 mmol, 80% yield).

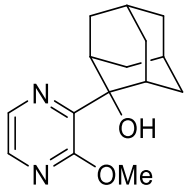
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.59 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.23 (m, 1H), 7.17 (d, *J* = 3.7 Hz, 1H), 7.03 (d, *J* = 3.7 Hz, 1H), 2.54 (dd, *J* = 3.0, 1.6 Hz, 1H), 2.43 (d, *J* = 3.1 Hz, 1H), 2.40 (d, *J* = 3.0 Hz, 2H), 2.10 – 2.06 (m, 1H), 2.03 – 1.96 (m, 2H), 1.93 (tt, *J* = 2.9, 1.3 Hz, 2H), 1.83 – 1.77 (m, 3H), 1.74 – 1.69 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.8, 143.1, 134.5, 129.0 (2C), 127.5, 125.8 (2C), 124.5, 122.6, 75.0, 47.1, 39.4, 38.2, 37.8, 35.3, 33.0, 27.5, 27.3, 27.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2900, 2853, 1720, 1701, 1599, 1498, 1464, 1446, 1388, 1352, 1314, 1283, 1258, 1224, 1210, 1172, 1156, 1115, 1101, 1071, 1058, 1043, 1035, 1028, 997, 964, 952,

933, 906, 886, 874, 841, 830, 803, 774, 753, 733, 688, 666, 637, 630, 616, 608, 604, 586, 580, 572, 551, 538, 532, 527, 516, 506, 488, 478, 471, 461, 456.

MS (EI, 70 eV): *m/z* (%) = 311 (14), 310 (65), 294 (18), 293 (88), 277 (40), 202 (10), 189 (53), 188 (12), 187 (100), 173 (31), 161 (43), 160 (16), 150 (14), 128 (16), 115 (30).

HRMS (EI): *m/z* calc. for [$C_{20}H_{22}OS$]: 310.1391; found 310.1389.

2-(3-Methoxypyrazin-2-yl)adamantan-2-ol (179ih)



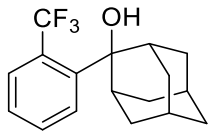
According to **TP20**, a solution 2-methoxypyrazine (**117i**, 22 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane: EtOAc = 9:1 → 7:3 → 1:1 → 3:7) afforded the title compound **179ih** as slightly yellow oil (42 mg, 0.16 mmol, 81% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11 (d, *J* = 2.7 Hz, 1H), 7.98 (d, *J* = 2.7 Hz, 1H), 4.01 (s, 3H), 3.13 (s, 1H), 2.65 (s, 2H), 2.48 – 2.34 (m, 2H), 2.10 – 1.81 (m, 3H), 1.78 – 1.71 (m, 5H), 1.67 – 1.60 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.8, 149.5, 138.7, 135.0, 77.7, 53.6, 38.0, 35.0 (2C), 34.9 (2C), 33.1 (2C), 27.4, 27.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2904, 2852, 1541, 1460, 1443, 1371, 1360, 1344, 1329, 1296, 1182, 1163, 1149, 1102, 1046, 1036, 1009, 972, 918, 841.

MS (EI, 70 eV): *m/z* (%) = 261 (11), 260 (60), 245 (12), 242 (13), 232 (36), 217 (36), 201 (14), 199 (11), 189 (16), 177 (11), 161 (17), 150 (19), 137 (23), 124 (20), 111 (100), 91 (19), 81 (10).

HRMS (EI): *m/z* calc. for [$C_{15}H_{20}N_2O_2$]: 260.1525; found 260.1517.

2-(2-(Trifluoromethyl)phenyl)adamantan-2-ol (179jh)



According to **TP20**, a solution of (trifluoromethyl)benzene (**117j**, 29 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179jh** as white crystals (25 mg, 0.08 mmol, 42% yield).

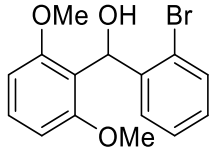
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.81 – 7.73 (m, 2H), 7.54 (td, *J* = 7.8, 1.5 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 2.72 (s, 2H), 2.45 (m, 2H), 2.29 (q, *J* = 4.2 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.82 – 1.61 (m, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.8, 131.9, 129.4, 129.13 (q, *J* = 7.4 Hz), 127.6 (q, *J* = 29.3 Hz), 127.5, 125.5 (q, *J* = 273.6 Hz), 37.6, 35.71 (q, *J* = 2.6 Hz). 35.0 (2C), 33.4 (2C), 27.2 (2C), 26.4 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3429, 2913, 2905, 2878, 2856, 1452, 1444, 1297, 1286, 1267, 1251, 1155, 1124, 1098, 1086, 1062, 1041, 1030, 1008, 996, 970, 964, 956, 935, 910, 774, 766, 757, 675.

MS (EI, 70 eV): *m/z* (%) = 278 (31), 276 (17), 256 (13), 200 (14), 173 (100), 161 (11), 155 (28), 151 (12), 145 (22), 133 (15), 131 (24), 127 (10), 123 (10), 93 (16), 91 (12), 81 (28), 80 (16), 79 (26).

HRMS (EI): *m/z* calc. for [[$C_{17}H_{19}F_3O$]: 296.1388; found 296.1384.

m.p. (°C): 68.3 – 71.3.

(2-Bromophenyl)(2,6-dimethoxyphenyl)methanol (179ch´´)



According to **TP20**, a solution of 1,3-dimethoxybenzene (**117c**, 28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2-bromobenzaldehyde (**112h´´**, 56 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179ch´´** as white powder (53 mg, 0.16 mmol, 82% yield).

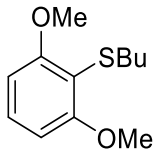
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41 – 7.35 (m, 2H), 7.25 – 7.19 (m, 3H), 6.60 (d, *J* = 8.4 Hz, 2H), 6.26 (d, *J* = 11.6 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 3.79 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.7, 144.0, 131.0 (2C), 129.3 (2C), 127.6 (2C), 120.4, 119.0, 104.6 (2C), 68.1, 56.0 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2941, 1592, 1474, 1458, 1435, 1404, 1338, 1290, 1275, 1242, 1219, 1197, 1185, 1167, 1102, 1070, 1027, 1008, 866, 841, 826, 803, 788, 770, 735, 722, 665.

MS (EI, 70 eV): *m/z* (%) = 306 (97), 304 (100), 243 (44), 225 (42), 210 (22), 197 (23), 185 (17), 182 (25), 181 (22), 171 (26), 169 (26), 167 (74), 165 (79), 152 (22), 151 (35), 149 (27), 139 (29), 137 (47), 135 (60), 122 (41), 109 (19), 107 (40), 91 (25), 77 (22).

HRMS (EI): *m/z* calc. for [$C_{15}H_{15}BrO_3$]: 322.0205; found 322.0198.

m.p. (°C): 126.5 – 128.7.

Butyl(2,6-dimethoxyphenyl)sulfane (179cq)



According to **TP20**, a solution of 1,3-dimethoxybenzene (**117c**, 28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfide (**112q**, 53 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases

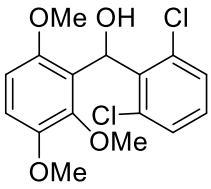
were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **179cq** as colorless oil (33 mg, 0.16 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30 – 7.22 (m, 1H), 6.59 (d, *J* = 8.4, 2H), 3.91 (s, 6H), 2.84 (dd, *J* = 7.9, 6.8, 2H), 1.56 – 1.35 (m, 4H), 0.89 (t, *J* = 7.2, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.2 (2C), 129.4, 110.6, 104.1 (2C), 56.3 (2C), 33.9, 31.8, 22.0, 13.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2871, 2836, 1579, 1467, 1430, 1378, 1291, 1267, 1246, 1172, 1102, 1060, 1033, 916, 771, 755, 748, 716.

MS (EI, 70 eV): *m/z* (%) = 226 (58), 170 (100), 168 (27), 167 (10), 155 (17), 124 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{18}O_2S$]: 226.1028; found 226.1022.

(2,6-Dichlorophenyl)(2,3,6-trimethoxyphenyl)methanol (179ki)



According to **TP20**, a solution of 1,2,4-trimethoxybenzene (**117k**, 34 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2,6-dichlorobenzaldehyde (**112i**, 53 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2 → 1:1) afforded the title compound **179ki** as slightly brown crystals (49 mg, 0.14 mmol, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 (d, *J* = 8.4 Hz, 2H), 7.07 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.57 (d, *J* = 9.0 Hz, 1H), 6.06 (d, *J* = 8.2 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.1, 148.0, 147.3, 139.4, 135.5, 129.1, 128.5, 122.8, 111.8 (2C), 106.8 (2C), 70.9, 60.8, 56.4, 56.3.

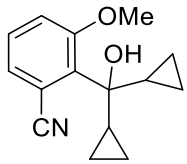
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3448, 2949, 2834, 1991, 1579, 1562, 1484, 1472, 1436, 1421, 1259, 1204, 1189, 1181, 1171, 1151, 1101, 1084, 1074, 1036, 1003, 970, 935, 909, 839, 788, 780, 772, 763, 740, 718, 702, 679.

MS (EI, 70 eV): *m/z* (%) = 344 (65), 343 (17), 342 (100), 312 (32), 310 (49), 277 (19), 275 (62), 239 (16), 217 (18), 197 (96), 195 (26), 182 (41), 181 (51), 175 (46), 173 (67), 169 (82), 167 (24), 165 (64), 161 (27), 159 (44), 154 (44), 152 (20), 139 (18), 138 (39), 137 (17).

HRMS (EI): *m/z* calc. for [$C_{16}H_{16}Cl_2O_4$]: 342.0426; found 342.0422.

m.p. (°C): 118.6 – 120.3.

2-(Dicyclopropyl(hydroxy)methyl)-3-methoxybenzonitrile (179lu)



According to **TP20**, a solution of 3-methoxybenzonitrile (**117l**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (**112u**, 33 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179lu** as slightly yellow solid (30 mg, 0.12 mmol, 62% yield).

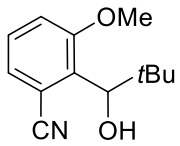
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 – 7.32 (m, 2H), 7.01 (dd, *J* = 7.6, 1.3, 1H), 3.90 (s, 3H), 1.65 – 1.55 (m, 2H), 0.69 – 0.60 (m, 2H), 0.53 (tdd, *J* = 8.7, 6.1, 4.5, 2H), 0.27 – 0.14 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.3, 154.2, 139.0, 130.7, 130.2, 115.6, 113.8, 88.3, 55.7, 17.3 (2C), 1.9 (2C), -0.1 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3232, 3006, 1744, 1665, 1604, 1490, 1465, 1436, 1378, 1349, 1326, 1276, 1240, 1226, 1213, 1184, 1174, 1126, 1106, 1080, 1069, 1045, 1024, 1014, 989, 967, 947, 919, 894, 874, 828, 820, 800, 783, 762, 740, 669.

MS (EI, 70 eV): *m/z* (%) = 216 (10), 215 (23), 203 (23), 202 (100), 160 (26).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}NO_2$]: 243.1259; found 243.1250.

m.p. (°C): 65.6 – 66.6.

2-(1-Hydroxy-2,2-dimethylpropyl)-3-methoxybenzonitrile (179le´´)



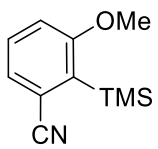
According to **TP20**, a solution of 3-methoxybenzonitrile (**117l**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of pivaldehyde (**112e´´**, 26 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **179le´´** as yellow oil (33 mg, 0.15 mmol, 75% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41 (d, *J* = 7.0, 2H), 6.99 (dd, *J* = 6.8, 2.1, 1H), 5.24 (s, 1H), 3.84 (s, 3H), 0.97 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.8, 154.9, 133.7, 132.8, 130.5, 115.8, 113.6, 90.4, 55.3, 38.0, 26.5 (3C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2870, 1761, 1683, 1599, 1489, 1464, 1442, 1397, 1364, 1326, 1312, 1299, 1266, 1219, 1192, 1175, 1102, 1066, 1052, 1034, 986, 963, 939, 922, 902, 861, 832, 803, 776, 748, 730, 659.

MS (EI, 70 eV): *m/z* (%) = 164 (10), 163 (100), 162 (95), 148 (13), 144 (32), 134 (25), 132 (12), 116 (20).

HRMS (EI): *m/z* calc. for [$C_{13}H_{17}NO_2$]: 219.1259; found 219.1252.

3-Methoxy-2-(trimethylsilyl)benzonitrile (179li´´)



According to **TP20**, a solution of 3-methoxybenzonitrile (**117l**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of TMSCl (**112i´´**, 40 µL, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179li´´** as colorless crystals (36 mg, 0.18 mmol, 88% yield).

According to **TP22,** a solution of 3-methoxybenzonitrile (**117l**, 27 mg, 0.20 mmol, 1.00 equiv) in THF (1.00 mL) and a solution of KDA (0.30 M in hexane) were prepared. The KDA solution (**112i´´**, 1.00 mL, 0.30 mmol, 1.50 equiv) was slowly added to **117l** at -78 °C and the mixture was stirred for 5 min. TMSCl (**112i´´**, 45 mg, 0.30 mmol, 1.50 equiv) was added to the reaction mixture and stirring at -78 °C was continued for 30 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179li´´** as colorless crystals (32 mg, 0.16 mmol, 78% yield).

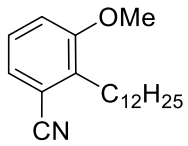
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.38 (t, *J* = 8.0, 1H), 7.28 (dd, *J* = 7.6, 1.0, 1H), 7.02 (dd, *J* = 8.4, 1.0, 1H), 3.82 (s, 3H), 0.41 (d, *J* = 1.3, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.6, 131.9, 131.0, 127.1, 120.3, 118.3, 114.0, 55.5, 0.8 (3C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3011, 2978, 2950, 2903, 2222, 1580, 1562, 1464, 1450, 1441, 1423, 1413, 1393, 1302, 1292, 1265, 1249, 1241, 1188, 1122, 1068, 1053, 895, 840, 789, 760, 744, 715, 689.

MS (EI, 70 eV): *m/z* (%) = 190 (55), 178 (16), 160 (100).

HRMS (EI): *m/z* calc. for [$C_{11}H_{15}NOSi$]: 205.0923; found 205.0917.

m.p. (°C): 95.2 – 100.1.

2-Dodecyl-3-methoxybenzonitrile (179lj´´)



According to **TP20**, a solution of 3-methoxybenzonitrile (**117l**, 27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (**112j´´**, 89 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **179lj´´** as white crystals (32 mg, 0.11 mmol, 53% yield).

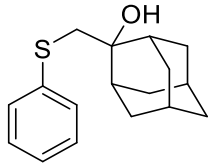
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.17 (m, 2H), 7.03 (dd, *J* = 7.9, 1.6, 1H), 3.84 (s, 3H), 2.90 – 2.78 (m, 2H), 1.61 – 1.53 (m, 2H), 1.26 (m, 19H), 0.90 – 0.85 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.7, 136.1, 127.5, 124.5, 118.3, 114.6, 113.6, 55.8, 32.1, 29.9, 29.8, 29.8, 29.8, 29.7 (2C), 29.6, 29.5, 29.1, 22.8, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2918, 2871, 2848, 2222, 1705, 1700, 1580, 1466, 1440, 1377, 1325, 1272, 1254, 1231, 1171, 1118, 1083, 1056, 1028, 788, 737, 724, 680.

MS (EI, 70 eV): *m/z* (%) = 216 (16), 202 (20), 188 (23), 175 (11), 174 (100), 172 (21), 161 (12), 160 (27), 159 (10), 147 (20), 146 (82), 132 (18), 118 (25), 116 (37), 89 (12).

HRMS (EI): *m/z* calc. for [$C_{20}H_{31}NO$]: 301.2406; found 301.2404.

m.p. (°C): 46.4 – 46.6.

2-((Phenylthio)methyl)adamantan-2-ol (183ah)



According to **TP20**, a solution of thioanisole (**180a**, 25 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.300 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream

passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.300 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **183ah** as slightly yellow crystals (54 mg, 0.20 mmol, 99% yield).

According to **TP22,** a solution of thioanisole (**180a**, 25 mg, 0.20 mmol, 1.00 equiv) in THF (1.00 mL) and a solution of KDA (0.30 M in hexane) were prepared. The KDA solution (1.00 mL, 0.30 mmol, 1.50 equiv) was slowly added to **180a** at -78 °C and the mixture was stirred for 5 min. Adamantanone (**112h**, 45 mg, 0.300 mmol, 1.50 equiv) was added to the reaction mixture and stirring at -78 °C was continued for 30 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **183ah** as slightly yellow crystals (52 mg, 0.19 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.48 – 7.40 (m, 2H), 7.32 – 7.23 (m, 2H), 7.23 – 7.14 (m, 1H), 3.39 (s, 2H), 2.39 (s, 1H), 2.31 – 2.20 (m, 2H), 1.91 – 1.65 (m, 10H), 1.59 – 1.50 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.1, 130.4 (2C), 129.1 (2C), 126.5, 74.8, 45.5, 38.3, 37.1 (2C), 34.6 (2C), 33.1 (2C), 27.4, 27.4.

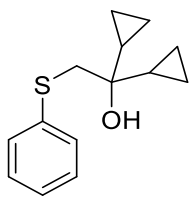
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2941, 2903, 2853, 2361, 1478, 1455, 1437, 1428, 1349, 1196, 1158, 1121, 1093, 1088, 1054, 1044, 1024, 1005, 996, 928, 730, 711, 698, 687, 668.

MS (EI, 70 eV): *m/z* (%) = 151 (34), 124 (100), 91 (18).

HRMS (EI): *m/z* calc. for [$C_{17}H_{22}OS$]: 274.1391; found 274.1388.

m.p. (°C): 69.3– 71.7.

1,1-Dicyclopropyl-2-(phenylthio)ethan-1-ol (183au)



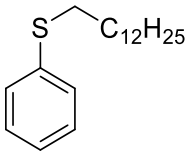
According to **TP20**, a solution of thioanisole (**180a**, 25 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (**112u**, 33 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **183au** as colorless oil (34 mg, 0.15 mmol, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 – 7.37 (m, 2H), 7.29 – 7.23 (m, 2H), 7.18 – 7.13 (m, 1H), 3.28 (s, 2H), 1.74 (s, 1H), 0.91 (tt, *J* = 8.4, 5.4, 2H), 0.53 – 0.41 (m, 4H), 0.41 – 0.33 (m, 2H), 0.33 – 0.25 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.6, 129.3 (2C), 129.0 (2C), 126.1, 70.5, 48.1, 18.7 (2C), 1.2 (2C), -0.0 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3490, 3084, 3007, 2921, 1583, 1480, 1465, 1439, 1424, 1382, 1310, 1231, 1169, 1158, 1111, 1088, 1070, 1048, 1022, 996, 930, 909, 876, 825, 778, 737, 690, 672.

MS (EI, 70 eV): *m/z* (%) = 123 (100), 122 (13), 111 (60), 69 (53), 41 (15).

HRMS (EI): *m/z* calc. for [$C_{14}H_{18}OS$]: 234.1078; found 234.1077.

Phenyl(tridecyl)sulfane (183aj´´)



According to **TP20**, a solution of thioanisole (**180a**, 25 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (**112j´´**, 89 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical

purification (silica gel, isohexane) afforded the title compound **183aj´´** as slightly yellow crystals (36 mg, 0.12 mmol, 62% yield).

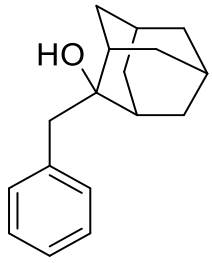
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35 – 7.24 (m, 4H), 7.19 – 7.12 (m, 1H), 2.92 (t, *J* = 7.5 Hz, 2H), 1.69 – 1.59 (m, 2H), 1.46 – 1.35 (m, 2H), 1.32 – 1.14 (m, 18H), 0.93 – 0.85 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.2, 129.0 (2C), 128.9 (2C), 125.7, 33.6, 32.1, 29.8, 29.8 (2C), 29.3, 29.6, 29.5, 29.3, 29.3, 29.0, 22.9, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 2953, 2916, 2871, 2848, 1585, 1480, 1473, 1463, 1438, 1094, 1072, 1023, 891, 729, 718, 702, 688.

MS (EI, 70 eV): *m/z* (%) = 292 (39), 123 (14), 110 (100).

HRMS (EI): *m/z* calc. for [$C_{19}H_{32}S$]: 292.2225; found 292.2221.

m.p. (°C): 40.2 – 42.4.

2-Benzyladamantan-2-ol (184bh)



According to **TP20**, toluene (**118b**) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.00 equiv) was prepared. The solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.00 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 99:1 → 95:5) afforded the title compound **184bh** as white solid (50 mg, 0.21 mmol, 69% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.28 – 7.20 (m, 2H), 7.17 (td, *J* = 6.2, 1.9 Hz, 3H), 2.92 (s, 2H), 2.12 – 2.01 (m, 4H), 1.88 – 1.82 (m, 1H), 1.76 – 1.69 (m, 3H), 1.62 (dt, *J* = 14.0, 3.2 Hz, 4H), 1.49 – 1.41 (m, 2H), 1.37 (s, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.4, 130.8 (2C), 128.4 (2C), 126.1, 74.8, 44.0, 38.6, 37.0 (2C), 34.7 (2C), 33.1 (2C), 27.6, 27.5.

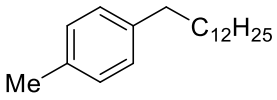
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3545, 3501, 2934, 2899, 2851, 1493, 1451, 1442, 1360, 1352, 1331, 1295, 1282, 1157, 1149, 1120, 1114, 1100, 1082, 1054, 1041, 1028, 1021, 1006, 987, 930, 891, 868, 802, 760, 701, 666.

MS (EI, 70 eV): *m/z* (%) = 152 (12), 151 (100), 150 (14), 91 (23).

HRMS (EI): *m/z* calc. for [$C_{17}H_{20}O$]: 240.1514; found 240.1508 (M – H_2).

m.p. (°C): 64.0 – 65.3.

1-Methyl-4-tridecylbenzene (184cj´´)



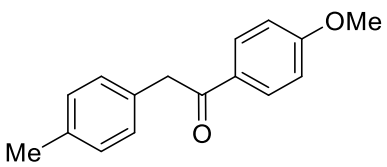
According to **TP20**, *p*-xylene (**118c**) (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.00 equiv) were prepared. The solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (**112j´´**, 89 mg, 0.30 mmol, 1.00 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane) afforded the title compound **184cj´´** as colorless oil (82 mg, 0.29 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.11 (d, *J* = 1.3, 4H), 2.63 – 2.54 (m, 2H), 2.35 (s, 3H), 1.67 – 1.57 (m, 2H), 1.29 (d, *J* = 2.4, 20H), 0.92 (t, *J* = 6.8, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.0, 135.1, 129.0 (2C), 128.4 (2C), 35.7, 32.1, 31.9, 29.9, 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 22.9, 21.2, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2922, 2853, 1516, 1465, 1378, 805, 721.

MS (EI, 70 eV): *m/z* (%) = 147 (10), 106 (29), 105 (100), 91 (18).

HRMS (EI): *m/z* calc. for [$C_{20}H_{34}$]: 274.2661; found 274.2665.

1-(4-Methoxyphenyl)-2-(*p*-tolyl)ethan-1-one (184cg´´)



According to **TP20**, *p*-xylene (**118c**) (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.00 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of *N*,*4*-dimethoxy-*N*-methylbenzamide (**112g´´**, 59 mg, 0.30 mmol, 1.00 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **184cg´´** as white crystals (69 mg, 0.29 mmol, 96% yield).

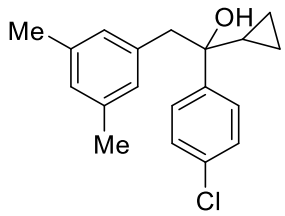
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 – 7.96 (m, 2H), 7.20 – 7.10 (m, 4H), 6.96 – 6.90 (m, 2H), 4.19 (s, 2H), 3.86 (s, 3H), 2.32 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.6, 163.6, 136.5, 132.0, 131.1 (2C), 129.8, 129.5 (2C), 129.3 (2C), 113.9 (2C), 55.6, 45.0, 21.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2920, 2904, 2854, 2842, 1678, 1596, 1576, 1517, 1507, 1459, 1452, 1441, 1418, 1334, 1321, 1304, 1260, 1254, 1228, 1221, 1209, 1199, 1177, 1165, 1122, 1108, 1027, 1011, 995, 987, 950, 915, 859, 844, 828, 818, 802, 774, 737.

MS (EI, 70 eV): *m/z* (%) = 135 (100).

HRMS (EI): *m/z* calc. for [$C_{16}H_{16}O_2$]: 240.1150; found 240.1147.

m.p. (°C): 91.5 – 91.7.

1-(4-Chlorophenyl)-1-cyclopropyl-2-(3,5-dimethylphenyl)ethan-1-ol (184ai´)



According to **TP20**, mesitylene (**118a**) (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.00 equiv) were prepared. The solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of (4-chlorophenyl)(cyclopropyl)methanone (**112i´**, 54 mg, 0.30 mmol, 1.00 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification

(silica gel, isohexane:EtOAc = 98:2) afforded the title compound **184ai´** as colorless crystals (80 mg, 0.28 mmol, 92% yield).

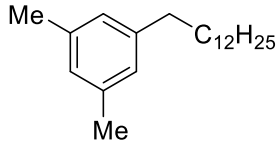
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 – 7.34 (m, 2H), 7.34 – 7.27 (m, 2H), 6.86 (s, 1H), 6.62 (s, 2H), 3.10 (d, *J* = 2.3, 2H), 2.23 (s, 6H), 1.66 (s, 1H), 1.36 – 1.26 (m, 1H), 0.50 – 0.43 (m, 1H), 0.39 – 0.25 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.3, 137.7 (2C), 135.8, 132.5, 128.6 (2C), 128.5, 128.0 (2C), 127.4 (2C), 74.3, 49.1, 21.4 (2C), 21.3, 2.0, 0.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3347, 3005, 2958, 2947, 2926, 2857, 1605, 1491, 1467, 1442, 1398, 1373, 1350, 1318, 1289, 1240, 1139, 1118, 1104, 1090, 1062, 1049, 1016, 996, 967, 945, 921, 905, 855, 831, 812, 729, 710, 672.

MS (EI, 70 eV): *m/z* (%) = 183 (29), 181 (100), 140 (22), 139 (77), 120 (54), 111 (10), 105 (14).

HRMS (EI): *m/z* calc. for [$C_{19}H_{21}ClO$]: 300.1281; found 300.1277.

m.p. (°C): 70.0 – 73.1.

1,3-Dimethyl-5-tridecylbenzene (184aj´´)



According to **TP20**, mesitylene (**118a**) (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.00 equiv) were prepared. The solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (**112j´´**, 89 mg, 0.30 mmol, 1.00 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane) afforded the title compound **184aj´´** as colorless oil (80 mg, 0.28 mmol, 89% yield). A scale-up of the reaction was performed increasing the volume of the loading coils ($V._{inj.}$ = 10 mL) as well as the run-time resulting in a 3.00 mmol scale reaction, which afforded the title compound as colorless oil (805 mg, 2.79 mmol, 93%).

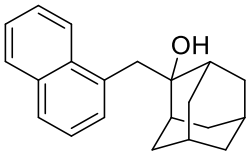
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.84 (d, *J* = 5.1, 3H), 2.63 – 2.47 (m, 2H), 2.31 (d, *J* = 3.7, 6H), 1.70 – 1.54 (m, 2H), 1.29 (m, 20H), 0.95 – 0.85 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.1, 137.8 (2C), 127.3, 126.4 (2C), 36.0, 32.1, 31.8, 29.9, 29.9 (2C), 29.8, 29.8, 29.7, 29.6, 29.5 (2C), 22.9, 21.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2922, 2853, 1607, 1465, 1377, 842, 721, 702.

MS (EI, 70 eV): *m/z* (%) = 133 (13), 121 (10), 120 (100), 119 (66), 105 (63), 91 (14).

HRMS (EI): *m/z* calc. for [$C_{21}H_{36}$]: 288.2817; found 288.2811.

2-(Naphthalen-1-ylmethyl)adamantan-2-ol (184eh)



According to **TP20**, a solution of 1-methylnaphthalene (**118e**, 28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 98.5:1.5) afforded the title compound **184eh** as white solid (50 mg, 0.18 mmol, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.29 (dd, *J* = 8.5, 1.2, 1H), 7.84 (dd, *J* = 8.0, 1.6, 1H), 7.77 (dt, *J* = 8.2, 1.1, 1H), 7.55 – 7.35 (m, 4H), 3.51 (s, 2H), 2.21 (ddd, *J* = 27.6, 13.1, 3.1, 4H), 1.99 (t, *J* = 3.2, 1H), 1.89 (ddt, *J* = 8.4, 3.9, 1.9, 4H), 1.78 (dt, *J* = 22.6, 3.4, 3H), 1.54 (ddd, *J* = 12.5, 3.0, 1.5, 2H), 1.16 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 134.2, 133.9, 133.9, 129.0, 128.7, 127.5, 126.0, 125.7, 125.6, 125.2, 75.9, 39.6, 38.6, 37.4 (2C), 35.0 (2C), 33.2 (2C), 27.7, 27.5.

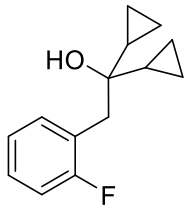
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3562, 2946, 2934, 2901, 2874, 2847, 1594, 1508, 1473, 1461, 1451, 1440, 1396, 1383, 1360, 1351, 1331, 1284, 1272, 1230, 1219, 1168, 1154, 1140, 1126, 1101, 1070, 1041, 1027, 1018, 1002, 986, 944, 929, 893, 864, 857, 807, 782, 742, 726.

MS (EI, 70 eV): *m/z* (%) = 275 (14), 274 (59). 151 (50), 141 (100), 140 (30).

HRMS (EI): *m/z* calc. for [$C_{21}H_{24}O$]: 292.1827; found 292.1819.

m.p. (°C): 98.5 – 102.7.

1,1-Dicyclopropyl-2-(2-fluorophenyl)ethan-1-ol (184qu)



According to **TP20**, a solution of 1-fluoro-2-methylbenzene (**118q**, 22 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (**112u**, 33 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **184qu** as colorless oil (29 mg, 0.13 mmol, 66% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.25 – 7.20 (m, 1H), 7.07 (dt, *J* = 7.6, 1.3, 1H), 7.05 – 7.01 (m, 1H), 6.96 – 6.89 (m, 1H), 2.87 (s, 2H), 0.89 (s, 1H), 0.81 – 0.69 (m, 2H), 0.42 – 0.33 (m, 6H), 0.32 – 0.25 (m, 2H).

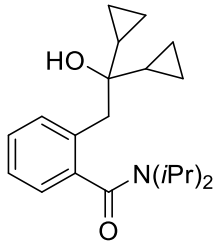
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.9 (d, *J* = 244.6), 140.8 (d, *J* = 7.3), 129.6 (d, *J* = 8.3), 126.9 (d, *J* = 2.7), 118.1 (d, *J* = 20.8), 113.5 (d, *J* = 21.0), 71.6, 48.9 (d, *J* = 1.7), 18.8 (2C), 1.7 (2C), 0.0 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3600, 3588, 3485, 3465, 3450, 3085, 3010, 2920, 2859, 1616, 1587, 1487, 1448, 1381, 1253, 1206, 1141, 1120, 1101, 1077, 1044, 1024, 996, 951, 925, 915, 891, 872, 828, 787, 758, 744, 707.

MS (EI, 70 eV): *m/z* (%) = 202 (12), 187 (33), 174 (10), 173 (36), 172 (12), 171 (15), 170 (10), 165 (12), 161 (28), 160 (15), 159 (84), 153 (21), 152 (25), 147 (14), 146 (77), 133 (50), 111 (100), 109 (61), 91 (15), 83 (21), 77 (10), 69 (77), 41 (15).

HRMS (EI): *m/z* calc. for [$C_{14}H_{17}FO$]: 220.1263; found 202.1151 [M – H_2O].

2-(2,2-Dicyclopropyl-2-hydroxyethyl)-*N*,*N*-diisopropylbenzamide (184ku)



According to **TP20**, a solution of *N*,*N*-diisopropyl-2-methylbenzamide (**118k**, 44 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, -40 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (**112u**, 33 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **184ku** as colorless oil (58 mg, 0.18 mmol, 88% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.49 – 7.46 (m, 1H), 7.29 (td, *J* = 7.6, 1.5, 1H), 7.20 (td, *J* = 7.5, 1.3, 1H), 7.08 (dd, *J* = 7.6, 1.5, 1H), 3.68 (p, *J* = 6.7, 1H), 3.52 (p, *J* = 6.8, 1H), 2.97 – 2.82 (m, 2H), 1.60 (d, *J* = 6.8, 3H), 1.53 (d, *J* = 6.8, 3H), 1.13 (d, *J* = 6.6, 3H), 1.08 (d, *J* = 6.7, 3H), 0.93 (tt, *J* = 8.2, 5.6, 1H), 0.83 – 0.77 (m, 1H), 0.63 – 0.55 (m, 1H), 0.41 (dtd, *J* = 9.2, 5.4, 3.6, 1H), 0.35 – 0.15 (m, 6H).

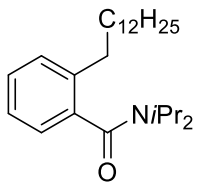
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 170.6, 144.5, 138.8, 134.4, 130.1, 127.5, 126.4, 124.8, 120.4, 51.0, 45.8, 21.0, 20.9, 20.6, 20.4, 14.2, 13.1, 6.2, 5.9, 5.9, 5.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 2965, 2927, 2856, 1630, 1597, 1480, 1449, 1434, 1369, 1336, 1233, 1209, 1186, 1163, 1154, 1136, 1112, 1079, 1032, 1022, 929, 895, 878, 842, 830, 759, 686.

MS (EI, 70 eV): *m/z* (%) = 312 (24), 311 (100), 226 (27), 184 (10), 43 (30).

HRMS (EI): *m/z* calc. for [$C_{21}H_{31}NO_2$]: 329.2355; found 311.2239 [M – H_2O].

***N*,*N*-Diisopropyl-2-tridecylbenzamide (184kj´´)**



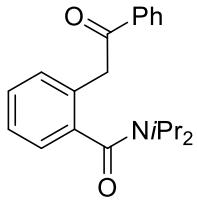
According to **TP20**, a solution of *N*,*N*-diisopropyl-2-methylbenzamide (**118k**, 44 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, -40 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (**112j´´**, 89 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 99:1) afforded the title compound **184kj´´** as colorless oil (58 mg, 0.15 mmol, 75% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.28 – 7.21 (m, 2H), 7.16 (td, *J* = 7.1, 1.9, 1H), 7.08 (dd, *J* = 7.5, 1.4, 1H), 3.68 (hept, *J* = 6.7, 1H), 3.50 (hept, *J* = 6.8, 1H), 2.59 (dd, *J* = 8.7, 7.5, 2H), 1.74 – 1.63 (m, 2H), 1.57 (dd, *J* = 6.8, 1.8, 6H), 1.37 – 1.21 (m, 19H), 1.10 (dd, *J* = 9.7, 6.7, 6H), 0.91 – 0.84 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 170.7, 139.0, 138.3, 129.4, 128.2, 125.8, 125.0, 50.8, 45.8, 33.1, 32.1, 31.2, 30.0, 29.8, 29.8 (2C), 29.8 (2C), 29.6, 29.5, 22.8, 20.9, 20.9, 20.8, 20.6, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2923, 2853, 1633, 1449, 1434, 1377, 1370, 1333, 1213, 1204, 1162, 1153, 1135, 1032, 771, 748, 721.

MS (EI, 70 eV): *m/z* (%) = 388 (10), 387 (42), 386 (31), 345 (25), 344 (100), 288 (24), 287 (85), 286 (22), 232 (14), 219 (10), 204 (36), 176 (10), 145 (14), 132 (13), 129 (13), 117 (12), 91 (14), 86 (15), 43 (10).

HRMS (EI): *m/z* calc. for [$C_{26}H_{45}NO$]: 387.3501; found 387.3498.

***N*,*N*-Diisopropyl-2-(2-oxo-2-phenylethyl)benzamide (184kk´´)**



According to **TP20**, a solution of *N*,*N*-diisopropyl-2-methylbenzamide (**118k**, 44 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 4 mL reactor tube (24 s, -40 °C) and was subsequently injected in a flask containing a stirred solution of *N*-methoxy-*N*-methylbenzamide (**112k´´**, 50 mg,

0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **184kk´´** as slightly yellow crystals (60 mg, 0.19 mmol, 93% yield).

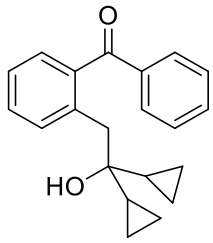
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.08 – 8.02 (m, 2H), 7.59 – 7.53 (m, 1H), 7.49 – 7.43 (m, 2H), 7.30 (ddd, *J* = 11.1, 7.3, 1.6, 2H), 7.24 – 7.17 (m, 2H), 4.65 – 4.19 (m, 2H), 3.82 (p, *J* = 6.6, 1H), 3.42 (p, *J* = 6.8, 1H), 1.52 (d, *J* = 6.8, 3H), 1.35 (d, *J* = 6.8, 3H), 1.12 (d, *J* = 6.7, 3H), 1.01 (d, *J* = 6.6, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 197.6, 170.4, 138.5, 136.6, 133.3, 131.8, 131.4, 128.8 (2C), 128.6, 128.6 (2C), 126.8, 125.1, 51.1, 45.9, 42.5, 20.9, 20.7, 20.6, 20.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2993, 2966, 2931, 2916, 2856, 1687, 1619, 1595, 1578, 1490, 1470, 1447, 1438, 1417, 1377, 1364, 1339, 1326, 1262, 1215, 1201, 1185, 1159, 1136, 1110, 1080, 1030, 993, 911, 851, 834, 795, 768, 752, 735, 700, 682, 658.

MS (EI, 70 eV): *m/z* (%) = 324 (12), 323 (47), 322 (37), 321 (10), 224 (23), 223 (100), 222 (38), 218 (17), 196 (16), 195 (99), 194 (23), 177 (14), 165 (13), 118 (10), 105 (88), 86 (30), 77 (24), 58 (14).

HRMS (EI): *m/z* calc. for [$C_{21}H_{25}NO_2$]: 323.1885; found 323.1884.

m.p. (°C): 105.0 – 108.4.

(2-(2,2-Dicyclopropyl-2-hydroxyethyl)phenyl)(phenyl)methanone (184ru)



According to **TP20**, a solution of phenyl(*o*-tolyl)methanone (**118r**, 39 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.18 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (**112u**, 33 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash

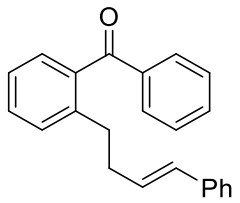
chromatographical purification (silica gel, isohexane:EtOAc = 98:2) afforded the title compound **184ru** as a yellow oil (55 mg, 0.18 mmol, 90% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.81 – 7.71 (m, 2H), 7.63 – 7.55 (m, 2H), 7.45 (m, 3H), 7.34 (dd, *J*=7.7, 1.3, 1H), 7.27 (td, *J*=7.7, 1.1, 1H), 4.00 (s, 1H), 3.04 (s, 2H), 0.90 – 0.81 (m, 2H), 0.49 – 0.41 (m, 2H), 0.41 – 0.27 (m, 4H), 0.27 – 0.17 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 199.8, 138.4, 138.4, 138.3, 133.9, 133.4, 130.9 (2C), 130.5, 130.37, 128.4 (2C), 125.4, 70.7, 45.6, 19.7 (2C), 0.6 (2C), 0.3 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3397, 3008, 1646, 1598, 1580, 1570, 1448, 1418, 1316, 1293, 1268, 1238, 1180, 1156, 1024, 1008, 940, 930, 906, 878, 826, 762, 728, 711, 701.

MS (EI, 70 eV): *m/z* (%) = 289 (25), 288 (100), 273 (57), 259 (13), 229 (16), 215 (18), 201 (10), 196 (10), 195 (33), 194 (16), 178 (15), 165 (34), 153 (11), 141 (13), 115 (12), 105 (35), 91 (12), 83 (10), 82 (11), 77 (18), 71 (16), 69 (13), 57 (15, 43 (10).

HRMS (EI): *m/z* calc. for [$C_{21}H_{22}O_2$]: 306.1620; found 288.1517 [M – H_2O].

Phenyl(2-(4-phenylbut-3-en-1-yl)phenyl)methanone (184rl´´)



According to **TP20**, a solution of phenyl(*o*-tolyl)methanone (**118r**, 39 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.18 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of cinnamyl bromide (**112l´´**, 59 mg, 0.30 mmol, 1.50 equiv) and CuCN·2LiCl (1.0 M in THF, 10 mol%) in THF. Stirring was continued for 10 min at -40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 →99:1) afforded the title compound **184rl´´** as colorless oil (45 mg, 0.14 mmol, 72% yield).

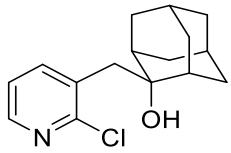
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.85 – 7.78 (m, 2H), 7.59 (t, J=7.4, 1H), 7.44 (t, J=7.7, 3H), 7.39 (d, J=7.3, 1H), 7.35 – 7.29 (m, 2H), 7.28 (d, J=3.8, 3H), 7.20 (dt, J=9.1, 4.6, 2H), 6.31 (dt, J=15.8, 1.4, 1H), 6.15 (dt, J=15.8, 6.8, 1H), 2.93 – 2.84 (m, 2H), 2.54 – 2.45 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 198.8, 140.9, 138.7, 137.9, 137.7, 133.3, 130.6, 130.5, 130.4, 130.4 (2C), 129.8, 128.8, 128.6 (4C), 127.0, 126.1 (2C), 125.5, 35.2, 33.3,
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3025, 2928, 1662, 1597, 1579, 1493, 1448, 1314, 1285, 1266, 1179, 1153, 965, 926, 762, 743, 709, 698.

MS (EI, 70 eV): *m/z* (%) = 221 (22), 195 (27), 194 (14), 193 (12), 192 (45), 165 (18), 118 (10), 117 (100), 115 (25), 104 (11), 90 (27), 85 (15), 71 (18), 57 (18).

HRMS (EI): *m/z* calc. for [$C_{23}H_{20}O$]: 312.1514; found 312.1520.

2-((2-Chloropyridin-3-yl)methyl)adamantan-2-ol (184sh)



According to **TP20**, a solution of 2-chloro-3-methylpyridine (**118s**, 26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (**112h**, 45 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 92.5:7.5) afforded the title compound **184sh** as white crystals (42 mg, 0.15 mmol, 75% yield).

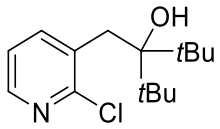
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.99 – 7.92 (m, 1H), 7.39 (dq, *J* = 7.0, 1.4 Hz, 1H), 6.71 (dd, *J* = 7.1, 5.2 Hz, 1H), 3.10 (t, *J* = 1.2 Hz, 2H), 2.45 – 2.38 (m, 2H), 1.94 (t, *J* = 2.9 Hz, 2H), 1.90 – 1.87 (m, 1H), 1.87 – 1.72 (m, 7H), 1.69 – 1.60 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.3, 146.5, 133.4, 120.2, 115.9, 91.1, 38.3, 37.6, 37.2 (2C), 34.5 (2C), 33.1 (2C), 26.7, 26.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2915, 2903, 2882, 2851, 1743, 1605, 1595, 1456, 1438, 1419, 1381, 1360, 1350, 1321, 1305, 1290, 1270, 1249, 1236, 1221, 1185, 1156, 1096, 1066, 1059, 1046, 1020, 982, 972, 958, 922, 901, 894, 873, 866, 827, 795, 775, 752, 740.

MS (EI, 70 eV): *m/z* (%) = 242 (31), 240 (44), 225 (17), 224 (100).

HRMS (EI): *m/z* calc. for [$C_{16}H_{20}ON$]: 242.1545; found 242.1497 (M – Cl).

m.p. (°C): 141.2 – 143.6.

3-((2-Chloropyridin-3-yl)methyl)-2,2,4,4-tetramethylpentan-3-ol (184sm´´)



According to **TP20**, a solution of 2-chloro-3-methylpyridine (**118s**, 26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 2,2,4,4-tetramethylpentan-3-one (**112m´´**, 43 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 92.5:7.5) afforded the title compound **184sm´´** slightly brown crystals (41 mg, 0.15 mmol, 76% yield).

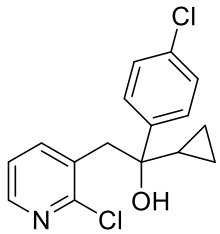
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.35 (dq, *J* = 7.1, 1.5 Hz, 1H), 6.68 (dd, *J* = 7.2, 5.2 Hz, 1H), 3.18 (d, *J* = 1.3 Hz, 2H), 1.69 (s, 1H), 1.09 (s, 18H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 169.1, 146.7, 132.6, 121.7, 115.7, 96.9, 42.1 (2C), 33.7, 28.3 (6C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 2926, 1744, 1602, 1492, 1476, 1458, 1424, 1402, 1392, 1369, 1342, 1294, 1264, 1248, 1220, 1180, 1171, 1044, 943, 921, 892, 782, 732.

MS (EI, 70 eV): *m/z* (%) = 176 (15), 120 (100).

HRMS (EI): *m/z* calc. for [$C_{11}H_{15}NO$]: 177.1154; found 177.1104 (M – C_4H_9Cl).

m.p. (°C): 81.7 – 84.3.

1-(4-Chlorophenyl)-2-(2-chloropyridin-3-yl)-1-cyclopropylethan-1-ol (184si´)



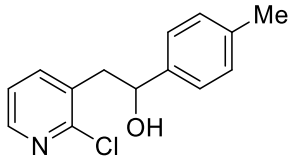
According to **TP20**, a solution of 2-chloro-3-methylpyridine (**118s**, 26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of (4-chlorophenyl)(cyclopropyl)methanone (**112i´**, 54 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 92.5:7.5) afforded the title compound **184si´** as brown oil (52 mg, 0.17 mmol, 96% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01 (dd, *J* = 5.2, 1.6, 1H), 7.48 – 7.38 (m, 3H), 7.35 – 7.28 (m, 2H), 6.78 (dd, *J* = 7.2, 5.2, 1H), 3.57 – 3.36 (m, 2H), 1.42 (tt, *J* = 7.7, 5.9, 1H), 1.25 (s, 1H), 0.62 – 0.37 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.2, 146.8, 143.9, 133.8, 133.3, 128.6 (2C), 126.7 (2C), 119.8, 117.0, 88.4, 41.5, 22.3, 1.9, 1.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 3009, 2924, 2853, 1712, 1641, 1599, 1550, 1490, 1460, 1420, 1400, 1335, 1294, 1247, 1232, 1184, 1104, 1091, 1063, 1045, 1025, 1011, 971, 909, 887, 823, 781, 758, 728, 716.

MS (EI, 70 eV): *m/z* (%) = 273 (20), 272 (18), 271 (74), 270 (52), 256 (20), 244 (31), 242 (98), 236 (35), 232 (31), 230 (100), 217 (26), 208 (35), 207 (18), 195 (18), 167 (69), 166 (33), 165 (18), 152 (22), 146 (17), 139 (25), 128 (42), 120 (20), 115 (18), 108 (19).

HRMS (EI): *m/z* calc. for [$C_{16}H_{15}Cl_2NO$]: 307.0531; found 271.0761 [M–HCl].

2-(2-Chloropyridin-3-yl)-1-(*p*-tolyl)ethan-1-ol (184sj)



According to **TP20**, a solution of 2-chloro-3-methylpyridine (**118s**, 26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 4-methylbenzaldehyde (**112j**, 36 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the

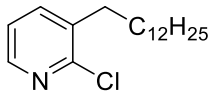
reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 92.5:7.5) afforded the title compound **184sj** as yellow oil (60 mg, 0.20 mmol, 97% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.12 – 7.94 (m, 1H), 7.46 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.81 (dd, *J* = 7.2, 5.2 Hz, 1H), 5.79 (dd, *J* = 9.5, 7.8 Hz, 1H), 3.74 – 3.58 (m, 1H), 3.26 – 3.03 (m, 1H), 2.35 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.2, 146.9, 138.3, 138.1, 133.7, 129.5 (2C), 125.7 (2C), 119.7, 116.9, 81.9, 37.0, 21.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 1652, 1599, 1557, 1516, 1459, 1424, 1335, 1306, 1287, 1238, 1222, 1182, 1174, 923, 879, 816, 786, 762.

MS (EI, 70 eV): *m/z* (%) = 210 (100), 194 (11), 193 (15), 192 (31), 183 (16), 166 (25), 120 (10), 118 (10).

HRMS (EI): *m/z* calc. for [$C_{14}H_{14}NO$]: 212.1075; found 212.1024 (M – Cl).

2-Chloro-3-tridecylpyridine (184sj´´)



According to **TP20**, a solution of 2-chloro-3-methylpyridine (**118s**, 26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (**112j´´**, 89 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 99:1) afforded the title compound **184sj´´** slightly yellow crystals (39 mg, 0.13 mmol, 66% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.23 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.16 (dd, *J* = 7.5, 4.7 Hz, 1H), 2.73 – 2.67 (m, 2H), 1.65 – 1.56 (m, 2H), 1.40 – 1.21 (m, 20H), 0.87 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.5, 147.2, 138.8, 137.0, 122.6, 33.3, 32.1, 29.8, 29.8, 29.8, 29.8, 29.7, 29.5, 29.5, 29.5, 29.3, 22.8, 14.3.

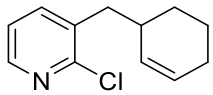
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2914, 2867, 2851, 1746, 1562, 1472, 1456, 1405, 1376, 1219, 1095, 1056, 838, 798, 748, 714, 686.

MS (EI, 70 eV): *m/z* (%) = 261 (19), 260 (100), 207 (15), 204 (10), 190 (10), 140 (23), 127 (23), 126 (16).

HRMS (EI): *m/z* calc. for [$C_{18}H_{29}NCl$]: 294.1989; found 294.1985 (M – H).

m.p. (°C): 35.3 – 37.2.

2-Chloro-3-(cyclohex-2-en-1-ylmethyl)pyridine (184se´)



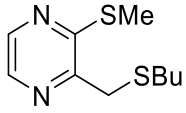
According to **TP20**, a solution of 2-chloro-3-methylpyridine (**118s**, 26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.18 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohex-1-ene (**112e´**, 48 mg, 0.30 mmol, 1.50 equiv) and CuCN·2LiCl (1.0 M in THF, 10 mol%) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 99:1) afforded the title compound **184se´** as slightly yellow oil (32 mg, 0.16 mmol, 77% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.54 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.18 (dd, *J* = 7.5, 4.7 Hz, 1H), 5.80 – 5.67 (m, 1H), 5.56 – 5.46 (m, 1H), 2.78 – 2.63 (m, 2H), 2.55 – 2.45 (m, 1H), 2.03 – 1.96 (m, 2H), 1.80 – 1.64 (m, 2H), 1.58 – 1.44 (m, 1H), 1.36 – 1.18 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.6, 147.3, 140.1, 135.2, 130.4, 128.3, 122.5, 39.7, 35.0, 28.8, 25.4, 21.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2857, 1744, 1678, 1562, 1448, 1434, 1407, 1222, 1196, 1165, 1123, 1075, 1060, 1048, 954, 809, 785, 747, 722, 690, 674.

MS (EI, 70 eV): *m/z* (%) = 129 (33), 127 (100), 81 (28), 79 (22).

HRMS (EI): *m/z* calc. for [$C_{12}H_{14}ClN$]: 207.0815; found 207.0810.

2-((Butylthio)methyl)-3-(methylthio)pyrazine (184tq)



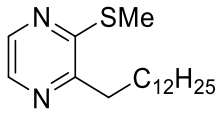
According to **TP20**, a solution of 2-methyl-3-(methylthio)pyrazine (**118t**, 28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfide (**112q**, 54 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5) afforded the title compound **184tq** as brown oil (43 mg, 0.19 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.30 (d, *J* = 2.6 Hz, 1H), 8.13 (d, *J* = 2.7 Hz, 1H), 3.85 (s, 2H), 2.58 (s, 3H), 2.57 – 2.53 (m, 2H), 1.57 (tt, *J* = 8.4, 6.8 Hz, 2H), 1.44 – 1.30 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.4, 151.4, 142.1, 137.3, 34.8, 31.9, 31.4, 22.1, 13.8, 13.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2926, 2871, 2857, 1744, 1514, 1444, 1413, 1365, 1220, 1210, 1191, 1142, 1121, 1097, 1087, 1060, 853.

MS (EI, 70 eV): *m/z* (%) = 140 (100), 139 (2), 107 (15).

HRMS (EI): *m/z* calc. for [$C_{10}H_{17}N_2S_2$]: 229.0833; found 229.0829 (M + H).

2-(Methylthio)-3-tridecylpyrazine (184tj´´)



According to **TP20**, a solution of 2-methyl-3-(methylthio)pyrazine (**118t**, 28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.50 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL/min flow rate in a T-mixer. The combined stream passed a 0.03 mL reactor tube (0.1 s, -78 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (**112j´´**, 89 mg, 0.30 mmol, 1.50 equiv) in THF. Stirring was continued for 10 min at -50 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases

were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane) afforded the title compound **184tj´´** as slightly yellow oil (49 mg, 0.16 mmol, 79% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 (d, *J* = 2.7 Hz, 1H), 8.13 (d, *J* = 2.7 Hz, 1H), 2.83 – 2.75 (m, 2H), 2.55 (s, 3H), 1.81 – 1.68 (m, 2H), 1.45 – 1.14 (m, 20H), 0.91 – 0.82 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.4, 154.8, 141.3, 137.2, 34.3, 32.0, 30.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.4, 29.4, 27.2, 22.7, 14.2, 12.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2922, 2852, 1518, 1465, 1447, 1371, 1322, 1206, 1149, 1103, 1094, 1062, 841, 722.

MS (EI, 70 eV): *m/z* (%) = 261 (11), 153 (12), 140 (100), 107 (12).

HRMS (EI): *m/z* calc. for [$C_{18}H_{32}N_2S$]: 308.2286; found 308.2283 (M – H)