Dissertation zur Erlangung des Doktorgrades

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Preparation of Lithium, Sodium and Potassium Organometallics by Metalation and Halogen/Metal Exchange in Continuous Flow

von

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aus

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Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Paul Knochel betreut.

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M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770.

2.) „Sodiation of Arenes and Heteroarenes in Continuous Flow"

N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10381.

3.) „Preparation of Functionalized Aryl, Heteroaryl and Benzylic Potassium Organometallics using Potassium Diisopropylamide in Continuous Flow"

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

4.) „Preparation of Diorganomagnesium Reagents by Halogen-Lithium Exchange of Functionalized Heteroaryl Halides and Subsequent *in situ* Trapping with $MgCl_2 \cdot LiCl$ in Continuous Flow"

R. H. V. Nishimura, N. Weidmann, P. Knochel, *Synthesis* **2020**, *52*, 3036.

5.) „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.

6.) „Halogen-Lithium Exchange of Sensitive (Hetero)Aromatic Halides under Barbier Conditions in a Continuous Flow Set-up"

N. Weidmann, R. H. V. Nishimura, J. H. Harenberg, P. Knochel, *Synthesis*, ahead of print.

7.) "Continuous Flow Sodiation of Substituted Acrylonitriles and Alkenyl Sulfides"

J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* ahead of print.

B) Poster presentation "Sodiation of Arenes and Heteroarenes in Continuous Flow"

1.) *ORCHEM*, **2018**, Berlin, Germany
2.) *Physical-Organic Chemistry at its Best: The Art of Chemical Problem Solving*, **2018**, Halle/Saale, Germany
3.) *Flow Chemistry Congress*, **2018**, Miami, USA
4.) *SFB 749 Meeting*, **2019**, Venice, Italy

Abbreviations

Physical constants are used according to the recommendations of the International System of Units (SI);[1] chemical structures are named according to the IUPAC conventions.[2] The following abbreviations will be used throughout this thesis:

Ac	acetyl
aq.	aqueous
Ar	undefined aryl substituent
ATR	attenuated total reflection
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BPR	back pressure regulator
bpy	2,2´-bipyridine
Bu	butyl
calcd.	calculated
CCDC	Cambridge Crystallographic Data Center
conc.	concentrated
Cy	cyclohexyl
d	doublet (NMR)
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMEA	dimethylethylamine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
d.r.	diastereomeric ratio
E-X	electrophile
e.g.	for example
EI	(electron ionization (MS)
equiv	equivalents

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[1] *THE INTERNATIONAL SYSTEM OF UNITS (SI) NIST SPECIAL PUBLICATION 330*, *2008 EDITION* (Eds.: B. N. Taylor, A. Thompson), 2008, https://www.nist.gov/pml/special-publication-330, 29.11.2019.

[2] Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names (Eds.: H. A. Favre, W. H. Powell), RCS, London, 2013.

ESI	electrospray ionization (MS)
Et	ethyl
FEP	fluorinated ethylene propylene
FG	functional group
g	gram
GC	gas chromatography
h	hour
Hal	halogen
Het	undefined heteroaryl substituent
Hex	hexyl
HMDS	bis(trimethylsilyl)amide
HRMS	high resolution mass spectrometry
i	iso
I.D.	inner diameter
i.e.	that means
inj.	injection
IR	infrared
J	coupling constant
KDA	potassium diisopropylamide
LDA	lithium diisopropylamide
M	$mol \cdot L^{-1}$
m	meta
Met	metal
Me	methyl
Mes	mesityl
min	minute
mL	millilitre
mm	millimetre
mmol	millimole
mol%	mole percent
m.p.	melting point

MS	mass spectrometry
NaDA	sodium diisopropylamide
NMR	nuclear magnetic resonance
o	ortho
Oct	octyl
p	para
Pent	pentyl
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	phenyl
Piv	pivaloyl
PMDTA	*N,N,N´,N´´,N´´*-pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
PTFE	polytetrafluoroethylene
q	quartet
R	undefined organic substituent
s	sec
s	singulet (NMR)
sat.	saturated
t	tert
tfp	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N´,N´*-tetramethylethylendiamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
UV	ultraviolet
Vol	volume

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A. INTRODUCTION

1. OVERVIEW

The formation of carbon-carbon and carbon-heteroatom bonds has always been one of the major tasks in organic synthesis. Although many different synthetic methodologies have been reported throughout the past centuries,[3] there is still a need for new and alternative bond formation reactions that complement current methods due to increasing complexity of organic molecules in pharmaceutical industry, applied sciences and agrochemistry.[4] In addition, in recent years a major goal of synthetic chemistry arose which is not related to the development of novel reaction methodologies but rather follows the principles of green and sustainable chemistry.[5] Industrial syntheses often require huge electrical energy input to obtain efficient heating or cooling. Further, undesired side products result in costly and uneconomic reaction pathways.[6] To address these needs, the thinking of organic synthetic chemists changed significantly. Sustainable, time-efficient, on-demand synthesis of target molecules is highly desired. Among established methods, continuous flow technology arose as a very successful technique to expand the toolbox of organic chemists and to overcome boundaries that limit batch reactions resulting in an exponential growth of publications in this area.[7] In recent years, flow chemistry demonstrated its potential to revolutionize the synthesis of complex organic molecules.[8] The use of automated flow set-ups with precise control over process parameters such as mixing[9] or temperature[10] in combination with enhanced data collection is enabling new ideas in chemical process development. Among those, reactions including organometallic intermediates display promising candidates for continuous flow technology. Especially highly reactive organolithiums and -magnesiums often suffer from the cost-intensive need of cryogenic temperatures and undesired side reactions.[11] Recent advances have considerably extended the scope of organometallic intermediates in continuous flow. Along with the development of on-line and in-line reaction monitoring *via* GCMS, IR or NMR spectroscopy, which has been developed to accurately track the reaction performances,[12] continuous flow technology displays a valuable tool to improve synthetical reactions, especially for the rapid scale-up of target molecules.

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[5] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273.

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[10] H. Wakami, J.-i. Yoshida, *Org. Process Res. Dev.* **2005**, *9*, 787.

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Among organometallic reactions, lithium chemistry is well-established due to its high reactivity. However, lithium has not only found wide applications in organometallic chemistry, but also in other areas such as energy storage, electromobility, in glass and ceramic as well as in pharmaceutical industry.[13] With its 0.002 to 0.007 weight percent within the earth crust, lithium is found rarely compared to its heavier analogues sodium and potassium.[14] In 2017, Bertau *et al.* already stated that the demand of lithium will increase by 8-11% annually resulting in a dramatic price explosion, which necessitates the investigation of cheaper and more earth-abundant options to well-established organolithium compounds for organic chemists.[13] According to the polarization of the carbon-metal bond, promising alternatives are found in the heavier alkali metals sodium and potassium.

Sodium with its 2.27 weight percent within the earth crust is not found in its elemental form in nature owing to the reactivity with water and the high reducing potential.[15] However, electrolysis of sodium salts enables an easy access to elemental sodium. Since the early discovery of a coupling reaction involving organosodiums by Wurtz and Fittig in the 19th century,[16] sodium chemistry did not receive much attention by synthetic chemists, which is mainly related to two major drawbacks: First, organosodium species are reported to be poorly soluble or insoluble in hydrocarbons or ethereal solvents, thereby limiting the scope of applications drastically.[17] Second, the high reactivity of organosodium reagents necessitates the need of cryogenic temperatures and hampers the applicability within organic syntheses.[18]

Potassium is the 17th most abundant element by weight on earth and is found in 2.60 weight percent within the earth crust.[19] As already described for sodium, its elemental form tents to form the corresponding hydroxide *via* a highly exothermic reaction when exposed to water. A reaction with oxygen, however, leads to the formation of potassium peroxides. Interestingly, potassium was already isolated in 1807 by Humphry Davy by electrolysis and thus, potassium is the first metal that was purely isolated by electrolysis.[20] However, it took more than a century until potassium dispersions were used to generate aliphatic and aromatic organopotassiums, again suffering from the low solubility in hydrocarbons or ethereal solvents and the generation of highly reactive potassium intermediates.[21]

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[16] (a) B. Tollens, R. Fittig, *Liebigs Ann. Chem.* **1864**, *131*, 303; (b) A. Wurtz, *Liebigs Ann. Chem.* **1855**, *96*, 364.

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2. FLOW CHEMISTRY

2.1 INTRODUCTION

We carry out synthesis in a 19th-century style – we have better glass, better analytical tools. But there hasn´t been a real advance.[22]

In 1998, A. J. Bard already stated that the technologies, chemists are using nowadays became obsolete. In fact, the way organic chemists are performing reactions did not change for decades. Mixing reagents in a flask or batch reactor, heating with oil baths or cooling with dry ice, extractions in separating funnels- these operations represent most of the daily processes in an organochemical laboratory. However, analytical tools such as IR or NMR spectroscopy were continuously improved. But why do chemists still stick to their thinking about conventional macrobatch technology? What about new ways to perform reactions in a different way? In the last decade, continuous flow technology arose as a promising technology to improve the performance of chemical reactions.[23] Continuous flow technology is a perfect example of thinking out of the box. Until twenty years ago, chemical reactions were performed almost unexceptionally in round bottom flask or special microwave set-ups. During the past decade the use of flow microreactors has been successfully established in both academic and industrial laboratories. Flow chemistry allows chemists to conduct a reaction in a continuous stream rather than in a flask by the use of special tubing, mixing and pumping devices. On the contrary to batch chemistry, which uses several macrobatch reactors to perform consecutive reactions, flow chemistry enables synthetic chemists to continuously manufacture desired products in microreactors often without the need of tedious isolation or purification of reaction intermediates. In the following chapters, the general set-up, applications and benefits of a continuous flow reaction are discussed.

2.2 CONTINUOUS FLOW SET-UP

One major advantage of flow technology results from the modular building blocks which are independently connected at any point of the continuous flow set-up. In general, most flow set-ups consist of six different flow elements, namely (I) reagent delivery (II) mixing unit (III) reactor unit (IV) pressure regulator (V) quenching unit and (VI) collection unit. Additional analytical or purification tools are further connected at any point of the flow set-up (Figure 1).[24]

The fundamental principle is the following: First, the reagents, stored either in reservoir flasks or loading coils, are directly pumped *via* tubing to a mixing device, followed by a reactor unit, which can both vary a lot depending on the special needs of the reaction conditions.

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[22] A. J. Bard, *Chem. Eng. News* **1998**.

[23] (a) K. S. Elvira, X. Casadevall-Solvas, R. C. R. Wootton, A. J. de Mello, *Nat. Chem.* **2013**, *5*, 905; (b) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849.

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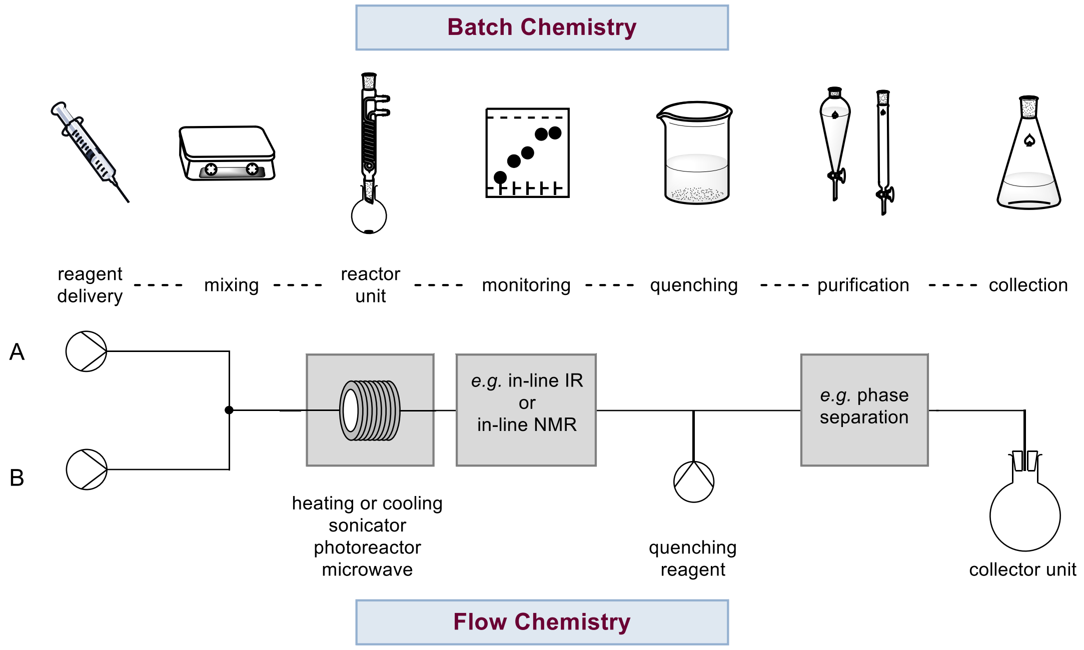

Figure 1: General continuous flow equipment with its macro batch counterparts.

The resulting reaction intermediate is either directly forwarded to a second reaction step, trapped by a quenching reagent delivered by another pumping device or directly trapped in a flask containing the corresponding quenching reagent. Additionally, pressure regulators are attached to the flow set-up, maintaining a constant pressure during the reaction. Lastly, the desired product is collected in a collection unit. By changing the flow-rates and the length or diameter of the reactor, residence and reaction time as well as stoichiometry of the reagents are precisely adjusted. Further, by placing the reactor unit in various surroundings, efficient heating or cooling, a microwave- or photochemical reaction and sonication can be achieved. Within the last decade, a lot of special equipment was designed allowing *e.g.* in-line monitoring, ultra-fast mixing, photochemical or multiphasic reactions in a continuous manner. In the following sections, a short introduction about the numerous building blocks is given.

2.2.1 Pumping Devices

Pumping devices play an important role within a flow set-up. They do not only deliver the reagents to the mixing and reactor unit, but also regulate the residence and reaction time by precise adjustment of the flow-rates. Thereby, pumping devices also directly influence the stoichiometry of the reagents. Overall, there are three prominent types of pumping devices used for continuous flow set-ups, each having various advantages and drawbacks. Before buying a flow set-up, the special needs of the reaction set-up must be considered to choose the most suitable pumping device.

First, syringe pumps are used, which consist of a pusher block, syringes, a syringe holder and a control unit (Figure 2). The pusher block moves the syringe piston forward, releasing the reagent directly from the syringes into the tubing with a controlled flow-rate. Recently, a major drawback of syringe pumps, namely that they are only able to deliver a defined amount of reagent limited by the syringe volume, was overcome by the development of syringe pump devices consisting of a delivery and loading syringe which are independently refilled when empty while the second syringe continuously delivers the corresponding reagent.[25] However, a second disadvantage of syringe pump set-ups is the pressure limitation. The connection between the syringes and the tubing can easily pop off at flow-rates above 1 $mL{\cdot}min^{-1}$. Nonetheless, syringe pumps are in particular used for a precise flow-rate control when using flow-rates below 1 $mL{\cdot}min^{-1}$ and because of their chemical robustness. Since only the syringes are in direct contact with the reagents, the scope of chemicals is only limited by the material of the syringes.

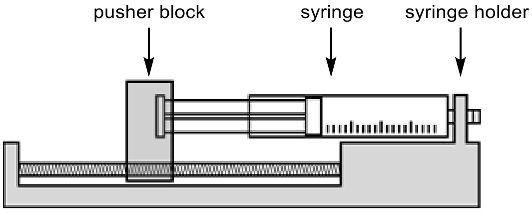

Figure 2: General working principle of a syringe pump.[26]

Piston pumps consist of a moving cam, which is directly attached to a piston (Figure 3).[27] When the piston moves out of the chamber, the inlet check valve opens and the reagent is sucked in from the inlet tubing. When the piston moves into the chamber, it directly closes the inlet check valve, whereas the piston pushes the reagent through the outlet check valve. Piston pumps are commonly used for flow-rates higher than 0.1 $mL{\cdot}min^{-1}$ and for reaction set-ups within a low- to high pressure range. However, a major drawback of piston pumps is observed when using volatile reagents or solvents such as Et_2O, DCM or $CHCl_3$. Further, the use of piston pumps leads to severe problems when using corrosive reagents. Since the piston is in direct contact with the reagent, the scope is limited to chemicals that do not interfere with the piston. A second disadvantage results from the discontinuous flow-rate which is a consequence of the stepwise filling and release of the pump.

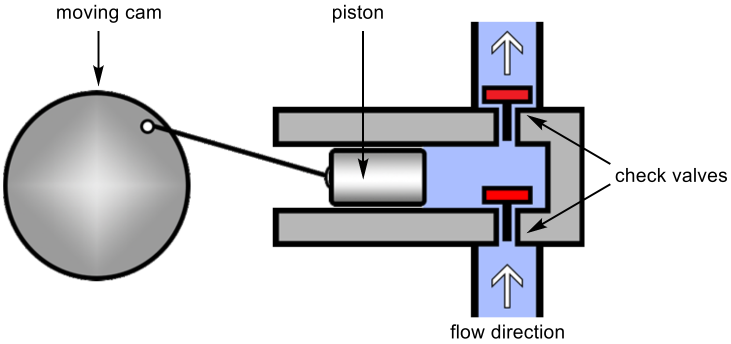

Figure 3: General working principle of a piston pump.[26]

Peristaltic pumps are used in many flow set-ups (Figure 4).[28] An elastic tubing is compressed by a moving rotor. Due to the speed of the rotation, a specific pressure arises inside the tubing,

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

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[27] (a) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; (b) *Fundamentals in Flow Chemistry* (Eds.: F. Darvas, V. Hessel, G. Dormán), de Gruyter, **2014**.
Flash Chemistry, Fast Organic Synthesis in Microsystems (Ed.: J.-i. Yoshida), Wiley-VCH, Chichester, **2008**.

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pushing the reagent to the mixing unit. Upon relaxation, the pressure decreases leading to a refill of the reagent from the reagent reservoir. However, as for piston pumps, the use of corrosive chemicals is limited to the material of the elastic tubing and further, the application of peristaltic pumps leads to a discontinuous flow-rate, caused by the wavelike pressure gradients.

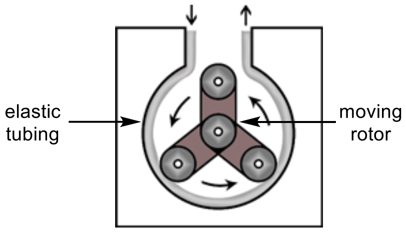

Figure 4: General working principle of a peristaltic pump[26]

For the delivery of gasses, special equipment is needed. Either, a direct connection of the gas bottle or the connection of a mass flow controller allow the successful utilization of gases in continuous flow. Whereas a gas bottle delivers gases in an undefined manner only controlled to some extent by a pressure reducer, mass flow controllers regulate the flow-rate *via* heat transfer phenomena exactly determining the flow-rate of a broad range of gases.[29]

2.2.2 Mixing Devices

The control of extremely fast reactions and the generation of highly reactive intermediates or products display one major benefit of flow chemistry. Roberge and co-workers determined that mainly reactions applying any reaction intermediate or product with a half-life of less than one second highly benefit from flow technology.[30] However, to achieve ultrafast mixing, fast telescoped reactions or efficient heat transfer, special mixing devices are particularly needed. In recent years, a huge variety of different mixing devices were developed, addressing special needs for reactions that could not be performed in a conventional batch reactor. In course of these studies, the group of Yoshida developed integrated micromixing devices to obtain residence times in the range of 10^{-2} to 10^{-4} s,[31] whereas conventional mixing devices can only obtain reaction times above 0.1 s.[32] In general, mixing is always directly proportional to the diffusion rate, hence one characteristic feature of mixing devices is their small diameter, thereby decreasing the diffusion length. Even if the volume of a mixing device is small, the total throughput can be significantly higher by simply increasing the run-time of flow reactions. Therefore, applications of flow chemistry are not only limited to academia but also found broad application in industry.

Due to the small volume of micromixers, they offer several advantageous characteristics over conventional macrobatch reactors. A mixing event is a result of molecular diffusion. Since the time for complete mixing is directly proportional to the square of the diffusion pathway (Equation 1, t = time since diffusion started, d = mean distance travelled by diffusing molecule,

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[29] L. D. Hinkle, C. F. Mariano, *J. Vac. Sci. Technol.* **1991**, *9*, 2043.

[30] D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, *Chem. Eng. Technol.* **2005**, *28*, 318.

[31] (a) A. Nagaki, Y. Takahashi, J.-i. Yoshida, *Chem. Eur. J.* **2014**, *20*, 7931; (b) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264.

[32] M. Colella, A. Nagaki, R. Luisi, *Chem. Eur. J.* **2020**, *26*, 19.

D = diffusion coefficient), shortening the diffusion pathway d leads to a significantly shorter mixing time t.[33]

$$t = \frac{d^2}{2 \cdot D} \tag{1}$$

Equation 1: Molecular difussion time t is directly proportional to the square of diffusion pathway d.

Additionally, the surface-to-volume ratio is considerably increased using micromixers. Since efficient heating and cooling are a result of a heat exchange between the interior and the exterior of a reaction system, heating and cooling are more efficient due to its increased surface avoiding hotspots or temperature gradients within the reaction mixture.[34] Furthermore, the increased surface-to-volume ratio has a great impact on biphasic reactions. The phase boundary of *e.g.* gas/liquid, solid/liquid or liquid/liquid reactions is enhanced allowing for a more efficient mass transfer between the different phases. Moreover, the use of micromixers in combination with defined flow-rates and reactor volumes enables a precise control of very short residence times in continuous flow. Due to the small diameters of mixing devices and reactors, short residence times not obtainable in macrobatch reactors can be easily achieved. Highly reactive and unstable intermediates or products can therefore be forwarded to a subsequent trapping reagent *via* another mixing device.

At this point, one fundamental question needs to be addressed: How can the efficiency of mixing be determined? Since it is hard to tell anything about the mixing efficiency within a mixing device, other methods have to be applied. Among those, the Villermaux-Dushman reaction, a competitive parallel reaction, was found to be the most convenient way.[35] The reaction consists of two independent processes: Protonation of an acetate anion by a strong acid and the formation of elemental iodine *via* redox comproportionation reaction of iodate and iodide ions catalyzed by oxonium ions (Scheme 1). Whereas the neutralisation of a base is an ultrafast reaction, the comproportionation reaction is only a fast reaction. Therefore, mixing of a strong acid with acetate anions in the presence of iodate and iodide ions provides a good evidence of the mixing efficiency. In case of ultrafast mixing, the neutralisation of the acetate anions outcompetes the slower redox formation of elemental iodine. On the other hand, if the mixing is slow, a local concentration gradient of acid is formed and a sufficient amount of protons is available to catalyze the redox reaction resulting in iodine formation. Lastly, the amount of *in situ* formed I_2 can be determined by UV analysis at 352 nm. The more iodine is formed, the higher is the absorption and the slower is the mixing.

$$\mathrm{CH_3COO^-} + \mathrm{H_3O^+} \longrightarrow \mathrm{CH_3COOH} + \mathrm{H_2O} \quad \textbf{(ultrafast)}$$

$$6\,\mathrm{H_3O^+} + \mathrm{IO_3^-} + 5\,\mathrm{I^-} \longrightarrow 3\,\mathrm{I_2} + 3\,\mathrm{H_2O} \quad \textbf{(fast)}$$

Scheme 1: Villermaux-Dushman reaction for the determination of mixing processes.

In the following sections, the basic principles of several mixing devices are introduced, showing the great potential of continuous flow technology. In general, a mixing unit consists

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[33] *Flash Chemistry, Fast Organic Synthesis in Microsystems* (Ed.: J.-i. Yoshida), Wiley-VCH, Chichester, **2008**.

[34] J.-i. Yoshida*, Chem. Commun.* **2005**, 4509.

[35] J. Villermaux, L. Falk, M.-C. Fournier, C. Detrez, *AIChE Symp. Ser.* **1992**, *286*, 6.

of small micrometer sized structures. They can be distinguished between static and dynamic micromixers. Dynamic mixers consist of an internal moving mixing unit such as a stirring bar. Moreover, complex external mixing instruments such as sonication or low-frequency vibrations have been developed. However, the simplicity of static mixers makes them more popular in modern flow applications. Static mixers are designed with a defined internal structure, which leads to efficient mixing either by turbulences or by an increased interface of the reagent streams.

The simplest static mixers are Y- and T-shaped mixers. Depending on the flow-rates, Y-shaped mixers usually lead to a laminar flow of the reagents (Figure 5a).[36] Due to the small diameter of the mixing device, the longitudinal interface is tremendous resulting in a high mixing rate: The smaller the diameter of the mixer, the faster the mixing. Mixing within a T-mixer, however, mainly depends on the flow-rate. At low flow-rates, the two reagent streams are mixed in a laminar manner. Using a fast flow-rate and a T-mixer usually results in a slug flow, where distinct small areas of reagent A and reagent B are formed (Figure 5b). As the interface between the slugs is increased, the diffusion is significantly enhanced compared to similar batch reactions. To simplify continuous flow reactions, many improvements in the design of a mixing device were made. Both, T- and Y-shaped reactors made from various materials and different sizes are commercially available. Noteworthy, simple T- and Y-shaped mixers are preferred in academia und industry over more complex mixers due to the reduced possibility of clogging. Further, microchip reactors with channels etched into the corresponding materials were developed recently, combining a T- or Y-mixer with a certain reactor volume.[37]

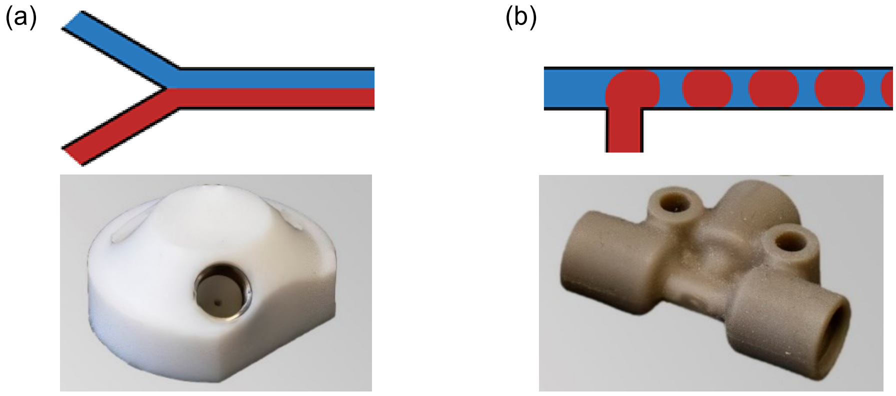

Figure 5: (a) Y-mixer with a longitudinal interface upon mixing; (b) T-mixer with a slug flow resulting in transverse interfaces of high area.[26]

To fulfil special requirements, various special mixing devices were developed such as multilaminar or split and recombine (SAR) mixers. Multilaminar mixers divide the reagent streams into numerous smaller streams and recombine those streams alternating with each other. Again, the ultrafast mixing is directly related to small diffusion pathways. To further improve the idea of multilaminar mixers, triangular shaped versions were developed. Due to thinning of the lamellae, the mixing efficiency is further improved. In contrast to multilaminar mixers, SAR mixers divide the reagent stream after mixing into two streams and recombine

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[36] S. Schwolow, J. Hollmann, B. Schenkel, T. Röder, *Org. Process Res. Dev.* **2012**, *16*, 1513.

[37] K. F. Jensen, B. J. Reizman, S. G. Newman, *Lab. Chip.* **2014**, *14*, 3206.

these streams again afterwards, resulting in turbulences, which mix the reagents more efficiently. The number of generated segments is doubled with every split-and-recombine event. Noteworthy, the number of segments increases exponentially along the reactor length with every split-and-recombine event resulting in an exceptional increased interphase of the reagent streams. Further improvements of SAR mixers were made leading to a splitting of the reagent streams not only in two but even more streams affording an enhanced mixing. Recent reports on special mixing devices mainly focus on mixers with additional mechanical obstacles, which further lead to more turbulences, or improved tolerance of various chemical reagents (*e.g.* foam-like, labyrinth-shaped or anti-fouling mixers).

Especially when using micromixers, it is worth mentioning, that the mixing devices already serves as a reactor due to the very fast reaction kinetics. Hence, it is expedient to continue with the special design of various reactors in the following chapter.

2.2.3 Reactor Design[38]

Reactor design displays an important role for almost every reaction performed in a continuous flow set-up. In general, reactor units are distinguished between coil-based reactors[39], chip reactors[40] and packed-bed reactors.[41] Due to their easy handling and low costs, simple coil reactors, which differ in their material (PTFE, hastelloy, stainless steel) are used most frequently. For elevated temperatures or pressurized reactions either hastelloy or stainless steel are applied, since the temperature is easily controlled by heating baths and the pressure is adjusted with back pressure regulators (BPRs). An increasing number of photochemical reactions are performed in a continuous flow set-up, as the light penetration is higher compared to batch reactions. To address the needs of photochemical reactions, coiled reactors made from UV/Vis transparent tubing such as fluorinated ethylene propylene (FEP) were developed.[42]

On the other hand, chip-based reactors are manufactured from ceramics, glass or silicon (Figure 6). The small diameters of the channels within a chip-reactor offer various advantages over coiled reactors. Due to the high surface-to-volume ratio, heat transfer and light penetration are increased. Further, specific materials allow for the functionalization of the channel walls by immobilization of a catalyst.[43] However, the chip-based reactors tend to clog during the reactions since even small precipitations lead to a blockage of the channels.

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[38] (a) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; (b) K. Geyer, J. D. C. Codée, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434.

[39] D. Cambie, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276.

[40] K. F. Jensen, B. J. Reizman, S. G. Newman, *Lab. Chip.* **2014**, *14*, 3206.

[41] J. R. Naber, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2010**, *49*, 9469.

[42] (a) B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry, K. I. Booker-Milburn, *J. Org. Chem.* **2005**, *70*, 7558; (b) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276; (c) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025.

[43] E. K. Lumley, C. E. Dyer, N. Pamme, R. W. Boyle, *Org. Lett.* **2012**, *14*, 5724.

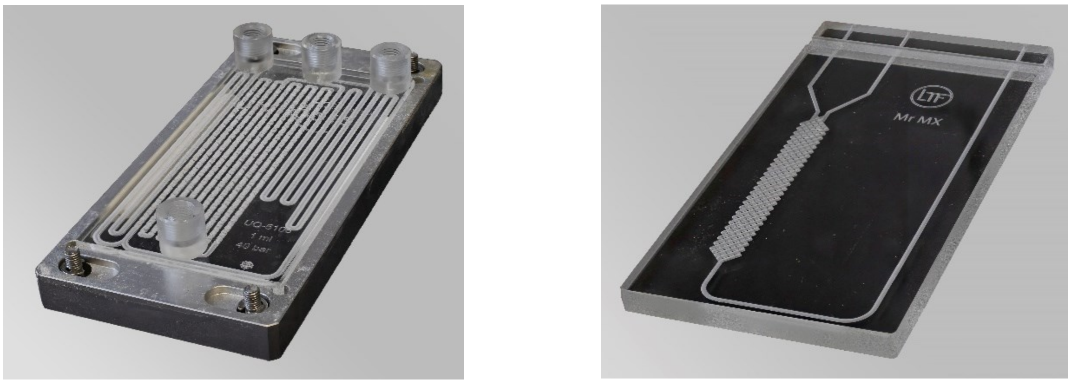

Figure 6: Chip-based reactors with a distinct inner volume and small channels sctratched into a glas plate, covered by a second glass plate.

Further, if heterogeneous catalysts or solid reagents should be used in continuous flow, packed-bed reactors are applied (Figure 7). In general, a column or cartridge is filled with the appropriate solid or heterogeneous catalyst, which are embedded through porous filters. A reagent solution is then flushed trough the cartridge affording the desired reaction within the cartridge. The particle size of the solids mainly influences the efficiency of the flow set-up. Huge particles do not provide a good surface-to-volume ratio and therefore the activity is decreased. However, small particles suffer from an inherent pressure increase or clogging of the porous filters. During the last years, different types of packed-bed reactors were developed, which allow the use of solids and heterogeneous catalysts. First of all, fluidized bed reactors consist of a cartridge or column loosely filled with the solid particles. Whenever a solvent or reagent stream passes through the cartridge, the particles are whirled up resulting in a heterogeneous mixture of reagent and particles. In contrast, fixed-bed reactors are packed tightly with the solid particles. The reagent stream surpasses the particles and the internal structure of the cartridge is fixed. Lastly, structured catalyzed bed reactors consist of small catalyst-covered channel walls. While the reagent stream surpasses the small channels, the particles efficiently catalyze the desired reactions. All packed-bed reactors have in common that the cartridges are sealed properly with porous filters in such a way that the particles are not released from the cartridge. In general, packed-bed reactors offer some major advantages: the catalysts do not poison the desired product and no expensive and time-consuming purification is needed. Further, a significantly higher effective molarity of the reagent or catalyst compared to batch reactions is achieved. Lastly, the reuse of the catalysts is often possible.

Figure 7: Glass column for the precise packing of a packed-bed reactor with various solids or heterogenous catalysts.

The research area of liquid-gas reactions represents another category of chemical modifications, which can be addressed by flow chemists. Ley *et al.* developed a so-called tube-in-tube reactor (Figure 8).[44] It consists of an inner and an outer tube, which are separated by a semipermeable Teflon AF-2400 membrane. The membrane is permeable for many commonly used gases whereas impermeable for most liquids. By flooding one tube with the desired gas and the other one with the reagent solution, the gas is able to diffuse into the solvent stream through the membrane resulting either in a saturated gas solution or in a direct liquid-gas reaction within the tube-in-tube reactor.

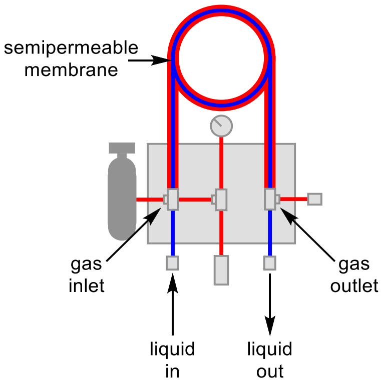

Figure 8: Working principle of a tube-in-tube reactor. The inner tubing allows gas diffusion by simultaneously preventing solvent diffusion resulting in a saturated gas solution or direct quenching with various gasses.[44]

Recent progress in the reactor design demonstrated the broad applications of continuous flow technology in various areas of organic chemistry. *E.g.* reactors allowing the performance of electrochemical[45] or photochemical reactions[46] were developed. Electrochemical microreactors were sufficiently tested avoiding large ohmic resistance between the electrodes. Furthermore, the application of photochemical microflow reactors tackles a well-known problem of photolytically activated reactions, namely the light penetration. Whereas on a small laboratory scale, light penetration is efficient in a small flask, their radiation in a macrobatch reactor is somewhat more complicated. The use of flow-microreactors leads to an increased surface-to-volume ratio, hence the light penetration is increased according to the Lambert-Beer law (Equation 2; E = attenuation of light, ε = absorptivity, c = concentration, d = optical path length, I_0 = intensity of incoming light, I_1 = intensity of outcoming light) resulting in an increased activation.

$$E = \varepsilon \cdot c \cdot d = lg \frac{I_0}{I_1} \tag{2}$$

Equation 2: Lambert-Beer law.

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[44] (a) M. Brzozowski, M. O´Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349; (b) C. J. Mallia, I. R. Baxendale, *Org. Process Rev. Dev.* **2016**, *20*, 327; (c) A. Polyzos, M. O´Brien, T. P. Petersen, I. R. Baxendale, S. V. Ley, *Angew. Chem. Int. Ed.* **2011**, *50*, 1190.

[45] (a) K. Watts, A. Baker, T. Wirth, *J. Flow Chem.* **2015**, *4*, 2; (b) R. A. Green, R. C. D. Brown, D. Pletcher, *J. Flow Chem.* **2016**, *6*, 191.

[46] (a) K. Loubière, M. Oelgemöller, T. Aillet, O. Dechy-Cabaret, L. Prat, *Chem. Eng. Process.* **2016**, *104*, 120; (b) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276; (c) L. D. Elliott, M. Berry, B. Harji, D. Klauber, J. Leonard, K. I. Booker-Milburn, *Org. Process Res. Dev.* **2016**, *20*, 1806.

2.2.4 Quenching Unit

A precise adjustment and control of the reaction time is often mentioned as one major benefit of flow chemistry. However, to sufficiently control the reaction time, it is mandatory to quench reactive intermediates or products before subsequent side reactions occur. Quenching of a reaction is achieved by different ways. In case of a photochemical or electrochemical reaction, the reaction in most cases takes place when the reagents are exposed to a light or current source. As soon as the reagent streams exit the photo- or electrochemical reactor, no further undesired activation occurs. However, trapping of highly reactive intermediates or products is usually achieved by thermal or chemical quenching. Thermal quenching refers to fast cooling after the desired reaction to stop undesired side reactions. Due to the increased surface-to-volume ratio within a flow reactor, rapid cooling can be achieved within milliseconds. Nevertheless, chemical quenches by the addition of a trapping reagent are by far the most applied method. Within a flow set-up, chemical quenches are achieved by adding the quenching reagent *via* an additional pumping device. These quenching methods altogether allow the precise control of the reaction time, in particular the performance of extremely fast reactions which cannot be done in a conventional macrobatch reactor.[47]

2.2.5 Pressure Regulating Unit

Pressure regulation units such as back pressure regulators (BPR) facilitate a constant pressure within a flow set-up. Especially for the application of volatile and gaseous reagents, a constant pressure within the flow system furnishes reproducible reactions. Furthermore, BPRs enable flow chemists to perform reactions above the boiling point of the appropriate solvents often resulting in a decreased reaction time. To meet the special needs of the flow set-up, preset BPRs, which generate a predefined back pressure, or adjustable BPRs are commercially available.[48]

2.2.6 Collection Unit

Albeit it is obvious that the resulting product has to be collected somehow, it is not always as trivial as it seems. For an optimized reaction affording the pure desired product, no special collection unit needs to be installed. A simple flask is sufficient to collect the product. However, while screening various conditions for the optimum reaction parameters, a fraction collector connected to in-line or on-line monitoring equipment considerably increases the efficiency of optimization studies.

2.2.7 Analysis and Purification Unit

Analysis and purification play an important role within a flow set-up. As previously mentioned, both tools can be attached at any point of the flow set-up, wherever analysis or purification is needed. In contrast to known batch processes, where chemists have to take aliquots and tediously analyse them *via* GC, HPLC, IR or NMR, flow technology allows for in-line or on-line analysis. This benefit facilitates not only optimization of reaction conditions but also

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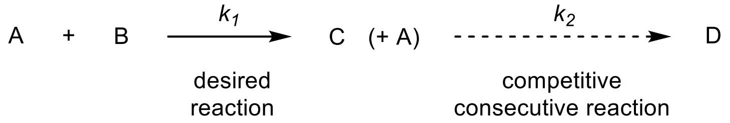
[47] J.-i. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896.

[48] R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 7502.

enables a permanent quality control of continuous processes through the observation of intermediates or products.[49] Further, it is highly desirable to obtain a pure, isolated product after laborious, consecutive flow reaction steps. Following the general concepts of batch chemistry, several purification tools were developed, *e.g.* liquid/liquid separation or scavenger cartridges. Liquid/liquid separation is based on a membrane separation technology, where the product is soluble in one solvent and the excess of reagents or side products are solubilized in a second immiscible solvent. With the help of a semipermeable membrane, the solvents are separated and the product stream is telescoped to the next reaction step.[50] Scavenger cartridges, which consist of a packed-bed reactor filled with a suitable material to trap the undesired side products, are an efficient method to remove impurities.[51]

2.3 MIXING VERSUS REACTION KINETICS

The selectivity of chemical reactions depends on their thermodynamics and kinetics. However, kinetics cannot be used to explain the selectivity of ultrafast reactions due to the lack of homogeneity within the reaction mixture in a macrobatch set-up. Therefore, it is essential for fast reactions that the mixing time is still shorter than the reaction time to obtain a homogeneous reaction mixture. Otherwise, competitive consecutive reactions can occur. Ideally, a reaction between reagent A and B leads solely to the desired product C with a rate constant k_1. In case of a competitive consecutive reaction, the resulting product C further reacts with remaining reagent A (or B) to an undesired side product D with a rate constant k_2 (Scheme 2).[52]



Scheme 2: General scheme of a desired reaction followed by an undesired competetive consecutive side reaction.

If $k_1 \leq k_2$, the *in situ* formed product C is subsequently converted to the undesired side product D and it is difficult to stop the reaction at the desired stage in a macrobatch reactor. However, if k_1 is significantly higher than k_2, it is in principle possible to stop the reaction at the level of product C. Nevertheless, the kinetic predictions are often disproved by the experimental observations in batch chemistry resulting in significant amounts of side product D even if $k_1 > k_2$ due to the lack of sufficient mixing. When the competitive consecutive side reaction is faster than the mixing, an interphase of product C is formed between reagent A and B. In a following step, product C can be converted to side product D at the periphery of reagent A (Figure 9).[52]

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[49] (a) B. J. Reizmann, K. F. Jensen, *Acc. Chem. Res.* **2016**, *49*, 1786; (b) J. Yue, J. C. Schouten, T. A. Nijhuis, *Ind. Eng. Chem. Res.* **2012**, *51*, 14583; (c) D. C. Fabry, E. Sugiono, M. Rueping, *React. Chem. Eng.* **2016**, *1*, 129.

[50] (a) K. Wang, G. Luo, *Chem. Eng. Sci.* **2017**, *169*, 18; (b) T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 5943; (c) A. G. O´Brien, Z. Horváth, F. Lévesque, J. W. Lee, A. Seidel-Morgenstern, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 7028.

[51] (a) S. V. Ley, *Chem. Rec.* **2012**, *12*, 378; (b) F. Venturoni, N. Nikbin, S. V. Ley, I. R. Baxendale, *Org. Biomol. Chem.* **2010**, *8*, 1798.

[52] *Flash Chemistry, Fast Organic Synthesis in Microsystems* (Ed.: J.-i. Yoshida), Wiley-VCH, Chichester, **2008**.

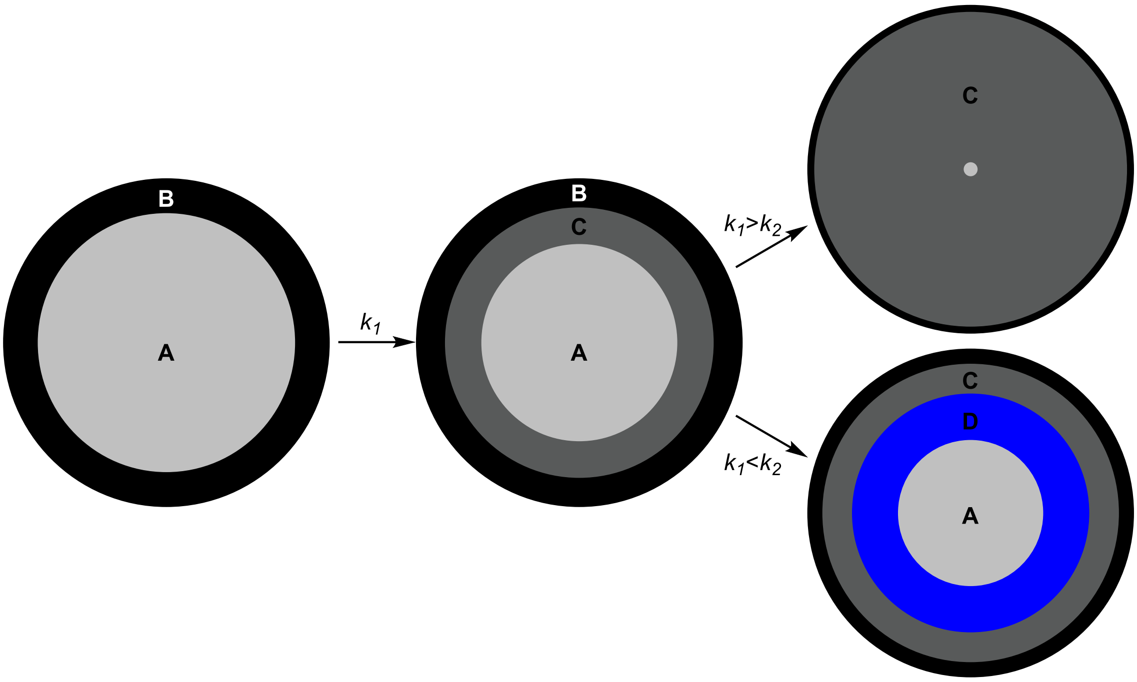

Figure 9: Graphical representation of competitive consecutive side reactions with $k_1>k_2$ (top) and $k_1<k_2$ (bottom).

To overcome these undesired side reactions in a macrobatch reactor, it is well-established to lower the reaction temperature resulting in a decreased reaction speed. The lower reaction speed allows for efficient mixing before any side reactions occur. Furthermore, lowering the reagent concentrations also leads to a slower reaction affording the same effect. However, both alternatives suffer from a significant decrease in the reaction speed and a need of huge amounts of solvent or expensive cooling to cryostatic temperatures.[53]

Ultrafast mixing is a necessary requirement to obtain a predictable selectivity close to the kinetically expected selectivity for fast reactions. Since the time for molecular diffusion is proportional to the square of the length of the diffusion path, shortening the diffusion path in a micromixing device results in a mixing speed not obtainable in a batch reactor. Therefore, the use of continuous flow chemistry and the application of special mixing devices address these needs and allow for the performance of extremely fast reactions that are completed within milliseconds and a homogeneous reaction environment by ultrafast mixing.

2.4 APPLICATION OF FLOW CHEMISTRY

On a laboratory scale we cannot perform reactions, which are too fast to control in a flask. However, flow chemistry allows the control of reactive intermediates affording the desired products within the reaction time range of milliseconds with high selectivity. Noteworthy, flow chemistry hereby does not change mechanistic pathways, kinetics or equilibria, which are known from the corresponding batch reactions. Rather, it opens up a new field of organic synthesis and provides a new method for performing extremely fast reactions that are difficult

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[53] *Flash Chemistry, Fast Organic Synthesis in Microsystems* (Ed.: J.-i. Yoshida), Wiley-VCH, Chichester, **2008**.

to perform in a conventional macrobatch set-up. In course of this chapter, a brief summary about reactions that benefit from flow technology is given.

2.4.1 Mixing as Crucial Parameter

As described in the previous chapter, one of the main advantages of continuous flow chemistry is the ultrafast mixing in special mixing devices. In the past, conducting an ultrafast reaction in a conventional macrobatch reactor in a selective manner was not possible due to side reactions leading to significant amounts of undesired byproducts. Generation of highly reactive intermediates that decompose within (milli)seconds is not possible in macrobatch reactors, whereas the in flow generated reactive intermediates can be directly transferred to the following reaction step without the need of long reaction times. Additionally, in some reactions the resulting products are not stable under the appropriate reaction conditions, leading to further reactions of the product resulting in undesired side products. By precise time control and quenching of the reaction, stopping the reaction at the desired product stage can be achieved.

Fast reactions are often exothermic. If a large number of molecules collides in a very short period of time, a huge release of energy proceeds in case of an exothermic reaction. To remove the heat from the reaction system, an efficient heat transfer is essential to conduct highly exothermic reactions in the absence of any side reactions or rapid boiling of the solvent, which can result in serious safety issues. Due to the high surface-to-volume ratio, continuous flow technology is able to provide an efficient heat transfer for highly exothermic reactions, whereas in a macrobatch reactor highly exothermic reactions are usually performed by slowly adding one reagent to a solution of a second reagent in an appropriate solvent. However, even by slow addition, the presence of local hotspots leading to undesired side reactions cannot be completely excluded.

Recently, the generation of halomethyllithiums in continuous flow was reported. Whereas batch reactions usually necessitate cryogenic temperatures to avoid decomposition of the intermediate halomethyllithiums resulting in carbenes, chloromethyllithium was generated at −40 °C within 0.31 s and subsequently trapped with aromatic aldehydes affording functionalized α-chloroalcohols in good to excellent yields (Scheme 3a).[54] The scope of this methodology was further extended to the direct lithiation of dichloromethane in continuous flow using *n*BuLi without the undesired formation of chlorocarbene. Trapping with aromatic aldehydes and further functionalization led to a series of aminothiazoles (Scheme 3b).[55]

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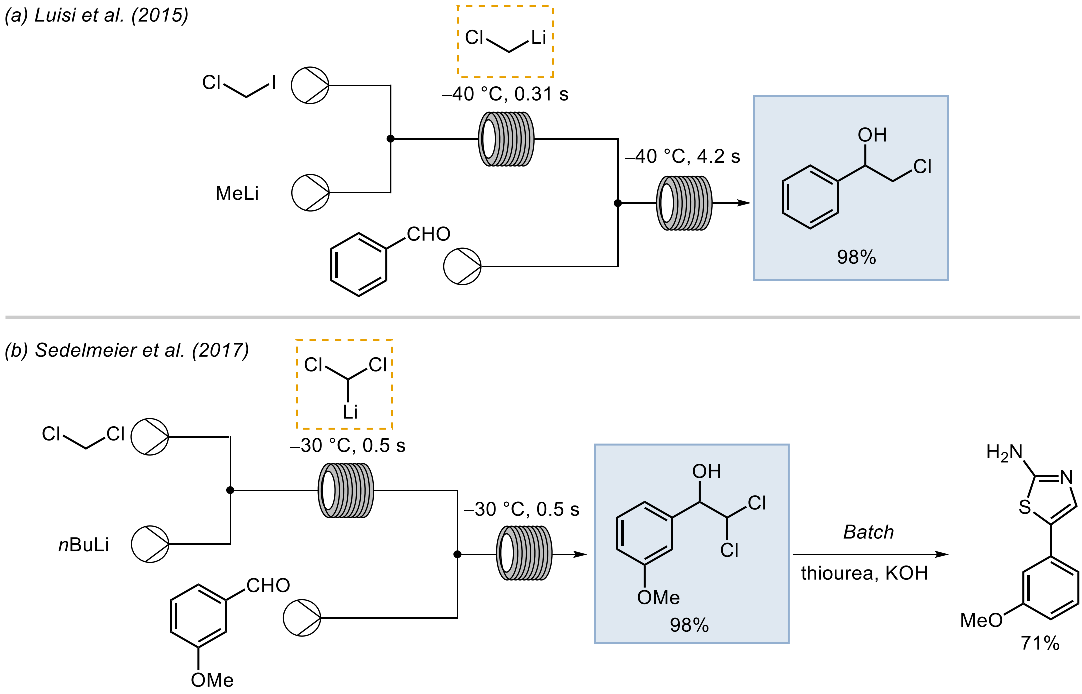
[54] L. Degennaro, F. Fanelli, A. Giovine, R. Luisi, *Adv. Synth. Catal.* **2015**, *357*, 21.

[55] A. Hafner, V. Mancino, M. Meisenbach, B. Schenkel, J. Sedelmeier, *Org. Lett.* **2017**, *19*, 786.



Scheme 3: Generation of highly reactive halomethyllithiums in a continuous flow set-up by (a) iodine-lithium exchange[54] and (b) direct metalation.[55]

2.4.1 Temperature-dependent reactions

It is well known that temperature is one of the key parameters that influences the performance of organic reactions. Whereas for fast reactions the temperature under standard batch conditions often needs to be lowered to cryogenic temperatures to control the reaction performance, heating of slow reactions can facilitate desired reaction pathways. Therefore, a reaction that is intrinsically slow and needs a long reaction time in batch displays a good candidate for the performance in continuous flow. Although in recent years microwave chemistry became a promising alternative for slow reactions, scaling-up a reaction is difficult since the microwave irradiation within a batch reactor is often not efficient.[56] However, flow technology provides synthetic chemists with a possibility to perform reactions upon efficient heating at high pressure even above the boiling point of the solvent at atmospheric pressure, speeding up the reaction rates in accordance to the Arrhenius equation (Equation 3):

$$k = A \cdot e^{-\frac{E_A}{R \cdot T}} \tag{3}$$

Equation 3: Arrhenius equation for the depence of the rate constants of chemical reactions and the temperature.

The Knochel group investigated direct magnesiations and zincation of acrylonitriles, acrylates and nitroolefins at elevated temperatures. Zincation using TMPZnCl·LiCl in THF was performed at 90 °C above the boiling point of THF by attaching a 2 bar BPR. Trapping of the resulting organozinc intermediates with various aldehydes afforded the functionalized alkenes within approximately three minutes (Scheme 4a).[57] To further demonstrate the potential of flow chemistry, the hydrolysis of α-aminonitriles is worth mentioning. α-Aminonitriles are

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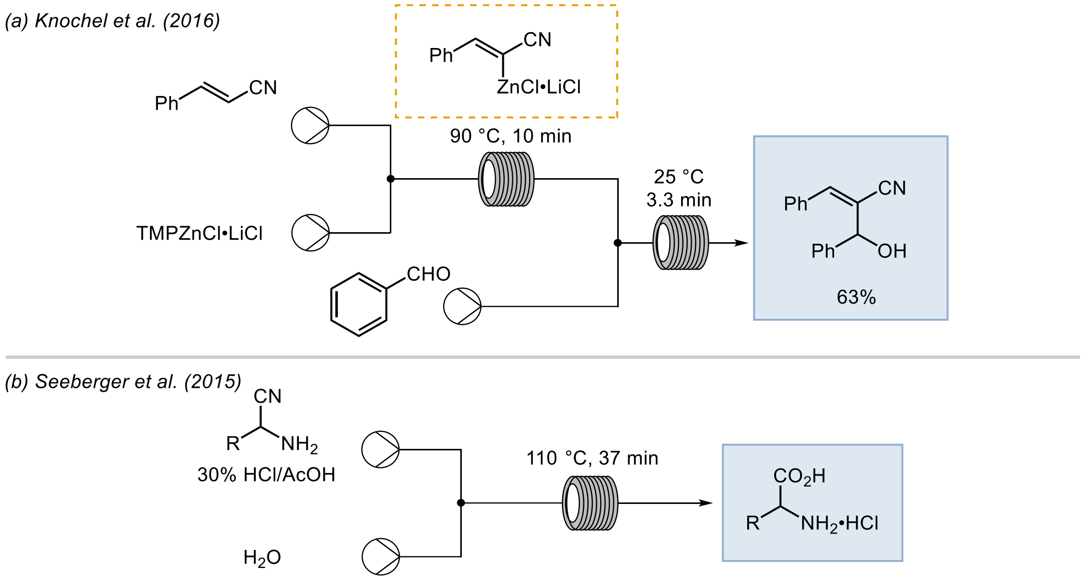
[56] T. N. Glasnov, C. O. Kappe, *Chem. – Eur. J.* **2011**, *17*, 11956.
[57] M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828.

commonly synthesized *via* the Strecker reaction from the corresponding aldehydes.[58] However, the hydrolysis of α-aminonitriles in a conventional batch reactor sometimes takes hours to days even at elevated temperatures. Seeberger *et al.* have reported a hydrolysis of α-aminonitriles using a continuous flow set-up at 110 °C. Performing the hydrolysis slightly above the boiling point of water resulted in a broad range of amino acids in good yields (Scheme 4b).[59]



Scheme 4: (a) Directed zincation of phenylacrylonitrile using TMPZnCl·LiCl in a continuous flow set-up at elevated temperatures.[57] (b) Hydrolysis of α-aminonitriles using a continuous flow set-up above the atmospherical boiling point of water.[59]

Furthermore, within a flow set-up a smaller temperature gradient is achieved. If there is an equilibrium between two starting materials and the activation energy for the transformation of the two starting materials is similar affording two different products according to the Curtin-Hammet principle, it is highly important to ensure a distinct temperature profile allowing only the desired reaction pathway. In fact, batch reactors usually have a large energy profile, which do not allow a precise product-to-side-product ratio control.

2.4.2 Multiphasic Reactions

Nowadays, many reactions for industrial applications or academic research are multiphasic, *e.g.* gas-liquid,[60] liquid-liquid, solid-liquid[61] or even triphasic transformations such as solid-liquid-gas reactions.[62] Even if several advances according to phase-transfer catalysts for immiscible liquid-liquid reactions in a conventional batch reactor were made, the majority of multiphasic reactions suffer from inefficient mixing. Most important for multiphasic transformations, either for standard batch or continuous flow reactions, is the interfacial area

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[58] J. Wang, X. Liu, X. Feng, *Chem. Rev.* **2011**, *111*, 6947.

[59] S. Vukelić, D. B. Ushakov, K. Gilmore, B. Koksch, P. H. Seeberger, *J. Org. Chem.* **2015**, *2015*, 3036.

[60] (a) C. A. Hone, D. M. Roberge, C. O. Kappe, *ChemSusChem* **2017**, *10*, 32; (b) A. Gavriilidis, A. Constantinou, K. Hellgardt, K. K. Hii, G. J. Hutchings, G. L. Brett, S. Kuhn, S. P. Marsden, *React. Chem. Eng.* **2016**, *1*, 595.

[61] (a) R. Munirathinam, J. Huskens, W. Verboom, Adv. Synth. Catal. 2015, 357, 1093; (b) R. Ricciardi, J. Huskens, W. Verboom, *ChemSusChem* **2015**, *8*, 2586.

[62] (a) P. J. Cossar, L. Hizartzidis, M. I. Simone, A. McCluskey, C. P. Gordon, *Org. Biomol. Chem.* **2015**, *13*, 7119; (b) C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327.

of two immiscible phases. In this sector, the beneficial application of flow technology for multiphasic reaction systems are briefly introduced.

A gas-liquid reaction in a conventional batch set-up usually suffers from a large stoichiometric excess of the gaseous reagent. Since the atom-economic properties of gas-liquid reactions often overcome the use of liquid or solid alternatives, many gas-liquid reactions are still run on a large scale. However, the use of gases or gaseous reagents in continuous flow can outcompete the need of large excesses of the gaseous components. Baxendale and co-workers calculated the interfacial areas for various reactors and flasks demonstrating that in a gas-liquid microchannel reactor the interfacial area is 3400-18000 $m^2 \cdot m^{-3}$, whereas for a 5 mL flask it is 141 $m^2 \cdot m^{-3}$. Especially an up-scaling of gaseous reactions strongly suffers from the loss of interfacial area. It was demonstrated that a half-filled 250 mL flask exhibits only 38 $m^2 \cdot m^{-3}$ interfacial area.[63] Therefore, gas-liquid reactions display a promising reaction type candidate for a transfer to continuous flow.

Depending on the flow-rate, gas-liquid reactions in continuous flow result either in bubble, slug or annular flow. Typical flow-rates, however, usually result in a slug flow with gaseous bubbles occupying the whole diameter of the tubing separated by liquid droplets. The faster the flow-rate, the smaller the gaseous bubbles become resulting in an increased number of bubbles per length unit and therefore an increased interfacial area. Furthermore, a highly desired alternative to slug flow is the Taylor flow. Herein, the slug flow bubbles adopt a special geometry, in which the gas is separated from the tubing wall by a thin film of liquid phase. Due to significantly increased interfacial area, the mass transfer is considerably increased.

Additionally, gas-liquid reactions performed in continuous flow benefit from the possibility to adjust higher pressure compared to conventional reaction set-ups resulting in an increased solubility of the gas. Lastly, many gases or gaseous reagents are toxic and dangerous to handle in a conventional batch reactor. However, the exposure to the chemists using a flow set-up is limited and, by *in situ* generation of the gas, it is completely avoided. These benefits are highlighted in the Heck-type carbonylation using stoichiometric amounts of *in situ* generated CO gas without any exposure of the synthetic chemists to toxic carbon monoxide by Ryu and co-workers (Scheme 5a).[64] Further, gaseous phosgene is usually avoided in academia and industry due to its high toxicity and difficulties while handling gaseous reagents. However, the use of phosgene displays an efficient method to activate carboxylic acids, which subsequently react with amines resulting in amide bonds. To combine safer handling and the high reactivity of phosgene, *in situ* generation was highly desired. Fortunately, mixing the corresponding carboxylic acid in DIPEA and DMF with triphosgene in MeCN afforded *in situ* generated phosgene within 0.5 s at 20 °C (Scheme 5b). The subsequent trapping of the activated acid with amines resulted in the corresponding amid bond formation in good to excellent yields.

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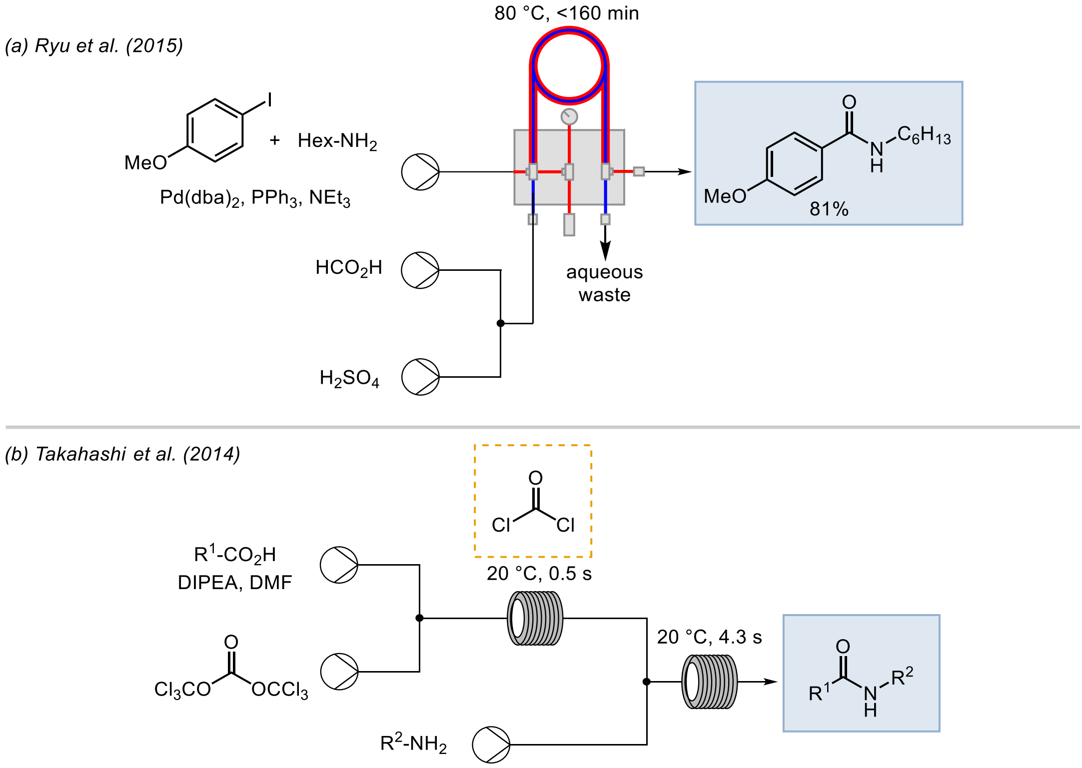
[63] C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327.

[64] (a) C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup, I. Ryu, *Org. Lett.* **2013**, *15*, 2794; (b) T. Fukuyama, Y. Mukai, I. Ryu, *J. Org. Chem.* **2011**, *7*, 1288.

Remaining phosgene is directly trapped by a batch quench with *aq.* HCl to avoid any exposure to highly toxic phosgene.[65]



Scheme 5: (a) Heck-type carbonylation using *in situ* generated CO.[64] (b) *In situ* generation of phosgene for the efficient amide bond formation using primary amines and carboxylic acids.[65]

Solid-liquid reactions also gain benefit from the easy separation and reusability of heterogeneous catalysts within packed-bed reactors. Depending on the particle size of the solids or the heterogeneous catalysts, the molar concentration of active catalysts is increased due to the increased interfacial surface facilitating an improved mass transfer. Especially triphasic reactions such as hydrogenation reactions with elemental hydrogen gas, using a heterogeneous catalyst in a packed-bed reactor and a solution of the unsaturated substrates, highly benefit from packed-bed reactor technology and efficient mixing within microchannel units.[66] Even enantioselective hydrogenations in continuous flow were reported. Ding and co-workers designed an insoluble polymeric chiral catalyst by mixing MonoPhos-based ligands and $[Rh(cod)_2]BF_4$ which was then filled in a packed-bed reactor performing asymmetric hydrogenations of α-dehydroamino acid methyl esters (Scheme 6).[67] Similarly, various other chiral catalytic systems including Ru, Pd and Ni with different ligands were reported.[68]

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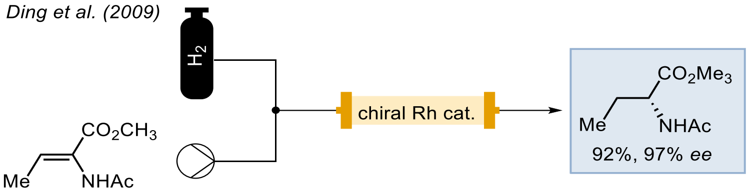
[65] (a) S. Fuse, N. Tanabe, T. Takahashi, *Chem. Commun.* **2011**, *46*, 12661; (b) S. Fuse, Y. Mifune, T. Takahashi, *Angew. Chem. Int. Ed.* **2014**, *53*, 851; (c) L. Cotarca, T. Geller, J. Répási, *Org. Process Res. Dev.* **2017**, *21*, 1439.

[66] M. Irfan, T. N. Glasnov, C. O. Kappe, *ChemSusChem.* **2011**, *4*, 300.

[67] L. Shi, X. Wang, C. A. Sandoval, Z. Wang, H. Li, J. Wu, L. Yu, K. Ding, *Chem. Eur. J.* **2009**, *15*, 9855.

[68] (a) C. de Bellefon, N. Tanchoux, S. Caravieilhes, P. Grenouillet, V. Hessel, *Angew. Chem. Int. Ed.* **2000**, *39*, 3442; (b) C. de Bellefon, R. Abdallah, T. Lamouille, N. Pestre, S. Caravieilhes, P. Grenouillet, *Chimia*, **2002**, *56*, 621; (c) C. de Bellefon, N. Pestre, T. Lamouille, P. Grenouillet, V. Hessel, *Adv. Synth. Catal.* **2003**, *345*, 190.



Scheme 6: Asymmetric hydrogenations of α-dehydroamino acids methyl esters using a triphasic continuous flow set-up.[67]

Nevertheless, by far the most organic syntheses are liquid-liquid reactions. In a continuous flow set-up two distinct flow regimes occur upon such reactions: laminar flow and slug flow. The choice of appropriate mixing devices strongly influences the resulting flow regimes. Whereas the use of a T-mixer often results in slug flow, laminar flow usually occurs using a Y-mixer. However, not only the design of the mixing unit, but also the flow-rates (Q), the viscosity of the reagent streams (v), the hydraulic diameter (D_H) and the channel width (A) impact the resulting flow regimes. Hence, the Reynolds number R_e is used to precisely calculate the flow regimes within a flow set-up (Equation 4):

$$R_e = \frac{Q \cdot D_H}{\nu \cdot A} \tag{4}$$

Equation 4: Reynolds number for the calculation of disctinct flow regimes. If $R_e < 2040$, it usually leads to laminar flow regimes.

Reactions with low flow-rates, viscous reagents and a large channel width usually lead to laminar flow regimes with Reynolds numbers $R_e < 2040$.[69] As a result of the huge longitudinal interface within laminar flow regimes and the numerous transverse interfaces occurring upon slug flow, liquid-liquid reactions often display a better performance in a continuous flow set-up compared to comparable batch reactions.

2.5 BENEFITS OF FLOW CHEMISTRY

Flow chemistry has truly the potential to revolutionize syntheses of organic molecules. In comparison to batch chemistry, typical benefits of flow chemistry are

(I) high surface-to-volume ratio of the reactor, which enables excellent temperature control and light penetration (useful *e.g.* in photochemical or highly exothermic reactions)

(II) the possibility to control the reactivity of unstable intermediates by consecutive, time-resolved quenching with suitable electrophiles

(III) performing reactions above the boiling point of the solvent by using a back pressure regulator or at elevated pressure

(IV) easy up-scaling of reactions by simply increasing the run-time

(V) safer handling of hazardous or explosive chemicals

(VI) Possibilities of in-line purification and analysis

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[69] K. Avila, D. Moxey, A. de Lozar, M. Avila, D. Barkley, B. Hof, *Science* **2011**, *333*, 192.

With these benefits in mind, there are many promising reactions, which were facilitated by flow chemistry to apply its advantages to well-known reaction pathways. At this point it is important to mention, that flow chemistry does not change the kinetics of a reaction. Rather, flow chemistry offers a mechanistic tool to reduce concentration or temperature gradients and therefore the formation of undesired side products. Even if mixing is not of main interest for a desired reaction, flow chemistry can still be beneficial. Highly exothermic reactions are complicated to handle in batch because the required cooling cannot be provided efficiently. On the other hand, the application of back pressure regulators allows chemists to equally heat the reaction mixtures to temperatures even above the boiling point of the solvents resulting in faster conversions with higher yields especially for intrinsically slow reactions. In case of multiphasic reactions, the application of flow technology often improves the efficiency of the desired reaction. Thus, flow chemistry has received a remarkably amount of attention because it enables new reaction methodologies, which were not known in conventional batch reactions. Hence, it is already used in both academia and industrial laboratories to a large extent. However, the use of one single reaction in continuous flow is the result of tedious, time-consuming screenings and optimizations not only of standard parameters such as temperature, stoichiometry, temperature, but also of the flow parameters, such as investigations of mixing and reactor units. Due to its complexity and the high costs compared to already existing batch equipment, it is definitely necessary to think about the desired benefits of flow technology in contrast to traditionally macrobatch chemistry for industrial applications. If the reaction is well-known in batch chemistry, resulting in excellent yields at ambient temperatures without the need of hazardous reagents, there is no need to optimize the reaction in a continuous flow set-up. However, reducing the exposure to toxic reagents or the generation of explosive intermediates often benefits from the application of flow chemistry. Due to the efficient mixing and working at elevated pressures, the use of gaseous reagents and gases is advantageous in a continuous flow set-up. Moreover, fast reactions which are difficult to scale-up or not selective in a batch reactor considerably gain profit in a continuous reaction. Lastly, the use of special reactor units allows for a better heat transfer, irradiation or electrochemical catalyses leading to a broad range of areas, where flow is applied in an advantageous manner.

3. ORGANOMETALLIC CHEMISTRY

3.1 PREPARATION OF ORGANOMETALLIC REAGENTS

Since many decades, numerous methodologies for the preparation and handling of organometallic reagents were investigated. The following chapter gives a brief overview about landmarks in organometallic chemistry. Depending on the availability of starting materials, the desired reaction conditions and the necessity for functional group tolerance, the accurate choice for a convenient preparation of the organometallic compound is essential. Its reactivity is in strong correlation with the polarization of the resulting carbon-metal bond. The more polarized the carbon-metal bond, the more reactive is the organometallic species, however with the major drawback of lowered functional group tolerance and stability of the inherently prepared organometallic species.[70] An indication for the polarization of a carbon-metal bond is derived from the Pauling electronegativity difference between carbon and the corresponding metal (Figure 10).

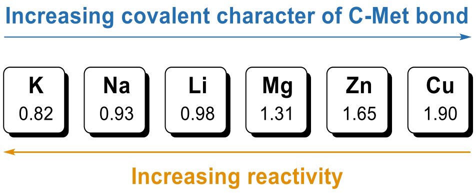

Figure 10: Increasing covalency of the C-Met bond results in a decreased reactivity of the organometallic reagent. Electronegativities according to Pauling.[71]

In general, the use of organometallics with highly polarized carbon-metal bonds such as organolithiums usually require costly cooling of the reaction mixture due to otherwise occurring side reactions and decomposition of the organometallics. Based on their intrinsical reactivity, there is usually no need of further activation of the organometallic reagents for their reactivity with a broad range of electrophiles such as aldehydes, ketones, Weinreb amides, imines or even epoxides.[70] On the other side, the use of less reactive organozinc reagents allows for a broad functional group tolerance, a significantly enhanced stability and thus the possibility to store organozinc reagents for months. However, the reactivity of organozinc compounds often requires the activation *via* transition metals and elevated temperatures to perform desired electrophile quenches or cross-coupling reactions. Nevertheless, it is worth mentioning that the direct generation of organozinc reagents is sometimes not possible and therefore its generation *via* transmetalation from a more reactive organometallic reagent already necessitates a consideration of functional group tolerance.[72] In the following sections, four ways to generate organometallic reagents in conventional batch reactors and in continuous flow are highlighted and their application, substrate scope and functional group tolerance are discussed.

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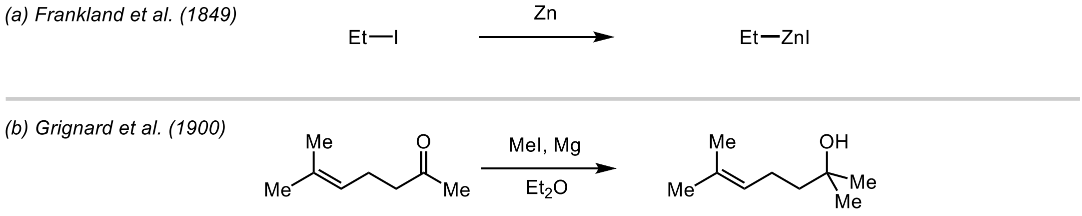
[70] (a) *Handbook of Functionalized Organometallics Vol 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**; (b) *Organometallchemie Vol 6*, (Ed.: C. Elschenbroich), Teubner, Wiesbaden, **2008**.

[71] D. R. Lide (Hrsg.): *Molecular Structure and Spectroscopy* in *CRC Handbook of Chemistry and Physics Vol 90*, (Ed. D. R. Lide), CRC Press/Taylor and Francis, Boca Raton, FL.

[72] E. Demory, V. Blandin, J. Einhorn, P. Y. Chavant, *Org. Process Res. Dev.* **2011**, *15*, 710.

3.1.1 Oxidative Insertion

Oxidative insertion is a powerful way to generate organometallic reagents. Since the development of the first organozinc reagent by Frankland in 1849 (Scheme 7a), who mixed zinc powder and ethyl iodide to perform an efficient insertion into the carbon-iodide bond, the field of oxidative insertion is continuously growing.[73] Due to the high atom- and cost-economy, oxidative insertion is still a considered method to generate organometallic reagents. Nevertheless, the generation of organozinc species suffers from the need of polar aprotic solvents and elevated temperatures. In 1900, Victor Grignard achieved a major breakthrough in oxidative insertions. While mixing methyl iodide and magnesium turnings, he generated methyl magnesium iodide, which is considered as the first organomagnesium reagent (Scheme 7b).[74]



Scheme 7: Seminal contributions for the generation of organometallic reagents by Frankland[73] (1849) and Grignard (1900).[74]

However, it turned out that elemental magnesium has some significant drawbacks in synthetic applications. Magnesium acts as a reducing agent which limits it substrate scope drastically. Organic halides containing *e.g.* nitro or azide functional groups are not tolerated upon oxidative insertion.[75] Moreover, magnesium needs to be activated prior to the oxidative insertion by iodine,[76] DIBAL-H[77] or dibromoethane[78] due to a passivation layer of MgO. Furthermore, the oxidative insertion is an exothermic reaction which is in particular problematic for a sufficient up-scale of desired reaction.[79]

In 2006, Knochel and co-workers developed an alternative way to perform oxidative insertions. While mixing various metals with LiCl, the oxidative insertion was promoted in such a way that the reaction proceeds without the need of additional heating at ambient temperatures (−20 °C to 25 °C) leading to an increased functional group tolerance. Further, the solubility of the resulting LiCl-complexed organometallic species was significantly increased (Scheme 8).[80]

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[73] (a) E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171; (b) D. Seyferth, *Organometallics* **2001**, *20*, 2940.

[74] (a) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322; (b) D. Seyferth, *Organometallics* **2009**, *28*, 1598.

[75] (a) O. Kamm, *Org. Synth.* **1941**, *1*, 445; (b) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983; (c) W. Lin, X. Zhang, Z. He, Y. Jin, L. Gong, A. Mi, *Synth. Commun.* **2002**, *32*, 3279.

[76] H. Gold, M. Lahed, P. Nilsson, *Synlett* **2005**, 1596.

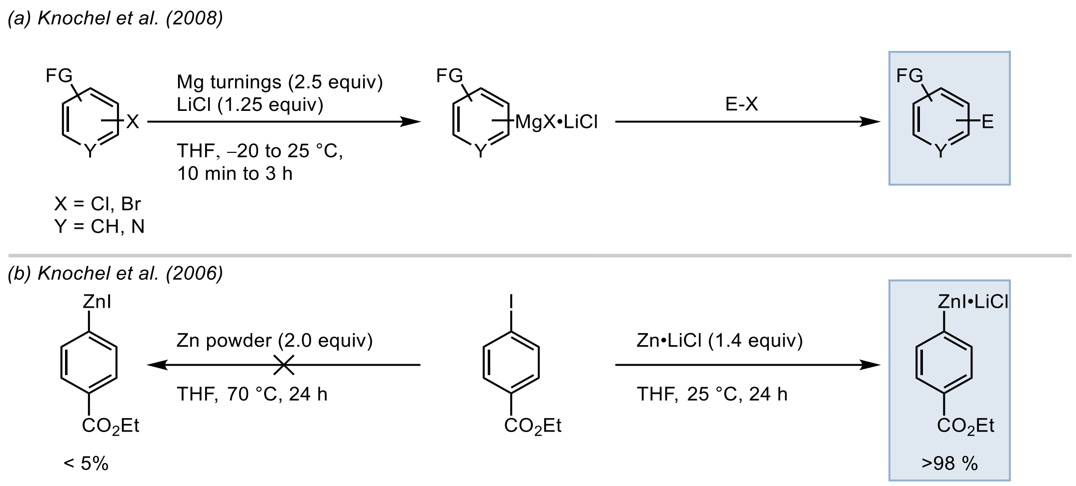
[77] U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.

[78] W. E. Lindsell, *Comprehensive Organometallic Chemistry I Vol 1* (Eds.: G. Wilkinson, F. G. S. Stone, G. E. Ebel) Pergamon Press, Oxford, **1982**.

[79] *Grignard Reagents, New Developments* (Ed.: H. G. Richey jr.) Wiley, New York, **2000**.

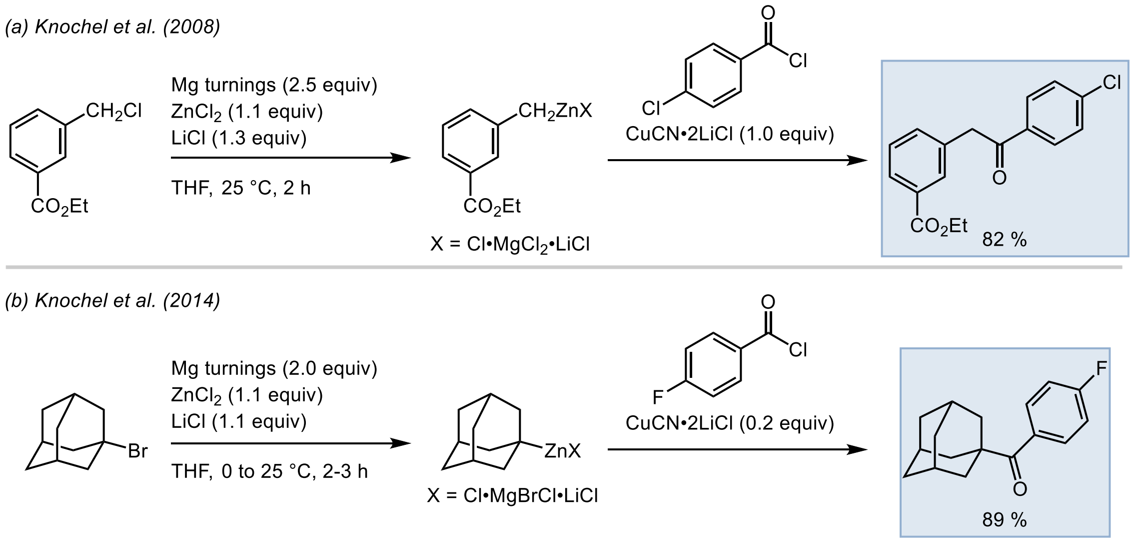
[80] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

In course of these studies, various organomagnesium,[81] -zinc,[82] -manganese[83] and -aluminium[84] intermediates were successfully synthesized.



Scheme 8: Oxidative insertions of magnesium or zinc in the presence of LiCl affording an organometallic species with enhanced solubility at ambient conditions. [81-82]

Additionally, Knochel *et al.* developed an *in situ* trapping method. It was found that the oxidative insertion of magnesium in the presence of *e.g.* $ZnCl_2$ still takes place (Scheme 9).[85] As soon as the organomagnesium species is formed, it is *in situ* trapped by the metal salt resulting in the more stable organometallic species, which allows a higher functional group tolerance.



Scheme 9: Oxidative insertions in the presence of LiCl and $ZnCl_2$ affording the *in situ* trapped organozinc reagents after oxidative insertion.[85]

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[81] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.

[82] (a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; (b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.

[83] Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198.

[84] T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313.

[85] (a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; (b) C. Sämann, V. Dhayalan, P. R. Schreiner, P. Knochel, *Org. Lett.* **2014**, *16*, 2418.

3.1.2 Halogen-Metal Exchange

In 1931, Prévost reported the first bromine-magnesium exchange using EtMgBr and cinnamoyl bromide in diethyl ether, opening up a new field of organometallic chemistry.[86] Wittig and Gilman further expanded the halogen-metal exchange reaction to the usage of BuLi as exchange reagent performing halogen-lithium exchanges.[87]

The generation of organometallic compounds *via* a halogen-metal exchange offers the great advantage of stereodefined intermediates.[88] Furthermore, no preactivation of the metal or the starting material is needed resulting in fast reaction rates. Additionally, the halogen-metal exchange can be performed at ambient temperatures without the need of heating. Since no elemental metal is used, the risk of reducing functional groups is lowered, hence the functional group tolerance is increased. However, the exchange reaction is an equilibrium reaction. During the reaction, the more stable carbanion is formed (Figure 11).[89]

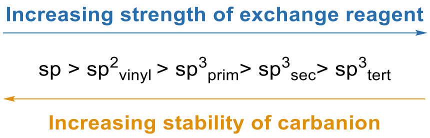

Figure 11: Depence of the stability of a carbanion and its strength as an exchange reagent.[89]

In course of halogen-lithium exchange studies, Parham and co-workers performed a halogen-lithium exchange in the presence of sensitive functional groups such as esters and nitro groups. However, the need of cryogenic temperatures was essential (Scheme 10a).[90] Knochel and co-workers further developed an iodide-lithium exchange reaction of vinyl iodides containing azides in the presence of $ZnCl_2$. The intermediate lithium species is *in situ* trapped by $ZnCl_2$ forming the more stable and less reactive zinc species, which further reacted with electrophiles without the attack of the azide (Scheme 10b).[91] Additionally, Yamamoto demonstrated the use of so-called super silyl protecting groups to perform an exchange reaction in the presence of esters (Scheme 10c).[92] However, the major drawbacks of halogen-lithium exchange reactions with moderate functional group tolerance are the need of cryogenic temperatures and uneconomic functional group protection.

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[86] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, 1372.

[87] (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.

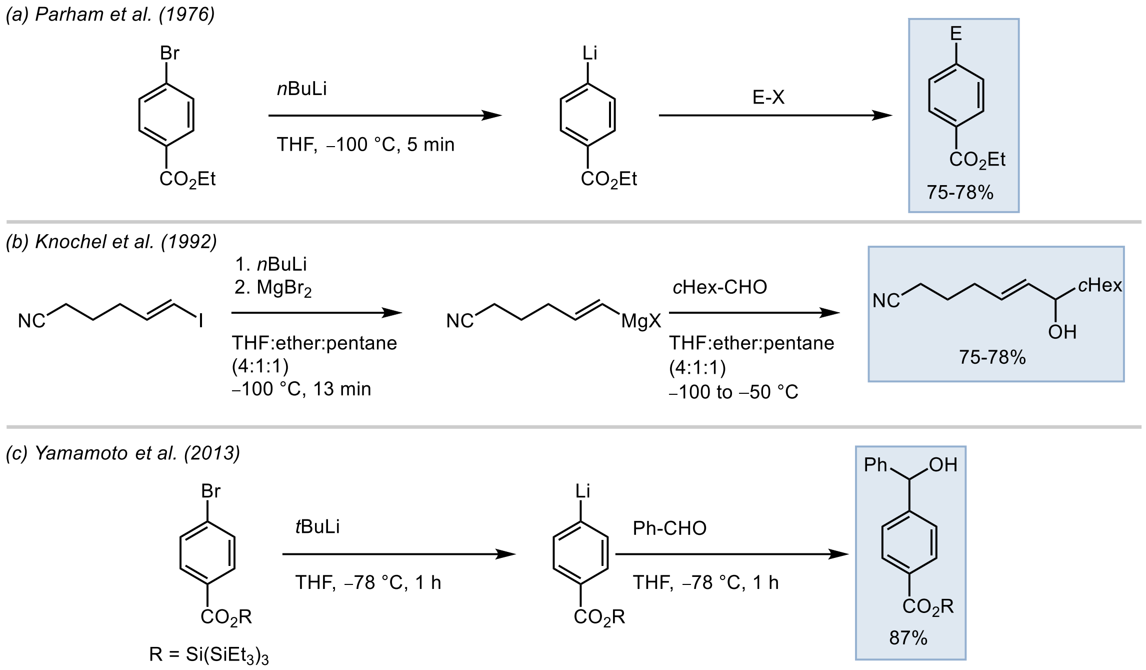
[88] (a) H. Neumann, D. Seebach, *Tetrahedron Lett.* **1976**, *52*, 4839; (b) K. Moriya, M. Simon, R. Mose, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10963.

[89] (a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; (b) D. E. Applequist, D. F. O´Brien, *J. Am. Chem. Soc.* **1962**, *85*, 74.

[90] (a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704; (b) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187; (c) W. E. Parham, C. K. Bradscher, *Acc. Chem. Res.* **1982**, *15*, 300.

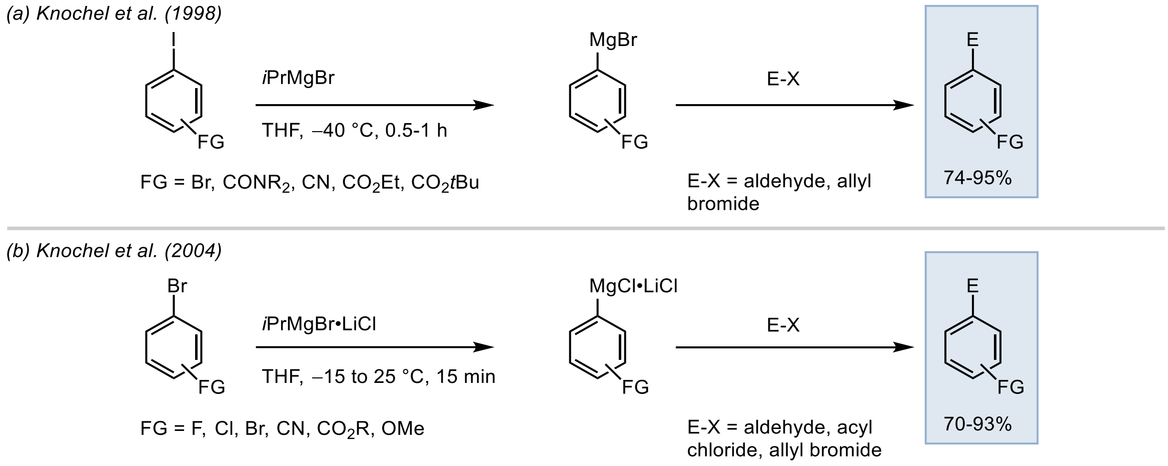
[91] (a) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983; (b) I. Klement, M. Rottländer, C. E. Tucker, T. N. Majid, P. Knochel, P. Venegas, G. Cahiez, *Tetrahedron* **1996**, *52*, 7301.

[92] S. Oda, H. Yamamoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 8165.



Scheme 10: Various strategies to perform halogen-lithium exchange in the presence of sensitive functional groups. (a) Cryogenic temperatures.[90] (b) *In situ* trapping of the aliphatic organilithium species.[91] (c) Sterically demanding protecting groups such as super silyl protecting group.[92]

Following seminal contributions of Prévost and Villieras, Knochel and co-workers have extended the halogen-lithium exchange to iodine-magnesium exchange reactions using *i*PrMgCl or PhMgCl to tolerate functional groups such as esters or nitro groups (Scheme 11a).[93] By adding LiCl to *i*PrMgCl, the so-called Turbo-Grignard was found to be more reactive in such a way that also a bromine-magnesium exchange was possible (Scheme 11b).[94]



Scheme 11: Iodine-magnesium exchange reactions using (a) *i*PrMgCl[93] or (b) Turbo-Grignard reagent.[94]

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[93] (a) C. Prévost, *Bull. Soc. Chem. Fr.* **1931**, *49*, 1372; (b) J. Villieras, *Bull. Soc. Chim. Fr.* **1967**, *5*, 1520; (c) L. Boymond, M. Rottänder, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.

[94] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

3.1.3 Directed Metalation

The preparation of organometallic compounds *via* directed metalation comprises some advantages over oxidative insertion and halogen-metal exchange. Directed metalation does not need any halogen at the desired position to perform a metalation. However, the need of strong bases cannot be precluded. In general, the use of strong alkyl lithium or lithium amide bases leads to a limited functional group tolerance of the directed metalation. Moreover, lithium amides of the general structure $LiNR_2$ such as LiHMDS, LDA and LiTMP are less nucleophilic than the alkyl lithium bases. Therefore, the application of lithium amides avoids undesired exchange reactions while maintaining a reactivity that is high enough to perform a directed metalation. However, the solubility of such bases at lower temperatures is limited.[95] To overcome these limitations, Hauser *et al.* investigated magnesium amides as metalating agents.[96] Eaton and Mulzer *et al.* continued the seminal work of Hauser and extended the use of magnesium amides to TMPMgCl and TMP_2Mg,[97] which allowed direct metalation of aromatics, pyridines and cyclopropanes. Nevertheless, the solubility of TMP-bases in THF remained low which allowed for the directed metalation solely at higher temperatures and with a large excess of TMP-base. To address these problems, the addition of LiCl increased the solubility of TMP-bases significantly while maintaining a high kinetical activity. Thus, the preparation of TMPMg·LiCl was straight forward: TMPH was directly mixed with *i*PrMgCl·LiCl achieving the TMPMgCl·LiCl base (Scheme 12a).[98] However, the directed metalation still suffered from limited functional group tolerance (Scheme 12b). The application of different metals led to a broad toolbox of various TMP-bases such as $(TMP)_2Mn\cdot 2MgCl_2\cdot 4LiCl$,[99] $(TMP)_2Fe\cdot 2MgCl_2\cdot 4LiCl$,[100] $(TMP)_3La\cdot 3MgCl_2\cdot 5LiCl$,[101] TMPZnCl·LiCl[102] and $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$[103] with varying functional group tolerance, regioselectivity and reactivity. Nevertheless, a scale up of directed metalations is still problematic due to the need of cryogenic temperatures.

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[95] (a) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306; (b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; (c) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; (d) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376.

[96] (a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; (b) F. C. Frostick, C. R. Hauser, *J. Am. Chem. Soc.* **1949**, *71*, 1350.

[97] (a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016; (b) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370.

[98] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.

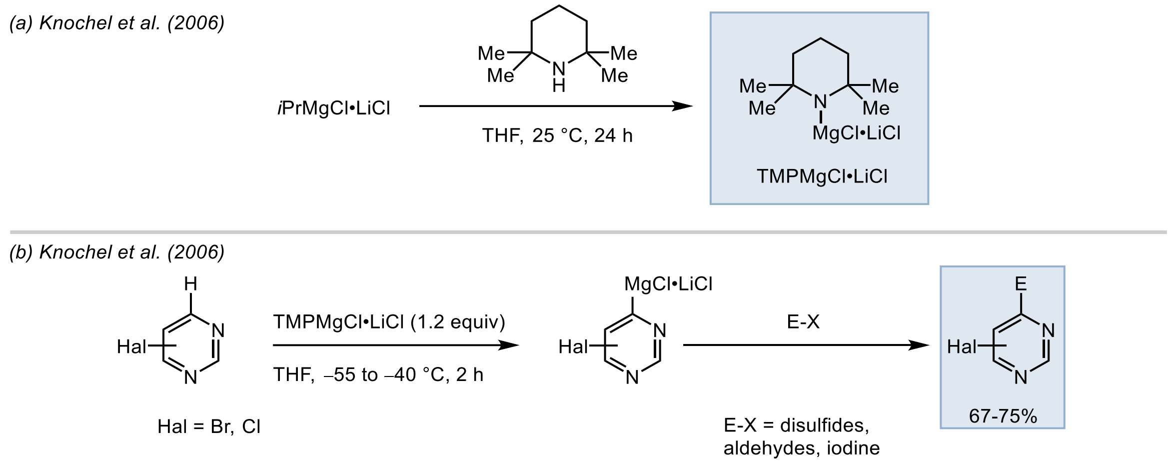
[99] S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.

[100] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.

[101] S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3304.

[102] (a) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; (b) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584.

[103] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.



Scheme 12: (a) Preparation of TMPMgCl·LiCl. (b) Directed metalation of pyrimidines using TMPMgCl·LiCl.[98]

3.1.4 *Transmetalation*

Transmetalation provides an efficient method to convert a reactive organometallic intermediate to a second, less reactive, hence more stable organometallic species. First reported by Gilman *et al.* in 1936, the concept of transmetalation arose as a promising tool especially with respect to functional group tolerance.[104] Mixing of a highly reactive organometallic species such as organolithiums with a less electropositive metal salt such as $MgCl_2$ or $ZnCl_2$ leads to the formation of the more stable organometallic species. The driving force for the transmetalation event is the generation of the more covalent carbon-metal bond and the formation of the more ionic metal salt due to the higher lattice energy.[104] Due to the fast halogen-lithium exchange and the application of strong lithium bases for direct metalation, the broad scope of substituted organolithiums is mainly limited by the functional group tolerance of the resulting lithium organometallics. Therefore, the generation of highly unstable organometallic species such as organolithiums necessitates a fast transmetalation event before undesired decomposition.

A second alternative reported by Knochel and co-workers is the *in situ* trapping approach. First, the starting material is premixed with a corresponding metal salt before the metalation is initiated. For instance, directed lithiation with TMPLi in the presence of magnesium, zinc or copper salts leads to the desired organomagnesium, -zinc or -copper intermediate with significantly enhanced stability and functional group tolerance.[105] In fact, the transmetalation of TMPLi to the more stable TMPMet species (Met = Mg, Zn or Cu) could be faster than the metalation event. However, calculations of the competing reactions showed, that the transmetalation of TMPLi is six-times slower than the directed metalation (Scheme 13). Therefore, the directed metalation occurs first, followed by a transmetalation to the more stable organometallic species. Nevertheless, the need of cryogenic temperatures displays a major drawback of transmetalations, in particularly for scaling-up these reactions.

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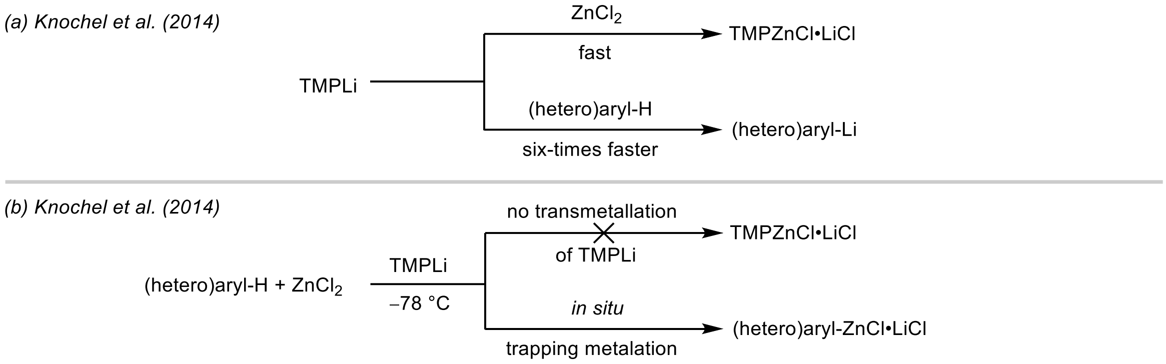
[104] *Organometallchemie Vol 6* (Ed.: C. Elschenbroich), Teubner, Wiesbaden, **2008**.

[105] 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.



Scheme 13: (a) Directed metalation is six-times faster than the transmetalation to the less reactive organozinc spezies; (b) Directed metalation of (hetero)arenes followed by *in situ* trapping with $ZnCl_2$.

3.2 ORGANOMETALLIC REAGENTS IN CONTINUOUS FLOW

In recent years, the beneficial merger of organometallic chemistry with flow chemistry was extensively studied. Hence an overview about organometallic chemistry in continuous flow is given in the following chapter.

Continuous flow chemistry offers several advantages compared to the classical batch approach. Due to a precise reaction time control, efficient mixing and an excellent heat transfer, the generation of organometallic compounds was achieved at ambient temperatures without the need of cryogenic temperatures.[106] Since only a very small amount of highly reactive intermediate is formed at a certain time, the electrophilic quench can be performed precisely without the occurrence of local concentration gradients or hotspots. Further, the use of continuous flow set-ups allowed the exploitation of unstable intermediates, which are difficult or impossible to handle under standard batch conditions.[107] By using a flow set-up with several pumping devices, multistep syntheses were implemented. Finally, the scale-up of previously reported syntheses is possible by simply increasing the run-time without the need of further optimizations. These technical capabilities led to numerous applications of flow technology in the area of organometallic chemistry, which are highlighted hereafter.

3.2.1 Oxidative Insertion in Continuous Flow

Oxidative insertions in continuous flow may offer significant benefits over their batch counterparts. The *in situ* prepared organometallic species is directly removed from the excess of solid metal avoiding side reactions according to the exothermic nature of the oxidative insertion. Efficient cooling of relatively small amounts of organometallics within a column or cartridge is easily afforded according to the enhanced surface-to-volume ratio. Hence, application of column and cartridge reactors allowed the usage of various metal powders in a continuous flow set-up. Alcázar and McQuade reported the first oxidative insertion of

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[106] (a) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892; (b) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688; (c) N. Kockmann, P. Thenée, C. Fleischer-Trebes, G. Laudadio, T. Noël, *React. Chem. Eng.* **2017**, *2*, 258; (d) *Flash Chemistry, Fast Organic Synthesis in Microsystems* (Ed.: J.-i. Yoshida), Wiley, Chichester, **2008**.

[107] (a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796; (b) D. E. Fitzpatrick, S. V. Ley, *Tetrahedron* **2018**, *74*, 3087; (c) *Micro Reaction Technology in Organic Synthesis* (Eds.: C. Wiles, P. Watts), CRC, Boca Raton, **2011**; (d) *Microreactors in Organic Chemistry and Catalysis, 2nd Ed.* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2013**.

elemental zinc into an alkylic or benzylic carbon-halide bond followed by a subsequent Negishi-cross coupling with aryl halides in a continuous flow set-up (Scheme 14a). First, the column reactor is filled with elemental zinc, which is preactivated by flashing with TMSCl and 1,2-dibromoethane. A solution of the alkyl- or benzylhalide is then passing by the packed-bed reactor for 10 min, affording the desired organozinc reagents. A subsequent in-line quench using aryl halides and a Silicat DPP-Pd column furnished the corresponding Negishi cross-coupling products in good to excellent yields.[108]

Similarly, de la Hoz and Alcázar have reported that magnesium turnings are preactivated by DIBAL-H, TMSCl and 1-bromo-2-chloroethane and stored in a packed-bed reactor. By pumping a THF solution of an alkyl or aryl halide through the column reactor, the corresponding magnesium species are obtained at elevated temperatures within 7.5 min. A subsequent in-line electrophile quench using aldehydes, Weinreb amides, anhydrides and isocyanates leads to the functionalized products in good yields (Scheme 14b).[109] Monitoring of the *in situ* generated Grignard reagent is achieved by on-line NMR spectroscopy.[110] Further, *in situ* trapping of the intermediate magnesium species with $ZnCl_2$ leads to the corresponding organozinc species, which undergoes a Nickel-mediated cross-coupling reaction with aryl iodides (Scheme 14c).[111] Noteworthy, these method tackles limitations, which are prone to oxidative insertions under batch conditions, *e.g.* the highly exothermic nature of the metal insertion is easily controlled and the subsequent trapping of the *in situ* generated organometallic species avoids any difficulties of storage and handling of air-sensitive organometallic reagents.

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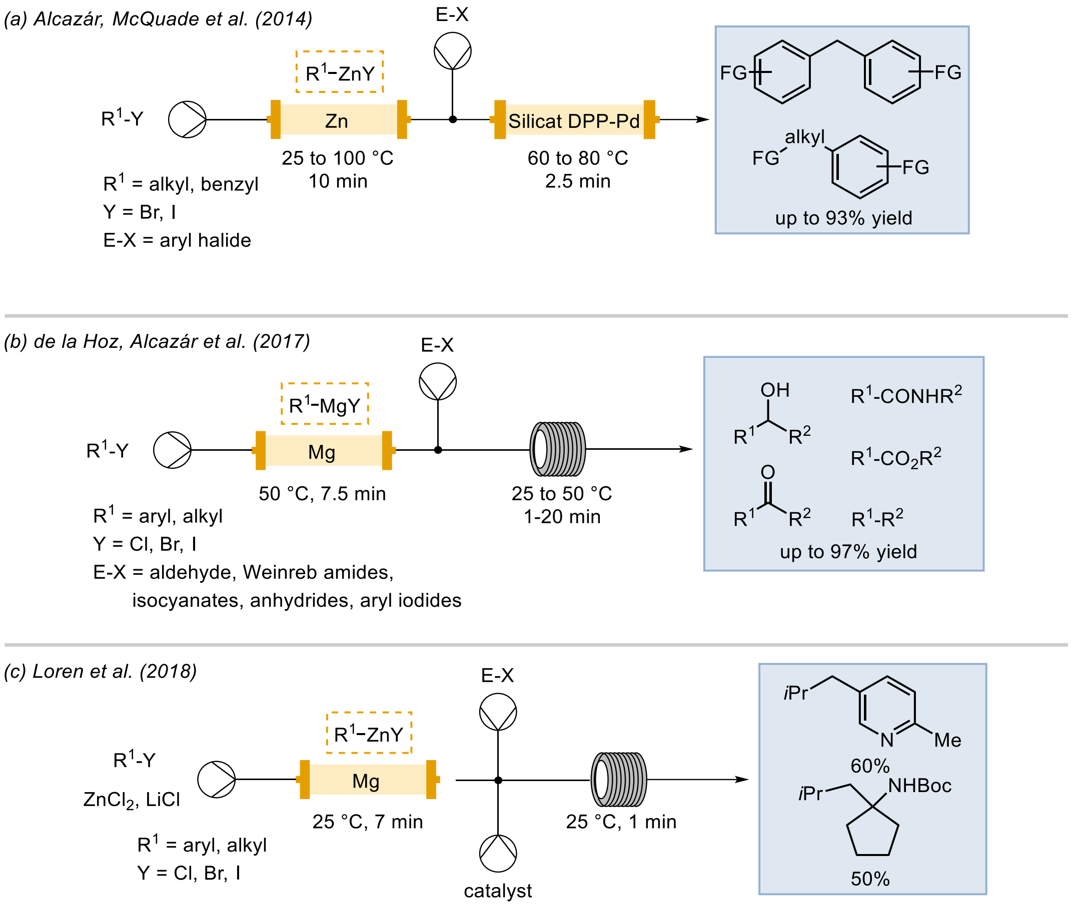
[108] (a) N. Alonso, L. Z. Miller, J. de Muñoz, J. Alcazar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3747; (b) M. Berton, L. Huck, J. Alcázar, *Nat. Protoc.* **2018**, *13*, 324; (c) I. Abdiaj, C. R. Horn, J. Alcázar, *J. Org. Chem.* **2019**, *84*, 4748.

[109] L. Huck, A. de la Hoz, A. Diaz-Ortiz, J. Alcázar, *Org. Lett.* **2017**, *19*, 3747.

[110] M. Goldbach, E. Danieli, J. Perlo, B. Kaptein, V. M. Litvinov, B. Blümich, F. Casanova, A. L. L. Duchateau, *Tetrahedron Lett.* **2016**, *57*, 122.

[111] A. Herath, V. Molteni, S. Pan, J. Loren, *Org. Lett.* **2018**, *20*, 7429.



Scheme 14: Oxidative insertion in a continuous flow set-up using packed-bed reactors with magnesium[109-111] or zinc.[108]

In summary, challenging steps of the oxidative insertion, such as the exothermal reaction conditions, can be avoided by the aid of continuous flow technology. Additionally, the immediate quench of the *in situ* formed organometallic species allows a broader scope of functional groups. It is worth mentioning that the generation of organometallic species in continuous flow *via* oxidative insertion usually does not increase the yield of the reaction significantly. Rather, the flow set-up is used for a precise reaction time control and an easier and safer preparation of the organometallic species.

3.2.2 Halogen-Metal Exchange in Continuous Flow

Within Yoshida´s pioneering work in halogen-metal exchange in continuous flow,[112] a custom-made ultrafast mixing devices was used, thereby affording reaction times of only a few milliseconds to perform halogen-lithium exchange reactions.[113] The unstable organolithiums were subsequently trapped with various electrophiles resulting in highly functionalized

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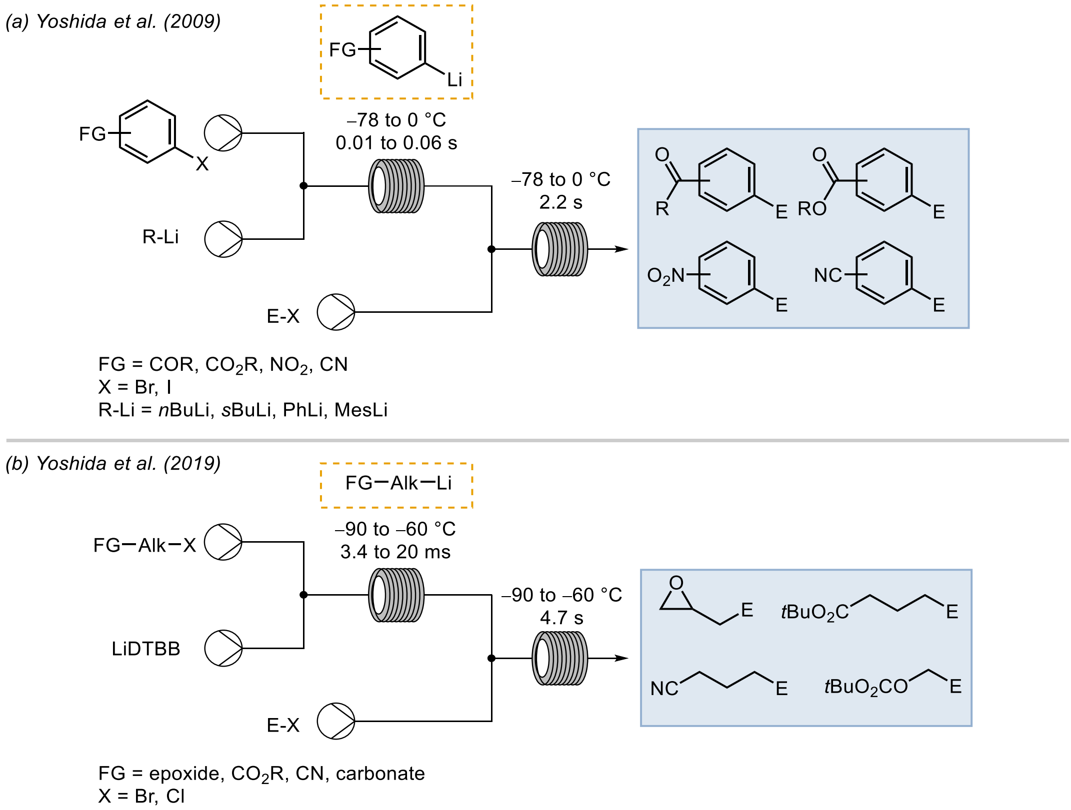
[112] (a) A. Nagaki, Y. Tomida, H. Usutani, H. Kim, N. Takabayashi, T. Nokami, H. Okamoto, J.-i. Yoshida, *Chem. Asian J.* **2007**, *2*, 1513; (b) Y. Ushiogi, T. Hase, Y. Iinuma, A. Takata, J.-i. Yoshida, *Chem. Commun.* **2007**, 2947; (c) A. Nagaki, N. Takabayashi, Y. Tomida, J.-i. Yoshida, *Org. Lett.* **2008**, *10*, 3037; (d) Y. Tomida, A. Nagaki, J.-i. Yoshida, *Org. Lett.* **2009**, *11*, 3614; (e) T. Asai, A. Takata, Y. Ushiogi, Y. Iinuma, A. Nagaki, J.-i. Yoshida, *Chem. Lett.* **2011**, *40*, 393; (f) Y. Tomida, A. Nagaki, J.-i. Yoshida, *J. Am. Chem. Soc.* **2011**, *133*, 3744.

[113] (a) H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691; (b) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J.-i. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046; (c) J.-i. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; (d) A. Nagaki, S. Ishiuchi, K. Imai, K. Sasatsuki, Y. Nakahara, J.-i. Yoshida, *React. Chem. Eng.* **2017**, *2*, 862.

products (Scheme 15a). Due to the fast iodine-lithium and bromine-lithium exchange reaction and the ultrafast mixing, the reaction times are adjusted in a way that even highly sensitive functional groups such as esters, nitriles and nitro groups are tolerated.[114] Pleasingly, the merger of continuous flow and halogen-metal exchange reactions avoids mostly the use of cryogenic temperatures and the need of bulky substituents on ester groups as reported for traditional batch chemistry and further facilitates the utilization of the highly reactive carbon-metal bond while obtaining an extended functional group tolerance. In course of Yoshida´s studies, several aryllithiums bearing electrophilic groups were synthesized which can either not be tolerated by standard batch conditions or at −100 °C.[115] Recently, Yoshida, Nagaki and co-workers expanded the scope of ultrafast halogen-lithium exchange reaction to alkyl halides bearing sensitive functional groups such as epoxides, esters, nitriles or carbonates. The highly unstable alkyllithiums were obtained within a retention time of 3.4 to 20 ms at −90 to −60 °C using a custom-made continuous flow set-up. Subsequent in-line trapping with various electrophiles afforded the desired polyfunctionalized alkanes in good yields (Scheme 15b).[116]



Scheme 15: (a) Halogen-lithium exchange using aryl- and alkyllithiums within a millisecond range and subsequent electrophile trapping.[114] (b) Generation of alkyllithiums bearing functional groups using LiDTBB and subsequent electrophile trapping.[116]

Yoshida *et al.* further demonstrated the application of ultrafast mixing for simultaneous competitive reactions such as undesired rearrangements or side reactions of lithium bases with

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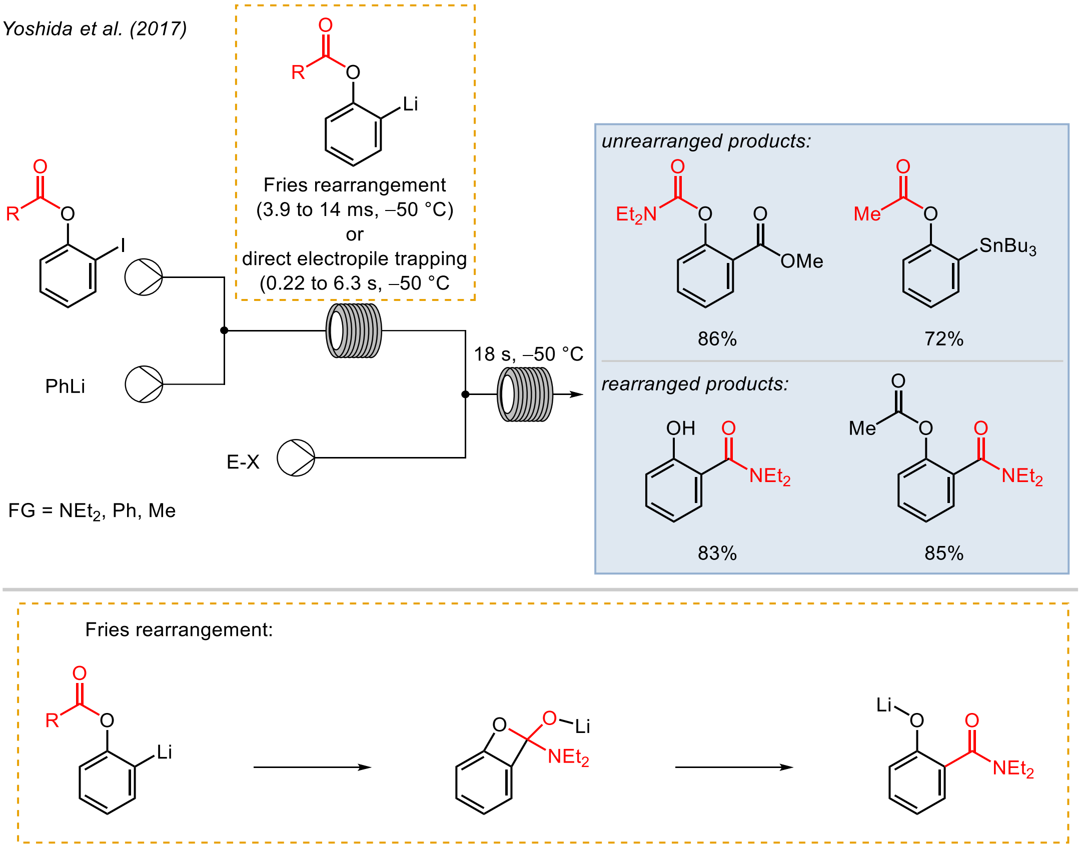
[114] (a) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; (b) A. Nagaki, H. Kim, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2008**, *47*, 7833; (c) A. Nagaki, H. Kim, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2009**, *48*, 8063; (d) A. Nagaki, H. Kim, Y. Moriwaki, C. Matsuo, J.-i. Yoshida, *Chem. Eur. J.* **2010**, *16*, 11167; (e) A. Nagaki, H. Kim, H. Usutani, C. Matsuo, J.-i. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; (f) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914.

[115] A. Nagaki, *Tetrahedron Lett.* **2019**, *60*, 150923.

[116] A. Nagaki, A. H. Yamashita, K. Hirose, Y. Tsuchihashi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2019**, *58*, 4027.

electrophilic groups within the starting material.[117] Hence, they reported the possibility to overcome side reactions occurring during a halogen-lithium exchange within a polyimide chip reactor. *E.g.* the Fries rearrangement of *ortho*-lithiated aryl carbamates and esters cannot be prevented in a macrobatch reactor. However, using a residence time of 0.33 ms afforded the *ortho*-functionalized carbamates and esters in good yields. On the other hand, by increasing the residence time to 628 ms, a Fries rearrangement occurs leading after subsequent in-line quench to the corresponding functionalized phenol derivatives (Scheme 16).[118]



Scheme 16: Selectively outcompeting the Fries rearrangement by ultrafast mixing performing an iodine-lithium exchange in a continuous flow set-up.[118]

Halogen-magnesium exchange reaction in continuous flow were reported by Yoshida, Ley and others. Yoshida reported the bromine-magnesium exchange using bromopentafluorobenzene and ethyl magnesium as exchange reagent. The *in situ* generated aryl magnesium reagent is subsequently trapped with BCl_3 or methanol resulting in the desired borate or hydrolysed pentafluorobenzene (Scheme 17a). Ley and co-workers, however, applied the Turbo-Grignard for successful generation of arylmagnesiums from the corresponding aryl bromides. Interestingly, the formation of the arylmagnesiums was monitored by in-line IR technology.[119] According to the investigations of Yoshida and Ley, it was possible to preclude the need of

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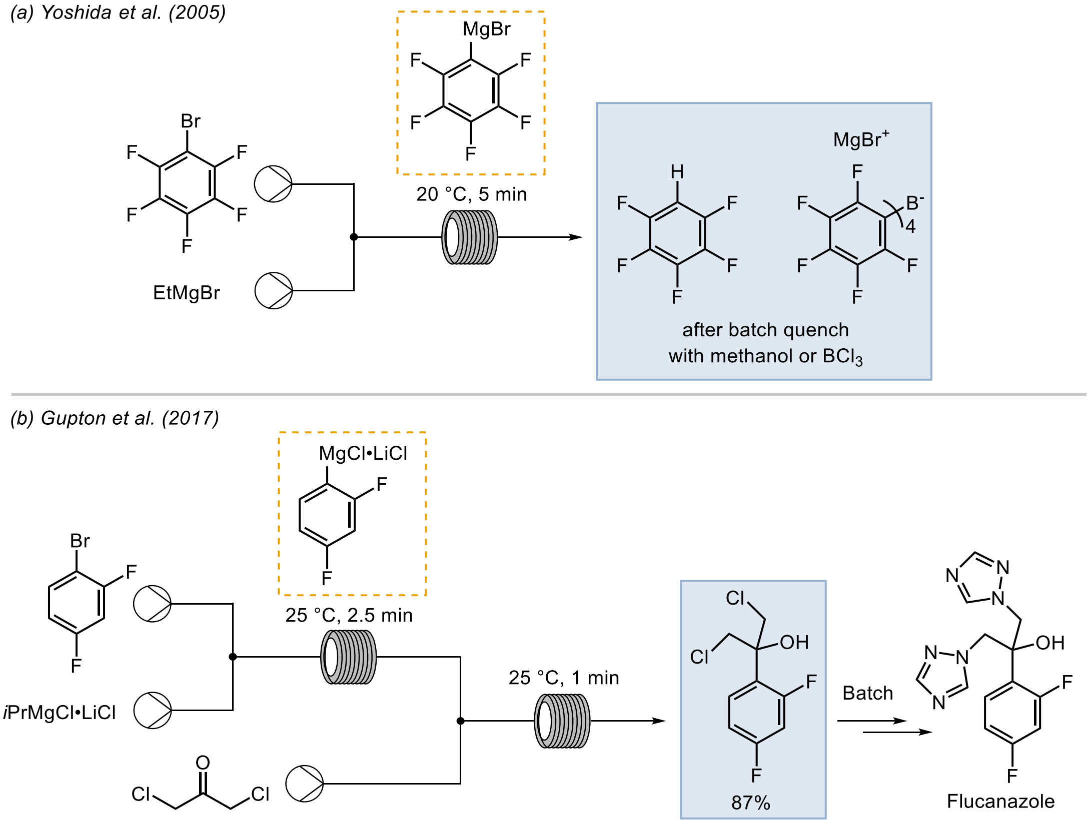
[117] (a) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; (b) H.-J. Lee, H. Kim, J.-i. Yoshida, D.-P. Kim, *Chem. Commun.* **2018**, *54*, 547; (c) A. Giovine, B. Musio, L. Degennaro, A. Falcicchio, A. Nagaki, J.-i. Yoshida, R. Luisi, *Chem. Eur. J.* **2013**, *19*, 1872.

[118] (a) H. Kim, K. I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691; (b) H. Kim, K. Inoue, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2017**, *56*, 7863.

[119] T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102.

cryogenic temperatures for halogen-magnesium exchange reactions. Noteworthy, the reaction times are significantly shortened compared to batch processes.[120]

Gupton and co-workers have highlighted the beneficial use of continuous flow technology for the halogen-metal exchange using Turbo-Grignard for the straight forward synthesis of the anti-fungal fluconazole. 1-Bromo-2,4-difluorobenzene is subjected to a bromine-magnesium exchange within 2.5 min at 25 °C. Subsequent trapping with 1,3-dichloroacetone under flow conditions led to the bis-chlorinated tertiary alcohol in 87% isolated yield. Further batch reactions furnished the desired anti-fungal fluconazole (Scheme 17b).[121]



Scheme 17: Halogen-magnesium exchange reaction using (a) EtMgBr[120] or (b) Turbo-Grignard as exchange reagent in a continuous flow set-up.[121]

3.2.3 *Directed Metalation in Continuous Flow*

To circumvent the need of an excess of metalating reagent and cryogenic temperatures, directed metalations are performed in continuous flow. Recently, Knochel, Ley and Yoshida have reported numerous applications in the area of directed metalation. Knochel *et al.* reported the metalation of substituted pyridines and pyrimidines under batch and flow conditions. Whereas for example the sensitive 2,3-dichloro-5-(trifluoromethyl)pyridine is metalated with TMPMgCl·LiCl using batch conditions at −40 °C within 2 h, the same reaction is performed within a flow set-up at 25 °C within 30 s. The resulting pyridylmagnesium species is quenched

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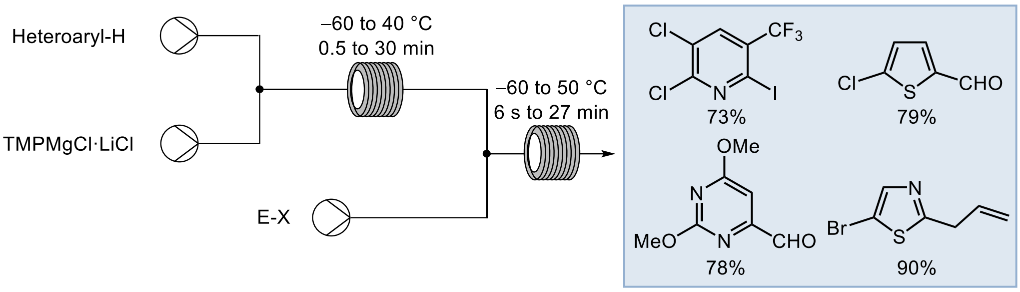
[120] (a) H. Wakami, J.-i. Yoshida, *Org. Process Res. Dev.* **2005**, *9*, 787; (b) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102; (c) Z. Qian, I. R. Baxendale, S. V. Ley, *Chem. Eur. J.* **2010**, *16*, 12342.

[121] S. Korwar, S. Amir, P. N. Tosso, B. K. Desai, C. J. Kong, S. Fadnis, N. S. Telang, S. Ahmad, T. D. Roper, B. F. Gupton, *Eur. J. Org. Chem.* **2017**, 6495.

with I_2 either in batch within 30 min (56% isolated yield) or in flow within 1 min resulting in a significantly increased yield of 73%. Applying the optimized reaction conditions to other nitrogen- and sulphur-containing heterocycles, a broad range of functionalized heterocycles was obtained after subsequent in-line quench with a large variety of electrophiles in good to excellent yields (Scheme 18).[122]



Scheme 18: Directed metalation in a continuous flow set-up using TMPMgCl·LiCl for the functionalization of heteroarenes.[122]

Moreover, Knochel and co-workers have demonstrated the advantageous use of continuous flow for the directed metalation of acrylonitriles, acrylates and nitroolefins. By using TMPZnCl·LiCl at 40 °C, it was possible to achieve a zincation of 3-ethoxyacrylonitrile within 10 minutes. Subsequent in-line quench afforded the desired allylated product in 78% yield. Further, magnesiations using TMPMgCl·LiCl allowed the generation of numerous metalation events at sp^2-carbon atoms at ambient temperatures resulting in various functionalized acrylonitriles, acrylates and nitroolefins in good yields (Scheme 19a).[123]

By the application of $(Cy_2N)_2Zn{\cdot}2LiCl$, Knochel *et al.* further extended the scope of directed metalations in continuous flow to sensitive (hetero)aromatics. The metalated species are formed at elevated temperatures (60 °C) by treating the (hetero)arenes with $(Cy_2N)_2Zn{\cdot}2LiCl$ within 10 minutes and a subsequent quench in a batch reactor with allyl bromides or Pd-catalyzed Negishi-cross couplings were performed (Scheme 19b).[124]

Furthermore, Knochel and co-workers have demonstrated a Barbier-type flow lithiation using LDA as metalating agent. Herein, a carbamoyl substrate is premixed with Weinreb amides or ketones followed by mixing with LDA at 25 °C. The carbamoyl lithium species is formed in the presence of the electrophile, instantaneously followed by the nucleophilic attack resulting in functionalized ketones and alcohols (Scheme 19c).[125]

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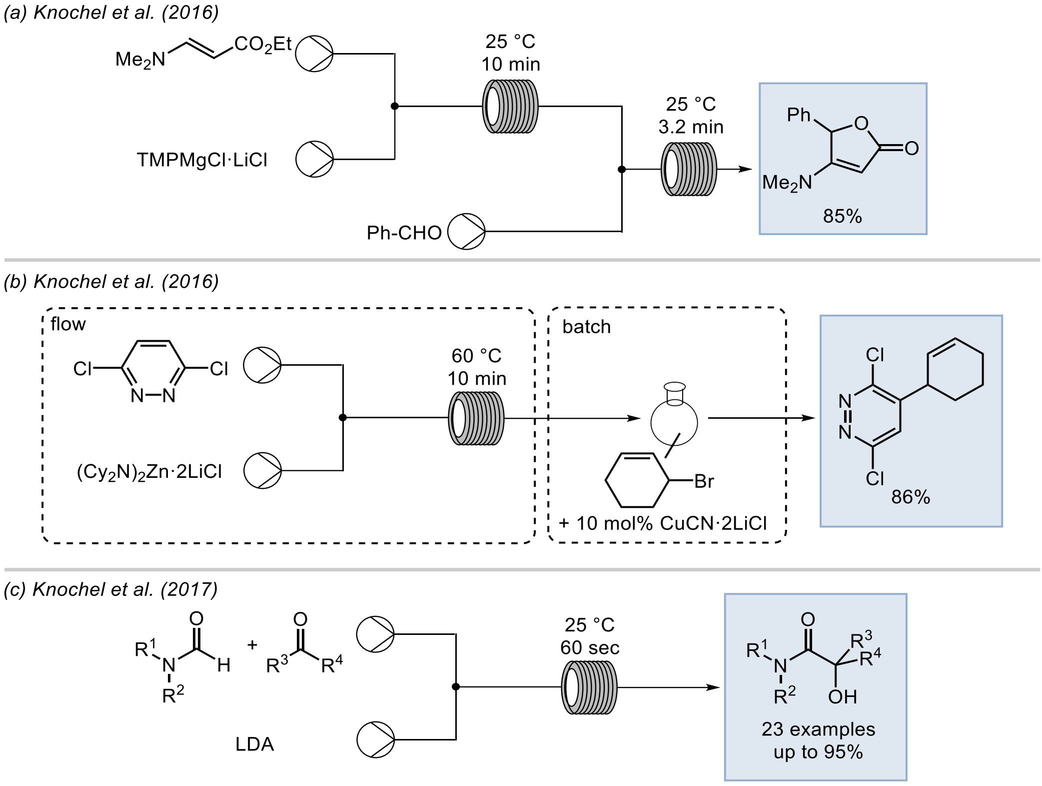
[122] (a) T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933; (b) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; (c) M. R. Becker, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501.

[123] M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828.

[124] M. R. Becker, P. Knochel, *Org. Lett.* **2016**, *18*, 1462.

[125] M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280.



Scheme 19: (a) Directed metalation of acrylonitriles, acrylates and nitroolefins using TMPZnCl·LiCl at 40 °C in continuous flow.[123] (b) Directed metalation of sensitive (hetero)arenes using $(Cy_2N)_2Zn \cdot 2LiCl$ at 60 °C in continuous flow.[124] (c) Barbier-type flow lithiation using LDA as metalating agent.[125]

In addition, the research groups of Stevens and Bio recently generated allenyllithiums in continuous flow. Due to the explosive manner and safety concerns of metalloallenes, the direct metalation of allenes is avoided in a macrobatch reaction. However, by applying continuous flow conditions, lithiated methoxyallene was generated by deprotonation with *n*BuLi. The afforded lithiated allene was subsequently trapped with benzophenone resulting in the desired tertiary alcohol in good yield (Scheme 20a).[126] Further, Bio and co-workers performed a lithiation reaction of gaseous allene with *n*HexLi. The resulting allenyllithium was transmetalated to a less reactive metal species such as allenylzinc, -magnesium or -boron and subjected to a trapping reagent. With respect to the metalation of allenes, the major benefit of flow chemistry results mainly from the safe handling of highly explosive reaction intermediates (Scheme 20b).[127]

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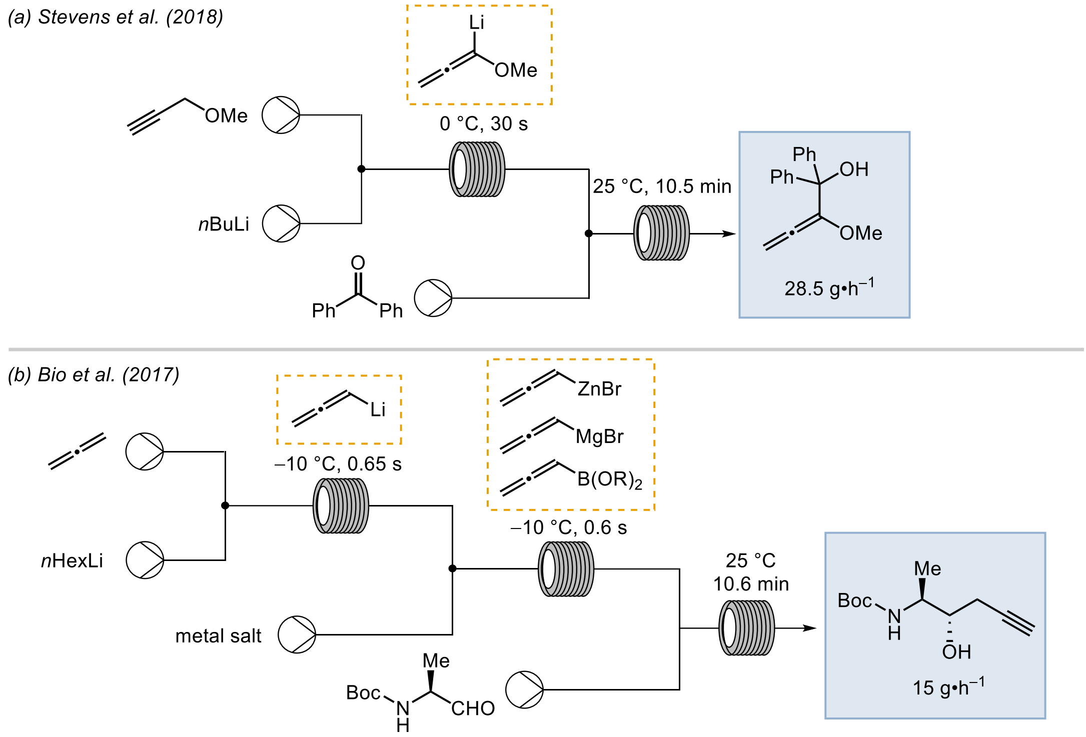
[126] S. Seghers, T. S. A. Heugebaert, M. Moens, J. Sonck, J. W. Thybaut, C. V. Stevens, *ChemSusChem.* **2018**, *11*, 2248.

[127] (a) H. Li, J. W. Sheeran, A. M. Clausen, Y.-Q. Fang, M. M. Bio, S. Bader, *Angew. Chem. Int. Ed.* **2017**, *56*, 9425; (b) J. Zhao, Y. Liu, S. Ma, *Org. Lett.* **2008**, *10*, 1521.



Scheme 20: Preperation of explosive metalloallenes *via* directed metallation using alkyllithiums in a continuous flow set-up.[126-127]

3.2.4 Transmetalation in Continuous Flow

A transmetalation event of less stable organometallic intermediates often suffers from the disadvantage, that the transmetalation needs to be very fast compared to any side reactions of the more reactive organometallic reagent. However, trapping of highly reactive organometallic intermediates with a less electropositive metal salt within very short reaction times in a continuous flow set-up and the application of *in situ* transmetalations may overcome these problems to some extent.

In 2014, Knochel and co-workers demonstrated a direct metalation with instantaneous in-line transmetalation. Therefore, various heterocycles were metalated in a commercially available continuous flow set-up using TMPMgCl·LiCl. A subsequent in-line quench with $ZnCl_2$ in the presence of $Pd(dba)_2$, P(*o*-furyl)$_3$ and aryl iodides, afforded the desired Negishi cross-coupling products *via* the transmetalated zinc species (Scheme 21a).[128]

Based on these promising results, the Knochel group investigated *in situ* transmetalations in continuous flow. In 2015, they reported an *in situ* trapping transmetalation protocol. A premixed solution of (hetero)arenes with metal salts such as $ZnCl_2{\cdot}2LiCl$, $MgCl_2$ or $LaCl_3{\cdot}2LiCl$ in THF was metalated with TMPLi or Cy_2NLi. Due to the presence of the metal salts, the less reactive (hetero)aryl organometallic species were formed, which were then directly quenched in a standard batch reaction with various electrophiles or further functionalized *via* Negishi cross-couplings (Scheme 21b). The scope of this method was

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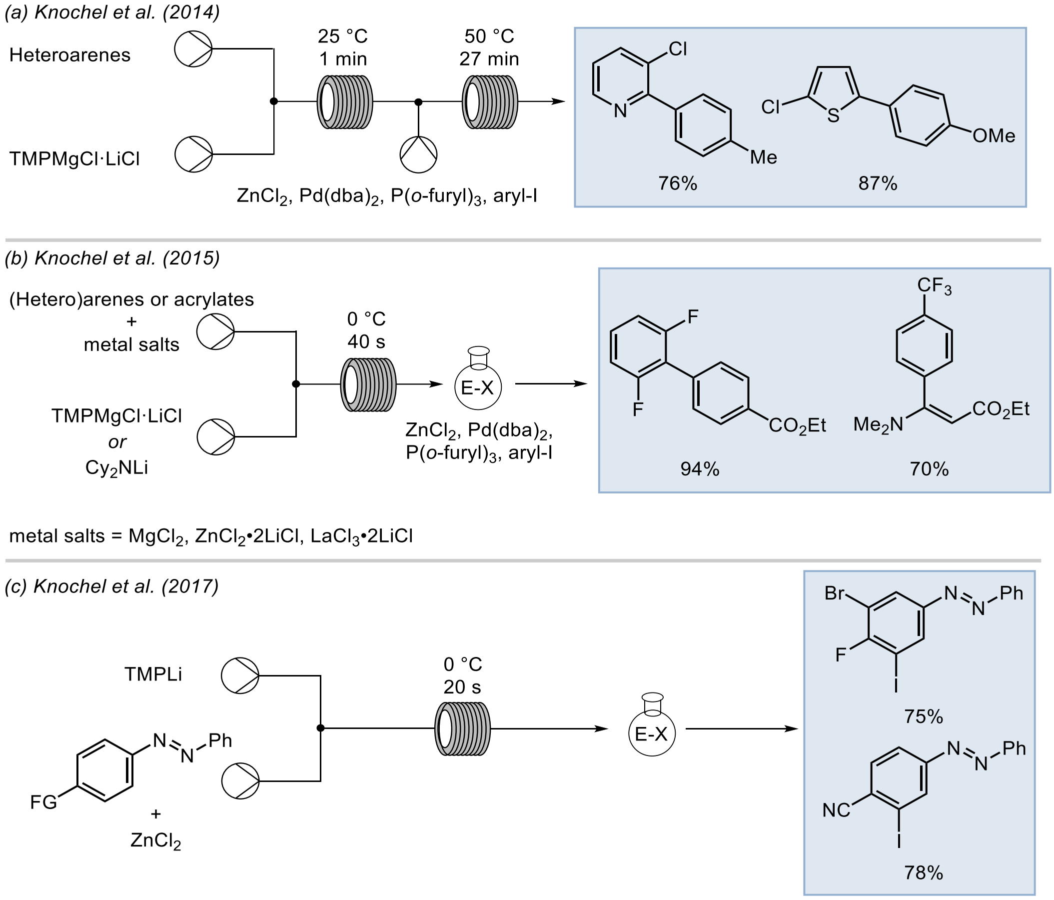
[128] T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933.

successfully extended to functionalized acrylates.[129] The *in situ* trapping with metal salts has recently been extended to highly reactive lithiated azobenzenes (Scheme 21c). Applying convenient flow conditions (0 °C, 20 s), unsymmetrical azobenzenes were lithiated. Noteworthy, azobenzenes, which did not contain sensitive functional groups, were directly trapped with various electrophiles. However, the presence of sensitive functional groups such as nitriles required the *in situ* transmetalation to less reactive magnesium or zinc azobenzenes. Subsequent batch quenching reactions with various electrophiles such as allylic halides, elemental bromine, acyl chlorides and aldehydes or Negishi cross-couplings were successfully performed.[130]



Scheme 21: Directed metalation with *in situ* transmetalation of various (hetero)arenes, acrylates and functionalized azobenzenes in the presence of various metal salts.[128-130]

Similarly, Buchwald *et al.* reported a stepwise metalation-transmetalation flow process. By using Schlosser base, a direct metalation of benzotrifluorides and fluorinated arenes and pyridines was performed. The metalated (hetero)arenes were then in a stepwise manner transmetalated to the corresponding zinc species by adding $ZnCl_2$ solution *via* a third pumping devices. In a third step, the organozinc reagents underwent Negishi cross-couplings using aryl bromides and a Pd-catalyst to access a broad range of fluorinated arenes and heteroarenes. In contrast to the previously described method of Knochel and co-workers, the stepwise procedure

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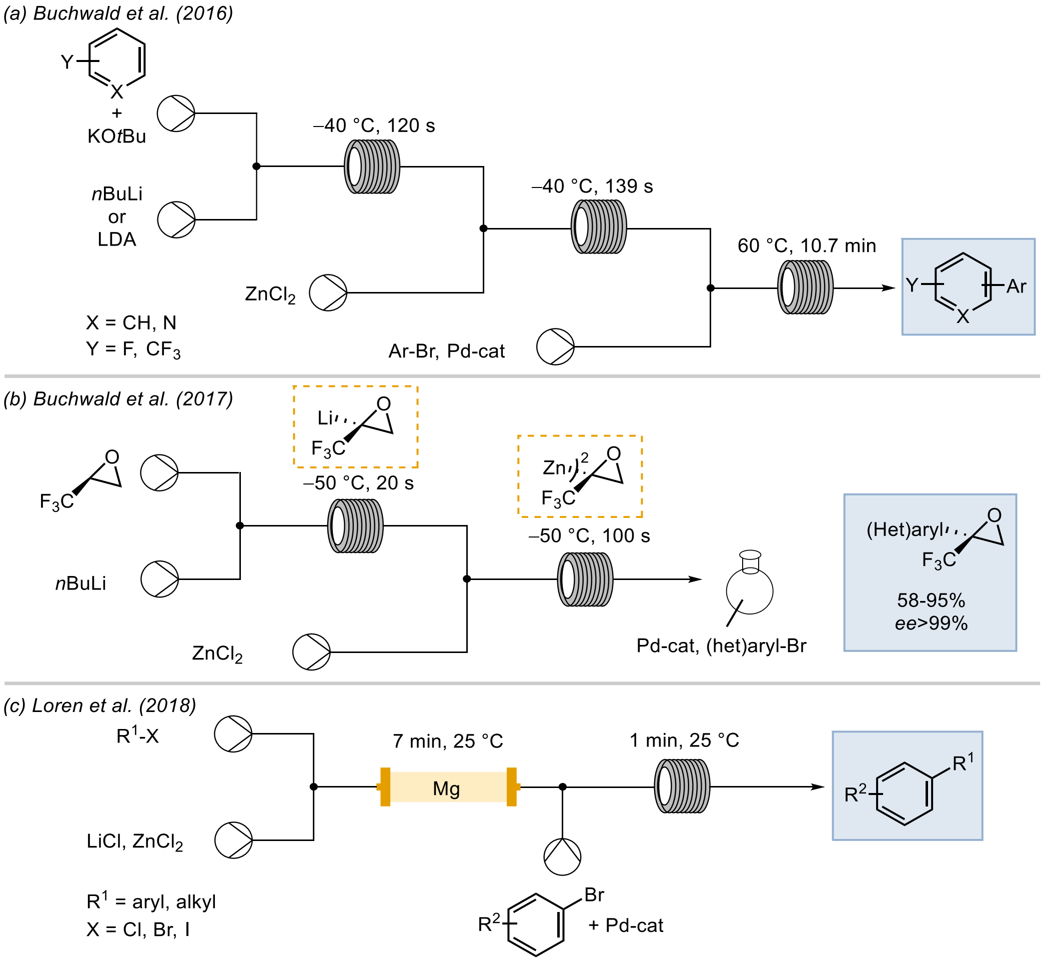
[129] (a) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; (b) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501.

[130] M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.* **2017**, *19*, 1666.

requires a tedious screening of the stability of the lithiated (hetero)arenes to avoid LiF elimination (Scheme 22a).[131] Buchwald successfully extended this method to the preparation of chiral α-CF_3-oxiranylzincates. Mixing 2,3-epoxy-1,1,1-trifluoropropane (TFPO) with *n*BuLi in continuous flow afforded the lithiated TFPO within 20 s at −50 °C. Addition of $ZnCl_2$ afforded the bis-organozinc species within 100 s. A subsequent Negishi cross-coupling reaction in batch resulted in enantioenriched 2-CF_3-2-(hetero)aryl-substituted oxiranes, which can be further functionalized *via* nucleophilic ring opening reactions leading to the corresponding tertiary CF_3-substituted alcohols (Scheme 22b).[132]



Scheme 22: (a) Directed metalation using *n*BuLi or LDA and stepwise transmetalation.[131] (b) Directed metalation of oxiranes using *n*BuLi and stepwise transmetalation using $ZnCl_2$.[132] (c) *In situ* trapping transmetalation of organomagnesium reagents generated in a continuous flow halogen-magnesium exchange by $ZnCl_2$.[133]

Recently, Loren and co-workers extended the scope of *in situ* trapping transmetalation to the generation of various alkyl and aryl organozinc compounds. Therefore, the corresponding aryl- or alkyl halide is mixed in a continuous flow set-up with a $ZnCl_2 \cdot LiCl$ solution. Then, the reagent mixture is pumped through a packed-bed reactor containing activated magnesium turnings. The *in situ* generated aryl- and alkylmagnesiums were directly transmetalated to the corresponding organozinc reagents, which were further telescoped to Negishi cross-coupling

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[131] S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463.
[132] H. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2017**, *139*, 11590.

reactions. Noteworthy, Loren *et al.* demonstrated the preparation of organozinc reagents, whose commercially availability is limited due to fast degradation (Scheme 22c).[133]

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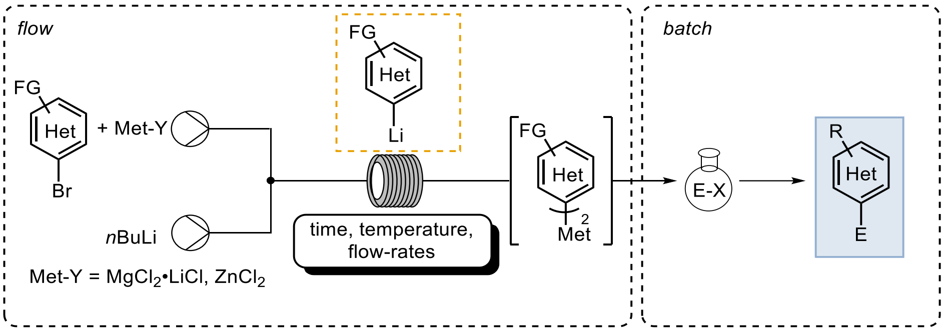
[133] A. Herath, V. Molteni, S. Pan, J. Loren, *Org. Lett.* **2018**, *20*, 7429.

4. OBJECTIVES

In the past decades, many improvements in the field of organolithium chemistry were made. Nevertheless, it is still an ongoing task to generate highly reactive lithium compounds containing sensitive functional groups such as isothiocyanates, esters, nitriles and azides. Among the top small molecule drugs by US retail sales in 2010 over 80% contain at least one heterocyclic fragment in their structure.[134] Owing to these facts, the synthesis of functionalized (hetero)aryllithiums should be the subject of intensive research. Previous results in the Knochel group showed the advantageous use of flow chemistry. Becker and co-workers were able to perform a direct lithiation using TMPLi in a commercially available flow set-up. The *in situ* generated lithium species was subsequently trapped by various metal salts (*e.g.* $ZnCl_2$, $CuCN{\cdot}2LiCl$) resulting in a less reactive and more stable organometallic species.[135] With these results in mind, a new methodology was envisioned combining the advantageous use of flow chemistry with halogen-lithium exchange of highly challenging aryl halides and an *in situ* trapping approach. It was proposed that (hetero)aryl halides perform a halogen-lithium exchange using *n*BuLi as exchange reagent. As previously demonstrated, the resulting lithium species should be trapped *in situ* with metal salts (*e.g.* $MgCl_2{\cdot}LiCl$ or $ZnCl_2$) resulting in the more stable organometallic species. Finally, batch quench with various electrophiles should afford highly functionalized (hetero)arenes (Scheme 23).[136]



Scheme 23: Halogen-lithium exchange of (hetero)arenes using *n*BuLi as exchange reagent in the presence of various metal salts in a continuous flow set-up affording the more stable (hetero)aromatic organometallic species, which should be trapped in batch by various electrophiles.

Furthermore, it was proposed to transfer the concept of *in situ* trapping with metal salts to a Barbier-type quenching with electrophiles, *i.e.* the electrophiles are already present during the halogen-lithium exchange event (Scheme 24). By premixing halogenated (hetero)arenes with suitable electrophiles and subsequent halogen-lithium exchange reaction using *n*BuLi and *t*BuLi as exchange reagent in a continuous flow set-up, *in situ* prepared (hetero)aryllithiums should be afforded. Due to the presence of suitable electrophiles, the organolithiums should be directly trapped before competitive side reactions such as decomposition of the organolithiums

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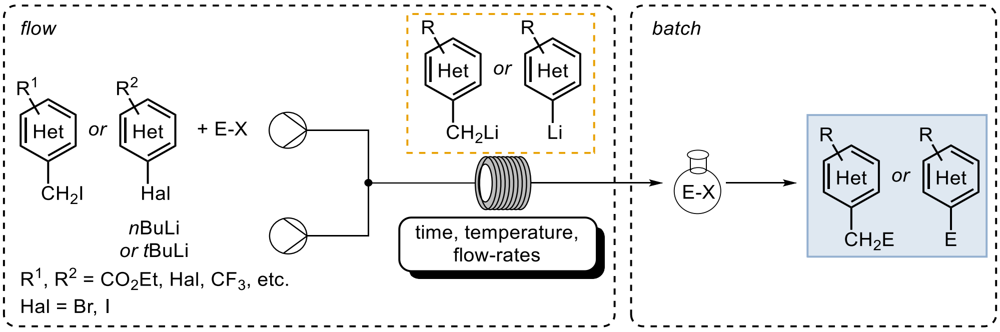
[134] D. J. Mack, M. L. Weinrich, E. Vitaku, J. T. Njardarson, http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster.

[135] M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501.

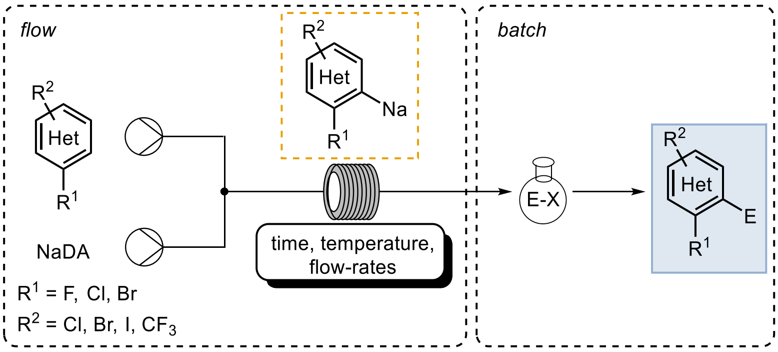
[136] This project was developed in cooperation with Dr. Marthe Ketels, Dr. Maximilian A. Ganiek and Dr. Rodolfo Hideki Vicente Nishimura, see: M. Ketels, Dissertation, LMU München, **2018** and M. A. Ganiek, Dissertation, LMU München, **2018**.

can occur.[137] Furthermore, an expansion of Barbier-type trapping to (hetero)benzylic lithium species, which should be prepared by an iodine-lithium exchange reaction using (hetero)benzylic iodides, was envisioned. The presence of electrophiles as trapping reagents should avoid the undesired Wurtz coupling, which is a typical side reaction of a batch reactions.[138]



Scheme 24: Barbier-type halogen-lithium exchange reaction of benzylic iodides and (hetero)aromatic halides in the presence of carbonyl-containing electrophiles affording the desired secondary and tertiary alcohols in a continuous flow set-up.

Recently, Collum and co-workers reported a straight forward synthesis of sodium diisopropylamide (NaDA), a sodium analogue of the frequently used LDA.[139] Collum and co-workers were able to perform a directed metalation of various aryl compounds using NaDA as metalating agent under batch conditions. Interestingly, substrates with *ortho*-halogen substituent were not applicable for the direct metalation due to a fast degradation of the intermediate sodium species *via* aryne formation.[140] Based on these results, a directed metalation of substituted (hetero)aryls in continuous flow using the soluble NaDA base was envisioned. It was anticipated that it should be possible to trap the highly reactive organosodium intermediates with various electrophiles by applying short reaction times of less than one second (Scheme 25).[141]



Scheme 25: Sodiation of (hetero)arenes using NaDA in a continuous flow set-up.

Moreover, the sodiation of (substituted) unsaturated alkenyl compounds was not yet described. Using NaDA in a continuous flow set-up should demonstrate an extension of the sodiation method to various (substituted) alkenyl nitriles and sulfides. Furthermore, it would be of great

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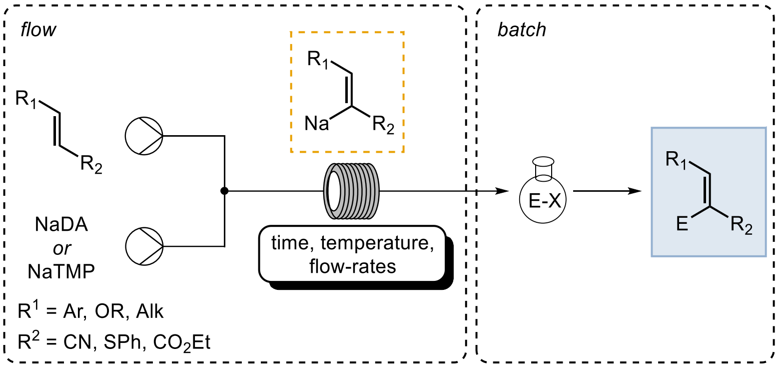
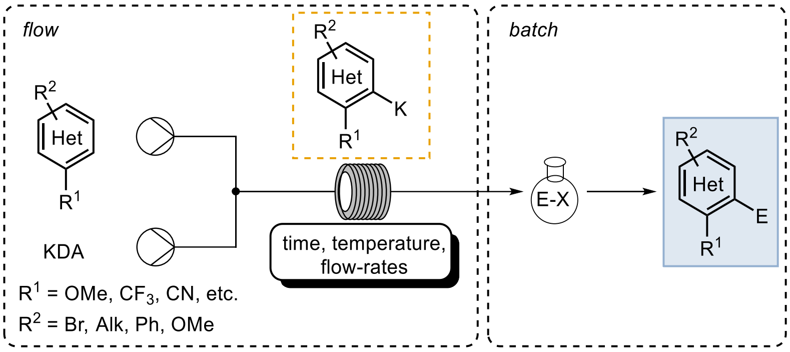
[137] This project was developed in cooperation with Dr. Rodolfo Hideki Vicente Nishimura.
[138] This project was developed in cooperation with Johannes H. Harenberg, see: J. H. Harenberg, Dissertation, LMU München.
[139] Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312.
[140] R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197.
[141] This project was developed in cooperation with Dr. Marthe Ketels, see: M. Ketels, Dissertation, LMU München, **2018**.

interest to investigate other sodium bases such as NaTMP, which are soluble not only in the uncommon solvent dimethylethylamine but rather in hydrocarbons or ethereal solvents (Scheme 26).[142]



Scheme 26: Sodiation of (substituted) alkenyl compounds using NaDA or NaTMP in a continuous flow set-up.

Finally, a flow procedure for a metalation using soluble potassium bases in a continuous flow set-up was envisioned. According to the increased bond polarity of the resulting organopotassiums compared to organolithiums and –sodiums, their reactivity should be further enhanced. Thus, it was estimated that ultrafast reaction times should play a crucial role for the efficient metalation with potassium bases. For that reason, it was anticipated that such a potassium metalation should be an excellent candidate for the beneficial use of continuous flow technology. In analogy to the efficient preparation of NaDA, a batch preparation of KDA using sliced potassium, diisopropylamine and isoprene in hydrocarbon solvents was proposed (Scheme 27).[142]



Scheme 27: Preparation of (hetero)aromatic potassium reagents by a directed metalation using KDA in a continuous flow set-up.

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[142] This project was developed in cooperation with Johannes H. Harenberg, see: J. H. Harenberg, Dissertation, LMU München.

B. RESULTS AND DISCUSSION

5. PREPARATION OF POLYFUNCTIONAL DIORGANO-MAGNESIUM AND -ZINC REAGENTS USING *IN SITU* TRAPPING HALOGEN-LITHIUM EXCHANGE OF HIGHLY FUNCTIONALIZED (HETERO)ARYL HALIDES IN CONTINUOUS FLOW

Organolithiums display an important role in the generation of organometallic intermediates in organic synthesis.[143] Among various methods for the preparation of organolithium compounds, the halogen-lithium exchange is a standard preparation method providing, after transmetalation to more electronegative metals, a broad range of organometallic intermediates.[144] However, the scope of halogen-lithium exchange is limited by the presence of sensitive functional groups such as azides, nitriles and esters.[145] To overcome these drawbacks, the use of cryogenic temperatures[146] or special protecting groups[147] proved to be successfully. Additionally, a fast subsequent transmetalation to a less reactive metal after the halogen-lithium exchange leads to more stable organometallics affording a better functional group tolerance even at higher temperatures.[148]

Within recent years, continuous flow techniques have emerged as a powerful tool for addressing synthetic problems.[149] Thus, Yoshida and co-workers have utilized ultra-fast mixing and a precise reaction time control for achieving the generation of lithiated arenes bearing sensitive functional groups such as nitro or cyano groups.[150] Recently, Knochel *et al.* have shown that the scope of arene-metalations with a strong base such as TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) is dramatically increased by performing these metalations in the presence of metallic salts.[151] The resulting organometallics were much more stable than the initially generated lithium reagents and could be broadly functionalized with a variety of electrophiles. The scope and reaction conditions of this *in situ* trapping procedure were now further improved by switching from a batch to a continuous flow set-up (Scheme 28a). Aware

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[143] (a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; (b) M. C. Whisler, S. Mac-Neil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

[144] D. R. Armstrong, E. Crosbie, E. Hevia, R. E. Mulvey, D. L. Ramsay, S. D. Robertson, *Chem. Sci.* **2014**, *5*, 3031.

[145] (a) M. Hatano, S. Suzuki, K. Ishihara, *Synlett* **2010**, 321; (b) T. Kim, K. Kim, *J. Heterocyclic Chem.* **2010**, *47*, 98; (c) K. Kobayashi, Y. Yokoi, T. Nakahara, N. Matsumoto, *Tetrahedron* **2013**, *69*, 10304; (d) A. Matsuzawa, S. Takeuchi, K. Sugita, *Chem. Asian J.* **2016**, *11*, 2863.

[146] W. E. Parham, C. K. Bradscher, *Acc. Chem. Res.* **1982**, *15*, 300.

[147] S. Oda, H. Yamamoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 8165.

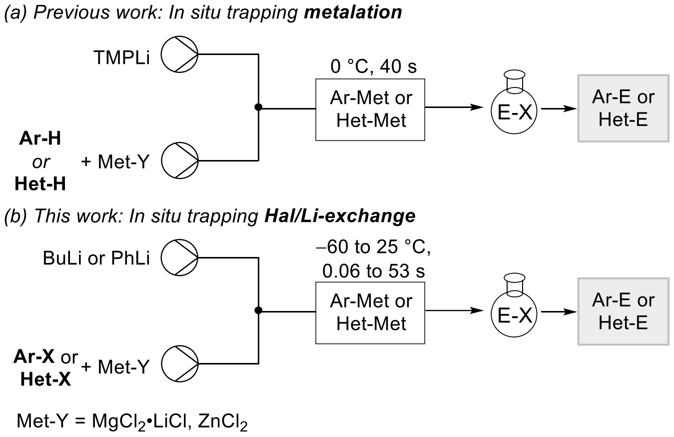
[148] (a) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983; (b) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463.

[149] For general advances in flow chemistry, see: (a) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102; (b) D. Ghislieri, K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 678; (c) M. Teci, M. Tilley, M. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967; (d) 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; (e) H. Seo, M. H. Katcher, T. F. Jamison, *Nat. Chem.* **2017**, *9*, 453.

[150] (a) A. Nagaki, H. Kim, H. Usutani, C. Matsuo J.-i. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; (b) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; (c) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; (d) H. Kim, H.-J. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 1877.

[151] (a) A. Frischmuth, M. Fernández, N. M. Barl, F. Achreiner, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53,* 7928; (b) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; (c) M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.* **2017**, *19*, 1666.

of the fast rate of the halogen-lithium exchange,[152] an analogous *in situ* trapping exchange procedure (Scheme 28b) was envisioned. This *in situ* trapping halogen-lithium exchange procedure has the general advantage that it provides excellent functional group tolerance including aryl azides and that it can be conducted using commercially available flow reactors.



Scheme 28: *In situ* trapping-metalation and -exchange using a commercially available continuous flow set-up.

5.1 OPTIMIZATION OF REACTION CONDITIONS

First, the reaction conditions were optimized performing an Br/Li-exchange for 4-bromobenzonitrile (**1a**) using BuLi as exchange reagent.[153] Without the addition of a metal salt, optimized flow conditions led after quenching with allyl bromide (**3a**, 2.5 equiv) and CuCN·2LiCl[154] (10 mol%) to the allylated arene **4aa** in 17% GC-yield (Table 1, entry 1). This low yield may be due to the competitive addition of the newly generated aryllithium of BuLi to the cyano group. Addition of soluble $MgCl_2 \cdot LiCl$ (1.1 equiv) to the aryl bromide **1a** afforded the desired allylated product in 57% GC-yield (entry 2). Using a substoichiometric amount of $MgCl_2 \cdot LiCl$ (0.5 equiv) and further optimization of the equivalents of *n*BuLi and the combined flow-rate led to the bis-organomagnesium species **2a** which, after trapping with allyl bromide in the presence of CuCN·2LiCl, resulted in 62-78% GC-yield (entries 3-5). Performing the reaction at 25 °C, the GC-yield dropped significantly to 38% (entry 6). Further optimizations of the *n*BuLi-equivalents provided the optimum conditions (1.5 equiv *n*BuLi; 0 °C; 12 $mL \cdot min^{-1}$ combined flow-rate; reaction time: 2.5 s) resulting in 85% GC-yield (entry 7). Instead of $MgCl_2 \cdot LiCl$, $ZnCl_2$ could also be used as an *in situ* transmetalating reagent leading to **4aa** in 82% GC-yield (entry 8). The use of 1.1 equivalents $ZnCl_2$ led to a slight decrease of GC-yield (71%, entry 9). To demonstrate that the exchange is faster than the transmetalation of the exchange reagent with the metal salt, a premixed solution of the corresponding metal salts and *n*BuLi were mixed at −78 °C and injected in flow. Not surprisingly, the yield of the exchange reaction dropped significantly (entries 10-11).

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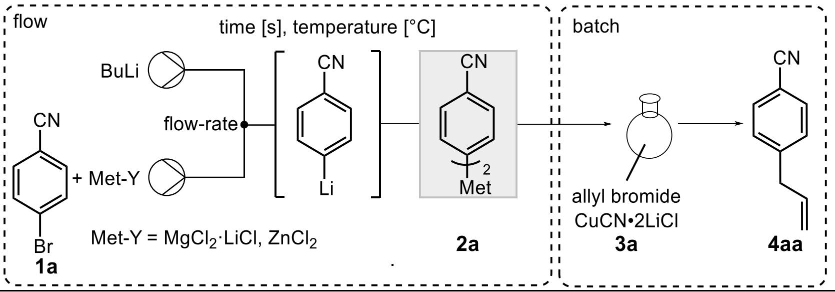
[152] W. F. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1996**, *27*, 1861.

[153] Commercially available equipment from Vapourtec and Uniqsis was used.

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

Table 1: Optimization of the bromine-lithium exchange in the presence of metal salts using continuous flow.



Entry	Metal salt (X equiv)	*n*BuLi (X equiv)	T [°C]	Flow-rate [mL·min^{-1}]	t [s]	GC-yield [%][a]
1	-	1.5	0	6.0	2.50	17
2	$MgCl_2 \cdot LiCl$ (1.1)	1.5	0	6.0	2.50	57
3	$MgCl_2 \cdot LiCl$ (0.5)	1.1	0	6.0	2.50	62
4	$MgCl_2 \cdot LiCl$ (0.5)	1.5	0	1.0	15.0	68
5	$MgCl_2 \cdot LiCl$ (0.5)	1.5	0	16.0	0.94	78
6	$MgCl_2 \cdot LiCl$ (0.5)	1.5	25	6.0	2.50	38
7	$MgCl_2 \cdot LiCl$ (0.5)	1.5	0	6.0	2.50	85
8	$ZnCl_2$ (0.5)	1.5	0	6.0	2.50	82
9	$CuCN \cdot 2LiCl$ (1.1)	1.5	0	6.0	2.50	71
10	$ZnCl_2$ (0.5)[b]	1.5	0	6.0	2.50	0
11	$MgCl_2 \cdot LiCl$ (0.5)[b]	1.5	0	6.0	2.50	26

[a] GC-yield determined using dodecane as an internal standard. [b] Metallic salt mixed with *n*BuLi in batch at −78 °C and then injected in flow.

5.2 INVESTIGATION OF THE ELECTROPHILE SCOPE

With the optimized conditions in hand, the electrophile scope was investigated. Therefore, the intermediate magnesium species **2a** was used in various quenching reactions such as iodolysis, addition to aldehydes and acylations resulting in functionalized benzonitriles **4ab**, **4ac** and **4ad** in 70-85% yield (Table 2, entries 1-3). The range of substrates was further extended to other bromobenzonitriles, which were converted to the corresponding diarylmagnesium species (**2b-c**). After batch-trapping with ketones, allyl bromides or acyl chlorides in the presence of $CuCN \cdot 2LiCl$, the corresponding products **4be**, **4cf** and **4cg** were afforded in 68-74% yield (entries 4-6). It was also possible to perform an I/Li exchange on 2-iodo-benzonitrile (**1d**) using similar conditions, providing the diarylzinc species **2d**. Allylation with 3-bromocyclohexene (**3h**) in the presence of $CuCN \cdot 2LiCl$ afforded the functionalized benzonitrile **4dh** in 80% yield (entry 7). Remarkably, these exchange reactions proceed at 0 °C in contrast to the standard halogen-lithium exchanges in batch, which are performed at −78 °C. Also, electron-rich aryl bromides (**1e-f**) were *in situ* transmetalated in the presence of $MgCl_2 \cdot LiCl$ and quenched with acyl chloride **3i** or subjected to a *Negishi* cross-coupling[155] after batch-transmetalation with

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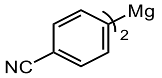
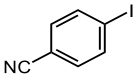
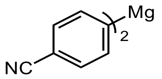
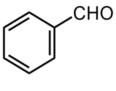
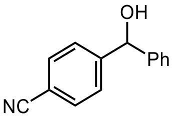
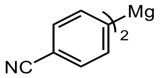
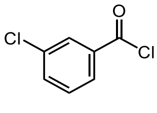
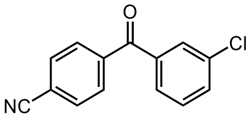
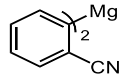
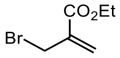
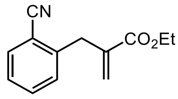
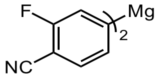
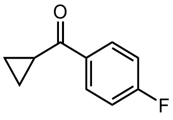
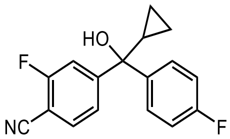
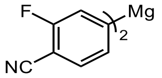
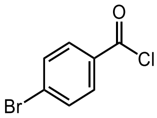
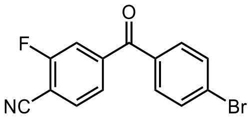
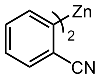
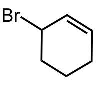
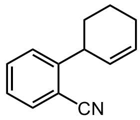
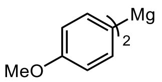
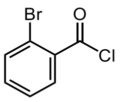
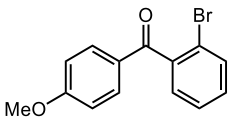
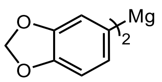
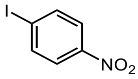
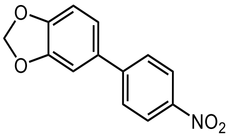
[155] E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298.

$ZnCl_2$. The resulting products **4ei**, **4fj** and **4fk** were obtained in 68-85% yield (entries 8-10). While most examples were performed on a 0.5 mmol scale, *in situ* trapping exchange reactions could be scaled up by simply extending the runtime. Thus, benzophenone **4cg** was prepared on a 10 mmol scale in 76% yield (entry 6) without further optimization.[156]

Table 2: *In situ* exchange-transmetalation for sensitive aryl halides of type **1** leading *via* intermediate diorgano-zincs or -magnesiums of type **2** to polyfunctional arenes of type **4**.

Entry	Metal Species T; flow-rate; t	Electrophile	Product[a]
1	 **2a**: 0 °C; 6 mL·min^{-1}; 2.5 s[b]	I_2 **3b**[c]	 **4ab**: 70%
2	 **2a**: 0 °C; 6 mL·min^{-1}; 2.5 s[b]	 **3c**[d]	 **4ac**: 83%
3	 **2a**: 0 °C; 6 mL·min^{-1}; 2.5 s[b]	 **3d**[e],[f]	 **4ad**: 85%
4	 **2b**: 0 °C; 9 mL·min^{-1}; 1.7 s[b]	 **3e**[g]	 **4be**: 68%
5	 **2c**: 0 °C; 9 mL·min^{-1}; 1.7 s[b]	 **3f**[d]	 **4cf**: 74%
6	 **2c**: 0 °C; 9 mL·min^{-1}; 1.7 s[b]	 **3g**[e],[f]	 **4cg**: 74% (76%)[h]
7	 **2d**: 0 °C; 6 mL·min^{-1}; 2.5 s[i]	 **3h**[g]	 **4dh**: 80%
8	 **2e**: 0 °C; 12 mL·min^{-1}; 2.5 s[b]	 **3i**[e],[f]	 **4ei**: 68%
9	 **2f**: 0 °C; 6 mL·min^{-1}; 2.5 s[b]	 **3j**[j]	 **4fj**: 85%

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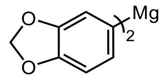
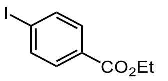
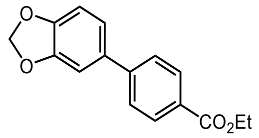
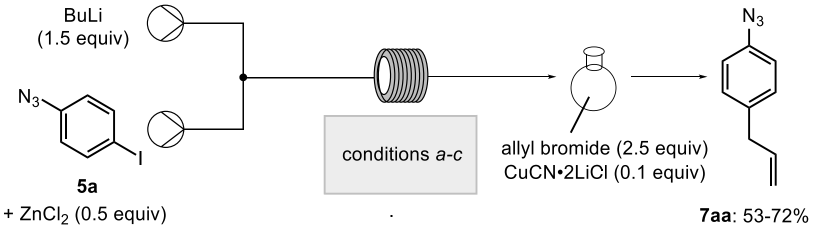
[156] (a) F. Ullah, T. Samarakoon, A. Rolfe, R. D. Kurtz, P. Hanson, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10959; (b) A. Hafner, P. Filipponi, L. Piccioni, M. Meisenbach, B. Schenkel, F. Venturoni, J. Sedelmeier, *Org. Process Res. Dev.* **2016**, *20*, 1833.

10	 **2f**: 0 °C; 6 mL·min^{-1}; 2.5 s[b]	 **3k**[j]	 **4fk**: 70%

[a] Yield of analytically pure isolated product. [b] Metal species prepared from the aryl bromide. [c] 2.0 equiv, 10 min, 25 °C. [d] 1.1-1.5 equiv, 1-2 h, 0 °C. [e] 1.1 equiv CuCN·2LiCl was added. [f] 1.5 equiv, 1-2 h, 0 °C. [g] 2.5 equiv, 0.1 equiv CuCN·2LiCl, 30 min, 0 °C. [h] Reaction performed on 10 mmol scale, 3 h, 0 °C. [i] Metal species prepared from the aryl iodide. [j] Negishi cross-coupling performed in batch, 1.5 equiv, 10 h, 25 °C after transmetalation to $ZnCl_2$ using PEPPSI-*i*Pr (2 mol%).

5.3 EXTENDING THE SUBSTRATE SCOPE TO ARYL HALIDES BEARING CHALLENGING FUNCTIONAL GROUPS

To further demonstrate the broad applicability of *in situ* trapping exchange reactions in flow, the compatibility with aryl halides bearing challenging functional groups such as esters, ketones, a nitro or heterocumulene groups *e.g.* azides or isothiocyanates was investigated. Notably, only halogen-lithium exchanges of *o*-nitroarenes[157] and an alkenyl iodide containing an aliphatic azide at −100 °C under batch conditions[158] are known, as well as several flow protocols for ester-, ketone- and nitro-containing arenes applying ultrafast micromixing and residence times down to a millisecond range.[159]



Scheme 29: I/Li-exchange in presence of an azide under various reaction conditions: (a) *In situ* exchange, 0 °C, 2.5 s, 6 mL·min^{-1}: **7aa**: 53% yield. (b) 0 °C, 2.5 s; No salt additive: no product and decomposition of reagents. (c) *In situ* exchange, −40 °C, 1.25 s, 12 mL·min^{-1}: **7aa**: 72% yield (1 mmol); 60% (5 mmol).

It was demonstrated that 4-iodophenyl azide[160] **(5a)** decomposes completely in the absence of a metal salt performing the reaction in flow. However, screening of various *in situ* trapping exchange conditions, *e.g* addition of soluble metal salts, flow-rate and temperature, led to the desired allylated phenyl azide **7aa** in 72% isolated yield (Scheme 29). Scale-up of this reaction from 1 to 5 mmol provided the aryl azide **7aa** in 60% yield. The analogous *m*-allyl azidobenzene (**7ba**) was obtained accordingly in 83% yield (Table 3, entry 1). Furthermore, nitro-, ketone- and ester-groups were investigated because of their pivotal role in organic synthesis due to competitive electron transfer and nucleophilic addition reactions.[161] In order

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[157] W. E. Parham, C. K. Bradscher, *Acc. Chem. Res.* **1982**, *15*, 300.

[158] (a) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983; (b) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463.

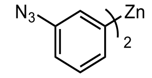
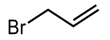
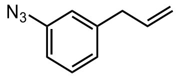
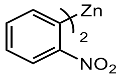
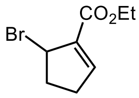
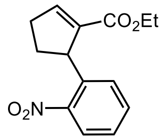
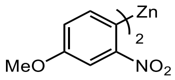
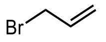
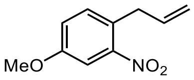
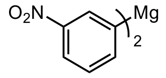
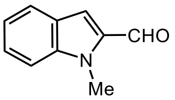
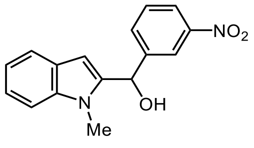
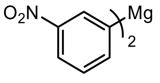
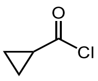
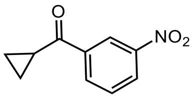
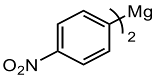
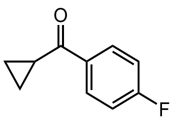
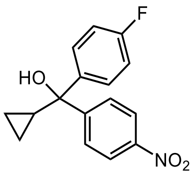
[159] (a) A. Nagaki, H. Kim, H. Usutani, C. Matsuo, J.-i. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; (b) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; (c) A.Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*,1914; (d) H. Kim, H.-J. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*,1877.

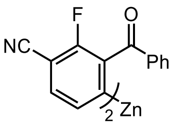
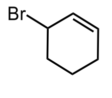
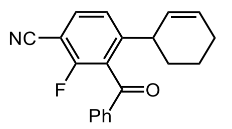
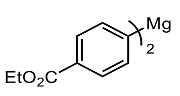
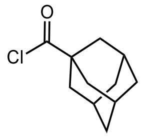
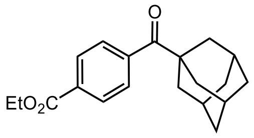
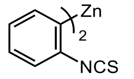
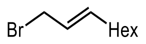
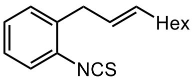
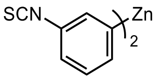
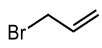
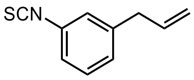
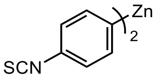
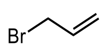
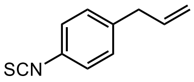
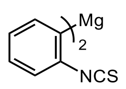
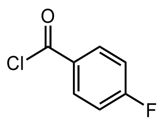
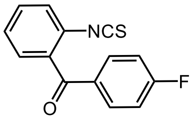
[160] For previous flow reactions with unstable aza-compounds, see: (a) C. J. Smith, N. Nikbin, S. V. Ley, H. Lange, I. R. Baxendale, *Org. Biomol. Chem.* **2011**, *9*, 1938; (b) F. R. Bou-Hamdan, F. Lévesque, A. G. O'Brien, P. H. Seeberger *Beilstein J. Org. Chem.* **2011**, *7,* 1124; (c) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Chem. Eur. J.* **2016**, *22*, 17407; (d) D. Dallinger, V. D. Pinho, B. Gutmann, C. O. Kappe, *J. Org. Chem.* **2016***,* 81, 5814; (e) H. Lehmann, *Green Chem.* **2017**, *19*, 1449.

[161] (a) M. Hatano, S. Suzuki, K. Ishihara, *Synlett* **2010**, 321; (b) T. Kim, K. Kim, *J. Heterocyclic Chem.* **2010**, *47*, 98; (c) K. Kobayashi, Y. Yokoi, T. Nakahara, N. Matsumoto, *Tetrahedron* **2013**, *69*, 10304; (d) A. Matsuzawa, S. Takeuchi, K. Sugita, *Chem. Asian J.* **2016**, *11*, 2863; (e) S. Oda, H. Yamamoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 8165.

to access aryl organometallics with such functional groups, the best lithiation exchange reagent was found to be PhLi instead of *n*BuLi. Using PhLi, the I/Li-exchange is also faster than a competitive transmetalation of PhLi, therefore allowing an efficient generation of diarylzincs and -magnesiums (**6c**-**h**). Thus, bis-(nitroaryl)zincs **6c**-**f** were generated from the corresponding aryl halides **5c**-**f**. Allylation, acylation and addition to indole aldehyde **3m** or ketone **3o** in batch furnished the desired functionalized nitro arenes **7cl**, **7da**, **7em**, **7en** and **7fo** in 60-78% yield (entries 2-6). Similarly, the ketone containing aryl bromide **5g** was functionalized by *in situ* trapping exchange reactions at −40 °C in the presence of $ZnCl_2$. Standard quenching conditions led to the allylated product **7gh** from the diarylzinc **6g** in 78% yield (entry 7). Furthermore, ethyl 4-iodobenzoate (**5h**) led to **7hp** *via* the diarylmagnesium **6h** in 70% (entry 8). It was further possible to perform an Br/Li-exchange on aryl bromides bearing an *p*-, *m*-, and *o*-isothiocyanate moiety without subsequent additions to the electrophilic isothiocyanate. After various copper mediated allylations or acylations, the desired products **7iq**, **7ja**, **7ka** and **7lr** were obtained in 63-68% yield (entries 9-12).

Table 3: *In situ* exchange-transmetalation for highly sensitive aryl halides of type **5** leading *via* intermediate diorgano-zincs or -magnesiums of type **6** to polyfunctional arenes of type **7**.

Entry	Metal species T; Flow-rate; t	Electrophile	Product[a]
1	 **6b**: −40 °C; 12 mL·min^{-1}; 1.25 s[b]	 **3a**[c]	 **7ba**: 83%
2	 **6c**: −20 °C; 12 mL·min^{-1}; 1.25 s[d]	 **3l**[c]	 **7cl**: 78%
3	 **6d**: −20 °C; 12 mL·min^{-1}; 0.10 s[d]	 **3a**[c]	 **7da**: 73%
4	 **6e**: −20 °C; 20 mL·min^{-1}; 0.06 s[b]	 **3m**[e]	 **7em**: 60%
5	 **6e**[b]	 **3n**[f]	 **7en**: 63%
6	 **6f**: −60 °C; 16 mL·min^{-1}; 0.08 s[b]	 **3o**[e]	 **7fo**: 73%

7	 **6g**: −40 °C; 20 mL·min^{-1}; 0.06 s[d]	 **3h**[c]	 **7gh**: 78%
8	 **6h**: −40 °C; 16 mL·min^{-1}; 0.94 s[b]	 **3p**[f]	 **7hp**: 70%
9	 **6i**: −20 °C; 12 mL·min^{-1}; 1.25 s[d]	 **3q**[c]	 **7iq**: 68%
10	 **6j**: −60 °C; 18 mL·min^{-1}; 0.07 s[d]	 **3a**[c]	 **7ja**: 65%
11	 **6k**: −60 °C; 9 mL·min^{-1}; 0.15 s[d]	 **3a**[c]	 **7ka**: 67%
12	 **6l**: −20 °C; 16 mL·min^{-1}; 0.94 s[d]	 **3r**[f]	 **7lr**: 63%

[a] Yield of analytically pure isolated product. [b] Metal species prepared from the aryl iodide. [c] 2.5 equiv, 0.1 equiv CuCN·2LiCl, 30 min, 0 °C. [d] Metal species prepared from the aryl bromide. [e] 1.1-1.5 equiv, 1-2 h, 0 °C. [f] 1.5 equiv, 1.1 equiv CuCN·2LiCl, 1-2 h, 0 °C.

5.4 PREPARATION OF POLYFUNCTIONAL HETEROCYCLIC ORGANOMETALLICS

Heterocycles are found in numerous target molecules due to their bioactive properties and agricultural and pharmaceutical applications.[162] Therefore, efficient functionalization of heterocycles has attracted considerable attention in the past decades.[163] Due to their high reactivity, organolithium compounds are standard organometallic reagents in organic syntheses[164] and have often been used to functionalize heterocycles. Nevertheless, preparation

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[162] (a) D. Astruc, *Modern Arene Chemistry*, Wiley-VCH: 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.

[163] (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; (f) F. H. Lutter, M. S. Hofmayer, J. M. Hammann, V. Malakhov, P. Knochel, *Organic Reactions: Generation and Trapping of Functionalized Aryl- and Heteroarylmagnesium and -Zinc Compounds,* (Ed.: S. E. Denmark), John Wiley & Sons, Hoboken, **2019**.

[164] (a) J. Clayden, *Organolithiums: Selectivity for Synthesis*; (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; (b) M. C. Whisler, S. Mac-Neil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; (c) K. Morija, K. Schwärzer, K. Karaghiosoff, P. Knochel, *Synthesis* **2016**, *48*, 3141; (d) A. B. Bellan, P. Knochel, *Synthesis* **2019**, *51*, 3536; (e) J. Skotnitzki, A. Kremsmair, P. Knochel, *Synthesis* **2020**, *52*, 189; (f) J. Skotnitzki, A. Kremsmair, B. Kicin, R. Saeb, V. Ruf, P. Knochel, *Synthesis* **2020**, *52*, 873.

and handling of heteroaromatic lithium compounds is still challenging, mainly because of their limited stability, low selectivity[165] and limited functional group tolerance.[166]

Among different methods to prepare heteroaromatic lithium species,[167] the halogen-lithium exchange was found to be one of the most efficient preparations of a broad variety of lithium compounds.[168] Recently, Knochel *et al.* have reported an *in situ* trapping transmetalation method using $MgCl_2$•LiCl for the direct preparation of the more stable organomagnesiums after halogen-lithium exchange reactions.[169] In recent years, continuous flow technology emerged as a promising technique to address current synthetic problems especially in organometallic chemistry.[170] Yoshida and others utilized (self-made) flow reactors to achieve ultra-fast mixing on a millisecond scale and precise control over reaction parameters such as reaction time and temperature and successfully applied continuous flow technology to halogen-lithium exchange reactions.[171]

5.5 OPTIMIZATION OF REACTION CONDITIONS

In preliminary experiments, the Br/Li-exchange of 3-bromoquinoline (**8a**) in the presence of $MgCl_2$•LiCl with *n*BuLi as exchange reagent was optimized leading to the corresponding diorganomagnesium reagent **9a** using a combined flow-rate of 12 mL·min^{-1} in a continuous flow set-up. Subsequent batch-trapping with cyclohexanone (**3s**) afforded the desired tertiary alcohol **10as**. At −78 °C, this reaction led to the functionalized quinoline **10as** in 62% GC-yield (Table 4, entry 1). Increasing the temperature resulted in a slightly increased GC-yield (65-67%, entries 2-3), whereas the GC-yield dropped dramatically at 0 °C (22%, entry 4). Addition of $MgCl_2$•LiCl (0.5 equiv) was mandatory for successful reactions since a reaction without $MgCl_2$•LiCl led to 18% GC-yield (entry 5), possibly due to a fast degradation of the heteroaryl lithium species. Increasing the amount of $MgCl_2$•LiCl (1.0 equiv) did not improve the yield (61%, entry 6). Replacing *n*BuLi by PhLi led to a slight decrease to 59% GC-yield (entry 7). Further optimization of the *n*BuLi concentration and reaction time increased the GC-yield of **10as** to 76% (isolated yield: 62%, entries 8-9). A scale-up of the reaction was performed by increasing the run-time from 10 s to 250 s. The desired tertiary

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[165] (a) T. Asai, A. Takata, Y. Ushiogi, Y. Iinuma, A. Nagaki, J.-i. Yoshida, *Chem. Lett.* **2011**, *40*, 393; (b) B. Iddon, *Heterocycles* **1983**, *20*, 1127; (c) A. Nagaki, S. Yamada, M. Doi, Y. Tomida, N. Takabayashi, J.-i. Yoshida, *Green Chem.* **2011**, *13*, 1110.

[166] (a) S. Oda, H. Yamamoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 8165; (b) H. Kim, K.-I. Min, K. Inoue, D.-J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 6286; (c) D. R. Armstrong, E. Crosbie, E. Hevia, R. E. Mulvey, D. L. Ramsay, S. D. Robertson, *Chem. Sci.* **2014**, *5*, 3031.

[167] (a) M. Yus, F. Foubelo, *Handbook of Functionalized Organometallics: Applications in Synthesis Vol. 1* (Ed.: P. Knochel), Wiley-VCH: Weinheim, **2005**; (b) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; (c) J. Skotnitzki, A. Kremsmair, D. Keefer, Y. Gong, R. de Vivie-Riedle, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 320; (d) D. J. Ramón, M. Yus, *Tetrahedron* **1996**, *52*, 13739; (e) R. A. Olofson, C. M. Dougherty *J. Am. Soc. Chem.* **1973**, *95*, 582.

[168] (a) H. R. Rogers, J. Houk, *J. Am. Chem. Soc.* **1982**, *104*, 522; (b) H. J. Reich, N. H. Phillips, I. L. Reich, *J. Am. Chem. Soc.* **1985**, *107*, 4101; (c) B. Jedlicka, R. H. Crabtree, P. E. M. Siebahn, *Organometallics* **1997**, *16*, 6021; (d) H. J. Reich, *J. Org. Chem.* **2012**, *77*, 5471.

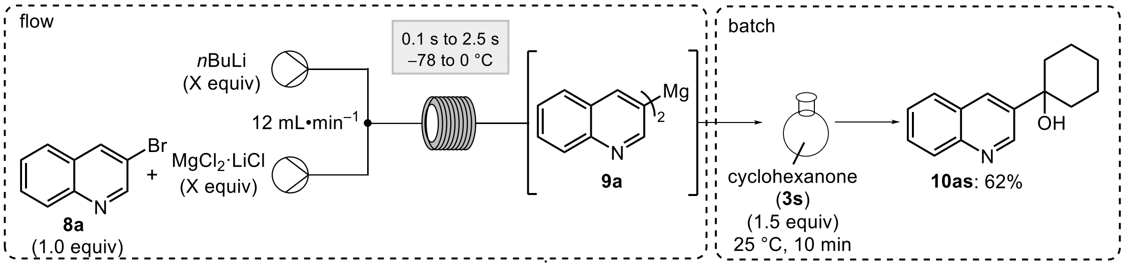
[169] (a) M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770; (b) B. Heinz, M. Balkenhohl, P. Knochel, *Synthesis* **2019**, *51*, 4452.

[170] General advances in flow chemistry: (a) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102; (b) D. Ghislieri, K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 678; (c) 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; (d) H. Seo, M. H. Katcher, T. F. Jamison, *Nat. Chem.* **2017**, *9*, 453.

[171] (a) A. Nagaki, H. Kim, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2008**, *47*, 7833; (b) J.-i. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; (c) J.-i. Yoshida, *Chem. Rec.* **2010**, *10*, 332; (d) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264.

alcohol **10as** was isolated in 61% yield on a 5 mmol scale, which was comparable with the yield obtained on a 0.20 mmol scale (62%, entry 9).

Table 4: Optimization of the bromine-lithium exchange in the presence of $MgCl_2 \cdot LiCl$ using continuous flow.

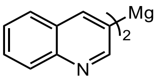
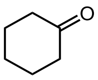
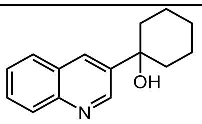


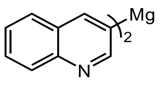
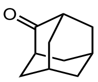
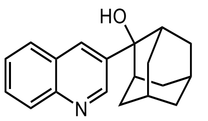
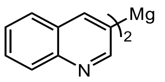
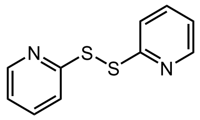
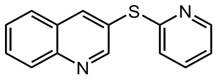
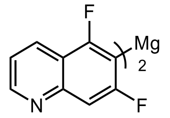
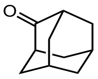
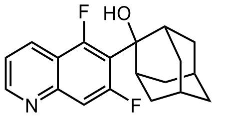
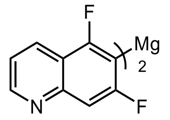
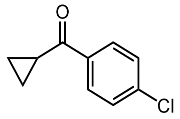
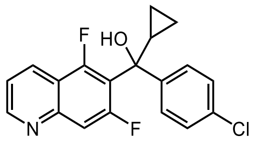
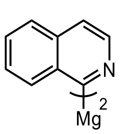
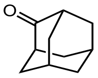
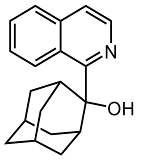
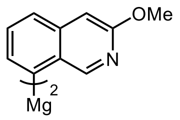
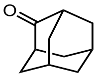
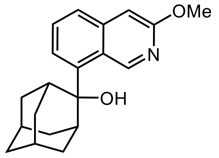
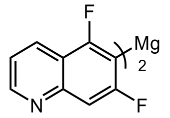
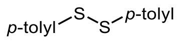
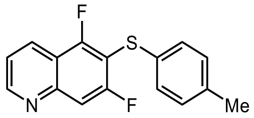
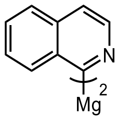
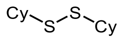
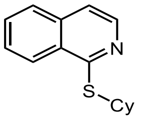
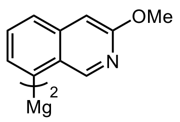
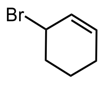
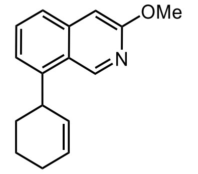
Entry	Base (X equiv)	T [°C]	Additives (X equiv)	Reaction time [s]	GC-yield [%][a]
1	*n*BuLi (1.0)	−78	$MgCl_2 \cdot LiCl$ (0.5)	2.5	62%
2	*n*BuLi (1.0)	−40	$MgCl_2 \cdot LiCl$ (0.5)	2.5	65%
3	*n*BuLi (1.0)	−20	$MgCl_2 \cdot LiCl$ (0.5)	2.5	67%
4	*n*BuLi (1.0)	0	$MgCl_2 \cdot LiCl$ (0.5)	2.5	22%
5	*n*BuLi (1.0)	−20	None	2.5	18%
6	*n*BuLi (1.0)	−20	$MgCl_2 \cdot LiCl$ (1.0)	2.5	61%
7	PhLi (1.0)	−20	$MgCl_2 \cdot LiCl$ (0.5)	2.5	59%
8	*n*BuLi (1.0)	−20	$MgCl_2 \cdot LiCl$ (0.5)	0.1	68%
9	***n*BuLi (1.5)**	**−20**	**$MgCl_2 \cdot LiCl$ (0.5)**	**0.1**	**76% (62%[b], 61%[c])**

[a] GC-yield determined using dodecane as an internal standard. [b] Yield of analytically pure isolated product. [c] Yield of analytically pure isolated product on a 5 mmol scale.

With these optimized conditions in hand, the *in situ* trapping halogen-exchange reaction on substituted (iso)quinolines was investigated. The intermediate diheteroarylmagnesium **9a** reacted with ketones such as cyclohexanone (**3s**) and adamantanone (**3t**) affording the tertiary alcohols **10as** and **10at** in 62-72% isolated yield (Table 5, entries 1-2). Using 2,2′-dipyridyl disulfide (**3u**) as electrophile afforded the thioether **10au** in 88% yield (entry 3). Further, the range of substrates was extended to various substituted bromo- and iodoquinolines and -isoquinolines of type **8** which were converted to the corresponding diheteroarylmagnesiums of type **9** and subsequently trapped with ketones or disulfides of type **3** resulting in functionalized (iso)quinolines of type **10**.

Table 5: *In situ* exchange-transmetalation for highly sensitive aryl halides of type **8** leading *via* intermediate diorganomagnesiums of type **9** to polyfunctional arenes of type **10**.

Entry	Diorganomagnesium species T [°C]; Flow-rate [mL·min−1], t [s]	Electrophile	Product[a]
1	 **9a**: −20; 12; 0.1[b,d]	 **3s**[e]	 **10as**: 62%

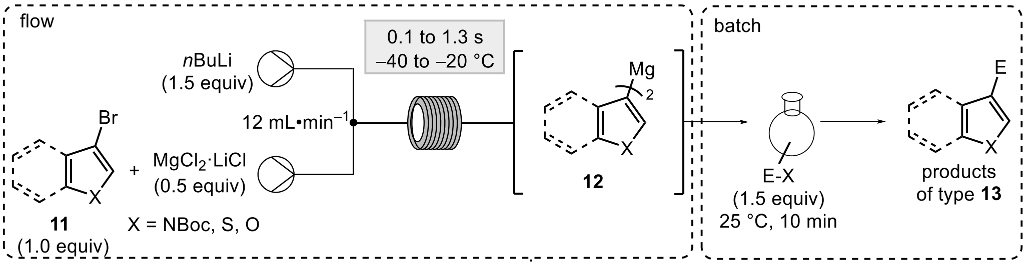
2	 **9a**: −20; 12; 0.1[b,d]	 **3t**[e]	 **10at**: 72%
3	 **9a**: −20; 12; 0.1[b,d]	 **3u**[e]	 **10au**: 88%
4	 **9b**: −78; 12; 0.1[b,d]	 **3t**[e]	 **10bt**: 95%
5	 **9b**: −78; 12; 0.1[b,d]	 **3f**[e]	 **10bf**: 95%
6	 **9c**: 0, 6, 2.5[c,d]	 **3t**[e]	 **10ct**: 73%
7	 **9d**: −20; 6; 2.5[b,d]	 **3t**[e]	 **10dt**: 73%
8	 **9b**: −78; 12; 0.1[b,d]	 **3v**[e]	 **10bv**: 73%
9	 **9c**: 0, 6, 2.5[c,d]	 **3w**[e]	 **10cw**: 90%
10	 **9d**: −20; 6; 2.5[b,d]	 **3h**[f]	 **10dh**: 71%

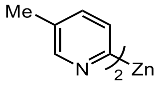
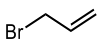
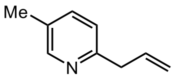
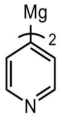
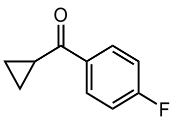
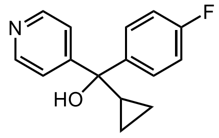
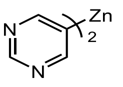
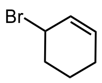
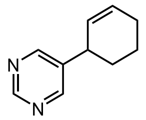
[a] Yield of analytically pure isolated product. [b] The diorganomagnesium species was prepared from the corresponding heteroaryl bromide. [c] The diorganomagnesium species was prepared from the corresponding heteroaryl iodide. [d] The diorganomagnesium species was prepared from *n*BuLi solution (0.30 M). [e] 1.5 equiv, 10 min, 25 °C. [f] 1.5 equiv, 0.1 equiv CuCN·2LiCl, 10 min, 25 °C.

Sterically hindered ketones such as adamantanone (**3t**) and 4-chlorophenyl cyclopropylketone (**3f**) gave the tertiary alcohols **10bt**, **10bf**, **10ct** and **10dt** in 73-95% yield (entries 4-7). Also, addition of the intermediate magnesium species **9b** and **9c** to the disulfides **3v** and **3w** led to the thioethers **10bv** and **10cw** in 73-90% yield (entries 8-9). Furthermore, allylation reactions were investigated. By adding 10 mol% CuCN·2LiCl, allylation of **2d** using cyclohexene bromide (**3h**) led to the functionalized isoquinoline **10dh** in 71% yield (entry 10).

To demonstrate the broad applicability of *in situ* trapping exchange reactions in continuous flow, various nitrogen-, sulfur- and oxygen-containing heterocycles of type **11** were investigated. First, (functionalized) pyridines and pyrimidines were subjected successfully to the Br/Li-exchange. Pyridine derivatives **11a**-**b** underwent the *in situ* trapping exchange reaction (Table 6, entries 1-2). Quenching of the bis-pyridyl-zinc and -magnesium reagents **12a** and **12b** in batch led to the allylated picoline **13aa** and the tertiary alcohol **13bo** in 62-63% yield (entries 1-2). Furthermore, 5-bromopyrimidine (**11c**) and the fully substituted iodopyrimidine **11d** were transmetalated *in situ* using short reaction times (0.06-1.25 s) at −40 to 0 °C (entries 3-4). An ester was tolerated using PhLi providing the acylated pyrimidine **13dx** in 68% yield (entry 4).[172] Interestingly, uracil derived, electron-rich iodopyrimidine **11e** underwent an efficient exchange using the same methodology and the reactive metal species **12e** was quenched with benzoyl chloride **3y** in a subsequent batch reaction leading to benzophenone **10f** in 72% yield (entry 5). Moreover, *N*-Boc-protected indole (**11f**) was converted to its magnesium species at −20 °C within 1.3 s. Subsequent batch-quench with cyclohexanone (**3s**) led to the tertiary alcohol **13fs** in 60% yield (entry 6).

Table 6: *In situ* exchange-transmetalation for highly sensitive aryl halides of type **11** leading *via* intermediate diorgano-zincs or -magnesiums of type **12** to polyfunctional arenes of type **13**.



Entry	Diorganomagnesium species of type **12** T [°C]; flow-rate [mL·min^{-1}], t [s]	Electrophile	Product of type **13**[a]
1	 **12a**: 0 °C; 6; 53 s[b,c]	 **3a**[d]	 **13aa**: 63%
2	 **12b**: 0 °C; 18; 0.83 s[c,e]	 **3o**[f]	 **13bo**: 62%
3	 **12c**: 0 °C; 12; 1.25 s[b,c]	 **3h**[d]	 **13ch**: 68%

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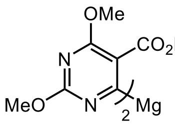
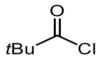
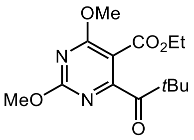
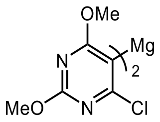
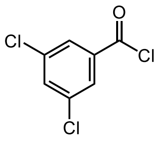
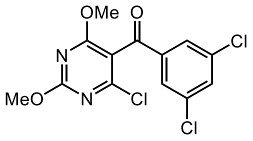
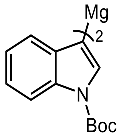
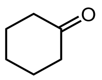
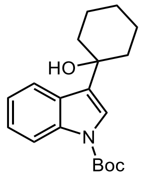
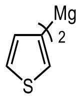
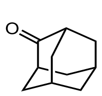
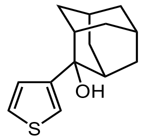
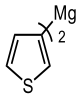
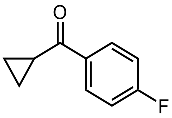
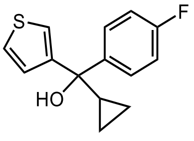
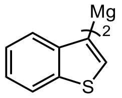
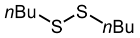
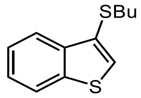
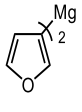
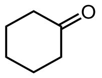
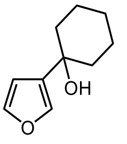
[172] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

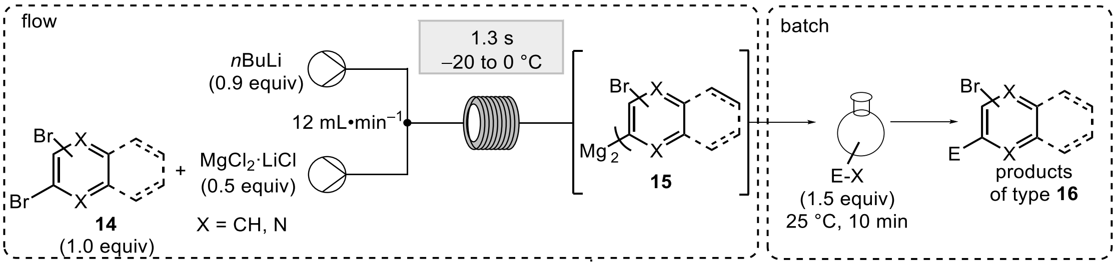
4	 **12d**: −40 °C; 20; 0.06 s[c,e]	 **3x**[d]	 **13dx**: 68%
5	 **12e**: −20; 9; 1.7[c,e]	 **3y**[d]	 **13ey**: 72%
6	 **12f**: −20; 12; 1.3[b,c]	 **3s**[f]	 **13fs**: 60% (61%)[g]
7	 **12g**: −20; 12; 1.3[b,c]	 **3t**[f]	 **13gt**: 92%
8	 **12g**: 0 °C; 6; 10 s[b,c]	 **3o**[f]	 **13go**: 77%
9	 **12h**: −20; 12; 1.3[b,c]	 **3z**[f]	 **13hz**: 94%
10	 **12i**: −40; 12; 0.1[b,c]	 **3s**[f]	 **13is**: 60%

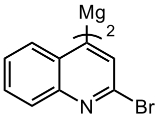
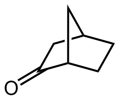
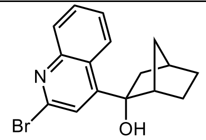
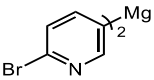
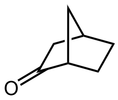
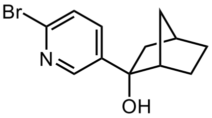
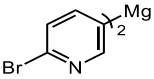
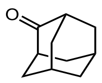
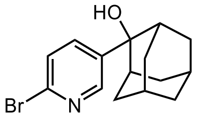
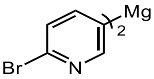
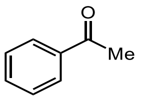
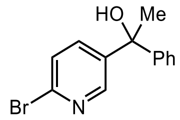
[a] Yield of analytically pure isolated product. [b] The diorganomagnesium species was prepared from the corresponding heteroaryl bromide. [c] The diorganomagnesium species was prepared from *n*BuLi solution (0.30 M). [d] 2.5 equiv, 0.1 equiv CuCN·2LiCl, 30 min, 0 °C. [e] Metal species prepared from the aryl iodide. [f] 1.5 equiv, 10 min, 25 °C. [g] Scale-up was performed on a 2 mmol scale.

Furthermore, a scale-up to 2.0 mmol was possible without any optimization by increasing the run-time resulting in a similar yield (61%). Applying the standard flow conditions to 3-bromothiophene (**11g**) afforded the functionalized thiophenes **13gt** and **13go** in 77-92% yield after batch quench with ketones **3t** and **3o** (entries 7-8). It was also possible to perform a Br/Li-exchange on 3-bromobenzothiophene (**11h**) applying the same conditions, providing diheteroarylmagnesium **12h**. A subsequent batch quench with Bu_2S_2 afforded 3-(butylthio)benzothiophene (**13hz**) in 94% yield (entry 9). Also, 3-bromofuran (**11i**) was converted to the corresponding bis-magnesium species **12i** within 0.1 s at −40 °C. Consecutive batch trapping with cyclohexanone (**3s**) led to the functionalized furan **13is** in 60% isolated yield (entry 10).

Notably, challenging substrates of type **14** bearing two bromides were successfully exchanged with excellent regioselectivity.[173] 2,4-Dibromoquinoline (**14a**) was selectively exchanged at 4-position using *n*BuLi (0.9 equiv). The resulting diorganomagnesium species **15a** was subsequently trapped with norcamphor (**3a’**) affording **16aa’** in 58% isolated yield (Table 7, entry 1). Interestingly, the exchange reaction of 2,5-dibromopyridine (**14b**) proceeded at 0 °C in contrast to batch reactions, which were usually performed at −78 °C. The diheteroarylmagnesium was selectively formed at 5-position. After batch addition to ketones **3a’**,**3t**, **3b’** and **3c’** or cyclohexene bromide (**3h**) using 10 mol% $CuCN\cdot 2LiCl$ as catalyst, the functionalized pyridines **16ba’**, **16bt**, **16bb’**, **16bc’** and **16bh** were obtained in 56-89% yield (entries 2-6). 2,5-Dibromopyrazine (**14c**) was exchanged using this method at −20 °C within 1.3 s reaction time. The resulting magnesium intermediate **15c** was directly quenched with cyclohexanone (**3s**) resulting in the corresponding tertiary alcohol **16cs** in 67% yield (entry 7). Noteworthy, using a 0.38 M *n*BuLi solution, it was shown that a double exchange was feasible without further optimization of the reaction conditions resulting in the bis-allylated product **16dh** in 62% yield (entry 8).

Table 7: *In situ* exchange-transmetalation for sensitive heteroaryl dibromides of type **15**, leading *via* intermediate diorganomagnesium species of type **16** to polyfunctional heteroarenes of type **16**.



Entry	Diorganomagnesium species of type **15** T [°C]; flow-rate [mL·min^{-1}], t [s]	Electrophile	Product of type **16**[a]
1	 **15a**: −20; 12; 1.3[b,c]	 **3a‘**[d]	 **16aa‘**: 58% *d.r.*>99:1
2	 **15b**: 0; 12; 1.3[b,c]	 **3a‘**[d]	 **16ba‘**: 68% *d.r.*>99:1
3	 **15b**: 0; 12; 1.3[b,c]	 **3t**[d]	 **16bt**: 67%
4	 **15b**: 0; 12; 1.3[b,c]	 **3b‘**[d]	 **16bb‘**: 56%

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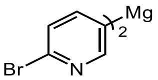
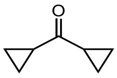
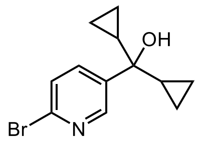
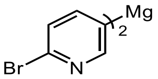
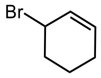
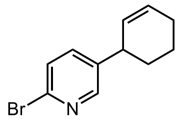
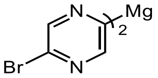
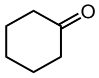
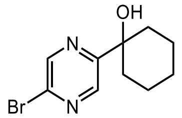
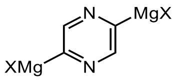
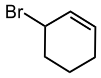
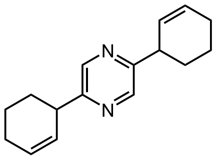
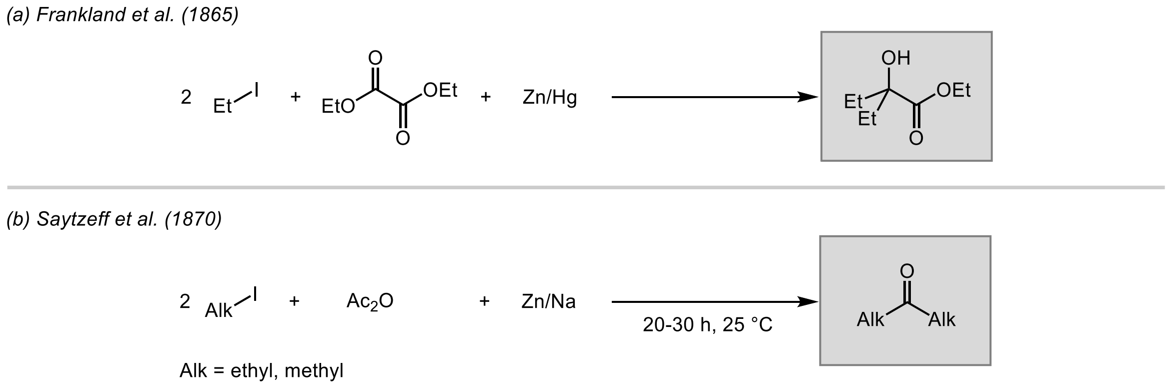
[173] (a) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525; (b) D. Soorukram, N. Boudet, V. Malakhov, P. Knochel, *Synthesis* **2007**, *24*, 3915.

5	 **15b**: 0; 12; 1.3[b,c]	 **3c‘**[d]	 **16bc‘**: 89%
6	 **15b**: 0; 12; 1.3[b,c]	 **3h**[e]	 **16bh**: 61%
7	 **15c**: −20; 12; 1.3[b,c]	 **3s**[d]	 **16cs**: 67%
8	 **15d**: −20; 12; 1.3[b,f]	 **3h**[g]	 **16dh**: 62%

[a] Yield of analytically pure isolated product. [b] The diorganomagnesium species was prepared from the corresponding heteroaryl bromide. [c] The diorganomagnesium species was prepared from *n*BuLi solution (0.18 M). [d] 1.5 equiv, 10 min, 25 °C. [e] 1.5 equiv, 0.1 equiv CuCN·2LiCl, 10 min, 25 °C. [f] The organomagnesium species was prepared from *n*BuLi solution (0.38 M). [g] 3.0 equiv, 0.2 equiv CuCN·2LiCl, 10 min, 25 °C.

6. HALOGEN-LITHIUM EXCHANGE OF SENSITIVE (HETERO)AROMATIC AND (HETERO)BENZYLIC HALIDES UNDER BARBIER CONDITIONS IN A CONTINUOUS FLOW SET-UP

Barbier(-type) reactions display a convenient way to handle reactive organometallic intermediates by *in situ* trapping with already present electrophiles. Seminal contributions resulting in Barbier-type reactions were made by Frankland and Saytzeff. Frankland already mixed oxalic ester with ethyl iodide and elemental zinc, affording the *in situ* generated diethyl zinc which was subsequently trapped by oxalic ester resulting in the desired tertiary alcohol (Scheme 30a).[174] In 1870, Saytzeff struggled with the synthesis of ketones such as butanone and acetone while mixing dialkyl zincs with acetic anhydride. However, a Barbier-type reaction, namely adding a mixture of alkyl iodides and acetic anhydride to a zinc/sodium mixture, afforded butanone and acetone after cautious distillation (Scheme 30b).[175]



Scheme 30: Seminal contributions regarding Barbier-type reactions by Frankland and Seytzeff in the late 19th century.[175-176]

Following these seminal results, Barbier replaced elemental zinc by magnesium to afford a tertiary alcohol in a one-step procedure by mixing methyl iodide, magnesium and 6-methylhept-5-en-2-one resulting in the first Barbier reaction in 1899 (Scheme 31a). In contrast, the Grignard reaction followed a stepwise procedure for the generation of the organomagnesium reagents and addition to the electrophile.[176] Based on these findings, many Barbier reactions were performed in the following years.[177] In the early 20th century, the investigation of allylic organomagnesiums in Barbier reactions led to the one-pot generation and addition of allylic organomagnesiums to ketones (Jaworsky reaction, Scheme 31b).[178] In 1911, Kipping and Davies further demonstrated that the generation of benzylic organomagnesium does not need a tedious preparation of the organometallic reagent and

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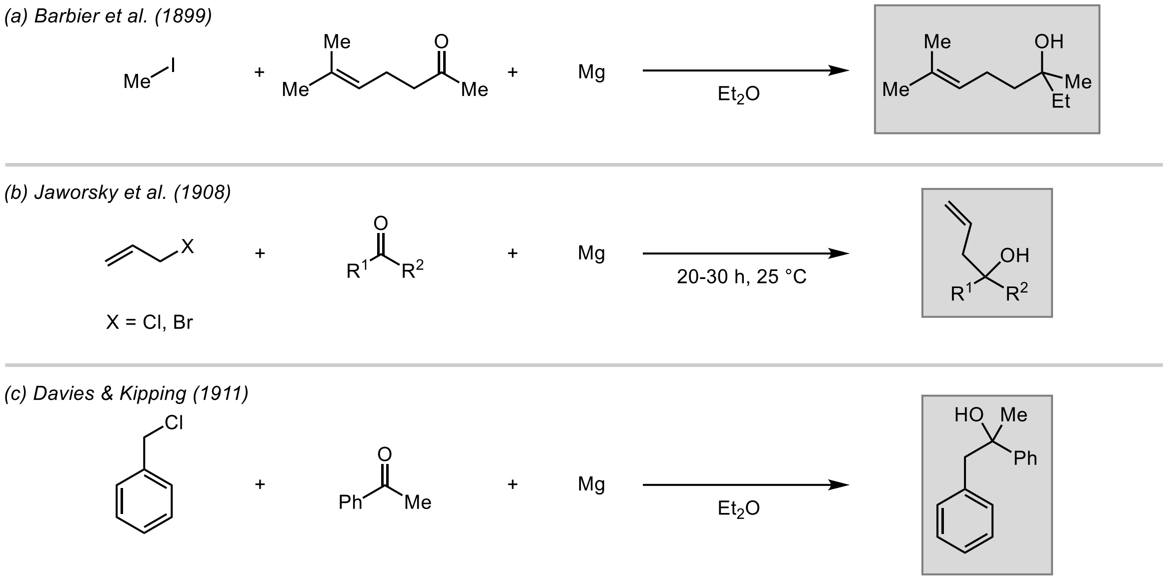
[174] E. Frankland, B. F. Duppa, *Justus Liebigs Ann. Chem.* **1865**, *133*, 80.
[175] A. Saytzeff, *T. f. Chemie* **1870**, *13*, 104.
[176] (a) P. Barbier, *Compt. Rend.* **1899**, *128*, 110; (b) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322.
[177] H. Gilman, J. H. McGlumphy, *Bull. Soc. Chim. France* **1928**, *43*, 1322.
[178] W. Jaworsky, *J. Russ. Phys.-Chem. Soc.* **1908**, *40*, 782; (b) W. Jaworsky, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 435.

transfer to the electrophile. Rather, a one-step procedure was possible without significant loss of yield (Scheme 31c).[179]



Scheme 31: A brief summary of the history of the Barbier(-type) reaction in the 20th century.

However, the Barbier procedure did not gain interest in the scientific community until Dreyfuss in 1963 successfully proved that Barbier-type protocols provide a useful tool for the *in situ* trapping of highly reactive intermediates.[180] Nevertheless, the amount of Grignard reactions outcompete the number of Barbier reactions by far, although an one-pot manner often provides a more economic method, which is highly desirable for industrial applications. However, not only the use of magnesium is of particular interest in organic syntheses. Organolithiums are more reactive than the corresponding organomagnesiums. Thus, the more electropositive lithium is enjoying increasing attention in recent years. In the late 1960´s, various intramolecular Barbier-type reactions with functionalized alkyl bromides and elemental lithium were reported (Scheme 32a).[181] Scilly and co-workers further extended the scope of lithium-Barbier-type reactions to aryl and alkyl halides in the presence of a large variety of aldehydes, ketones and esters (Scheme 32b).[182] Instead of using elemental lithium for the generation of organolithiums, Kobayashi and co-workers developed a strategy to perform an iodine-lithium exchange using *n*BuLi and aromatic iodides. Intramolecular trapping with a ketone afforded the tertiary alcohol in 69% isolated yield (Scheme 32c).[183]

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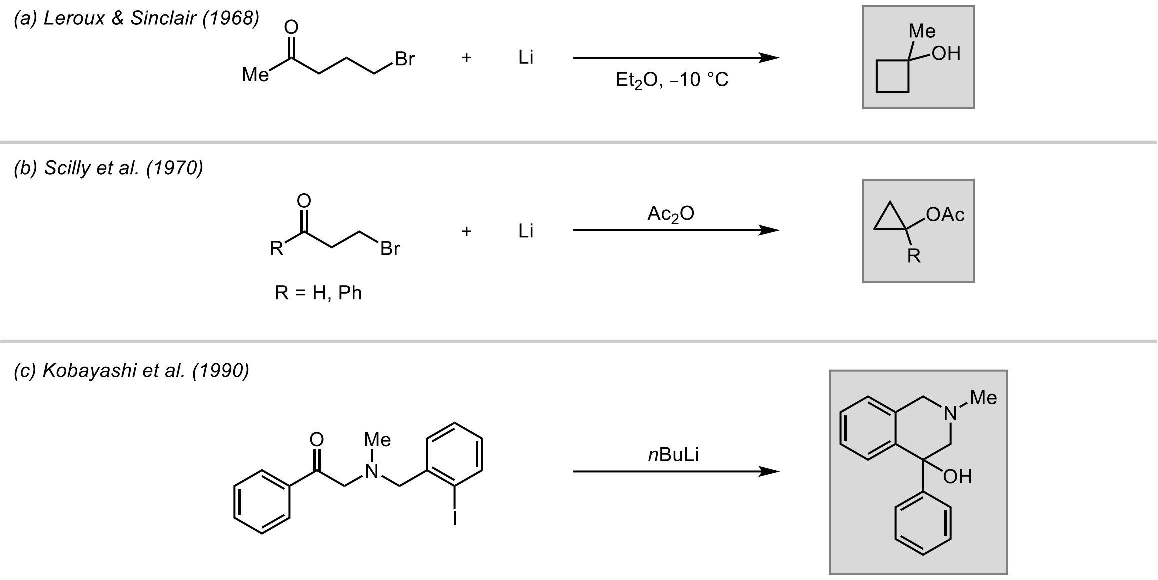
[179] H. Davies, F. J. Kipping, *J. Chem. Soc. Trans.* **1911**, *99*, 296.

[180] M. Dreyfuss, *J. Org. Chem.* **1963**, *28*, 3269.

[181] (a) Y. Leroux, *Bull. Soc. Chim. France* **1968**, 359; (b) D. P. G. Hamon, R. W. Sinclair, *J. Chem. Soc. Chem. Commun.* **1968**, 890.

[182] (a) P. J. Pearce, D. H. Richards, N. F. Scilly, *J. Chem. Soc. Chem. Commun.* **1970**, 1160; (b) P. J. Pearce, D. H. Richards, N. F. Scilly, *J. Chem. Soc. Perkin Trans. I* **1972**, 1655.

[183] M. Kihara, M. Kashimoto, Y. Kobayashi, S. Kobayashi, *Tetrahedron Lett.* **1990**, *37*, 5347.



Scheme 32: Barbier-type halogen-lithium exchange reactions using elemental lithium or *n*BuLi as exchange reagent.

However, the field of Barbier-type reactions using elemental lithium or alkyl lithium reagents for exchange reactions is still underdeveloped. Therefore, investigations on Barbier-type reactions is still an ongoing task. In the following, two methods for the generation of highly reactive (hetero)aromatic and (hetero)benzylic organolithiums are introduced highlighting the benefits of Barbier-type reactions in a continuous flow set-up.

6.1 INTRODUCTION

Functionalized (hetero)arenes play an important role in the elaboration of pharmaceuticals and agrochemicals.[184] New strategies for the functionalization of aromatics and heteroaromatics are still needed for extending the reaction scope.[185] In the past, lithium bases have been used to produce various lithiated aromatics and heteroaromatics.[186] However, some major drawbacks, *e.g.* a low functional group tolerance and moderate stability of the resulting (hetero)aryllithium have been noticed.[187] To overcome these limitations, other organometallic reagents, such as organomagnesium and organozinc species with increased stability, were used. Nevertheless, their low reactivity towards electrophiles often requires the presence of transition metal

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[184] (a) D. Astruc, *Modern Arene Chemistry*, Wiley-VCH: 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.

[185] (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.

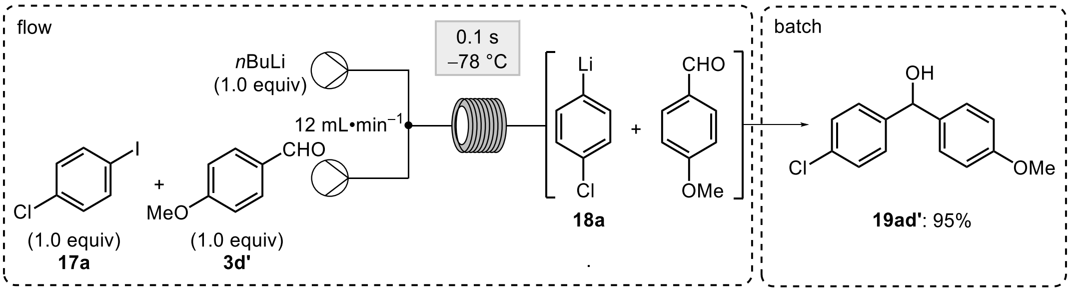
[186] (a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187; (b) W. E. Parham, L. D. Jones, Y. Sayed, *J. Org. Chem.* **1975**, *40*, 239; (c) W. E. Parham, R. M. Piccirilli, *J. Org. Chem.* **1977**, *42*, 257; (d) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; (e) L. Morija, K. Schwärzer, K. Karaghiosoff, P. Knochel, *Synthesis* **2016**, *48*, 3141; (f) A. B. Bellan, P. Knochel, *Synthesis* **2019**, *51*, 3536; (g) J. Skotnitzki, A. Kremsmair, P. Knochel, *Synthesis* **2020**, *52*, 189; (h) J. Skotnitzki, A. Kremsmair, B. Kicin, R. Saeb, V. Ruf, P. Knochel, *Synthesis* **2020**, *52*, 873.

[187] (a) M. Hatano, S. Suzuki, K. Ishihara, *Synlett* **2010**, 321; (b) T. Kim, K. Kim, *J. Heterocycl. Che*m. **2010**, *47*, 98; (c) K. Kobayashi, Y. Yokoi, T. Nakahara, N. Matsumoto, *Tetrahedron* **2013**, *69*, 10304; (d) A. Matsuzawa, S. Takeuchi, K. Sugita, *Chem. Asian J.* **2016**, *11*, 2863.

catalysts.[188] Recently, Yoshida and others reported an increased compatibility of lithiated compounds bearing functional groups under continuous flow conditions.[189] Inspired by Yoshida's work and having in mind, that the halogen-lithium exchange is a fast reaction for the generation of lithiated (hetero)aromatics,[190] the preparation of (hetero)aryl lithium derivatives in the presence of various electrophiles was envisioned. In addition, the precise control of reaction parameters such as temperature, reaction time and ultra-fast mixing using a commercial flow set-up allowed convenient reaction conditions at non cryogenic temperatures and scale-ups without further optimization of the reaction conditions.[191]

6.2 SCREENING OF OPTIMIZED REACTION CONDITIONS

Herein, a Barbier-type halogen-lithium exchange reaction of sensitive (hetero)aromatic halides of type **17** using *n*BuLi or *t*BuLi as exchange reagents in the presence of various electrophiles of type **3** using a commercially available flow set-up is reported. The resulting lithiated (hetero)aromatic species of type **18** were quenched *in situ* with various electrophiles resulting in a broad range of functionalized (hetero)aromatics of type **19**. First, the stoichiometry of 1-chloro-4-iodobenzene (**17a**) and *p*-anisaldehyde (**3d'**, playing the role of the *in situ* electrophile) were screened as well as the reaction time and temperature. It was found that by using a combined flow-rate of 12 mL·min^{-1} at −78 °C a complete iodine-lithium exchange of arene **17a** (1.0 equiv) in the presence of *p*-anisaldehyde (**3d'**) (1.5 equiv) and *n*BuLi (1.5 equiv) as exchange reagent was afforded within 0.1 s leading to the secondary alcohol **19ad'** in 72% GC-yield.



Scheme 33: Halogen-lithium exchange reaction of functionalized (hetero)aryl halides of type **17** under Barbier conditions and *in situ* trapping with various electrophiles of type **3** affording polyfunctionalized (hetero)aryls of type **19** using a commercial continuous flow set-up.

Increasing the reaction time (up to 24 s) or conducting the reaction at elevated temperatures (up to 0 °C) led to a decreased GC-yield of 62-65%. Finally, optimal results were achieved using aromatic iodide **17a** (1.0 equiv), aldehyde **3d'** (1.0 equiv) and *n*BuLi (1.0 equiv) as exchange reagent. The addition of *n*BuLi to *p*-anisaldehyde (**3d'**) leading to a secondary

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[188] (a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; (b) M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56, 12770;* (c) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 1992; (d) B. Heinz, M. Balkenhohl, P. Knochel, *Synthesis* **2019**, *51*, 4452.

[189] (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*, 6286; (e) A. Nagaki, Y. Tsuchihashi, S. Haraki, J.-i. Yoshida, *Org. Biomol. Chem.* **2015**, *13*, 7140.

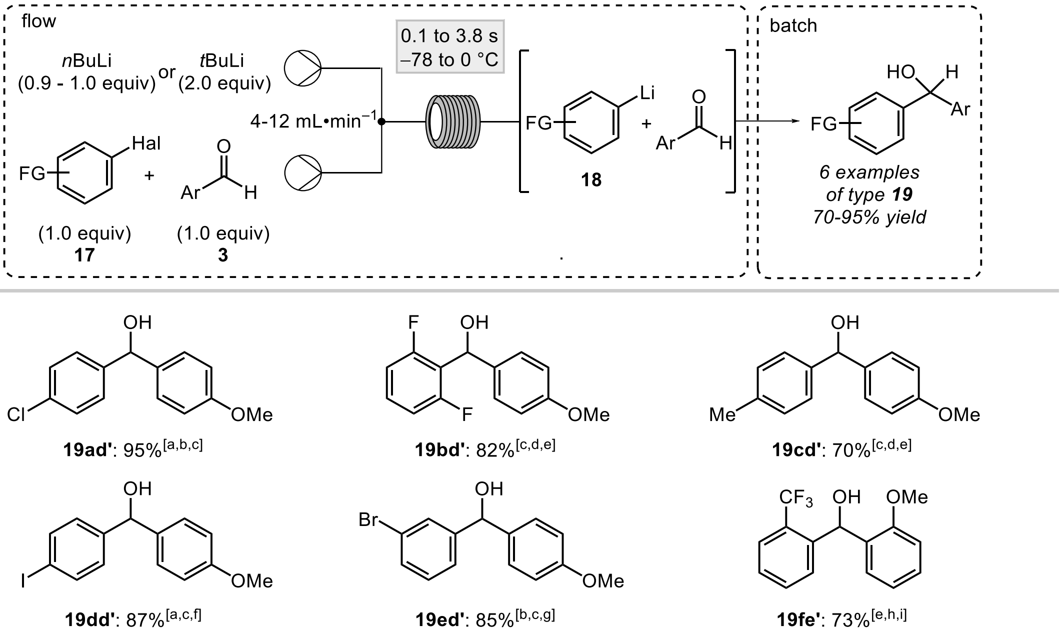
[190] H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130.

[191] (a) M. B. Plutschack, B. Piber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796; (b) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892; (c) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463.

alcohol was a negligible side-reaction and **19ad’** was obtained in 95% isolated yield (Scheme 33).

6.3 EXPANDING THE SUBSTRATE SCOPE

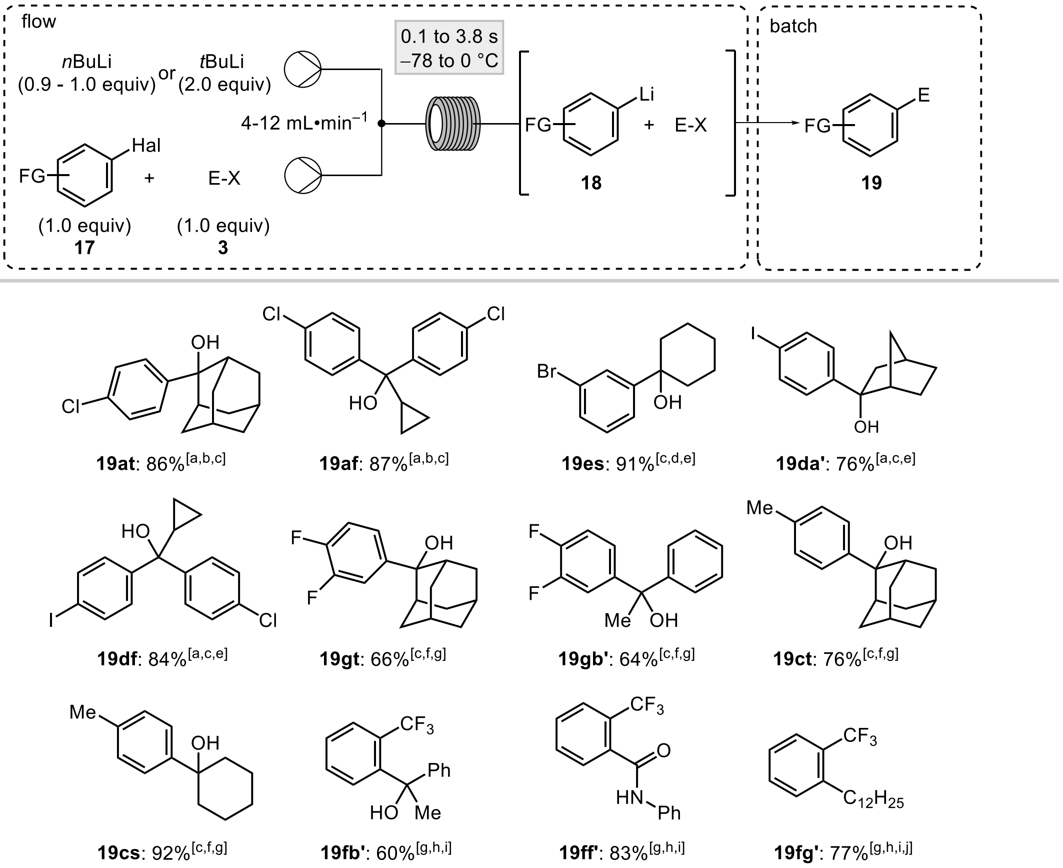
Similarly, 1,3-difluoro-2-iodobenzene (**17b**) gave the organolithium reagent **18b** at −20 °C within 1.9 s, which was subsequently trapped with **3d’** resulting in the secondary alcohol **19bd’** in 82% yield (Scheme 34). The reaction of 1-methyl-4-iodobenzene (**17c**) with *p*-anisaldehyde (**3d’**) afforded the desired product **19cd’** in 70% isolated yield. This procedure was applied to dihalogenated starting materials such as 1,4-diiodobenzene (**17d**) and 1-bromo-2 iodobenzene (**17e**). The *in situ* generated organolithiums **18d-18e** were immediately trapped with **3d’** resulting in the corresponding alcohols **19dd’** and **19ed’** in 85-87% yield. As expected, using 1,4-diiodobenzene (**17d**) merely one iodine was exchanged. Additionally, 1-bromo-3-iodobenzene (**17e**) underwent a clean I/Li exchange providing the benzhydryl alcohol **19ed’** in 85% yield. The exchange of 1-iodo-2-(trifluoromethyl)benzene (**17f**) using *n*BuLi only led to the undesired BuLi-addition to the aldehyde. However, by using *t*BuLi (2.0 equiv) the desired organolithium **18f** was obtained. After *in situ* trapping with *o*-anisaldehyde (**3e’**), the desired alcohol **19fe’** was isolated in 73% yield.



Scheme 34: Halogen-lithium exchange reaction of functionalized aryl halides under Barbier conditions and *in situ* trapping with aldehydes using a commercial continuous flow set-up. [a] −78 °C, 12 mL·min^{-1}, 0.1 s. [b] *n*BuLi = 1.0 equiv. [c] From the corresponding iodide. [d] −20 °C, 8 mL·min^{-1}, 1.9 s. [e] *t*BuLi = 2.0 equiv. [f] *n*BuLi = 0.9 equiv. [g] 0 °C, 12 mL·min^{-1}, 0.1 s. [h] −20 °C, 4 mL·min^{-1}, 3.8 s. [i] From the corresponding bromide.

6.4 TRAPPING OF HIGHLY REACTIVE ORGANOLITHIUMS WITH (STERICALLY HINDERED) KETONES

In contrast to the less reactive magnesium or zinc species, the corresponding highly reactive lithium species was trapped *in situ* using Barbier conditions with various ketones resulting in tertiary alcohols. Remarkably, sterically hindered ketones, which are prone to undergo a reduction with lithium reagents,[192] such as adamantanone (**3t**) and 4-chlorophenyl cyclopropyl ketone (**3f**) were satisfactory used as trapping agents (Scheme 35). Thus, the aryllithium **18a** was quenched with **3t** and **3f** resulting in the tertiary alcohols **19at** and **19af** in 86-87% isolated yield. Then, arenes bearing fluoro-, bromo- and iodo-substituents were investigated using the optimum flow conditions. The *in situ* generated aryllithiums **18d**, **18e** and **18g** were subsequently trapped by cyclohexanone (**3s**), norcamphor (**3a'**), 4-chlorophenyl cyclopropylketone (**3f**) or adamantanone (**3t**) affording the functionalized arenes **19es**, **19da'**, **19df** and **19gt** in 66-91% yield. Moreover, 1,2-difluoro-4-iodobenzene (**17g**) reacted instantaneously with acetophenone (**3b'**) affording the alcohol **19gb'** in 64% yield without any detection of the aldol side product. Similarly, 1-methyl-4-iodobenzene (**17c**) led, after *in situ* trapping of the lithiated species **18c** with adamantanone (**3t**) and cyclohexanone (**3s**), to the corresponding tertiary alcohols **19ct** and **19cs** in 76-92% yield. Noteworthy, lithiation of 1-iodo-2-(trifluoromethyl)benzene (**17f**) using the optimum conditions resulted in the organolithium **18f**, which after *in situ* trapping with acetophenone (**3b'**) afforded the alcohol **19fb'** in 60% yield. Extending the flow procedure to isocyanates as *in situ* trapping reagents was also possible. Thus, the addition of **18f** to phenyl isocyanate (**3f'**) under standard conditions afforded the corresponding amide **19ff'** in 83% yield.



19at: 86%[a,b,c] **19af**: 87%[a,b,c] **19es**: 91%[c,d,e] **19da'**: 76%[a,c,e]

19df: 84%[a,c,e] **19gt**: 66%[c,f,g] **19gb'**: 64%[c,f,g] **19ct**: 76%[c,f,g]

19cs: 92%[c,f,g] **19fb'**: 60%[g,h,i] **19ff'**: 83%[g,h,i] **19fg'**: 77%[g,h,i,j]

Scheme 35: Halogen-lithium exchange reaction of functionalized aryl halides under Barbier conditions and *in situ* trapping with sterically hindered ketones, phenylisocyanate and dodecyl iodide using a continuous flow set-up. [a] −78 °C, 12 mL·min⁻¹, 0.1 s. [b] *n*BuLi = 1.0 equiv. [c] From the corresponding iodide. [d] 0 °C, 6 mL·min⁻¹, 0.1 s. [e] *n*BuLi = 0.9 equiv. [f] −20 °C, 8 mL·min⁻¹, 1.9 s. [g] *t*BuLi = 2.0 equiv. [h] −20 °C, 4 mL·min⁻¹, 3.8 s. [i] From the corresponding bromide. [j] Dodecyl iodide (1.5 equiv) was used.

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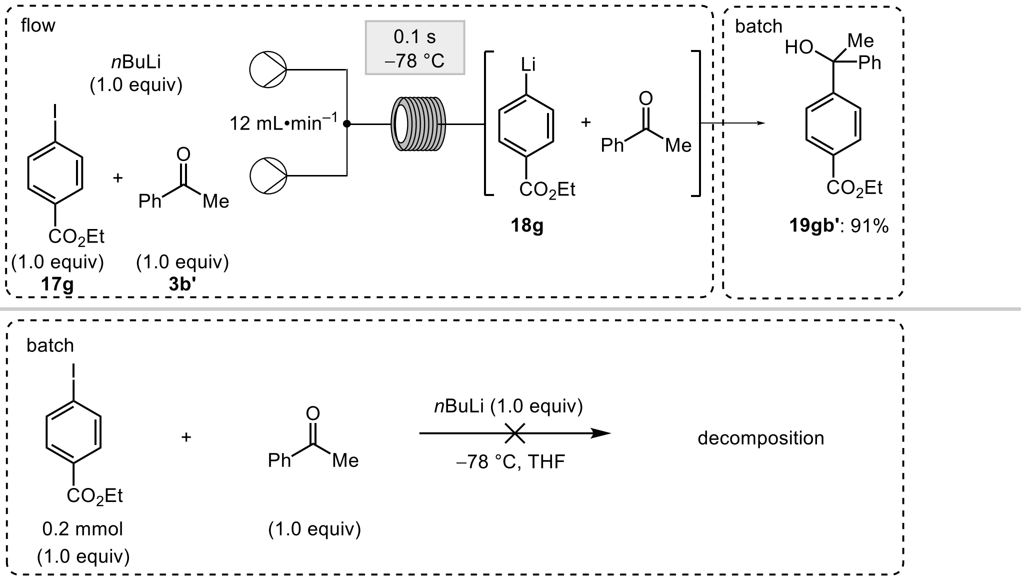
[192] H. Yamataka, N. Miyano, T. Hanafusa, *J. Org. Chem.* **1991**, *56*, 2573.

Next, a Wurtz-Fittig-type coupling[11] using dodecyl iodide (**3g'**, 1.5 equiv) in the absence of any transition metal catalyst was examined. Pleasingly, the alkylated arene **19fg'** was obtained in 77% yield.

6.5 FLOW VERSUS BATCH REACTION OF ETHYL 4-IODOBENZOATE

Next, the behavior of aromatic esters such as ethyl 4-iodobenzoate (**17h**) was examined, which are usually not tolerated under batch conditions using lithium bases. However, with a flow set-up it was possible to perform an iodine-lithium exchange in the presence acetophenone (**3b'**, 1.0 equiv). The *in situ* trapping of the lithiated arene **18h** afforded the desired tertiary alcohol **19hb'** in 91% yield, whereas a batch reaction led to undesired side reactions and decomposition of ester **17h** (Scheme 36).



Scheme 36: *In situ* trapping iodine-lithium exchange reaction of highly sensitive ethyl 4-iodobenzoate (**17h**) under Barbier conditions using a commercial continuous flow set-up.

6.6 BARBIER HALOGEN-LITHIUM EXCHANGE OF FUNCTIONALIZED HETEROCYCLES

The functionalization of heterocycles is a key synthetic task for the elaboration of pharmacological active compounds and agrochemicals.[193] To demonstrate the broad applicability of Barbier-type halogen-lithium exchange reactions, its compatibility with heteroaromatic halides of type **20** was investigated, affording functionalized heterocycles of type **22** *via* the heteroaryllithium species of type **21**. Notably, 2-bromopyridine (**20a**) was used to generate the highly reactive intermediate 2-pyridyllithium (**21a**) at −78 °C within 0.1 s. Trapping of **21a** with sterically demanding ketones **3h', 3t** and **3f** afforded the tertiary alcohols **22ah'**, **22at** and **22af** in 93-99% yield (Table 8, entries 1-3). Quenching with Weinreb amide **3i'** and imine **3j'** led to the desired ketone **22ai'** and secondary amine **22aj'** in 59-62% yield (entries 4-5). The tertiary alcohol **22bt** was obtained after *in situ* quenching of organolithium

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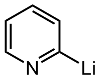
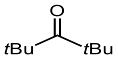
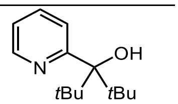
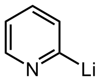
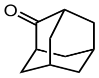
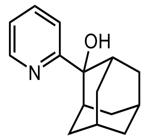
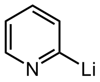
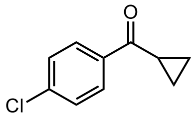
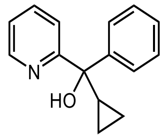
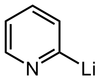
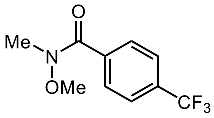
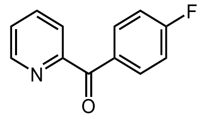
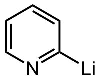
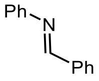
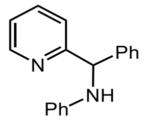
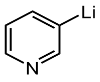
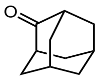
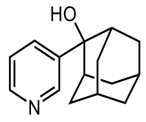
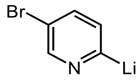
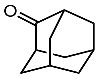
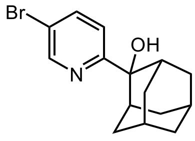
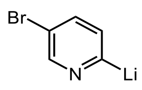
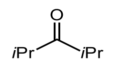
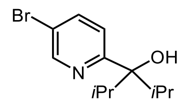
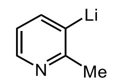
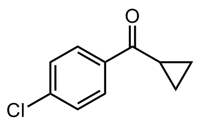
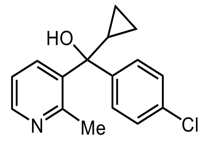
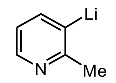
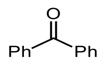
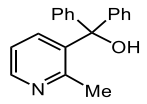
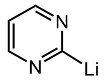
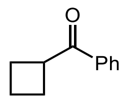
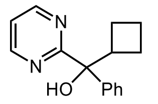
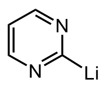
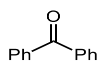
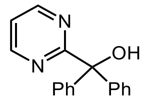
[193] (a) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306; (b) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; (c) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667; (d) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; (e) F. Foubelo, M. Yus, *Chem. Soc. Rev.*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

21b at 0 °C within 7.5 s from 3-bromopyridine (**20b**), whereas the bromine-lithium exchange under batch conditions usually was performed at −78 °C (entry 6). Further, 2,5-dibromopyridine (**20c**) was lithiated in continuous flow with *n*BuLi (0.9 equiv) with complete regioselectivity. Upon immediate quench of resulting lithium species **21c** with various sterically demanding ketones, such as adamantanone (**3t**) and 2,4-dimethylpentan-3-one (**3k'**), solely the 2-substituted pyridines **22ct** and **22ck'** were obtained in 53-64% yield (entries 7-8). Further, 3-iodo-2-methylpyridine (**20d**) was subjected to these conditions affording the desired tertiary alcohols **22df** and **22dl'** in 81-92% yield after *in situ* trapping with ketones **3f** and **3l'** (entries 9-10). 2-Iodopyrimidine (**20e**) was lithiated at −78 °C within 0.1 s affording *via* Barbier-type trapping with ketones **3m'** and **3l'** the sterically demanding tertiary alcohols **22em'** and **22el'** in 79-99% yield (entries 11-12).

Table 8: Halogen-lithium exchange reaction of functionalized heteroaryl halides of type **20** under Barbier conditions and *in situ* trapping of intermediate organolithiums of type **21** with electrophiles of type **3** affording functionalized heteroaryls of type **22** in continuous flow.

Entry	Metal species T[°C]; t[s] Flow-rate [mL·min^{-1}]	Electrophile	Product[a]
			
1	**21a**: −40; 0.1, 12	**3h'**	**22ah'**: 93%[b]
			
2	**21a**: −40; 0.1, 12	**3t**	**22at**: 98%[c]
			
3	**21a**: −40; 0.1, 12	**3f**	**22af**: 99%[c]
			
4	**21a**: −40; 0.1, 12	**3i'**	**22ai'**: 62%[c]
			
5	**21a**: −40; 0.1, 12	**3j'**	**22aj'**: 59%[c]
			
6	**21b**: 0; 7.5; 2	**3t**	**22bt**: 60%[b]
			
7	**21c**: −78; 0.15; 8	**3t**	**22ct**: 64%[c]

8	 **21c**: −78; 0.15; 8	 **3k‘**	 **22ck‘**: 53%[c]
9	 **21d**: −78; 0.1; 12	 **3f**	 **22df**: 81%[c]
10	 **21d**: −78; 0.1; 12	 **3l‘**	 **22dl‘**: 92%[c]
11	 **21e**: −78; 0.1; 12	 **3m‘**	 **22em‘**: 79%[c]
12	 **21e**: −78; 0.1; 12	 **3l‘**	 **22el‘**: 99%[c]

[a] Yield of analytically pure isolated product. [b] *t*BuLi = 2.0 equiv, prepared from the corresponding bromide. [c] *n*BuLi = 0.9 equiv, prepared from the corresponding iodide.

6.7 BARBIER-TYPE REACTION OF (FUNCTIONALIZED) BENZYLIC IODIDES

Although substituted benzylic lithiums were previously prepared by halogen-lithium exchange or insertion reactions from the corresponding benzylic halides (Scheme 37a),[194] their synthesis is often accompanied by side reactions such as Wurtz-homocouplings.[195] Furthermore, the iodine-lithium exchange on alkyl iodides is virtually instantaneous, even outcompeting the deprotonation of MeOH.[196] Based on those facts, it was envisioned to overcome the need of an ultrafast in-line quench or *in situ* trapping with metal salts by adding an electrophile to the starting material solution (Barbier-type conditions).

In course of these studies, an iodine-lithium exchange using benzylic iodides of type **23** in the presence of carbonyl electrophiles of type **3** in a microflow reactor set-up is reported.[197] The resulting benzylic lithium species of type **24** was instantaneously trapped in a Barbier-type reaction by electrophiles of type **3** already present in the reaction solution affording the desired secondary and tertiary alcohols of type **25** (Scheme 37b).

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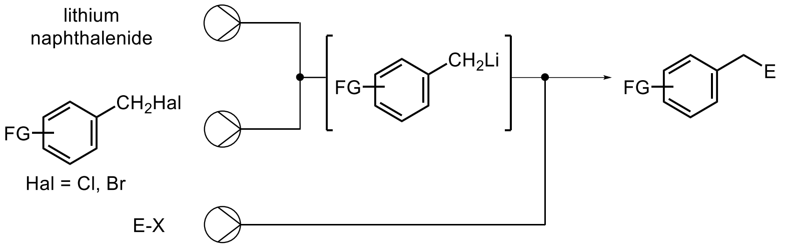
[194] A. Nagaki, K. Sasatsuki, S. Ishiuchi, N. Miuchi, M. Takumi, J.-i. Yoshida, *Chem. – Eur. J.* **2019**, *25*, 4946; (b) H.-j. Lee, H. Kim, J.-i. Yoshida, D.-P. Kim, *Chem. Commun.* **2018**, *54*, 547; (c) H. Kim, Y. Yonekura, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2018**, *57*, 4063; (d) H. Kim, 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.-i. Yoshida, *Org. Biomol. Chem.* **2015**, *13*, 7140.

[195] (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. A. McNinch, D. Wittenberg, *J. Org. Chem.* **1958**, *23*, 2044.

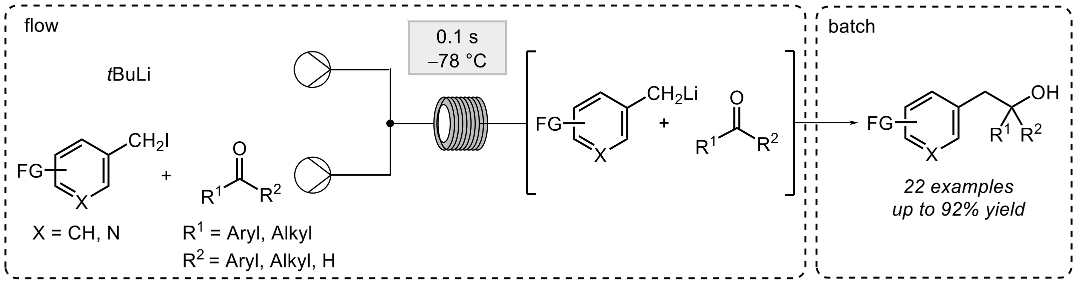
[196] (a) W. F. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861; (b) C. A. Stein, T. H. Morton, *Tetrahedron Lett.* **1973**, *14*, 4933.

[197] For applications of benzyl lithium in flow see: A. Nagaki, Y. Tsuchihashi, S. Haraki, J.-i. Yoshida, *Org. Biomol. Chem.* **2015**, *13*, 7140. For usage of benzyl lithium under barbier conditions see: (a) C. Gómez, F. F. Huerta, M. Yus, *Tetrahedron* **1997**, *40*, 13897; (b) C. Gómez, F. F. Huerta, M. Yus, *Tetrahedron* **1998**, *54*, 1853.

(a) Previous work: Benzylic lithiums via ***lithium insertion*** *with ultrafast reaction times (Yoshida)*



(b) This work: (Hetero)benzylic lithiums via in situ **I/Li-*exchange***



Scheme 37: (a) Lithium insertion into benzylic halides using ultrafast in-line electrophile quench. (b) Iodine-lithium exchange on (hetero)benzylic iodides under Barbier conditions.

6.8 SCREENING OF OPTIMIZED REACTION CONDITIONS FOR BENZYLIC IODIDES

First, the generation of benzyllithium (**24a**) under Barbier-type conditions from benzyl iodide (**23a**, 65 mg, 0.20 mmol, 1.0 equiv) using *n*BuLi (0.25 mmol, 1.25 equiv) as exchange reagent in the presence of benzaldehyde (**3c**, 32 mg, 0.30 mmol, 1.5 equiv) was examined at 0 °C using a combined flow-rate of 2.0 mL·min^{-1}, resulting in 50% GC-yield with a significant amount of *n*BuLi addition to benzaldehyde and Wurtz-type homocoupling (Table 9, entry 1).[198] Decreasing the reactor volume had no impact on the conversion and GC-yield (entry 2). Investigation of various lithium bases such as *s*BuLi, *t*BuLi, *n*HexLi, neo-pentyllithium led to a significant increase of the GC-yield using *t*BuLi (74%, entry 3). The reaction conditions were further optimized by increasing the flow-rate and lowering the temperature, resulting in 87% GC-yield (−78 °C, 10 mL·min^{-1} combined flow-rate, 0.02 mL reactor volume, 0.1 s). Entries 1-8 demonstrate the strong mixing dependence of the iodine-lithium exchange using benzylic iodides. In accordance with the literature,[199] higher flow-rates and smaller reactor diameters resulted in more efficient mixing favouring the exchange reaction. Coordinating additives such as TMEDA (*N,N,N',N'*-tetramethylethylenediamine) and PMDTA (*N,N,N',N'',N''*-pentamethyldiethylenetriamine) afforded the secondary alcohol **25ac** in only 10-13% GC-yield (entries 9-10) with the Wurtz-type coupling as a major side reaction.[200] Using *n*BuLi as exchange reagent at the optimized conditions led to a decreased conversion and GC-yield (entry 11). Under the optimized reaction conditions (entry 8), the desired alcohol **25ac** was obtained in 79% isolated yield. A scale-up was possible without further optimization

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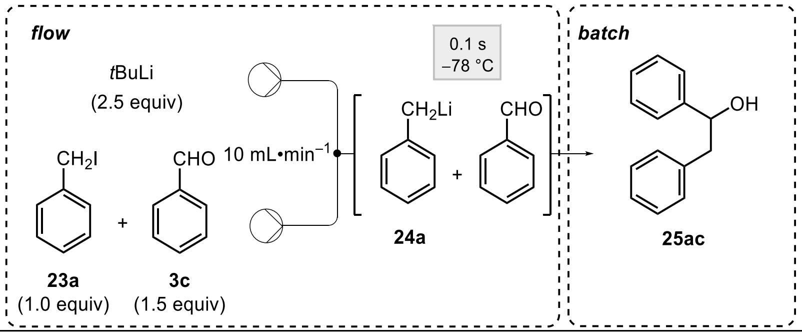
[198] For detailed flow screening conditions including the major side products see experimental part.

[199] (a) A. Soleymani, H. Yousefi, I. Turunen, *Chem. Eng. Sci.* **2008**, *63*, 5291; (b) M. B. Plutschak, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.

[200] For detailed screening of coordinating ligands see experimental part.

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 78% isolated yield. Interestingly, performing the reaction under batch conditions led to a significantly decreased yield of 15%.[201]

Table 9: Optimization of reaction conditions for iodine-lithium exchange of benzylic iodide (**23a**) with lithium bases and *in situ* Barbier-type reaction with benzaldehyde (**3c**) enabled by continuous flow.



Entry	Base (X equiv)	Reaction time [s]	V_R [mL]	Flow-rate [mL·min^{-1}]	Temperature [°C]	Conversion [%]	GC-yield [%][a]
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

For further screening results see experimental part [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.

6.9 EXPANDING THE SCOPE TO SUBSTITUTED ELECTRON-RICH AND -DEFICIENT BENZYLIC IODIDES

Having these optimized conditions in hand, the scope of various carbonyl derivatives and substituted benzylic iodides was investigated (Table 10).[202] Benzyllithium (**24a**) was generated in the presence of *m*-anisaldehyde (**3n'**) resulting in 63% isolated yield of the secondary alcohol **25an'** (entry 2). However, using aliphatic aldehydes such as 2-ethylbutanal or non-cyclic

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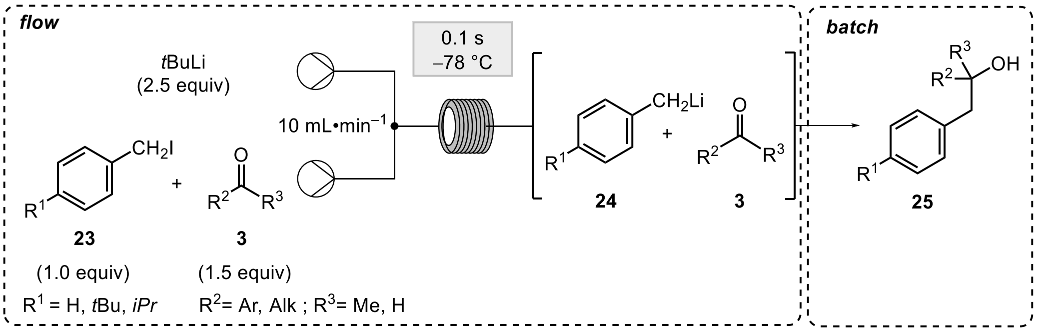
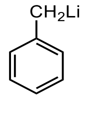
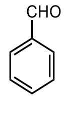
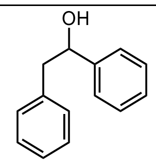
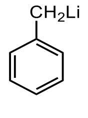
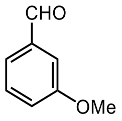
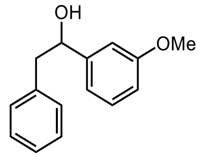
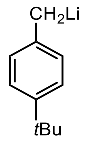
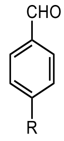
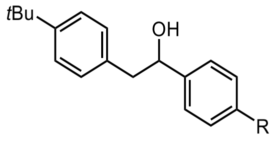
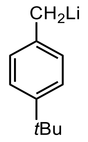
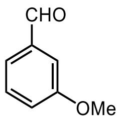
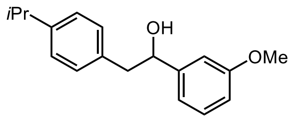
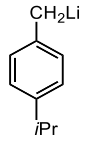
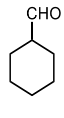
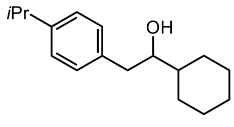
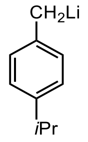
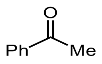
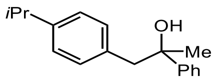
[201] For detailed batch screening conditions see experimental part

[202] A temperature screening was conducted separately for each reaction.

ketones such as 2-hexanone under Barbier-type reaction conditions afforded the desired aliphatic alcohols in lower GC-yields, possibly due to the enolization of the aldehydes and ketones. Alkyl-substituted substrates such as 4-*tert*butylbenzyl iodide (**23b**) or 4-*iso*propylbenzyl iodide (**23c**) afforded the desired benzylic alcohols **25bc**, **25bd'**, **25bn'** and **25co'** after *in situ* quench with aromatic and aliphatic aldehydes in 56-76% yield (entries 3-6).

Table 10: *In situ* exchange reaction and subsequent Barbier-type reaction of (sterically demanding) benzylic iodides of type **23** leading *via* reactive benzylic lithium species of type **24** to functionalized alcohols of type **25**.



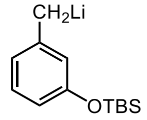
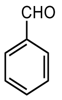
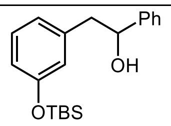
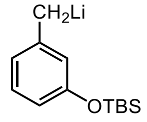
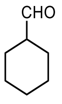
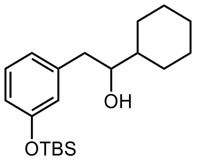
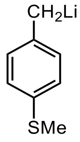
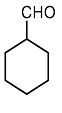
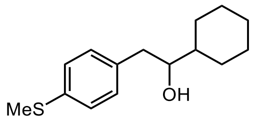
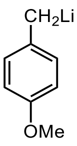
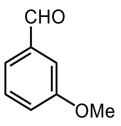
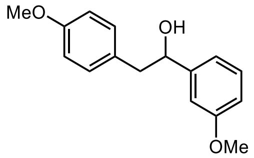
Entry	Metal species	Electrophile	Product[a]
1	 **24a**	 **3c**	 **25ac**: 79%[b]
2	 **24a**	 **3n'**	 **25an'**: 63%[b]
3	 **24b**	 **3c**: R=H	 **25bc**: 65%[b]
4	**24b**	**3d'**: R=OMe	**25bd'**: 56%[b]
5	 **24b**	 **3n'**	 **25bn'**: 71%[c]
6	 **24c**	 **3o'**	 **25co'**: 76%[d]
7	 **24c**	 **3b'**	 **25cb'**: 68%[c]

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

Interestingly, the addition to ketones, which is typically slower than the addition to aldehydes,[203] was also possible without a significant loss of yield. Using **23c** and acetophenone (**3b'**), the tertiary alcohol **25cb'** was obtained in 68% yield (entry 7).

Next, electron-rich benzylic iodides bearing a TBS-substituted alcohol, thioether or methoxy substituent were subjected to the optimized flow conditions (Table 11). Thus, 3-OTBS-substituted benzylic iodide (**26a**) was lithiated at −40 °C within 0.1 s providing the secondary alcohol **28ac** in 50% yield after *in situ* quench with benzaldehyde (**3c**, entry 1). Alternatively, benzylic organolithium **27a** reacted with cyclohexyl carboxaldehyde (**3o'**) leading to the aliphatic alcohol **28ao'** in 62% isolated yield (entry 2). Flow-lithiation of thioether-substituted benzylic iodide (**26b**) and *in situ* trapping with **3o'** led to the desired carbinol **28bo'** in 68% yield (entry 3). *Meta*- and *para*-methoxy-substituted benzylic organolithiums (**27c-d**) were prepared from the corresponding iodides (**26c-d**) affording the secondary benzylic alcohols **28cn'** and **28dp'** in 53-67% yield (entries 4-5). Additionally, Barbier-type reactions with sterically demanding ketones such as norcamphor (**3a'**) and adamantanone (**3t**) were possible without further optimization of the flow conditions resulting in the tertiary alcohols **28da'**, **28dt** and **28bt** in 59-85% isolated yield (entries 6-8). Using Barbier conditions in batch led to **28dt** in only 40% isolated yield, which is significantly lower compared to continuous flow conditions (85% yield).

Table 11: *In situ* exchange reaction and subsequent Barbier-type reaction of electron-rich benzylic iodides of type **26** leading *via* reactive benzylic lithium species of type **27** to functionalized alcohols of type 28.

Entry	Metal species	Electrophile	Product[a]
1	 **27a**	 **3c**	 **28ac**: 50%[b]
2	 **27a**	 **3o'**	 **28ao'**: 62%[c]
3	 **27b**	 **3o'**	 **28bo'**: 68%[d]
4	 **27c**	 **3n'**	 **28cn'**: 67%[e]

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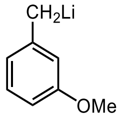
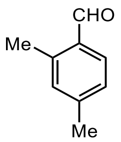
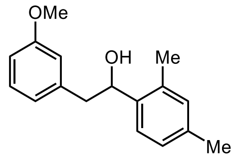
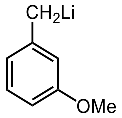
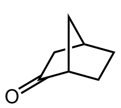
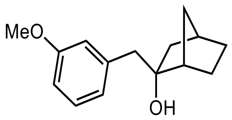
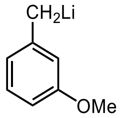
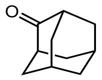
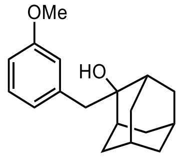
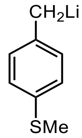
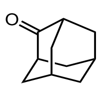
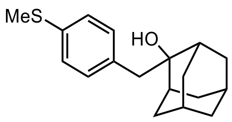
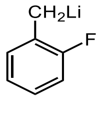
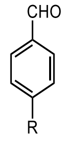
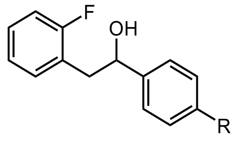
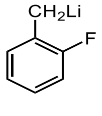
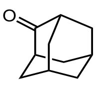
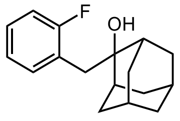
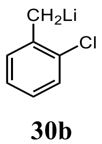
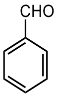
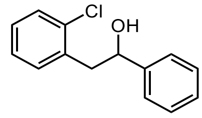
[203] A. Nagaki, Y. Tsuchihashi, S. Haraki, J.-i. Yoshida, *Org. Biomol. Chem.* **2015**, *13*, 7140.

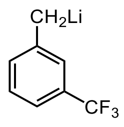
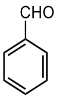
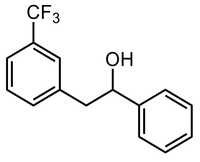
5	 **27d**	 **3p'**	 **28dp'**: 53%[d]
6	 **27d**	 **3a'**	 **28da'**: 59%, *d.r.*>99:1[d]
7	 **27d**	 **3t**	 **28dt**: 85% (40%)[f]
8	 **27b**	 **3t**	 **28bt**: 76%[d]

[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 (for detailed information see experimental part)

To further extend the scope of the lithiation protocol, it was applied to electron-deficient benzylic substrates (Table 12). Thus, 2-fluoro- and 2-chloro-substituted benzylic iodides (**29a-b**) were converted to the corresponding lithiated species **30a-b** within 0.1 s. Trapping the intermediates of type **30** with aldehydes **3c** or **3d'** and ketone **3t** gave the desired alcohols **31ac**, **31ad'**, **31at** and **31bc** in 44-80% yield (entries 1-4). The presence of a trifluoromethyl group in *meta* position was also tolerated and resulted in the secondary alcohol **31cc** in 64% isolated yield after reaction with **3c** (entry 5).

Table 12: *In situ* exchange and subsequent Barbier-type reaction of electron-poor benzylic iodides of type **29** leading *via* reactive lithium species of type **30** to functionalized alcohols of type **31**.

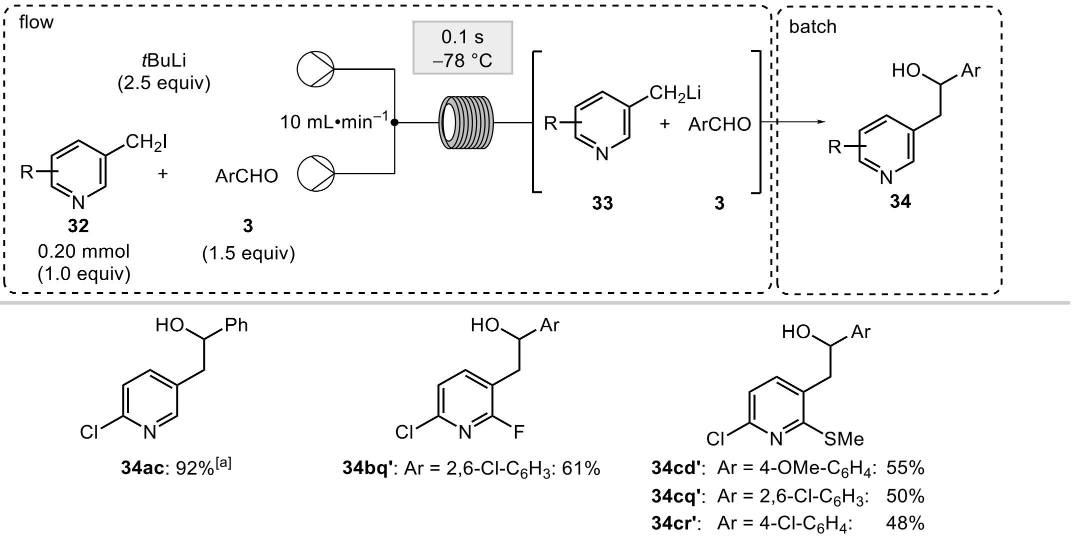
Entry	Metal species	Electrophile	Product[a]
1	 **30a**	 **3c**: R=H[b]	 **31ac**: 70%
2	**30a**	**3d'**: R=OMe[b]	**31ad'**: 53%
3	 **30a**	 **3t**[c]	 **31at**: 44%
4	 **30b**	 **3c**[b]	 **31bc**: 80%

5	 **30c**	 **3c**[b]	 **31cc**: 64%

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

6.10 FUNCTIONALIZATION OF HETEROBENZYLIC IODIDES

Having in mind that the functionalization of heteroaromatics is an important synthetic goal[204] and that heterocycles display one of the most important structural motifs in current research due to their wide range of bioactive properties and frequent use in agrochemical and pharmaceutical chemistry,[205] heterobenzylic iodides were investigated (Scheme 38).[206] It was found that readily prepared 2-chloro-5-(iodomethyl)pyridine (**32a**) reacted instantaneously with *t*BuLi (2.5 equiv) to the corresponding pyridylmethyllithium **33a**. In the presence of benzaldehyde (**3c**), the benzylic alcohol **34ac** was obtained in 92% isolated yield, whereas no product was detected on GCMS under various batch conditions.[207]



Scheme 38: *In situ* exchange reaction and subsequent Barbier-type reaction of heterobenzylic iodides of type **32** leading *via* highly reactive lithium species of type **33** to functionalized alcohols of type **34**. [a] No product detected under various batch conditions.

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[204] (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.

[205] (a) D. Astruc, *Modern Arene Chemistry,* Wiley-VCH, 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. Mueller, K. Karaghiosoff, P. Knochel, *Synthesis* **2018**, *50*, 4383; (f) B. Heinz, M. Balkenhohl, P. Knochel, *Synthesis* **2019**, *51*, 4452.

[206] N. M. Barl, E. Sansiaume-Dagousset, G. Monzon, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422; (b) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, *44*, 5824.

[207] For detailed batch screening conditions see experimental part.

6-Chloro-2-fluoro-3-(iodomethyl)pyridine (**32b**) was lithiated at −78 °C within 0.1 s affording the desired secondary alcohol **34bq'** in 61% yield *via* Barbier-trapping with 2,6-dichlorobenzaldehyde (**3q'**). Further, flow-exchange reaction of 6-chloro-3-(iodomethyl)-2-(methylthio)pyridine (**32c**) led to the corresponding pyridylmethyllithium **33c** which was instantaneously quenched *in situ* by various aromatic aldehydes affording the secondary alcohols **34cd'**, **34cq'** and **34cr'** in 48-55% yield.

7. SODIATION OF ARENES AND HETEROARENES IN CONTINUOUS FLOW

In the 19th century, Wurtz and Fittig demonstrated the utilization of elemental sodium for Wurtz(-Fittig) reactions affording alkyl-alkyl, aryl-alkyl or aryl-aryl cross couplings by mixing the corresponding aryl or alkyl halides in the presence of sodium.[208] However, the scope of the Wurtz-Fittig reactions remained very limited due to various side reactions such as undesired homocoupling and elimination.[209] Moreover, one major drawback of organosodiums is their poor solubility resulting in heterogeneous reactions affording lower yields compared to the soluble lithium analogues.[210] Nevertheless, it was reported that complexation with amine ligands such as TMEDA considerably increased the solubility of sodium bases. For instance, *n*BuNa, which was prepared by mixing NaO*t*Bu and *n*BuLi, was dissolved by addition of TMEDA.[211] Besides other alkyl- and arylsodiums such as phenyl sodium, isopropyl or pentyl sodium, which have been synthesized thereafter, sodium amides were also successfully investigated. Among those, sodium tetramethylpiperidide, sodium hexamethyldisilazide and sodium diisopropylamide display interesting properties regarding solubility, reactivity and selectivity of the metalation event, *e.g.* NaTMP/TMEDA is highly soluble in hexane.[212] Further, NaDA was first synthesized by Levine in 1960 by mixing phenyl sodium and diisopropylamine in benzene. However, this procedure resulted in an insoluble NaDA suspension.[213] Further optimizations of the NaDA preparation using *n*BuNa and diisopropylamine or LDA and NaO*t*Bu in aromatic hydrocarbons did not increase the solubility. Following these seminal contribution, Wakefield and co-workers have reported a synthesis of NaDA in the absence of any lithium salts by simply adding diisopropylamine to a mixture of sodium dispersion and isoprene in cyclohexane. Herein, isoprene acts as electron transfer reagent affording NaDA without the need of any lithium reagent.[214] However, the use of sodium bases is still limited to a minimum due to inherent problems with the control of the reactivity of organosodiums, their solubility and their stability. Collum and co-workers recently tackled these problems by the utilization of dimethylethylamine as a coordinating solvent resulting in a brownish NaDA solution which can be stored for months at −20 °C.[215]

7.1 INTRODUCTION

In recent years, organolithium compounds were widely used in industry and academic research.[216] Due to their high reactivity, lithium species display a promising opportunity to

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[208] A. Wurtz, *Ann. Chem. Chim. Phys.* **1855**, *44*, 275; (b) A. Wurtz, *Ann.* **1855**, *96*, 364; (c) D. C. Billington, *Comp. Org. Synth.* **1991**, *3*, 413.

[209] D. Seyferth, *Organometallics* **2006**, *25*, 2.

[210] C. Schade, W. Bauer, P. von Ragué Schleyer, *J. Organomet. Chem.* **1985**, *295*, 25; (b) G. Trimitsis, A. Tungay, R. Beyer, K. Kettermann, *J. Org. Chem.* **1973**, *38*, 1491.

[211] D. Seyferth, *Organometallics* **2006**, *25*, 2.

[212] D. Armstrong, D. Graham, A. Kennedy, R. Mulvey, C. O´Hara, *Chem. Eur. J.* **2008**, *14*, 8025; (b) B. Bernet, A. Vasella, *Tetrahedron Lett.* **1983**, *24*, 5491.

[213] S. Raynolds, R. Levine, *J. Am. Chem. Soc.* **1960**, *82*, 472; (b) A. Miller, C. Osuch, N. Goldberg, R. Levine, *J. Am. Chem. Soc.* **1956**, *78*, 674.

[214] D. Barr, A. Dawson, B. Wakefield, *J. Chem. Soc. Chem. Commun.* **1992**, 204.

[215] R. Algera, Y. Ma, D. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 7921.

[216] *Modern Arene Chemistry* (Ed: D. Astruc), Wiley-VCH, Weinheim, **2002**.

functionalize various carbon scaffolds. Nevertheless, preparation and handling of (hetero)aromatic lithium compounds is still challenging, mainly because of their fast degradation, low selectivity and limited functional group tolerance.[217] To overcome these drawbacks, milder magnesium and zinc bases have been developed resulting in a higher functional group tolerance allowing the preparation of functionalized (hetero)aromatics.[218] Furthermore, the synthesis of sodium species is desired due to the more polar, hence more reactive carbon-sodium bond. However, sodium bases have received only little attention due to the high reactivity and poor solubility of reported sodium compounds. Furthermore, sodium is about 1500 times more earth abundant than lithium in the earth crust, while the lithium demand and therefore the price is increasing significantly in recent years.[219] Although Schlosser, Mulvey and others[220] have already demonstrated the high potential of sodium organometallic chemistry,[221] the use of sodium compounds is certainly underexploited in organic synthesis. Recently, Collum reported the sodiation of aromatic and heterocyclic substrates using sodium diisopropylamide (NaDA) as a soluble base in dimethylethylamine (DMEA) at cryogenic temperatures.[222]

However, the use of (hetero)aromatic sodium compounds requires short reaction times and a precise control of reaction parameters, especially to achieve a moderate functional group tolerance. To address these needs, Yoshida,[223] Ley[224] and others[225] demonstrated a high compatibility with sensitive functional groups by using commercially available or custom-made flow set-ups. These flow set-ups have numerous advantageous, such as short reaction times allowing for milder reaction conditions and easy scale-ups without the need of tedious optimization studies of the reaction conditions.[226]

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[217] (a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; (b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.

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

[220] (a) M. Schlosser, J. Hartmann, M. Stähle, J. Kramar, A. Walde, A. Mordini, *Chimia* **1986**, *40*, 306; (b) A. J. Martínez-Martínez, A. R. Kenneddy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834; (c) J. A. Garden, D. R. Armstrong, W. Clegg, J. Garcia-Alvarez, E. Hevia, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, L. Russo, *Organometallics* **2013**, *32*, 5481; (d) 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; (e) A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 340.

[221] (a) M. Schlosser, *Angew. Chem. Int. Ed.* **1964**, *3*, 287; (b) D. Seyferth, *Organometallics* **2009**, *28*, 2; (c) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470.

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

[223] (a) H. Kim, Y. Yonekura, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2018**, *57,* 4063*;* (b) A. Nagaki, Y. Takahashi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2016**, *55*, 5327*; (*c) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264.

[224] (a) 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; (b) J. A. Newby, D. W. Blaylock, P. M. Witt, R. M. Turner, P. L. Heider, B. H. Harji, D. L. Browne, S. V. Ley, *Org. Process Res. Dev.* **2014**, *18*, 1221; (c) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102.

[225] (a) M. Ketels, M. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770; *(*b) M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.* **2017**, *19*, 1666; (c) M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280; (d) C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4945; (e) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; (f) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463; (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. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967.

[226] (a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796; (b) B. Gutmann, C. O. Kappe, *J. Flow. Chem.* **2017**, *7*, 65; (c) J. Britton, T. F. Jamison, *Nat. Protoc.* **2017**, *12*, 2423.

7.2 LIMITATIONS IN BATCH CHEMISTRY

Since Collum observed some limitation for the use of NaDA in batch, it was envisioned to overcome these problems by using continuous flow technology. *Ortho*-halide substituted aryl sodium compounds are prone to undergo aryne formation *via* elimination of sodium halide.[227] In course of these studies, the first sodiation of arenes and heteroarenes in a microflow reactor set-up is reported resulting in a broad range of (hetero)aryl sodium intermediates. These sodiated compounds are directly quenched with various electrophiles such as aldehydes, ketones, isocyanates and alkyl halides forming an enormous number of functionalized (hetero)arenes. Remarkably, the scope of this sodiation protocol is significantly broader compared to batch limitations.

7.3 OPTIMIZATION OF SODIUM DIISOPROPYLAMIDE (NADA) SYNTHESIS AND REACTION CONDITIONS

First of all, the previously reported NaDA synthesis was optimized slightly compared to the previously reported Collum synthesis.[228] Using less equivalents of sodium, the concentration of NaDA solution remained approximately 1.0 M, which was diluted with DMEA to the desired concentration of 0.21 M. According to a tedious screening, a concentration of 0.21 M was ideal for the sodiation in continuous flow avoiding clogging either of the mixing device or the reactor.

To optimize the reaction conditions, the sodiation of 1,3-dichlorobenzene (**35a**) and subsequent electrophile quench using iodine (**3b**) was investigated (Table 13). Using 1.2 equivalents NaDA at 0 °C and a 0.25 mL reactor with a combined flow-rate of 10 $mL\cdot min^{-1}$, the starting material completely decomposed possibly due to aryne formation. To avoid sodium chloride elimination, the reactor volume was decreased to 0.08 mL, resulting in a significantly shorter reaction time (0.5 s) and 30% GC yield. At −20 °C, the GC yield was increased to 89%, resulting in an isolated yield of the analytically pure iodinated product (84% yield). Unfortunately, a higher NaDA concentration (0.50 M) led to clogging of the reactor possibly due to the precipitation of sodium chloride. Increasing the combined flow-rate to 16 $mL\cdot min^{-1}$ had no effect on the GC yield (89%), but the risk of blockages was significantly higher. By exchanging the uncommon solvent DMEA to other coordinating solvents such as PMDTA or TMEDA, the GC yield dropped to 69-72%. Unfortunately, the use of Et_3N was not possible, since the concentration of the resulting sodium base was lower than 0.20 M. However, using the optimized conditions (combined flow-rate: 10 $mL\cdot min^{-1}$, 0.08 mL reactor, −20 °C), it was possible to achieve full sodiation of 1,3-dichlorobenzene within 0.5 s. A subsequent batch quench with iodine (**3b**) afforded the iodinated arene **37ab** in 84% isolated yield (Table 14, entry 1).

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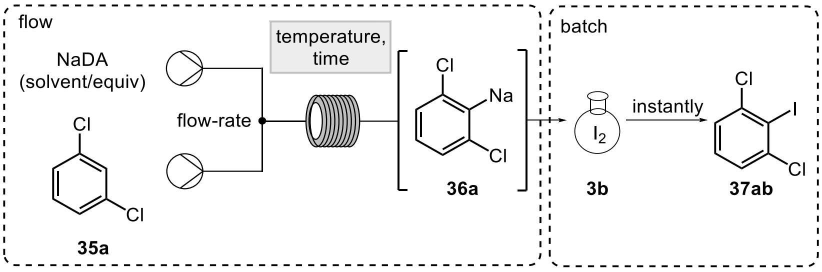
[227] (a) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 7921; (b) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544; (c) Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312.

[228] R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197.

Table 13: Optimization of flow-conditions for the sodiation of 1,3-dichlorobenzene (**35a**).



Entry	Base/Solvent (equiv)	Flow Conditions (T, flow-rate, Vol$_R$)	Result
1	NaDA in DMEA (0.24 M, 1.20 equiv)	0 °C, 10 mL·min^{-1} 0.25 mL reactor	decomposition
2	NaDA in DMEA (0.21 M, 1.05 equiv)	0 °C, 10 mL·min^{-1} 0.08 mL reactor with changing diameter	30% GC-yield
3	**NaDA in DMEA** **(0.21 M, 1.05 equiv)**	**−20 °C, 10 mL·min^{-1},** **0.08 mL reactor with changing diameter**	**89% GC-yield** **(84% isolated yield)**
4	NaDA in DMEA (0.50 M, 1.05 equiv)	−20 °C, 10 mL·min^{-1} 0.08 mL reactor with changing diameter	blockage
5	NaDA in DMEA (0.21 M, 1.05 equiv)	−20 °C, 16 mL·min^{-1} 0.08 mL reactor with changing diameter	89% GC-yield
6	NaDA in DMEA (0.21 M, 1.05 equiv)	−20 °C, 10 mL·min^{-1} 0.08 mL reactor with changing diameter	72% GC-yield[a]
7	NaDA in DMEA (0.21 M, 1.05 equiv)	−20 °C, 10 mL·min^{-1} 0.08 mL reactor with changing diameter	69% GC-yield[b]
8	NaDA in Et_3N	-	solubility not high enough

[a] PMDTA (1.0 equiv) was added. [b] TMEDA (1.0 equiv) was added.

7.4 SODIATION OF ARENES

With the optimized flow conditions in hand, the substrate scope was investigated. 2,6-dichlorophenylsodium (**36a**) was quenched in batch with benzaldehyde (**3c**), PPh_2Cl (**3s'**, followed by the addition of sulfur), phenylisocyanate (**3f'**) and S-(4-fluorophenyl)benzenesulfonothioate (**3t'**) affording the desired products **37ac**, **37as'**, **37af'** and **37at'** in 64-95% yield (Table 14, entries 2-5). Interestingly, no benzyne formation was observed under these flow conditions. Then, substitution reactions (Wurtz-Fittig-couplings) were examined.[229] Whereas the use of an allylic bromide such as cyclohexenyl bromide (**3f**) required copper-catalysis,[230] methyl iodide (**3g**) and *n*butyl bromide (**3h**) reacted instantly at −20 °C in the absence of any transition metal catalyst with the in flow generated arylsodium **36a** affording the cross-coupling products **37ah**, **37au'** and **37av'** in 53-75% yield (entries 6-8).

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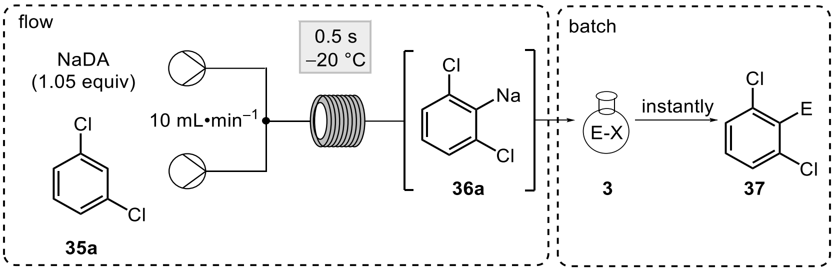
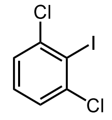
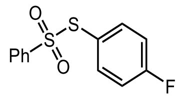
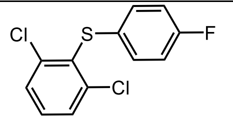
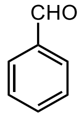
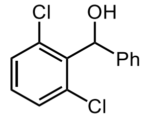
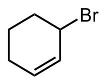
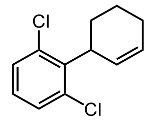
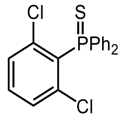
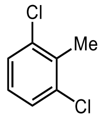
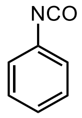
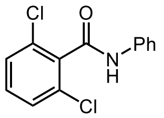
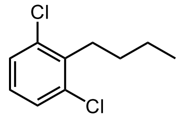
[229] (a) B. Tollens, R. Fittig, *Liebigs Ann. Chem.* **1864**, *131*, 303; (b) A. Wurtz, *Liebigs Ann. Chem.* **1855**, *96*, 364; (c) J. B. Campbell, R. F. Dedinas, S. Trumbower-Walsh, *Synlett* **2010**, 3008; (d) A. S. Jeevan Chakravarthy, M. S. Krishnamurthy, N. S. Begum, S. H. Prasad, *Tetrahedron Lett.* **2016**, *57*, 3231; (e) P. F. Hudrlik, W. D. Arasho, A. M. Hudrlik, *J. Org. Chem.* **2007**, *72*, 8107.

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

Table 14: Sodiation of 1,3-dichlorobenzene (**35a**) using a microflow reactor and subsequent batch quench of the intermediate organosodium **36a** with various electrophiles of type **3** leading to functionalized dichlorobenzenes of type **37**.



Entry	Electrophile	Product[a]	Entry	Electrophile	Product[a]
1	I_2 **3b**[b]	 **37ab**: 84%	5	 **3t’**[b]	 **37at’**: 75%
2	 **3c**[c]	 **37ac**: 95%	6	 **3h**[e]	 **37ah**: 75%
3	PPh_2Cl + S_8 **3s’**[d]	 **37as’**: 74%	7	MeI **3u’**[f]	 **37au’**: 53%
4	 **3f’**[b]	 **37af’**: 64%	8	*n*Bu-Br **3v’**[g]	 **37av’**: 53%

[a] Yield of analytically pure isolated product. [b] 2.5 equiv E-X. [c] 1.5 equiv E-X. [d] 2.5 equiv PPh_2Cl, then 10.0 equiv S_8, overnight. [e] 5 mol% CuCN·2LiCl, 2.5 equiv E-X. [f] 5.0 equiv E-X. [g] 10.0 equiv E-X.

Furthermore, related arenes bearing chloro-, iodo-, fluoro- or trifluoromethyl-substituents were subjected to the optimized flow conditions. 1,3-Difluorobenzene (**35b**) was sodiated at −40 °C providing the corresponding arylsodium (**36b**), which was subsequently quenched in batch with aldehyde providing the secondary alcohol in 88% yield (Table 15, entry 1). Alternatively, arylsodium **36b** was trapped with benzoyl chloride (**3x’**) in the absence of any transition metal catalyst leading to benzophenone derivate **37bx’** in 71% yield (entry 2). Flow-sodiation of 2-fluoroiodobenzene (**35c**) and subsequent quench with aldrithiol (**3u**) led to the corresponding thioether **37cu** in 62% yield (entry 3). In addition, trifluoromethyl-substituted arene **35d** was sodiated at −40 °C and quenched with aldehyde **3y** leading to alcohol **37dy** in 85% yield (entry 4). Furthermore, the optimized flow conditions were applied to the sodiation of heteroarenes. Thus, 2-chloropyridine (**35e**) was sodiated in flow at convenient conditions (–20 °C, 0.5 s using a flow-rate of 10 mL·min^{-1}; compared to –78 °C in batch[231]) and the intermediate 2-chloro-3-pyridyl sodium (**36e**) was subsequently trapped with iodine (**3b**) and Bu_2S_2 (**3z**) leading to the functionalized pyridines **37eb** and **37ez** in 53-89% yield (entries 5-6). Trifluoromethyl-substituted pyridine **35f** was sodiated in flow and trapped with aldehyde **3q’** yielding the secondary alcohol **37fq’** in 68% yield (entry 7).

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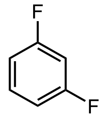
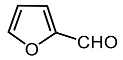
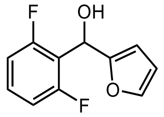
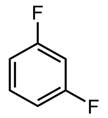
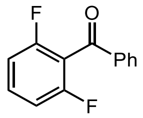
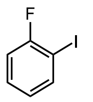
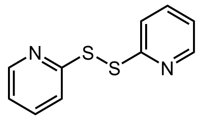
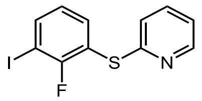
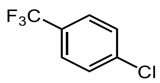
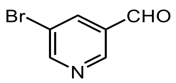
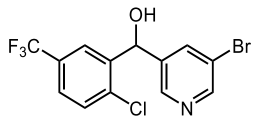
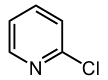
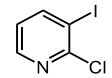
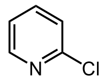
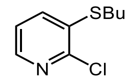
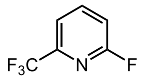
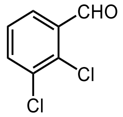
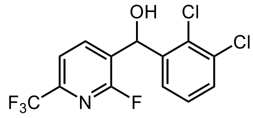
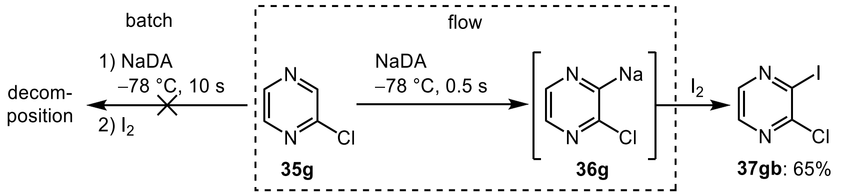
[231] R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197.

Table 15: Sodiation of arenes and heteroarenes of type **35** leading *via* intermediate organosodiums of type **36** to polyfunctional arenes and heteroarenes of type **37**.

Entry	Substrate (Sodiation Temperature)	Electrophile	Product[a]
1	 **35b** (–40 °C)	 **3w'**[b]	 **37bw'**: 88%
2	 **35b** (–40 °C)	Ph-COCl **3x'**[c]	 **37bx'**: 71%
3	 **35c** (–40 °C)	 **3u**[c]	 **37cu**: 62%
4	 **35d** (–40 °C)	 **3y**[b]	 **37dy**: 85%
5	 **35e** (–20 °C)	I_2 **3b**[c]	 **37eb**: 53%
6	 **35e** (–20 °C)	Bu_2S_2 **3z**[c]	 **37ez**: 89%
7	 **35f** (–40 °C)	 **3q'**[b]	 **37fq'**: 68%

[a] Yield of analytically pure isolated product. [b] 1.5 equiv E-X. [c] 2.5 equiv E-X.

7.5 Sodiation of Sensitive Arenes and Heteroarenes



Scheme 39: Sodiation of sensitive heteroarene 2-chloropyrazine (**35g**) in a microflow reactor and under batch conditions and subsequent trapping with iodine (**3b**) leading to functionalized heteroarene **37gb** or decomposition.

This flow sodiation procedure extends considerably the scope of such metalations and applies it to sensitive substrates that decompose under batch sodiation conditions.[232] Thus, for example, 2-chloropyrazine (**35g**) cannot be sodiated in batch with NaDA at –78 °C. However, under optimized flow conditions (–78 °C, 0.5 s using a flow-rate of 10 mL·min^{-1}) a complete

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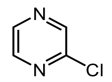
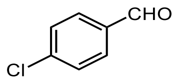
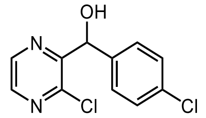
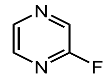
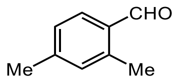
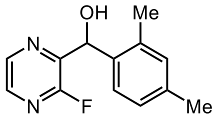
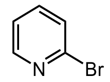
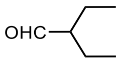
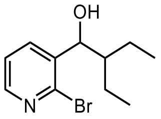
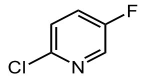
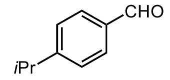
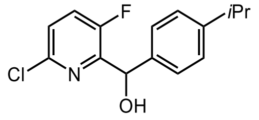
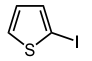
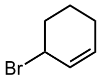
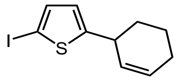
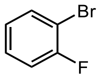
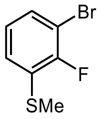
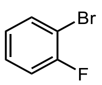
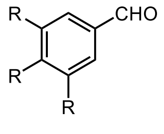
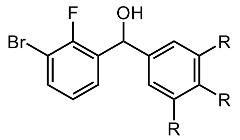
[232] R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197.

consumption of the starting material was observed affording the pyrazine **37gb** in 65% yield after iodolysis (Scheme 39). In addition to 2-chloropyrazine (**35g**), 2-fluoropyrazine (**35h**) and substituted pyridines **35i** and **35j**, which decompose upon batch-sodiation, were successfully sodiated under flow conditions and trapped with aldehydes, yielding functionalized heteroarenes **37gr'**, **37hp'**, **37iz'** and **37ja''** in 65-97% yield (Table 16, entries 1-4). Copper-catalyzed[233] batch allylation of sodiated 2-iodothiophene (**35k**) under flow-conditions led to the functionalized thiophene **37kh** in 76% yield (entry 5).

Table 16: Sodiation of sensitive arenes and heteroarenes of type **35** leading *via* intermediate organosodiums of type **36** to polyfunctional arenes and heteroarenes of type **37**.

Entry	Substrate (Sodiation Temperature)	Electrophile	Product[a]
1	 **35g** (–78 °C)	 **3r'**[b]	 **37gr'**: 79%
2	 **35h** (–60 °C)	 **3p'**[b]	 **37hp'**: 97%
3	 **35i** (–78 °C)	 **3z'**[b]	 **37iz':** 65%
4	 **35j** (–78 °C)	 **3a''**[b]	 **37ja''**: 77%
5	 **35k** (–78 °C)	 **3h**[c]	 **37kh**: 76%
6	 **35l** (–60 °C)	Me_2S_2 **3b''**[d]	 **37lb''**: 70%
7	 **35l** (–60 °C)	 **3c'':** R = OMe[b]	 **37lc'':** R = OMe; 80%
8	**35l** (–60 °C)	**3c:** R = H[b]	**37lc:** R = H; 81%

[a] Yield of analytically pure isolated product. [b] 1.5 equiv E-X. [c] 5 mol% CuCN·2LiCl, 2.5 equiv E-X. [d] 2.5 equiv E-X.

At −60 °C it was possible to sodiate 2-bromofluorbenzene (**35l**) without aryne formation. Instant reaction of the sodiated intermediate **36l** with dimethyl disulfide (**3b''**) or aromatic

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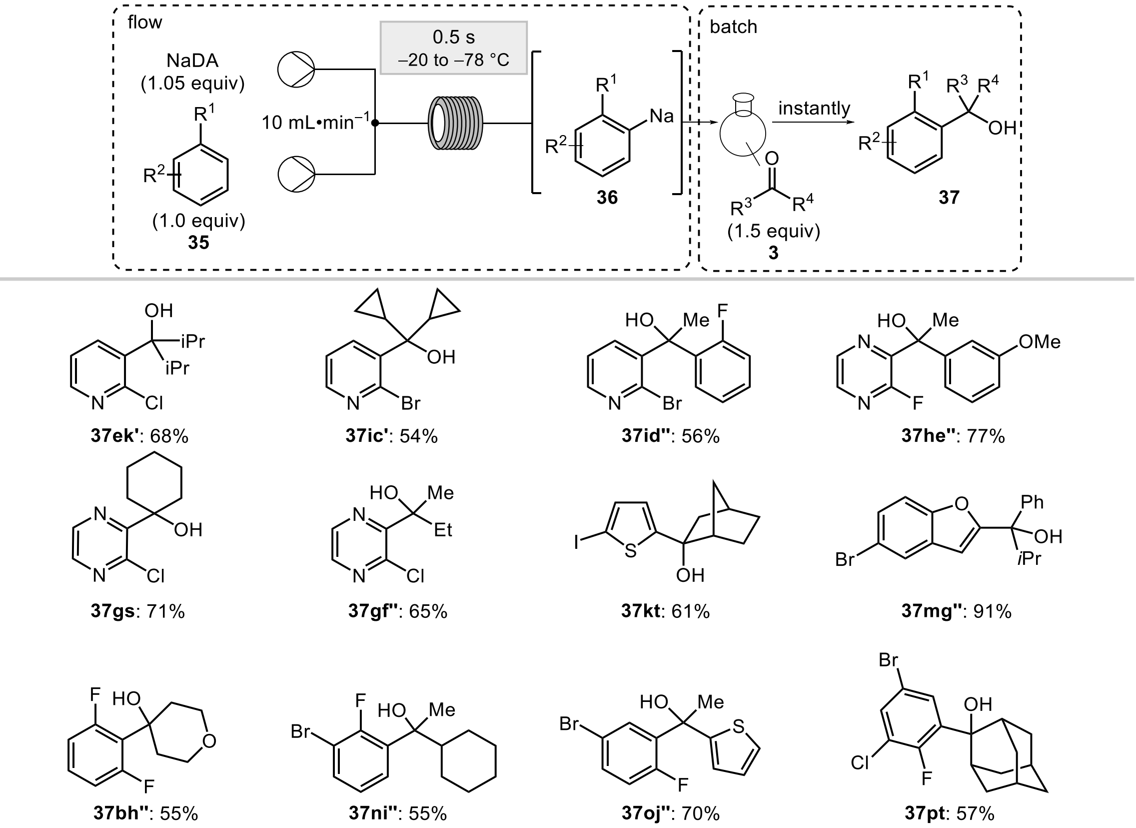
[233] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

aldehydes **3c’’** and **3c** furnished functionalized arenes **37lb’’**, **37lc’’** and **37lc** in 70-81% yield (entries 6-8).

7.6 ADDITION OF (HETERO)ARYL SODIUMS TO KETONES

Addition of organometallics to ketones is always subject to side reactions.[234] In particular, sterically hindered ketones are prone to undergo reduction instead of addition reactions using alkyl lithium or -magnesium species.[235] Remarkably, the in flow generated sodium derivatives of type **36** underwent reactions with ketones of type **3**, leading to tertiary alcohols of type **37**. Thus, numerous polyfunctional arenes and heteroarenes were obtained in up to 91% yield (Scheme 40).



Scheme 40: Sodiation of (hetero)arenes of type **35** and subsequent batch quench with ketones of type **3** leading to tertiary alcohols of type **37**.

7.7 FUNCTIONAL GROUP TOLERANCE AND SCALE UP

Noteworthy, sodiation of 4-fluorobenzonitrile (**38a**) at –78 °C led to the desired sodium arene **39a** without the attack at the nitrile functionality.[236] Batch quench with benzaldehyde (**3c**), ketone **3k’’** and disulfide **3u** led instantly to functionalized benzonitriles **40ac**, **40ak’’** and **40au**

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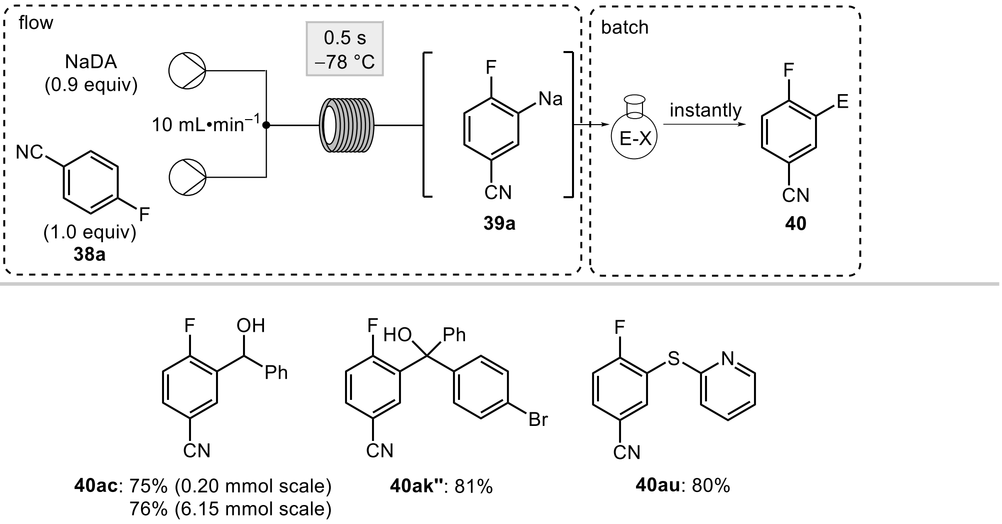
[234] (a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; (b) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998; (c) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *J. Org. Chem.* **2010**, *75*, 5008; noteworthy exceptions: (d) C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy, E. Hevia, *Angew. Chem. Int. Ed.* **2014**, *53*, 5969; (e) L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salmone, S. Florio, V. Capriati, *Chem. Sci.* **2016**, *7*, 1192.

[235] H. Yamataka, N. Miyano, T. Hanafusa, *J. Org. Chem.* **1991**, *56*, 2573.

[236] 0.9 equiv NaDA were used as the limiting reagent to avoid double metalation.

in 75-81% yield (Scheme 41). Additionally, a scale-up was possible without any further optimization by simply extending the runtime. Thus, a scale-up by factor 30 was conducted and the functionalized benzonitrile **40ac** was obtained in 76% yield on a gram scale (Scheme 41).



Scheme 41: Sodiation of highly sensitive 4-fluorobenzonitrile (**38a**) and subsequent batch quench with electrophiles yielding functionalized benzonitriles of type **40**.

8. CONTINUOUS FLOW SODIATION OF SUBSTITUTED ACRYLONITRILES AND ALKENYL SULFIDES

The metalation of unsaturated nitriles and sulfides is an important synthetic procedure.[237] After quenching with various electrophiles, highly functionalized unsaturated products are obtained, which are useful building blocks for biologically active heterocycles and natural products.[238] The batch-metalation of alkenylnitriles or -sulfides with lithium bases is often complicated due to competitive allylic lithiations.[239] The use of stronger, more polar bases such as sodium or potassium amides may avoid such limitations. However, the sodiation of unsaturated compounds is much less explored.[240] Moreover, the use of sodium organometallics is of high interest due to the low price, high abundancy and low toxicity of sodium salts.[241] Recently, arylsodium compounds have been prepared by Collum using NaDA (sodium diisopropylamide) as deprotonating agent[242] and by Asako and Takai who have investigated the utility of arylsodiums in catalytic cross-couplings.[243] Yoshida, Ley, Organ and others have demonstrated a high functional group tolerance performing challenging metalations in a continuous flow set-up.[244] Based on these studies, the Collum procedure was extended to the preparation of sodiated aryl and heteroaryl derivatives, which are difficult to generate otherwise and decompose upon batch-sodiation.[245] KDA · TMEDA (potassium diisopropyl-

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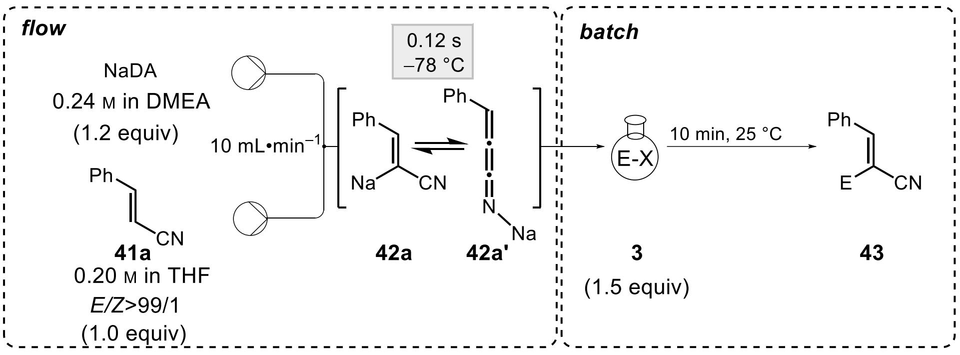
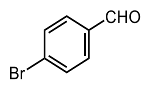
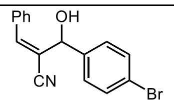
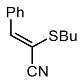
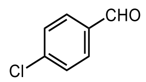
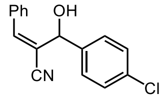
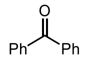
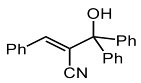
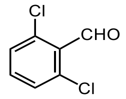
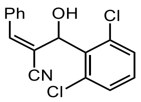
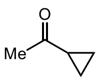
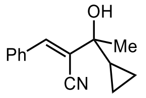
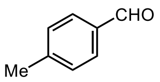
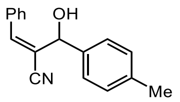
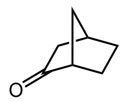
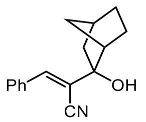
amide · *N*,*N*,*N'*,*N'*-tetramethylethylenediamine) in hexane was used in continuous flow for similar metalations.[246] In course of these studies, it is reported that NaDA and NaTMP were efficient bases for the regioselective flow-metalation of various substituted acrylonitriles and alkenyl sulfides.[247]

8.1 OPTIMIZATION STUDIES OF CINNAMONITRILE SODIATION

In first experiments, the sodiation of cinnamonitrile (**41a**) was optimized. It was found that sodiation with NaDA (0.24 M in DMEA (dimethylethylamine), 1.2 equiv) at −78 °C using a combined flow-rate of 10 mL·min^{-1} and a 0.02 mL reactor proceeded best with a residence time of 0.12 s affording organosodium **42a** and **42a'**. Subsequent trapping with electrophiles of type **3** such as aldehydes, ketones, disulfides and allylic bromides afforded 2-substituted cinnamonitriles of type **43** with usually high *E/Z* ratios (Table 17, entries 1-10).

Table 17: Sodiation of cinnamonitrile (**41a**) using a microflow reactor and subsequent batch quench of the intermediate sodium organometallic **42a** with various electrophiles of type **3** leading to functionalized cinnamonitriles of type **43**.



Entry	Substrate	Product[a]	Entry	Substrate	Product[a]
1	 **3l“**	 **43al”**: 95%, *Z/E*>99/1	6	Bu_2S_2 **3z**	 **43az**: 93%, *Z/E*=54/46
2	 **3r‘**	 **43ar’**: 92%, *Z/E*>99/1	7	 **3l‘**	 **43al‘**: 82%, *E/Z*>99/1[b]
3	 **3q‘**	 **43aq’**: 74%, *Z/E*=89/11	8	 **3n“**	 **43an“**: 78%, *E/Z*>99/1[d]
4	 **3m“**	 **43am”**: 93%, *Z/E*>99/1[b]	9	 **3a‘**	 **43aa‘**: 82%, *E/Z*>99/1[b] *d.r.*>99/1

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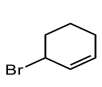
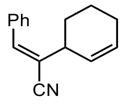
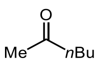
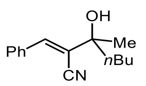
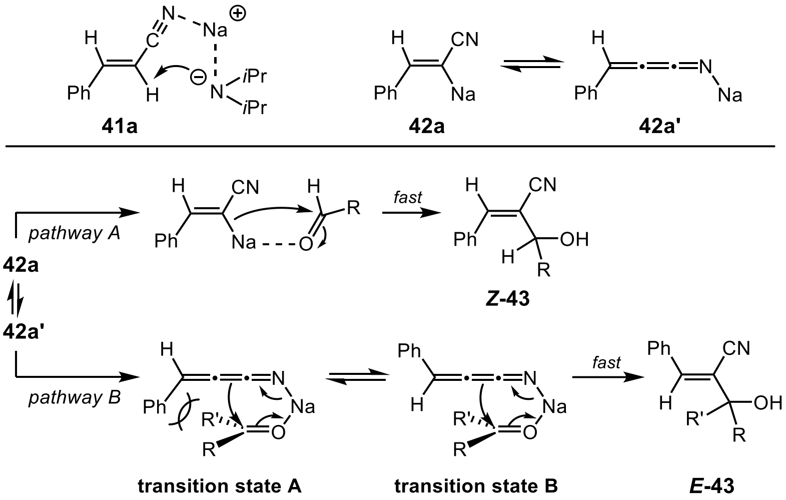
[246] J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*; 12321; *Angew. Chem.* **2020**, *132*, 12419.

[247] Commercially available equipment from *Uniqsis* was used. For a detailed optimization, see experimental part.

5	 **3h**[b]	 **43ah**: 93%, *E/Z*=90/10	10	 **3o“**	 **43ao“**: 87%, *E/Z*>99/1[d]

[a] Yield of analytically pure product. [b] The diastereoselectivity was confirmed by crystal structure analyses. [c] 10 mol% CuCN·2LiCl. [d] According to the proposed mechanism, ketone-quenches were assumed to be *E*-diastereoselective.

The diastereoselectivity of products of type **43** obtained after the addition to a carbonyl electrophile was tentatively explained by assuming that the sodiated nitrile **42a’** reacted fast with an aldehyde (RCHO) according to pathway A (Scheme 42) leading to the allylic alcohol ***Z*-43**. In contrast, by using ketones, an equilibration to the cummulene form **42a’** may occur and the cyclic transition state **A** would be disfavoured due to steric hindrance. *E/Z* isomerization of the cummulene structure **42a’** occurred affording the ***E*-43** product *via* transition state **B** (Scheme 42).



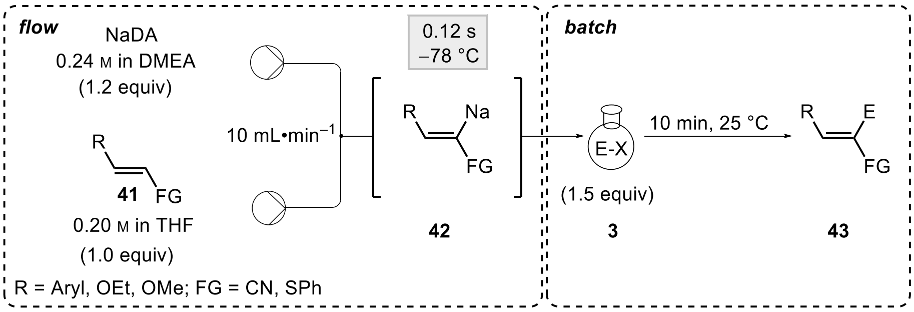
Scheme 42: Proposed mechanism for the stereoselective addition of sodiated phenylacrylonitrile **42a’** to aldehydes or ketones.

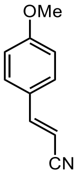
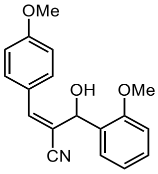
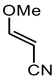
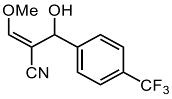
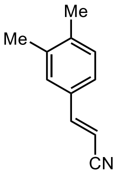
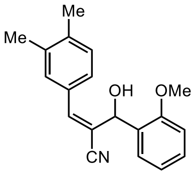
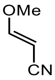
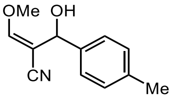
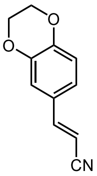
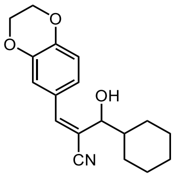
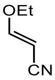
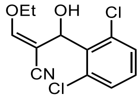
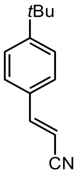
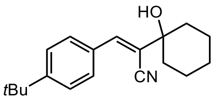
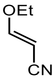
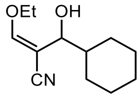
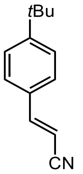
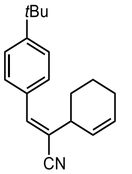
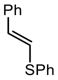
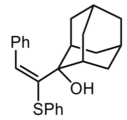
8.2 SODIATION OF SUBSTITUTED (ARYL)ACRYLONITRILES

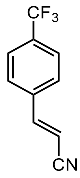
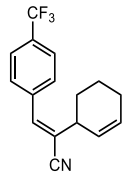
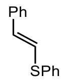
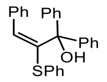
This flow procedure was then extended to various functionalized arylacrylonitriles of type **41**. Electron-rich cinnamonitrile derivatives (**41b**-**41e**) were selectively metalated in 2-position using NaDA in a continuous flow set-up within 0.12 s at −78 °C. The resulting organosodiums (**42b-e**) were trapped in batch with various carbonyl electrophiles, such as *m*-anisaldehyde (**3e’**), cyclohexanecarboxaldehyde (**3o’**) or cyclohexanone (**3s**), and with 3-bromocyclohexene (**3h**) using 10 mol% CuCN·2LiCl as catalyst, affording the desired alcohols (**43be’**, **43ce’**, **43do’** and **43es**) and an allylated cinnamonitrile derivative (**43eh**) in 57-97% yield with *Z/E* ratios up to >99/1 (Table 18, entries 1-5). Similarly, regioselective sodiation of electron-deficient 3-(4-(trifluoromethyl)phenyl)acrylonitrile (**41f**) followed by copper-catalyzed allylation with 3-bromocyclohexene (**3h**) led to the functionalized phenylacrylonitrile (**43fh**) in 66% yield with an *E/Z* ratio >99/1. Furthermore, an extension to methoxy- and ethoxyacrylonitriles **41g** and **41h** was possible resulting in secondary alcohols (**43gp’’**, **43gm’’**, **43hq’** and **43ho’**) after batch-quench with aromatic aldehydes (**3p’’**, **3m’’** and **3q’**), and aliphatic aldehyde (**3o’**) in 91-98% and *Z/E* ratios >99/1 (entries 7-10). An alkenyl sulfide such as phenyl(styryl)sulfane (**41i**) provided the sodium derivative (**42i)** upon metalation with

NaDA. Trapping with sterically demanding ketones such as adamantanone (**3t**) and benzophenone (**3l’**) gave tertiary alcohols (**43it** and **43il’**) in 85-95% yield and comparable *E/Z* ratios to the starting material **41i** (entries 11-12).

Table 18: Sodiation of substituted acrylonitriles and alkenyl sulfides of type **41** using a microflow reactor and subsequent batch quench of the intermediate sodium organometallics of type **42** with various electrophiles of type **3** leading to functionalized phenylacrylonitriles and alkenyl sulfides of type **43**.



Entry	Substrate	Product[a]	Entry	Substrate	Product[a]
1	 **41b** *E/Z*=76/24	 **43be‘**: 97% *Z/E*=89/11	7	 **41g** *E/Z*=83/17	 **43gp‘‘**: 93%[b] *Z/E*>99/1
2	 **41c** *E/Z*=79/21	 **43ce‘**: 84%[b] *Z/E*=90/10	8	 **41g** *E/Z*=83/17	 **43gm‘‘**: 98%[b] *Z/E*>99/1
3	 **41d** *E/Z*=83/17	 **43do‘**: 74% *Z/E*>99/1	9	 **41h** *E/Z*=68/32	 **43hq‘**: 95%[b] *Z/E*>99/1
4	 **41e** *E/Z*=79/21	 **43es**: 67%[b] *E/Z*>99/1	10	 **41h** *E/Z*=68/32	 **43ho‘**: 91%[b] *Z/E*>99/1
5	 **41e**[c] *E/Z*=79/21	 **43eh**: 57% *E/Z*>99/1	11	 **41i** *E/Z*=71/29	 **43it**: 95%[b] *E/Z*=77/23

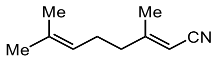
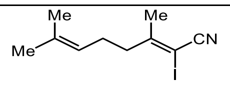
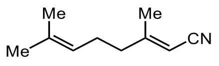
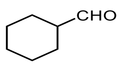
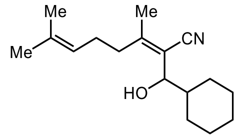
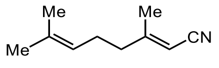
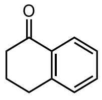
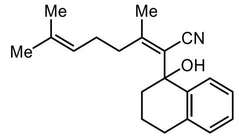
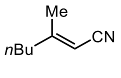
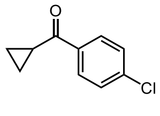
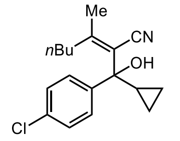
6	 **41f**[c] *E*/*Z*=78/22	 **43fh**: 66%[b] *E*/*Z*>99/1	12	 **41i** *E*/*Z*=71/29	 **43il'**: 85%, *E*/*Z*=68/32

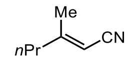
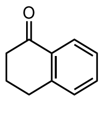
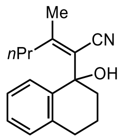
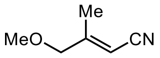
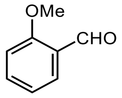
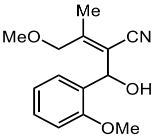
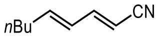
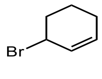
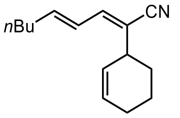
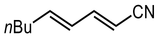
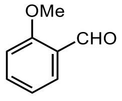
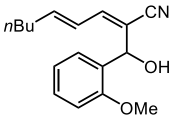
[a] Yield of analytically pure product. [b] The diastereoselectivity was confirmed by crystal structure analyses. [c] 10 mol% CuCN·2LiCl.

8.3 EXPANDING THE REACTION SCOPE TO ALKYL-SUBSTITUTED ACRYLONITRILES AND ALKENYL SULFIDES

Extension to alkyl-substituted acrylonitriles such as geranylnitrile (**44a**, *E*/*Z*=50/50) and the related nitrile **44b** (*E*/*Z*=65/35) was possible under the standard sodiation conditions providing after electrophilic quench the desired functionalized nitriles (**46ab**, **46ao'**, **46aq''**, **46bf**) in 60-98% yield as *E*/*Z* mixtures (Table 3, entries 1-4). Interestingly, starting from the diastereoselectively pure acrylonitrile **44c** (*E*/*Z*>99/1) the desired product **46cq''** was obtained in 67% yield (*Z*/*E*=58/42) after quench with α-tetralone (**3q''**) (entry 5) showing the prevalence of the cumulene structure of the sodiated nitriles (see **42a** in Table 17). However, the methoxy-substituted acrylonitrile **44d** (*E*/*Z*=80/20) afforded after continuous flow sodiation and quenching with *o*-anisaldehyde (**3e'**) the allylic alcohol **46de'** 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 **44e** was sodiated in flow and trapped with an allylic bromide (**3h**) or an aldehyde (**3e'**), furnishing the functionalized dienylnitriles (**46eh** and **46ee'**) in 74-82% yield (entries 7-8).

Table 19: Sodiation of alkyl- and alkenyl-substituted acrylonitriles of type **44** using a microflow reactor and subsequent batch quench of the intermediate sodium organometallics of type **45** with various electrophiles of type **3** leading to functionalized alkyl- and alkenyl-substituted acrylonitriles of type **46**.

Entry	Substrate	Electrophile	Product[a]
1	 **44a**, *E*/*Z*=50/50	I_2 **3b**	 **46ab**: 75%, *Z*/*E*=68/32
2	 **44a**, *E*/*Z*=50/50	 **3o'**	 **46ao'**: 60%, *Z*/*E*=64/36
3	 **44a**, *E*/*Z*=50/50	 **3q''**	 **46aq''**: 98%, *Z*/*E*=53/47
4	 **44b**, *E*/*Z*=65/35	 **3f**	 **46bf**: 85%, *Z*/*E*=55/45

5	 **44c**, *E*/*Z*>99/1	 **3q''**	 **46cq''**: 67%, *Z*/*E*=58/42
6	 **44d**, *E*/*Z*=80/20	 **3e'**	 **46de'**: 58%, *Z*/*E*>99/1
7	 **44e**, 2*E*/2*Z*=69/31	 **3h**[b]	 **46eh**: 74%, 2*E*/2*Z*=77/23
8	 **44e**, 2*E*/2*Z*=69/31	 **3e'**	 **46ee'**: 82%. 2*Z*/2*E*=76/24

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

8.4 SODIATION USING LITHIUM-FREE NATMP IN CONTINUOUS FLOW

Recently, Takai and Asako published a straightforward synthesis of lithium-free sodium 2,2,6,6-tetramethylpiperidide (NaTMP) in hexane by using sodium dispersion, TMPH, TMEDA and isoprene.[248] This method would avoid the use of DMEA as solvent and therefore making this method more practical. Using the Takai procedure, hexane-soluble NaTMP·TMEDA[249] was prepared and an efficient continuous flow sodiation of cinnamonitrile (**41a**) was performed selectively in 2-position within 0.12 s at −78 °C. A subsequent batch trapping of **42a** with various ketones of type **3** afforded the desired tertiary alcohols of type **43** in 58-83% yield as single regioisomers with a *Z*/*E* ratio >99/1 (Scheme 43). Similarly, ethoxyacrylonitrile **41h** gave, after batch quench with *m*-anisaldehyde (**3e'**) and benzophenone (**3l'**), the allylic alcohols **43he'** and **43hl'** in 65-78% yield (*Z*/*E*>99/1). Further, geranylnitrile (**44a**) provided the organosodium **45a** upon metalation with NaTMP·TMEDA, which after a copper-catalyzed allylation using 3-bromocyclohexene (**3h**) led to the desired product **46ah** in 54% yield with a *E*/*Z* ratio of 52/48.

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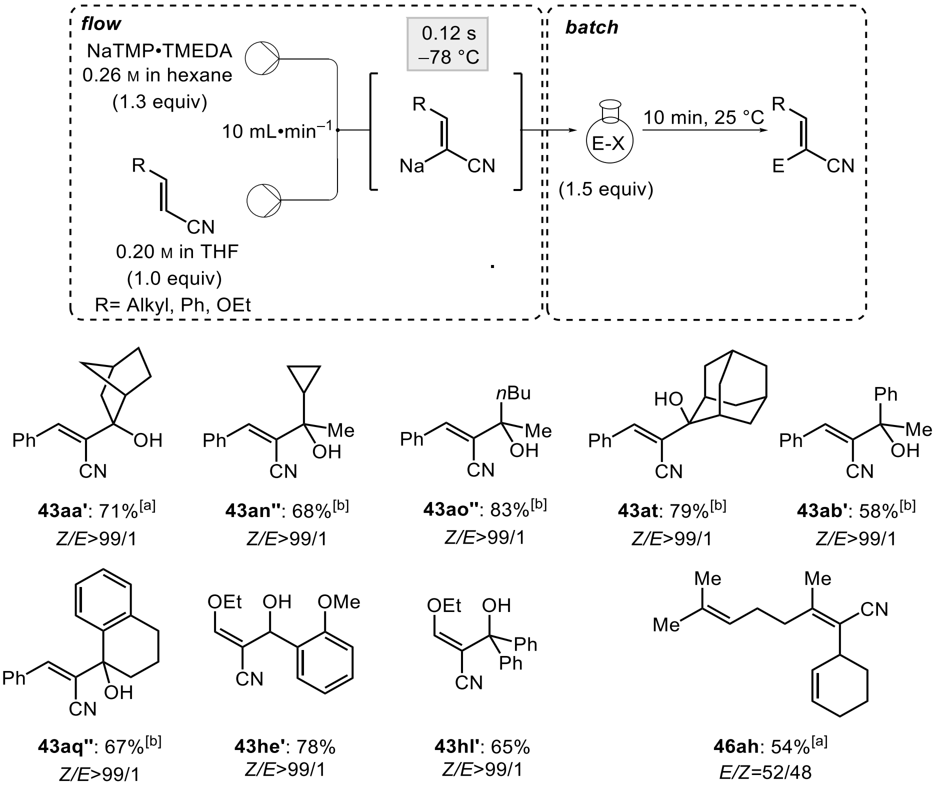
[248] (a) S. Asako, M. Kodera, H. Nakajima, K. Takai, *Adv. Synth. Catal.* **2019**, *361*, 3120; (b) D. R. Armstrong, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2011**, *17*, 8820; (c) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470; (d) R. McLellan, 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.

[249] For the synthesis of NaTMP·TMEDA, see experimental part.



[a] The diastereoselectivity was confirmed by crystal structure analyses. [b] According to the proposed mechanism, ketone-quenches were assumed to be *E*-diastereoselective.

Scheme 43: 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] 10 mol% CuCN·2LiCl.

8.5 SODIATION OF CHALLENGING ACRYLATES BY USING BARBIER-TYPE CONDITIONS

However, the sodiation of other acrylates still remained challenging. Applying the standard sodiation method to ethyl cinnamate (**47a**) afforded solely the condensation product **49a** showing that the sodiation of **47a** was possible, but difficult to control. Thus, the intermediate organosodium **48a** reacted instantaneously with another molecule of **47a** before the desired electrophile quench proceeded (Scheme 44a). To prevent this self-condensation reaction, sterically hindered *tert*-butyl cinnamate (**47b**) was used affording organosodium **48b** after continuous flow sodiation. A copper-catalyzed batch allylation with 3-bromocyclohexene (**3h**) gave the desired product **49bh** in 61% yield with an *E/Z* ratio >99/1 (Scheme 44b). To overcome the need of sterically hindered esters, a Barbier-type *in situ* trapping[250] of the highly reactive organosodiums of type **48** was envisioned. Interestingly, ethyl cinnamate (**47a**), which underwent self-condensation side reactions applying the standard flow conditions (Scheme 44a), was sodiated at −78 °C under Barbier-conditions and afforded organosodium **48a**, which was instantaneously trapped by adamantanone (**3t**), outcompeting self-condensation and resulting in the tertiary alcohol **49at** in 66% yield (*E/Z*>99/1). Similarly,

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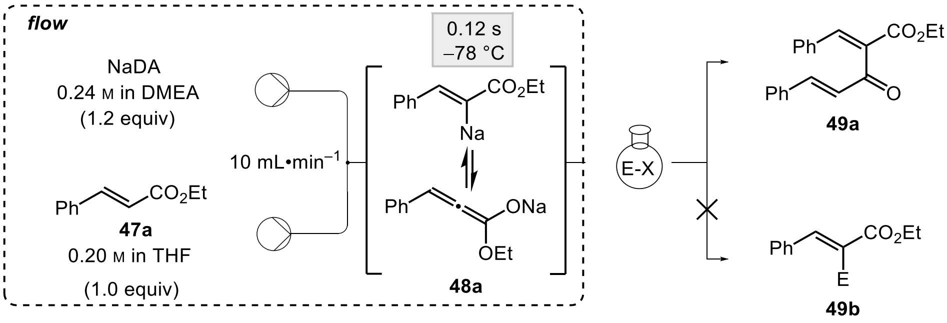
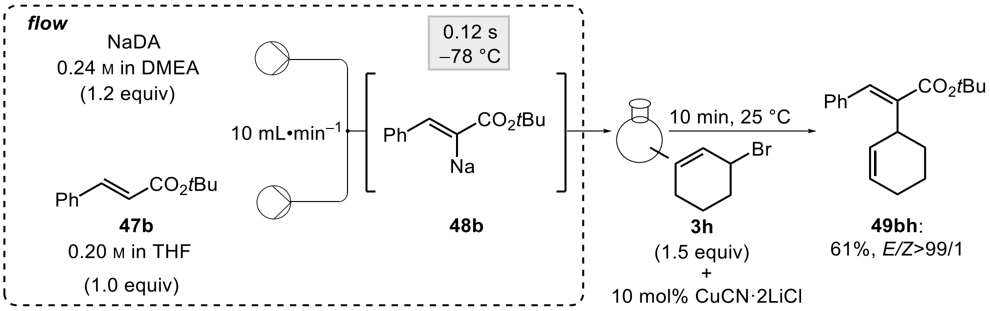
[250] (a) M. G. Ganiek, M. V. Ivanova, B. Martin, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 17249; (b) M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280; (c) N. Weidmann, J. H. Harenberg, P. Knochel, *Org. Lett. Org. Lett.* **2020**, *22*,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

methyl-3-methoxyacrylate (**47c**) was sodiated in 3-position in the presence of adamantanone (**3t**) using NaDA (1.2 equiv) affording the spirolactone **49ct** in 58% yield (Scheme 44c).

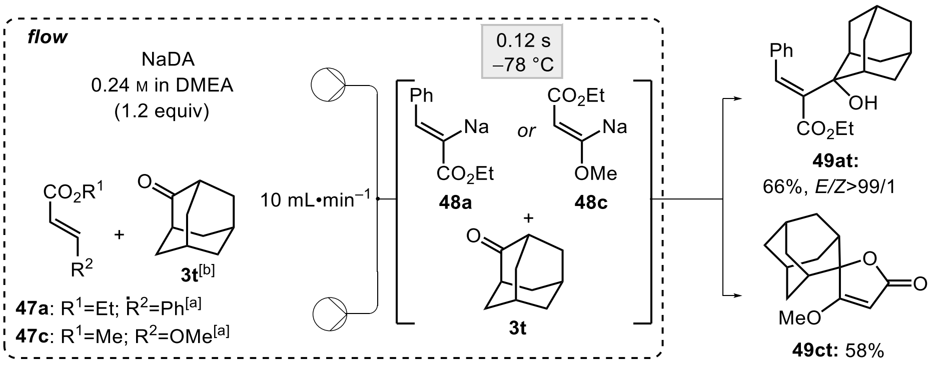
a) Sodiation of ethyl cinnamate ***11a*** *leading to self-condensation side product:*



b) Sodiation of sterically hindered acrylates and subsequent batch trapping:



c) Sodiation of acrylates using Barbier-type trapping conditions:



Scheme 44: Sodiation of substituted acrylates of type **47** using a microflow reactor under Barbier conditions. *In situ* or consecutive batch quench of the intermediate sodium organometallics of type **48** afforded functionalized acrylates of type **49**. [a] 0.20 M in THF, 1.0 equiv. [b] 0.30 M in THF, 1.5 equiv.

9. PREPARATION OF FUNCTIONALIZED ARYL, HETEROARYL AND BENZYLIC POTASSIUM ORGANOMETALLICS USING POTASSIUM DIISOPROPYLAMIDE IN CONTINUOUS FLOW

From all the alkali metals, lithium has by far received the most applications in organic synthesis.[251] However, the use of sodium and potassium organometallic intermediates has been explored since more than a century[252] 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.[253] Recently, it was reported that the use of continuous flow techniques[254] considerably facilitates the use of sodium bases such as NaDA (sodium diisopropylamide) for the selective sodiation of aromatics and heterocycles.[255] In course of these studies, 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 is reported.

9.1 PREPARATION OF POTASSIUM DIISOPROPYLAMIDE (KDA)

Whereas KDA was usually prepared according to the Schlosser method by mixing LDA (lithium diisopropylamide) with *t*BuOK,[256] it was envisioned to prepare this base in the absence of any lithium salts, using a modified procedure of Collum for the preparation of NaDA.[257] 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

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[251] (a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; (b) T. 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.

[252] (a) D. Seyferth, *Organometallics* **2006**, *25*, 2; (b) D. Seyferth, *Organometallics* **2009**, *28*, 2; (c) G. B. Buckton, *Proc. R. Soc. London* **1859**, *9*, 685; (d) G. B. Buckton, *Liebigs Ann. Chem.* **1859**, *112*, 220; (e) W. H. Carothers, D. D. Coffman, *J. Am. Chem. Soc.* **1930**, *52*, 1254; (f) J. A. Wanklyn, *Liebigs Ann. Chem.* **1858**, *108*, 67.

[253] (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, *Organometallics in Synthesis,* John Wiley & Sons, Hoboken, **2013**; (e) M. Schlosser J. Hartmann, M. Stähle, J. Kramer, A. Walde, A. Mordini, *Chimia* **1986**, *40*, 306.

[254] (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; For recent reviews about flow chemistry see: (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.

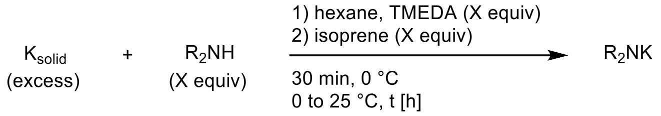
[255] N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018,** *57*, 10748.

[256] (a) A 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. Pospišil, D. Lim, *Tetrahedron Lett.* **1966**, *2*, 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. Alvarez, *Angew. Chem. Int. Ed.* **2010**, *49*, 318.

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

6 h reaction time to a dark solution (Table 20, entries 1-6). The resulting KDA 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 yield was calculated based on diisopropylamine (1.0 equiv). The equivalents of TMEDA and isoprene (entries 1-4) were varied and it was 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). Longer stirring did not improve the yield. Such KDA 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, the KDA preparation conditions described in entry 4 were used.

Table 20: Optimization of the preparation of potassium amide bases using solid potassium, secondary amides, TMEDA and isoprene in hexane.

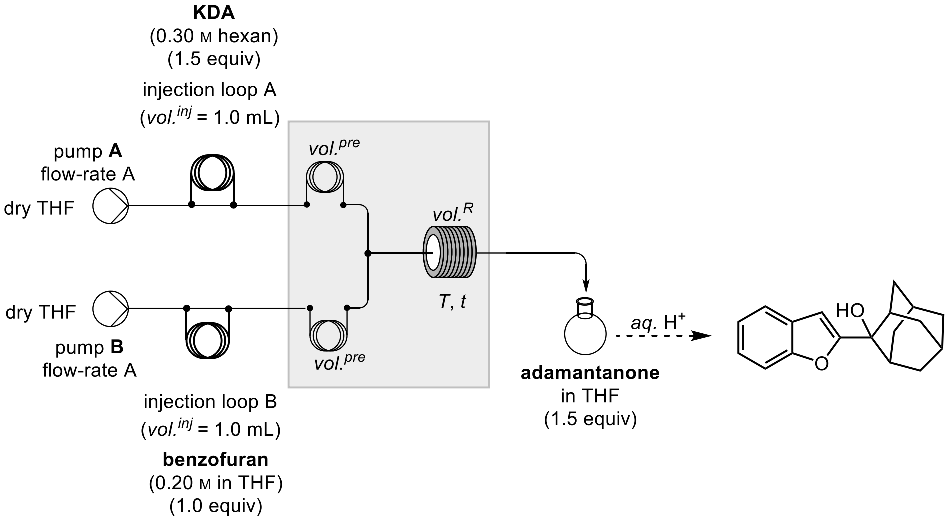


$$\underset{\text{(excess)}}{K_{solid}} + \underset{\text{(X equiv)}}{R_2NH} \xrightarrow[\text{30 min, 0 °C; 0 to 25 °C, t [h]}]{\text{1) hexane, TMEDA (X equiv); 2) isoprene (X equiv)}} R_2NK$$

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

9.2 OPTIMIZATION SCREENING OF FLOW CONDITIONS FOR BENZOFURAN METALATION USING KDA AS EXAMPLE FOR GENERAL FLOW OPTIMIZATIONS



Scheme 45: Flow set-up for the metalation of benzofuran with KDA and batch quench with adamantanone.

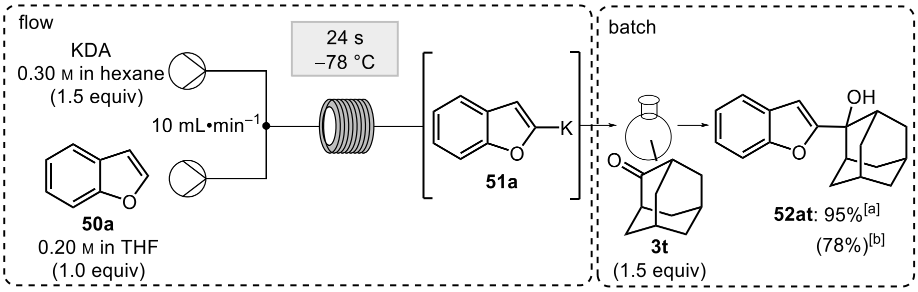
In preliminary experiments, the reaction conditions for performing metalations with KDA in hexane and in continuous flow using benzofuran (**50a**) in THF as substrate and adamantanone (**3t**) as quenching reagent were optimized. A KDA solution (0.30 M, 1.5 equiv) in hexane and a solution of the benzofuran **50a** (0.20 M, 1.0 equiv) in THF were prepared. Injection loop A (vol^{inj} =1.0 mL) was loaded with the KDA solution and injection loop B (vol^{inj} =1.0 mL) was loaded with a solution of substrate **50a**. The solutions were simultaneously injected into separate streams of THF (flow-rates: see screening table 21), which each passed a precooling loop (vol^{pre} = 1.0 mL, T [°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 (vol^{R} = see table 21; residence time: t, T [°C]) and was subsequently injected in a flask containing a stirred solution of adamantanone (**3t**, 1.5 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 21: Optimization screening of flow conditions for benzofuran (**50a**) metalation using KDA.

Entry	T^1 [°C]	Vol^R [mL]	Flow-rate [mL·min^{-1}]	t^1 [s]	GC-yield
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

By varying temperature, flow-rate and reactor size (reactor volume), it was found that it was best to perform the metalation at −78 °C using 1.5 equiv of KDA, a 4 mL tube reactor and a combined flow-rate of 10 mL·min^{-1} leading to a reaction time of 24 s for the metalation.[258] The resulting potassium organometallic **51a** was then quenched with adamantanone (**3t**, 1.5 equiv) at −40 °C for 10 min leading to the tertiary alcohol **52at** in 95% isolated yield (Scheme 46).



Scheme 46: Metalation of benzofuran (**50a**) with KDA and subsequent trapping with adamantanone (**3t**) in continuous flow. [a] Isolated yield of analytically pure product. [b] Cyclohexane was used as solvent.

9.3 INVESTIGATION OF THE ELECTROPHILE SCOPE

These potassium organometallics display a high reactivity and the metalation of benzothiazole **50b** under optimum conditions[259] (flow-rate: 10 mL·min^{-1}; reaction time: 0.18 s; reactor volume: 0.03 mL; reaction temperature: −78 °C) furnished the potassium intermediate **51b**, which was trapped with various electrophiles such as ketones (adamantanone (**3t**) or norcamphor (**3a’**)) leading to the tertiary alcohols **52bt** and **52ba’** in 74–77% yield (Table 22, entries 1-2). Using Barbier-type conditions,[260] *i.e.* metalation of a mixture of **50b** (1.0 equiv) and **3t** (1.5 equiv) with KDA (1.5 equiv) under the same flow conditions led to the alcohol **52bt** in 74% yield (entry 1). Quenching of **51b** with pivaldehyde (**52br’’**) afforded the alcohol **53br’’** in 75% yield. Weinreb amides were excellent acylation reagents for potassium organometallics and the trapping of **51b** with **3s’’** and **3t’’** gave the corresponding ketones in 91-93% yield (entries 4-5). Thiolation of **51b** with Bu_2S_2 (**3z**) led to the thioether **52bz** in 92%

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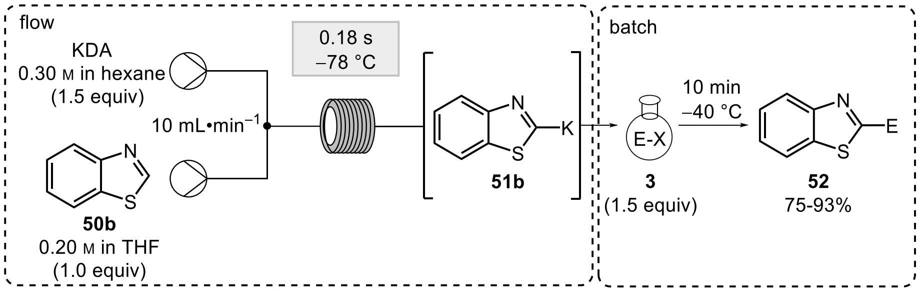
[258] Commercially available equipment from *Uniqsis* was used.

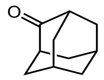
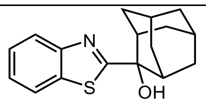
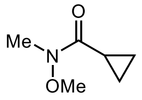
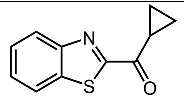
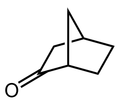
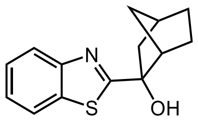
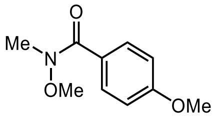
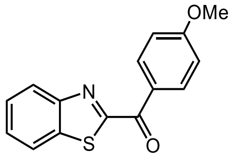
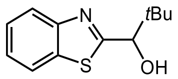
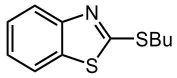
[259] Optimization studies of the flow conditions were separately conducted for each substrate.

[260] (a) P. Barbier, *Compt. Rend.* **1899**, *128*, 110; (b) P. Barbier, *C. R. Acad. Sci. Paris* **1899**, *128*, 110; (c) C. Blomberg, F. A. Hartog, *Synthesis* **1977**, *18*.

yield. The corresponding Barbier-type reaction proceeded in this case with only 47% yield (entry 6).

Table 22: Metalation of benzothiazole (**50b**) using KDA in continuous flow and subsequent batch quench with various electrophiles of type **3** leading to functionalized benzothiazole derivatives of type **52**.



Entry	Electrophile	Product[a]	Entry	Electrophile	Product[a]
1	 **3t**	 **52bt**: 77%, (74%)[b]	4	 **3s''**	 **52bs''**: 91%
2	 **3a'**	 **52ba'**: 77%	5	 **3t''**	 **52bt''**: 93%
3	Pivaldehyde **3r''**	 **52br''**: 75%	6	Bu_2S_2 **3z**	 **52bz**: 92%, (47%)[b]

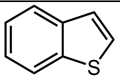
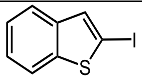
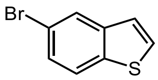
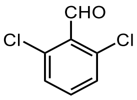
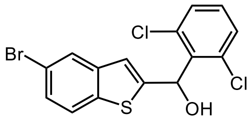
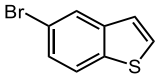
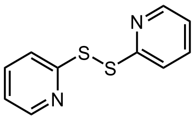
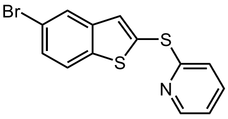
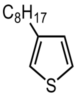
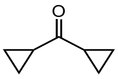
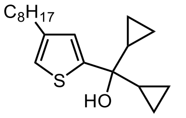
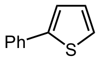
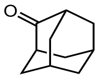
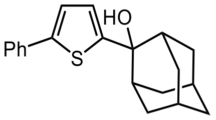
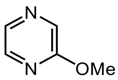
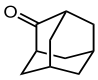
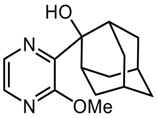
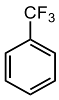
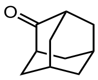
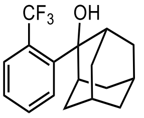
[a] Yield of analytically pure isolated product. [b] Barbier-type reaction using a pre-mixed solution of benzothiazole (**50b**, 1.0 equiv) and electrophile (1.5 equiv), instant quench with NH_4Cl.

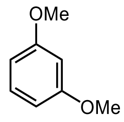
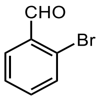
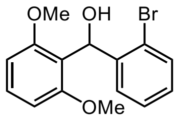
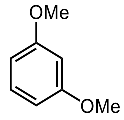
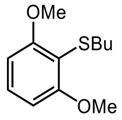
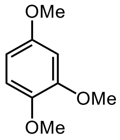
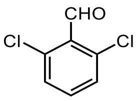
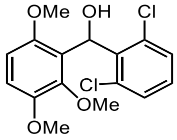
9.4 Expanding the (Hetero)Aromatic Substrate Scope

The reaction scope was then extended to various heterocyclic and aromatic substrates. For example, benzothiophene derivatives **50c** and **50d** were metalated with KDA and quenched with iodine (**3b**) or the aromatic aldehyde **3q'** as well as the aldrithiol (**3u**) leading to the desired products (**52cb**, **52dq'** and **52du**) in 63-98% yield (Table 23, entries 1-3). A complete regioselectivity of the metalation of 3-octylthiophene (**50e**) was observed and addition to dicyclopropyl ketone (**3c'**) gave the tertiary alcohol **52ec'** in 65% yield (entry 4). Similarly, 2-phenylthiophene **50f** was metalated with KDA and trapped with **3t** affording **52ft** in 80% yield (entry 5). 2-Methoxypyrazine (**50g**) was regioselectively metalated at position 3 with KDA (−78 °C, 0.18 s using a combined flow-rate of 10 mL·min^{-1}). Addition of ketone **3t** gave the desired alcohol **52gt** in 81% yield (entry 6). Extension to various aromatic substrates was possible. Electron-poor trifluoromethylbenzene (**50h**) was metalated in *ortho*-position with KDA (−78 °C, 24 s reaction time, 10 mL·min^{-1} combined flow-rate) providing after addition of **3t** the alcohol **52ht** in 42% yield (entry 7). Electron-rich substrates such as

1,3-dimethoxybenzene (**52i**) and 1,2,4-trimethoxybenzene (**52j**) were metalated with KDA and gave after batch quenching with aldehydes **3u''** and **3q'** and Bu_2S_2 (**3z**) the corresponding adducts **52iu''**, **52iz** and **52jq'** in 71-82% yield (entries 8-10).

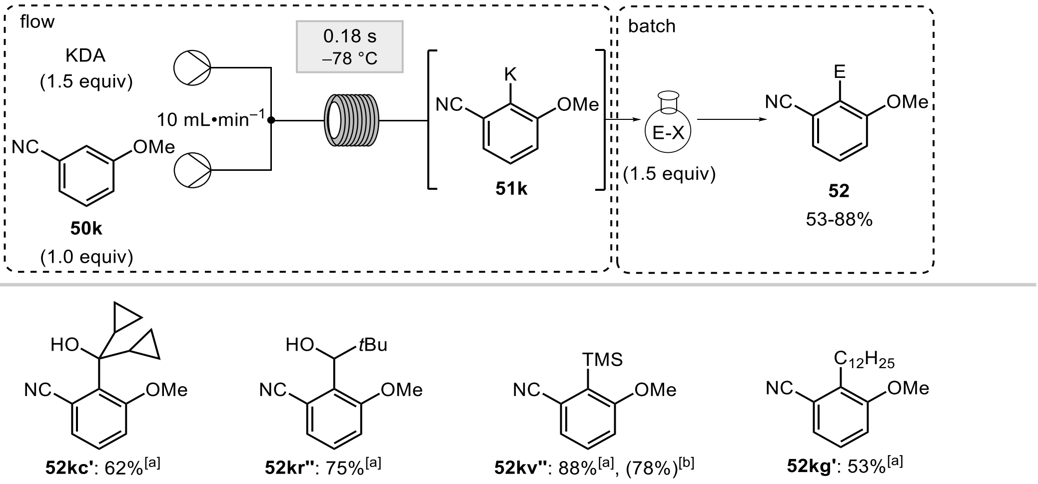
Table 23: Metalation of (hetero)arenes of type **50** using KDA in continuous flow and subsequent batch quench with various electrophiles of type **3** leading to functionalized (hetero)arenes of type **52**.

Entry	Substrate T [°C], t [s], flow-rate [mL·min^{-1}]	Electrophile [a]	Product [b]
1	 **50c:** −78, 24, 10	I_2 **3b**	 **52cb:** 63%[c]
2	 **50d:** −78, 0.18, 10	 **3q'**	 **52dq':** 98%
3	 **50d:** −78, 0.18, 10	 **3u**	 **52du:** 93%
4	 **50e:** −78, 0.18, 10	 **3c'**	 **52ec':** 65%
5	 **50f:** −78, 0.18, 10	 **3t**	 **52ft:** 80%
6	 **50g:** −78, 0.18, 10	 **3t**	 **52gt:** 81%
7	 **50h:** −78, 24, 10	 **3t**	 **52ht:** 42%

8	 **50i:** −78, 24, 10	 **3u''**	 **52iu'':** 82%
9	 **50i:** −78, 24, 10	Bu_2S_2 **3z**	 **52iz:** 73%
10	 **50j:** −78, 0.18, 10	 **3q'**	 **52jq':** 71%

[a] 1.5 equiv of electrophile were used. [b] Yield of analytically pure isolated product. [c] KDA was prepared in cyclohexane. [d] Barbier-type reaction using a pre-mixed solution of 1,3-dimethoxybenzene (**50i**, 28 mg, 0.20 mmol, 1.0 equiv) and adamantanone (**3t**, 45 mg, 0.30 mmol, 1.5 equiv), instant quench with NH_4Cl.

Interestingly, aromatic nitriles were tolerated in such metalations and 3-methoxybenzonitrile (**50k**) was deprotonated at position 2 by KDA (−78 °C, reaction time: 0.18 s). The resulting arylpotassium derivative **51k** reacted with various electrophiles (ketone **3c'**, pivaldehyde (**3r''**) and TMS-Cl (**3v''**)) leading to the expected products **52kc'**, **52kr''**and **52kg'** in 62-88% yield. Performing the metalation of **50k** with KDA in batch followed by Me_3SiCl quenching afforded the product **52kv''** in 78% yield. A Wurtz-type coupling[261] using primary alkyl iodides such as dodecyl iodide (**3g'**) led to the alkylated 3-methoxybenzonitrile **52kg'** in 53% yield. (Scheme 47).



Scheme 47: Metalation of 3-methoxy benzonitrile (**50k)** with KDA 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.

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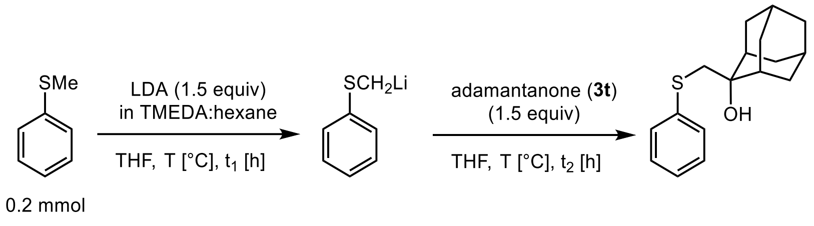
[261] (a) A. Wurtz, *Ann. Chim. Phys.* **1955**, *44*, 275; (b) A. Wurtz, *Ann. Chim. Phys.* **1855**, *96*, 364.

9.5 LATERAL METALATIONS IN BATCH AND CONTINUOUS FLOW

Whereas lateral alkali-metalations of arenes were well described in batch,[262] the corresponding reactions in flow are rare.[263] Therefore, substrates being able to undergo lateral metalation were investigated. Thioanisole (**53a**) was previously lithiated with BuLi and DABCO or HMPA leading to $PhSCH_2Li$ (**54a**).[264] However, LDA did not achieve a lithiation neither in batch nor in flow.



53a **54a** **55at**

Scheme 48: Attempted metalation of thioanisole **53a** under batch conditions using LDA as base and subsequent quench with adamantanone (**3t**).

LDA in TMEDA:hexane (1.0 mL, 0.30 M, 0.30 mmol, 1.5 equiv) was added to thioanisole (**53a**) (25 mg, 0.20 mmol, 1.0 equiv), dissolved in THF (1.0 mL), at the indicated temperature and stirred for the indicated time. Then, adamantanone (**3t**) (45 mg, 0.30 mmol 1.5 equiv), dissolved in THF (1.0 mL), was added to the mixture and stirred at the indicated temperature for the indicated time. After quenching with *sat. aq.* NH_4Cl, yields were determined using GC-analyses, demonstrating that a metalation using LDA in a conventional batch reactor did not provide the desired lithiated species.

Table 24: Attempts to lithiate **53a** under batch conditions using LDA and subsequent quench using **3t**.

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

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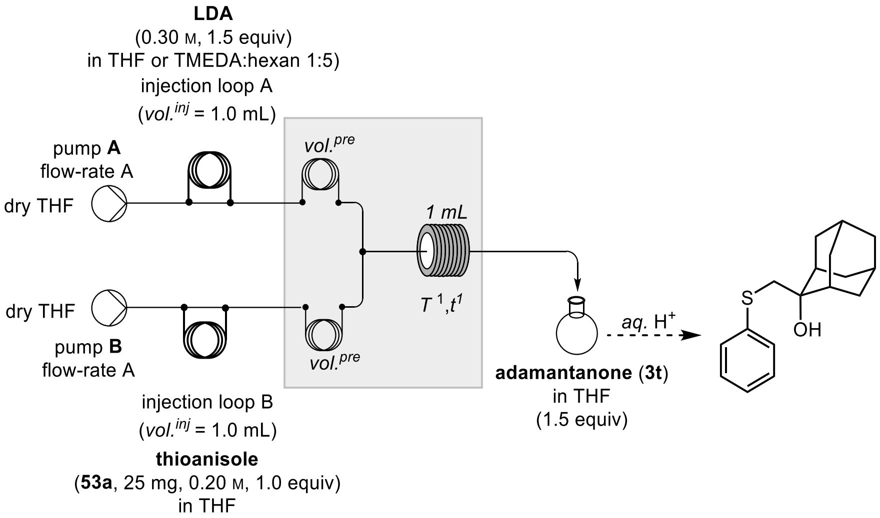
[262] (a) P. Fleming, D. F. O´Shea, *J. Am. Chem. Soc.* **2011**, *133*, 1698; (b) A. Manvar, P. Fleming, D. F. O´Shea, *J. Org. Chem.* **2015,** *80*, 8727; (c) F. Gualtieri, A. Mordini, S. Pecchi, S. Scapecchi, *Synlett* **1996**, *5*, 447; (d) M. A. J. Miah, M. P. Sibi, S. Chattopadhyay, O. B. Familoni, V. Snieckus, *Eur. J. Org. Chem.* **2018**, *4*, 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.

[263] (a) F. Venturoni, N. Nikzad, 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.

[264] (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.



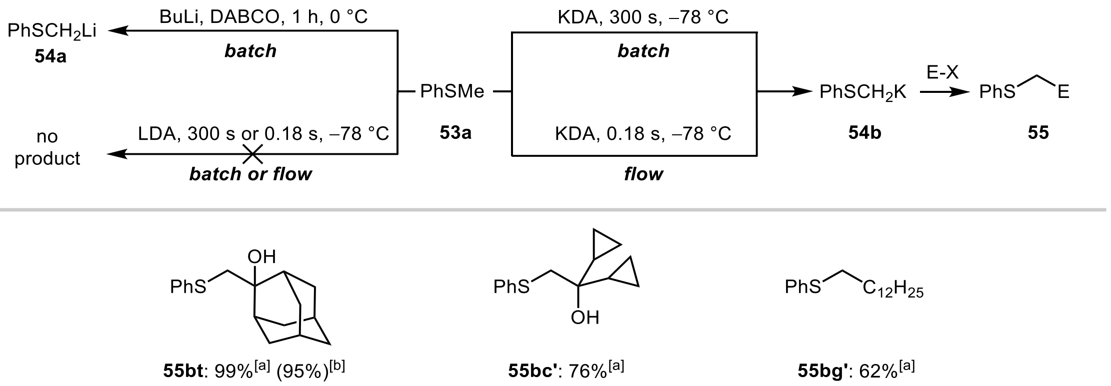
Scheme 49: Flow set-up for the metalation of thioanisole **53a** with LDA and batch quench with adamantanone **3t.**

A LDA solution (0.30 M, 1.5 equiv) in TMEDA:hexane (1:5) or THF and a solution of thioanisole **53a** (0.20 M, 1.0 equiv) in THF were prepared. Injection loop A (vol^{inj} =1.0 mL) was loaded with the LDA solution and injection loop B (vol^{inj} =1.0 mL) was loaded with the solution of **53a**. The solutions were simultaneously injected into separate streams of THF (flow-rates: 5 mL·min^{-1}), which each passed a precooling loop (vol^{pre} = 1.0 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 (vol^R = 1.0 mL; residence time: t^1 = 6 s, T^1 [°C]) and was subsequently injected in a flask containing a stirred solution of adamantanone (**3t**) (1.5 equiv) in THF. The reaction mixture was stirred for 30 min at −40 °C and quenched with *sat. aq.* NH_4Cl. Yields were determined using GC-analyses. Similarly to the metalation in batch, no lithiated thioanisole derivative was observed using continuous flow conditions.

Table 25: Attempts to lithiate **53a** under continuous flow conditions using LDA and subsequent batch quench using **3t**.

Entry	Solvent	T^1 [°C]	Conversion [%]	GC-yield
1	TMEDA:hexane	0	15	n.d.
2	TMEDA:hexane	−40	25	n.d.
3	TMEDA:hexane	−78	20	n.d.
4	THF	0	13	n.d.
5	THF	−40	10	n.d.
6	THF	−78	7	traces

On the other hand, KDA successfully deprotonated **53a** in batch as well as in flow (Scheme 50) affording $PhSCH_2K$ (**7a**), which was quenched with ketones **3t** and **3c’** and alkyl iodide **3g’** resulting in the desired products **55bt**, **55bc’** and **55bg’** in 62-99% yield.



Scheme 50: Metalation of thioanisole (**53a**) using 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.

The use of KDA was quite advantageous for the metalation of methyl-substituted arenes (Scheme 51). Preliminary results show, that a 0.20 M solution of toluene (**56a**) led to unsatisfactory results, however the injection of neat toluene (**56a**) improved considerably the flow metalation with KDA. 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 using a combined flow-rate of 10 mL·min^{-1}. Under these convenient conditions, a subsequent batch-trapping with ketone **3t** gave **58at** in 69% yield. Similarly, *p*-xylene (**56b**) provided the mono-potassium derivative **56b**, which after addition to **3t** gave the alcohol **58bt** in 94% yield. Quenching the potassium derivative **56b** with dodecyl iodide (**3g'**) or Weinreb amide **3t''** afforded the products **58bg'** and **58bt''** in 95-96% yield. Mesitylene (**56c**) was metalated neat and after quenching with ketone **3f** and dodecyl iodide (**3g'**) gave the arenes **58cf** and **58cg'** in 89-92% yield. In the case of the Wurtz-type coupling with **3g'**, the reaction was ten-fold scaled up to a 3 mmol scale,[265] providing **58bg'** in 93% yield. For 1-methylnaphthalene (**56d**), a 0.20 M solution in THF was used and standard KDA-metalation led after trapping with ketones **3t** and **3c'** to the corresponding naphthylmethyl alcohols **58dt** and **58dc'** in 61-92% yield. Functionalized substrates such as 2-fluorotoluene (**56e**) were metalated at the benzylic position, affording the potassium organometallic **57e**, which after quenching with ketones **3t** and **3c'** led to the tertiary alcohols **58et** and **58ec'** in 66-67% yield. *N,N*-diisopropyl-2-methylbenzamide (**56f**) led upon reaction with KDA at −40 °C (reaction time: 24 s) solely to the lateral metalated species **57f**, completely avoiding *ortho* metalation.[266] Trapping with various electrophiles such as ketones **3t** and **3c'**, alkyl iodide **3g'** and Weinreb amide **3w''** gave the expected products **58ft**, **58fc'**, **58fg'** and **58fw''** in 75-95% yield. Further, ketones were successfully tolerated. For example, lateral metalation of ketone **56g** using KDA proceeded smoothly at −40 °C within 0.18 s using a flow-rate of 10 mL·min^{-1}. Batch trapping with ketone **3c'** and cinnamyl bromide (**3x''**) in the presence of 10% CuCN·2LiCl resulted in the tertiary alcohol **58gc'** and the allylated ketone **58gx''** in 72-90% yield. The substrate scope was further extended to methyl-substituted heterocycles such as 2-chloro-3-methyl-pyridine (**56h**). Metalation of **56h** at the 2-methyl substituent using KDA

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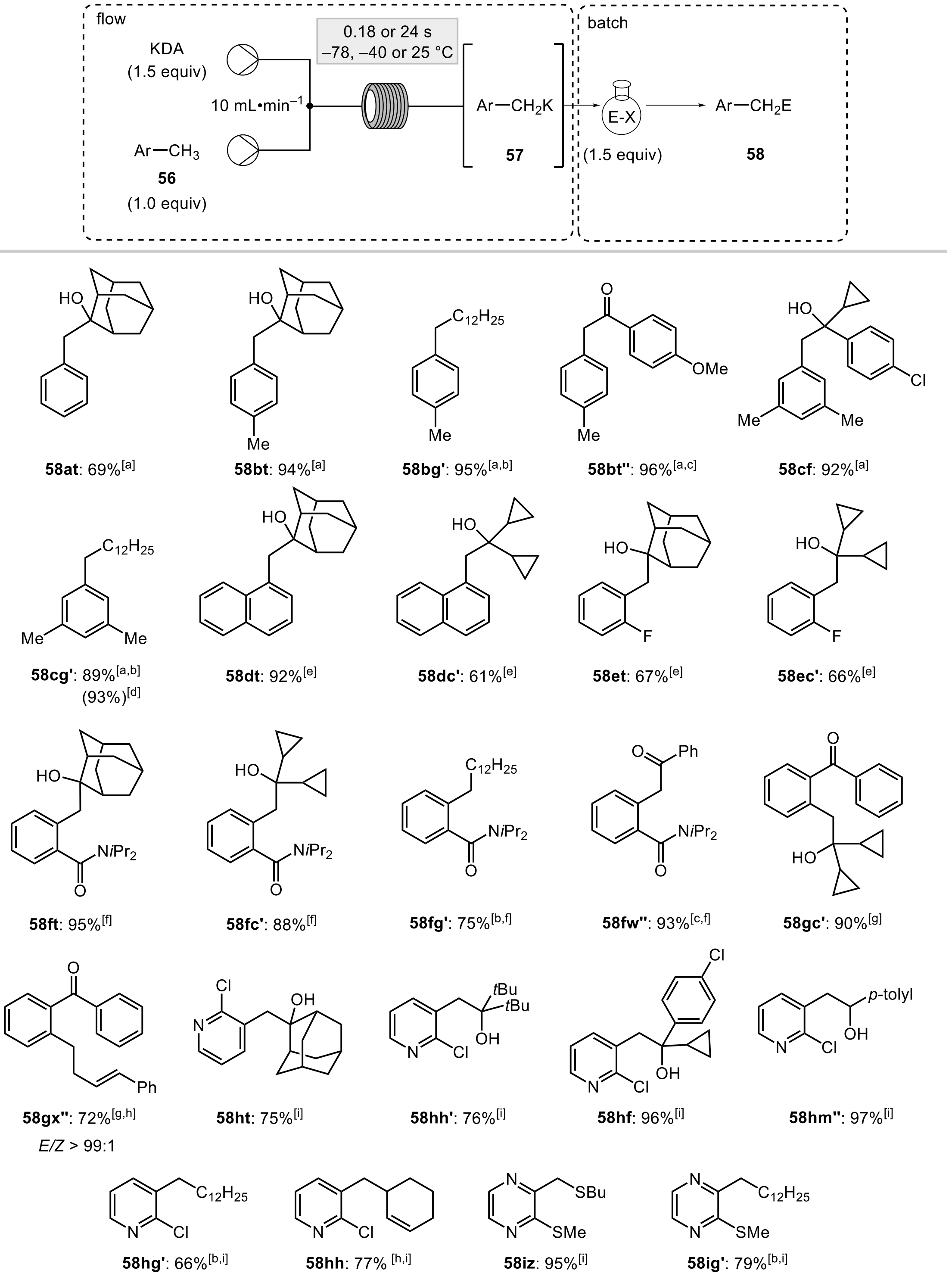
[265] (a) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Chem. Eur. J.* **2016**, *22*, 17407; (b) A. Hafner, P. Filipponi, L. Piccioni, M. Meisenbach, B. Schenkel, F. Venturoni, J. Sedelmeier, *Org. Process Res. Dev.* **2016**, *20*, 1833.

[266] (a) L. Balloch, A. R. Kennedy, R. E. Mulvey, T. Rantanen, S. D. Robertson, V. Snieckus O*rganometallics* **2011**, *30*, 145; (b) K. J. Singh, A. C. Hoepker, D. B. Collum, *J. Am. Soc. Chem.* **2008**, *130*, 18008.

led to the corresponding organopotassium species **57h**, which after batch quench with various carbonyl electrophiles (**3t**, **3h'**, **3f** and **3m''**) gave the corresponding alcohols **58ht**, **58hh'**, **58hf** and **58hm''** in 75-97% yield. Trapping **57h** with alkyl iodide **3g'** and cinnamyl bromide **3x''** (in the presence of 10% CuCN·2LiCl) led to the corresponding products **58hg'** and **58hx''** in 66-77% yield. Pyrazine **56i** was also metalated in continuous flow with KDA. It was found that after metalation at the methyl-substituent the heterobenzylic potassium organometallic **57i** was obtained. Batch trapping with dibutyl disulfide (**3z**) and dodecyl iodide (**3g'**) gave the functionalized pyrazines **58iz** and **58ig'** in 79-95% isolated yield.

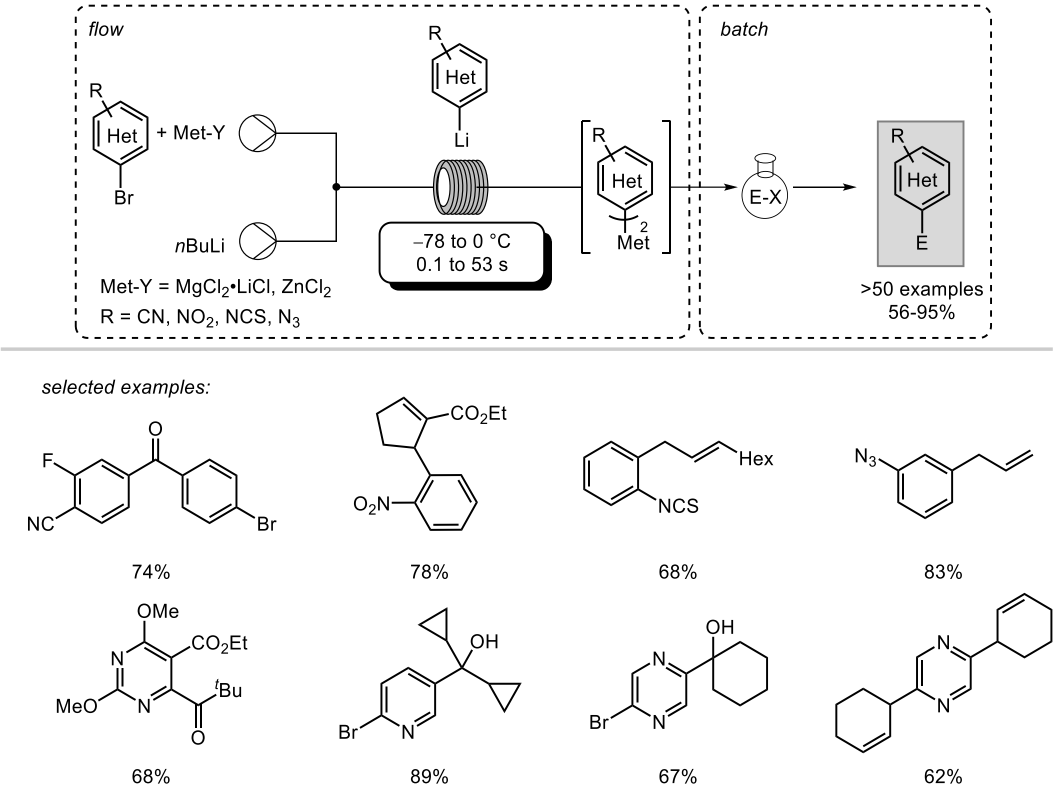


Scheme 51: Lateral metalation of methyl-substituted (hetero)arenes of type **56** using KDA in continuous flow leading to organopotassium species of type **57**. Subsequent batch trapping with various electrophiles afforded functionalized methyl-substituted (hetero)arenes of type **58**. Yields of analytically pure isolated products. [a] Substrate (neat), E-X (0.30 mmol, 1.0 equiv), KDA (1.1 equiv), 25 °C, 24 s, 10 mL·min^{-1}. [b] Wurtz-type coupling product obtained 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^{-1}. [f] −40 °C, 24 s, 10 mL·min^{-1}. [g] −40 °C, 0.18 s, 10 mL·min^{-1}. [h] 10 mol% CuCN·2LiCl. [i] −78 °C, 0.18 s, 10 mL·min^{-1}.

10. SUMMARY

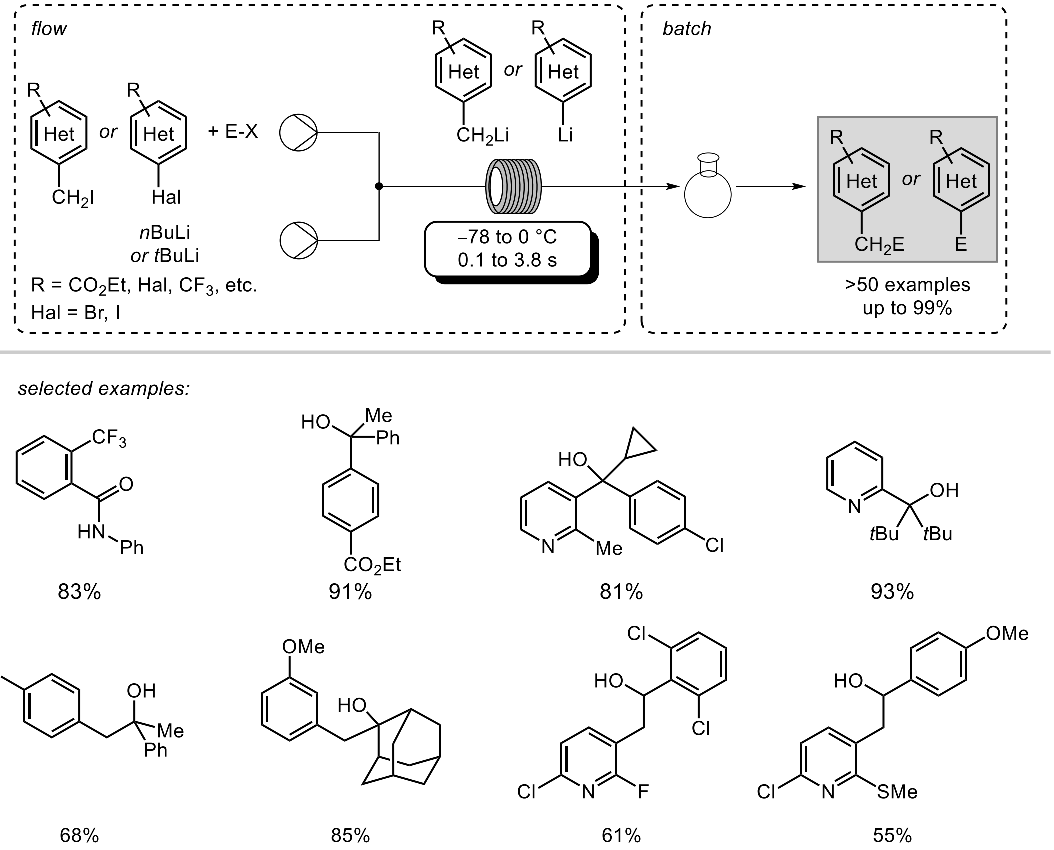
In course of these studies, the beneficial merger of continuous flow technology with metalorganic chemistry was investigated. By using a continuous flow set-up, a precise control of the reaction temperature and reaction time was possible and thereby the generation and handling of highly reactive organometallic intermediates was achieved. As already stated, continuous flow technology offers many advantages, especially for the preparation of unstable reactive intermediates as well as for ultrafast reactions, which proceed on a timescale less than a minute. Therefore, fast transformations such as halogen-lithium exchange reactions with *in situ* transmetalation and subsequent batch trapping or direct batch trapping of organolithiums were investigated to overcome limiting drawbacks of organolithium chemistry. Furthermore, directed metalations using sodium diisopropylamide and potassium diisopropylamide and the reactivity of intermediate organosodium and organopotassium reagents was extensively studied using a continuous flow set-up.

First, the preparation of polyfunctional diorgano-magnesiums and -zinc reagents using *in situ* trapping halogen-lithium exchange of highly functionalized (hetero)aryl halides was investigated (Scheme 52). Halogen-metal exchange displays a general method to prepare metalated (hetero)arenes. However, the synthesis of aryllithiums always suffers from low functional group tolerance and the need of cryogenic temperatures. Based on the previously reported *in situ* trapping of lithiated (hetero)arenes generated *via* directed metalation, a halogen-lithium exchange in the presence of various metal salts such as $ZnCl_2$ or $MgCl{\cdot}LiCl$ was investigated. First results using 4-bromobenzonitrile and *n*BuLi as exchange reagent under various flow conditions demonstrated the necessity of a metal salt for the *in situ* trapping event. Without any metal salt, decomposition and attack at the nitrile functionality occurred as major side reactions. However, the use of $ZnCl_2$ or $MgCl{\cdot}LiCl$ afforded the desired diorgano-metal species, which was subsequently trapped with various electrophiles. The scope of *in situ* trapping halogen-lithium exchange was successfully extended to various substituted arenes. In particular, the tolerance of functional groups was tremendously enhanced, *e.g.* azides, isothiocyanates, nitro- and ester-containing arenes were functionalized in a continuous flow set-up, which was not possible under conventional batch conditions demonstrating the beneficial application of flow technology. Additionally, a halogen-lithium exchange reaction in the presence of $MgCl_2$ using a broad range of heteroarenes was reported. Interestingly, heterocyclic substrates bearing two bromides were successfully exchanged with excellent regioselectivity affording the monofunctionalized pyridines and pyridazines. However, by increasing the equivalents of *n*BuLi, the bisfunctionalized heteroarenes were also obtained in moderate yields.



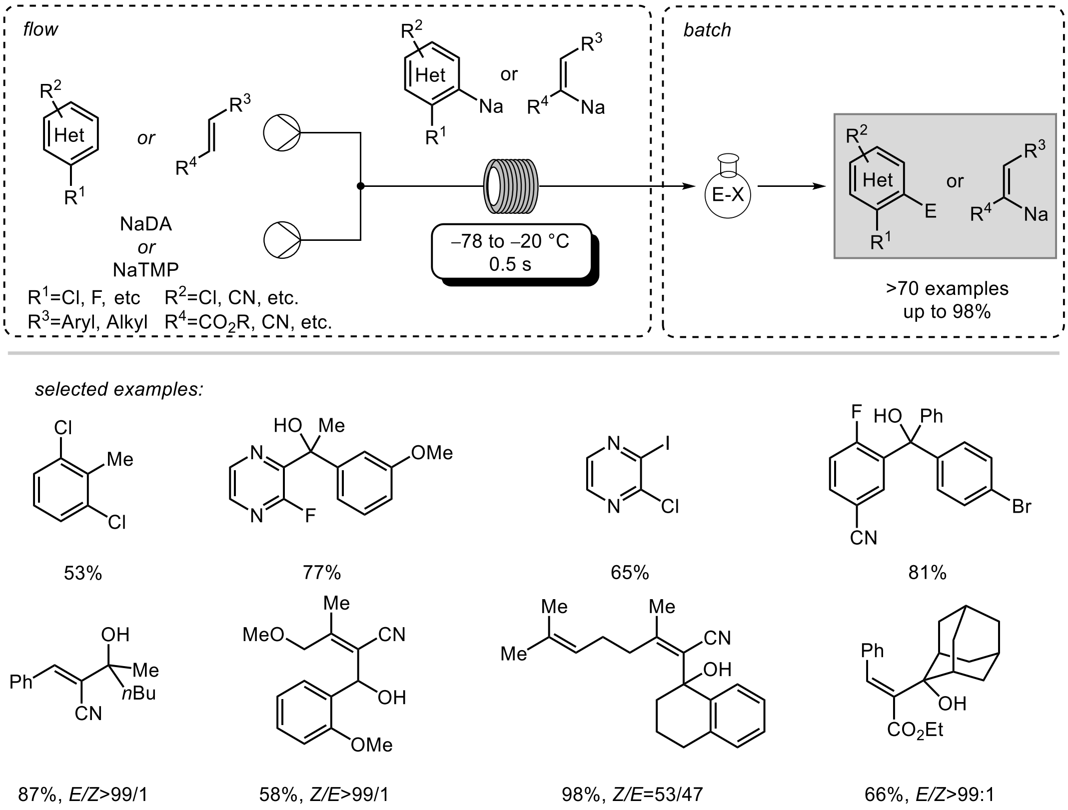
Scheme 52: Selected examples of the halogen-lithium exchange reaction of (hetero)arenes using a continuous flow set-up.

Continuing on these results, a Barbier-type halogen-lithium exchange reaction of (hetero)arenes was envisioned (Scheme 53). Whereas trapping with metal salts such as $ZnCl_2$ or MgCl·LiCl afforded the corresponding diorgano-magnesium and -zinc reagents in good to excellent yields, it was proposed to overcome degradation of the intermediate organolithiums by premixing the aryl halides and the desired electrophile before performing the halogen-lithium exchange reaction. Indeed, it was found that the halogen-lithium exchange in the presence of electrophiles using *n*BuLi as exchange reagent afforded the desired functionalized arenes outcompeting side reactions such as the addition of BuLi to the electrophile. *In situ* trapping with various electrophiles such as aldehydes, ketones, imines, Weinreb amides, isocyanates and alkyl halides led to a broad range of functionalized (hetero)arenes in good to excellent yields. Interestingly, sensitive functional groups such as esters were successfully tolerated, whereas a Barbier-type batch reaction solely led to degradation of the ester demonstrating the necessity of ultrafast mixing within a continuous flow set-up. An extension of this Barbier-type trapping reaction to heteroarenes afforded a broad range of functionalized pyridines and pyrimidines, showing the general applicability of this method. To further test the limitations of the Barbier-type reactions, an extension to benzylic halides was proposed. The generation of benzylic lithiums by halogen-lithium exchange reactions is often accompanied by side reactions such as Wurtz-type homocouplings. However, it was found that benzylic iodides undergo an iodine-lithium exchange in the presence of carbonyl-containing electrophiles. Interestingly, enolisable aliphatic and aromatic ketones were tolerated without a significant loss of yield. Both, electron-rich and electron-demanding benzylic iodides were successfully implemented within this continuous flow method. To demonstrate the broad applicability of the method, heterobenzylic iodides were successfully functionalized by premixing with the desired aromatic aldehydes.



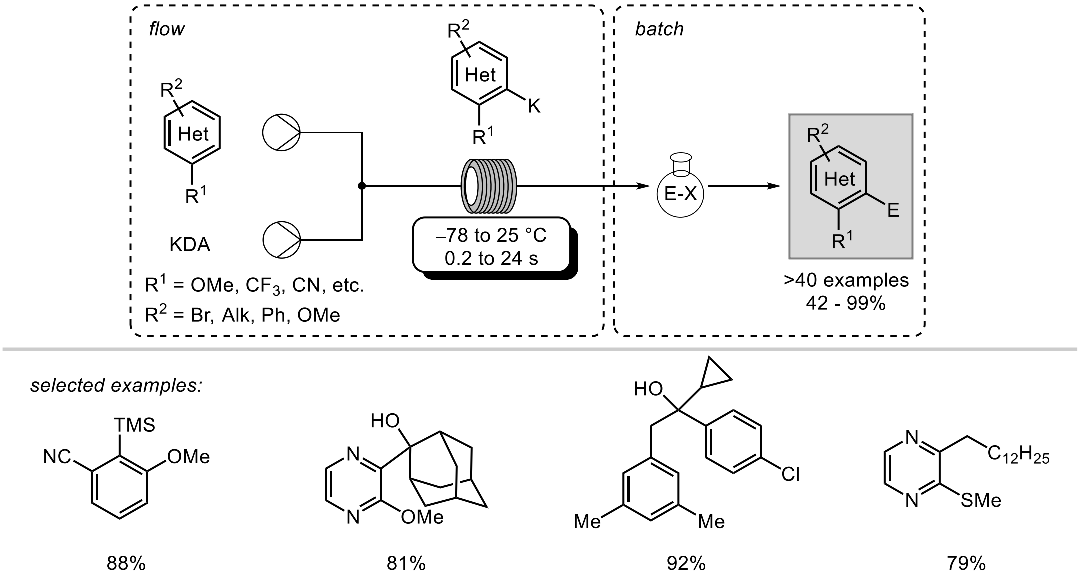
Scheme 53: Selected examples of the Barbier-type halogen-lithium exchange of sensitive (hetero)aromatic halides and benzylic iodides using a continuous flow set-up.

A third project focused on the sodiation of (hetero)arenes and substituted acrylonitriles and alkenyl sulfides using a continuous flow set-up (Scheme 54). Collum and co-workers already reported the sodiation of arenes using the soluble NaDA (sodium diisopropylamide) base. However, the *ortho*-metalation of halogenated arenes often led to aryne formation *via* sodium halide elimination. To overcome the elimination, a sodiation using a continuous flow set-up was proposed. By ultrafast mixing, an efficient synthesis of the desired organosodiums was envisioned. Using very short reaction times, the electrophile quench was assumed to be faster than the undesired elimination reaction. According to a slightly modified procedure from Collum and co-workers, a 1.0 M solution of NaDA in DMEA was prepared, which was subsequently used for flow-sodiations. In fact, 2,6-dichlorophenylsodium was prepared in a continuous flow set-up within 0.5 s at −20 °C using NaDA (1.05 equiv), which was directly trapped in batch with various electrophiles such as iodine, aromatic aldehydes, isocyanates or allylic bromides. Even a Wurtz-Fittig-type coupling using methyl iodide or butyl bromide was possible affording the desired alkylated arenes in good yields. Interestingly, no aryne formation was observed upon sodiation of *ortho*-halogenated arenes. It was demonstrated that arenes and heteroarenes were sodiated in a continuous flow set-up using NaDA and the resulting sodiated (hetero)aromatics reacted instantly under batch conditions with a broad range of electrophiles affording the desired functionalized (hetero)aromatics. Moreover, the addition of organometallics to ketones is always subject to side reactions such as reduction of the ketones. However, addition of (hetero)arylsodiums to ketones furnished the desired tertiary alcohols in good to excellent yield. Furthermore, 2-chloropyrazine was reported to decompose upon aryne formation under conventional batch conditions. However, by using a continuous flow set-up, the desired heteroarylsodium spezies was obtained and subsequently trapped with iodine affording the iodinated pyrazine in 65% isolated yield. Finally, tolerating sensitive functional groups such as nitriles was demonstrated by using 4-fluorobenzonitrile at −78 °C. To further broaden the scope of sodiated organometallics, this protocol was applied to alkenyl sulfides and acrylonitriles. The resulting sodiated intermediates were subsequently trapped with various electrophiles affording functionalized alkenyl sulfides and acrylonitriles. Since DMEA, which is used as solvent for NaDA, is an uncommon, toxic and expensive solvent, it was envisioned to overcome the need of DMEA. In fact, it was found that NaTMP in hexane could also be used for sodiations in a continuous flow set-up without further optimization. Tolerating sensitive functional groups such as esters was achieved either by using sterically demanding esters or a Barbier-type protocol with a premixed solution of electrophile and acrylate affording functionalized acrylates.



Scheme 54: Selected examples of the sodiation of (hetero)arenes and acrylonitriles or alkenyl sulfides with NaDA or NaTMP and subsequent batch quench with various electrophiles using a continuous flow set-up.

Inspired by the generation of highly reactive organosodiums, an extension of directed metalation to organopotassium reagents was envisioned (Scheme 55). However, one major drawback of potassium reagents was the absence of pure potassium bases. Previously reported syntheses of *e.g.* KDA (potassium diisopropylamide) always included the usage of lithium bases such as *n*BuLi and therefore, a mixed K/Li-species was obtained. Nonetheless, a preparation of lithium salt-free KDA was proposed. Indeed, a KDA-solution in hexane (approximately 0.6 M) was obtained by mixing TMEDA, diisopropylamine and isoprene with sliced elemental potassium. To afford the desired (hetero)aromatic potassium reagents, a flow-metalation was performed between −78 °C and 25 °C with reaction times between 0.2 s and 24 s using a commercial flow set-up. These potassium organometallics reacted instantaneously with various electrophiles, such as ketones, aldehydes, alkyl and allylic halides, disulfides, Weinreb amides and Me_3SiCl, affording functionalized (hetero)arenes in high yields. Again, aromatic nitriles were tolerated by ultrafast mixing within 0.2 s. This flow procedure was successfully extended to the lateral metalation of methyl-substituted arenes and heteroarenes affording functionalized (hetero)benzylic products.



Scheme 55: Selected examples of the preparation of functionalized aryl-heteroaryl and benzylic potassium organometallics using a continuous flow set-up.

11. OUTLOOK

The development of various continuous flow techniques, special equipment, new reactor and mixing devices, each addressing special needs of synthetic chemists, provides a very powerful toolbox to handle extremely fast reactions. Beside other advantages such as safer handling of hazardous or toxic reagents or intermediates, continuous flow technology further allows for the performance of reactions, which are too fast to control under conventional batch conditions. Hence, reactions that are supposed to be impossible in a batch reactor can become possible resulting in yet unknown reaction pathways. Further, the controlled transfer of highly reactive intermediates to a second location, where they can perform desired functionalizations, offers new possibilities for ultrafast reactions. Organometallic chemistry is one area among many others that benefits significantly from the application of flow technology. Due to the highly reactive carbon-metal bond, organometallic intermediates display many potential intermediates that can either not be generated in a conventional batch reactor or that are difficult to store for a longer period of time. The merger of continuous flow technology and organometallic chemistry, in particularly with regard to highly reactive organolithium, -sodium and -potassium reagents, displays a promising approach to get access to organometallic intermediates, which are difficult to control and handle under standard batch conditions. Furthermore, not only the taming of highly reactive intermediates on a small scale remains challenging, but large scale reactions including metalorganic reagents also often suffer from side reactions due to local concentration gradients or hotspots. However, scaling up a reaction in a continuous flow set-up is often achieved by simply increasing the run-time. Moreover, automatization of multiple reaction steps using flow technology will lead to a rapid build-up of huge small molecule libraries by synthesizing thousands of molecules within a couple of days. Further, the shift of a laboratory synthesis to the desired industrial production can be rapidly carried out by using special mixing devices and reactors, which can save a lot of time and manpower during the scale-up.

C. EXPERIMENTAL PART

12. GENERAL INFORMATION

12.1 SOLVENTS

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves.

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

***i*$\mathbf{Pr_2NH}$** (DIPA) was freshly distilled from calcium hydride under argon and stored under argon.

Solvents for column chromatography were distilled prior to use.

12.2 REAGENTS

All reagents were obtained from commercial sources and used without further purification unless otherwise stated.

BuLi solution in hexane was purchased from Albermarle and the concentration was determined by titration against 1,10-phenanthroline in THF with *i*PrOH.

PhLi solution in dibutyl ether was purchased from Sigma Aldrich and the concentration was determined by titration against 1,10-phenanthroline in THF with *i*PrOH.

NaDA solution (ca. 1.0 M in DMEA) was prepared according to a slightly modified procedure reported by Collum.[267] It was demonstrated that a quantity reduction of sodium dispersion did not influence the concentration of resulting NaDA solution. Optimized preparation 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 diisopropylamine (4.2 mL, 29.8 mmol) were added. After cooling the solution to 0 °C, isoprene (1.52 mL, 15.0 mmol) was added dropwise and the solution was allowed to warm to room temperature over 2 h. The concentration of the resulting yellow NaDA solution was determined by titration with diphenylacetic acid. Prior to use the solution was diluted to a concentration close to 0.20 M.

TMPNa solution (ca. 1.0 M in hexane) was prepared according to a slightly modified procedure reported by Takai.[268] 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 *n*hexane (3×3 mL). Distilled *n*hexane (15.0 mL), TMEDA (3.4 mL, 22.4 mmol, 1.0 equiv) and diisopropylamine

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[267] R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197.

[268] S. Asako, M. Kodera, H. Nakajima, K. Takai, *Adv. Synth. Catal.* **2019**, *361*, 3120.

(3.2 mL, 22.4 mmol, 1.0 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 solution.

Titration of KDA was done using a standardized solution of *n*BuOH (0.4 M) in distilled *n*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 12).

Figure 12: Titration of KDA (a) base before titration; (b) titration mixture after reaching the endpoint.

$CuCN\cdot 2LiCl$[269] solution (1.0 M in THF) was prepared by drying CuCN (9.0 g, 100 mmol) and LiCl (8.5 g, 200 mmol) in a Schlenk-flask under high 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.

$ZnCl_2$ solution (1.0 M in THF) was prepared by drying $ZnCl_2$ (27.3 g, 200 mmol) in a Schlenk flask under vacuum at 150 °C for 5 h. After cooling to 25 °C, dry THF (200 mL) was added and stirred until the salts were dissolved.

$MgCl_2\cdot LiCl$. solution (0.5 M in THF) was prepared by drying LiCl (4.2 g, 100 mmol) in a Schlenk flask equipped with a magnetic stirrer and a septum under vacuum for 5 h at 150 °C. After cooling to 25 °C Mg turnings (2.6 g, 105 mmol) and THF (200 mL) were added. 1,2-Dichloroethane (9.9 g, 100 mmol, 7.9 mL) was added dropwise over 1 h. The reaction mixture was stirred at 25 °C until gas evolution was complete.

12.3 CHROMATOGRAPHY

Flash column chromatography was performed using SiO2 60 (0.040 0.063 mm, 230 400 mesh ASTM) from Merck. Thin layer chromatography (TLC) was performed using aluminum plates covered with SiO2 (Merck 60, F 254). Spots were visualized under UV light.

12.4 ANALYTICAL DATA

Yields refer to isolated yields of compounds estimated to be >95% pure as determined by 1H-NMR (25 °C) and capillary GC-analyses. 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: $CDCl_3$ (*δ*H: 7.26; δC: 77.16). For the description 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.

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

Infrared spectra were recorded from 4000-400 cm^{-1} on a Nicolet 510 FT-IR or a Perkin-Elmer 281 IR spectrometer. Samples were measured neat (Smiths Detection DuraSampl IR II Diamond ATR). The 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).

12.5 SINGLE CRYSTAL X-RAY DIFFRACTION STUDIES

Single crystals of crystaline compounds, suitable for X-ray diffraction, were obtained by slow evaporation of acetonitrile or DCM 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.270 Absorption correction using the multiscan methoda) was applied. The structures were solved with SHELXS-97,271 refined with SHELXL-97272 and finally checked using PLATON.273 Details for data collection and structure refinement are summarized in the corresponding tables.

12.6 GENERAL REMARKS ON FLOW AND SUBSEQUENT BATCH QUENCHING REACTIONS

Tetradecane ($n\mathrm{C}_{14}\mathrm{H}_{30}$), dodecane ($n\mathrm{C}_{12}\mathrm{H}_{26}$) or undecane ($n\mathrm{C}_{11}\mathrm{H}_{24}$) 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 or a Uniqsis FlowSyn system was used. If the Vapourtec System was used, *n*hexane solutions of *n*BuLi or PhLi and THF solutions of the remaining reactants were kept in flasks with rubber septa under an argon atmosphere during the reactions. If the Uniqsis system was used, carrier solvents as well as reactant solutions were stored under argon and injected to carrier solvent streams. 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,

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[270] Program package CrysAlisPro 1.171.38.46 (Rigaku OD, 2015).

[271] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.

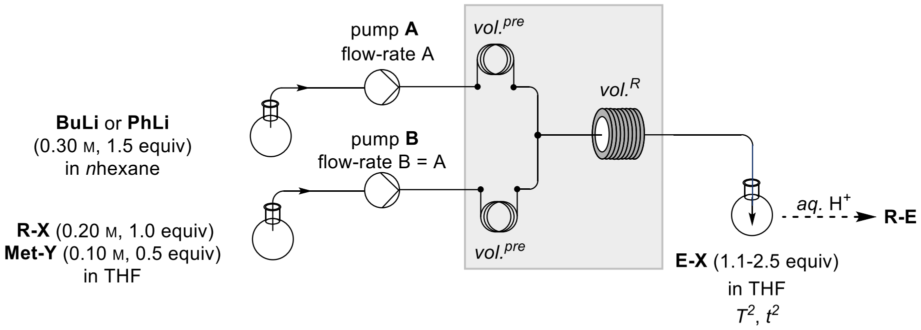
[272] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.

[273] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

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: 1.0 $\mathrm{mL \cdot min^{-1}}$; run-time: 10-30 min).

13. PREPARATION OF POLYFUNCTIONAL DIORGANO-MAGNESIUM AND -ZINC REAGENTS USING *IN SITU* TRAPPING HALOGEN-LITHIUM EXCHANGE OF HIGHLY FUNCTIONALIZED (HETERO)ARYL HALIDES IN CONTINUOUS FLOW

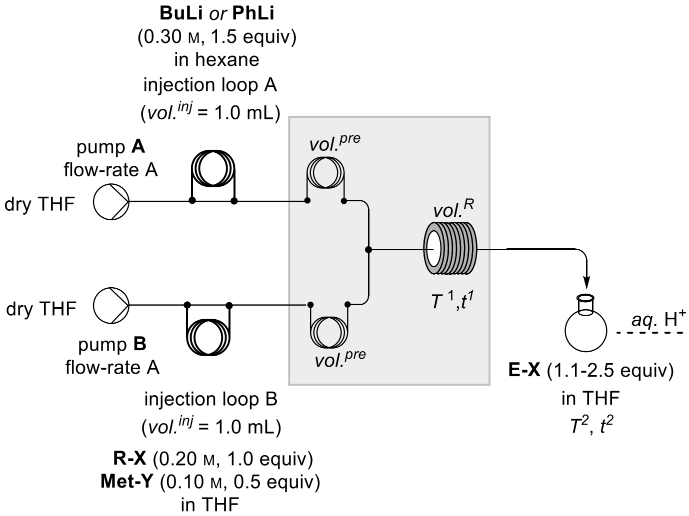
13.1 TYPICAL PROCEDURE 1 (TP1)



Scheme 56: Vapourtec flow set-up for the halide-lithium exchange and of substrates R-X with aryllithium reagents in the presence of a metallic salt (Met-Y) and batch quench with an electrophile (E-X).

A BuLi or PhLi solution in hexane (0.30 M, 1.5 equiv) and a solution of the aryl halide substrate (R-X, 0.20 M, 1.0 equiv) and metallic salt (Met-Y, 0.10 M, 0.5 equiv) in THF were prepared. The solutions were pumped from their flasks through a suction needle at flow-rate A = 3.0-10.0 mL·min^{-1} and flow-rate B = flow-rate A. After passing a PTFE tubing (vol^{pre} = 1.0-2.0 mL, T^1 = −78 - 0°C, residence time: 6 – 20 s) for precooling, the solutions were mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (Vol^R = 0.02 – 5.3 mL; residence time: t^1 = 0.06 – 53.0 s, T^1 = −78 to 25 °C) and was subsequently injected in a flask containing a stirred, cooled (T^1 = −40 to 25°C) solution of an electrophile E-X (1.2-2.5 equiv) and catalyst, if applicable, in 1 mL THF per mmol of substrate. The reaction mixture was stirred further for the indicated times and temperatures (T^2, reaction time: t^2) 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 with suited isohexane:EtOAc mixtures afforded the pure products R-E.

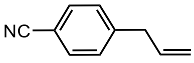
13.2 TYPICAL PROCEDURE 2 (TP2)



Scheme 57: Uniqsis flow set-up for the halide-lithium exchange and of substrates R-X with aryllithium reagents in the presence of a metallic salt (Met-Y) and batch quench with an electrophile (E-X).

A BuLi or PhLi solution in hexane (0.30 M, 1.5 equiv) and a solution of the aryl halide substrate (R-X, 0.20 M, 1.0 equiv) and metallic salt (Met-Y, 0.10 M, 0.5 equiv) in THF were prepared. Injection loop A (vol^{inj}=1.0-2.0 mL) was loaded with the exchange reagent (BuLi or PhLi) and injection loop B (vol^{inj}=1.0-2.0 mL) was loaded with the solution of the substrate (R-X) and the metallic salt Met-Y The solutions were simultaneously injected into separate streams of hexane and THF, respectively (pump A: THF; pump B: THF, flow-rates: 3.0-10.0 mL·min^{-1}), which each passed a precooling loop (vol^{pre} = 1.0 – 2.0 mL, T^1 = −78 - 0°C, residence time: 6 - 20 s), before they were mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (Vol^R = 0.02 – 5.3 mL; residence time: t^1 = 0.06-53.0 s, T^1 = −78 to 25 °C) and was subsequently injected in a flask containing a stirred, cooled (T^1 = −40 to 25°C) solution of an electrophile E-X (1.1 – 2.5 equiv) and catalyst, if applicable, in THF. The reaction mixture was stirred further for the indicated times and temperatures (T^2, reaction time: t^2) 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 with suited isohexane:EtOAc mixtures afforded the pure products R-E.

4-Allylbenzonitrile (4aa)



According to TP1, a solution of 4-bromobenzonitrile (0.20 M, 0.4 mmol) and $MgCl_2$·LiCl (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (121 mg, 1.0 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 10 min at 25 °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 *in vacuo*, purification *via* HPLC afforded the title compound as a pale yellow oil (40 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.58 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.92 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.17 – 5.04 (m, 1H), 3.44 (d, *J* = 6.7 Hz, 2H).

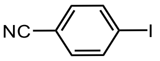
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 145.79, 135.78, 132.39 (2C), 129.53 (2C), 119.17, 117.38, 110.21, 40.32.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2922, 2854, 2228, 1608, 1458, 1374, 1260, 1176, 1096, 994, 918, 814, 702.

MS (EI, 70 eV): *m/z* (%) = 144 (11), 143 (98), 142 (100), 140 (20), 116 (37), 115 (75), 89 (15).

HRMS (EI): *m/z* calc. for [$C_{10}H_8N$]: 142.0657; found 142.0650 (M – H).

4-Iodobenzonitrile (4ab)



According to the TP1, a solution of 4-bromobenzonitrile (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of iodine (254 mg, 1.0 mmol, 2.5 equiv) in THF. Stirring was continued for 10 min at 25 °C before *sat. aq.* $Na_2S_2O_3$ 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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 49:1) afforded the title compound as a pale yellow powder (75 mg, 0.33 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 – 7.73 (m, 2H), 7.46 – 7.30 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 138.7 (2C), 133.3 (2C), 118.3, 111.9, 100.4.

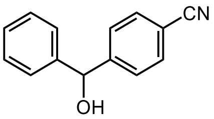
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2958, 2926, 2870, 2226, 1910, 1684, 1644, 1588, 1578, 1474, 1390, 1370, 1342, 1302, 1274, 1244, 1222, 1204, 1112, 1056, 1010, 962, 816, 766, 732, 700.

MS (EI, 70 eV): *m/z* (%) = 229 (100), 130 (12).

HRMS (EI): *m/z* calc. for [C_7H_4IN]: 228.9388; found 228.9382.

m.p. (°C): 170.20 – 170.8.

4-(Hydroxy(phenyl)methyl)benzonitrile (4ac)



According to the TP1, a solution of 4-bromobenzonitrile (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 $mL \cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of benzaldehyde (64 mg, 0.60 mmol, 1.5 equiv) in THF. Stirring was continued for 1 h at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 4:1) afforded the title compound as colorless crystals (58 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.67 – 7.55 (m, 2H), 7.56 – 7.45 (m, 2H), 7.45 – 7.27 (m, 5H), 5.84 (s, 1H), 2.65 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 149.0, 142.9, 132.3 (2C), 129.0 (2C), 128.4, 127.1 (2C), 126.8 (2C), 118.9, 111.2, 75.7.

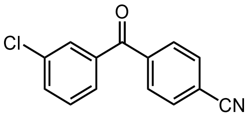
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3462, 3418, 2926, 2882, 2870, 2232, 2226, 1663, 1608, 1599, 1513, 1503, 1491, 1450, 1404, 1339, 1320, 1276, 1230, 1187, 1172, 1114, 1079, 1044, 1027, 1018, 862, 846, 802, 770, 732, 723, 702, 675.

MS (EI, 70 eV): *m/z* (%) = 209 (53), 208 (16), 190 (11), 130 (24), 107 (13), 105 (34), 104 (27), 103 (10), 102 (14), 79 (28), 78 (14), 77 (29), 61 (12), 45 (13), 42 (100).

HRMS (EI): *m/z* calc. for [$C_{14}H_{11}NO$]: 209.0841; found 209.0835.

m.p. (°C): 80.7 – 81.0.

4-(3-Chlorobenzoyl)benzonitrile (4ad)



According to the TP1, a solution of 4-bromobenzonitrile (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 $mL \cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-chlorobenzoyl chloride (105 mg, 0.60 mmol, 1.5 equiv) and $CuCN \cdot 2LiCl$ solution (0.44 mL, 1.0 M in THF, 1.1 equiv) in THF. Stirring was continued for 1 h at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 49:1) afforded the title compound as a white solid (81 mg, 0.34 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 – 7.84 (m, 2H), 7.84 – 7.78 (m, 2H), 7.76 (t, *J* = 1.8 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.46 (t, *J* = 7.9 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.7, 140.6, 138.1, 135.1, 133.4, 132.4 (2C), 130.3 (2C), 130.1, 130.0, 128.2, 118.0, 116.2.

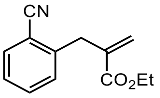
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3091, 3076, 3064, 2923, 2854, 2228, 1728, 1646, 1606, 1588, 1567, 1463, 1416, 1403, 1312, 1292, 1279, 1268, 1247, 1180, 1149, 1120, 1074, 1019, 999, 969, 961, 929, 900, 853, 817, 789, 753, 730, 707, 672, 663.

MS (EI, 70 eV): *m/z* (%) = 241 (35), 226 (11), 225 (14), 191 (10), 190 (45), 140 (22), 139 (100), 130 (45), 111 (37), 102 (36), 75 (13), 50 (10), 44 (30), 43 (17).

HRMS (EI): *m/z* calc. for [$C_{14}H_8ClNO$]: 241.0294; found 241.0286.

m.p. (°C): 95.4 – 95.8.

Ethyl 2-(2-cyanobenzyl)acrylate (4be)



According to the TP1, a solution of 2-bromobenzonitrile (0.20 M, 0.50 mmol) and $MgCl_2\cdot LiCl$ (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 9 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of ethyl 2-(bromomethyl)acrylate (138 µL, 1.0 mmol, 2.0 equiv) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 30 min at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 9:1) afforded the title compound as a colorless oil (73 mg, 0.34 mmol, 68% yield).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 7.62 (ddd, *J* = 7.6, 1.3, 0.5 Hz, 1H), 7.51 (td, *J* = 7.7, 1.4 Hz, 1H), 7.36 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H), 6.32 (q, *J* = 0.9 Hz, 1H), 5.56 (q, *J* = 1.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

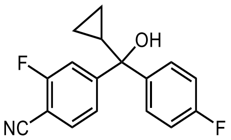
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.28, 142.71, 138.24, 132.99, 132.82, 130.28, 127.59, 127.13, 118.01, 113.08, 61.07, 36.62, 14.19.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 2226, 1712, 1634, 1600, 1486, 1448, 1368, 1302, 1254, 1198, 1138, 1094, 1024, 952, 930, 858, 816, 760, 680.

MS (EI, 70 eV): *m/z* (%) = 355 (12), 341 (11), 299 (20), 281 (31), 225 (21), 221 (14), 215 (15), 214 (19), 207 (14), 207 (19), 171 (15), 149 (38), 147 (21), 141 (11), 131 (11), 130 (17), 129 (13), 128 (15), 119 (13), 117 (19), 115 (23), 105 (19), 104 (14), 103 (27), 91 (39), 79 (13), 78 (16), 77 (11), 76 (11), 73 (25), 45 (25), 44 (30), 43 (100), 42 (11), 41 (17).

HRMS (EI): *m/z* calc. for [$C_{13}H_{13}NO_2$]: 215.0946; found 215.0939.

4-(Cyclopropyl(4-fluorophenyl)(hydroxy)methyl)-2-fluorobenzonitrile (4cf)



According to the TP1, a solution of 4-bromo-2-fluorobenzonitrile (0.20 M, 0.50 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 9 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl(4-fluorophenyl)methanone (90 mg, 0.55 mmol, 1.1 equiv) in THF. Stirring was continued for 2 h at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 92:8) afforded the title compound as colorless crystals (105 mg, 0.37 mmol, 74% yield).

^{1}H-NMR (600 MHz, CDCl$_3$): δ / ppm = 7.53 (dd, *J* = 8.1, 6.5 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.34 (dd, *J* = 10.4, 1.6 Hz, 1H), 7.24 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.07 – 6.97 (m, 2H), 2.08 (s, 1H), 1.63 – 1.50 (m, 1H), 0.82 – 0.68 (m, 1H), 0.60 – 0.40 (m, 3H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 163.99 (d, *J* = 78.8 Hz), 161.47 (d, *J* = 67.7 Hz), 156.20 (d, *J* = 6.9 Hz), 141.38 (d, *J* = 3.3 Hz), 133.02, 128.91 (d, *J* = 8.2 Hz, 2C), 123.16, 123.13, 115.41 (d, *J* = 21.4 Hz, 2C), 114.70 (d, *J* = 20.8 Hz), 114.13, 99.71 (d, *J* = 15.6 Hz), 21.51, 2.68, 1.30.

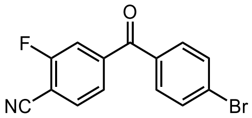
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3418, 2244, 1618, 1602, 1568, 1504, 1496, 1422, 1342, 1220, 1158, 1106, 1044, 996, 874, 824, 800, 736.

MS (EI, 70 eV): *m/z* (%) = 258 (16), 259 (100), 244 (12), 161 (11), 148 (18), 148 (59), 123 (25), 109 (26).

HRMS (EI): *m/z* calc. for [$C_{17}H_{13}F_2NO$]: 285.0965; found 285.0961.

m.p. (°C): 78.4-78.9.

4-(4-Bromobenzoyl)-2-fluorobenzonitrile (4cg)



According to TP1, a solution of 4-bromo-2-fluorobenzonitrile (0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 9 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-bromobenzoyl chloride (165 mg, 0.75 mmol, 1.5 equiv) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv) in THF. Stirring was continued for 2 h at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 97:3) afforded the title compound as a colorless crystals (112 mg, 0.37 mmol, 74% yield).

In addition, a sufficient scale-up of the reaction according to TP2 was demonstrated. A solution of 4-bromo-2-fluorobenzonitrile (0.20 M, 10 mmol) and $MgCl_2$·LiCl (0.10 M, 5 mmol, 0.5 equiv) in THF (total volume: 40 mL) and a solution of BuLi (0.30 M in hexane, 15 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 9 mL·min^{-1} flow-rate in a T-mixer over. The flow-rates were constant over a total runtime of 667 sec. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-bromobenzoyl chloride (3.30 g, 11 mmol, 1.1 equiv) in THF. Stirring was continued for 3 h at 0 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. 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 *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 92:8) afforded the title compound as colorless crystals (2.31 g, 7.6 mmol, 76%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.78 (dd, *J* = 7.8, 6.4 Hz, 1H), 7.71 – 7.56 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 192.6 (d, *J* = 1.7 Hz), 163.0 (d, *J* = 261.9 Hz), 143.4 (d, *J* = 6.5 Hz), 134.6, 133.9, 132.3 (2C), 131.5 (2C), 129.2, 125.8 (d, *J* = 3.9 Hz), 117.5 (d, *J* = 20.9 Hz), 113.2, 105.2 (d, *J* = 15.8 Hz).

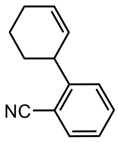
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2236, 1660, 1584, 1564, 1494, 1418, 1396, 1298, 1274, 1216, 1104, 1068, 1010, 896, 872, 858, 840, 826, 754, 686.

MS (EI, 70 eV): *m/z* (%) = 185 (13), 185 (97, 183 (13), 183 (100), 157 (19), 155 (19), 148 (15), 148 (10), 100 (11), 76 (10), 75 (10).

HRMS (EI): *m/z* calc. for [$C_{14}H_7BrFNO$]: 302.9695; found 302.9687.

m.p. (°C): 114.0-115.4.

1',2',3',4'-Tetrahydro-[1,1'-biphenyl]-2-carbonitrile (4dh)



According to the TP1, a solution of 2-iodobenzonitrile (0.20 M, 0.40 mmol) and $ZnCl_2$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 $mL\cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-bromocyclohexene (161 mg, 1.00 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 10 min at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 99:1) afforded the title compound as pale yellow oil (59 mg, 0.32 mmol, 80% yield).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 7.62 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.39 – 7.35 (m, 1H), 7.29 (td, *J* = 7.6, 1.2 Hz, 1H), 6.02 – 5.97 (m, 1H), 5.67 – 5.62 (m, 1H), 3.89 – 3.84 (m, 1H), 2.18 – 2.09 (m, 3H), 1.77 – 1.64 (m, 2H), 1.57 – 1.50 (m, 1H).

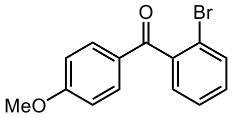
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 150.4, 133.0, 132.9, 130.1, 128.4, 128.1, 126.7, 118.2, 112.1, 40.2, 31.7, 25.0, 21.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 2932, 2860, 2838, 2222, 1684, 1652, 1598, 1480, 1446, 1432, 1346, 1322, 1296, 1284, 1248, 1206, 1164, 1136, 1094, 1046, 1038, 984, 956, 902, 884, 876, 848, 702, 760, 746, 722, 686, 662.

MS (EI, 70 eV): *m/z* (%) = 183 (79), 182 (100), 168 (37), 167 (19), 166 (21), 165 (21), 156 (11), 154 (43), 142 (14), 141 (10), 140 (30), 129 (30), 128 (18), 127 (18), 116 (22), 115 (25), 89 (14), 77 (20), 76 (11), 63 (16), 54 (14), 43 (13), 42 (11), 41 (31).

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}N$]: 182.0970; found 182.0960 ($M^+ - H$).

(2-Bromophenyl)(4-methoxyphenyl)methanone (4ei)



According to the TP1, a solution of 1-bromo-4-methoxybenzene (0.20 M, 0.50 mmol) and $MgCl_2\cdot LiCl$ (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 9 $mL\cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 5 mL reactor tube (12 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 2-bromobenzoyl chloride (165 mg, 0.75 mmol, 1.5 equiv) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv) in THF. Stirring was continued for 2 h at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 95:5) afforded the title compound as colorless crystals (98 mg, 0.34 mmol, 68% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.81 – 7.76 (m, 2H), 7.63 (ddd, J = 8.0, 1.1, 0.5 Hz, 1H), 7.40 (td, J = 7.4, 1.1 Hz, 1H), 7.35 – 7.30 (m, 2H), 6.95 – 6.91 (m, 2H), 3.87 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 194.6, 164.2, 141.2, 133.2, 132.8 (2C), 131.0, 129.2, 128.9, 127.3, 119.5, 114.0 (2C), 55.7.

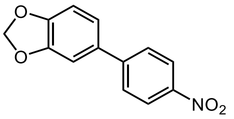
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2972, 2840, 1654, 1596, 1572, 1510, 1486, 1428, 1308, 1292, 1246, 1178, 1150, 1112, 1020, 926, 860, 822, 760, 734, 692, 654.

MS (EI, 70 eV): m/z (%) = 292 (16), 290 (16), 135 (100).

HRMS (EI): m/z calc. for [$C_{14}H_{11}BrO_2$]: 289.9942; found 289.9937.

m.p. (°C): 92.2-93.5.

5-(4-Nitrophenyl)benzo[*d*][1,3]dioxole (4fj)



According to the TP1, a solution of 5-bromobenzo[*d*][1,3]dioxole (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 18 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 5.0 mL reactor tube (16.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of $ZnCl_2$ (0.44 mL, 1.0 M in THF, 1.1 equiv) in THF. The mixture was stirred for 15 min and then PEPPSI-*i*Pr (5.4 mg, 2 mol%) and 1-iodo-4-nitrobenzene (149 mg, 0.60 mmol, 1.5 equiv) were added. Stirring was continued overnight at 25 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 99:1) afforded the title compound as a yellow solid (82 mg, 0.34 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 (dt, J = 9.0, 2.6, 2.0 Hz, 2H), 7.65 (dt, J = 9.0, 2.5, 2.0 Hz, 2H), 7.15 – 7.06 (m, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.04 (s, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.7, 148.6, 147.4, 146.9, 133.1, 127.5 (2C), 124.3 (2C), 121.6, 109.0, 107.7, 101.7.

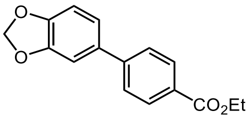
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2854, 1594, 1506, 1494, 1478, 1440, 1410, 1334, 1294, 1280, 1258, 1232, 1202, 1186, 1154, 1110, 1032, 1012, 974, 962, 926, 876, 846, 810, 752, 740, 720, 692, 658.

MS (EI, 70 eV): *m/z* (%) = 243 (100), 242 (11), 213 (24), 185 (15), 167 (11), 139 (76).

HRMS (EI): *m/z* calc. for [$C_{13}H_9NO_4$]: 243.0532; found 243.0527.

m.p. (°C): 124.0 – 124.9.

Ethyl 4-(benzo[*d*][1,3]dioxol-5-yl)benzoate (4fk)



According to the TP1, a solution of 5-bromobenzo[*d*][1,3]dioxole (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 18 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 5.0 mL reactor tube (16.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of $ZnCl_2$ (0.44 mL, 1.0 M in THF, 1.1 equiv) in THF. The mixture was stirred for 15 min and then PEPPSI-*i*Pr (5.4 mg, 2 mol%) and ethyl 4-iodobenzoate (166 mg, 0.60 mmol, 1.5 equiv) were added. Stirring was continued overnight at 25 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 24:1) afforded the title compound as colorless crystals (75 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.07 (dt, *J* = 8.6, 2.2 Hz, 2H), 7.57 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.13 – 7.05 (m, 2H), 6.95 – 6.81 (m, 1H), 6.01 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 166.6, 148.4, 147.9, 145.3, 134.4, 130.2 (2C), 129.0, 126.7 (2C), 121.1, 108.8, 107.8, 101.4, 61.1, 14.5.

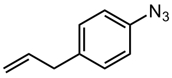
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2986, 2942, 2902, 2788, 1704, 1604, 1522, 1502, 1484, 1440, 1410, 1368, 1314, 1288, 1270, 1254, 1234, 1180, 1148, 1102, 1034, 1020, 1010, 932, 890, 856, 848, 812, 768, 738, 700, 656.

MS (EI, 70 eV): *m/z* (%) = 271 (18), 270(100), 242 (51), 241 (28), 226 (11), 225 (75), 197 (11), 139(61).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}O_4$]: 270.0892; found 270.0887.

m.p. (°C): 92.9 – 93.2.

1-Allyl-4-azidobenzene (7aa)



According to the TP1, a solution of 1-azido-4-iodobenzene (0.20 M, 1.00 mmol) and $ZnCl_2$ (0.10 M, 0.50 mmol, 0.5 equiv) in THF (total volume: 5.00 mL) and a solution of BuLi (0.30 M in hexane, 1.50 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 $mL\cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of allyl bromide (0.22 mL, 2.5 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 1.5 h at −40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×60 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 as a pale yellow oil (114 mg, 0.72 mmol, 72% yield).

Scale-up of the reaction was achieved according to the TP1. A solution of azido-4-iodobenzene (0.20 M, 4.90 mmol) and $ZnCl_2$ (0.10 M, 2.45 mmol, 0.5 equiv) in THF (total volume: 24.50 mL) and a solution of BuLi (0.30 M in hexane, 7.35 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 $mL\cdot min^{-1}$ flow-rate in a T-mixer over a total runtime of 250 sec. The combined stream passed a 0.25 mL reactor tube (1.25 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of allyl bromide (1.06 mL, 12.25 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.49 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 1 h at −40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×150 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 as a pale yellow oil (464 mg, 2.91 mmol, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.17 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.3 Hz, 2H), 6.02 – 5.87 (m, 1H), 5.12 – 5.06 (m, 1H), 5.10 – 5.02 (m, 1H), 3.40 – 3.33 (m, 2H).

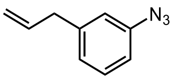
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 138.0, 137.3, 137.0, 130.1 (2C), 119.2 (2C), 116.2, 39.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2108, 1611, 1510, 1505, 1434, 1357, 1284, 1184, 1120, 1082, 994, 805, 735.

MS (EI, 70 eV): *m/z* (%) = 159(20), 132(15), 131(100), 130(82), 128(17), 127(12), 116(18), 104(23), 103(28), 97(13), 95(14), 91(15), 85(13), 83(14), 81(14), 78(23), 77(20), 71(17), 69(21), 63(11), 57(21), 55(13), 41(28), 40(15).

HRMS (EI): *m/z* calc. for [$C_9H_9N_3$]: 159.0796; found 159.0788.

3-Allyl-4-azidobenzene (7ba)



According to the TP1, a solution of 1-azido-4-iodobenzene (0.20 M, 1.00 mmol) and $ZnCl_2$ (0.10 M, 0.50 mmol, 0.5 equiv) in THF (total volume: 5.00 mL) and a solution of BuLi (0.30 M in hexane, 1.50 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of allyl bromide (0.22 mL, 2.5 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 1.5 h at −40 °C before *sat. aq.* NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted three times with EtOAc (3×60 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 as a pale yellow oil (132 mg, 0.83 mmol, 83%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 7.28 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.86 (s, 1H), 5.95 (ddt, *J* = 18.8, 9.5, 6.7 Hz, 1H), 5.12 (s, 1H), 5.14 – 5.06 (m, 1H), 3.38 (d, *J* = 6.7 Hz, 2H).

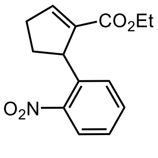
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 142.2, 140.2, 136.8, 129.9, 125.4, 119.3, 116.9, 116.6, 40.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3047, 2924, 2108, 1603, 1558, 1483, 1444, 1356, 1288, 1203, 1168, 1101, 1073, 1021, 994, 941, 914, 885, 775, 695.

MS (EI, 70 eV): *m/z* (%) = 133(17), 132(27), 131(100), 116(24), 115(17), 111(17), 106(19), 104(26), 103(23), 97(23), 91(30), 85(23), 83(28), 78(23), 77(50), 71(27), 69(32), 65(16), 57(43), 55(26), 51(16), 44(59), 43(27), 41(36).

HRMS (EI): *m/z* calc. for [$C_9H_9N_3$]: 159.0796; found 159.0791.

Ethyl 5-(2-nitrophenyl)cyclopent-1-ene-1-carboxylate (7cl)



According to the TP1, a solution of 1-bromo-2-nitrobenzene (0.20 M, 0.40 mmol) and $ZnCl_2$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of ethyl 5-bromocyclopent-1-ene-1-carboxylate (131 mg, 0.60 mmol, 1.5 equiv) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv) in THF.

Stirring was continued for 1 h at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound as a brown-red oil (81 mg, 0.31 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.12 – 7.06 (m, 1H), 4.72 – 4.54 (m, 1H), 4.07 – 3.91 (m, 2H), 2.82 – 2.53 (m, 2H), 1.98 – 1.88 (m, 1H), 1.33 – 1.17 (m, 1H), 1.03 (t, *J* = 7.1 Hz, 3H).

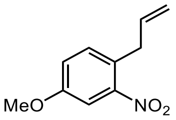
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.3, 149.5, 146.6, 140.1, 138.3, 133.0, 128.2, 127.0, 124.3, 60.3, 45.4, 33.8, 32.1, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2936, 2906, 2872, 1758, 1710, 1634, 1608, 1578, 1522, 1478, 1446, 1352, 1292, 1266, 1204, 1188, 1140, 1098, 1032, 1018, 956, 930, 902, 852, 824, 784, 746, 708, 684, 662.

MS (EI, 70 eV): *m/z* (%) = 216 (79), 205 (15), 198 (20), 188 (26), 187 (24), 185 (30), 172 (80), 171 (49), 170 (100), 169 (15), 168 (21), 161 (16), 160 (37), 159 (16), 157 (21), 155 (18), 154 (53), 146 (16), 145 (89), 144 (22), 143 (38), 142 (40), 141 (59), 140 (18), 139 (34), 130 (30), 129 (37), 128 (52), 127 (32), 117 (21), 116 (22), 115 (98), 77 (17), 55 (32).

HRMS (EI): *m/z* calc. for [$C_{12}H_{10}NO_3$]: 216.0661; found 216.0669 ($M^+ - C_2H_5O$).

1-Allyl-4-methoxy-2-nitrobenzene (7da)



According to the TP1, a solution of 1-bromo-4-methoxy-2-nitrobenzene (0.20 M, 0.40 mmol) and $ZnCl_2$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.10 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (121 mg, 1.0 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 10 min at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 49:1) afforded the title compound as a red-brown oil (56 mg, 0.29 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.44 (d, *J* = 2.7 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.09 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.04 – 5.79 (m, 1H), 5.22 – 4.92 (m, 2H), 3.85 (s, 3H), 3.61 (dt, *J* = 6.4, 1.5 Hz, 2H).

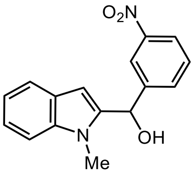
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 158.5, 149.7, 135.6, 132.9, 126.9, 119.9, 116.8, 109.4, 55.9, 36.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 2942, 2840, 1640, 1622, 1572, 1524, 1498, 1462, 1440, 1410, 1348, 1322, 1286, 1248, 1186, 1146, 1066, 1034, 996, 916, 856, 832, 810, 792, 760, 738, 676.

MS (EI, 70 eV): *m/z* (%) = 192 (11), 176 (70), 175 (19), 164 (41), 163 (15), 161 (15), 160 (10), 159 (100), 148 (15), 147 (11), 146 (35), 133 (56), 132 (15), 131 (29), 130 (10), 129 (28), 117 (14), 115 (24), 105 (18), 103 (57), 102 (11), 91 (16), 89 (11), 78 (10), 88 (26).

HRMS (EI): *m/z* calc. for [$C_{10}H_{11}NO_3$]: 193.0739; found 193.0732.

(1-Methyl-1*H*-indol-2-yl)(3-nitrophenyl)methanol (7em)



According to the TP1, a solution of 1-iodo-3-nitrobenzene (0.20 M, 0.40 mmol) and MgCl$_2$·LiCl (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 20 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 1-methyl-1*H*-indole-3-carbaldehyde (96 mg, 0.60 mmol, 1.5 equiv) in THF. Stirring was continued for 1.5 h at 0 °C before *sat. aq.* NH$_4$Cl 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 *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 4:1) afforded the title compound as a red gel (67 mg, 0.24 mmol, 60% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.44 – 8.28 (m, 1H), 8.14 – 7.99 (m, 1H), 7.92 – 7.73 (m, 1H), 7.59 – 7.43 (m, 2H), 7.40 – 7.20 (m, 2H), 7.17 – 7.04 (m, 1H), 6.85 (s, 1H), 6.19 (s, 1H), 3.74 (s, 3H), 2.62 – 2.49 (m, 1H).

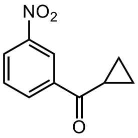
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 148.4, 146.1, 137.6, 132.5, 129.2, 127.7, 125.9, 122.5, 122.3, 121.4, 119.9, 119.5, 117.2, 109.7, 69.2, 32.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2932, 2826, 1702, 1614, 1582, 1524, 1474, 1446, 1424, 1370, 1346, 1330, 1252, 1234, 1200, 1156, 1130, 1090, 1062, 1036, 1012, 906, 806, 788, 730, 684.

MS (EI, 70 eV): *m/z* (%) = 283 (20), 282 (100), 266 (16), 265 (64), 219 (16), 218 (18), 160 (38), 158 (16), 132 (39), 129 (10), 117 (15).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}N_2O_3$]: 282.1004; found 282.0997.

Cyclopropyl(3-nitrophenyl)methanone (7en)



According to the TP1, a solution of 1-iodo-3-nitrobenzene (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 20 $mL \cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropanecarbonyl chloride (63 mg, 0.60 mmol, 1.5 equiv) and $CuCN \cdot 2LiCl$ solution (0.44 mL, 1.0 M in THF, 1.1 equiv) in THF. Stirring was continued for 1.5 h at 0 °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 *in vacuo*, purification *via* HPLC afforded the title compound as a white solid (48 mg, 0.25 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.84 (t, J = 1.9 Hz, 1H), 8.42 (dq, J = 8.2, 2.3, 1.1 Hz, 1H), 8.32 (dq, J = 7.8, 1.6, 1.1 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 2.81 – 2.58 (m, 1H), 1.37 – 1.26 (m, 2H), 1.20 – 1.08 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 198.5, 148.5, 139.3, 133.7, 129.9, 127.2, 123.1, 17.7, 12.7 (2C).

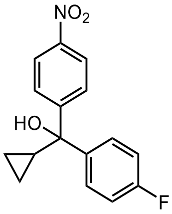
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3094, 1662, 1614, 1580, 1526, 1476, 1440, 1418, 1384, 1350, 1316, 1282, 1222, 1172, 1110, 1080, 1046, 1016, 1000, 922, 894, 878, 850, 822, 802, 752, 716, 686, 664.

MS (EI, 70 eV): *m/z* (%) = 150 (150), 104 (19), 76 (12).

HRMS (EI): *m/z* calc. for $[C_{10}H_8NO_3]$: 190.0504; found 190.0497 (M^+ – H).

m.p. (°C): 73.9 – 75.0.

Cyclopropyl(4-fluorophenyl)(4-nitrophenyl)methanol (7fo)



According to the TP1, a solution of 1-iodo-4-nitrobenzene (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 16 $mL \cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.08 s, −60 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl-4-fluorophenyl)methanone (99 mg, 0.60 mmol, 1.5 equiv) in THF. Stirring was continued for 1.5 h at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 9:1) afforded the title compound as an orange oil (82 mg, 0.29 mmol, 73% yield).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.15 (dt, J = 9.0, 2.0 Hz, 2H), 7.57 (dt, J = 9.0, 2.1 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.05 – 6.98 (m, 2H), 1.98 (s, 1H), 1.63 – 1.57 (m, 1H), 0.77 – 0.69 (m, 1H), 0.59 – 0.50 (m, 2H), 0.50 – 0.45 (m, 1H).

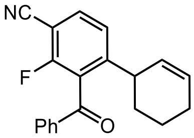
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 162.3 (d, J = 247.3 Hz), 154.5, 147.0, 141.2, 129.0 (d, J = 8.1 Hz, 2C), 127.6 (2C), 123.3 (2C), 115.3 (d, J = 21.3 Hz, 2C), 76.6, 21.7, 2.6, 1.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3538, 3082, 3010, 1602, 1506, 1424, 1408, 1346, 1316, 1224, 1160, 1108, 1098, 1026, 1014, 988, 964, 930, 906, 878, 852, 830, 804, 750, 708, 696.

MS (EI, 70 eV): *m/z* (%) = 260 (15), 259 (100), 246 (14), 183 (11), 165 (11), 150 (37), 123 (37), 109 (13).

HRMS (EI): *m/z* calc. for [$C_{16}H_{13}FNO_3$]: 286.0879; found 286.0868 (M^+ – H).

2-Benzoyl-3-fluoro-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-4-carbonitrile (7gh)



According to the TP1, a solution of 3-benzoyl-4-bromo-2-fluorobenzonitrile (0.20 M, 0.40 mmol) and $ZnCl_2$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 20 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-bromocyclohexene (161 mg, 1.00 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 30 min at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 19:1) afforded the title compound as a colorless oil (94 mg, 0.31 mmol, 78% yield).

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 7.80 (dd, J = 8.2, 1.1 Hz, 2H), 7.68 – 7.64 (m, 2H), 7.52 – 7.49 (m, 2H), 7.31 (d, J = 8.2 Hz, 1H), 5.95 – 5.90 (m, 1H), 5.52 (dd, J = 10.5, 2.1 Hz, 1H), 3.41 – 3.34 (m, 1H), 2.10 – 1.99 (m, 2H), 1.96 – 1.90 (m, 1H), 1.71 – 1.65 (m, 1H), 1.52 – 1.41 (m, 2H).

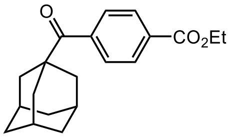
^{13}C-NMR (201 MHz, CDCl$_3$): δ / ppm = 192.4, 160.2, 158.9, 153.3, 136.7, 134.8, 133.9, 130.6, 129.6 (2C), 129.2 (2C), 127.8, 125.0, 113.7, 99.4, 39.2, 32.0, 24.7, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3026, 2934, 2862, 2838, 2236, 1672, 1614, 1596, 1562, 1476, 1448, 1428, 1392, 1344, 1316, 1284, 1248, 1174, 1160, 1136, 1074, 1056, 1012, 1002, 984, 954, 910, 896, 868, 834, 772, 760, 728, 714, 686, 676.

MS (EI, 70 eV): *m/z* (%) = 305 (11), 287 (40), 272 (16), 258 (13), 250 (21), 210 (14), 209 (100), 208 (48), 207 (13), 91 (18), 77 (10).

HRMS (EI): *m/z* calc. for [$C_{20}H_{16}FNO$]: 305.1216; found 305.1210.

Ethyl 4-(adamantane-1-carbonyl)benzoate (7hp)



According to the TP1, a solution of ethyl 4-iodobenzoate (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 16 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of 1-adamantanecarbonyl chloride (119 mg, 0.60 mmol, 1.5 equiv) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv) in THF. Stirring was continued for 2 h 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 *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 99:1) afforded the title compound **7i** as a colorless oil (86 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.05 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 2.09 – 2.04 (m, 3H), 2.00 – 1.92 (m, 6H), 1.79 – 1.66 (m, 6H), 1.40 (t, J = 7.1 Hz, 3H).

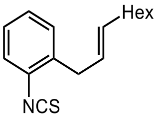
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 210.3, 166.1, 144.0, 131.7, 129.3 (2C), 126.8 (2C), 61.4, 47.1, 39.0 (3C), 36.6 (3C), 28.1 (3C), 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2904, 2850, 2167, 1717, 1674, 1608, 1569, 1503, 1475, 1452, 1400, 1367, 1345, 1269, 1231, 1198, 1179, 1161, 1021, 988, 951, 931, 860, 829, 776, 767, 716, 696, 662.

MS (EI, 70 eV): *m/z* (%) = 312 (13), 136 (25), 135 (100), 93 (18), 79 (21).

HRMS (EI): *m/z* calc. for [$C_{20}H_{24}O_3$]: 312.1725; found 312.1721.

1-Isothiocyanato-2-(non-1-en-3-yl)benzene (7iq)



According to the TP1, a solution of 1-bromo-2-isothiocyanatobenzene (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 16 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of (*E*)-1-bromonon-2-ene (123 mg, 0.60 mmol, 1.5 equiv) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 1.1 equiv) in THF. Stirring was continued for 1 h at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane) afforded the title compound as a pale yellow oil (70 mg, 0.27 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.18 (m, 4H), 5.60 – 5.45 (m, 2H), 3.40 (d, *J* = 5.6 Hz, 2H), 2.03 (q, *J* = 6.4 Hz, 2H), 1.38 – 1.21 (m, 8H), 0.91 – 0.83 (m, 3H).

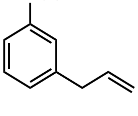
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 137.7, 133.6, 130.1, 127.6, 127.6, 127.3, 126.5, 126.4, 35.6, 32.7, 31.9, 29.5, 29.0, 22.8, 22.8, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2924, 2870, 2854, 2176, 2076, 1598, 1578, 1484, 1450, 1378, 966, 934, 904, 752, 724, 672.

MS (EI, 70 eV): *m/z* (%) = 258 (61), 226 (92), 216 (23), 202 (32), 188 (30), 174 (33), 170 (17), 168 (22), 163 (48), 162 (100), 161 (45), 156 (42), 155 (30), 154 (34), 149 (64), 148 (60), 130 (54), 129 (26), 128 (33), 121 (15), 118 (20), 117 (31), 116 (26), 115 (32).

HRMS (EI): *m/z* calc. for [$C_{16}H_{20}NS$]: 258.1316; found 258.1312 (M^+ – H).

1-Allyl-3-isothiocyanatobenzene (7ja)



According to the TP1, a solution of 1-bromo-3-isothiocyanatobenzene (0.20 M, 0.50 mmol) and $ZnCl_2$ (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 18 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.022 mL reactor tube (0.07 s, −60 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (151 mg, 1.25 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 30 min at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane) afforded the title compound as a colorless oil (57 mg, 0.33 mmol, 65% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.27 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.11 (dddd, *J* = 7.7, 1.5, 1.0, 0.4 Hz, 1H), 7.09 – 7.04 (m, 2H), 5.93 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.15 – 5.06 (m, 2H), 3.37 (dtd, *J* = 6.8, 1.4, 0.7 Hz, 2H).

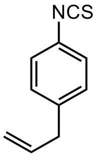
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.06, 136.36, 136.36, 131.36, 129.59, 127.83, 126.00, 123.51, 116.88, 39.82.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2978, 2906, 2246, 2050, 2042, 1640, 1600, 1580, 1482, 1438, 1410, 1292, 1164, 1080, 992, 916, 898, 822, 780, 702, 680, 654.

MS (EI, 70 eV): *m/z* (%) = 175 (74), 174 (12), 118 (10), 117 (100), 116 (22), 115 (70).

HRMS (EI): *m/z* calc. for [$C_{10}H_9NS$]: 175.0456; found 175.0448.

1-Allyl-4-isothiocyanatobenzene (7ka)



According to the TP1, a solution of 1-bromo-4-isothiocyanatobenzene (0.20 M, 0.50 mmol) and $ZnCl_2$ (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 9 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.022 mL reactor tube (0.15 s, −60 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (151 mg, 1.25 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 30 min at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane) afforded the title compound as a colorless oil (59 mg, 0.34 mmol, 67% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.16 (d, *J* = 0.7 Hz, 4H), 5.93 (ddt, *J* = 16.8, 10.2, 6.7 Hz, 1H), 5.13 – 5.04 (m, 2H), 3.38 (dt, *J* = 6.7, 1.5 Hz, 2H).

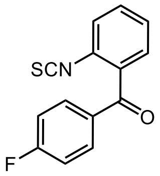
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.73, 136.61 (2C), 129.85 (3C), 125.85 (2C), 116.66, 39.86.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 2978, 2902, 2180, 2050, 2042, 1638, 1604, 1502, 1432, 1418, 1294, 1248, 1196, 1106, 992, 916, 838, 800, 722, 676.

MS (EI, 70 eV): *m/z* (%) = 176 (11), 175 (100), 148 (22), 117 (93), 116 (24), 115 (59).

HRMS (EI): *m/z* calc. for [$C_{10}H_9NS$]: 175.0456; found 175.0449.

(4-Fluorophenyl)(2-isothiocyanatophenyl)methanone (7lr)



According to the TP1, a solution of 1-bromo-2-isothiocyanatobenzene (0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 16 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-fluorobenzoyl chloride (95 mg, 0.60 mmol, 1.5 equiv) and $CuCN \cdot 2LiCl$ solution (0.44 mL, 1.0 M in THF, 1.1 equiv) in THF. Stirring was continued for 1.5 h at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane:EtOAc = 24:1) afforded the title compound as a light yellow oil (64 mg, 0.25 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.89 – 7.81 (m, 2H), 7.56 – 7.45 (m, 2H), 7.41 – 7.33 (m, 2H), 7.21 – 7.13 (m, 2H).

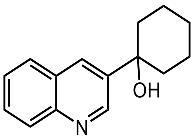
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.0, 166.3 (d, *J* = 256.2 Hz), 135.0, 133.2 (d, *J* = 3.0 Hz, 2C), 132.8, 132.9, 132.1, 130.1, 129.8, 127.5, 127.1, 116.1 (d, *J* = 22.1 Hz, 2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 2926, 2166, 2062, 1662, 1594, 1572, 1532, 1504, 1478, 1444, 1410, 1378, 1304, 1288, 1262, 1230, 1200, 1148, 1102, 1094, 1042, 1012, 938, 926, 890, 848, 816, 778, 752, 734, 706, 678, 660.

MS (EI, 70 eV): *m/z* (%) = 257 (56), 256 (33), 197 (53), 162 (90), 134 (36), 123 (19), 123 (100), 95 (17), 75 (12).

HRMS (EI): *m/z* calc. for [$C_{14}H_8FNOS$]: 257.0311; found 257.0304.

1-(Quinolin-3-yl)cyclohexanol (10as)



According to the TP1, a solution of 3-bromoquinoline (42 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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 a flask containing a stirred solution of cyclohexanone (30 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as white solid (28 mg, 0.12 mmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.02 (d, *J* = 2.3 Hz, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 2.35 (s, 1H), 1.96 – 1.75 (m, 7H), 1.72 – 1.65 (m, 2H), 1.40 – 1.25 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 149.1, 147.1, 142.0, 131.3, 129.2, 129.0, 128.1, 127.8, 126.8, 72.4, 38.8 (2C), 25.4, 22.1 (2C).

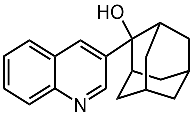
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3153, 3059, 2926, 2900, 2851, 1574, 1495, 1448, 1427, 1369, 1267, 1235, 1183, 1151, 1131, 1041, 982, 972, 967, 961, 918, 896, 817, 785, 749.

MS (EI, 70 eV): *m/z* (%) = 227 (13), 225 (21), 209 (38), 208 (21), 207 (14), 205 (29), 204 (24), 194 (19), 185 (13), 184 (100), 181 (12), 180 (77), 171 (43), 168 (10), 167 (27), 166 (18), 156 (53), 154 (10), 152 (10), 142 (10), 130 (11), 128 (51), 115 (13).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}NO$]: 227.1310; found 227.1315.

m.p. (°C): 153.5 – 155.0.

2-(Quinolin-3-yl)adamantan-2-ol (10at)



According to the TP1, a solution of 3-bromoquinoline (42 mg, 0.20 M, 0.20 mmol) and $MgCl_2$·LiCl (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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 a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as white solid (40 mg, 0.143 mmol, 72% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 9.13 (d, *J* = 2.4 Hz, 1H), 8.23 (d, *J* = 2.2 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 2.73 (s, 2H), 2.47 (d, *J* = 11.9 Hz, 2H), 1.99 – 1.94 (m, 1H), 1.86 – 1.71 (m, 9H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 149.6, 147.4, 137.9, 132.8, 129.6, 129.1, 128.2 (2C), 126.9, 75.3, 37.7, 35.8 (2C), 35.0 (2C), 32.9 (2C), 27.6, 26.9.

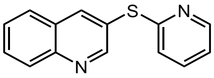
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2907, 2896, 2889, 1493, 1104, 1089, 1052, 1026, 921, 907, 783, 747.

MS (EI, 70 eV): *m/z* (%) = 278 (18), 260 (15), 253 (24), 251 (14), 227 (19), 226 (12), 225 (100), 209 (36), 207 (51), 191 (11), 150 (27), 129 (59), 128 (19), 102 (15), 91 (13), 80 (12), 79 (30), 78 (16), 42 (15).

HRMS (EI): *m/z* calc. for [$C_{19}H_{20}NO$]: 278.1550; found 278.1540 (M – H).

m.p. (°C): 239.1 – 240.0.

3-(Pyridin-2-ylthio)quinoline (10au)



According to the TP1, a solution of 3-bromoquinoline (42 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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 a flask containing a stirred solution of 1,2-di(pyridin-2-yl)disulfane (66 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 9:1 → 8:2 → 7:3) afforded the title compound as yellow solid (42 mg, 0.18 mmol, 88% yield).

^{1}H-NMR (600 MHz, CDCl$_3$): δ / ppm = 8.97 (d, *J* = 2.2 Hz, 1H), 8.42 (d, *J* = 1.9 Hz, 1H), 8.42 – 8.40 (m, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.83 – 7.81 (m, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.59 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.5, 1.9 Hz, 1H), 7.07 – 7.03 (m, 2H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ / ppm = 159.5, 154.9, 150.0, 147.6, 141.9, 137.0, 130.6, 129.6, 128.4, 127.9, 127.4, 125.3, 122.0, 120.8.

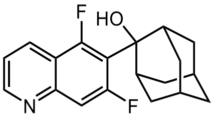
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3043, 2985, 1568, 1556, 1488, 1443, 1419, 1370, 1352, 1324, 1277, 1256, 1227, 1150, 1144, 1123, 1086, 1043, 1017, 984, 960, 946, 916, 866, 788, 761, 750, 724.

MS (EI, 70 eV): *m/z* (%) = 238 (13), 237 (100).

HRMS (EI): *m/z* calc. for [$C_{14}H_9N_2S$]: 237.0492; found 237.0483 (M – H).

m.p. (°C): 90.9 – 92.8.

2-(5,7-Difluoroquinolin-6-yl)adamantan-2-ol (10bt)



According to the TP1, a solution of 6-bromo-5,7-difluoroquinoline (49 mg, 0.20 M, 0.20 mmol) and $MgCl_2\cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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 a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 8:2) afforded the title compound as white solid (60 mg, 0.19 mmol, 95% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.90 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.36 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.54 (d, *J* = 14.8 Hz, 1H), 7.40 (dd, *J* = 8.5, 4.3 Hz, 1H), 2.94 (s, 2H), 2.63 (s, 1H), 2.44 (d, *J* = 10.9 Hz, 2H), 1.93-1.84 (m, 4H), 1.77 (s, 3H), 1.70 (d, *J* = 12.1 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.8 (dd, *J* = 252.9, 12.5 Hz), 155.9 (dd, *J* = 259.7, 11.8 Hz), 152.5, 147.2 (dd, *J* = 16.7, 6.0 Hz), 130.3 (dd, *J* = 8.5, 1.8 Hz), 120.9 (t, *J* = 2.8 Hz), 119.9 (dd, *J* = 16.9, 13.1 Hz), 117.4 (dd, *J* = 21.0, 1.2 Hz), 110.9 (dd, *J* = 26.7, 4.2 Hz), 79.9 (dd, *J* = 3.2, 2.3 Hz), 37.6 (3C), 33.2 (2C), 26.6 (3C), 26.5.

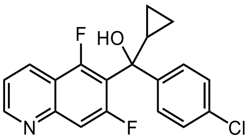
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3311, 3280, 2968, 2937, 2915, 2897, 2891, 2848, 1633, 1626, 1576, 1483, 1457, 1406, 1382, 1369, 1358, 1353, 1328, 1285, 1272, 1193, 1177, 1164, 1103, 1084, 1057, 1049, 1033, 1026, 1014, 1000, 971, 939, 853, 820, 805, 760.

MS (EI, 70 eV): *m/z* (%) = 315 (87), 298 (14), 297 (57), 220 (22), 219 (24), 207 (16), 195 (31), 194 (100), 193 (14), 192 (99), 179 (14), 178 (27), 166 (12), 165 (30), 164 (16), 121 (23), 93 (16), 91 (11), 81 (28), 80 (17), 79 (35), 77 (11), 67 (21), 43 (20), 41 (18).

HRMS (EI): *m/z* calc. for [$C_{19}H_{19}F_2NO$]: 315.1435; found 315.1430.

m.p. (°C): 201.5 – 202.9.

(4-Chlorophenyl)(cyclopropyl)(5,7-difluoroquinolin-6-yl)methanol (10bf)



According to the TP1, a solution of 6-bromo-5,7-difluoroquinoline (49 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 $mL \cdot min^{-1}$ 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 a flask containing a stirred solution of (4-chlorophenyl)(cyclopropyl)methanone (54 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 8:2) afforded the title compound as white solid (66 mg, 0.19 mmol, 95% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.94 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.42 – 8.40 (m, 1H), 7.54 (d, *J* = 13,3 Hz, 1H), 7.46 (dd, *J* = 8.5, 4.3 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.31 – 7.27 (m, 2H), 3.17 (dd, *J* = 7.7, 3.4 Hz, 1H), 1.92-1.84 (m, 1H), 0.79-0.73 (m, 1H), 0.69-0.58 (m, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.2 (dd, *J* = 250.2, 10.3 Hz), 155.4 (dd, *J* = 258.9, 10.3 Hz), 152.7, 147.6 (dd, *J* = 16.1, 5.4 Hz), 145.0, 133.4, 130.2 (dd, *J* = 7.2, 1.8 Hz), 128.4 (2C), 127.1 (2C), 121.2 (t, *J* = 2.7 Hz), 120.7 (dd, *J* = 17.3, 12.6 Hz), 117.1 (d, *J* = 19.3 Hz), 110.6 (dd, *J* = 24.6, 4.5 Hz), 77.3 (d, *J* = 2.5 Hz), 22.1 (dd, *J* = 7.4, 2.7 Hz), 2.5 (t, *J* = 2.9 Hz, 2C).

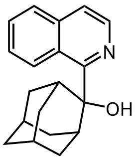
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1642, 1580, 1488, 1380, 1366, 1328, 1171, 1143, 1106, 1102, 1092, 1055, 1021, 1011, 974, 849, 837, 829, 818, 812, 804, 762.

MS (EI, 70 eV): *m/z* (%) = 319 (34), 318 (20), 317 (100), 192 (54), 165 (12), 164 (12), 139 (20), 111 (11), 43 (17).

HRMS (EI): *m/z* calc. for [$C_{19}H_{14}ClF_2NO$]: 345.0732; found 345.0741.

m.p. (°C): 170.6 – 172.0.

2-(Isoquinolin-1-yl)adamantan-2-ol (10ct)



According to the TP1, a solution of 1-iodoisoquinoline (**1c**, 51 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 $mL \cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a

0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 9:1) afforded the title compound as white solid (41 mg, 0.15 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.92 (d, J = 8.8 Hz, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.60 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.52 – 7.48 (m, 2H), 2.82 (s, 2H), 2.57 (d, J = 10.9 Hz, 2H), 2.20 (s, 1H), 2.06 – 2.00 (m, 3H), 1.78 – 1.71 (m, 7H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.4, 139.8, 137.8, 129.2, 128.5, 127.7, 126.6, 125.8, 120.6, 80.5, 47.1, 39.4, 38.2, 38.0 (2C), 35.2, 33.6, 27.7, 27.4.

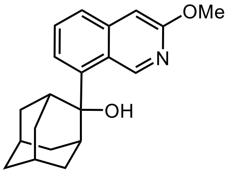
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3424, 3052, 2951, 2939, 2932, 2920, 2903, 2894, 2848, 1619, 1590, 1556, 1467, 1451, 1442, 1350, 1342, 1315, 1310, 1304, 1286, 1174, 1137, 1103, 1073, 1044, 1035, 1013, 992, 962, 938, 914, 867, 820, 805, 799, 744, 694, 681, 665.

MS (EI, 70 eV): *m/z* (%) = 279 (21), 278 (100), 260 (80), 253 (18), 225 (70), 218 (26), 209 (26), 207 (67), 204 (18), 184 (27), 180 (26), 168 (24), 167 (29), 166 (23), 156 (28), 150 (31), 146 (17), 143 (21), 130 (29), 129 (87), 128 (63), 102 (22), 91 (19), 79 (38), 77 (17).

HRMS (EI): *m/z* calc. for [$C_{19}H_{20}NO$]: 278.1550; found 278.1544 (M – H).

m.p. (°C): 174.1 – 176.0.

2-(3-Methoxyisoquinolin-8-yl)adamantan-2-ol (10dt)



According to the TP1, a solution of 8-bromo-3-methoxyisoquinoline (48 mg, 0.20 M, 0.20 mmol) and $MgCl_2\cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 8:2) afforded the title compound as white crystals (45 mg, 0.5 mmol, 73% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 9.97 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 6.96 (s, 1H), 4.02 (s, 3H), 2.80 (s, 2H), 2.63 (d, *J* = 12.6 Hz, 2H), 2.06 (s, 1H), 1.96 – 1.93 (m, 1H), 1.82 – 1.67 (m, 9H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 160.2, 151.2, 142.4, 141.6, 128.8, 126.3, 123.6, 123.3, 102.0, 77.9, 54.2, 38.4 (2C), 37.9 (2C), 33.5, 27.8 (2C), 27.1 (2C).

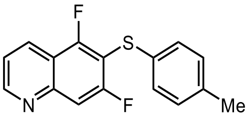
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3411, 2956, 2935, 2913, 2902, 2887, 2855, 2845, 1618, 1592, 1484, 1462, 1447, 1427, 1381, 1339, 1321, 1308, 1289, 1257, 1250, 1225, 1188, 1162, 1147, 1103, 1095, 1077, 1037, 1017, 1007, 996, 965, 948, 869, 805, 762, 736, 704, 664.

MS (EI, 70 eV): *m/z* (%) = 309 (19), 291 (21), 290 (12), 188 (17), 187 (12), 186 (100), 172 (14), 165 (12), 160 (31), 159 (26), 158 (27), 157 (26), 150 (20), 129 (10), 115 (12), 91 (20), 81 (11), 80 (13), 79 (42), 77 (16).

HRMS (EI): *m/z* calc. for [$C_{20}H_{23}NO_2$]: 309.1729; found 309.1725.

m.p. (°C): 190.0 – 193.2.

5,7-Difluoro-6-(*p*-tolylthio)quinoline (10bv)



According to the TP1, a solution of 6-bromo-5,7-difluoroquinoline (49 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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 a flask containing a stirred solution of 1,2-di-tolyldisulfane (74 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 8:2) afforded the title compound as yellow solid (42 mg, 0.146 mmol, 73% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.95 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.37 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.63 (dd, *J* = 9.6, 1.1 Hz, 1H), 7.44 (dd, *J* = 8.5, 4.3 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 2.30 (s, 3H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 161.9 (dd, *J* = 250.9, 5.5 Hz), 158.9 (dd, *J* = 257.4, 6.7 Hz), 152.9, 148.5 (dd, *J* = 14.2, 4.9 Hz), 137.6, 130.8 (2C), 130.4 (3C), 130.1, 129.8 (dd, *J* = 4.2, 2.1 Hz), 121.1 (t, *J* = 2.7 Hz), 116.6 (dd, *J* = 18.0, 1.7 Hz), 110.0 (dd, *J* = 23.2, 4.8 Hz), 21.2.

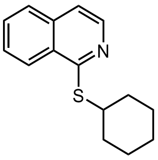
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2853, 1628, 1589, 1573, 1555, 1490, 1483, 1455, 1431, 1397, 1376, 1362, 1342, 1333, 1302, 1280, 1203, 1162, 1146, 1116, 1088, 1082, 1041, 1018, 1013, 850, 837, 804, 758, 703, 695.

MS (EI, 70 eV): *m/z* (%) = 287 (71), 286 (10), 269 (16), 268 (72), 267 (40), 266 (27), 254 (10), 253 (30), 143 (26), 91 (31), 85 (11), 83 (11), 69 (16), 65 (18), 57 (22), 55 (22), 43 (22), 41 (18).

HRMS (EI): *m/z* calc. for [$C_{16}H_{11}F_2NS$]: 287.0580; found 287.0583.

m.p. (°C): 99.5 – 101.5.

1-(Cyclohexylthio)isoquinoline (10cw)



According to the TP1, a solution of 1-iodoisoquinoline (51 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of dicyclohexyldisulfide (69 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 98:2 → 19:1) afforded the title compound as pale yellow oil (44 mg, 0.18 mmol, 90% yield).

^{1}H-NMR (600 MHz, CDCl$_3$): δ / ppm = 8.30 (d, *J* = 5.7 Hz, 1H), 8.22 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.64 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.54 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.32 (d, *J* = 5.7 Hz, 1H), 4.17-4.13 (m, 1H), 2.18-2.15 (m, 2H), 1.83-1.79 (m, 2H), 1.68-1.65 (m, 1H), 1.61-1.49 (m, 4H), 1.38-1.33 (m, 1H).

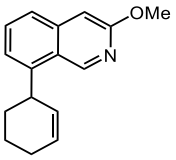
^{13}C-NMR (150 MHz, CDCl$_3$): δ / ppm = 159.8, 142.0, 135.6, 130.3, 127.4, 127.2, 127.0, 124.9, 117.1, 42.6, 33.4 (2C), 26.3, 26.0 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3048, 2924, 2849, 1619, 1582, 1549, 1493, 1460, 1447, 1333, 1307, 1297, 1260, 1227, 1204, 1182, 1147, 1142, 1025, 1013, 997, 987, 886, 864, 841, 811, 793, 782, 741, 704, 675.

MS (EI, 70 eV): *m/z* (%) = 210 (17), 162 (11), 161 (100), 134 (12), 128 (18), 67 (17).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}NS$]: 243.1082; found 243.1081.

8-(Cyclohex-2-en-1-yl)-3-methoxyisoquinoline (10dh)



According to the TP1, a solution of 8-bromo-3-methoxyisoquinoline (48 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 $mL \cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohex-1-ene (48 mg, 0.30 mmol, 1.5 equiv) and $CuCN \cdot 2LiCl$ solution (0.02 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 8:2) afforded the title compound as pale yellow oil (34 mg, 0.14 mmol, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.29 (s, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.48 (dd, J = 8.3, 6.9 Hz, 1H), 7.23 (dd, J = 6.9, 0.9 Hz, 1H), 7.01 (s, 1H), 6.05 – 6.00 (m, 1H), 5.81 (dq, J = 10.1, 2.6 Hz, 1H), 4.24 (m, 1H), 4.04 (s, 3H), 2.22 – 2.15 (m, 3H), 1.80 – 1.67 (m, 3H).

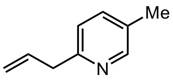
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.1, 147.4, 143.5, 140.3, 130.3, 129.5, 129.4, 124.4, 123.7, 123.2, 102.0, 54.3, 37.1, 31.6, 25.3, 21.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3017, 2928, 2857, 2833, 1621, 1590, 1567, 1487, 1465, 1445, 1422, 1391, 1349, 1318, 1289, 1258, 1247, 1228, 1222, 1176, 1169, 1146, 1133, 1074, 1038, 1018, 975, 882, 876, 852, 796, 765, 743, 723, 694, 681, 664.

MS (EI, 70 eV): *m/z* (%) = 239 (69), 238 (100), 234 (23), 210 (90), 196 (32), 184 (30), 182 (45), 180 (49), 168 (37), 167 (63), 166 (46), 165 (35), 158 (38), 154 (52), 153 (26), 152 (40), 140 (25), 139 (44), 128 (23), 126 (21), 115 (47), 89 (20), 79 (41), 78 (20).

HRMS (EI): *m/z* calc. for [$C_{16}H_{17}NO$]: 239.1310; found 239.1309.

2-Allyl-5-methylpyridine (13aa)



According to the TP1, a solution of 2-bromo-5-methylpyridine (0.20 M, 1.00 mmol) and $ZnCl_2$ (0.10 M, 0.50 mmol, 0.5 equiv) in THF (total volume: 5.00 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 $mL \cdot min^{-1}$ flow-rate in a T-mixer. The combined stream passed a 5.0 mL reactor tube (53 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (302 mg, 2.50 mmol, 2.5 equiv) in THF. Stirring was continued for 1 h at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 8:2) afforded the title compound as pale yellow oil (84 mg, 0.63 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.34 (d, *J* = 2.2 Hz, 1H), 7.38 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.10 – 5.92 (m, 1H), 5.18 – 5.03 (m, 2H), 3.57 – 3.46 (m, 2H), 2.27 (s, 3H).

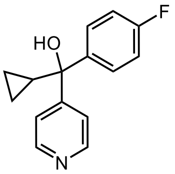
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.2, 149.8, 137.1, 136.1, 130.5, 122.3, 116.6, 42.5, 18.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2927, 2861, 1665, 1602, 1568, 1484, 1448, 1380, 1254, 1186, 1132, 1029, 886, 830, 745, 723.

MS (EI, 70 eV): *m/z* (%) = 134(0.5), 133(10), 132(100), 117(36).

HRMS (EI): *m/z* calc. for [$C_9H_{11}N$]: 133.0891; found 132.0808 [M-H].

Cyclopropyl(4-fluorophenyl)(pyridin-4-yl)methanol (13bo)



According to the TP1, a solution of 4-iodopyridine (0.20 M, 0.50 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 18 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.83 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl(4-fluorophenyl)methanone (90 mg, 0.55 mmol, 1.1 equiv) in THF. Stirring was continued for 2 h at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 3:7) afforded the title compound as colorless crystals (76 mg, 0.31 mmol, 62% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.47 (s, 2H), 7.47 – 7.39 (m, 2H), 7.33 – 7.28 (m, 2H), 7.05 – 6.97 (m, 2H), 2.55 (s, 1H), 1.56 (tt, *J* = 8.0, 5.5 Hz, 1H), 0.72 – 0.64 (m, 1H), 0.58 – 0.44 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.13 (d, *J* = 247.1 Hz), 155.94, 149.39 (2C), 141.70 (d, *J* = 3.3 Hz), 128.80 (d, *J* = 8.1 Hz, 2C), 121.55 (2C), 115.07 (d, *J* = 21.3 Hz, 2C), 75.92, 21.24, 2.23, 1.28.

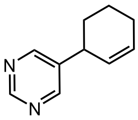
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3186, 3004, 1602, 1506, 1422, 1408, 1358, 1300, 1222, 1194, 1158, 1148, 1068, 1028, 1016, 994, 968, 878, 840, 816, 802, 730, 686.

MS (EI, 70 eV): *m/z* (%) = 216 (15), 215 (100), 202 (14), 123 (32), 109 (13), 106 (17), 95 (15), 78 (13).

HRMS (EI): *m/z* calc. for [$C_{15}H_{14}FNO$] [M]: 243.1049; found 243.1062.

m.p. (°C): 154.3-156.8.

5-(Cyclohex-2-en-1-yl)pyrimidine (13ch)



According to the TP1, a solution of 5-bromopyrimidine (0.20 M, 0.40 mmol) and $ZnCl_2$ (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-bromocyclohexene (161 mg, 1.00 mmol, 2.5 equiv) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 10 min at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane) afforded the title compound as a light brown oil (43 mg, 0.27 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.08 (s, 1H), 8.59 (s, 2H), 6.04 – 5.97 (m, 1H), 5.69 – 5.61 (m, 1H), 3.48 – 3.38 (m, 1H), 2.17 – 2.00 (m, 3H), 1.79 – 1.50 (m, 3H).

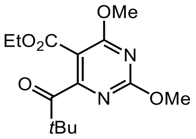
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.0, 156.5 (2C), 139.2, 130.6, 127.3, 37.3, 32.1, 24.9, 20.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3022, 2928, 2858, 2838, 1716, 1672, 1610, 1560, 1432, 1408, 1370, 1346, 1326, 1302, 1256, 1230, 1184, 1164, 1136, 1110, 1078, 1046, 1036, 984, 958, 910, 890, 880, 848, 824, 794, 758, 722, 704, 668.

MS (EI, 70 eV): *m/z* (%) = 160 (81), 159 (27), 146 (10), 145 (100), 132 (16), 131 (53), 118 (15), 105 (13), 104 (15), 78 (12).

HRMS (EI): *m/z* calc. for [$C_{10}H_{12}N_2$]: 160.1000; found 160.0994.

Ethyl 2,4-dimethoxy-6-pivaloylpyrimidine-5-carboxylate (13dx)



According to the TP1, a solution of ethyl 4-iodo-2,6-dimethoxypyrimidine-5-carboxylate (0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.10 M, 0.20 mmol, 0.5 equiv) in THF (total volume: 2.0 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 20 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of pivaloyl chloride (72 mg, 0.60 mmol, 1.5 equiv) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv) in THF. Stirring was continued for 2 h at 0 °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 *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 19:1) afforded the title compound as a pale yellow oil (79 mg, 0.27 mmol, 68% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 4.29 (q, J = 7.1 Hz, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 1.34 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H).

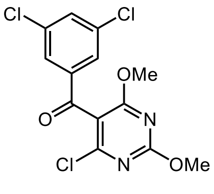
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 208.2, 170.0, 169.2, 164.8, 163.9, 105.7, 61.8, 55.7, 55.1, 43.7, 27.2 (3C), 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 2962, 2936, 2874, 1740, 1704, 1568, 1552, 1484, 1460, 1374, 1360, 1274, 1236, 1200, 1120, 1060, 1032, 986, 946, 872, 860, 824, 786, 768, 726, 680.

MS (EI, 70 eV): *m/z* (%) = 251 (16), 239 (67), 211 (89), 185 (14), 167 (100), 140 (25), 139 (40), 109 (24).

HRMS (EI): *m/z* calc. for [$C_{14}H_{20}N_2O_5$]: 296.1372; found 296.1367.

(4-Chloro-2,6-dimethoxypyrimidin-5-yl)(3,5-dichlorophenyl)methanone (13ey)



According to the TP1, a solution of 4-chloro-5-iodo-2,6-dimethoxypyrimidine (0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 9 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.08 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3,5-dichlorobenzoyl chloride (157 mg, 0.75 mmol, 1.5 equiv) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv) in THF.

Stirring was continued for 2 h at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 9:1) afforded the title compound as a white solid (125 mg, 0.36 mmol, 72% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.66 (d, *J* = 1.9 Hz, 2H), 7.60 (t, *J* = 1.9 Hz, 1H), 4.09 (s, 3H), 3.96 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 188.51, 169.61, 164.74, 158.63, 138.92, 136.10 (2C), 133.90, 127.72 (2C), 111.74, 56.02, 55.47.

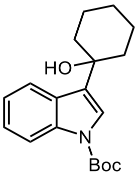
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1676, 1564, 1536, 1464, 1390, 1328, 1244, 1202, 1160, 1084, 1034, 968, 942, 874, 796, 770, 744, 664.

MS (EI, 70 eV): *m/z* (%) = 348 (11), 346 (12), 203 (33), 201 (100), 173 (10), 76 (15).

HRMS (EI): *m/z* calc. for [$C_{13}H_9Cl_3N_2O_3$] [M-H]: 345.9679; found 345.9671.

m.p. (°C): 83.1-84.0.

***tert*-Butyl 3-(1-hydroxycyclohexyl)-1*H*-indole-1-carboxylate (13fs)**



According to the TP1, a solution of *N*-Boc-3-bromoindole (59 mg, 0.20 M, 0.20 mmol) and $MgCl_2$·LiCl (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexanone (30 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 8:2) afforded the title compound as white solid (38 mg, 0.12 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.49 (s, 1H), 7.30 (ddd, *J* = 8.4, 7.3, 1.2 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 2.04 – 1.98 (m, 4H), 1.87 – 1.71 (m, 5H), 1.67 (s, 11H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 150.0, 136.3, 129.0, 128.5, 124.3, 122.4, 121.7, 121.5, 115.5, 83.8, 71.1, 38.0 (2C), 28.4 (3C), 25.9, 22.1 (2C).

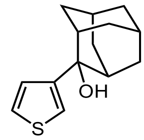
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3530, 2939, 2923, 2853, 1704, 1473, 1454, 1442, 1380, 1365, 1349, 1306, 1298, 1275, 1261, 1253, 1228, 1190, 1182, 1148, 1141, 1119, 1091, 1055, 1047, 1031, 1019, 983, 966, 907, 852, 842, 809, 771, 765, 747, 713, 655.

MS (EI, 70 eV): *m/z* (%) = 259 (31), 242 (11), 241 (68), 216 (17), 198 (13), 197 (67), 196 (26), 182 (10), 172 (29), 170 (11), 168 (43), 167 (16), 154 (11), 144 (10), 130 (21), 117 (20), 61 (10), 57 (100), 56 (13), 55 (14), 45 (12), 44 (23), 43 (81), 41 (47).

HRMS (EI): *m/z* calc. for [$C_{19}H_{25}NO_3$]: 315.1834; found 315.1824.

m.p. (°C): 128.6 – 130.3.

Adamanton-2-yl(thiophen-3-yl)methanol (13gt)



According to the TP1, a solution of 3-bromothiophene (33 mg, 0.20 M, 0.20 mmol) and $MgCl_2\cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5) afforded the title compound as pale yellow oil (43 mg, 0.18 mmol, 92% yield).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ / ppm = 7.31 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.27 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.19 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.37 (d, *J* = 9.9 Hz, 4H), 1.86 (s, 1H), 1.75 – 1.67 (m, 9H), 1.57 (s, 1H).

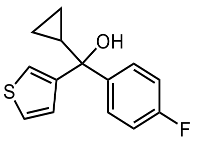
^{13}C-NMR (100 MHz, CD_2Cl_2): δ / ppm = 149.0, 126.3, 126.1, 121.6, 74.6, 38.3, 37.9 (2C), 35,6 (2C), 33.4 (2C), 28.1, 27.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3552, 3442, 3106, 2901, 2854, 1468, 1449, 1409, 1352, 1324, 1287, 1264, 1233, 1184, 1172, 1102, 1078, 1042, 1007, 999, 980, 941, 927, 888, 868, 844, 795, 781, 766, 736, 670.

MS (EI, 70 eV): *m/z* (%) = 234 (21), 219 (13), 217 (37), 216 (12), 187 (10), 150 (26), 111 (20), 79 (13), 42 (25).

HRMS (EI): *m/z* calc. for [$C_{14}H_{18}OS$]: 234.1078; found 234.1075.

Cyclopropyl(4-fluorophenyl)(thiophen-3-yl)methanol (13go)



According to the TP1, a solution of 3-bromothiophene (0.20 M, 0.50 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.25 mmol, 0.5 equiv) in THF (total volume: 2.5 mL) and a solution of BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 1 mL reactor tube (10 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl(4-fluorophenyl)methanone (90 mg, 0.55 mmol, 1.1 equiv) in THF. Stirring was continued for 2 h at 0 °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 Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 9:1) afforded the title compound as a yellow oil (95 mg, 0.39 mmol, 77% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.38 (m, 2H), 7.32 (ddd, *J* = 3.0, 1.4, 0.4 Hz, 1H), 7.25 (ddd, *J* = 5.0, 3.0, 0.4 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.94 (ddd, *J* = 5.0, 1.4, 0.4 Hz, 1H), 2.01 (s, 1H), 1.65 – 1.55 (m, 1H), 0.70 – 0.59 (m, 1H), 0.58 – 0.42 (m, 3H).

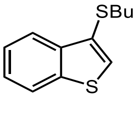
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.27, 140.71, 139.68, 135.58, 131.27, 128.79, 128.64 (d, *J* = 11.2 Hz, 2C), 128.70 (d, *J* = 179.5 Hz, 2C), 126.19, 61.03, 33.32, 14.30.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3496, 3104, 3006, 1658, 1588, 1506, 1430, 1410, 1394, 1282, 1222, 1158, 1144, 1046, 1024, 968, 860, 850, 832814, 764, 740, 684.

MS (EI, 70 eV): *m/z* (%) = 220 (67), 207 (22), 136 (12), 123 (100), 111 (16).

HRMS (EI): *m/z* calc. for [$C_{14}H_{13}FOS$]: 248.0671; found 248.0666.

3-(Butylthio)benzo[*b*]thiophene (13hz)



According to the TP1, a solution of 3-bromobenzo[*b*]thiophene (43 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of dibutyldisulfide (54 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 99:1) afforded the title compound as pale yellow oil (42 mg, 0.19 mmol, 94% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.95 – 7.93 (m, 1H), 7.88 – 7.85 (m, 1H), 7.44 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.40 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.38 (s, 1H), 2.90 (t, *J* = 7.2 Hz, 2H), 1.66 – 1.58 (m, 2H), 1.50-1.41 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

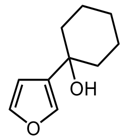
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 140.0, 139.3, 127.5, 126.2, 124.9, 124.5, 123.0, 122.7, 34.6, 31.7, 21.9, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3096, 3060, 2954, 2925, 2869, 1737, 1480, 1463, 1453, 1435, 1419, 1377, 1308, 1272, 1253, 1223, 1146, 1099, 1062, 1018, 962, 937, 914, 825, 780, 753, 730, 723, 703.

MS (EI, 70 eV): *m/z* (%) = 222 (32), 166 (100), 165 (14), 134 (12), 121 (20).

HRMS (EI): *m/z* calc. for [$C_{12}H_{14}S_2$]: 222.0537; found 222.0532.

1-(Furan-3-yl)cyclohexan-1-ol (13is)



According to the TP1, a solution of 3-bromofuran (29 mg, 0.20 M, 0.20 mmol) and MgCl$_2$·LiCl (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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 a flask containing a stirred solution of cyclohexanone (30 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °C before *sat. aq.* NH$_4$Cl 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 Na$_2$SO$_4$ and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound as pale yellow oil (20 mg, 0.12 mmol, 60% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.38-7.36 (m, 2H), 6.42 (dd, *J* = 1.6, 1.1 Hz, 1H), 1.86 – 1.78 (m, 3H), 1.75 – 1.67 (m, 3H), 1.63 – 1.49 (m, 4H), 1.37 – 1.29 (m, 1H).

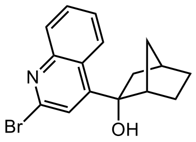
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 143.2, 138.3, 108.5 (2C), 69.4, 38.7 (2C), 25.7, 22.3 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3445, 2930, 2857, 2360, 1753, 1633, 1448, 1341, 1318, 1280, 1260, 1178, 1161, 1147, 1134, 1114, 1088, 1052, 1033, 1021, 972, 956, 929, 888, 872, 837, 787, 725.

MS (EI, 70 eV): *m/z* (%) = 166 (77), 151 (12), 148 (26), 137 (14), 133 (14), 123 (100), 110 (19), 108 (11), 95 (58), 91 (27), 81 (28), 77 (13), 67 (28).

HRMS (EI): *m/z* calc. for [$C_{10}H_{14}O_2$]: 166.0994; found 166.0988.

2-(2-Bromoquinolin-4-yl)bicyclo[2.2.1]heptan-2-ol (16aa')



According to the TP1, a solution of 2,4-dibromoquinoline (57 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of norcamphor (33 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 9:1) afforded the title compound as white solid (33 mg, 0.11 mmol, 58% yield, *d.r.* > 99/1).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.46 (dd, *J* = 8.6, 1.0 Hz, 1H), 8.00 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.49 (s, 1H), 2.92 (d, *J* = 3.5 Hz, 1H), 2.33 (t, *J* = 3.9 Hz, 1H), 2.29 – 2.20 (m, 2H), 2.04 (s, 1H), 1.95 (dd, *J* = 13.3, 3.3 Hz, 1H), 1.76 – 1.51 (m, 5H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 155.5, 150.3, 141.8, 130.0, 129.7, 127.9, 126.5, 125.4, 121.3, 80.5, 48.3, 46.2, 39.2, 37.6, 29.0, 22.0.

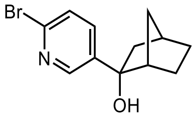
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3378, 2961, 2940, 2928, 2867, 1572, 1554, 1500, 1409, 1357, 1339, 1312, 1280, 1267, 1254, 1225, 1165, 1147, 1096, 1084, 1045, 1023, 1002, 994, 959, 888, 872, 836, 796, 770, 753, 692.

MS (EI, 70 eV): *m/z* (%) = 251 (58), 249 (62), 238 (43), 236 (36), 234 (37), 232 (26), 210 (25), 209 (37), 208 (38), 207 (37), 206 (39), 192 (24), 182 (28), 170 (100), 154 (42), 153 (25), 152 (26), 142 (49), 140 (53), 128 (77), 127 (88), 115 (84), 77 (26), 75 (30), 67 (54).

HRMS (EI): *m/z* calc. for [$C_{16}H_{16}BrNO$]: 317.0415; found 317.0410.

m.p. (°C): 216.8 – 218.2.

2-(6-Bromopyridin-3-yl)bicyclo[2.2.1]heptan-2-ol (16ba')



According to the TP1, a solution of 2,5-dibromopyridine (47 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of norcamphor (33 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as white solid (33 mg, 0.12 mmol, 68% yield, *d.r.* > 99/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 (dd, *J* = 2.7, 0.6 Hz, 1H), 7.70 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.43 (dd, *J* = 8.4, 0.7 Hz, 1H), 2.51 (d, *J* = 3.5 Hz, 1H), 2.36 (t, *J* = 4.2 Hz, 1H), 2.21 (ddd, *J* = 13.3, 4.8, 2.8 Hz, 1H), 2.18 - 2.11 (m, 1H), 1.92 (s, 1H), 1.69 – 1.63 (m, 1H), 1.53 – 1.48 (m, 3H), 1.47 – 1.42 (m, 1H), 1.38 (dq, *J* = 10.3, 1.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.2, 143.7, 140.5, 137.0, 127.7, 79.5, 47.6, 47.0, 38.8, 37.8, 28.9, 22.3.

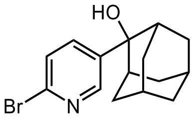
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3352, 2952, 2870, 2360, 1576, 1558, 1457, 1358, 1310, 1294, 1147, 1089, 1022, 974, 958, 909, 829, 731.

MS (EI, 70 eV): *m/z* (%) = 214 (38), 212 (39), 202 (31), 201 (58), 200 (33), 199 (60), 188 (32), 186 (98), 184 (100), 158 (18), 156 (18), 133 (20).

HRMS (EI): *m/z* calc. for [$C_{12}H_{14}BrNO$]: 267.0259; found 267.0252.

m.p. (°C): 150.8 – 152.3.

2-(6-Bromopyridin-3-yl)adamantan-2-ol (16bt)



According to the TP1, a solution of 2,5-dibromopyridine (47 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as white solid (37 mg, 0.12 mmol, 67% yield).

^{1}H-NMR (400 MHz, CDCl3): δ / ppm = 8.47 (d, *J* = 2.6 Hz, 1H), 7.69 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 2.49 (s, 2H), 2.38 (d, *J* = 12.0 Hz, 2H), 1.91 (t, *J* = 2.8 Hz, 1H), 1.87 (s, 1H), 1.82 – 1.70 (m, 7H), 1.60 (d, *J* = 13.4 Hz, 2H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 148.5, 140.9, 140.2, 136.6, 128.2, 74.8, 37.6, 35.6 (2C), 34.8 (2C), 32.8 (2C), 27.4, 26.7.

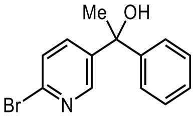
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3356, 2906, 2855, 2361, 1575, 1559, 1458, 1364, 1090, 1049, 1008, 969, 912, 831.

MS (EI, 70 eV): *m/z* (%) = 309 (20), 307 (23), 291 (98), 289 (100), 228 (32), 210 (16), 207 (16), 200 (16), 189 (19), 188 (32), 187 (21), 186 (61), 184 (63), 159 (26), 158 (24), 157 (28), 156 (26), 151 (58), 133 (27), 93 (25), 91 (23), 81 (43), 79 (39), 77 (15).

HRMS (EI): *m/z* calc. for [$C_{15}H_{18}BrNO$]: 307.0572; found 307.0566.

m.p. (°C): 163.0 – 164.8.

1-(6-Bromopyridin-3-yl)-1-phenylethan-1-ol (16bb')



According to the TP1, a solution of 2,5-dibromopyridine (47 mg, 0.20 M, 0.20 mmol) and MgCl$_2$·LiCl (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of acetophenone (28 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °C before *sat. aq.* NH$_4$Cl 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 Na$_2$SO$_4$ and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as colorless oil (28 mg, 0.10 mmol, 56% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.40 (d, *J* = 2.6 Hz, 1H), 7.57 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 3H), 7.34 (td, *J* = 6.8, 1.8 Hz, 2H), 7.28 (dt, *J* = 7.1, 1,4 Hz, 1H), 2,43 (s, 1H), 1.96 (s, 3H).

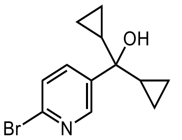
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 148.1, 146.4, 143.0, 140.7, 136.7, 128.7 (2C), 127.8, 127.6, 125.8 (2C), 74.9, 30.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920, 2361, 2342, 2332, 1576, 1559, 1457, 1449, 1374, 1093, 1022, 766, 700.

MS (EI, 70 eV): *m/z* (%) = 265 (12), 264 (96), 263 (13), 262 (100), 186 (63), 184 (64), 158 (15), 156 (15).

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}BrNO$]: 277.0102; found 277.0098.

(6-Bromopyridin-3-yl)dicyclopropylmethanol (16bc')



According to the TP1, a solution of 2,5-dibromopyridine (47 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropylketone (33 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as colorless oil (43 mg, 0.16 mmol, 89% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.57 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.73 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.43 (dd, *J* = 8.4, 0.7 Hz, 1H), 1.47 (s, 1H), 1.18 – 1.09 (m, 2H), 0.64 – 0.54 (m, 4H), 0.46 – 0.33 (m, 4H).

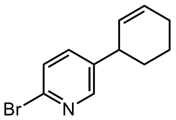
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.1, 142.2, 140.4, 136.3, 127.1, 72.6, 20.4 (2C), 2.3 (2C), 0.1 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3354, 3086, 3008, 1575, 1560, 1451, 1427, 1355, 1288, 1165, 1138, 1122, 1084, 1022, 999, 969, 926, 913, 872, 858, 827, 735.

MS (EI, 70 eV): *m/z* (%) = 241 (56), 239 (57), 238 (10), 228 (58), 226 (62), 224 (26), 199 (25), 197 (23), 186 (95), 184 (100), 160 (26), 158 (26), 156 (26), 145 (15).

HRMS (EI): *m/z* calc. for [$C_{12}H_{14}BrNO$]: 267.0259; found 268.0333 [M + H].

2-Bromo-5-(cyclohex-2-en-1-yl)pyridine (16bh)



According to the TP1, a solution of 2,5-dibromopyridine (47 mg, 0.20 M, 0.20 mmol) and $MgCl_2 \cdot LiCl$ (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohex-1-ene (48 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl solution (0.02 mL, 1.0 M in THF, 0.1 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as colorless oil (26 mg, 0.11 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (t, J = 1.6 Hz, 1H), 7.39 (d, J = 1.6 Hz, 2H), 5.97 – 5.92 (m, 1H), 5.64 – 5.60 (m, 1H), 3.43 – 3.37 (m, 1H), 2.12 – 2.06 (m, 2H), 2.01 – 1.98 (m, 1H), 1.74 – 1.57 (m, 2H), 1.53 – 1.45 (m, 1H).

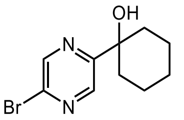
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 150.0, 141.3, 139.7, 138.1, 130.1, 128.2, 127.8, 38.8, 32.4, 24.9, 20.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3021, 2931, 2860, 2836, 2360, 2342, 1670, 1653, 1576, 1559, 1451, 1395, 1377, 1346, 1300, 1131, 1088, 1022, 882, 848, 829, 793, 737, 724.

MS (EI, 70 eV): *m/z* (%) = 239 (38), 238 (10), 237 (40), 236 (11), 224 (45), 222 (46), 211 (16), 210 (33), 209 (17), 208 (34), 173 (12), 171 (12), 158 (70), 156 (10), 143 (31), 142 (14), 131 (10), 130 (100), 128 (19), 117 (16), 104 (10), 103 (16), 77 (12).

HRMS (EI): m/z calc. for [$C_{11}H_{12}BrN$]: 237.0153; found 237.0145.

1-(5-Bromopyrazin-2-yl)cyclohexan-1-ol (16cs)



According to the TP1, a solution of 2,5-dibromopyrazine (47 mg, 0.20 M, 0.20 mmol) and $MgCl_2$·LiCl (0.10 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexanone (30 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2)) afforded the title compound as white solid (31 mg, 0.12 mmol, 67% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.59 (s, 2H), 3.09 (s, 1H), 1.92 – 1.64 (m, 9H), 1.39 – 1.28 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.5, 145.5, 142.0, 138.9, 73.1, 37.9 (2C), 25.3, 21.8 (2C).

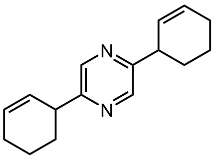
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3460, 2917, 2851, 1737, 1727, 1443, 1377, 1365, 1353, 1303, 1271, 1259, 1227, 1158, 1144, 1132, 1118, 1108, 1099, 1037, 1028, 1014, 981, 927, 905, 891, 851, 835, 764.

MS (EI, 70 eV): *m/z* (%) = 230 (84), 228 (88), 227 (14), 215 (54), 213 (54), 203 (15), 201 (28), 199 (28), 187 (95), 186 (15), 185 (100), 183 (15), 175 (33), 174 (75), 173 (35), 172 (79), 160 (22), 159 (31), 158 (23), 157 (29).

HRMS (EI): *m/z* calc. for [$C_{10}H_{13}BrN_2O$]: 256.0211; found 256.0205.

m.p. (°C): 70.4 – 72.8.

2,5-Di(cyclohex-2-en-1-yl)pyrazine (16dh)



According to the TP1, a solution of 2,5-dibromopyrazine (47 mg, 0.20 M, 0.20 mmol) and $MgCl_2\cdot LiCl$ (0.20 M, 0.10 mmol, 0.5 equiv) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.48 M in hexane, 0.48 mmol, 2.4 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohex-1-ene (97 mg, 0.60 mmol, 3.0 equiv) and $CuCN\cdot 2LiCl$ solution (0.04 mL, 1.0 M in THF, 0.2 equiv) in THF. Stirring was continued for 10 min at 25 °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 Na_2SO_4 and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 4:1) afforded the title compound as colorless oil (30 mg, 0.13 mmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.42 (s, 2H), 5.99 – 5.96 (m, 2H), 5.77 (d, *J* = 10.1 Hz, 2H), 3.62 – 3.58 (m, 2H), 2.17 – 2.05 (m, 6H), 1.80 – 1.65 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.9, 143.1, 129.8, 127.7, 41.5, 41.0, 30.5, 25.0 (2C), 24.0, 21.1 (2C), 21.0, 17.6, 17.4, 14.8.

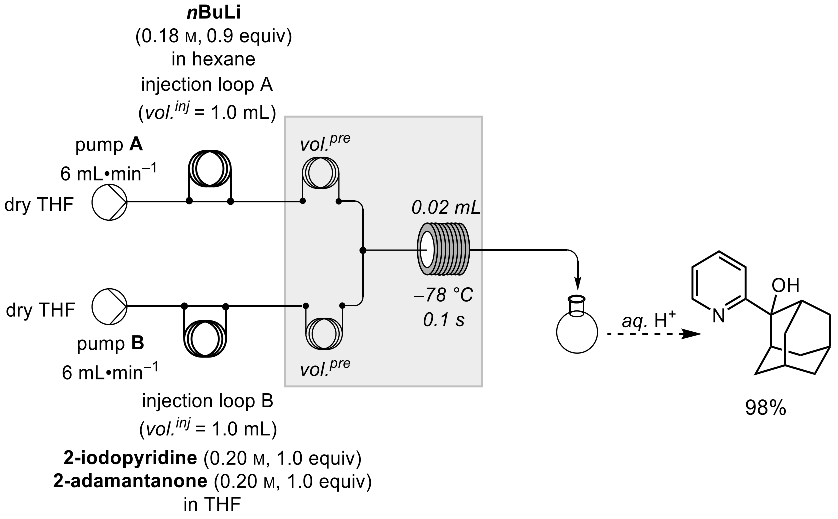
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3021, 2928, 2859, 2836, 1476, 1447, 1432, 1340, 1145, 1129, 1032, 988, 896, 879, 724.

MS (EI, 70 eV): *m/z* (%) = 241 (11), 240 (67), 239 (32), 225 (18), 212 (34), 211 (100), 199 (20), 197 (16), 186 (14), 185 (11), 183 (24), 174 (72), 173 (29), 171 (14), 169 (17), 159 (25), 157 (28), 146 (14), 145 (25), 120 (21), 77 (11).

HRMS (EI): *m/z* calc. for [$C_{16}H_{20}N_2$]: 240.1626; found 240.1622.

14. Halogen-Lithium Exchange of Sensitive (Hetero)Aromatic Halides under Barbier Conditions in a Continuous Flow Set-up

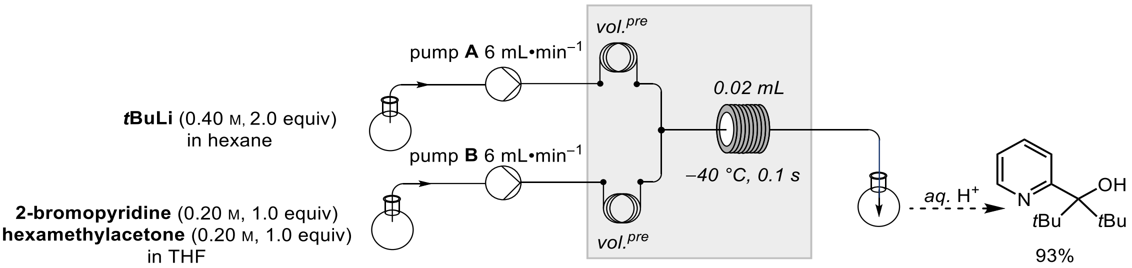
14.1 Typical Procedure 3 (TP3)



Scheme 58: Uniqsis flow set-up for the halogen-lithium exchange of (hetero)arenes with *n*BuLi in the presence of various electrophiles.

A *n*BuLi solution in hexane (0.18 M, 0.9 equiv) and a solution of 2-iodopyridine (41 mg, 0.20 M, 1.0 equiv) and 2-adamantanone (30 mg, 0.20 M, 1.0 equiv) in THF were prepared. Injection loop A (vol^{inj} =1.0 mL) was loaded with *n*BuLi as exchange reagent and injection loop B (vol^{inj} =1.0 mL) was loaded with a solution containing 2-iodopyridine and 2-adamantanone. The solutions were simultaneously injected into separate streams of THF, respectively (pump A: THF; pump B: THF, flow-rates: 6.0 mL·min^{-1}), which each passed a precooling loop (vol^{pre} = 1.0 mL, T^1 = −78 °C, residence time: 10 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (Vol^{R} = 0.02 mL; residence time: t^1 = 0.1 s, T^1 = −78 °C) and was subsequently collected flask. The reaction mixture was quenched with a *sat. aq.* NH$_4$Cl 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 → 8:2) afforded the title compound as white crystals (45 mg, 0.18 mmol, 98%).

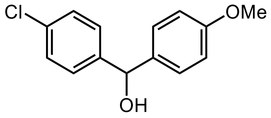
14.2 TYPICAL PROCEDURE 4 (TP4)



Scheme 59: Vapourtec E-series Integrated Flow Chemistry System for the halogen-lithium exchange of (hetero)arenes with *t*BuLi in the presence of various electrophiles.

A *t*BuLi solution in hexane (0.40 M, 2.0 equiv) and a solution of the 2-bromopyridine (32 mg, 0.20 M, 1.0 equiv) and hexamethylacetone (28 mg, 0.20 M, 1.0 equiv) in THF were prepared. The solutions were pumped from their flasks through a suction needle with a flow-rate of 6.0 mL·min^{-1}. After passing a PTFE tubing (vol^{pre} = 1.0 mL, T^1 = −40 °C, residence time: 10 s) for precooling, the solutions were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (Vol^R = 0.02 mL; residence time: t^1 = 0.1 s, T^1 = −40 °C) and was subsequently collected in an empty flask. The reaction mixture was 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 → 8:2) afforded the title compound as yellow solid (41 mg, 0.19 mmol, 93%).

(4-Chlorophenyl)(4-methoxyphenyl)methanol (19ad')



According to the TP3, a solution of 1-chloro-4-iodobenzene (0.20 M, 48 mg, 0.20 mmol) and *p*-anisaldehyde (0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 = 100:0 → 95:5 → 7:3) afforded the title compound as white solid (47 mg, 0.19 mmol, 95%).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ / ppm = 7.34 – 7.29 (m, 4H), 7.28 – 7.22 (m, 2H), 6.89 – 6.84 (m, 2H), 5.76 (s, 1H), 3.77 (s, 3H), 2.42 (s, 1H).

^{13}C-NMR (100 MHz, CD_2Cl_2): δ / ppm = 159.8, 143.6, 136.6, 133.4, 128.9 (2C), 128.3 (4C), 114.4 (2C), 75.5, 55.8.

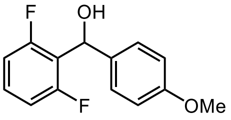
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3265, 2956, 2931, 2836, 1609, 1584, 1510, 1487, 1462, 1455, 1440, 1402, 1301, 1248, 1171, 1111, 1088, 1034, 1012, 1006, 859, 831, 813, 800, 770.

MS (EI, 70 eV): *m/z* (%) = 248 (14), 231 (12), 196 (11), 153 (11), 152 (20), 141 (15), 139 (46), 137 (14), 135 (85), 109 (100), 108 (39), 94 (15), 77 (15).

HRMS (EI): *m/z* calc. for [$C_{14}H_{13}ClO_2$]: 248.0604; found 248.0599.

m.p. (°C): 54.2 – 56.7.

(2,6-Difluorophenyl)(4-methoxyphenyl)methanol (19bd')



According to the TP3, a solution of 1,3-difluoro-2-iodobenzene (0.20 M, 50 mg, 0.20 mmol) and *p*-anisaldehyde (0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 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. 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 = 100:0 → 95:5 → 8:2) afforded the title compound as colorless oil (41 mg, 0.16 mmol, 82%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.35 – 7.29 (m, 2H), 7.25 (tt, *J* = 8.4, 6.4 Hz, 1H), 6.95 – 6.83 (m, 4H), 6.19 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 2.73 (dt, *J* = 9.4, 2.4 Hz, 1H).

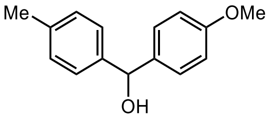
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 160.9 (dd, *J* = 248.2, 8.3 Hz, 2C), 159.2, 134.4, 129.6 (t, *J* = 10.7 Hz), 127.1 (2C), 119.6 (t, *J* = 16.4 Hz), 113.9 (2C), 112.4 – 111.8 (m, 2C), 67.6 (t, *J* = 3.5 Hz), 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3415, 2936, 2838, 1623, 1612, 1588, 1510, 1468, 1443, 1418, 1303, 1246, 1231, 1199, 1169, 1113, 1064, 1029, 1010, 991, 868, 841, 805, 789, 766, 721, 692.

MS (EI, 70 eV): *m/z* (%) = 250 (45), 233 (27), 189 (13), 141 (98), 137 (34), 135 (15), 109 (100), 108 (29), 94 (22).

HRMS (EI): *m/z* calc. for [$C_{14}H_{12}F_2O_2$]: 250.0805; found 250.0799.

(4-Methoxyphenyl)(*p*-tolyl)methanol (19cd')



According to the TP4, a solution of 1-iodo-4-methylbenzene (0.20 M, 44 mg, 0.20 mmol) and *p*-anisaldehyde (0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 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. 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 as white solid (32 mg, 0.14 mmol, 70%).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ / ppm = 7.31 – 7.19 (m, 4H), 7.19 – 7.10 (m, 2H), 6.89 – 6.81 (m, 2H), 5.75 (d, *J* = 3.4 Hz, 1H), 3.77 (s, 3H), 2.32 (s, 3H), 2.25 (dd, *J* = 3.5, 0.6 Hz, 1H).

^{13}C-NMR (100 MHz, CD_2Cl_2): δ / ppm = 159.6, 142.1, 137.7, 137.2, 129.6 (2C), 128.2 (2C), 126.7 (2C), 114.3 (2C), 76.0, 55.8, 21.3.

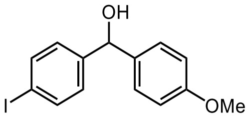
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3297, 1741, 1737, 1610, 1510, 1253, 1234, 1217, 1171, 1030, 1015, 1007, 824, 820, 809, 770.

MS (EI, 70 eV): *m/z* (%) = 228 (20), 211 (16), 165 (11), 152 (12), 137 (11), 135 (100), 119 (40), 109 (33), 108 (57), 91 (14).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}O_2$]: 228.1150; found 228.1139.

m.p. (°C): 63.8 – 64.7.

(4-Iodophenyl)(4-methoxyphenyl)methanol (19dd')



According to the TP3, a solution of 1,4-diiodobenzene (0.20 M, 66 mg, 0.20 mmol) and *p*-anisaldehyde (0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 as white solid (53 mg, 0.16 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.68 – 7.62 (m, 2H), 7.25 – 7.21 (m, 2H), 7.14 – 7.09 (m, 2H), 6.88 – 6.82 (m, 2H), 5.72 (d, *J* = 2.9 Hz, 1H), 3.79 (s, 3H), 2.30 (d, *J* = 3.1 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 159.4, 143.8, 137.5 (2C), 135.8, 128.5 (2C), 128.0 (2C), 114.1 (2C), 93.0, 75.4, 55.4.

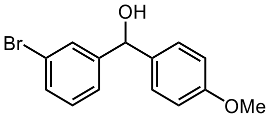
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3253, 2833, 1741, 1609, 1510, 1481, 1392, 1249, 1217, 1172, 1110, 1031, 1019, 1000, 856, 830, 813, 799, 773.

MS (EI, 70 eV): *m/z* (%) = 340 (28), 323 (10), 231 (50), 181 (11), 153 (10), 152 (24), 137 (16), 135 (100), 109 (70), 108 (31), 94 (14), 77 (11).

HRMS (EI): *m/z* calc. for [$C_{14}H_{13}IO_2$]: 339.9960; found 339.9955.

m.p. (°C): 94.6 – 96.0.

(3-Bromophenyl)(4-methoxyphenyl)methanol (19ed')



According to the TP3, a solution of 1-bromo-3-iodobenzene (0.20 M, 57 mg, 0.20 mmol) and *p*-anisaldehyde (0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 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. 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 = 100:0 → 95:5 → 9:1) afforded the title compound as yellow oil (45 mg, 0.15 mmol, 85%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.57 (t, *J* = 1.8 Hz, 1H), 7.40 (ddd, *J* = 7.9, 2.1, 1.1 Hz, 1H), 7.32 – 7.25 (m, 3H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.92 – 6.87 (m, 2H), 5.76 (s, 1H), 3.82 (s, 3H), 2.37 (s, 1H).

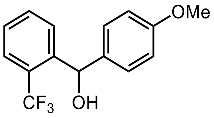
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 159.4, 146.4, 135.7, 130.5, 130.1, 129.5, 128.1 (2C), 125.1, 122.7, 114.2 (2C), 75.3, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3372, 3062, 3001, 2955, 2931, 2836, 1610, 1594, 1586, 1569, 1510, 1464, 1441, 1425, 1303, 1245, 1172, 1111, 1092, 1069, 1029, 1008, 997, 872, 829, 811, 788, 758, 732, 692, 670.

MS (EI, 70 eV): *m/z* (%) = 294 (11), 292 (11), 185 (30), 183 (30), 181 (10), 165 (10), 157 (10), 155 (10), 153 (15), 152 (33), 137 (55), 135 (88), 109 (100), 108 (19), 94 (26), 77 (26).

HRMS (EI): *m/z* calc. for [$C_{14}H_{13}BrO_2$]: 292.0099; found 292.0096.

(4-Methoxyphenyl)(2-(trifluoromethyl)phenyl)methanol (19fe')



According to the TP4, a solution of 1-bromo-2-(trifluoromethyl)benzene (0.20 M, 45 mg, 0.20 mmol) and *p*-anisaldehyde (0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 4 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (3.8 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. 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 → 85:15) afforded the title compound as pale yellow oil (39 mg, 0.14 mmol, 69%).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ / ppm = 7.73 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28 – 7.23 (m, 2H), 6.88 – 6.83 (m, 2H), 6.23 (d, *J* = 2.9 Hz, 1H), 3.77 (s, 3H), 2.46 (d, *J* = 3.6 Hz, 1H).

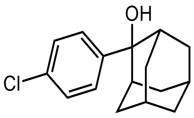
^{13}C-NMR (100 MHz, CD_2Cl_2): δ / ppm = 159.7, 143.3, 135.8, 132.9, 129.7, 128.4 (2C), 128.2, 127.6 (q, *J* = 30.1 Hz), 126.1 (q, *J* = 5.9 Hz), 125.1 (q, *J* = 274.0 Hz), 114.2 (2C), 71.1 (q, *J* = 2.4 Hz), 55.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3397, 2837, 1610, 1584, 1511, 1462, 1454, 1443, 1310, 1272, 1249, 1157, 1118, 1060, 1035, 1009, 959, 844, 833, 807, 768, 743, 669.

MS (EI, 70 eV): *m/z* (%) = 282 (20), 261 (10), 241 (16), 231 (14), 211 (17), 137 (58), 109 (100), 108 (25), 94 (19).

HRMS (EI): *m/z* calc. for [$C_{15}H_{13}F_3O_2$]: 282.0868; found 282.0855.

Adamanton-2-yl(4-chlorophenyl)methanol (19at)



According to the TP3, a solution of 1-chloro-4-iodobenzene (0.20 M, 48 mg, 0.20 mmol) and 2-adamantanone (0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 = 100:0 → 95:5) afforded the title compound as white solid (45 mg, 0.17 mmol, 86%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.49 – 7.44 (m, 2H), 7.36 – 7.31 (m, 2H), 2.50 (s, 2H), 2.38 (d, *J* = 12.5 Hz, 2H), 1.90 (t, *J* = 2.9 Hz, 1H), 1.73 (d, *J* = 12.9 Hz, 7H), 1.64 (d, *J* = 13.4 Hz, 2H), 1.55 (s, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 144.0, 133.1, 128.9 (2C), 127.2 (2C), 75.4, 37.7, 35.8 (2C), 34.9 (2C), 33.0 (2C), 27.5, 26.9.

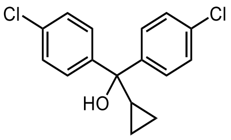
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 2905, 2896, 2849, 1493, 1448, 1093, 1044, 1014, 1000, 970, 932, 911, 822, 720.

MS (EI, 70 eV): *m/z* (%) = 253 (21), 251 (11), 165 (10), 153 (12), 152 (14), 141 (33), 139 (100), 125 (15), 115 (15), 93 (12), 91 (25), 81 (20), 80 (19), 79 (45), 78 (12), 77 (18), 67 (12).

HRMS (EI): *m/z* calc. for [$C_{16}H_{19}ClO$]: 262.1124; found 262.1121.

m.p. (°C): 84.2 – 85.7.

Bis(4-chlorophenyl)(cyclopropyl)methanol (19af)



According to the TP3, a solution of 1-chloro-4-iodobenzene (0.20 M, 48 mg, 0.20 mmol) and (4-chlorophenyl)(cyclopropyl)methanone (0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 = 100:0 → 95:5) afforded the title compound as colorless oil (51 mg, 0.17 mmol, 87%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.38 – 7.33 (m, 4H), 7.30 – 7.26 (m, 4H), 1.87 (s, 1H), 1.60 – 1.51 (m, 1H), 0.63 – 0.58 (m, 2H), 0.47 – 0.42 (m, 2H).

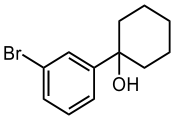
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 145.4 (2C), 133.3 (2C), 128.4 (4C), 128.3 (4C), 76.6, 21.7, 1.9 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3579, 3479, 3083, 3005, 2915, 1902, 1592, 1573, 1486, 1399, 1317, 1296, 1166, 1145, 1090, 1033, 1025, 1012, 984, 960, 944, 927, 895, 879, 872, 814, 740, 726, 718, 699.

MS (EI, 70 eV): *m/z* (%) = 274 (12), 266 (13), 264 (22), 263 (18), 261 (26), 241 (14), 239 (46), 226 (17), 225 (30), 205 (10), 204 (61), 203 (50), 202 (63), 200 (11), 199 (14), 191 (21), 190 (12), 189 (40), 181 (14), 178 (10), 176 (16), 165 (26), 163 (16), 151 (10), 149 (36), 141 (32), 139 (100), 128 (10), 125 (27), 111 (12), 101 (15), 89 (10), 75 (17).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}Cl_2O$]: 292.0422; found 292.0418.

1-(3-Bromophenyl)cyclohexanol (19es)



According to the TP3, a solution of 1-bromo-3-iodobenzene (0.20 M, 57 mg, 0.20 mmol) and cyclohexanone (0.20 M, 20 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 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. 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 = 100:0 → 95:5 → 9:1) afforded the title compound as colorless oil (42 mg, 0.16 mmol, 91%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.66 (t, *J* = 1.9 Hz, 1H), 7.42 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.37 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 1.85 – 1.62 (m, 11H).

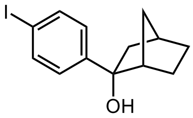
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 152.0, 129.9, 129.8, 128.2, 123.4, 122.6, 73.1, 38.9 (2C), 25.5, 22.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3382, 3064, 2929, 2851, 1673, 1593, 1564, 1473, 1461, 1447, 1416, 1407, 1350, 1314, 1258, 1205, 1171, 1147, 1133, 1074, 1035, 1026, 996, 971, 914, 883, 874, 849, 833, 780, 737, 693, 674.

MS (EI, 70 eV): *m/z* (%) = 238 (13), 236 (13), 213 (20), 211 (20), 200 (25), 198 (26), 185 (27), 183 (27), 175 (22), 158 (10), 157 (22), 156 (10), 142 (13), 141 (12), 133 (10), 132 (100), 131 (18), 129 (60), 128 (42), 115 (25), 91 (15), 77 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{15}BrO$]: 254.0306; found 254.0301.

2-(4-Iodophenyl)bicyclo[2.2.1]heptan-2-ol (19da')



According to the TP3, a solution of 1,4-diiodobenzene (0.20 M, 66 mg, 0.20 mmol) and norcamphor (0.20 M, 22 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 $mL\cdot min^{-1}$ 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. 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 as white crystals (43 mg, 0.14 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.68 – 7.63 (m, 2H), 7.29 – 7.24 (m, 2H), 2.54 – 2.51 (m, 1H), 2.31 (td, *J* = 5.9, 5.3, 2.5 Hz, 1H), 2.23 (ddd, *J* = 13.2, 4.9, 2.8 Hz, 1H), 2.19 – 2.10 (m, 1H), 1.68 (s, 1H), 1.66 – 1.60 (m, 1H), 1.55 – 1.41 (m, 4H), 1.34 (ddt, *J* = 10.1, 3.4, 1.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.9, 137.4 (2C), 128.2 (2C), 92.5, 80.7, 47.4, 46.9, 38.9, 37.7, 29.1, 22.4.

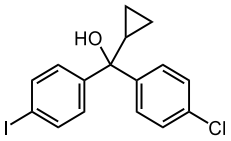
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3336, 2941, 2865, 1740, 1579, 1481, 1449, 1385, 1309, 1229, 1142, 1075, 1019, 1000, 972, 958, 869, 846, 816, 810, 752, 698.

MS (EI, 70 eV): *m/z* (%) = 259 (11), 246 (55), 231 (100), 187 (57), 169 (14), 141 (14), 132 (23).

HRMS (EI): *m/z* calc. for [$C_{13}H_{15}IO$]: 314.0168; found 314.0163.

m.p. (°C): 92.8 – 94.9.

(4-Chlorophenyl)(cyclopropyl)(4-iodophenyl)methanol (19df)



According to the TP3, a solution of 1,4-diiodobenzene (**0**.20 M, 66 mg, 0.20 mmol) and (4-chlorophenyl)(cyclopropyl)methanone (0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 $mL\cdot min^{-1}$ 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. 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 as pale yellow oil (58 mg, 0.15 mmol, 84%).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ / ppm = 7.67 – 7.63 (m, 2H), 7.40 – 7.35 (m, 2H), 7.32 – 7.27 (m, 2H), 7.21 – 7.16 (m, 2H), 2.00 (s, 1H), 1.56 (tt, *J* = 8.3, 5.5 Hz, 1H), 0.62 – 0.55 (m, 2H), 0.43 (tdd, *J* = 5.2, 4.2, 1.7 Hz, 2H).

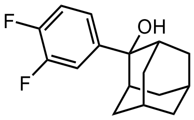
^{13}C-NMR (100 MHz, CD_2Cl_2): δ / ppm = 147.3, 146.0, 137.6 (2C), 133.5, 129.4 (2C), 128.9 (2C), 128.6 (2C), 93.3, 77.0, 21.8, 2.2, 2.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3575, 3476, 3079, 3005, 1902, 1593, 1583, 1483, 1399, 1390, 1367, 1362, 1316, 1296, 1164, 1144, 1090, 1060, 1026, 1013, 1005, 982, 959, 943, 926, 894, 877, 871, 810, 761, 733, 723, 701, 682, 677.

MS (EI, 70 eV): *m/z* (%) = 358 (32), 357 (16), 356 (100), 343 (19), 231 (36), 166 (10), 165 (16), 152 (10), 141 (15), 139 (46).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}ClIO$]: 383.9778; found 383.9775.

2-(3,4-Difluorophenyl)adamantan-2-ol (19gt)



According to the TP4, a solution of 4-bromo-1,2-difluorobenzene (0.20 M, 39 mg, 0.20 mmol) and 2-adamantanone (0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 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. 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 → 8:2) afforded the title compound as white solid (35 mg, 0.13 mmol, 66%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 (ddd, *J* = 12.5, 7.7, 2.3 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.15 (dt, *J* = 10.1, 8.4 Hz, 1H), 2.46 (t, *J* = 2.9 Hz, 2H), 2.41 – 2.31 (m, 2H), 1.90 (h, *J* = 3.1 Hz, 1H), 1.80 – 1.68 (m, 7H), 1.64 (dt, *J* = 13.6, 2.5 Hz, 2H), 1.53 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.3 (dd, *J* = 120.5, 12.6 Hz), 148.8 (dd, *J* = 121.6, 12.6 Hz), 142.8 (t, *J* = 4.2 Hz), 121.8 (dd, *J* = 6.1, 3.5 Hz), 117.4 (d, *J* = 16.9 Hz), 115.1 (d, *J* = 17.8 Hz), 75.3, 37.6, 35.9 (2C), 34.9 (2C), 33.0 (2C), 27.4, 26.8.

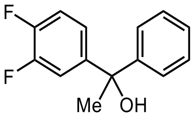
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3320, 2939, 2906, 2853, 1605, 1520, 1509, 1449, 1423, 1389, 1361, 1276, 1216, 1191, 1148, 1125, 1112, 1102, 1079, 1045, 1010, 999, 984, 945, 929, 889, 868, 816, 779, 768, 713.

MS (EI, 70 eV): *m/z* (%) = 264 (13), 247 (15), 246 (100), 221 (15), 204 (13), 141 (43), 127 (11), 115 (10), 91 (10), 81 (11), 79 (12).

HRMS (EI): *m/z* calc. for [$C_{16}H_{18}F_2O$]: 264.1326; found 264.1313.

m.p. (°C): 89.9 – 90.4.

1-(3,4-Difluorophenyl)1-phenylethan-1-ol (19gb')



According to the TP4, a solution of 4-bromo-1,2-difluorobenzene (0.20 M, 39 mg, 0.20 mmol) and acetophenone (0.20 M, 24 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 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. 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 → 8:2) afforded the title compound as pale yellow oil (30 mg, 0.13 mmol, 64%).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ / ppm = 7.42 - 7.39 (m, 2H), 7.35 - 7.24 (m, 4H), 7.13 - 7.09 (m, 2H), 2.34 (s, 1H), 1.92 (s, 3H).

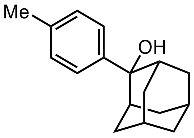
^{13}C-NMR (100 MHz, CD_2Cl_2): δ / ppm = 150.4 (dd, *J* = 246.6, 12.7 Hz), 149.6 (dd, *J* = 246.6, 12.7 Hz), 147.9, 146.3 (dd, *J* = 4.7, 3.8 Hz), 128.9 (2C), 127.8, 126.2 (2C), 122.5 (dd, *J* = 6.3, 3.5 Hz), 117.2 (d, *J* = 16.9 Hz), 115.7 (d, *J* = 18.3 Hz), 76.0 (d, *J* = 1.3 Hz), 31.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3417, 3060, 2981, 1608, 1510, 1493, 1446, 1420, 1373, 1326, 1298, 1275, 1205, 1157, 1111, 1101, 1068, 1027, 940, 917, 903, 875, 822, 802, 774, 759, 709, 697, 681.

MS (EI, 70 eV): *m/z* (%) = 220 (13), 219 (100).

HRMS (EI): *m/z* calc. for [$C_{14}H_{12}F_2O$]: 234.0856; found 234.0844.

2-(*p*-Tolyl)adamantan-2-ol (19ct)



According to the TP4, a solution of 1-iodo-4-methylbenzene (0.20 M, 44 mg, 0.20 mmol) and 2-adamantanone (0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a

0.25 mL reactor tube (1.9 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. 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 as white solid (37 mg, 0.15 mmol, 76%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.44 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 2.55 (s, 2H), 2.41 (d, J = 12.3 Hz, 2H), 2.35 (s, 3H), 1.91 (s, 1H), 1.76 – 1.70 (m, 9H), 1.48 (s, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 142.6, 137.0, 129.5 (2C), 125.5 (2C), 75.6, 37.8, 35.8 (2C), 35.1 (2C), 33.1 (2C), 27.6, 27.1, 21.1.

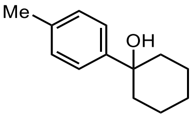
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3450, 2930, 2902, 2887, 2850, 1514, 1449, 1349, 1282, 1192, 1101, 1082, 1047, 1020, 999, 971, 934, 912, 815, 794, 724.

MS (EI, 70 eV): *m/z* (%) = 242 (34), 227 (29), 224 (43), 199 (16), 121 (19), 119 (100), 106 (11), 105 (10), 93 (17), 91 (28).

HRMS (EI): *m/z* calc. for [$C_{17}H_{22}O$]: 242.1671; found 242.1659.

m.p. (°C): 73.6 – 75.4.

1-(*p*-Tolyl)cyclohexan-1-ol (19cs)



According to the TP4, a solution of 1-iodo-4-methylbenzene (0.20 M, 44 mg, 0.20 mmol) and cyclohexanone (0.20 M, 20 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 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. 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 as white solid (35 mg, 0.18 mmol, 92%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.41 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 2.35 (s, 3H), 1.86 – 1.71 (m, 7H), 1.66 – 1.61 (m, 2H), 1.57 (s, 1H), 1.36 – 1.26 (m, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 146.6, 136.4, 129.0 (2C), 124.6 (2C), 73.1, 39.0 (2C), 25.7, 22.4 (2C), 21.1.

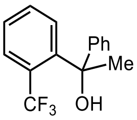
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3419, 3366, 2933, 2921, 2843, 1741, 1513, 1493, 1445, 1372, 1349, 1317, 1266, 1256, 1205, 1170, 1144, 1135, 1129, 1114, 1036, 1015, 968, 960, 940, 926, 904, 848, 832, 808, 796, 697.

MS (EI, 70 eV): *m/z* (%) = 190 (25), 175 (27), 157 (10), 148 (11), 147 (100), 134 (79), 129 (23), 119 (41), 91 (21), 55 (21).

HRMS (EI): *m/z* calc. for [$C_{13}H_{18}O$]: 190.1358; found 190.1347.

m.p. (°C): 53.3 – 55.2.

1-Phenyl-1-(2-(trifluoromethyl)phenyl)ethan-1-ol (19fb')



According to the TP4, a solution of 1-bromo-2-(trifluoromethyl)benzene (0.20 M, 45 mg, 0.20 mmol) and acetophenone (0.20 M, 24 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 4 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (3.8 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. 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 → 85:15) afforded the title compound as pale yellow oil (32 mg, 0.12 mmol, 60%).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ / ppm = 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.57 (td, *J* = 7.8, 0.9 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.32 – 7.21 (m, 5H), 2.52 (s, 1H), 1.98 (s, 3H).

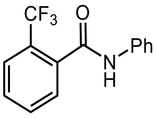
^{13}C-NMR (100 MHz, CD_2Cl_2): δ / ppm = 148.8 (d, *J* = 1.3 Hz), 146.5 (d, *J* = 1.3 Hz), 132.0 (d, *J* = 1.1 Hz), 129.8, 128.8 (q, *J* = 6.8 Hz), 128.6 (2C), 128.3 (q, *J* = 31.2 Hz), 128.1, 127.5, 125.8 (2C), 125.2 (q, *J* = 273.9 Hz), 77.6, 33.2 (d, *J* = 1.4 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3455, 2983, 1601, 1494, 1445, 1374, 1303, 1290, 1270, 1221, 1163, 1121, 1095, 1080, 1070, 1054, 1032, 1001, 959, 927, 909, 764, 754, 697, 652.

MS (EI, 70 eV): *m/z* (%) = 251 (46), 232 (14), 231 (97), 212 (15), 211 (100), 183 (26).

HRMS (EI): *m/z* calc. for [$C_{15}H_{13}F_3O$]: 266.0918; found 266.0906.

N-phenyl-2-(trifluoromethyl)benzamide (19ff')



According to the TP3, a solution of 1-iodo-2-(trifluoromethyl)benzene (0.20 M, 54 mg, 0.20 mmol) and phenylisocyanate (0.20 M, 24 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 = 9:1) afforded the title compound as white crystals (42 mg, 0.15 mmol, 83%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.74 (d, *J* = 7.6 Hz, 1H), 7.64 (dd, *J* = 4.2, 1.3 Hz, 2H), 7.61 – 7.56 (m, 4H), 7.37 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 165.9, 137.5, 135.9 (q, *J* = 2.0 Hz), 132.3, 130.3, 129.3 (2C), 128.7, 127.5 (q, *J* = 31.7 Hz), 126.6 (q, *J* = 4.9 Hz), 125.2, 123.7 (q, *J* = 273.8 Hz), 120.4 (2C).

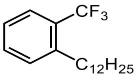
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3319, 3279, 3260, 1664, 1649, 1620, 1601, 1543, 1515, 1500, 1489, 1442, 1330, 1314, 1270, 1173, 1165, 1130, 1120, 1107, 1080, 1072, 1054, 1033, 896, 778, 761, 753, 725, 696, 686.

MS (EI, 70 eV): *m/z* (%) = 265 (16), 173 (100), 145 (42).

HRMS (EI): *m/z* calc. for [$C_{14}H_{10}F_3NO$]: 265.0714; found 265.0707.

m.p. (°C): 145.1 – 147.7.

1-Dodecyl-2-(trifluoromethyl)benzene (19fg')



According to the TP4, a solution of 1-iodo-2-(trifluoromethyl)benzene (0.20 M, 45 mg, 0.20 mmol) and dodecyl iodide (0.30 M, 89 mg, 0.30 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 4 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (3.8 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. The aqueous phase was extracted three times with hexane (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) afforded the title compound as colorless oil (48 mg, 0.15 mmol, 77%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.60 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 15.3 Hz, 1H), 3.19 (t, *J* = 7.1 Hz, 3H), 2.80 – 2.71 (m, 2H), 1.82 (p, *J* = 7.1 Hz, 3H), 1.66 – 1.51 (m, 2H), 1.39 (dt, *J* = 9.1, 4.1 Hz, 7H), 0.88 (t, *J* = 6.8 Hz, 8H).

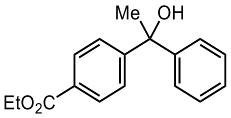
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 141.8 (q, *J* = 1.6 Hz), 131.6, 130.9, 128.3 (q, *J* = 29.7 Hz), 125.8 (q, *J* = 5.8 Hz), 125.6, 124.7 (d, *J* = 273.9 Hz), 33.6, 32.8, 32.0, 30.5, 29.7, 29.6, 29.5, 29.4, 28.6, 22.7, 14.2, 7.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2922, 2853, 1466, 1456, 1312, 1167, 1122, 1060, 1035, 766, 721, 654.

MS (EI, 70 eV): *m/z* (%) = 161 (10), 160 (100), 159 (43), 109 (10), 91 (21).

HRMS (EI): *m/z* calc. for [$C_{19}H_{29}F_3$]: 314.2221; found 314.2213.

Ethyl 4-(1-hydroxy-1-phenylethyl)benzoate (19gb')



According to the TP3, a solution of ethyl 4-iodobenzoate (0.20 M, 55 mg, 0.20 mmol) and acetophenone (0.20 M, 24 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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$_4$Cl 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 Na$_2$SO$_4$ and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as pale yellow oil (49 mg, 0.18 mmol, 91%).

^{1}H-NMR (400 MHz, CD$_2$Cl$_2$): δ / ppm = 7.98 – 7.93 (m, 2H), 7.53 – 7.48 (m, 2H), 7.43 – 7.39 (m, 2H), 7.35 – 7.29 (m, 2H), 7.27 – 7.22 (m, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 1H), 1.96 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).

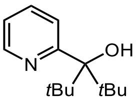
^{13}C-NMR (100 MHz, CD$_2$Cl$_2$): δ / ppm = 166.8, 153.7, 148.1, 129.8 (2C), 129.7, 128.8 (2C), 127.7, 126.3 (2C), 126.3 (2C), 76.5, 61.4, 31.0, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3478, 2981, 2934, 1713, 1697, 1610, 1575, 1493, 1463, 1446, 1407, 1368, 1311, 1272, 1184, 1107, 1098, 1069, 1018, 954, 925, 910, 860, 829, 777, 760, 707, 698.

MS (EI, 70 eV): *m/z* (%) = 256 (17), 255 (100), 177 (34), 149 (16), 105 (34)

HRMS (EI): *m/z* calc. for [$C_{17}H_{18}O_3$]: 270.1256; found 270.1253.

2,2,4,4-Tetramethyl-3-(pyridin-2-yl)pentan-3-ol (22ah')



According to the TP4, a solution of 2-bromopyridine (0.20 M, 31 mg, 0.20 mmol) and 2,2,4,4-tetramethylpentan-3-one (0.20 M, 28 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 → 8:2) afforded the title compound as yellow solid (41 mg, 0.19 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.50 (ddd, *J* = 5.0, 1.7, 1.2 Hz, 1H), 7.64 (ddd, *J* = 8.9, 6.9, 1.8 Hz, 1H), 7.60 (dt, *J* = 8.2, 1.3 Hz, 1H), 7.20 (ddd, *J* = 6.9, 5.0, 1.3 Hz, 1H), 1.04 (s, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.5, 145.9, 135.1, 123.4, 121.9, 82.0, 41.5 (2C), 29.6 (6C).

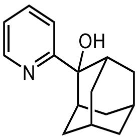
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3270, 3010, 2962, 2917, 2872, 1592, 1569, 1479, 1466, 1434, 1401, 1389, 1366, 1357, 1229, 1212, 1156, 1065, 1053, 1001, 952, 809, 761.

MS (EI, 70 eV): *m/z* (%) = 165 (11), 164 (100), 150 (37), 148 (13), 147 (10), 146 (96), 132 (15), 131 (79), 130 (52), 121 (44), 120 (39), 117 (19), 106 (30), 93 (15), 80 (12), 79 (49), 78 (33), 57 (11), 41 (20).

HRMS (EI): *m/z* calc. for [$C_{10}H_{14}NO$]: 164.1075; found 164.1070 (M – C_4H_9).

m.p. (°C): 42.7 – 43.8.

2-(Pyridin-2-yl)adamantan-2-ol (22at)



According to the TP3, a solution of 2-iodopyridine (0.20 M, 41 mg, 0.20 mmol) and 2-adamantanone (0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 → 8:2) afforded the title compound as white crystals (45 mg, 0.18 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.58 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 7.68 (td, *J* = 7.8, 1.9 Hz, 1H), 7.49 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.16 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 2.67 (q, *J* = 3.3 Hz, 2H), 2.49 – 2.35 (m, 2H), 2.16 (s, 1H), 1.90 (p, *J* = 3.1 Hz, 1H), 1.83 – 1.60 (m, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.3, 149.4, 136.7, 122.2, 120.3, 37.9, 35.1 (2C), 35.0 (2C), 33.0 (2C), 27.5, 27.2.

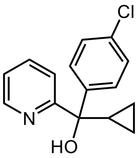
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3362, 2954, 2931, 2903, 2850, 1592, 1571, 1474, 1450, 1432, 1387, 1365, 1351, 1334, 1312, 1304, 1292, 1283, 1178, 1148, 1104, 1087, 1052, 1044, 1014, 999, 973, 938, 917, 837, 806, 794, 756.

MS (EI, 70 eV): *m/z* (%) = 229 (23), 228 (18), 211 (17), 201 (46), 200 (100), 170 (32), 168 (36), 158 (26), 156 (20), 146 (38). 144 (17), 134 (24), 132 (18), 130 (28), 120 (18), 118 (24), 117 (25), 106 (45), 93 (43), 91 (26), 80 (71), 79 (80), 78 (86), 77 (34), 41 (26).

HRMS (EI): *m/z* calc. for [$C_{15}H_{19}NO$]: 229.1467; found 229.1462.

m.p. (°C): 109.6 – 110.3.

(4-Chlorophenyl)(cyclopropyl)(pyridin-2-yl)methanol (22af)



According to the TP3, a solution of 2-iodopyridine (0.20 M, 41 mg, 0.20 mmol) and (4-chlorophenyl)(cyclopropyl)methanone (0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 → 8:2) afforded the title compound as colorless oil (50 mg, 0.18 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.48 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H), 7.63 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.28 – 7.15 (m, 4H), 5.74 (s, 1H), 1.59 (tt, *J* = 8.2, 5.3 Hz, 1H), 0.67 – 0.54 (m, 2H), 0.45 (dtd, *J* = 9.5, 5.5, 4.3 Hz, 1H), 0.35 (dddd, *J* = 9.0, 8.1, 6.1, 4.2 Hz, 1H).

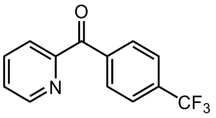
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 163.8, 147.1, 145.3, 137.1, 133.1, 128.7 (2C), 128.3 (2C), 122.4, 121.2, 75.0, 20.5, 1.9, 0.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3339, 3009, 1592, 1571, 1489, 1469, 1433, 1397, 1356, 1302, 1294, 1211, 1192, 1152, 1091, 1048, 1014, 994, 958, 884, 872, 824, 772, 749, 733, 720, 684.

MS (EI, 70 eV): *m/z* (%) = 258 (14), 244 (10), 240 (16), 230 (16), 225 (20), 218 (23), 207 (19), 204 (14), 167 (16), 154 (10), 148 (13), 141 (25), 139 (78), 134 (58), 132 (20), 125 (17), 124 (12), 115 (13), 106 (28), 96 (54), 93 (21), 79 (37), 78 (100), 75 (28).

HRMS (EI): *m/z* calc. for [$C_{15}H_{14}ClNO$]: 259.0764; found 258.0680 (M – H).

Pyridin-2-yl(4-(trifluoromethyl)phenyl)methanone (22ai')



According to the TP3, a solution of 2-iodopyridine (0.20 M, 41 mg, 0.20 mmol) and *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (0.20 M, 33 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 as yellow oil (30 mg, 0.11 mmol, 62%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.73 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.23 – 8.09 (m, 3H), 7.95 (td, *J* = 7.7, 1.7 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.54 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H).

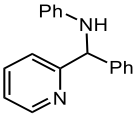
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 192.9, 154.2, 148.8, 139.4, 137.5, 133.9 (q, *J* = 32.6 Hz), 131.4 (2C), 126.9, 125.2 (q, *J* = 3.7 Hz, 2C), 124.9, 123.8 (q, *J* = 273 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 1953, 1671, 1583, 1570, 1509, 1436, 1408, 1324, 1312, 1306, 1282, 1242, 1166, 1123, 1110, 1064, 1046, 1018, 995, 935, 856, 807, 781, 752, 741, 723, 690, 665.

MS (EI, 70 eV): *m/z* (%) = 250 (76), 224 (13), 223 (100), 222 (14), 203 (24), 202 (11), 182 (27), 173 (46), 154 (56), 145 (82), 125 (16).

HRMS (EI): *m/z* calc. for [$C_{13}H_8F_3NO$]: 251.0558; found 251.0557.

N-(phenyl(pyridin-2-yl)methyl)aniline (22aj')



According to the TP3, a solution of 2-iodopyridine (0.20 M, 41 mg, 0.20 mmol) and *N*,1-diphenylmethanimine (0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 as brown oil (29 mg, 0.12 mmol, 59%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.60 (d, *J* = 4.3 Hz, 1H), 7.62 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.19 – 7.08 (m, 3H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 2H), 5.59 (s, 1H), 5.46 (s, 1H).

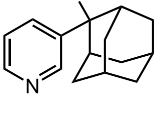
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.9, 149.2, 147.0, 142.5, 136.9, 129.2 (2C), 128.9 (2C), 127.6, 127.4 (2C), 122.3, 121.9, 117.5, 113.6 (2C), 63.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3386, 1708, 1600, 1570, 1503, 1473, 1453, 1427, 1361, 1319, 1264, 1221, 994, 747, 693.

MS (EI, 70 eV): *m/z* (%) = 260 (24), 183 (13), 182 (100), 169 (10), 168 (77), 167 (67), 166 (12), 77 (10).

HRMS (EI): *m/z* calc. for [$C_{18}H_{16}N_2$]: 260.1313; found 260.1308.

2-(Pyridin-3-yl)adamantan-2-ol (22bt)



According to the TP4, a solution of 3-bromopyridine (0.20 M, 31 mg, 0.20 mmol) and 2-adamantanone (0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 → 8:2) afforded the title compound as white crystals (27 mg, 0.12 mmol, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.63 (d, *J* = 2.4 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.82 (dt, *J* = 8.1, 2.1 Hz, 1H), 7.27 (dd, *J* = 8.0, 4.7 Hz, 1H), 2.53 (q, *J* = 3.1 Hz, 2H), 2.42 (dd, *J* = 12.8, 3.2 Hz, 2H), 1.91 (t, *J* = 3.2 Hz, 1H), 1.81 – 1.67 (m, 7H), 1.61 (dt, *J* = 13.2, 2.7 Hz, 2H), 1.24 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.8, 147.5, 141.0, 133.9, 123.7, 74.6, 37.7, 35.4 (2C), 34.7 (2C), 32.8 (2C), 27.5, 26.9.

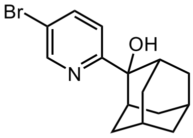
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3153, 2909, 2895, 2851, 1449, 1418, 1104, 1048, 1044, 1028, 1016, 970, 939, 808, 714, 702.

MS (EI, 70 eV): *m/z* (%) = 228 (22), 211 (100), 186 (16), 168 (21), 156 (16), 151 (56), 134 (28), 132 (16), 130 (19), 122 (18), 118 (19), 117 (25), 109 (21), 108 (47), 106 (79), 93 (25), 91 (43), 81 (57), 80 (63), 79 (86), 78 (76), 77 (40), 67 (22).

HRMS (EI): *m/z* calc. for [$C_{15}H_{19}NO$]: 229.1467; found 229.1462.

m.p. (°C): 148.0 – 148.7.

2-(5-Bromopyridin-2-yl)adamantan-2-ol (22ct)



According to the TP3, a solution of 5-bromo-2-iodopyridine (0.20 M, 47 mg, 0.20 mmol) and 2-adamantanone (0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.88 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. 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 → 8:2) afforded the title compound as white crystals (37 mg, 0.12 mmol, 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.73 (d, *J* = 2.3 Hz, 1H), 8.59 (d, *J* = 2.4 Hz, 1H), 7.98 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.80 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.28 (dd, *J* = 8.5, 0.8 Hz, 1H), 2.61 (t, *J* = 2.9 Hz, 2H), 2.39 (dd, *J* = 12.7, 3.1 Hz, 2H), 2.19 (s, 1H), 1.93 – 1.86 (m, 1H), 1.81 – 1.66 (m, 6H), 1.60 (dt, *J* = 13.3, 2.7 Hz, 3H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 163.3, 162.9, 155.2, 150.3, 145.0, 139.3, 122.4, 121.9, 119.1, 91.6, 37.7, 35.1, 35.0, 34.9, 32.9, 32.9, 27.4, 27.0.

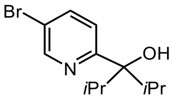
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3367, 2946, 2916, 2892, 2854, 1462, 1451, 1406, 1372, 1354, 1336, 1102, 1092, 1056, 1045, 1004, 975, 942, 916, 841, 832.

MS (EI, 70 eV): *m/z* (%) = 307 (19), 206 (11), 205 (10), 158 (10), 88 (22), 86 (13), 84 (18), 73 (15), 70 (16), 61 (36), 45 (11), 43 (100).

HRMS (EI): *m/z* calc. for [$C_{15}H_{18}BrNO$]: 307.0572; found 307.0576.

m.p. (°C): 115.7 – 117.3.

3-(5-Bromopyridin-2-yl)-2,4-dimethylpentan-3-ol (22ck')



According to the TP3, a solution of 5-bromo-2-iodopyridine (0.20 M, 47 mg, 0.20 mmol) and 2,4-dimethylpentan-3-one (0.20 M, 23 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.15 s, −78 °C) and was subsequently injected in an empty flask. Stirring was continued for 10 min at 25 °C before *sat. aq.* NH$_4$Cl 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 Na$_2$SO$_4$ and filtrated. After removal of the solvent flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound as yellow oil (27 mg, 0.11 mmol, 53%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.74 (dd, *J* = 2.1, 0.8 Hz, 1H), 8.60 (dd, J = 2.3, 0.8 Hz, 1H), 8.45 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.96 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.60 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.19 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.09 (dd, *J* = 8.4, 0.9 Hz, 1H), 4.98 (s, 1H), 2.33 – 2.24 (m, 2H), 0.80 (d, *J* = 6.7 Hz, 6H), 0.76 (d, *J* = 6.9 Hz, 6H).

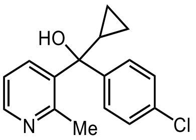
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 160.6, 153.2, 152.0, 148.3, 144.2, 140.5, 138.7, 136.2, 122.7, 122.1, 118.9, 91.0, 80.1, 34.4, 17.6, 16.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3417, 2963, 2933, 2876, 1464, 1440, 1381, 1359, 1318, 1288, 1237, 1209, 1178, 1158, 1136, 1128, 1100, 1092, 1068, 1017, 1001, 957, 926, 918, 874, 865, 827, 762, 738.

MS (EI, 70 eV): *m/z* (%) = 61 (15), 45 (12), 43 (100).

HRMS (EI): *m/z* calc. for [$C_{12}H_{18}BrNO$]: 271.0572; found 229.9995 (M – C_3H_8).

(4-Chlorophenyl)(cyclopropyl)(2-methylpyridin-3-yl)methanol (22df)



According to the TP3, a solution of 3-iodo-2-methylpyridine (0.20 M, 44 mg, 0.20 mmol) and (4-chlorophenyl)(cyclopropyl)methanone (0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 = 6:4) afforded the title compound as white solid (42 mg, 0.15 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.40 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.32 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.29 – 7.21 (m, 3H), 2.57 (s, 1H), 2.19 (s, 3H), 1.59 (tt, *J* = 8.0, 5.6 Hz, 1H), 0.73 – 0.58 (m, 3H), 0.49 – 0.40 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 158.3, 147.9, 144.0, 140.1, 134.8, 133.0, 128.3 (2C), 127.7 (2C), 120.6, 76.1, 24.5, 22.1, 2.2, 2.0.

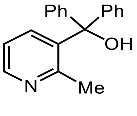
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1576, 1494, 1484, 1456, 1431, 1194, 1178, 1144, 1104, 1092, 1024, 1013, 988, 976, 963, 890, 878, 829, 804, 792, 784, 735, 728, 716.

MS (EI, 70 eV): *m/z* (%) = 247 (29), 246 (16), 245 (88), 232 (23), 141 (11), 139 (31), 120 (32), 93 (10), 92 (18), 88 (15), 73 (13), 70 (15), 61 (23), 45 (14), 43 (100).

HRMS (EI): *m/z* calc. for [$C_{16}H_{16}ClNO$]: 273.0920; found 273.0909.

m.p. (°C): 173.3 – 174.1.

(2-Methylpyridin-3-yl)diphenylmethanol (22dl')



According to the TP3, a solution of 3-iodo-2-methylpyridine (0.20 M, 44 mg, 0.20 mmol) and benzophenone (0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 = 6:4) afforded the title compound as white crystals (49 mg, 0.17 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.40 (dt, *J* = 4.9, 1.6 Hz, 1H), 7.39 – 7.28 (m, 6H), 7.25 – 7.18 (m, 4H), 7.10 – 6.94 (m, 2H), 3.20 (dd, *J* = 10.0, 3.6 Hz, 1H), 2.36 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.0, 148.0, 145.8 (2C), 140.3, 136.9 (2C), 128.4 (4C), 127.7 (5C), 120.1, 82.2, 25.5.

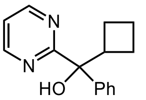
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079, 1588, 1575, 1489, 1434, 1339, 1266, 1186, 1159, 1118, 1047, 1026, 908, 899, 806, 756, 738, 701.

MS (EI, 70 eV): *m/z* (%) = 198 (35), 196 (12), 184 (14), 183 (100), 155 (15), 154 (24), 120 (37), 105 (75), 93 (64), 92 (23), 77 (25).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}NO$]: 275.1310; found 275.1306.

m.p. (°C): 146.1 – 148.1.

Cyclobutyl(phenyl)(pyrimidin-2-yl)methanol (22em')



According to the TP3, a solution of 2-iodopyrimidine (0.20 M, 41 mg, 0.20 mmol) and cyclobutyl(phenyl)methanone (0.20 M, 32 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 → 8:2) afforded the title compound as white solid (37 mg, 0.14 mmol, 79%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.70 (d, *J* = 4.8 Hz, 2H), 7.75 – 7.66 (m, 2H), 7.29 (ddd, *J* = 7.7, 6.9, 1.2 Hz, 2H), 7.22 – 7.17 (m, 1H), 7.15 (t, *J* = 4.9 Hz, 1H), 5.50 (d, *J* = 0.7 Hz, 1H), 3.85 – 3.66 (m, 1H), 2.21 – 2.08 (m, 1H), 2.02 – 1.88 (m, 1H), 1.88 – 1.71 (m, 3H), 1.64 – 1.52 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 171.8, 156.8 (2C), 144.3, 128.0 (2C), 127.0, 126.4 (2C), 119.2, 78.7, 44.1, 22.4, 21.7, 17.4.

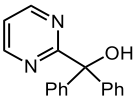
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3441, 2982, 2937, 2856, 1562, 1490, 1446, 1434, 1412, 1369, 1320, 1243, 1214, 1189, 1149, 1092, 1070, 1031, 1010, 996, 968, 920, 899, 891, 826, 810, 788, 756, 733, 702, 684.

MS (EI, 70 eV): *m/z* (%) = 186 (13), 185 (100), 107 (14), 105 (12), 97 (10), 79 (10), 77 (10).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}N_2O$]: 240.1263; found 240.1256.

m.p. (°C): 84.8 – 85.6.

Diphenyl(pyrimidin-2-yl)methanol (22el')



According to the TP3, a solution of 2-iodopyrimidine (0.20 M, 41 mg, 0.20 mmol) and benzophenone (0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL·min^{-1} 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. 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 → 8:2) afforded the title compound as white solid (51 mg, 0.18 mmol, 99%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.78 (d, *J* = 4.9 Hz, 2H), 7.48 – 7.43 (m, 4H), 7.34 – 7.26 (m, 6H), 7.24 (d, *J* = 4.9 Hz, 1H), 6.05 (s, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 172.1, 156.8 (3C), 145.3, 128.1 (4C), 128.0 (4C), 127.5 (2C), 119.4, 81.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3382, 3064, 1597, 1564, 1493, 1483, 1448, 1434, 1418, 1381, 1320, 1251, 1211, 1178, 1166, 1101, 1091, 1077, 1051, 1033, 997, 987, 943, 934, 923, 898, 857, 846, 813, 796, 765, 756, 724, 700, 660.

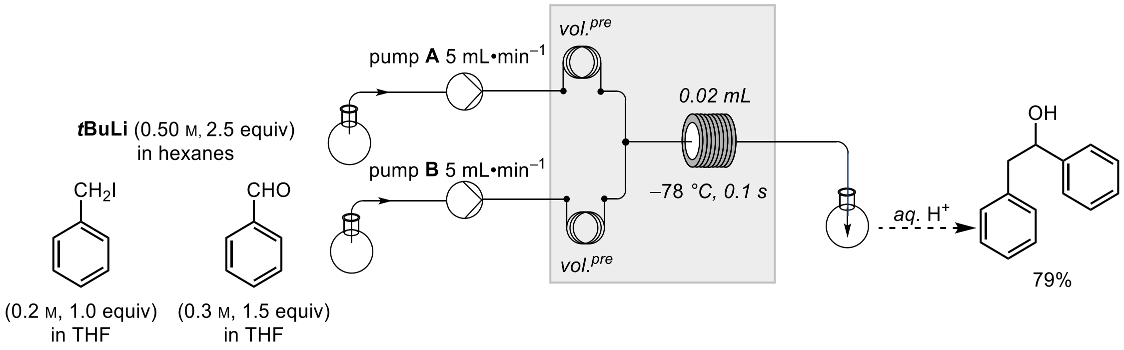
MS (EI, 70 eV): *m/z* (%) = 263 (11), 262 (54), 185 (56), 183 (35), 165 (13), 157 (31), 152 (11), 107 (23), 105 (100), 80 (14), 79 (24), 77 (76).

HRMS (EI): *m/z* calc. for [$C_{17}H_{14}N_2O$]: 262.1106; found 262.1099.

m.p. (°C): 111.8 – 113.7.

15. CONTINUOUS FLOW PREPARATION OF (HETERO)BENZYLIC LITHIUMS VIA IODINE-LITHIUM EXCHANGE REACTION UNDER BARBIER CONDITIONS

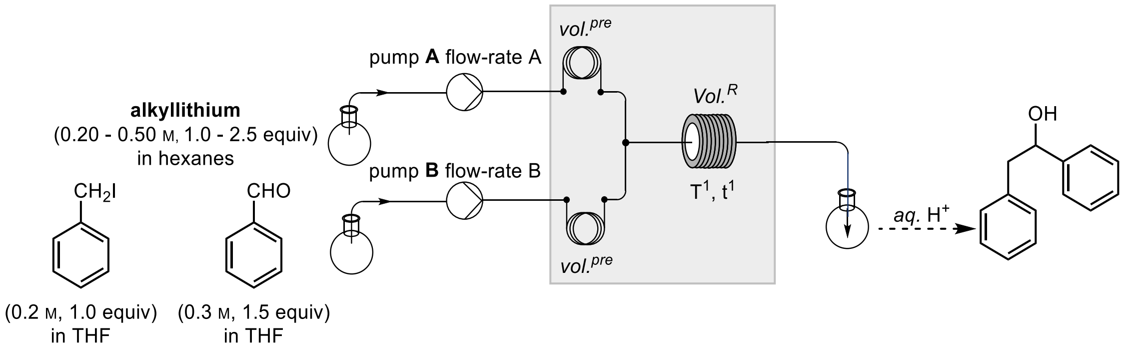
15.1 TYPICAL PROCEDURE 5 (TP5)



Scheme 60: 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 (0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (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^{-1} 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 as a white amorphous solid (31 mg, 0.16 mmol, 79% yield).

Reaction screening



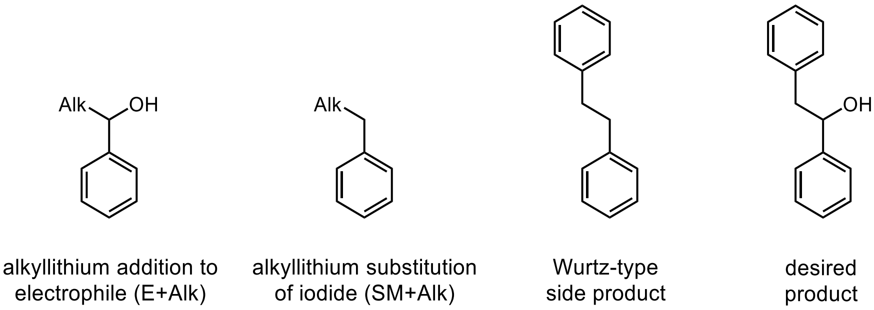
Scheme 61: General scheme for the optimization screening of 1,2-diphenylethan-1-ol.

Table 26: Optimization screening of 1,2-diphenylethan-1-ol.

Entry	Base [equiv]	t [s]	$\text{Vol}_{\text{reactor}}$ [mL]	Flow-rate [$\text{mL}\cdot\text{min}^{-1}$]	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
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**

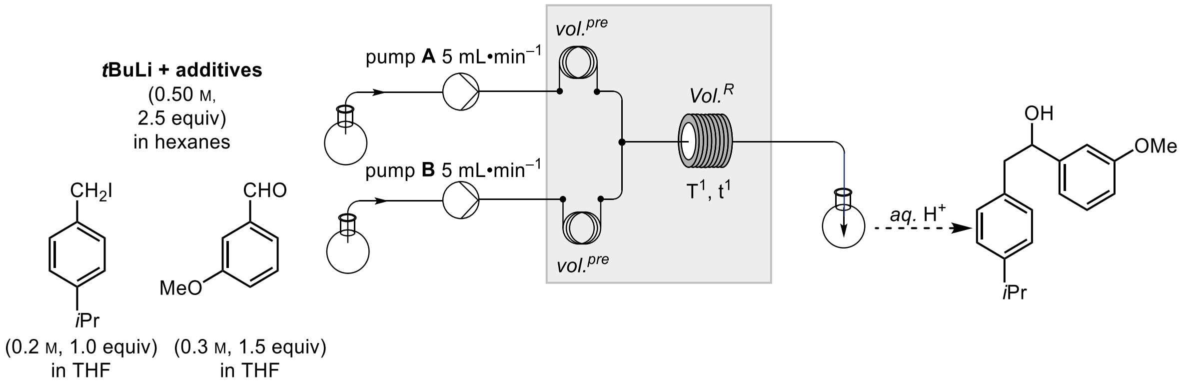
49	*t*BuLi (2.5)[a]	0.1	0.02	10	−78	0.27	0.20	1.65	100	13
50	*t*BuLi (2.5)[b]	0.1	0.02	10	−78	0.00	0.11	1.78	100	10
51	*s*BuLi (1.1)	0.1	0.02	10	−78	n.d	n.d	n.d	75	59
52	*n*HexLi (1.1)	0.1	0.02	10	−78	n.d	n.d	n.d	68	57
53	neopentyl Li (1.1)	0.1	0.02	10	−78	n.d	n.d	n.d	83	62

[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.



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. The values for the addition of alkyllithium to the benzaldehyde as well as the substitution product of alkyllithium at the benzyl iodide are not directly comparable.

Screening of different additives

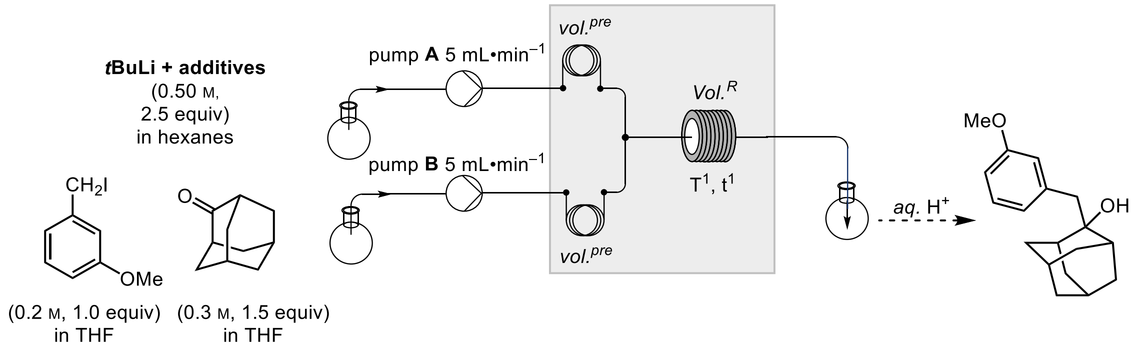


Scheme 62: General scheme for the additive screening of Barbier-type reaction of 4-*iso*propyliodomethylbenzene and *m*-anisaldehyde affording 2-(4-*iso*propylphenyl)-1-(3-methoxyphenyl)ethan-1-ol.

Table 27: Additive screening of Barbier-type reaction of 4-*iso*propyliodomethylbenzene and *m*-anisaldehyde affording product 2-(4-*iso*propylphenyl)-1-(3-methoxyphenyl)ethan-1-ol .

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 $x = \frac{\text{GC value}}{\text{Standard value}}$.



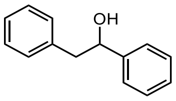
Scheme 63: General scheme for the additive screening of Barbier-type reaction of *m*-methoxyiodomethylbenzene and adamantanone affording 2-(3-methoxybenzyl)adamantan-2-ol.

Table 28: Additive screening of Barbier-type reaction of *m*-methoxyiodomethylbenzene and adamantanone affording 2-(3-methoxybenzyl)adamantan-2-ol .

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 $x = \frac{\text{GC value}}{\text{Standard value}}$.

1,2-Diphenylethan-1-ol (25ac)



According to the TP5, a solution of benzyl iodide (0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (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^{-1} 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 as a white amorphous solid (31 mg, 0.16 mmol, 79% yield).

In addition, a convenient scale-up of the reaction according to TP5 was demonstrated. A solution of benzyl iodide (0.20 M, 4.00 mmol, 1.0 equiv) and benzaldehyde (**2a**, 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^{-1} 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 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.

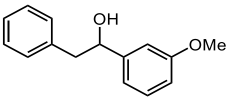
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3294, 3026, 2922, 2855, 1495, 1453, 1445, 1072, 1039, 1026, 1016, 952, 778, 760, 741, 696.

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 (25an')



According to the TP5, a solution of benzyl iodide (0.20 M, 0.20 mmol, 1.0 equiv) and *p*-anisaldehyde (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^{-1} 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 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.

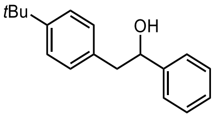
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3294, 3026, 2922, 2855, 1495, 1453, 1445, 1316, 1072, 1039, 1026, 1016, 952, 917, 778, 760, 741, 696.

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 (25bc)



According to the TP5, a solution of 1-(*tert*-butyl)-4-(iodomethyl)benzene (0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (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^{-1} 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 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).

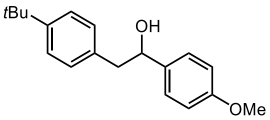
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3560, 2951, 1509, 1493, 1453, 1360, 1269, 1049, 1028, 910, 817, 755, 731, 699.

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 (25bd’)



According to the TP5, a solution of 1-(*tert*-butyl)-4-(iodomethyl)benzene (0.20 M, 0.20 mmol, 1.0 equiv) and *p*-anisaldehyde (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^{-1} 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 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).

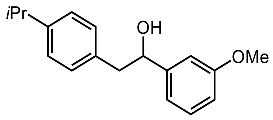
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3557, 2952, 1608, 1509, 1249, 1178, 1106, 1047, 1028, 878, 829, 814.

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 (25bn’)



According to the TP5, a solution of 1-(iodomethyl)-4-isopropylbenzene (0.20 M, 0.20 mmol, 1.0 equiv) and *m*-anisaldehyde (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^{-1}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 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).

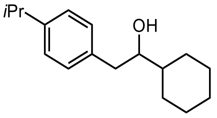
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 159.8, 147.4, 145.8, 135.4, 129.6, 129.5 (2C), 126.8 (2C), 118.3, 113.3, 111.3, 75.4, 55.4, 45.9, 33.9, 24.2 (2C).

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 (25co')



According to the TP5, a solution of 1-(iodomethyl)-4-isopropylbenzene (0.20 M, 0.20 mmol, 1.0 equiv) and cyclohexanecarboxaldehyde (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^{-1} 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$_4$Cl 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$_2$SO$_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound 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.

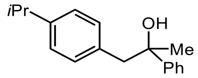
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3314, 2957, 2928, 2919, 2891, 2844, 1514, 1445, 1418, 1335, 1293, 1105, 1084, 1057, 1030, 1005, 891, 866, 847, 838, 812.

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 (25cb')



According to the TP5, a solution of 1-(iodomethyl)-4-isopropylbenzene (0.20 M, 0.20 mmol, 1.0 equiv) and acetophenone (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^{-1} 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 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).

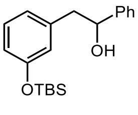
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.9, 147.4, 134.0, 130.7 (2C), 128.2 (2C), 126.7, 126.4 (2C), 125.1 (2C), 74.5, 50.1, 33.8, 29.6, 24.1, 24.1.

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 (28ac)



According to the TP5, a solution of *tert*-butyl(3-(iodomethyl)phenoxy)dimethylsilane (0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (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^{-1} 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 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).

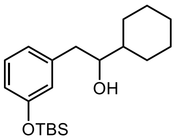
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 155.9, 143.8, 139.6, 129.6, 128.5 (2C), 127.7, 126.0 (2C), 122.6, 121.4, 118.5, 75.4, 46.1, 25.8 (3C), 18.3, -4.3 (2C).

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 (28ao')



According to the TP5, a solution of *tert*-butyl(3-(iodomethyl)phenoxy)dimethylsilane (0.20 M, 0.20 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (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^{-1} 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$_4$Cl 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$_2$SO$_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound 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).

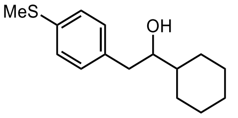
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 155.9, 140.8, 129.6, 122.5, 121.3, 118.2, 77.0, 43.2, 40.9, 29.5, 28.1, 26.7, 26.5, 26.3, 25.8 (3C), 18.3, -4.2 (2C).

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 (28bo')



According to the TP5, a solution of (4-(iodomethyl)phenyl)(methyl)sulfane (0.20 M, 0.20 mmol, 1.0 equiv) and cyclohexanecarboxaldehyde (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^{-1} 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 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).

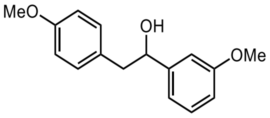
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 136.3, 136.2, 130.0 (2C), 127.2 (2C), 77.0, 43.3, 40.3, 29.5, 28.1, 26.7, 26.4, 26.7, 16.3.

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 (28cn')



According to the TP5, a solution of 1-(iodomethyl)-4-methoxybenzene (0.20 M, 0.20 mmol, 1.0 equiv) and *m*-anisaldehyde (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^{-1} 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 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).

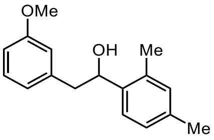
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.8, 158.5, 145.7, 130.6 (2C), 130.0, 129.5, 118.4, 114.1 (2C), 113.3, 111.4, 75.5, 55.4, 55.4, 45.3.

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 (28dp')



According to the TP5, a solution of 1-(iodomethyl)-3-methoxybenzene (0.20 M, 0.20 mmol, 1.0 equiv) and 2,4-dimethylbenzaldehyde (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^{-1} 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 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).

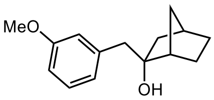
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 159.8, 140.2, 139.2, 137.0, 134.4, 131.2, 129.7, 127.1, 125.3, 121.9, 115.2, 112.1, 71.7, 55.3, 45.2, 21.1, 19.1.

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 (28da')



According to the TP5, a solution of 1-(iodomethyl)-3-methoxybenzene (0.20 M, 0.20 mmol, 1.0 equiv) and norcamphor (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^{-1} 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 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).

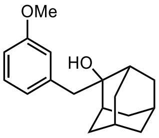
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 159.6, 139.4, 129.4, 123.1, 116.4, 111.9, 79.3, 55.3, 48.0, 45.9, 45.8, 38.7, 37.5, 28.8, 22.2.

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 (28dt)



According to the TP5, a solution of 1-(iodomethyl)-3-methoxybenzene (0.20 M, 0.20 mmol, 1.0 equiv) and adamantanone (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^{-1} 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 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.

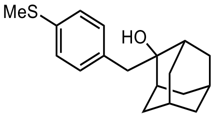
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3510, 2962, 2942, 2930, 2899, 2853, 1742, 1600, 1590, 1489, 1471, 1462, 1432, 1374, 1260, 1228, 1168, 1123, 1101, 1084, 1061, 1035, 1010, 993, 929, 922, 791, 739, 716, 694.

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 (28bt)



According to the TP5, a solution of (4-(iodomethyl)phenyl)(methyl)sulfane (0.20 M, 0.20 mmol, 1.0 equiv) and adamantanone (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^{-1} 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 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).

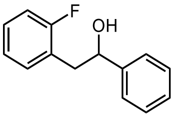
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 136.4, 134.3, 131.2 (2C), 126.7 (2C), 74.8, 43.4, 38.5, 36.9 (2C), 34.7 (2C), 33.1 (2C), 27.6, 27.4, 16.1.

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 (31ac)



According to the TP5, a solution of 1-fluoro-2-(iodomethyl)benzene (0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (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^{-1} 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 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).

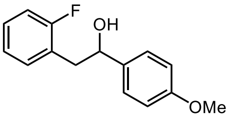
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 163.0 (d, *J* = 245.7 Hz), 143.7, 140.7 (d, *J* = 7.3 Hz), 130.0 (d, *J* = 8.3 Hz), 128.7, 128.0 (2C), 126.0 (2C), 125.3 (d, *J* = 2.8 Hz), 116.5 (d, *J* = 21.0 Hz), 113.6 (d, *J* = 21.0 Hz), 75.3, 45.8.

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$_2$O] calcd for $C_{14}H_{11}F$ 198.0845; Found 198.0803.

2-(2-Fluorophenyl)-1-(4-methoxyphenyl)ethan-1-ol (31ad')



According to the TP5, a solution of 1-fluoro-2-(iodomethyl)benzene (0.20 M, 0.20 mmol, 1.0 equiv) and *p*-methoxybenzaldehyde (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^{-1} 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$_4$Cl 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$_2$SO$_4$ and filtrated. After removal of the solvent, flash chromatographical purification (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound 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).

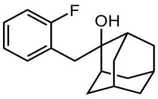
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 162.8 (d, *J* = 245.7 Hz), 159.2, 140.8 (d, *J* = 7.3 Hz), 135.7, 129.8 (d, *J* = 8.4 Hz), 127.2 (2C), 125.2 (d, *J* = 2.8 Hz), 116.4 (d, *J* = 21.0 Hz), 113.9 (2C), 113.4 (d, *J* = 21.0 Hz), 74.8, 55.3, 45.6.

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 (31at)



According to the TP5, a solution of 1-fluoro-2-(iodomethyl)benzene (0.20 M, 0.20 mmol, 1.0 equiv) and adamantanone (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^{-1} 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 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.

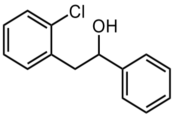
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3478, 2905, 2855, 1616, 1586, 1487, 1444, 1251, 1141, 1098, 1042, 1018, 1010, 994, 927, 786, 747, 718, 688.

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 (31bc)



According to the TP5, a solution of 1-chloro-2-(iodomethyl)benzene (0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (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^{-1} 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 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.

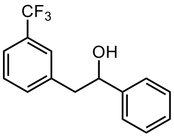
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3288, 3260, 3234, 3192, 3061, 3030, 2927, 1472, 1444, 1418, 1400, 1326, 1288, 1203, 1049, 1040, 1030, 1002, 994, 910, 874, 747, 695, 682.

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 (31cc)



According to the TP5, a solution of 1-(iodomethyl)-3-(trifluoromethyl)benzene (0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (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^{-1} 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 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).

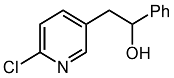
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 143.5, 139.1, 133.0 (d, *J* = 1.4 Hz), 130.6 (q, *J* = 32.2 Hz), 128.7, 128.6 (2C), 127.9, 126.3 (q, *J* = 3.8 Hz), 125.9 (2C), 124.2 (q, *J* = 272.6 Hz), 123.4 (q, *J* = 3.8 Hz), 75.2, 45.6.

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 (34ac)



According to the TP5, a solution of 2-chloro-5-(iodomethyl)pyridine (0.20 M, 0.20 mmol, 1.0 equiv) and benzaldehyde (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^{-1} 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 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.

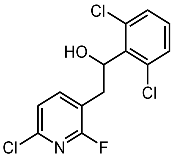
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3345, 2917, 1586, 1568, 1459, 1434, 1407, 1386, 1312, 1302, 1292, 1214, 1202, 1140, 1110, 1092, 1076, 1060, 1027, 1003, 826, 813, 763, 738, 699, 685.

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 (34bq')



According to the TP5, a solution of 6-chloro-2-fluoro-3-(iodomethyl)pyridine (0.20 M, 0.20 mmol, 1.0 equiv) and 2,6-dichlorobenzaldehyde (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^{-1} 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 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).

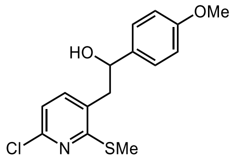
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.0 (d, *J*=245.4), 147.0 (d, *J*=14.0), 144.2 (d, *J*=5.6, 2C), 136.2 (2C), 134.4, 129.7 (2C), 121.8 (d, *J*=5.1), 118.1 (d, *J*=29.3), 71.5, 34.1 (d, *J*=2.7).

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 (34cd')



According to the TP5, a solution of 6-chloro-3-(iodomethyl)-2-(methylthio)pyridine (0.20 M, 0.20 mmol, 1.0 equiv) and *p*-methoxybenzaldehyde (**2c**, 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^{-1} 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 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.

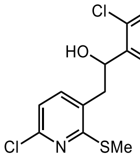
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3342, 3284, 2923, 2853, 2838, 1610, 1575, 1549, 1511, 1461, 1439, 1412, 1366, 1343, 1322, 1296, 1246, 1219, 1202, 1178, 1168, 1132, 1073, 1058, 1045, 1026, 1001, 861, 838, 822, 782, 736, 726, 705.

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 (34cq')



According to the TP5, a solution of 6-chloro-3-(iodomethyl)-2-(methylthio)pyridine (0.20 M, 0.20 mmol, 1.0 equiv) and 2,6-dichlorobenzaldehyde (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^{-1} 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 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.

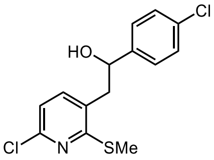
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3402, 2926, 1577, 1554, 1435, 1409, 1364, 1312, 1297, 1248, 1220, 1202, 1170, 1148, 1132, 1087, 1078, 1056, 971, 964, 862, 835, 811, 778, 766, 751, 722, 710, 666.

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 (34cr')



According to the TP5, a solution of 6-chloro-3-(iodomethyl)-2-(methylthio)pyridine (0.20 M, 0.20 mmol, 1.0 equiv) and 4-chlorobenzaldehyde (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^{-1} 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 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).

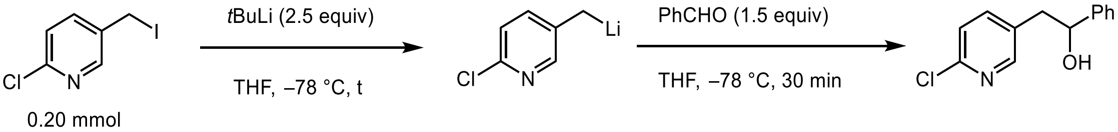
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.3, 149.2, 142.3, 139.9, 133.6, 129.7, 128.8 (2C), 127.2 (2C), 119.0, 71.9, 42.0, 13.6.

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.

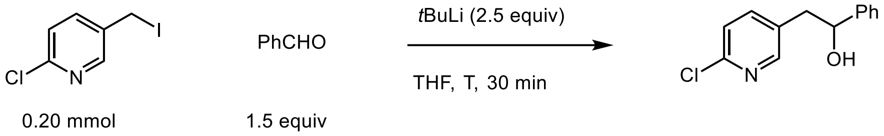
Typical procedure for the sequential batch method



Scheme 64: Typical procedure for the sequential batch method.

To 2-chloro-5-(iodomethyl)pyridine (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 (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.

Typical procedure for the Barbier-type batch method

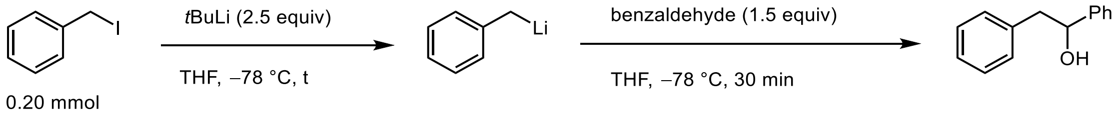


Scheme 65:Typical procedure for the Barbier-type batch method

To 2-chloro-5-(iodomethyl)pyridine (0.20 mmol, 1.0 equiv) and benzaldehyde (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.

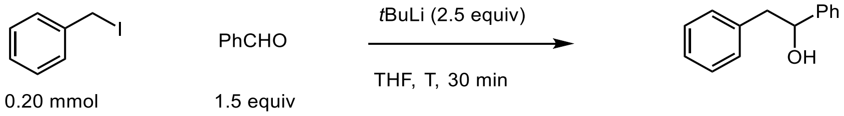
Batch screening results

1,2-Diphenylethan-1-ol



Scheme 66: Screening results for sequential batch method of benzyl lithium with benzaldehyde.

According to the typical procedure for the sequential batch approach, to a solution of benzyl iodide (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 (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 67: Screening results for Barbier-type batch method of benzyl lithium with benzaldehyde affording 1,2-diphenylethan-1-ol.

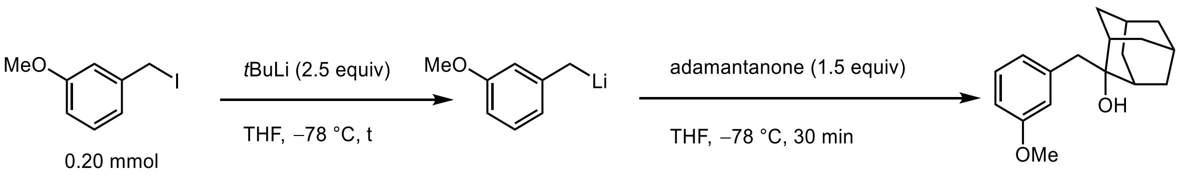
According to the typical procedure for the Barbier-type batch reactions, to a solution of benzyl iodide (44 mg, 0.20 mmol, 1.0 equiv) and benzaldehyde (32 mg, 0.30 mmol, 1.5 equiv) in THF (1.0 mL), *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv) was added at an indicated temperature T (T_1 = −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 analysed *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. The title compound was obtained as colorless crystals (16 mg, 0.08 mmol, 40% yield).

Table 29: Batch screening of reaction between benzyl iodide and benzaldehyde affording 1,2-diphenylethan-1-ol .

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

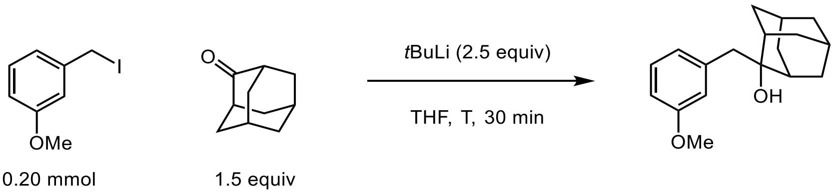
GC-yields were calculated by normation of the isolated yield. [a] Isolated yield.

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



Scheme 68: Screening results for sequential batch method of 3-methoxyiodomethylbenzene with adamantanone.

According to the typical procedure for the sequential batch approach, to a solution of 3-methoxyiodomethylbenzene (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 (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 69: Screening results for Barbier-type batch method of 3-methoxyiodomethylbenzene with adamantanone.

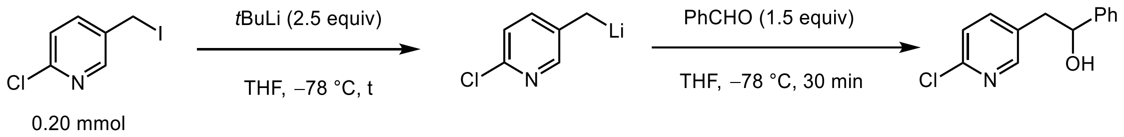
According to the typical procedure for the Barbier-type batch reactions, to a solution of 3-methoxyiodomethylbenzene (50 mg, 0.20 mmol, 1.0 equiv) and adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF (1.0 mL), *t*BuLi (1.0 mL, 0.50 M in hexane, 0.50 mmol, 2.5 equiv) was added at an indicated temperature 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 analysed *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. The title compound was obtained as colorless crystals (8 mg, 0.03 mmol, 15% yield).

Table 30: Batch screening of reaction between 3-methoxyiodomethylbenzene and adamantanone affording product 2-(3-methoxybenzyl)adamantan-2-ol.

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

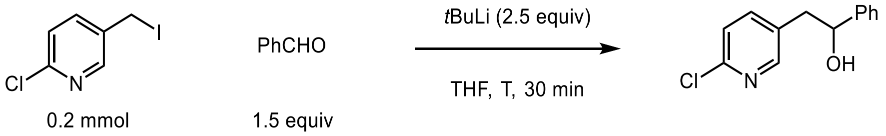
GC-yields were calculated by normation using the isolated yield. [a] Isolated yield.

2-(6-Chloropyridin-3-yl)-1-phenylethan-1-ol



Scheme 70: Screening results for sequential batch method of 2-chloroiodomethylpyridine with benzaldehyde.

According to the typical procedure for the sequential batch approach, to a solution of 2-chloro-5-iodomethylpyridine (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 (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.



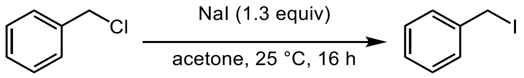
Scheme 71: Screening results for Barbier-type batch method of 2-chloroiodomethylpyridine with benzaldehyde.

According to the typical procedure for the Barbier-type batch reactions, to a solution of 2-chloro-5-iodomethylpyridine (51 mg, 0.20 mmol, 1.0 equiv) and benzaldehyde (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 31: Batch screening of reaction between 2-chloroiodomethylpyridine and benzaldehyde affording product 2-(6-chloropyridin-3-yl)-1-phenylethan-1-ol .

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

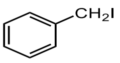
Typical procedure for the preparation of (hetero)benzylic iodides



Scheme 72: Typical procedure for the preparation of (hetero)benzylic iodides.

(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 (23a)



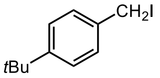
(Chloromethyl)benzene (1.26 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred 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.[274]

1-(*Tert*-butyl)-4-(iodomethyl)benzene (23b)



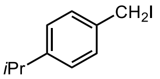
1-(*Tert*-butyl)-4-(chloromethyl)benzene (1.82 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues 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).

^{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.[275]

1-(Iodomethyl)-4-*iso*propylbenzene (23c)



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

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[274] S. H. Combe, A. Hosseini, L. Song, H. Hausmann, P. R. Schreiner, *Org. Lett.* **2017**, *19*, 6156.

[275] J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson, *ACS Catal.* **2019**, *9*, 9568.

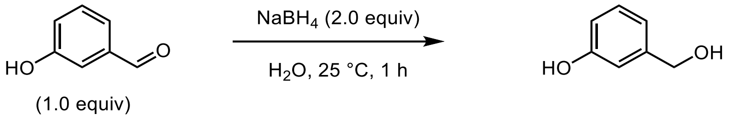
added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as brown oil (2.18 g, 8.4 mmol, 84% yield), which was stored at −24 °C together with a copper turning.

^{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.[276]

3-(Hydroxymethyl)phenol



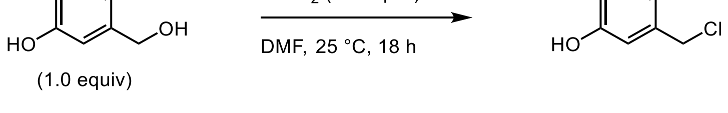
According to literature[277], 2-hydroxybenzaldehyde (3.96 g, 32.4 mmol, 1.0 equiv) was dissolved in water (90 mL). NaBH$_4$ (2.45 g, 64.8 mmol, 2.0 equiv) was added in portions and the mixture was stirred for 1 h at 25 °C. The reaction mixture was cooled to 0 °C and 6 M HCl was added until pH 5 was reached. 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.

^{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.[278]

3-(Chloromethyl)phenol



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

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[276] J. S. Ruso, N. Rajendiran, R. S. Kumaran, *J. Korean Chem. Soc.* **2014**, *58*, 39.
[277] M. Guiso, A. Betrow, C. Marra, *Eur. J. Org. Chem.* **2008**, *11*, 1967.
[278] S. Aoun, P. Sierocki, A. Lebreton, M. Mathé-Allainmat, *Synthesis* **2019**, *51*, 3556.

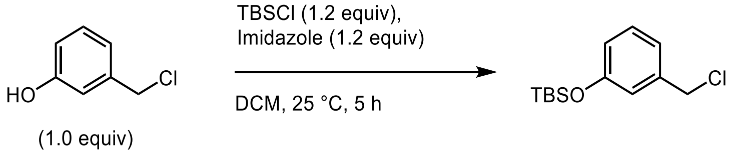
(5x100 mL) and dried over $MgSO_4$. Solvents were removed *in vacuo* and the residue was purified by flash column chromatography (isohexane:EtOAc = 9:1) to obtain the title compound as yellow oil (1.15 g, 8.1 mmol, 29% yield).

^{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.[279]

Tert-butyl(3-(chloromethyl)phenoxy)dimethylsilane



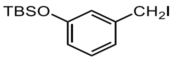
To a solution of 3-(Chloromethyl)phenol (1.15 g, 8.1 mmol, 1.0 equiv) and imidazole (0.66 g, 9.7 mmol, 1.2 equiv) in DCM (40 mL) TBSCl (1. 46 g, 9.7 mmol, 1.2 equiv) was added in portions. The mixture was stirred for 5 h at 25 °C. After the reaction was completed, water (50 mL) was added and the aqueous 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).

^{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.[280]

Tert-butyl(3-(iodomethyl)phenoxy)dimethylsilane (26a)



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

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[279] M.-F. Pouliot, O. Mahé, J.-D. Hamel, J. Desroches, J.-F. Paquin, *Org. Lett.* **2012**, *14*, 5428.

[280] P. H. Huy, I. Filbrich, *Chem. Eur. J.* **2018**, *24*, 7410.

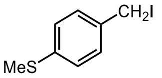
turning was added to the filtrate and the solvents were removed *in vacuo* to obtain the desired product as a slightly brown amorphous solid (1.95 g, 5.6 mmol, 56% yield), which was stored at −24 °C together with a copper turning.

^{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.[281]

(4-(Iodomethyl)phenyl)(methyl)sulfane (26b)



(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 $MgSO_4$. 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).

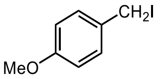
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 138.7, 136.1, 129.3 (2C), 126.8 (2C), 15.8, 5.9.

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 (26c)



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

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[281] D. B. Berkowitz, J. M. McFadden, M. K. Sloss, *J. Org. Chem.* **2000**, *65*, 2907.

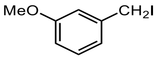
covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with *sat. aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined 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.[282]

1-(Iodomethyl)-3-methoxybenzene (26d)



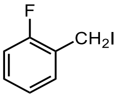
1-(Chloromethyl)-3-methoxybenzene (1.56 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues 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.[283]

1-Fluoro-2-(iodomethyl)benzene (29a)



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

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[282] N. Iranpoor, H. Firouzabadi, A. Jamalian, F. Kazemi, *Tetrahedron*, **2005**, *61*, 5699.

[283] M. Rafiee, F. Wang, D. P. Hruszkewycz, S. S. Stahl, *J. Am. Chem. Soc.* **2018**, *140*, 22.

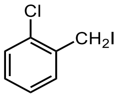
aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were transferred with Et_2O (30 mL) into a separatory funnel and washed with *sat. aq.* $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers 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.[284]

1-Chloro-2-(iodomethyl)benzene (29b)



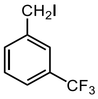
1-Chloro-2-(chloromethyl)benzene (1.61 g, 10.0 mmol, 1.0 equiv) was dissolved in dry acetone (120 mL) and NaI (2.18 g, 13.0 mmol, 1.3 equiv) was added in a flame dried flask covered in aluminium foil. The mixture was stirred for 16 h at 25 °C. Solvents were evaporated *in vacuo*. The crude residues were 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.[285]

1-(Iodomethyl)-3-(trifluoromethyl)benzene (29c)



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[284] J. A. Ayres, M. W. Ashford, Y. Stöckl, V. Prudhomme, K. B. Ling, J. A. Platts, L. C. Morrill, *Org. Lett.* **2017**, *19*, 3835.

[285] S. H. Combe, A. Hosseini, L. Song, H. Hausmann, P. R. Schreiner, *Org. Lett.* **2017**, *19*, 6156.

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).

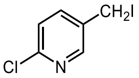
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.4, 132.2 (d, *J*=1.4), 131.3 (q, *J*=32.6), 129.5, 125.5 (q, *J*=3.8), 124.8 (q, *J*=3.8), 124.0 (q, *J*=272.3 Hz), 3.6.

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 (32a)



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 crystals (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).

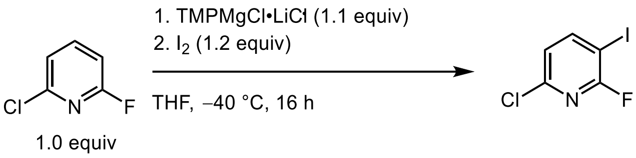
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 150.7, 149.2, 139.4, 134.5, 124.6, -0.8.

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



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).

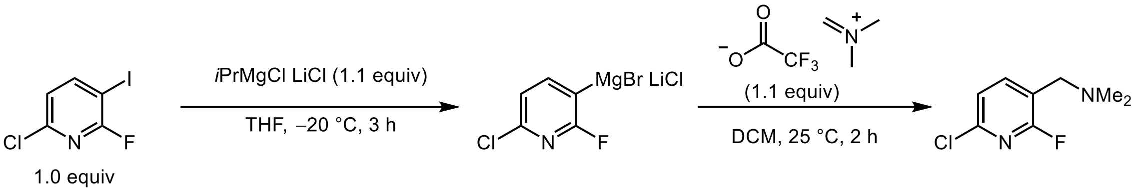
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.1 (d, *J*=241.5), 151.8 (d, *J*=3.0), 149.2 (d, *J*=12.6), 123.4 (d, *J*=5.4), 73.3 (d, *J*=41.4).

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.[286]

1-(6-Chloro-2-fluoropyridin-3-yl)-*N,N*-dimethylmethanamine



According to literature,[Fehler! Textmarke nicht definiert.] to 6-chloro-2-fluoro-3-iodopyridine (7.70 g, 3 0 mmol, 1.0 equiv) 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

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[286] N. M. Barl, E. Sansiaume-Dagousset, G. Monzón, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422.

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 (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).

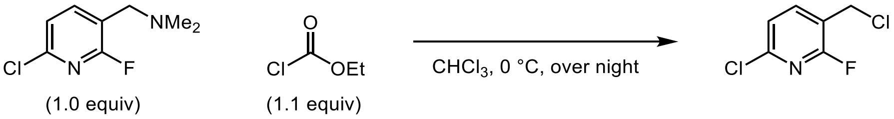
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.6 (d, *J*=245.8), 147.4, 144.13 (d, *J*=5.3), 122.0, 121.9, 55.5 (d, *J*=2.7), 45.2 (2C).

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.[287]

6-Chloro-3-(chloromethyl)-2-fluoropyridine



According to literature, 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.[287]

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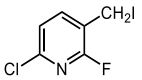
[287] N. M. Barl, E. Sansiaume-Dagousset, G. Monzón, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422.

6-Chloro-2-fluoro-3-(iodomethyl)pyridine (32b)



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.

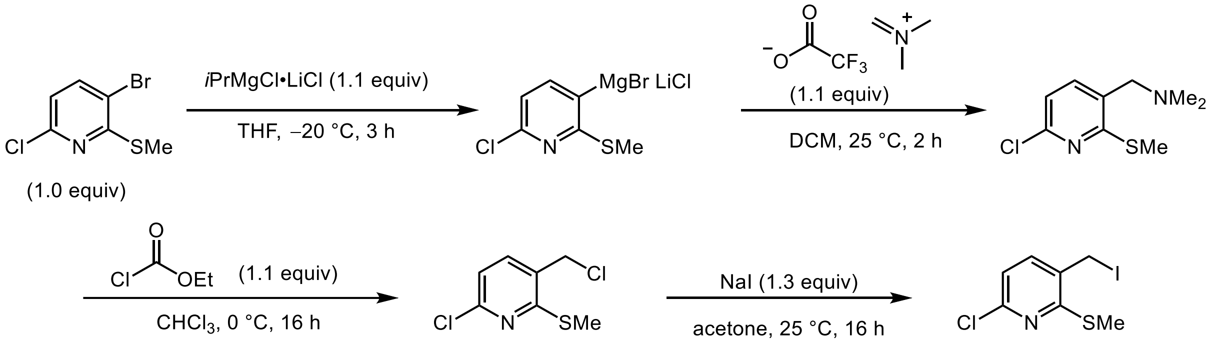
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 (dd, *J*=9.5, 7.8, 1H), 7.20 (dd, *J*=7.8, 0.9, 1H), 4.35 (s, 2H).

^{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 (32c)



According to literature,[288] 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 mL, 14.9 mmol, 1.1 equiv) in DCM (15 mL)

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[288] N. M. Barl, E. Sansiaume-Dagousset, G. Monzón, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422.

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,[289] 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).

^{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).

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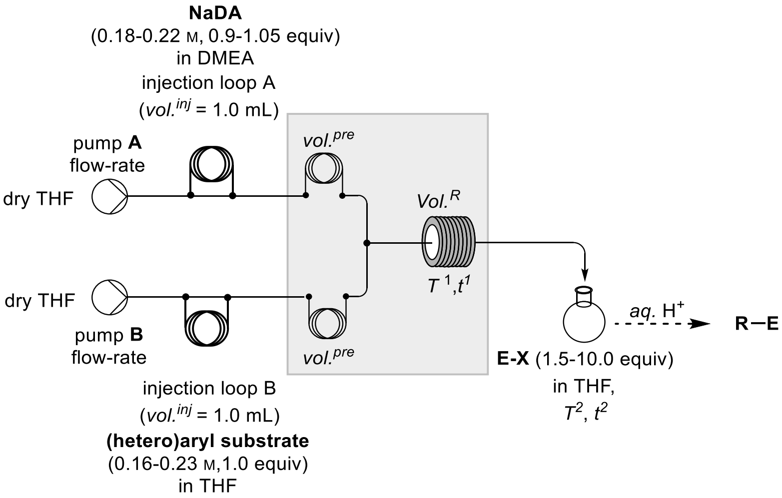
[289] N. M. Barl, E. Sansiaume-Dagousset, G. Monzón, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422.

HRMS (EI-orbitrap): *m/z:* [M] calcd for C_7H_7ClINS 298.9032; Found 298.9024.

m.p. (°C): 87.5 – 89.9.

16. SODIATION OF ARENES AND HETEROARENES IN CONTINUOUS FLOW

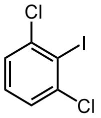
16.1 TYPICAL PROCEDURE 6 (TP6)



Scheme 73: Uniqsis flow set-up for the metalation of (hetero)aryls with sodium reagents and batch quench with an electrophile (E-X).

A NaDa solution (0.18 – 0.22 M, 0.90 or 1.05 equiv) in DMEA and a solution of the (hetero)aryl substrate (0.16 – 0.23 M, 1.0 equiv) in THF were prepared. Injection loop A (vol^{inj} =1.0 mL) was loaded with the NaDA solution and injection loop B (vol^{inj} =1.0 mL) was loaded with the solution of the substrate. The solutions were simultaneously injected into separate streams of THF (flow-rates: 5 mL·min^{-1}), which each passed a precooling loop (vol^{pre} = 1.0 mL, T^1 = –20 to –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 and stainless steel needle (vol^R = 0.08 mL; residence time: t^1 = 0.5 s, T^1 = –20 to –78 °C) changing diameter from 0.25 mm to 0.8 mm and thus achieving better mixing and was subsequently injected into a flask containing a stirred, cooled (T^2 = 0 °C) solution of an electrophile E-X (1.5 – 10.0 equiv) in THF. The reaction mixture was stirred further for the indicated times and temperatures (T^2, reaction time: t^2) and quenched with an indicated *sat. aq.* solution. The aqueous phase was extracted with EtOAc or hexane and the organic phases were dried and filtrated. After removal of the solvent in vacuo, flash column chromatographical purification with suited isohexane:EtOAc mixtures afforded the pure products R-E.

1,3-Dichloro-2-iodobenzene (37ab)



According to the TP6, a solution of 1,3-dichlorobenzene (0.18 M, 0.18 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.18 M in DMEA, 0.18 mmol, 1.05 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 (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of iodine (222 mg, 0.88 mmol, 5.0 equiv) in THF. The reaction mixture was instantly quenched by the addition of *sat. aq.* $Na_2S_2O_3$. 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 as white crystals (40 mg, 0.15 mmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 140.8, 129.8 (2C), 127.4 (2C), 103.9.

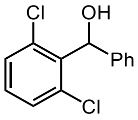
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2921, 2850, 1556, 1421, 1392, 1252, 1184, 1147, 1130, 1080, 1012, 967, 893, 769, 697, 684.

MS (EI, 70 eV): *m/z* (%) = 276 (10), 274 (64), 272 (100), 175 (19), 173 (30), 127 (23), 109 (17).

HRMS (EI): *m/z* calc. for [$C_6H_3Cl_2I$]: 271.8656; found 271.8651.

m.p. (°C): 54.7 – 58.7.

(2,6-Dichlorophenyl)(phenyl)methanol (37ac)



According to the TP6, a solution of 1,3-dichlorobenzene (0.17 M, 0.17 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.18 M in DMEA, 0.18 mmol, 1.05 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 (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred benzaldehyde solution (26 µL, 0.25 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a colorless liquid (40 mg, 0.16 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.32 (m, 4H), 7.32 – 7.27 (m, 3H), 7.22 (dd, *J* = 8.6, 7.4 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 3.43 (d, *J* = 10.3 Hz, 1H).

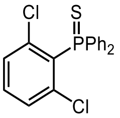
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 141.6, 137.9, 135.3 (2C), 129.6, 129.5 (2C), 128.4 (2C), 127.4 (2C), 125.5, 72.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3563, 3435, 3060, 3028, 1601, 1579, 1562, 1494, 1449, 1435, 1400, 1250, 1176, 1148, 1089, 1020, 916, 865, 826, 778, 766, 734, 695, 660.

MS (EI, 70 eV): *m/z* (%) = 254 (39), 252 (59), 251 (14), 199 (26), 177 (10), 175 (63), 173 (100), 165 (10), 152 (14), 79 (21), 78 (27), 77(14).

HRMS (EI): *m/z* calc. for [$C_{13}H_{10}Cl_2O$]: 252.0109; found 252.0105.

(2,6-Dichlorophenyl)diphenylphosphine sulfide (37as')



According to the TP6, a solution of 1,3-dichlorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of chlorodiphenylphosphane (90 µL, 0.50 mmol, 2.5 equiv) in THF. Stirring was continued for 30 min at 0 °C before sulfur (513 mg, 2.00 mmol, 10.0 equiv) was added in portions. After stirring the solution for 16 h at 25 °C, 2.0 M NaOCl was added to quench the reaction mixture. 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 as a highly viscose yellow liquid (53 mg, 0.15 mmol, 74% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.98 – 7.91 (m, 4H), 7.49 – 7.37 (m, 6H), 7.34 – 7.31 (m, 3H).

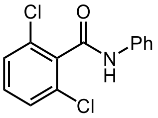
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 139.5, 139.4, 135.2, 134.4, 132.5, 132.4, 131.3 (4C), 131.2 (2C), 131.1 (2C), 128.8 (2C), 128.6 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 2977, 1732, 1568, 1552, 1480, 1437, 1416, 1372, 1395, 1240, 1185, 1146, 1093, 1044, 998, 900, 773, 722, 694, 688.

MS (EI, 70 eV): *m/z* (%) = 329 (33), 328 (19), 327 (100), 219 (15), 217 (47), 183 (28), 181 (14).

HRMS (EI): *m/z* calc. for [$C_{18}H_{13}Cl_2PS$]: 361.9850; found 361.9846.

2,6-Dichloro-*N*-phenylbenzamide (37af')



According to the TP6, a solution of 1,3-dichlorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of isocyanatobenzene (55 µL, 0.50 mmol, 2.5 equiv) in THF. The reaction mixture was instantly 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 as a white solid (34 mg, 0.13 mmol, 64% yield).

^{1}H-NMR (400 MHz, CD_3CN): δ / ppm = 8.87 (s, 1H), 7.67 – 7.60 (m, 2H), 7.48 – 7.44 (m, 2H), 7.43 – 7.36 (m, 3H), 7.21 – 7.15 (m, 1H).

^{13}C-NMR (100 MHz, CD_3CN): δ / ppm = 163.5, 139.3, 137.0, 132.6, 132.2 (2C), 130.0 (2C), 129.1 (2C), 125.6, 120.7 (2C).

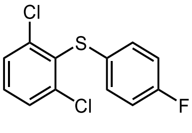
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3240, 2193, 3131, 3064, 3042, 1653, 1620, 1598, 1579, 1552, 1534, 1491, 1448, 1430, 1376, 1324, 1268, 1235, 1194, 1177, 1145, 1087, 1026, 915, 887, 798, 778, 759, 744, 701, 685.

MS (EI, 70 eV): *m/z* (%) = 177 (10), 175 (64), 109 (11).

HRMS (EI): *m/z* calc. for [$C_{10}H_8N$]: 265.0061; found 265.0056.

m.p. (°C): 175.5 – 177.5.

(2,6-Dichlorophenyl)(4-fluorophenyl)sulfane (37at')



According to the TP6, a solution of 1,3-dichlorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of (4-fluorophenyl)benzenesulfonothioate (134 mg, 0.50 mmol, 2.5 equiv) in THF. The reaction mixture was instantly quenched by the addition of 2.0 M NaOCl. 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 as a colorless liquid (41 mg, 0.15 mmol, 75% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.48 – 7.44 (m, 2H), 7.31 – 7.28 (m, 1H), 7.25 – 7.19 (m, 2H), 7.01 – 6.95 (m, 2H).

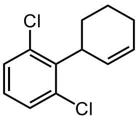
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 161.9 (d, *J* = 246.5 Hz), 141.8, 132.3 (2C), 130.9 (d, *J* = 2.1 Hz), 130.8 (2C), 130.6 (d, *J* = 3.3 Hz, 2C), 129.1, 116.3 (d, *J* = 22.1 Hz, 2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1589, 1565, 1553, 1487, 1423, 1400, 1292, 1226, 1187, 1155, 1140, 1106, 1088, 1042, 1012, 821, 773, 734, 711, 698, 676, 667, 659.

MS (EI, 70 eV): *m/z* (%) = 274 (21), 272 (30), 203 (12), 202 (100), 157 (12).

HRMS (EI): *m/z* calc. for [$C_{12}H_7Cl_2FS$]: 271.9630; found 271.9623.

2',6'-Dichloro-1,2,3,4-tetrahydro-1,1'-biphenyl (37ah)



According to the TP6, a solution of 1,3-dichlorobenzene (0.17 M, 0.17 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.18 M in DMEA, 0.18 mmol, 1.05 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 (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohex-1-ene (49 µL, 0.42 mmol, 2.5 equiv) and CuCN·2LiCl (20 µL, 0.02 mmol, 0.1 equiv) in THF. The reaction mixture was instantly 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 as a colorless oil (28 mg, 0.13 mmol, 75% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.33 – 7.26 (m, 2H), 7.08 (t, *J* = 8.0 Hz, 1H), 5.80 (dddd, *J* = 7.8, 5.0, 2.9, 1.0 Hz, 1H), 5.64 (ddd, *J* = 10.1, 2.9, 1.5 Hz, 1H), 4.34 (dddd, *J* = 12.0, 7.0, 4.0, 2.5 Hz, 1H), 2.20 – 1.67 (m, 6H).

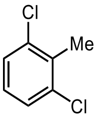
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 140.4, 129.1 (2C), 127.7 (3C), 126.8 (2C), 40.0, 26.5, 24.6, 23.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2931, 2859, 1580, 1559, 1430, 1246, 1182, 1149, 1080, 1045, 983, 933, 900, 846, 797, 775, 761, 729, 718, 690.

MS (EI, 70 eV): *m/z* (%) = 226 (100), 213 (28), 211 (45), 191 (18), 187 (15), 185 (23), 176 (17), 174 (47), 172 (75), 165 (27), 163 (88), 161 (13), 159 (22), 156 (12), 155 (29), 150 (20), 149 (26), 137 (19), 128 (65), 127 (19), 115 (25), 76 (14), 67 (13).

HRMS (EI): *m/z* calc. for [$C_{12}H_{12}Cl_2$]: 226.0316; found 226.0311.

1,3-Dichloro-2-methylbenzene (37au')



According to the TP6, a solution of 1,3-dichlorobenzene (0.19 M, 0.38 mmol) in THF (total volume: 2 mL) and a solution of NaDA (0.20 M in DMEA, 0.400 mmol, 1.05 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 (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of iodomethane (60 µL, 1.90 mmol, 5.0 equiv) in THF. The reaction mixture was instantly quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with hexane (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, pentane) afforded the title compound as a colorless liquid (33 mg, 0.21 mmol, 54% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.27 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 1H), 2.47 (s, 3H).

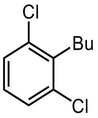
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 135.6 (2C), 134.6, 127.9 (2C), 127.3, 17.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2854, 1561, 1434, 1378, 1269, 1202, 1153, 1086, 1054, 1000, 804, 769, 759, 692.

MS (EI, 70 eV): *m/z* (%) = 162 (31), 160 (49), 127 (33), 125 (100), 89 (28).

HRMS (EI): *m/z* calc. for [$C_7H_6Cl_2$]: 159.9847; found 159.9840.

2-Butyl-1,3-dichlorobenzene (37av')



According to the TP6, a solution of 1,3-dichlorobenzene (0.19 M, 0.19 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.05 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 (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of *n*butyl bromide (0.20 mL, 1.90 mmol, 10.0 equiv) in THF. The reaction mixture was instantly quenched by the addition of *sat. aq.* NH_4Cl. The aqueous phase was extracted three times with hexane (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, pentane) afforded the title compound as a colorless liquid (20 mg, 0.10 mmol, 53% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.26 (d, *J* = 8.0 Hz, 2H), 7.06 – 7.01 (m, 1H), 3.08 – 2.79 (m, 2H), 1.62 – 1.51 (m, 2H), 1.50 – 1.40 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

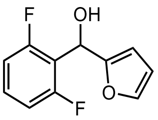
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 138.9 (2C), 135.4, 128.2 (2C), 127.4, 31.2, 30.5, 22.9, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2928, 2871, 2860, 1582, 1561, 1466, 1456, 1434, 1379, 1265, 1192, 1182, 1152, 1104, 1086, 1078, 962, 927, 822, 799, 790, 771, 758, 721.

MS (EI, 70 eV): *m/z* (%) = 204 (20), 202 (31), 163 (11), 162 (23), 161 (65), 160 (35), 159 (100), 127 (12), 125 (34), 123 (19), 89 (20).

HRMS (EI): *m/z* calc. for [$C_{10}H_{12}Cl_2$]: 202.0316; found 202.0308.

(2,6-Difluorophenyl)(furan-2-yl)methanol (37bw')



According to the TP6, a solution of 1,3-difluorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –40 °C) and was subsequently injected in a flask containing a stirred solution of furan-2-carbaldehyde (25 µL, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly quenched by the addition of *sat. aq.* NH$_4$Cl. 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 = 10:1) afforded the title compound as a highly viscose brown liquid (37 mg, 0.18 mmol, 88% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.40 (d, *J* = 1.0 Hz, 1H), 7.34 – 7.24 (m, 1H), 6.93 (t, *J* = 8.4 Hz, 2H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.21 (d, *J* = 3.3 Hz, 1H), 6.17 (s, 1H), 2.92 (s, 1H).

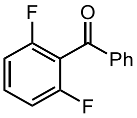
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 161.0 (dd, *J* = 248.9, 7.9 Hz, 2C), 153.8, 142.8, 130.1 (t, *J* = 10.7 Hz), 116.9 (t, *J* = 16.5 Hz), 112.0 (d, *J* = 25.5 Hz, 2C), 110.6, 107.3, 62.3 (t, *J* = 4.3 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3410, 3115, 2926, 2855, 1758, 1703, 1624, 1593, 1468, 1396, 1336, 1270, 1233, 1192, 1144, 1086, 994, 940, 898, 886, 783, 740, 722.

MS (EI, 70 eV): *m/z* (%) = 210 (20), 193 (26), 183 (10), 182 (100), 173 (11), 164 (21), 153 (15), 141 (88), 138 (10), 133 (14), 127 (12).

HRMS (EI): *m/z* calc. for [$C_{11}H_8F_2O_2$]: 210.0492; found 210.0487.

(2,6-Difluorophenyl)(phenyl)methanone (37bx')



According to the TP6, a solution of 1,3-difluorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –40 °C) and was subsequently injected in a flask containing a stirred solution of benzoyl chloride (57 µL, 0.49 mmol, 2.5 equiv) in THF. The reaction mixture was instantly 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 = 95:5) afforded the title compound as a colorless liquid (30 mg, 0.14 mmol, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 – 7.85 (m, 2H), 7.66 – 7.59 (m, 1H), 7.53 – 7.40 (m, 3H), 7.06 – 6.96 (m, 2H).

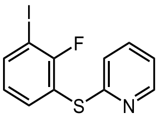
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 189.1, 160.0 (dd, *J* = 251.7, 7.6 Hz, 2C), 137.0, 134.4, 132.0 (t, *J* = 9.9 Hz), 129.8 (2C), 128.9 (2C), 117.2 (t, *J* = 21.8 Hz), 112.2 – 111.8 (m, 2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1672, 1621, 1588, 1583, 1462, 1449, 1316, 1294, 1275, 1266, 1233, 1180, 1145, 1072, 1026, 1004, 926, 847, 800, 762, 732, 696, 686.

MS (EI, 70 eV): *m/z* (%) = 218 (57), 198 (34), 141 (97), 114 (15), 105 (100), 77 (53), 74 (10), 63 (27).

HRMS (EI): *m/z* calc. for [$C_{13}H_8F_2O$]: 218.0543; found 218.0538.

2-((2-Fluoro-3-iodophenyl)thio)pyridine (37cu)



According to the TP6, a solution of 1-fluoro-2-iodobenzene (0.19 M, 0.19 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.05 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 (0.5 s, –40 °C) and was subsequently injected in a flask containing a stirred solution of aldrithiol (105 mg, 0.48 mmol, 2.5 equiv) in THF. The reaction mixture was instantly quenched by the addition of 2.0 M NaOCl. 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 as a white solid (39 mg, 0.12 mmol, 62% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.41 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.82 (ddd, *J* = 7.9, 5.7, 1.6 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.09 – 7.01 (m, 2H), 6.95 (td, *J* = 7.8, 0.7 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 161.5 (d, *J* = 247.0 Hz), 158.4 (d, *J* = 1.3 Hz), 149.9, 141.0 (d, *J* = 1.8 Hz), 137.2, 136.9, 126.5 (d, *J* = 4.6 Hz), 121.9, 120.7, 119.3 (d, *J* = 21.1 Hz), 82.3 (d, *J* = 27.5 Hz).

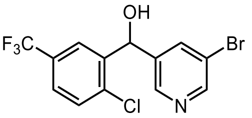
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1574, 1559, 1556, 1447, 1428, 1418, 1277, 1223, 1152, 1129, 1087, 1082, 1055, 1046, 990, 882, 819, 776, 770, 760, 741, 724, 711.

MS (EI, 70 eV): *m/z* (%) = 312 (19), 205 (12), 204 (100), 203 (11), 185 (16), 127 (47).

HRMS (EI): *m/z* calc. for [$C_{11}H_7FINS$]: 330.9328; found 330.9325.

m.p. (°C): 72.3 – 74.1.

(5-Bromopyridin-3-yl)(2-chloro-5-(trifluoromethyl)phenyl)methanol (37dy)



According to the TP6, a solution of 1-chloro-4-(trifluoromethyl)benzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –40 °C) and was subsequently injected in a flask containing a stirred solution of 5-bromonicotinaldehyde (93 mg, 0.50 mmol, 1.5 equiv) in THF. The reaction mixture was instantly quenched by the addition of *sat. aq.* NH$_4$Cl. 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 as a colorless viscous liquid (62 mg, 0.17 mmol, 85% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.48 (d, *J* = 17.6 Hz, 2H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.83 (t, *J* = 2.0 Hz, 1H), 7.54 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 6.21 (s, 1H), 3.86 (s, 1H).

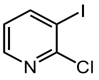
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 150.3, 146.7, 140.9, 139.2, 137.5, 135.9, 135.9, 130.5, 130.3 (q, *J* = 33.2 Hz), 126.4 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 3.8 Hz), 122.4 (q, *J* = 272.4 Hz), 69.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3165, 2848, 1611, 1583, 1562, 1478, 1421, 1323, 1275, 1248, 1202, 1167, 1122, 1099, 1079, 1036, 1021, 916, 886, 873, 826, 768, 737, 708, 695, 661, 654.

MS (EI, 70 eV): *m/z* (%) = 209 (26), 207 (24), 184 (11), 179 (28), 163 (25), 161 (82), 160 (32), 159 (12), 158 (99), 157 (13), 156 (100), 145 (58), 144 (15), 143 (17), 131 (27), 129 (26), 125 (41), 78 (23), 76 (34), 75 (13), 74 (12), 39 (36), 50 (18).

HRMS (EI): *m/z* calc. for [$C_{13}H_8BrClF_3NO$]: 364.9430; found 364.9415.

3-(Butylthio)-2-chloropyridine (37eb)



According to the TP6, a solution of 2-chloropyridine (0.17 M, 0.17 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.18 M in DMEA, 0.18 mmol, 1.05 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 (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of iodine (216 mg, 0.84 mmol, 5.0 equiv) in THF. The reaction mixture was instantly quenched by the addition of *sat. aq.* $Na_2S_2O_3$. 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 as white crystals (24 mg, 0.09 mmol, 53% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.37 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.15 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.8, 4.7 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 154.6, 148.9, 148.8, 123.2, 94.9.

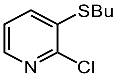
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920, 2851, 1554, 1546, 1385, 1252, 1208, 1135, 1057, 1011, 1004, 982, 794, 742, 720.

MS (EI, 70 eV): *m/z* (%) = 241 (32), 239 (100), 127 (20), 114 (11), 112 (31), 76 (15).

HRMS (EI): *m/z* calc. for [C_5H_3ClIN]: 238.8999; found 238.8993.

m.p. (°C): 92.7 – 93.7.

3-(Butylthio)-2-chloropyridine (37ez)



According to the TP6, a solution of 2-chloropyridine (0.17 M, 0.17 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.18 M in DMEA, 0.18 mmol, 1.05 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 (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfid (94 µL, 0.42 mmol, 2.5 equiv) in THF. The reaction mixture was instantly quenched by the addition of 2.0 M NaOCl. 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 as an orange oil (26 mg, 0.13 mmol, 89% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.19 (dd, *J* = 7.8, 4.7 Hz, 1H), 2.93 (t, *J* = 7.3, 2H), 1.75 – 1.64 (m, 2H), 1.56 – 1.45 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

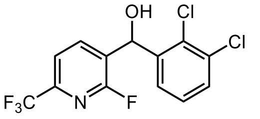
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 149.1, 145.1, 135.2, 135.1, 122.7, 31.8, 30.5, 22.2, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2929, 2872, 1547, 1464, 1433, 1379, 1346, 1212, 1143, 1128, 1064, 1042, 1035, 787, 757, 728, 655.

MS (EI, 70 eV): *m/z* (%) = 201 (25), 147 (36), 145 (100), 108 (21).

HRMS (EI): *m/z* calc. for [$C_9H_{12}ClNS$]: 201.0379; found 201.0374.

(2,3-Dichlorophenyl)(2-fluoro-6-(trifluoromethyl)pyridin-3-yl)methanol (37fq')



According to the TP6, a solution of 2-fluoro-6-(trifluoromethyl)pyridine (0.19 M, 0.19 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.05 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 (0.5 s, –40 °C) and was subsequently injected in a flask containing a stirred solution of 2,3-dichlorobenzaldehyde (84 mg, 0.29 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a colorless highly viscous liquid (46 mg, 0.13 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 – 7.89 (m, 1H), 7.58 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 1H), 6.44 (s, 1H), 2.82 (s, 1H).

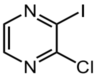
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.3 (d, *J* = 246.3 Hz), 145.6 (dd, *J* = 36.3, 13.8 Hz), 140.7 (d, *J* = 4.9 Hz), 140.1, 133.8, 131.0, 130.6, 127.9 (q, *J* = 120.7 Hz), 127.8, 126.2, 121.4 (q, *J* = 272.8 Hz), 118.5 (dq, *J* = 6.0, 3.0 Hz), 67.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1611, 1587, 1568, 1476, 1451, 1410, 1350, 1279, 1193, 1173, 1141, 1117, 1103, 1051, 1035, 974, 924, 878, 858, 821, 784, 773, 747, 742, 721, 699, 678.

MS (EI, 70 eV): *m/z* (%) = 341 (12), 339 (18), 304 (26), 194 (23), 192 (100), 177 (20), 175 (44), 174 (27), 173 (68), 166 (44), 165 (66), 164 (19), 149 (31), 148 (14), 147 (47), 146 (54), 145 (11), 139 (18), 138 (11), 126 (10), 114 (10), 111 (19), 109 (12), 75 (15).

HRMS (EI): *m/z* calc. for [$C_{13}H_7Cl_2F_4NO$]: 338.9841; found 338.9833.

2-Chloro-3-iodopyrazine (37gb)



According to the TP6, a solution of 2-chloropyrazine (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of iodine (127 mg, 0.50 mmol, 2.5 equiv) in THF. The reaction mixture was instantly quenched by the addition of *sat. aq.* $Na_2S_2O_3$. 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 = 95:5) afforded the title compound as light yellow crystals (31 mg, 0.13 mmol, 65% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.30 (d, *J* = 2.4 Hz, 1H), 8.28 (d, *J* = 2.4 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 154.8, 142.7, 142.1, 119.7.

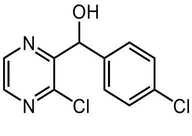
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2920, 2849, 1820, 1721, 1531, 1494, 1463, 1424, 1409, 1377, 1336, 1311, 1253, 1228, 1181, 1170, 1139, 1056, 1024, 858, 778.

MS (EI, 70 eV): *m/z* (%) = 242 (32), 240 (100), 127 (36), 115 (25), 113 (73), 88 (10), 86 (30).

HRMS (EI): *m/z* calc. for [$C_4H_2ClIN_2$]: 239.8951; found 239.8945.

m.p. (°C): 77.0 – 78.8.

(4-Chlorophenyl)(3-chloropyrazin-2-yl)methanol (37gr')



According to the TP6, a solution of 2-chloropyrazine (0.19 M, 0.19 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.05 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 4-chlorobenzaldehyde (40 mg, 0.29 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a yellow liquid (38 mg, 0.15 mmol, 79% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.56 (d, J = 2.5 Hz, 1H), 8.38 (d, J = 2.5 Hz, 1H), 7.32 – 7.27 (m, 4H), 6.00 (d, J = 7.3 Hz, 1H), 4.66 (d, J = 7.8 Hz, 1H).

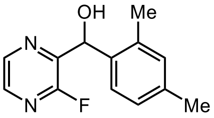
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 154.4, 147.7, 143.4, 141.4, 139.0, 134.4, 129.0 (2C), 129.0 (2C), 71.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3397, 1489, 1401, 1368, 1291, 1243, 1187, 1152, 1105, 1087, 1037, 1013, 946, 875, 836, 821, 805, 779, 764, 749, 732, 722, 690, 674, 661, 658, 652.

MS (EI, 70 eV): *m/z* (%) = 256 (17), 254 (26), 143 (16), 141 (48), 141 (34), 140 (20), 139 (100), 125 (12), 116 (14), 115 (22), 114 (45), 113 (24), 111 (11), 79 (15), 77 (40), 75 (12).

HRMS (EI): *m/z* calc. for [$C_{11}H_8Cl_2N_2O$]: 254.0014; found 254.0007.

(2,4-Dimethylphenyl)(3-fluoropyrazin-2-yl)methanol (37hp')



According to the TP6, a solution of 2-fluoropyrazine (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –60 °C) and was subsequently injected in a flask containing a stirred solution of 2,4-dimethylbenzaldehyde (40 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 = 8:2) afforded the title compound as a pale yellow oil (45 mg, 0.19 mmol, 97% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.57 – 8.45 (m, 1H), 8.30 – 8.06 (m, 1H), 7.02 (s, 1H), 6.96 – 6.85 (m, 2H), 6.19 (s, 1H), 2.46 (s, 3H), 2.28 (s, 3H).

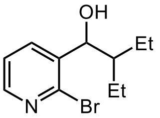
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.5 (d, J = 255.0 Hz), 146.0 (d, J = 29.2 Hz), 140.6 (d, J = 8.4 Hz), 140.3 (d, J = 4.9 Hz), 138.3, 136.5, 135.6, 131.9, 127.3, 127.1, 67.8 (d, J = 5.9 Hz), 21.2, 19.21 (d, J = 1.6 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3391, 3014, 2922, 1710, 1614, 1537, 1502, 1453, 1407, 1379, 1265, 1198, 1171, 1110, 1037, 932, 893, 859, 838, 810, 762, 718.

MS (EI, 70 eV): *m/z* (%) = 216 (11), 214 (13), 213 (100), 201 (23), 199 (13), 135 (16), 134 (99), 133 (61), 107 (25), 105 (26), 99 (10), 91 (23), 79 (10).

HRMS (EI): *m/z* calc. for [$C_{13}H_{13}FN_2O$]: 232.1012; found 232.1006.

1-(2-Bromopyridin-3-yl)-2-ethylbutan-1-ol (37iz')



According to the TP6, a solution of 2-bromopyridine (0.19 M, 0.19 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.05 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 2-ethylbutanal (29 mg, 0.29 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a yellow oil (32 mg, 0.12 mmol, 65% yield).

^{1}H-NMR (600 MHz, CDCl$_3$): δ / ppm = 8.25 (dd, *J* = 4.7, 2.0 Hz, 1H), 7.86 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.29 (dd, *J* = 7.7, 4.6 Hz, 1H), 5.07 (t, *J* = 4.0 Hz, 1H), 2.15 (s, 1H), 1.70 – 1.63 (m, 1H), 1.57 – 1.49 (m, 1H), 1.40 – 1.29 (m, 3H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H).

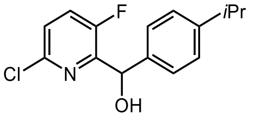
^{13}C-NMR (150 MHz, CDCl$_3$): δ / ppm = 148.7, 141.9, 140.6, 137.4, 122.9, 72.9, 45.6, 22.7, 19.9, 11.7, 11.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2931, 2873, 1575, 1559, 1458, 1401, 1379, 1181, 1130, 1103, 1065, 1052, 1040, 1016, 837, 805, 773, 754, 744, 735, 705.

MS (EI, 70 eV): *m/z* (%) = 189 (55), 188 (98), 187 (56), 186 (100), 185 (17), 183 (12), 158 (10), 156 (11), 130 (23), 122 (29), 108 (14), 107 (38), 106 (25), 105 (24), 81 (17), 79 (58), 78 (46).

HRMS (EI): *m/z* calc. for [$C_{11}H_{16}BrNO$]: 257.0415; found 257.0407.

(6-Chloro-3-fluoropyridin-2-yl)(4-isopropylphenyl)methanol (37ja'')



According to the TP6, a solution of 2-chloro-5-fluoropyridine (0.19 M, 0.19 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.05 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 4-isopropylbenzaldehyde (42 mg, 0.29 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as white crystals (41 mg, 0.15 mmol, 77% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.04 (s, 1H), 7.69 (d, *J* = 5.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.01 (d, *J* = 3.0 Hz, 1H), 2.89 (h, *J* = 13.9, 7.0 Hz, 1H), 2.70 (s, 1H), 1.23 (d, *J* = 6.9 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 155.9 (d, *J* = 255.2 Hz), 149.8, 146.8 (d, *J* = 2.9 Hz), 143.3 (d, *J* = 12.9 Hz), 138.2, 137.2 (d, *J* = 26.5 Hz), 127.2 (2C), 126.7 (d, *J* = 1.1 Hz, 2C), 122.1 (d, *J* = 1.9 Hz), 69.5 (d, *J* = 1.8 Hz), 34.0, 24.0 (2C).

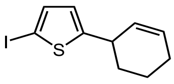
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3262, 3246, 3241, 3227, 2956, 1605, 1462, 1427, 1422, 1353, 1297, 1285, 1256, 1244, 1194, 1180, 1164, 1090, 1052, 1018, 921, 895, 849, 837, 831, 814, 755, 717, 663.

MS (EI, 70 eV): *m/z* (%) = 264 (22), 262 (13), 261 (11), 248 (11), 238 (18), 236 (56), 160 (31), 159 (16), 158 (100), 147 (13), 130 (17), 119 (22), 115 (11), 105 (12), 91 (24), 59 (10).

HRMS (EI): *m/z* calc. for [$C_{15}H_{15}ClFNO$]: 279.0826; found 279.0822.

m.p. (°C): 105.8 – 107.2.

2-(Cyclohex-2-en-1-yl)-5-iodothiophene (37kh)



According to the TP6, a solution of 2-iodothiophene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohexene (79 mg, 0.49 mmol, 2.5 equiv) and CuCN·2LiCl (0.01 mL of 1.0 M solution in THF, 5 mol%) in THF. The reaction mixture was instantly 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 as a pale brown oil (43 mg, 0.15 mmol, 76% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.06 (d, *J* = 3.6 Hz, 1H), 6.52 (dd, *J* = 3.7, 0.9 Hz, 1H), 5.92 – 5.82 (m, 1H), 5.74 (dd, *J* = 9.9, 3.2 Hz, 1H), 3.73 – 3.61 (m, 1H), 2.13 – 1.95 (m, 3H), 1.79 – 1.58 (m, 3H).

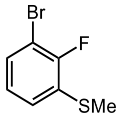
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 156.8, 136.6, 129.1, 129.0, 125.4, 70.1, 37.1, 32.4, 25.0, 20.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3018, 2919, 2849, 1720, 1646, 1587, 1455, 1444, 1428, 1402, 1377, 1347, 1309, 1295, 1253, 1133, 1050, 973, 940, 894, 869, 790, 753, 721, 684.

MS (EI, 70 eV): *m/z* (%) = 163 (4), 135 (5), 127 (100).

HRMS (EI): *m/z* calc. for [$C_{10}H_{11}IS$]: 289.9626; found 289.9618.

(3-Bromo-2-fluorophenyl)(methyl)sulfane (37lb'')



According to the TP6, a solution of 1-bromo-2-fluorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –60 °C) and was subsequently injected in a flask containing a stirred solution of dimethyldisulfide (57 mg, 0.60 mmol, 3.0 equiv) in THF. The reaction mixture was instantly quenched by the addition of 2.0 M NaOCl. 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 as a light orange oil (31 mg, 0.14 mmol, 70% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.39 – 7.33 (m, 1H), 7.21 – 7.16 (m, 1H), 7.01 – 6.95 (m, 1H), 2.48 (s, 3H).

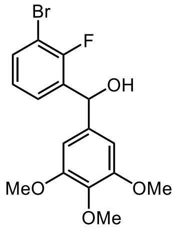
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 156.5 (d, *J* = 244.6 Hz), 130.5, 127.8 (d, *J* = 18.3 Hz), 127.6 (d, *J* = 2.1 Hz), 125.3 (d, *J* = 4.5 Hz), 109.4 (d, *J* = 21.5 Hz), 15.8 (d, *J* = 2.8 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3069, 2923, 2853, 1710, 1583, 1559, 1442, 1434, 1319, 1286, 1234, 1203, 1158, 1093, 1080, 1058, 970, 957, 880, 820, 758, 704.

MS (EI, 70 eV): *m/z* (%) = 222 (99), 220 (100), 189 (41), 187 (41), 176 (15), 174 (16), 140 (14), 126 (55).

HRMS (EI): *m/z* calc. for [C_7H_6BrFS]: 219.9358; found 219.9351.

(3-Bromo-2-fluorophenyl)(3,4,5-trimethoxyphenyl)methanol (37lc'')



According to the TP6, a solution of 1-bromo-2-fluorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –60 °C) and was subsequently injected in a flask containing a stirred solution of 3,4,5-trimethoxybenzaldehyde (59 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 → 4:1 → 2:1) afforded the title compound as a colorless liquid (59 mg, 0.16 mmol, 80% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.49 – 7.43 (m, 2H), 7.03 (td, *J* = 7.9, 0.8 Hz, 1H), 6.60 (s, 2H), 6.05 (s, 1H), 3.82 (s, 6H), 3.81 (s, 3H).

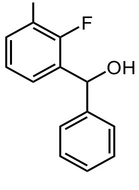
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.2 (d, *J* = 247.1 Hz), 153.4 (2C), 138.1, 137.6, 132.7 (d, *J* = 14.0 Hz), 132.7, 126.7 (d, *J* = 3.5 Hz), 125.4 (d, *J* = 4.4 Hz), 109.2 (d, *J* = 21.2 Hz), 103.4 (d, *J* = 0.8 Hz, 2C), 70.1 (d, *J* = 2.9 Hz), 60.9, 56.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3480, 3393, 2966, 2936, 2836, 2827, 1592, 1505, 1450, 1415, 1400, 1331, 1310, 1273, 1227, 1183, 1177, 1122, 1083, 1070, 1059, 996, 970, 921, 883, 861, 838, 829, 796, 785, 766, 753, 734, 714, 677.

MS (EI, 70 eV): *m/z* (%) = 372 (49), 370 (54), 203 (60), 201 (65), 169 (100), 154 (13), 138 (21).

HRMS (EI): *m/z* calc. for [$C_{16}H_{16}BrFO_4$]: 370.0216; found 370.0208.

(3-Bromo-2-fluorophenyl)(phenyl)methanol (37lc)



According to the TP6, a solution of 1-bromo-2-fluorobenzene (0.21 M, 0.21 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.22 M in DMEA, 0.22 mmol, 1.05 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 (0.5 s, –60 °C) and was subsequently injected in a flask containing a stirred solution of benzaldehyde (33 mg, 0.32 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a pale yellow oil (48 mg, 0.17 mmol, 81% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.54 – 7.43 (m, 2H), 7.41 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 7.08 – 7.01 (m, 1H), 6.13 (s, 1H), 2.39 (s, 1H).

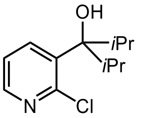
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.2 (d, *J* = 247.3 Hz), 142.3, 132.9, 132.7 (2C), 128.8 (2C), 128.2, 126.8 (d, *J* = 3.6 Hz), 126.5 (d, *J* = 0.8 Hz), 125.4 (d, *J* = 4.4 Hz), 109.3 (d, *J* = 21.2 Hz), 70.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3320, 3064, 3031, 2915, 1950, 1881, 1809, 1683, 1602, 1573, 1493, 1450, 1314, 1226, 1190, 1168, 1127, 1081, 1036, 1023, 918, 870, 818, 773, 725, 696.

MS (EI, 70 eV): *m/z* (%) = 283 (13), 282 (86), 281 (13), 280 (88), 279 (14), 205 (10), 203 (100), 201 (100), 185 (11), 184 (11), 183 (52), 172 (11), 165 (11), 152 (11), 123 (11), 107 (17), 105 (91), 96 (20), 94 (18), 79 (56), 78 (70), 77 (33).

HRMS (EI): *m/z* calc. for [$C_{13}H_{10}BrFO$]: 279.9899; found 279.9893.

3-(2-Chloropyridin-3-yl)-2,4-dimethylpentan-3-ol (37ek')



According to the TP6, a solution of 2-chloropyridine (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –20 °C) and was subsequently injected in a flask containing a stirred solution of 2,4-dimethylpentan-3-one (33 mg, 0.29 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 → 1:1) afforded the title compound as colorless crystals (30 mg, 0.13 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.28 (dd, *J* = 4.6, 1.9 Hz, 1H), 8.09 (s, 1H), 7.24 (dd, *J* = 7.9, 4.5 Hz, 1H), 2.77 (s, 2H), 0.95 (d, *J* = 6.7 Hz, 6H), 0.81 (d, *J* = 6.9 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.6, 147.5, 140.1, 121.7, 81.6, 34.3 (2C), 18.6 (2C), 17.2 (2C).

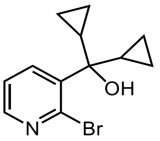
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3374, 2993, 2962, 2935, 2877, 2848, 1591, 1573, 1554, 1463, 1454, 1384, 1371, 1330, 1321, 1296, 1235, 1224, 1177, 1167, 1151, 1119, 1097, 1059, 1013, 996, 987, 956, 912, 869, 834, 809, 752, 747, 658.

MS (EI, 70 eV): *m/z* (%) = 186 (30), 184 (91), 182 (10), 148 (100), 142 (24), 140 (77), 133 (14), 130 (34), 120 (20), 117 (11), 112 (17), 106 (15), 92 (10), 78 (23), 77 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{16}ClN$] ($M^+ - H_2O$): 209.0971; found 209.0965 ($M^+ - H_2O$).

m.p. (°C): 113.8 – 115.4.

(2-Bromopyridin-3-yl)dicyclopropylmethanol (37ic')



According to the TP6, a solution of 2-bromopyridine (0.18 M, 0.18 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.19 M in DMEA, 0.19 mmol, 1.05 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropylmethanone (31 µL, 0.27 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as colorless crystals (26 mg, 0.10 mmol, 54% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.25 (dd, *J* = 4.6, 1.9 Hz, 1H), 8.07 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.25 (dd, *J* = 7.8, 4.6 Hz, 1H), 1.95 (s, 1H), 1.65 (tt, *J* = 8.2, 5.7 Hz, 2H), 0.81 – 0.72 (m, 2H), 0.62 (tdd, *J* = 8.3, 7.0, 4.6 Hz, 2H), 0.42 – 0.32 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.9, 144.0, 140.5, 137.2, 122.5, 73.0, 19.3 (2C), 4.2 (2C), 1.1 (2C).

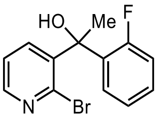
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3377. 3083, 3007, 1571, 1555, 1434, 1427, 1389, 1314, 1261, 1234, 1212, 1184, 1169, 1120, 1110, 1049, 1040, 1006, 973, 958, 920, 909, 853, 824, 795, 780, 735, 731, 662.

MS (EI, 70 eV): *m/z* (%) = 241 (21), 239 (23), 228 (53), 226 (53), 199 (12), 197 (11), 186 (95), 184 (100), 160 (74), 158 (15), 156 (15), 154 (12), 132 (10), 130 (43), 118 (16), 117 (42), 115 (10), 91 (14), 89 (13), 81 (13), 79 (13), 78 (17), 69 (19).

HRMS (EI): *m/z* calc. for [$C_{10}H_{10}BrNO$] ($M^+ - C_2H_4$): 238.9946; found 238.9939 ($M^+ - C_2H_4$).

m.p. (°C): 137.9 – 139.7.

1-(2-Bromopyridin-3-yl)-1-(2-fluorophenyl)ethan-1-ol (37id'')



According to the TP6, a solution of 2-bromopyridine (0.18 M, 0.18 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.19 M in DMEA, 0.19 mmol, 1.05 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 1-(2-fluorophenyl)ethan-1-one (33 µL, 0.27 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a grey solid (30 mg, 0.10 mmol, 56% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.28 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.20 – 8.15 (m, 1H), 7.70 (td, *J* = 8.1, 1.8 Hz, 1H), 7.35 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.19 (td, *J* = 7.6, 1.3 Hz, 1H), 6.92 (ddd, *J* = 11.8, 8.1, 1.3 Hz, 1H), 2.02 (d, *J* = 0.8 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.6 (d, *J* = 246.3 Hz), 148.8, 142.7 (d, *J* = 1.3 Hz), 140.5, 136.5 (d, *J* = 2.9 Hz), 132.6 (d, *J* = 10.7 Hz), 129.8 (d, *J* = 8.6 Hz), 128.8 (d, *J* = 3.6 Hz), 124.0 (d, *J* = 3.4 Hz), 122.9, 116.3 (d, *J* = 22.4 Hz), 74.2, 28.1 (d, *J* = 1.3 Hz).

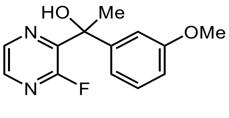
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3262, 3076, 2982, 2923, 2867, 1770, 1728, 1609, 1574, 1556, 1485, 1451, 1440, 1404, 1389, 1367, 1277, 1248, 1231, 1225, 1200, 1185, 1160, 1134, 1101, 1087, 1052, 1039, 1031, 991, 922, 863, 845, 816, 803, 757, 748, 726, 661.

MS (EI, 70 eV): *m/z* (%) = 283 (13), 282 (98), 281 (12), 280 (100), 200 (21), 198 (39), 186 (20), 184 (22), 178 (14), 173 (10), 172 (40), 170 (16), 159 (25), 157 (23), 139 (25), 123 (20).

HRMS (EI): *m/z* calc. for [$C_{13}H_{11}BrFNO$]: 295.0008; found 294.9996.

m.p. (°C): 101.8 – 102.0.

1-(3-Fluoropyrazin-2-yl)-1-(3-methoxyphenyl)ethan-1-ol (37he'')



According to the TP6, a solution of 2-fluoropyrazine (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –60 °C) and was subsequently injected in a flask containing a stirred solution of 1-(3-methoxyphenyl)ethan-1-one (45 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a slightly yellow oil (38 mg, 0.15 mmol, 77% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.53 – 8.46 (m, 1H), 8.22 (t, *J* = 2.2 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.06 – 7.00 (m, 2H), 6.87 – 6.82 (m, 1H), 5.35 (s, 1H), 3.82 (s, 3H), 2.06 (d, *J* = 1.8 Hz, 3H).

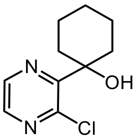
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.0, 157.5 (d, *J* = 255.4 Hz), 148.9 (d, *J* = 27.1 Hz), 146.3, 141.1 (d, *J* = 8.6 Hz), 139.6 (d, *J* = 5.0 Hz), 129.5, 118.2 (d, *J* = 1.8 Hz), 112.9, 112.0 (d, *J* = 1.5 Hz), 74.1 (d, *J* = 6.8 Hz), 55.4, 26.6 (d, *J* = 4.0 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3428, 3071, 2983, 2938, 2836, 1600, 1584, 1538, 1486, 1452, 1433, 1399, 1366, 1317, 1289, 1249, 1195, 1164, 1115, 1088, 1040, 996, 935, 857, 787, 769, 700, 684.

MS (EI, 70 eV): *m/z* (%) = 249 (11), 248 (81), 233 (30), 229 (17), 205 (20), 151 (100), 150 (21), 135 (37), 125 (33), 99 (10), 97 (28), 77 (11), 43 (23).

HRMS (EI): *m/z* calc. for [$C_{13}H_{13}FN_2O_2$]: 248.0961; found 248.0955.

1-(3-Chloropyrazin-2-yl)cyclohexan-1-ol (37gs)



According to the TP6, a solution of 2-chloropyrazine (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexanone (29 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as colorless crystals (30 mg, 0.14 mmol, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (d, *J* = 2.4 Hz, 1H), 8.34 (d, *J* = 2.4 Hz, 1H), 4.90 (s, 1H), 2.48 (td, *J* = 13.1, 4.5 Hz, 2H), 1.95 – 1.76 (m, 3H), 1.74 – 1.66 (m, 2H), 1.62 – 1.52 (m, 2H), 1.45 – 1.33 (m, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 158.4, 147.1, 142.4, 140.1, 73.8, 34.3 (2C), 25.3, 22.0 (2C).

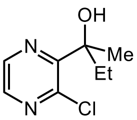
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3413, 2953, 2922, 2890, 2852, 1446, 1440, 1388, 1365, 1341, 1327, 1272, 1236, 1183, 1130, 1087, 1063, 1035, 1014, 982, 913, 867, 835, 789, 771.

MS (EI, 70 eV): *m/z* (%) = 212 (20), 194 (10), 186 (17), 184 (47), 171 (11), 149 (80), 141 (45), 130 (12), 128 (35), 116 (11), 115 (19), 114 (25), 99 (11), 98 (25), 79 (13), 57 (18), 56 (12), 55 (15), 44 (100), 43 (47), 42 (15), 41 (28).

HRMS (EI): *m/z* calc. for [$C_{10}H_{13}ClN_2O$]: 212.0716; found 212.0707.

m.p. (°C): 71.6 – 73.1.

2-(3-Chloropyrazin-2-yl)butan-2-ol (37gf'')



According to the TP6, a solution of 2-chloropyrazine (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of butan-2-one (22 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a pale yellow oil (24 mg, 0.13 mmol, 65% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.46 (d, *J* = 2.4 Hz, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 5.34 (s, 1H), 2.33 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.97 (dq, *J* = 14.2, 7.5 Hz, 1H), 1.68 (s, 3H), 0.69 (t, *J* = 7.4 Hz, 3H).

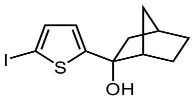
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 157.8, 147.0, 142.6, 139.9, 74.6, 32.5, 26.5, 8.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 2971, 2932, 2877, 1726, 1551, 1457, 1436, 1371, 1351, 1286, 1236, 1197, 1130, 1061, 1035, 996, 927, 858, 796, 776.

MS (EI, 70 eV): *m/z* (%) = 159 (29), 115 (17), 43 (37).

HRMS (EI): *m/z* calc. for [$C_8H_{11}ClN_2O$]: 186.0560; found 186.0545.

2-(5-Iodothiophen-2-yl)bicyclo[2.2.1]heptan-2-ol (37kt)



According to the TP6, a solution of 2-iodothiophene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of bicyclo[2.2.1]heptan-2-one (32 mg, 0.29 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 = 95:5) afforded the title compound as a colorless liquid (38 mg, 0.12 mmol, 61% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.07 (d, *J* = 3.8 Hz, 1H), 6.65 (d, *J* = 3.8 Hz, 1H), 2.43 (d, *J* = 2.7 Hz, 1H), 2.34 – 2.29 (m, 1H), 2.24 (ddd, *J* = 13.1, 4.8, 2.8 Hz, 1H), 2.15 – 2.05 (m, 1H), 2.02 (s, 1H), 1.68 – 1.57 (m, 2H), 1.53 – 1.37 (m, 3H), 1.37 – 1.31 (m, 1H).

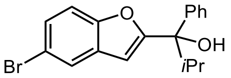
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 161.2, 136.5, 124.6, 79.6, 72.5, 50.0, 48.1, 38.9, 37.3, 28.8, 22.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3409, 2948, 2867, 1731, 1474, 1452, 1445, 1423, 1373, 1308, 1291, 1252, 1228, 1212, 1188, 1163, 1130, 1121, 1069, 1041, 1002, 964, 952, 929, 918, 821, 790, 753.

MS (EI, 70 eV): *m/z* (%) = 302 (19), 274 (100), 252 (13), 237 (12), 193 (12), 175 (37), 147 (36), 127 (55).

HRMS (EI): *m/z* calc. for [$C_{11}H_{13}IOS$]: 319.9732; found 319.9726.

1-(5-Bromobenzofuran-2-yl)-2-methyl-1-phenylpropan-1-ol (37mg’’)



According to the TP6, a solution of 5-bromobenzofuran (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of 2-methyl-1-phenylpropan-1-one (43 mg, 0.29 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 = 95:5) afforded the title compound as a colorless viscous liquid (61 mg, 0.18 mmol, 91% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.64 (d, *J* = 1.8 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.39 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 6.68 (s, 1H), 2.80 (hept, *J* = 6.8 Hz, 1H), 2.44 (s, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

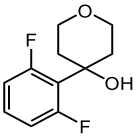
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 163.2, 153.6, 143.1, 130.4, 128.3 (2C), 127.4, 126.8, 125.7 (2C), 123.7, 116.0, 112.8, 102.4, 78.8, 36.3, 17.4, 16.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3572, 3475, 3058, 3025, 2966 2931, 2874, 1609, 1599, 1585, 1490, 1442, 1386, 1366, 1343, 1317, 1258, 1242, 1163, 1147, 1117, 1077, 1049, 1013, 981, 938, 901, 865, 793, 749, 699, 673.

MS (EI, 70 eV): *m/z* (%) = 328 (27), 326 (27), 324 (12), 303 (16), 302 (17), 300 (19), 231 (18), 225 (23), 223 (27), 215 (13), 207 (24), 202 (20), 198 (11), 196 (12), 169 (10), 167 (10), 129 (15), 128 (13), 117 (14), 115 (33), 105 (79), 103 (10), 98 (18), 96 (19), 91 (12), 89 (10), 82 (31), 81 (100), 79 (91), 78 (18), 77 (26).

HRMS (EI): *m/z* calc. for [$C_{18}H_{15}BrO$] ($M^+ - H_2O$): 326.0306; found 326.0300 ($M^+ - H_2O$).

4-(2,6-Difluorophenyl)tetrahydro-2*H*-pyran-4-ol (37bh'')



According to the TP6, a solution of 1,3-difluorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –40 °C) and was subsequently injected in a flask containing a stirred solution of tetrahydro-4*H*-pyran-4-one (57 mg, 0.29 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a white solid (23 mg, 0.11 mmol, 55% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.25 – 7.17 (m, 1H), 6.88 (dd, *J* = 10.9, 8.4 Hz, 2H), 4.00 (t, *J* = 11.0 Hz, 2H), 3.81 (dd, *J* = 10.3, 5.0 Hz, 2H), 2.77 – 2.72 (m, 1H), 2.44 (td, *J* = 13.5, 4.8 Hz, 2H), 2.01 (d, *J* = 13.8 Hz, 2H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 161.0 (dd, *J* = 247.8, 9.0 Hz, 2C), 129.1 (t, *J* = 12.1 Hz, 2C), 122.3 (t, *J* = 13.2 Hz), 114.3 – 111.5 (m), 71.9 (t, *J* = 2.3 Hz), 63.6 (2C), 38.0 (t, *J* = 4.6 Hz, 2C).

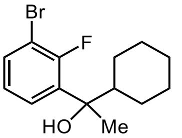
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3357, 2975, 2962, 2935, 2923, 2881, 2853, 1618, 1578, 1571, 1464, 1454, 1429, 1391, 1362, 1329, 1305, 1290, 1260, 1230, 1208, 1141, 1122, 1093, 1076, 1029, 1019, 988, 966, 915, 836, 796, 730, 706.

MS (EI, 70 eV): *m/z* (%) = 214 (17), 196 (47), 185 (15), 170 (100), 169 (18), 168 (76), 158 (14), 156 (56), 142 (23), 141 (74), 140 (36), 139 (10), 127 (49), 114 (28), 113 (19), 100 (31), 73 (10), 72 (13), 57 (10), 43 (74), 42 (53).

HRMS (EI): *m/z* calc. for [$C_{11}H_{12}F_2O_2$]: 214.0805; found 214.0804.

m.p. (°C): 76.9 – 78.8.

1-(3-Bromo-2-fluorophenyl)-1-cyclohexylethan-1-ol (37ni'')



According to the TP6, a solution of 1-bromo-2-fluorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –60 °C) and was subsequently injected in a flask containing a stirred solution of 1-cyclohexylethan-2-one (38 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a highly viscose colorless liquid (33 mg, 0.11 mmol, 55% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.49 (td, *J* = 7.6, 1.7 Hz, 1H), 7.44 (ddd, *J* = 8.0, 6.4, 1.7 Hz, 1H), 6.99 (td, *J* = 7.9, 0.8 Hz, 1H), 1.90 – 1.76 (m, 4H), 1.72 – 1.61 (m, 2H), 1.59 (d, *J* = 1.8 Hz, 3H), 1.36 – 0.96 (m, 6H).

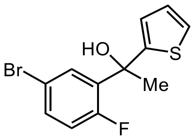
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 155.6 (d, *J* = 246.2 Hz), 136.7 (d, *J* = 13.4 Hz), 132.1, 127.4 (d, *J* = 4.5 Hz), 124.7 (d, *J* = 4.2 Hz), 110.0 (d, *J* = 23.5 Hz), 76.6 (d, *J* = 4.8 Hz), 46.5 (d, *J* = 3.2 Hz), 27.5, 27.0, 26.7 (d, *J* = 0.5 Hz), 26.5, 26.0, 26.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3603, 3473, 2929, 2852, 1600, 1565, 1437, 1374, 1334, 1293, 1245, 1225, 1197, 1175, 1159, 1127, 1086, 1059, 1030, 1004, 971, 939, 906, 892, 868, 847, 822, 800, 778, 762, 731, 673, 656.

MS (EI, 70 eV): *m/z* (%) = 219 (96), 217 (100), 216 (10).

HRMS (EI): *m/z* calc. for [$C_{14}H_{18}BrFO$]: 300.0525; found 300.0510.

1-(5-Bromo-2-fluorophenyl)-1-(thiophen-2-yl)ethan-1-ol (37oj'')



According to the TP6, a solution of 1-bromo-4-fluorobenzene (0.20 M, 0.20 mmol) 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·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –40 °C) and was subsequently injected in a flask containing a stirred solution of 1-(furan-2-yl)ethan-1-one (38 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a pale orange oil (42 mg, 0.14 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (dd, *J* = 7.2, 2.6 Hz, 1H), 7.40 (ddd, *J* = 8.6, 4.3, 2.6 Hz, 1H), 7.25 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.96 – 6.86 (m, 3H), 2.66 (d, *J* = 3.1 Hz, 1H), 2.05 (d, *J* = 1.1 Hz, 3H).

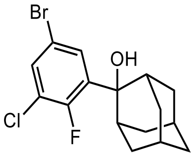
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.1 (d, *J* = 247.6 Hz), 151.3 (d, *J* = 1.0 Hz), 136.3 (d, *J* = 12.4 Hz), 132.4 (d, *J* = 8.7 Hz), 130.2 (d, *J* = 3.6 Hz), 126.8, 125.3, 124.3 (d, *J* = 1.7 Hz), 118.1 (d, *J* = 24.7 Hz), 116.9 (d, *J* = 3.3 Hz), 72.8 (d, *J* = 2.0 Hz), 30.1 (d, *J* = 3.7 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3422, 3104, 3072, 2976, 2934, 1572, 1475, 1447, 1434, 1391, 1374, 1351, 1322, 1254, 1234, 1219, 1195, 1163, 1127, 1087, 1078, 1053, 1015, 917, 893, 859, 843, 813, 785, 749, 698, 669.

MS (EI, 70 eV): *m/z* (%) = 287 (10), 285 (11), 284 (61), 281 (15), 203 (26), 202 (100), 201 (14), 184 (15), 183 (15), 170 (31), 159 (13), 157 (15), 101 (18).

HRMS (EI): *m/z* calc. for [$C_{12}H_{10}BrFOS$]: 299.9620; found 299.9612.

2-(5-Bromo-3-chloro-2-fluorophenyl)adamantan-2-ol (37pt)



According to the TP6, a solution of 4-bromo-2-chloro-1-fluorobenzene (0.19 M, 0.19 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 1.05 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of adamantan-2-one (45 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a white solid (40 mg, 0.11 mmol, 57% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.48 (s, 1H), 7.46 (s, 1H), 2.60 (s, 2H), 2.39 (dd, J = 12.8, 3.0 Hz, 2H), 1.91 – 1.78 (m, 4H), 1.76 – 1.65 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.6 (d, J = 252.0 Hz), 136.0 (d, J = 11.3 Hz), 132.1, 130.3 (d, J = 4.6 Hz), 123.8 (d, J = 21.8 Hz), 116.4 (d, J = 4.2 Hz), 77.1 (d, J = 2.3 Hz), 37.5, 35.8, 35.8, 35.2 (2C) , 33.0 (2C), 27.1, 26.6 (d, J = 1.0 Hz).

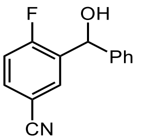
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3358, 3335, 2935, 2899, 2847, 1562, 1451, 1388, 1384, 1355, 1331, 1244, 1220, 1195, 1173, 1166, 1161, 1102, 1082, 1052, 1009, 997, 985, 942, 921, 877, 854, 838, 754, 735, 688, 668.

MS (EI, 70 eV): *m/z* (%) = 342 (31), 340 (25), 237 (31), 235 (24), 225 (20), 223 (12), 210 (14), 208 (11), 207 (31), 206 (19), 184 (12), 183 (28), 171 (11), 170 (26), 165 (11), 151 (24), 149 (18), 133 (15), 128 (16), 121 (13), 93 (39), 92 (11), 91 (52), 81 (75), 80 (23), 79 (100), 78 (31), 77 (19), 67 (25), 45 (17), 44 (66), 42 (27).

HRMS (EI): *m/z* calc. for [$C_{16}H_{17}BrClFO$]: 358.0135; found 358.0131.

m.p. (°C): 98.2 – 101.0.

4-Fluoro-3-(hydroxy(phenyl)methyl)benzonitrile (40ac)



According to the TP6, a solution of 4-fluorobenzonitrile (0.22 M, 0.22 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.20 M in DMEA, 0.20 mmol, 0.9 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of benzaldehyde (35 mg, 0.33 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as a colorless crystals (34 mg, 0.15 mmol, 75% yield).

In addition, a convenient scale-up of the reaction according to the TP6 was demonstrated. A solution of 4-fluorobenzonitrile (0.23 M in THF) (total volume: 30 mL) and a solution of NaDA (0.21 M in DMEA, 30 mL, 0.9 equiv) were prepared. The solutions were injected into 6 mL loading coils and subsequently precooled and mixed with an overall 10 mL·min^{-1} flow-rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of benzaldehyde (1.05 g, 9.90 mmol, 1.5 equiv) in THF. This procedure was repeated 5 times, leading to a total amount of 30 mL collected in the same flask. Stirring was continued for 5 min at 0 °C before *sat. aq.* NH_4Cl 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 $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, isohexane: EtOAc = 9:1) afforded the title compound as colorless crystals (1.06 g, 4.67 mmol, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 – 7.93 (m, 1H), 7.56 (ddd, *J* = 8.5, 4.8, 2.2 Hz, 1H), 7.43 – 7.29 (m, 5H), 7.10 (dd, *J* = 9.6, 8.5 Hz, 1H), 6.10 (s, 1H), 2.51 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.1 (d, *J* = 256.6 Hz), 141.7, 133.5 (d, *J* = 9.6 Hz), 133.2 (d, *J* = 14.6 Hz), 132.2 (d, *J* = 5.6 Hz), 129.0 (2C), 128.5 (2C), 126.5 (d, *J* = 1.2 Hz), 118.3, 116.9 (d, *J* = 23.3 Hz), 108.8 (d, *J* = 3.8 Hz), 69.6 (d, *J* = 2.8 Hz).

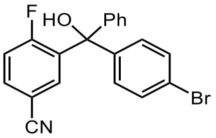
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3496, 2922, 2904, 2232, 1606, 1586, 1486, 1453, 1412, 1393, 1346, 1300, 1280, 1244, 1219, 1190, 1133, 1112, 1076, 1044, 1026, 927, 911, 837, 808, 760, 695, 685, 656.

MS (EI, 70 eV): *m/z* (%) = 227 (58), 225 (19), 208 (24), 205 (11), 149 (12), 148 (100), 122 (17), 121 (37), 105 (66), 100 (10), 79 (43), 78 (17), 77 (33).

HRMS (EI): *m/z* calc. for [$C_{14}H_{10}FNO$]: 227.0746; found 227.0741.

m.p. (°C): 103.7 – 105.6.

3-((4-Bromophenyl)(hydroxy)(phenyl)methyl)-4-fluorobenzonitrile (40ak'')



According to the TP6, a solution of 4-fluorobenzonitrile (0.23 M, 0.23 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.21 M in DMEA, 0.21 mmol, 0.9 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of (4-bromophenyl)(phenyl)methanone (90 mg, 0.35 mmol, 1.5 equiv) in THF. The reaction mixture was instantly 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 as white crystals (71 mg, 0.19 mmol, 81% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.66 (ddd, *J* = 8.4, 4.6, 2.2 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.40 – 7.35 (m, 3H), 7.33 (dd, *J* = 7.4, 2.2 Hz, 1H), 7.25 – 7.13 (m, 5H), 3.28 (d, *J* = 6.8 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 163.0 (d, *J* = 256.7 Hz), 143.8, 143.4, 135.9 (d, *J* = 11.7 Hz), 134.4 (d, *J* = 10.3 Hz), 134.2 (d, *J* = 4.7 Hz), 131.6 (2C), 129.3 (d, *J* = 1.1 Hz), 128.7, 128.6 (3C), 127.3, 122.5, 118.1, 118.1, 117.8, 108.7 (d, *J* = 3.7 Hz), 80.3.

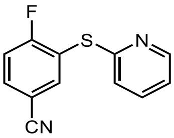
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3453, 2237, 1585, 1484, 1446, 1403, 1398, 1338, 1262, 1236, 1195, 1189, 1171, 1134, 1108, 1073, 1033, 1021, 1008, 970, 917, 892, 835, 829, 816, 768, 734, 727, 707, 702, 691, 675, 667, 659, 654.

MS (EI, 70 eV): *m/z* (%) = 304 (10), 281 (12), 263 (22), 261 (22), 226 (10), 207 (45), 185 (37), 183 (36), 154 (13), 148 (100), 105 (30), 77 (12).

HRMS (EI): *m/z* calc. for [$C_{20}H_{13}BrFNO$]: 381.0165; found 381.0160.

m.p. (°C): 168.1 – 170.3.

4-Fluoro-3-(pyridin-2-ylthio)benzonitrile (40au)



According to the TP6, a solution of 4-fluorobenzonitrile (0.23 M, 0.23 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.21 M in DMEA, 0.21 mmol, 0.9 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 (0.5 s, –78 °C) and was subsequently injected in a flask containing a stirred solution of aldrithiol (126 mg, 0.57 mmol, 2.5 equiv) in THF. The reaction mixture was instantly quenched by the addition of 2.0 M NaOCl. 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 as white crystals (38 mg, 0.17 mmol, 80% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.41 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.89 (dd, *J* = 6.4, 2.1 Hz, 1H), 7.70 (ddd, *J* = 8.6, 4.6, 2.1 Hz, 1H), 7.59 (ddd, *J* = 8.0, 7.5, 1.9 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 7.20 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 164.8 (d, *J* = 258.2 Hz), 156.3 (d, *J* = 1.3 Hz), 150.2, 140.0 (d, *J* = 2.4 Hz), 137.3, 135.0 (d, *J* = 9.4 Hz), 122.9, 121.7 (d, *J* = 19.7 Hz), 121.5, 117.6 (d, *J* = 24.4 Hz), 117.5, 109.5 (d, *J* = 4.3 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2228, 1576, 1559, 1483, 1456, 1415, 1389, 1267, 1245, 1115, 1070, 1044, 985, 906, 830, 759, 735, 731, 721, 713, 676.

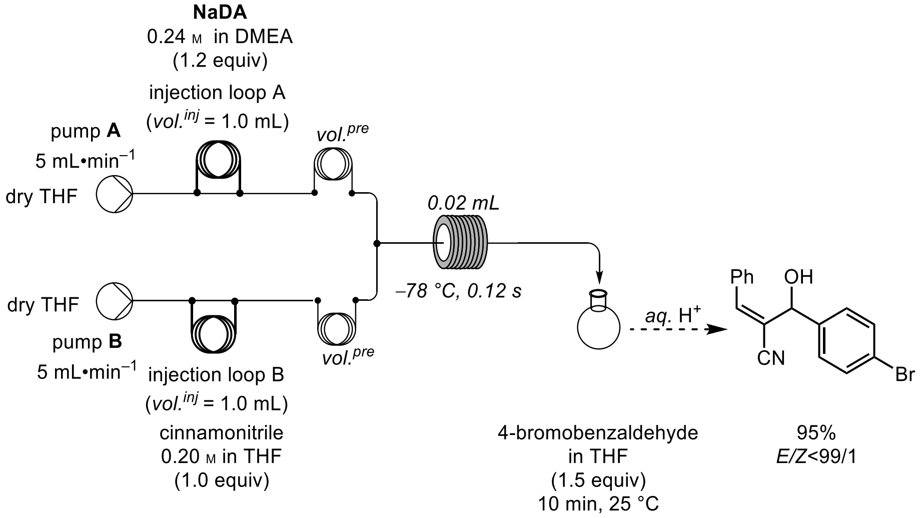
MS (EI, 70 eV): *m/z* (%) = 230 (20), 212 (10), 211 (100), 78 (19).

HRMS (EI): *m/z* calc. for [$C_{12}H_6FN_2S$] ($M^+ - H$): 229.0236; found 229.0231 ($M^+ - H$).

m.p. (°C): 106.7 – 108.3.

17. CONTINUOUS FLOW SODIATION OF SUBSTITUTED ACRYLONITRILES AND ALKENYL SULFIDES

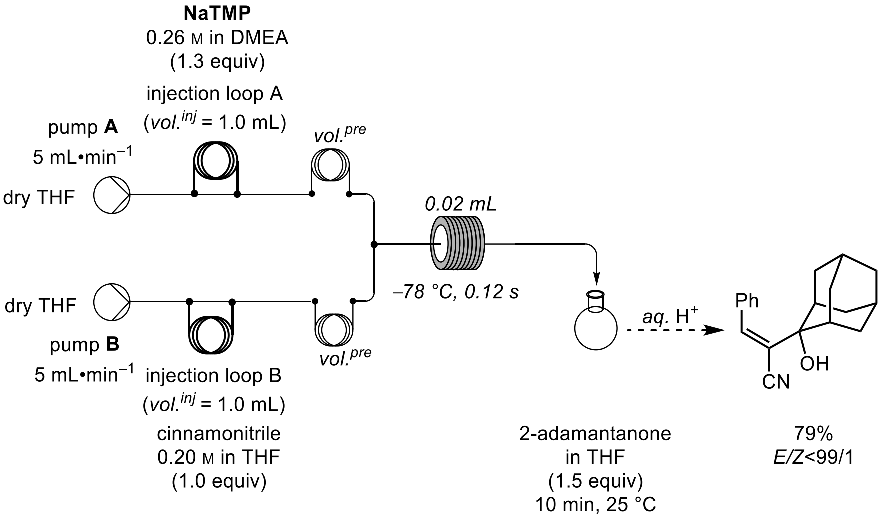
17.1 TYPICAL PROCEDURE 7 (TP7)



Scheme 74: Uniqsis flow setup for the sodiation of cinnamonitrile using a microflow reactor and subsequent batch quench of the intermediate organosodium with 4-bromobenzaldehyde leading to (*Z*)-2-((4-bromophenyl)(hydroxy)methyl)-3-phenylacrylonitrile.

A NaDa solution (0.24 M, 1.2 equiv) in DMEA and a solution of cinnamonitrile (0.20 M, 26 mg, 1.0 equiv) in THF were prepared. Injection loop A (vol^{inj} =1.0 mL) was loaded with the NaDA solution and injection loop B (vol^{inj} =1.0 mL) was loaded with the solution of cinnamonitrile (**1a**). The solutions were simultaneously injected into separate streams of THF (flow-rates: 5 mL·min^{-1}), which each passed a pre-cooling loop (vol^{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 (vol^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 (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 as colorless crystals (64 mg, 0.19 mmol, 95% yield; *Z/E* > 99/1).

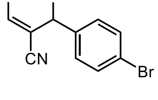
17.2 TYPICAL PROCEDURE 8 (TP8)



Scheme 75: Uniqsis flow setup for the sodiation of cinnamonitrile using a microflow reactor and subsequent batch quench of the intermediate organosodium with 2-adamantanone leading to (Z)-2-(2-hydroxyadamantan-2-yl)-3-phenylacrylonitrile

A NaTMP solution (0.26 M, 1.2 equiv) in hexane and a solution of cinnamonitrile (0.20 M, 26 mg, 1.0 equiv; *E/Z* > 99/1) in THF were prepared. Injection loop A (vol$^{\text{inj}}$ =1.0 mL) was loaded with the NaTMP solution and injection loop B (vol$^{\text{inj}}$ =1.0 mL) was loaded with the solution of cinnamonitrile (**1a**). The solutions were simultaneously injected into separate streams of THF (flow-rates: 5 mL·min^{-1}), which each passed a pre-cooling loop (vol$^{\text{pre}}$ = 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 (vol$^{\text{R}}$ = 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 (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 as colorless oil (44 mg, 0.16 mmol, 79% yield; *Z/E* > 99/1).

(*Z*)-2-((4-Bromophenyl)(hydroxy)methyl)-3-phenylacrylonitrile (43al'')



According to the TP7, a solution of cinnamonitrile (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 (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 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.

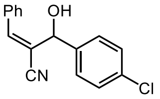
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3480, 2213, 1616, 1591, 1574, 1488, 1447, 1399, 1391, 1361, 1292, 1283, 1248, 1218, 1194, 1159, 1136, 1108, 1074, 1030, 1012, 977, 946, 934, 906, 866, 847, 827, 778, 759, 699, 657.

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 (43ar')



According to the TP7, a solution of cinnamonitrile (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 (42 mg, 0.30 mmol, 1.7 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH$_4$Cl. 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 as colorless crystals (45 mg, 0.17 mmol, 92% yield; *Z/E* > 99/1).

^{1}H-NMR (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.

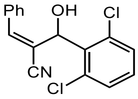
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3398, 2922, 2852, 2219, 1616, 1596, 1575, 1490, 1464, 1456, 1447, 1404, 1091, 1042, 1013, 836, 799, 777, 755, 728, 697.

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 (43aq')



According to the TP7, a solution of cinnamonitrile (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 (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 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.

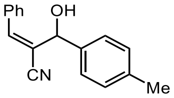
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3492, 3437, 3066, 2923, 2854, 2211, 1792, 1683, 1601, 1579, 1561, 1492, 1446, 1437, 1305, 1228, 1202, 1184, 1148, 1093, 1077, 1033, 983, 943, 890, 826, 793, 782, 767, 756, 720, 696.

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 (43am'')



According to the TP7, a solution cinnamonitrile (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 (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 as a pale yellow solid (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.

Table 32: Details for X-ray data collection and structure refinement for compound **43am''**.

	43am''
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	$P21/c$
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

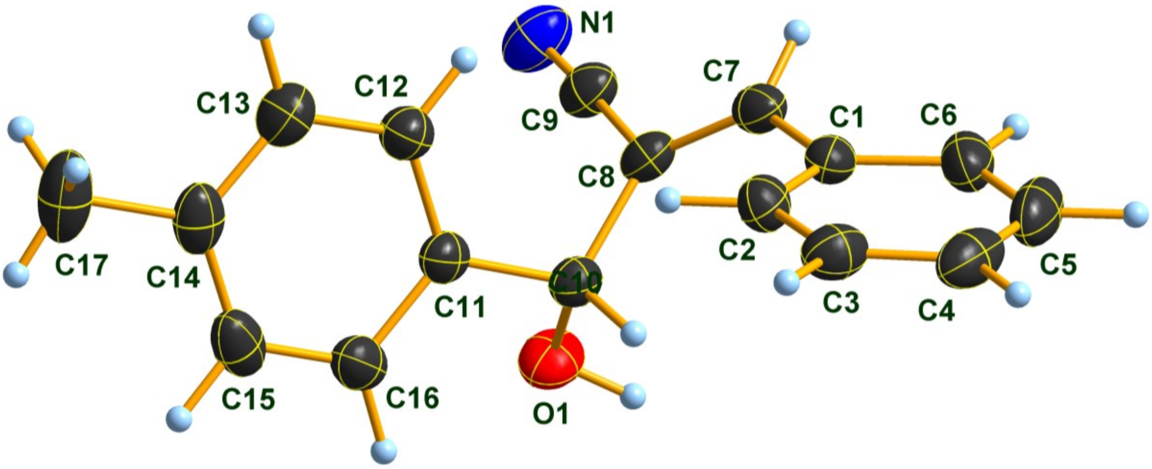


Figure 13: Molecular structure of compound **43am'** in the crystal, DIAMOND[290] representation; thermal ellipsoids are drawn at 50 % probability level.

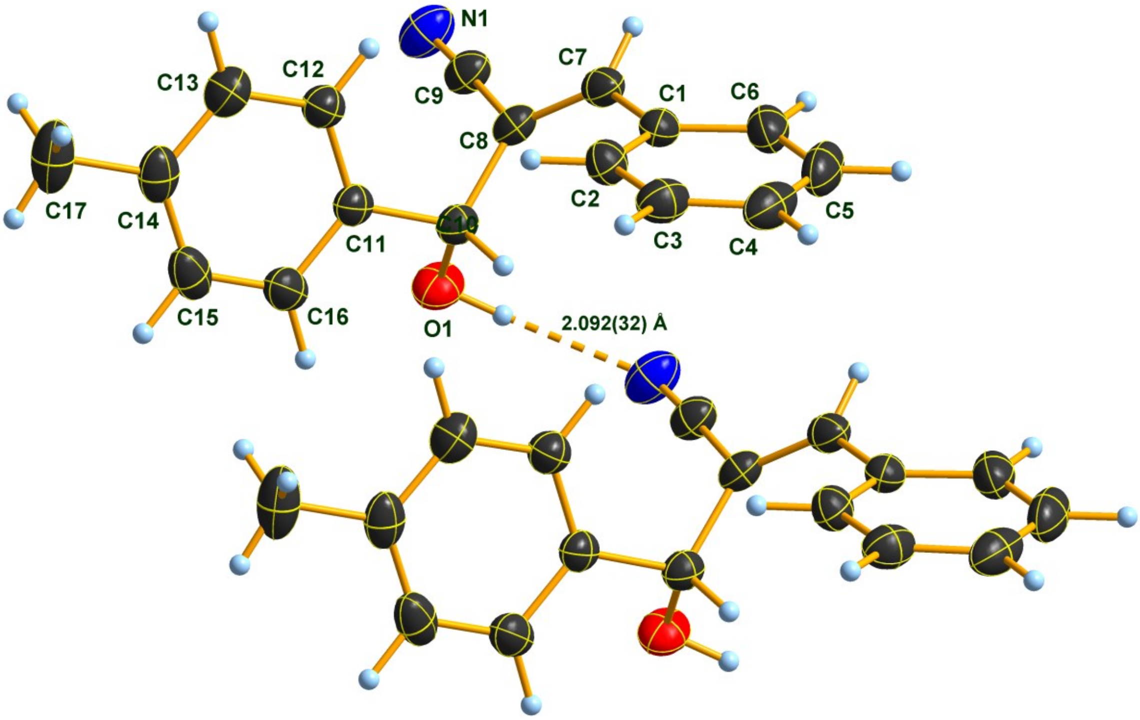


Figure 14: Hydrogen bonding in the crystal of compound **43am'**, DIAMOND[290] representation; thermal ellipsoids are drawn at 50 % probability level. Symmetry code for the second (not labeled) molecule: 1+x, y, z.

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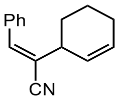
[290] DIAMOND, Crystal Impact GbR., Version 3.2i.

2-(Cyclohex-2-en-1-yl)-3-phenylacrylonitrile (43ah)



According to the TP7, a solution cinnamonitrile (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 (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 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.

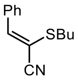
(*Z*)-2-(Cyclohex-2-en-1-yl)-3-phenylacrylonitril:e δ / ppm = 143.2, 134.2, 131.5, 130.0, 128.8 (2C), 128.4 (2C), 126.3, 121.1, 119.7, 41.7, 29.8, 25.0, 20.1.

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 (43az)



According to the TP7, a solution cinnamonitrile (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 (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 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.

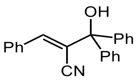
(*E*)-2-(Butylthio)-3-phenylacrylonitrile: δ / ppm = 142.7, 134.2, 130.7, 130.5 (2C), 128.7 (2C), 115.8, 105.5, 34.2, 32.0, 21.8, 13.7.

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 (43al')



According to the TP7, a solution of cinnamonitrile (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 (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 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.

Table 33: Details for X-ray data collection and structure refinement for compound **43al'**.

	43al'
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)
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

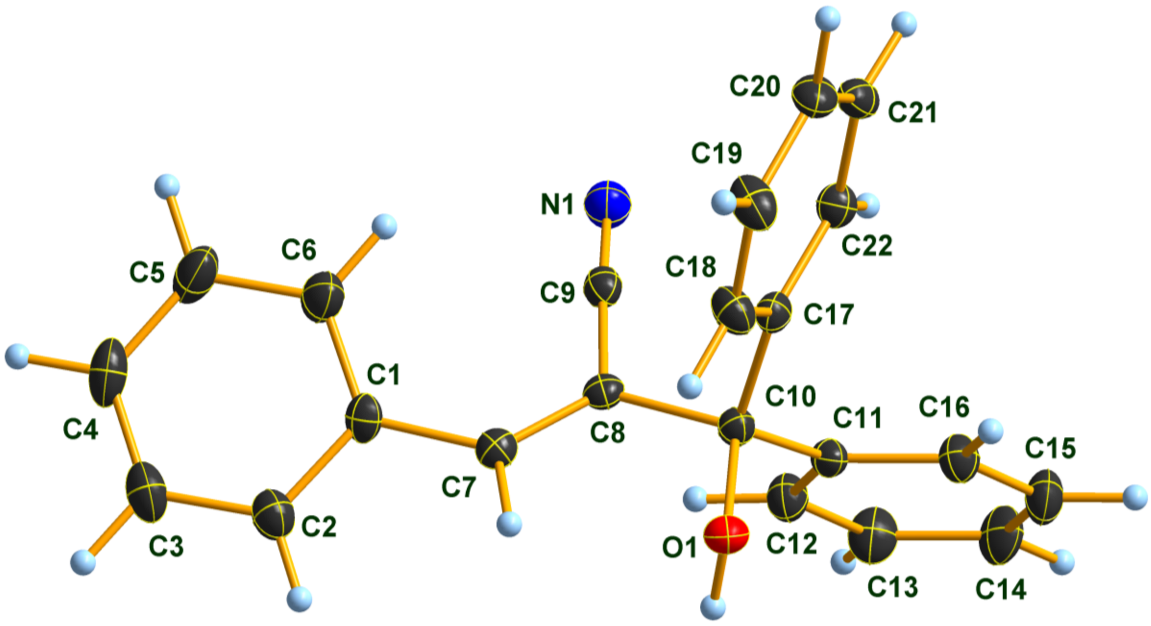


Figure 15: Molecular structure of compound **43al'** in the crystal. DIAMOND[291] representation; thermal ellipsoids are drawn at 50 % probability level.

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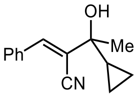
[291] DIAMOND, Crystal Impact GbR., Version 3.2i.

(*E*)-2-Benzylidene-3-cyclopropyl-3-hydroxybutanenitrile (43an'')



According to the TP7, a solution of cinnamonitrile (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 (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 as a yellow oil (30 mg, 0.14 mmol, 78% yield; *E/Z* > 99/1).

According to the TP8, a solution of cinnamonitrile (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 (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 as a yellow oil (29 mg, 0.14 mmol, 68% yield; *Z*/*E* > 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).

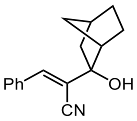
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.1, 133.6, 130.3, 129.2 (2C), 128.9 (2C), 119.1, 118.3, 72.9, 26.9, 21.1, 2.2, 1.2.

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

2-(2-Hydroxybicyclo[2.2.1]heptan-2-yl)-3-phenylacrylonitrile (43aa’)



According to the TP7, a solution of cinnamonitrile (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 (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 as a colorless solid (39 mg, 0.16 mmol, 82% yield; *E/Z* > 99/1, *d.r.* > 99/1).

According to the TP8, a solution of cinnamonitrile (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 (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 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.

Table 34: Details for X-ray data collection and structure refinement for compound **43aa'**.

	43aa'
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
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

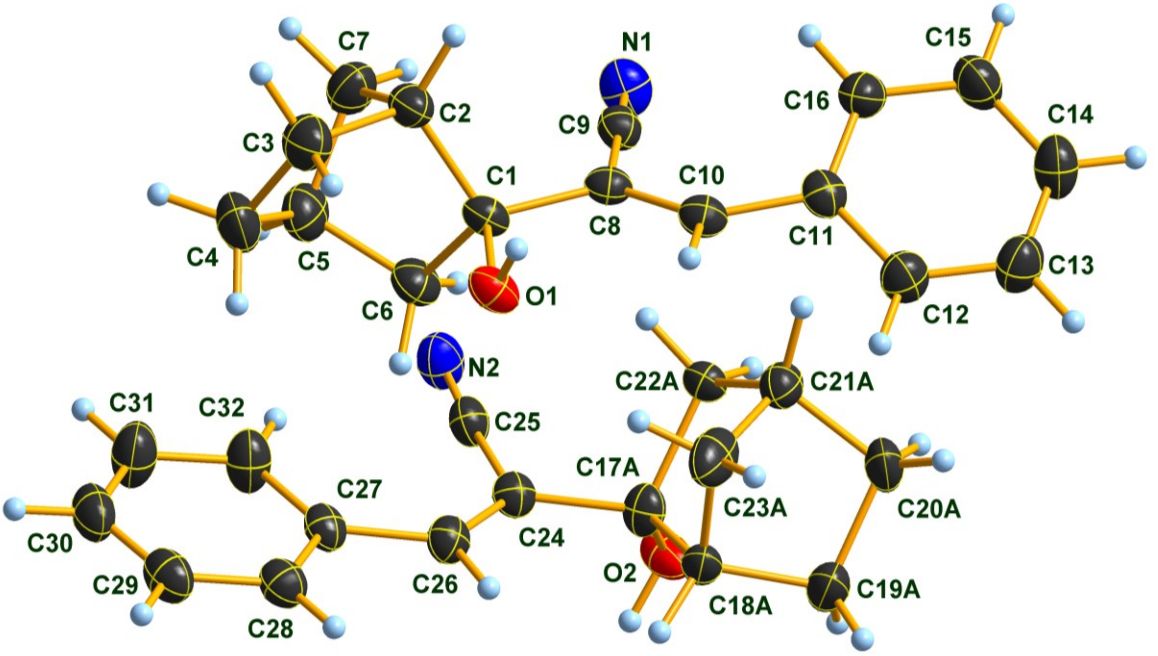
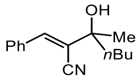


Figure 16: Molecular structure of compound **43aa’** in the crystal; view of the two crystallographically independent molecules. In one of the molecules (bottom) the norbornane ring is disordered over two positions. Only the position with higher occupancy (70 %) has been shown for clarity. DIAMOND[292] representation; thermal ellipsoids are drawn at 50 % probability level.

(*E*)-2-Benzylidene-3-hydroxy-3-methylheptanenitrile (43ao’’)



According to the TP7, a solution of cinnamonitrile (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 (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 as a colorless oil (40 mg, 0.17 mmol, 87% yield; *E/Z* > 99/1).

According to the TP8, a solution of cinnamonitrile (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 (30 mg,

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[292] DIAMOND, Crystal Impact GbR., Version 3.2i.

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 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).

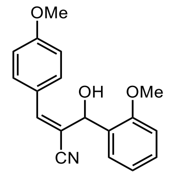
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.5, 133.5, 130.3, 129.1 (2C), 129.0 (2C), 118.7,118.1, 74.8, 41.2, 28.4, 258, 23.0, 14.1.

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 (43be')



According to the TP7, a solution of 3-(4-methoxyphenyl)acrylonitrile (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 (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 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.

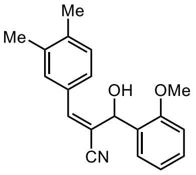
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3431, 3005, 2959, 2932, 2928, 2838, 2359, 2210, 1602, 1570, 1512, 1490, 1463, 1439, 1424, 1404, 1399, 1388, 1306, 1288, 1256, 1179, 1162, 1136, 1110, 1046, 1028, 832, 791, 756.

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 (43ce’)



According to the TP7, a solution of 3-(3,4-dimethylphenyl)acrylonitrile (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 (41 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH$_4$Cl. 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 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.

Table 35: Details for X-ray data collection and structure refinement for compound **43ce'**.

	43ce'
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

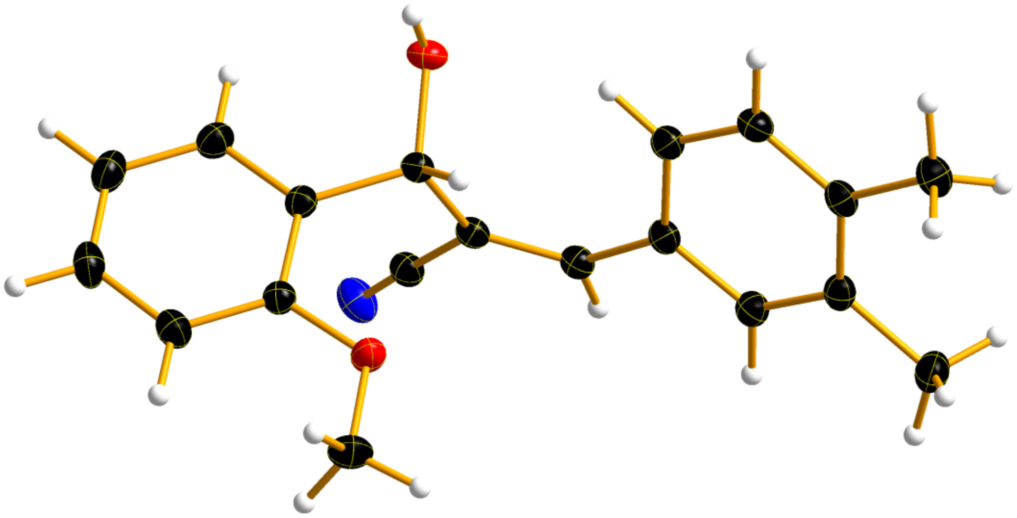


Figure 17: Molecular structure of compound **43ce’** in the crystal, DIAMOND[293] representation; thermal ellipsoids are drawn at 50 % probability level.

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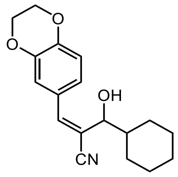
[293] DIAMOND, Crystal Impact GbR., Version 3.2i.

(*Z*)-2-(Cyclohexyl(hydroxy)methyl)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile (43do')



According to the TP7, a solution of 3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile (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 (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 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).

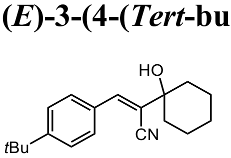
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 146.1, 145.1, 143.6, 126.8, 123.2, 118.9, 118.4, 117.7, 117.0, 71.8, 64.6, 64.3, 42.7, 29.2, 29.0, 26.2, 25.8, 25.6.

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 (43es)



According to the TP7, a solution of 3-(4-(*tert*-butyl)phenyl)-2-(cyclohexyl(hydroxy)methyl)acrylonitrile (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 (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 as a colorless solid (34 mg, 0.5 mmol, 67% yield; *Z/E* > 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.

Table 36: Details for X-ray data collection and structure refinement for compound **43es**.

	43es
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
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

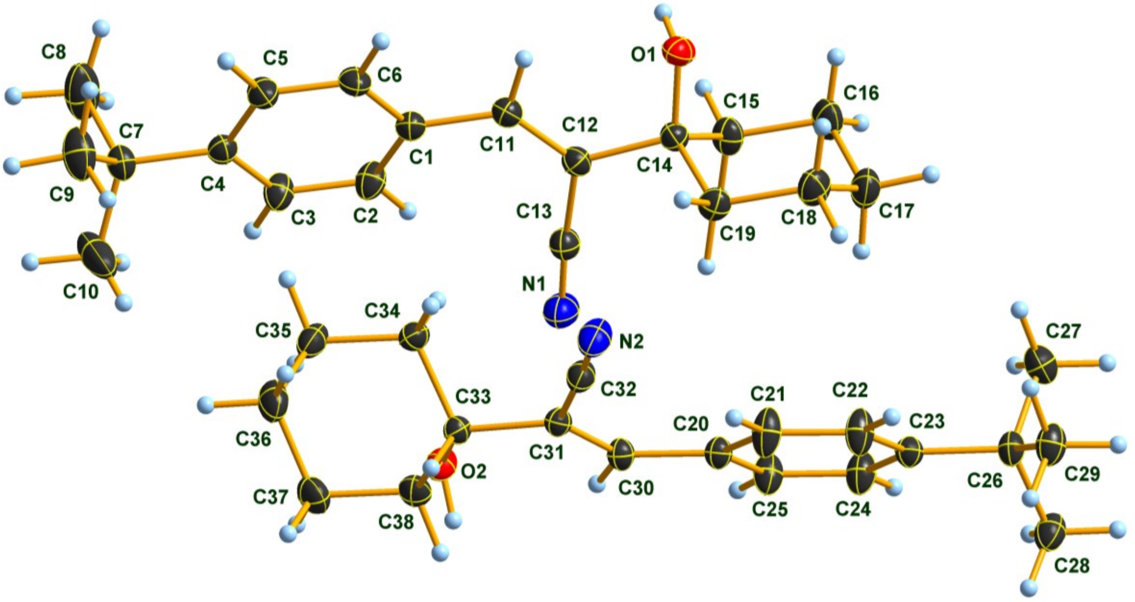


Figure 18: Molecular structure of compound **43es** in the crystal. DIAMOND[294] representation; thermal ellipsoids are drawn at 50 % probability level.

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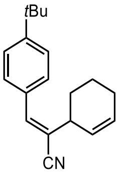
[294] DIAMOND, Crystal Impact GbR., Version 3.2i.

(*E*)-3-(4-(*Tert*-butyl)phenyl)-2-(cyclohex-2-en-1-yl)acrylonitrile (43eh)



According to the TP7, a solution of 3-(4-(*tert*-butyl)phenyl)acrylonitrile (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 (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 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).

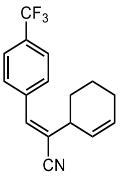
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.9, 143.8, 131.4, 131.3, 129.1 (2C), 126.7, 125.9 (2C), 120.2, 119.9, 35.6, 35.0, 31.3 (3C), 28.5, 24.6, 21.4.

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 (43fh)



According to the TP7, a solution of 3-(4-(trifluoromethyl)phenyl)acrylonitrile (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 (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 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.

Table 37: Details for X-ray data collection and structure refinement for compound **43fh**.

	43fh
Empirical formula	$C_{16}H_{14}F_3N$
Formula mass	277.28
T[K]	143(2)
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

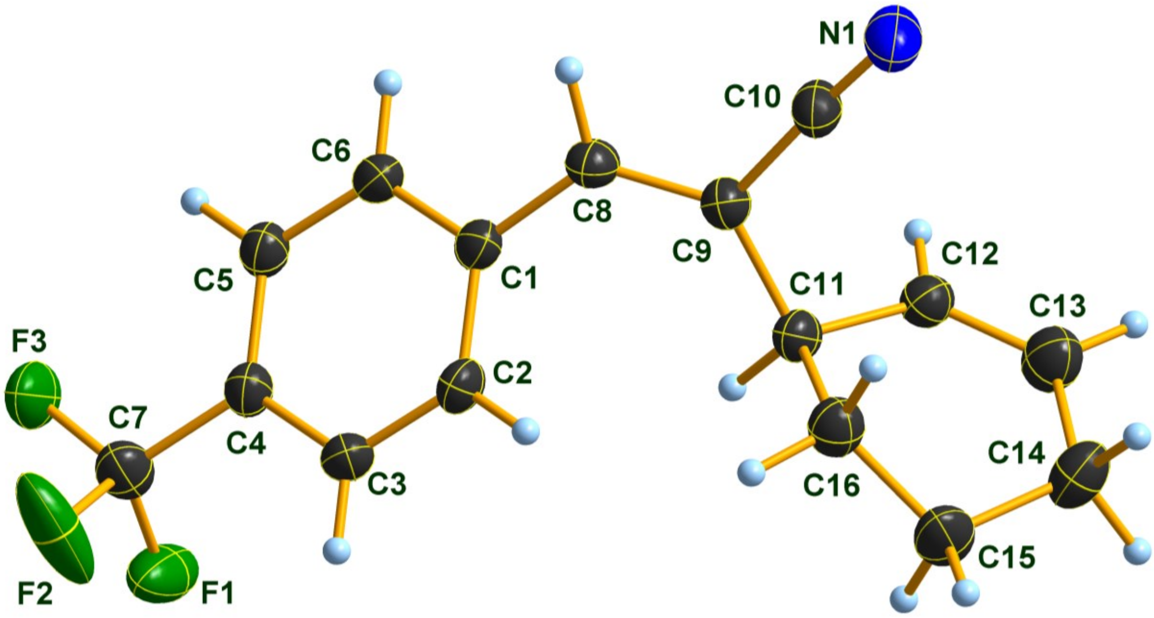


Figure 19: Molecular structure of compound **43fh** in the crystal. DIAMOND[e)295] representation; thermal ellipsoids are drawn at 50 % probability level.

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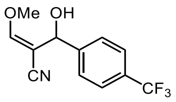
[295] DIAMOND, Crystal Impact GbR., Version 3.2i.

(*Z*)-4-Hydroxy-3-methoxy-4-(4-(trifluoromethyl)phenyl)but-2-enenitrile (43gp'')



According to the TP7, a solution 3-methoxyacrylonitrile (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·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 (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 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.

Table 38: Details for X-ray data collection and structure refinement for compound **43gp''**.

	43gp''
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
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

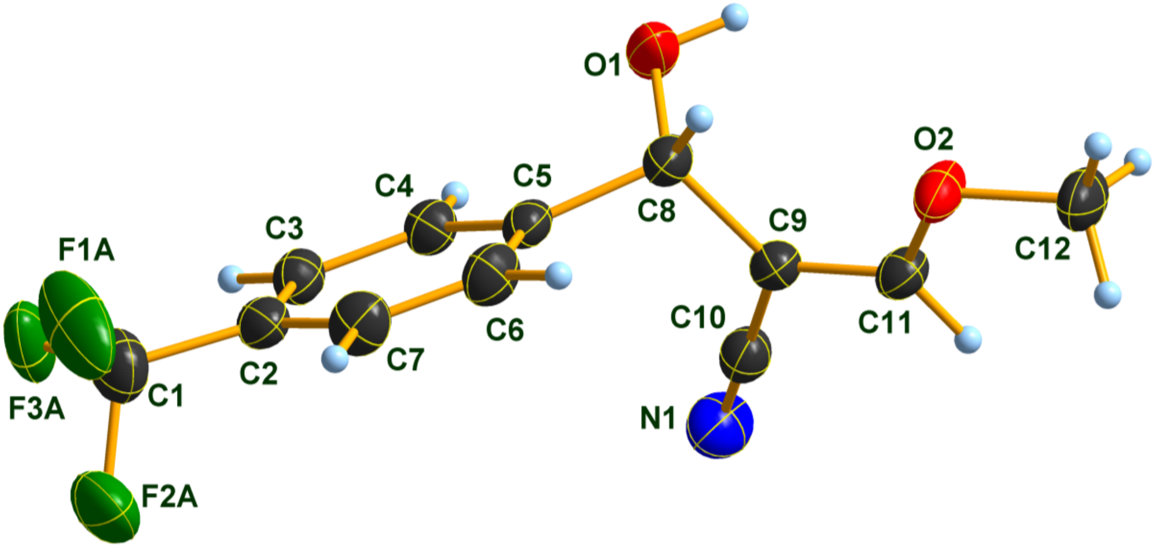


Figure 20: Molecular structure of compound **43gp''** in the crystal, DIAMOND[296] representation; thermal ellipsoids are drawn at 50 % probability level. The CF_3 group is disordered over two positions; only one position is shown for clarity.

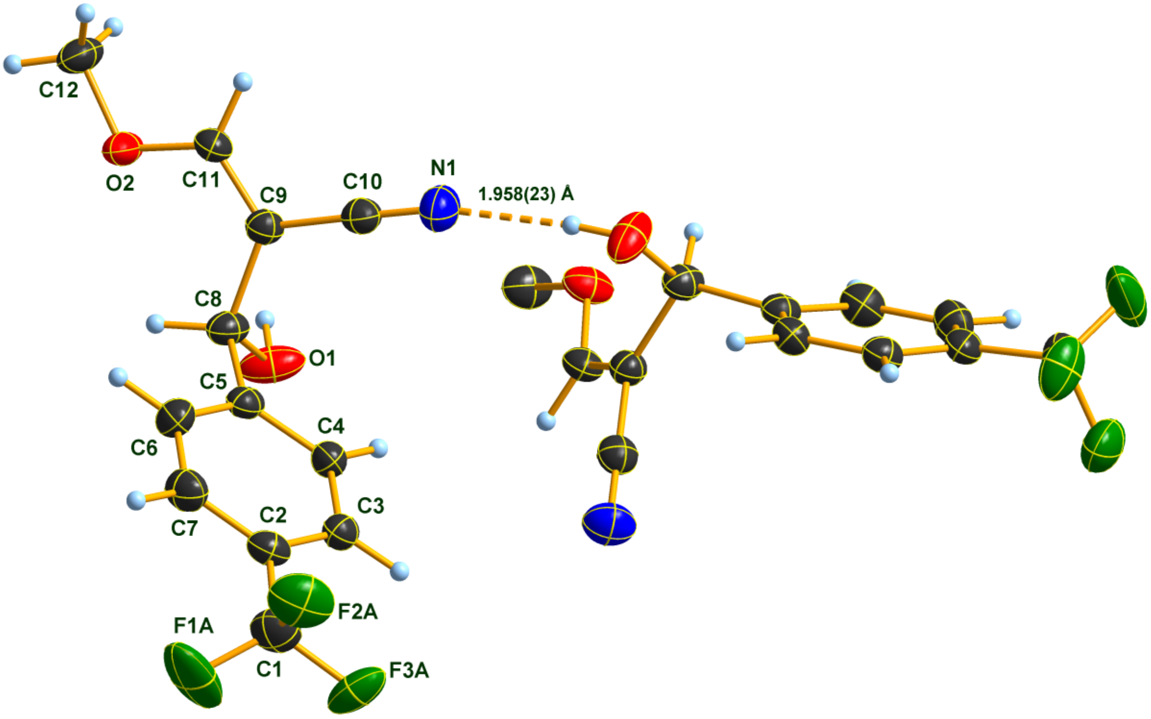


Figure 21: Hydrogen bonding in the crystal of compound **43gp''**, DIAMOND[296] representation; thermal ellipsoids are drawn at 50 % probability level. Symmetry code for the second (not labeled) molecule: -x, -0.5+y, 0.5-z.

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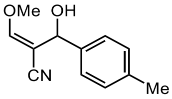
[296] DIAMOND, Crystal Impact GbR., Version 3.2i.

(*Z*)-2-(Hydroxy(*p*-tolyl)methyl)-3-methoxyacrylonitrile (43gm'')



According to the TP7, a solution of 3-methoxyacrylonitrile (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 (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 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.

Table 39: Details for X-ray data collection and structure refinement for compound **43gm''**.

	43gm''
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
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

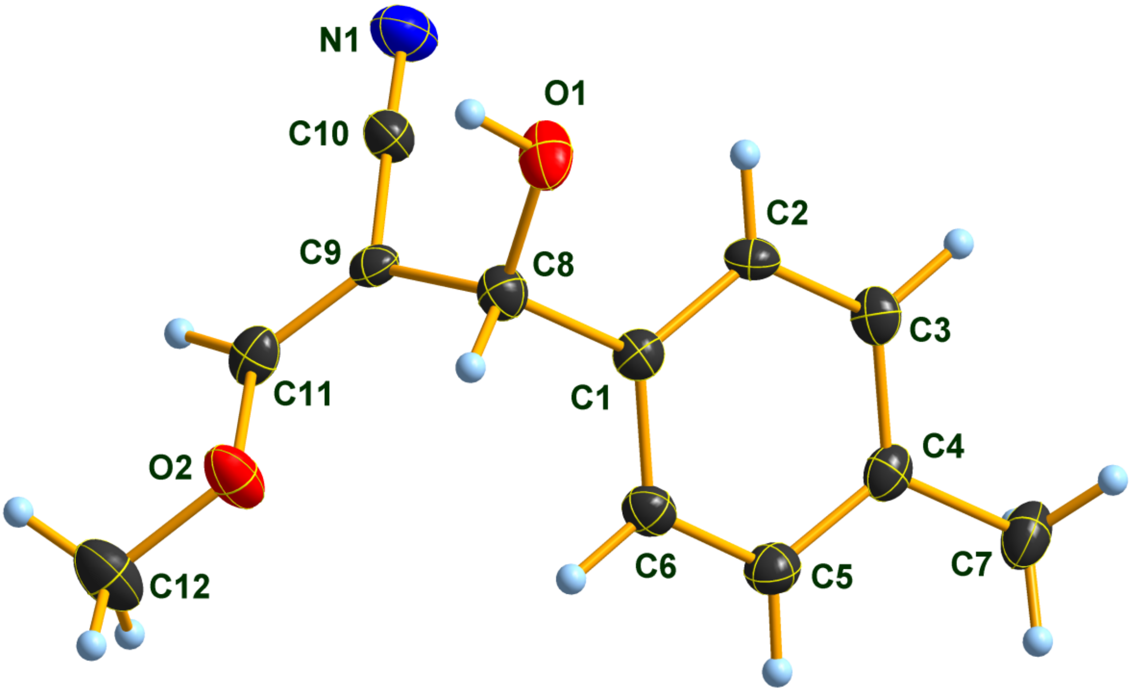
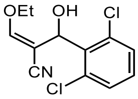


Figure 22: Molecular structure of compound **43gm''** in the crystal. DIAMOND[297] representation; thermal ellipsoids are drawn at 50 % probability level.

(*Z*)-2-((2,6-Dichlorophenyl)(hydroxy)methyl)-3-ethoxyacrylonitrile (43hq')



According to the TP7, a solution of 3-ethoxyacrylonitrile (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 (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 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).

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[297] DIAMOND, Crystal Impact GbR., Version 3.2i.

^{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.

Table 40: Details for X-ray data collection and structure refinement for compound **43hq’**.

	43hq’
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	$-10 \leq h \leq 10$
	$-17 \leq k \leq 17$
	$-25 \leq l \leq 25$
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

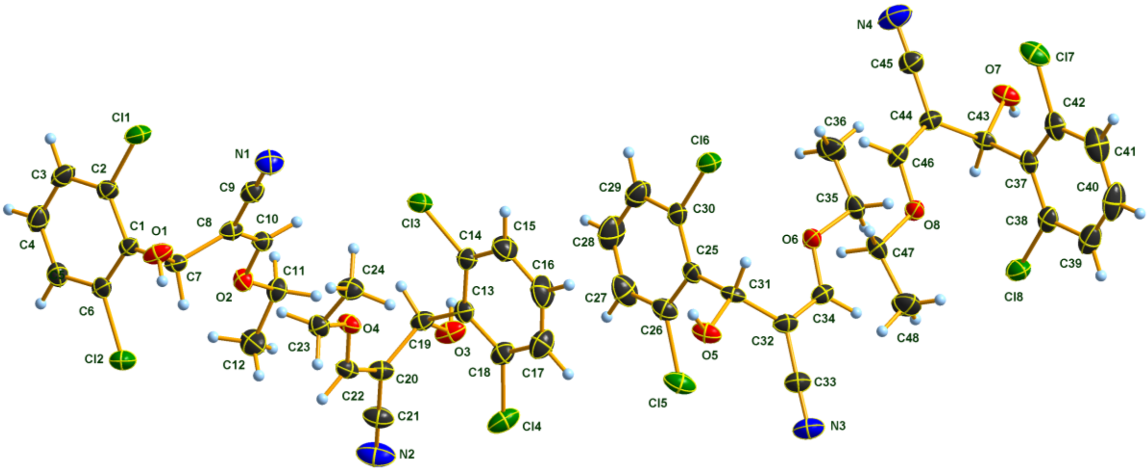
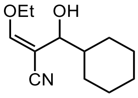


Figure 23: Molecular structure of compound **43hq'** in the crystal. DIAMOND[298] representation; thermal ellipsoids are drawn at 50 % probability level.

(*Z*)-4-Cyclohexyl-3-ethoxy-4-hydroxybut-2-enenitrile (43ho')



According to the TP7, a solution 3-ethoxyacrylonitrile (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 (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 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,

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[298] DIAMOND, Crystal Impact GbR., Version 3.2i.

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).

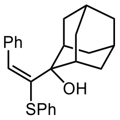
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 159.3, 118.2, 96.4, 71.2, 70.0, 42.6, 29.1, 28.7, 26.4, 25.9, 25.7, 15.3.

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 (43it)



According to the TP7, a solution (*E*)-phenyl(styryl)sulfane (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 (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 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.

Table 41: Details for X-ray data collection and structure refinement for compound **43it**.

	43it
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)
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

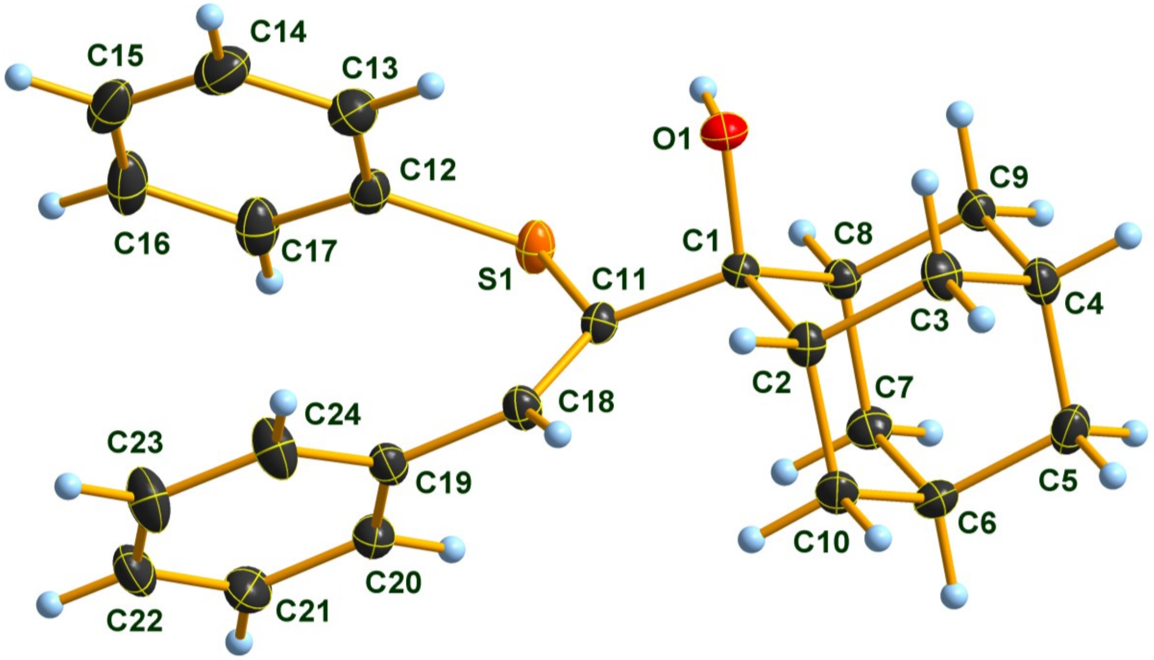
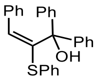


Figure 24: Molecular structure of compound **43it** in the crystal. DIAMOND[299] representation; thermal ellipsoids are drawn at 50 % probability level.

1,1,3-Triphenyl-2-(phenylthio)prop-2-en-1-ol (43il')



According to the TP7, a solution (*E*)-phenyl(styryl)sulfane (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 (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

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[299] DIAMOND, Crystal Impact GbR., Version 3.2i.

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 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, $CDCl_3$):

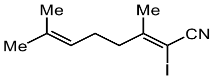
(*E*/*Z*)-1,1,3-Triphenyl-2-(phenylthio)prop-2-en-1-ol: δ / ppm = 146.4, 145.2, 144.5, 140.1, 137.3, 135.4, 133.1, 131.3, 129.6, 129.5, 128.9, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 127.9, 127.9, 127.8, 127.7, 127.0, 125.8, 84.6, 82.9.

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 (46ab)



According to the TP7, a solution geranyl nitrile (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 (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 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.

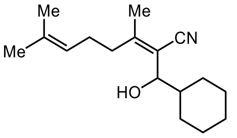
(*Z*)-2-(Hydroxyiodomethyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 166.9, 134.2, 121.7, 117.6, 54.6, 38.7, 29.9, 27.3, 25.6, 17.8.

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 (46ao')



According to the TP7, a solution geranyl nitrile (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 (34 mg, 0.30 mmol, 1.7 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH$_4$Cl. 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 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.

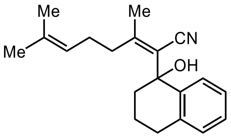
(*Z*)-2-(Cyclohexyl(hydroxy)methyl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 157.5, 133.5, 122.5, 117.3, 114.3, 73.1, 42.9, 39.0, 29.3, 28.9, 26.4 (2C), 26.0, 25.8, 23.0, 18.8, 17.8.

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 (46aq'')



According to the TP7, a solution geranyl nitrile (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 (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 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.

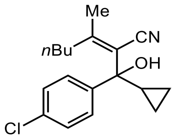
(*Z*)-2-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3,7-dimethylocta-2,6-dienenitrile: δ / ppm = 157.0, 140.1, 137.2, 133.2, 129.5, 128.3, 127.6, 127.2, 122.6, 120.4, 118.1, 72.9, 39.9, 37.3, 29.7, 26.6, 25.6, 19.8, 19.2, 17.8.

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 (46bf)



According to the TP7, a solution 3-methylhept-2-enenitrile (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 (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 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.

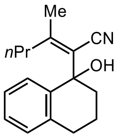
(*E*)-2-((4-Chlorophenyl)(cyclopropyl)(hydroxy)methyl)-3-methylhept-2-enenitrile: δ / ppm = 164.3, 143.3, 133.2, 128.4 (2C), 127.3 (2C), 118.5, 118.2, 74.8, 39.7, 30.2, 24.0, 23.6, 20.5, 14.1, 2.3, 2.2.

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 (46cq'')



According to the TP7, a solution (*E*)-3-methylhex-2-enenitrile (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 (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 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).

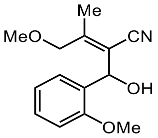
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 157.5, 140.1, 137.2, 129.6, 128.3, 127.6, 127.3, 120.3, 118.2, 72.9, 41.8, 37.4, 29.7, 21.4, 19.6, 19.2, 13.7.

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 (46de')



According to the TP7, a solution of 4-methoxy-3-methylbut-2-enenitrile (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 *m*-anisaldehyde (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 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.

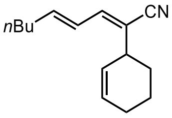
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3416, 3353, 2938, 2843, 2217, 1600, 1590, 1488, 1463, 1449, 1438, 1377, 1290, 1266, 1245, 1190, 1166, 1133, 1114, 1095, 1079, 1042, 1030, 958, 942, 834, 790, 780, 756, 721, 661.

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 (46eh)



According to the TP7, a solution of (*2E,4E*)-nona-2,4-dienenitrile (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 (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 as a yellow oil (32 mg, 0.15 mmol, 74% yield; 2*Z*/2*E* = 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).

(2Z,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.

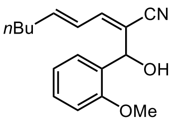
(2*Z*,4*E*)-2-(Cyclohex-2-en-1-yl)nona-2,4-dienenitrileenenitrile: δ / ppm = 144.2, 143.6, 131.0, 127.1, 126.4, 118.2, 115.5, 39.6, 32.8, 31.6, 31.1, 29.8, 24.9, 22.4, 20.1.

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 (46ee')



According to the TP7, a solution of (*2E,4E*)-nona-2,4-dienenitrile (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 *m*-anisaldehyde (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 as off-white solid (45 mg, 0.16 mmol, 82% yield; 2*Z*/2*E* = 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.

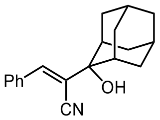
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 2961, 2928, 2856, 2838, 2220, 1633, 1599, 1588, 1488, 1462, 1436, 1407, 1383, 1370, 1324, 1304, 1285, 1251, 1235, 1200, 1188, 1173, 1161, 1148, 1119, 1053, 1046, 1023, 981, 947, 940, 931, 917, 860, 843, 789, 754, 724, 688.

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 (43at)



According to the TP7, a solution of cinnamonitrile (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 (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 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).

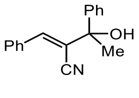
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.0, 133.6, 130.6, 129.2 (2C), 129.0 (2C), 118.4, 117.8, 75.7, 37.4, 35.7 (2C), 34.6 (2C), 32.7 (2C), 27.1, 26.9.

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 (43ab‘)



According to the TP8, a solution of cinnamonitrile (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 (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 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).

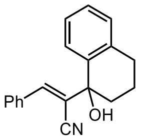
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 143.8, 141.6, 133.3, 130.5, 129.2 (2C), 129.0 (2C), 128.9 (2C), 128.4, 125.7 (2C), 119.1, 117.9, 75.8, 28.7.

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 (43aq'')



According to the TP8, a solution of cinnamonitrile (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 (44 mg, 0.30 mmol, 1.5 equiv) in THF. The reaction was instantaneously quenched by the addition of *sat. aq.* NH$_4$Cl. 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 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).

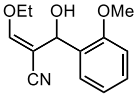
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 142.8, 138.0, 137.7, 133.4, 130.4, 129.7, 129.2 (2C), 129.0 (2C), 128.9, 127.7, 127.1, 119.1, 118.0, 75.1, 37.2, 29.5, 19.3.

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 (43he')



According to the TP8, a solution of 3-ethoxyacrylonitrile (0.20 M, 19 mg, 0.20 mmol, 1.0 equiv) 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 *m*-anisaldehyde (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 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.

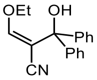
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3387, 2935, 2840, 2212, 1637, 1599, 1587, 1488, 1462, 1438, 1392, 1371, 1355, 1325, 1306, 1290, 1242, 1216, 1190, 1171, 1161, 1146, 1108, 1091, 1027, 1013, 949, 940, 920, 892, 855, 790, 768, 756, 732, 688.

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 (43hl')



According to the TP8, a solution of 3-ethoxyacrylonitrile (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 (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 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).

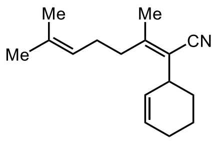
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.2, 143.8 (2C), 128.5 (4C), 128.3 (2C), 127.3 (4C), 116.4, 98.7, 78.8, 71.1, 15.3.

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 (46ah)



According to the TP8, a solution of geranyl nitrile (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 (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 as a yellow oil (25 mg, 0.11 mmol, 54% yield; *Z*/*E* = 52/48).

^{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).

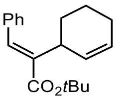
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 154.9, 154.8, 133.4, 133.1, 130.4, 130.3, 127.6, 127.5, 122.7, 122.6, 118.7, 118.4, 115.4, 115.1, 38.8, 36.2, 36.0, 34.0, 28.6, 28.2, 26.6, 26.5, 25.8, 25.8, 24.6, 24.6, 23.0, 21.7, 21.6, 18.4, 17.8 (2C).

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 (49bh)



According to the TP8, a solution *tert*-butyl cinnamate (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 (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 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).

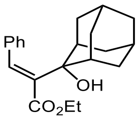
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 167.5, 138.7, 138.6, 136.2, 130.5, 129.1 (2C), 128.4 (2C), 128.0, 126.2, 80.9, 36.2, 28.3, 28.3 (3C), 24.8, 22.9.

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 (49at)



A solution of ethyl cinnamate (0.20 M, 35 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* > 99/1) and adamantanone (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 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.

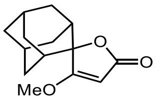
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3407, 2958, 2917, 2903, 2856, 1708, 1678, 1636, 1468, 1459, 1446, 1410, 1392, 1375, 1352, 1338, 1319, 1296, 1284, 1231, 1208, 1130, 1118, 1110, 1104, 1095, 1072, 1040, 1003, 962, 936, 926, 911, 874, 857, 756, 732, 702, 683.

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 (49ct)



A solution of methyl (*E*)-3-methoxyacrylate (0.20 M, 23 mg, 0.20 mmol, 1.0 equiv; *E*/*Z* > 99/1) and adamantanone (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 **13co** 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.

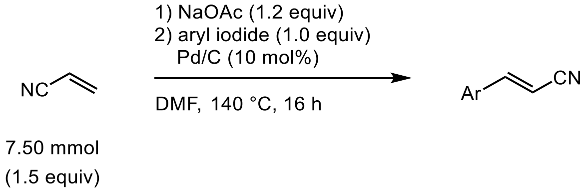
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3111, 2946, 2908, 2895, 2864, 2851, 1754, 1619, 1471, 1455, 1436, 1377, 1346, 1315, 1286, 1254, 1203, 1177, 1113, 1104, 1066, 1050, 1041, 1018, 1009, 1002, 959, 954, 934, 924, 888, 866, 826, 802, 777, 753, 739, 709, 666.

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.

17.3 TYPICAL PROCEDURE 9 (TP9)



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 mol% 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.[300]

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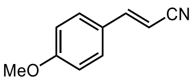
[300] P. An, Z. Yu, Q. Lin, *Org. Lett.* **2013**, *15*, 5496.

3-(4-Methoxyphenyl)acrylonitrile (41b)



According to the TP9, 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% 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).

(*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.

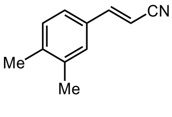
(Z)- 3-(4-Methoxyphenyl)acrylonitrile: δ / ppm = 148.8, 131.3 (2C), 130.3, 130.2, 126.6, 118.6 (2C), 93.5, 19.8.

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 (41c)



According to the TP9, 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% 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.

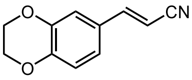
(*Z*)-3-(3,4-Dimethylphenyl)acrylonitrile: δ / ppm = 148.9, 140.5, 137.4, 131.5, 130.4, 130.3, 126.7, 113.9, 93.6, 20.1, 19.9.

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 (41d)



According to the TP9, 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% 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.

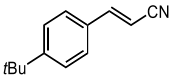
(*Z*)- 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylonitrile: δ / ppm = 148.1, 129.0, 123.2, 118.2, 117.8, 117.6, 116.4, 92.8, 64.8, 64.3.

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 (41e)



According to the TP9, 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% 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).

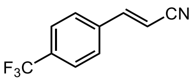
(*Z*)-3-(4-(*Tert*-butyl)phenyl)acrylonitrile: δ / ppm = 154.8, 148.7, 131.1, 129.1 (2C), 126.0 (2C), 117.1, 94.1, 35.1, 31.2 (3C).

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 (41f)



According to the TP9, 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% 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.

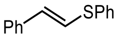
(*Z*)- 3-(4-(Trifluoromethyl)phenyl)acrylonitrile: δ / ppm = 147.2, 136.8, 132.9 (q, *J* = 32.6 Hz), 129.3 (2C), 126.1 (q, *J* = 3.9 Hz, 2C), 123.7 (d, *J* = 272.2 Hz), 116.8, 98.1.

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 (41i)



Phenylacetylene (1.0 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).[301]

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[301] I. P. Beletskaya, I. G. Trostyanskaya, *Synlett*, **2012**, *4*, 535.

^{1}H-NMR (400 MHz, CDCl$_3$):

(*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.

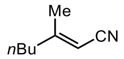
(*Z*)-Phenyl(styryl)sulfane: δ / ppm = 136.6, 135.4, 132.0, 130.0 (2C), 129.3 (2C), 128.8 (2C), 127.7 (2C), 127.1, 126.2, 123.5.

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 (44b)



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).[302]

^{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).

(*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$_3$):

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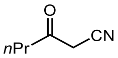
[302] S. A. DiBiase, B. A. Lipisko, A. Haag, A. W. Raymond, G. W. Gokel, *J. Org. Chem.* **1979**, *44*, 4640.

(*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.[303]

3-Oxohexanenitrile

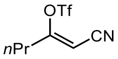


According to the literature,[304] to a solution of ethyl butyrate (23.2 g, 26.4 mL, 200 mmol, 1.0 equiv) and acetonitrile (12.3 g, 15.6 mL, 300 mmol, 1.5 equiv) in THF (400 mL) was added NaH (60% dispersion in mineral oil, 12.0 g, 300 mmol, 1.5 equiv) in small portions. The mixture was heated to reflux 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[305].

(*Z*)-1-Cyanopent-1-en-2-yl 4-methylbenzenesulfonate



According to the literature,[306] 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 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).

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[303] T. T. Vasilev, N. A. Kuzmina, O. V. Chakovskaya, N. E. Mysova, A. B. Terentev, *Russ. J. Org. Chem.* **2004**, *40*, 174.

[304] S. Havel, P. Khirsariya, N. Akavaram, K. Paruch, B. Carbain *J. Org. Chem.* **2018**, *83*, 15380.

[305] Y. Chen, S. McN. Sieburth, *Synthesis*, **2002**, *15*, 2191.

[306] 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.

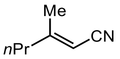
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.4, 118.4 (q, *J*=320.5), 111.9, 92.0, 36.4, 19.5, 13.2.

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 (44c)



According to the literature,[307] 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).

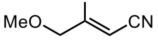
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 165.4, 117.4, 95.2, 40.7, 21.0, 20.4, 13.6.

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 (44d)



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 cyanomethylphosphonate (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

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[307] A. Jolit, P. M. Walleser, G. P. A. Yap, M. A. Tius, *Angew. Chem. Int. Ed.* **2014**, *53*, 6180; *Angew. Chem.* **2014**, *126*, 6294.

1 h. 1-Methoxypentan-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).[308]

^{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.

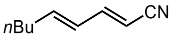
(*Z*)-4-Methoxy-3-methylbut-2-enenitrile: δ / ppm = 161.3, 116.0, 97.1, 73.2, 58.6, 20.6.

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.

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 (44e)



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).[309]

^{1}H-NMR (400 MHz, $CDCl_3$):

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[308] 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.

[309] J. K. Gawronski, H. M. Walborsky, *J. Org. Chem.* **1986**, *51*, 2863.

(*2E,4E*)-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).

(*2Z,4E*)-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).

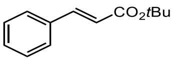
^{13}C-NMR (100 MHz, CDCl$_3$):

(*2E,4E*)-nona-2,4-dienenitrile: δ / ppm = 151.1, 146.2, 128.1, 118.6, 96.5, 32.7, 30.7, 22.4, 14.0.

(*2Z,4E*)-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.[310]

(E)-Tert-butyl cinnamate (47b)



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.[311]

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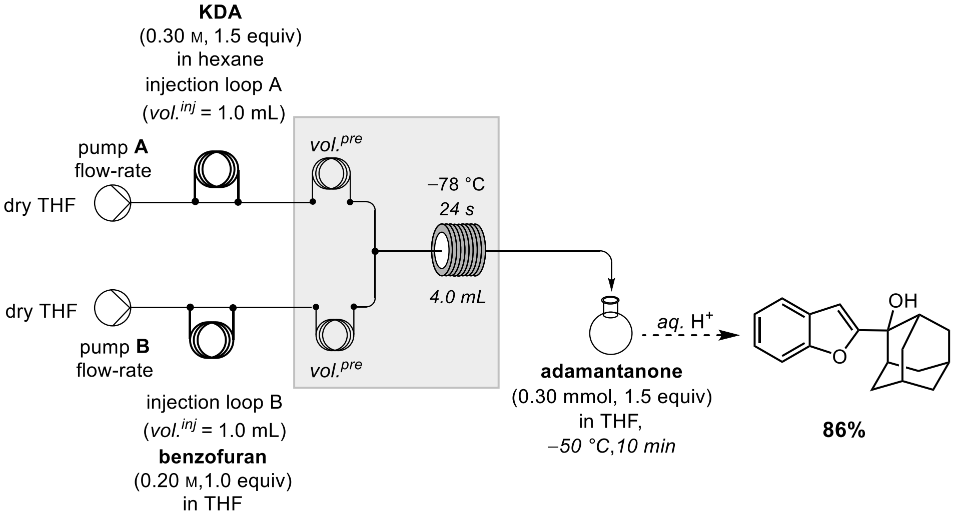
[310] C. H. Yoon, K. S. Yoo, S. W. Yi, R. K. Mishra, K. W. Jung, *Org. Lett.* **2004**, *6*, 4037.

[311] T. Onozawa, M. Kitajima, N. Kogure, H. Takayama, *J. Org. Chem.* **2018**, *83*, 15312.

18. PREPARATION OF FUNCTIONALIZED POTASSIUM ARYL, HETEROARYL AND BENZYLIC ORGANOMETALLICS USING POTASSIUM DIISOPROPYLAMIDE IN CONTINUOUS FLOW

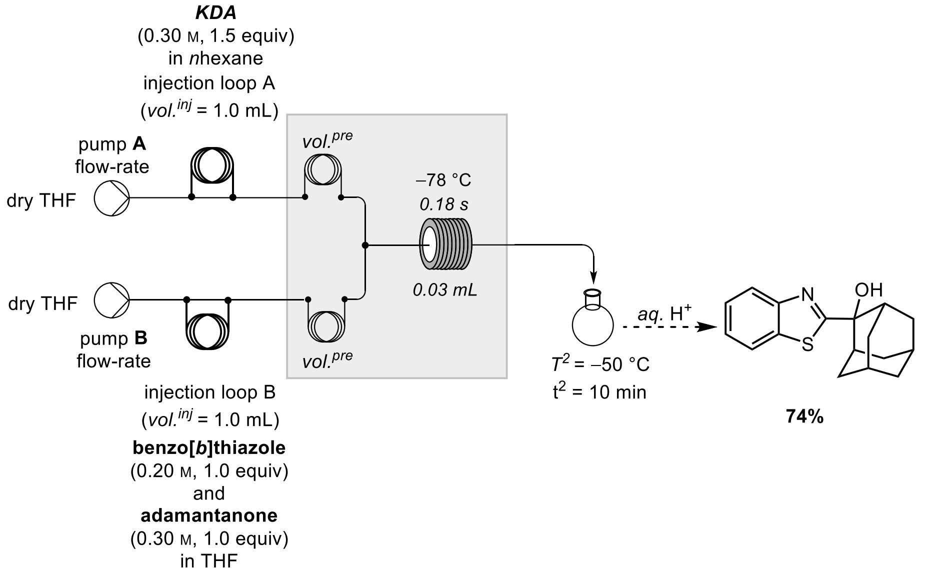
18.1 TYPICAL PROCEDURE 10 (TP10)



Scheme 76: Flow set-up for the deprotonation of (hetero)aromatic substrates with KDA and batch quench with an electrophile (E-X).

A solution of benzofuran (24 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 equiv) were prepared. Injection loop A (vol^{inj} =1.0 mL) was loaded with KDA and injection loop B (vol^{inj} =1.0 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^{-1}), which each passed a precooling loop (vol$_{pre}$ = 1.0 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 (Vol^R = 4.0 mL; residence time: t^1 = 24 s, T^1 = −78 °C) and was subsequently injected in a flask containing a stirred solution of an adamantanone (45 mg, 0.30 M, 1.5 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 as white crystals (47 mg, 0.18 mmol, 86% yield).

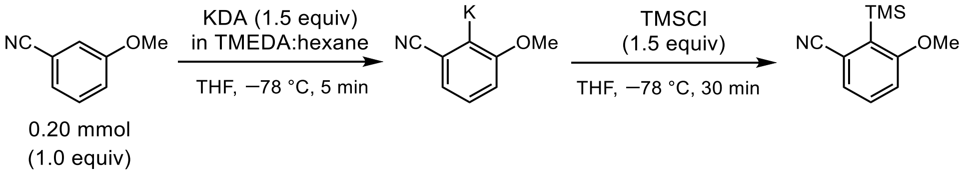
18.2 TYPICAL PROCEDURE 11 (TP11)



Scheme 77: Flow set-up for the deprotonation of (hetero)aromatic substrates with KDA in the presence of an electrophile (E-X). See text for abbreviations.

A KDA solution in hexane (0.30 M, 1.5 equiv) and a solution of benzo[*b*]thiazole (27 mg, 0.20 M, 1.0 equiv) and 2-adamantanone (45 mg, 0.30 M, 1.5 equiv) in dry THF were prepared. Injection loop A (vol^{inj} =1.0 mL) was loaded with KDA and injection loop B (vol^{inj} = 1.0 mL) was loaded with the solution of benzo[*b*]thiazole and 2-adamantanone. The solutions were simultaneously injected into separate streams of THF, respectively (pump A: THF; pump B: THF, combined flow-rates: 10 mL·min^{-1}), which each passed a precooling loop (vol^{pre} = 1.0 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 (Vol^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 as white crystals (42 mg, 0.15 mmol, 74% yield).

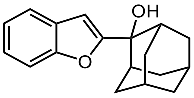
Typical procedure for the metalation using KDA in batch



Scheme 78: Typical procedure for the metalation of arenes using KDA in batch.

A solution of 3-methoxybenzonitrile (27 mg, 0.20 mmol, 1.0 equiv) in THF (1.0 mL) and a solution of KDA (0.30 M in hexane) were prepared. The KDA solution (1.0 mL, 0.30 mmol, 1.5 equiv) was slowly added to 3-methoxybenzonitrile at −78 °C and the mixture was stirred for 5 min. TMSCl (45 mg, 0.30 mmol, 1.5 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 as colorless crystals (32 mg, 0.16 mmol, 78% yield).

2-(Benzofuran-2-yl)adamantan-2-ol (52at)



According to the TP10, a solution of benzofuran (24 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 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.

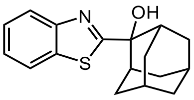
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3528, 3424, 2956, 2916, 2904, 2891, 2852, 1469, 1451, 1402, 1360, 1352, 1332, 1286, 1262, 1248, 1233, 1193, 1181, 1167, 1159, 1116, 1102, 1082, 1052, 1044, 1016, 1006, 997, 982, 949, 930, 908, 900, 886, 876, 858, 806, 749, 740, 706, 680.

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 (52bt)



According to the TP10, a solution of benzo[*b*]thiazole (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 as white crystals (54 mg, 0.19 mmol, 95% yield).

According to the TP11, a solution of benzo[*b*]thiazole (0.20 M, 0.20 mmol) and 2-adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 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 as white crystals (42 mg, 0.15 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.

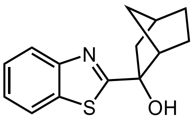
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3372, 3331, 2942, 2921, 2902, 2882, 2854, 1504, 1454, 1437, 1372, 1358, 1350, 1324, 1314, 1279, 1244, 1240, 1233, 1207, 1168, 1152, 1124, 1102, 1084, 1066, 1045, 1034, 1018, 1010, 996, 959, 937, 908, 885, 812, 804, 755, 727, 712, 696, 690.

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 (52ba')



According to the TP10, a solution of benzothiazole (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of norcamphor (33 mg, 0.30 mmol, 1.5 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 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.

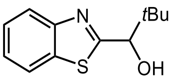
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3330, 2971, 2949, 2940, 2925, 2868, 1503, 1493, 1455, 1446, 1437, 1416, 1325, 1313, 1294, 1278, 1251, 1238, 1176, 1165, 1152, 1130, 1123, 1079, 1065, 1046, 1022, 972, 953, 937, 885, 809, 756, 730, 710, 698.

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 (52br'')



According to the TP10, a solution of benzothiazole (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of pivaldehyde (26 mg, 0.30 mmol, 1.5 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 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).

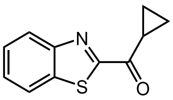
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3423, 2962, 2869, 1510, 1501, 1476, 1464, 1455, 1437, 1392, 1368, 1360, 1329, 1313, 1284, 1237, 1218, 1188, 1168, 1154, 1126, 1086, 1075, 1061, 1016, 900, 764, 757, 731, 708, 687.

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 (52bs'')



According to the TP10, a solution of benzothiazole (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of *N*-methoxy-*N*-methylcyclopropanecarboxamide (39 mg, 0.30 mmol, 1.5 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 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.

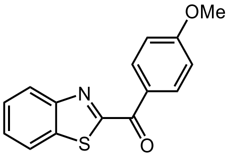
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 3049, 3012, 2924, 2854, 1738, 1668, 1626, 1592, 1550, 1486, 1462, 1456, 1443, 1427, 1414, 1381, 1316, 1277, 1238, 1213, 1184, 1163, 1117, 1094, 1070, 1036, 1013, 951, 879, 831, 806, 760, 726, 708, 694.

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 (52bt'')



According to the TP10, a solution of benzothiazole (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 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 (59 mg, 0.30 mmol, 1.5 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 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.

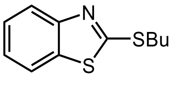
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 1628, 1593, 1569, 1554, 1509, 1490, 1455, 1438, 1425, 1322, 1300, 1273, 1260, 1240, 1177, 1129, 1115, 1065, 1025, 891, 865, 839, 820, 778, 761, 753, 724, 707, 696.

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 (52bz)



According to the TP10, a solution of benzothiazole (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfide (54 mg, 0.30 mmol, 1.5 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 as orange oil (41 mg, 0.18 mmol, 92% yield).

According to the TP11, a solution of benzothiazole (0.20 M, 0.20 mmol) and dibutyl disulfide (54 mg, 0.30 mmol, 1.5 equiv) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 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 as yellow oil (21 mg, 0.09 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).

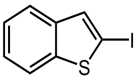
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.6, 153.5, 135.2, 126.1, 124.2, 121.6, 121.0, 33.5, 31.4, 22.1, 13.8.

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 (52cb)



According to the TP10, a solution of benzo[*b*]thiophene (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in cyclohexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of I_2 (76 mg, 0.30 mmol, 1.5 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 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).

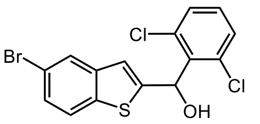
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.5, 140.9, 133.9, 124.6, 124.5, 122.4, 121.4, 78.5.

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 (52dq')



According to the TP10, a solution of 5-bromobenzo[*b*]thiophene (43 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2,6-dichlorobenzaldehyde (53 mg, 0.30 mmol, 1.5 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 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).

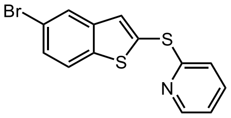
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.9, 141.4, 138.5, 136.4, 135.1 (2C), 130.3, 129.6 (2C), 127.3, 126.3, 123.8, 119.7, 118.5, 70.4.

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 (52du)



According to the TP10, a solution of 5-bromobenzo[*b*]thiophene (43 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 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 (66 mg, 0.30 mmol, 1.5 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 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).

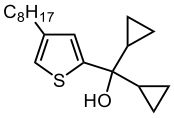
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.1, 149.8, 142.0, 141.2, 137.2, 133.2, 132.3, 128.6, 126.6, 123.6, 121.2, 120.8, 118.8.

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 (52ec')



According to the TP10, a solution of 3-octylthiophene (39 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (33 mg, 0.30 mmol, 1.5 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 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).

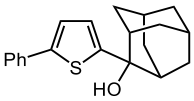
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.0, 142.7, 124.9, 118.7, 72.8, 32.0, 30.8, 30.5, 29.6, 29.6, 29.4, 22.8, 21.4 (2C), 14.3, 1.7 (2C), 1.0 (2C).

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 (52ft)



According to the TP10, a solution of 2-phenylthiophene (32 mg, 0.17 M, 0.17 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.26 M in hexane, 0.26 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 as 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).

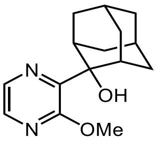
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.8, 143.1, 134.5, 129.0 (2C), 127.5, 125.8 (2C), 124.5, 122.6, 75.0, 47.1, 39.4, 38.2, 37.8, 35.3, 33.0, 27.5, 27.3, 27.2.

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 (52gt)



According to the TP10, a solution 2-methoxypyrazine (22 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 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).

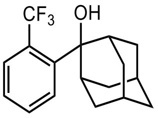
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.8, 149.5, 138.7, 135.0, 77.7, 53.6, 38.0, 35.0 (2C), 34.9 (2C), 33.1 (2C), 27.4, 27.2.

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 (52ht)



According to the TP10, a solution of (trifluoromethyl)benzene (29 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 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).

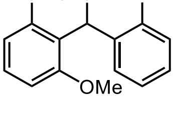
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3429, 2913, 2905, 2878, 2856, 1452, 1444, 1297, 1286, 1267, 1251, 1155, 1124, 1098, 1086, 1062, 1041, 1030, 1008, 996, 970, 964, 956, 935, 910, 774, 766, 757, 675.

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 (52iu'')



According to the TP10, a solution of 1,3-dimethoxybenzene (28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-bromobenzaldehyde (56 mg, 0.30 mmol, 1.5 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 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).

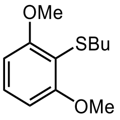
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2941, 1592, 1474, 1458, 1435, 1404, 1338, 1290, 1275, 1242, 1219, 1197, 1185, 1167, 1102, 1070, 1027, 1008, 866, 841, 826, 803, 788, 770, 735, 722, 665.

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 (52iz)



According to the TP10, a solution of 1,3-dimethoxybenzene (28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfide (53 mg, 0.30 mmol, 1.5 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 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).

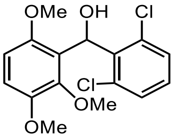
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 161.2 (2C), 129.4, 110.6, 104.1 (2C), 56.3 (2C), 33.9, 31.8, 22.0, 13.8.

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 (52jq')



According to the TP10, a solution of 1,2,4-trimethoxybenzene (34 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2,6-dichlorobenzaldehyde (53 mg, 0.30 mmol, 1.5 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 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.

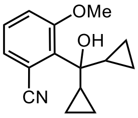
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3448, 2949, 2834, 1991, 1579, 1562, 1484, 1472, 1436, 1421, 1259, 1204, 1189, 1181, 1171, 1151, 1101, 1084, 1074, 1036, 1003, 970, 935, 909, 839, 788, 780, 772, 763, 740, 718, 702, 679.

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 (52kc')



According to the TP10, a solution of 3-methoxybenzonitrile (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (33 mg, 0.30 mmol, 1.5 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 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).

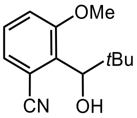
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3232, 3006, 1744, 1665, 1604, 1490, 1465, 1436, 1378, 1349, 1326, 1276, 1240, 1226, 1213, 1184, 1174, 1126, 1106, 1080, 1069, 1045, 1024, 1014, 989, 967, 947, 919, 894, 874, 828, 820, 800, 783, 762, 740, 669.

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 (52kr'')



According to the TP10, a solution of 3-methoxybenzonitrile (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of pivaldehyde (26 mg, 0.30 mmol, 1.5 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 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).

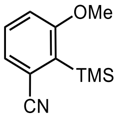
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.8, 154.9, 133.7, 132.8, 130.5, 115.8, 113.6, 90.4, 55.3, 38.0, 26.5 (3C).

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 (52kv'')



According to the TP10, a solution of 3-methoxybenzonitrile (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of TMSCl (40 µL, 0.30 mmol, 1.5 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 as colorless crystals (36 mg, 0.18 mmol, 88% yield).

According to TP12**,** a solution of 3-methoxybenzonitrile (, 27 mg, 0.20 mmol, 1.0 equiv) in THF (1.0 mL) and a solution of KDA (0.30 M in hexane) were prepared. The KDA solution (1.0 mL, 0.30 mmol, 1.5 equiv) was slowly added to 3-methoxybenzonitrile at −78 °C and the mixture was stirred for 5 min. TMSCl (45 mg, 0.30 mmol, 1.5 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 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).

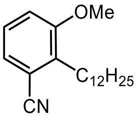
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3011, 2978, 2950, 2903, 2222, 1580, 1562, 1464, 1450, 1441, 1423, 1413, 1393, 1302, 1292, 1265, 1249, 1241, 1188, 1122, 1068, 1053, 895, 840, 789, 760, 744, 715, 689.

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 (52kg’)



According to the TP10, a solution of 3-methoxybenzonitrile (27 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (89 mg, 0.30 mmol, 1.5 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 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.

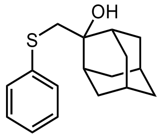
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2918, 2871, 2848, 2222, 1705, 1700, 1580, 1466, 1440, 1377, 1325, 1272, 1254, 1231, 1171, 1118, 1083, 1056, 1028, 788, 737, 724, 680.

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 (55bt)



According to the TP10, a solution of thioanisole (25 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 as slightly yellow crystals (54 mg, 0.20 mmol, 99% yield).

According to TP12**,** a solution of thioanisole (25 mg, 0.20 mmol, 1.0 equiv) in THF (1.0 mL) and a solution of KDA (0.30 M in hexane) were prepared. The KDA solution (1.0 mL, 0.30 mmol, 1.5 equiv) was slowly added to thioanisole at −78 °C and the mixture was stirred for 5 min. Adamantanone (45 mg, 0.30 mmol, 1.5 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 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.

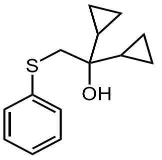
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2941, 2903, 2853, 2361, 1478, 1455, 1437, 1428, 1349, 1196, 1158, 1121, 1093, 1088, 1054, 1044, 1024, 1005, 996, 928, 730, 711, 698, 687, 668.

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 (55bc')



According to the TP10, a solution of thioanisole (25 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (33 mg, 0.30 mmol, 1.5 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 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).

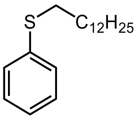
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.6, 129.3 (2C), 129.0 (2C), 126.1, 70.5, 48.1, 18.7 (2C), 1.2 (2C), -0.0 (2C).

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 (55bg')



According to the TP10, a solution of thioanisole (25 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (89 mg, 0.30 mmol, 1.5 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 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.

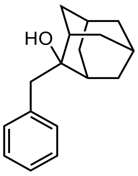
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 2953, 2916, 2871, 2848, 1585, 1480, 1473, 1463, 1438, 1094, 1072, 1023, 891, 729, 718, 702, 688.

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 (58at)



According to the TP10, toluene and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.0 equiv) was prepared. The solutions were mixed with an overall 10 mL·min^{-1} 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 (45 mg, 0.30 mmol, 1.0 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 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.

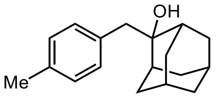
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3545, 3501, 2934, 2899, 2851, 1493, 1451, 1442, 1360, 1352, 1331, 1295, 1282, 1157, 1149, 1120, 1114, 1100, 1082, 1054, 1041, 1028, 1021, 1006, 987, 930, 891, 868, 802, 760, 701, 666.

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.

2-(4-Methylbenzyl)adamantan-2-ol (58bt)



According to the TP10, *p*-xylene (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.0 equiv) were prepared. The solutions were mixed with an overall 10 mL·min^{-1} 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 (45 mg, 0.30 mmol, 1.0 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 = 97:3) afforded the title compound as yellow crystals (76 mg, 0.28 mmol, 94% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.12 (s, 4H), 2.96 (s, 2H), 2.33 (s, 3H), 2.20 – 2.13 (m, 2H), 2.10 (dd, *J* = 13.0, 3.1, 2H), 1.95 – 1.88 (m, 1H), 1.83 – 1.74 (m, 3H), 1.73 – 1.64 (m, 5H), 1.52 (ddd, *J* = 12.4, 3.0, 1.6, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 136.2, 134.2, 130.6 (2C), 129.1 (2C), 74.7, 43.5, 38.5, 36.9 (2C), 34.7 (2C), 33.1 (2C), 27.6, 27.5, 21.2.

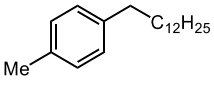
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3545, 3436, 3397, 2912, 2902, 2854, 1514, 1472, 1453, 1442, 1411, 1377, 1352, 1333, 1300, 1283, 1203, 1170, 1155, 1117, 1099, 1059, 1042, 1023, 1007, 992, 926, 908, 893, 880, 868, 849, 812, 753, 731, 727, 695, 668.

MS (EI, 70 eV): *m/z* (%) = 238 (25), 150 (100), 107 (12), 106 (92), 105 (18), 91 (15).

HRMS (EI): *m/z* calc. for [$C_{18}H_{24}O$]: 256.1827; found 256.1822.

m.p. (°C): 62.5 – 67.9.

1-Methyl-4-tridecylbenzene (58bg’)



According to the TP10, *p*-xylene (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.0 equiv) were prepared. The solutions were mixed with an overall 10 mL·min^{-1} 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 (89 mg, 0.30 mmol, 1.0 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 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).

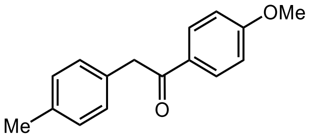
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.0, 135.1, 129.0 (2C), 128.4 (2C), 35.7, 32.1, 31.9, 29.9, 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 22.9, 21.2, 14.3.

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 (58bt'')



According to the TP10, *p*-xylene (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.0 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 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 (59 mg, 0.30 mmol, 1.0 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 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.

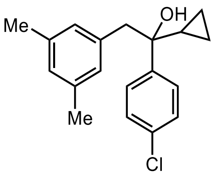
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2920, 2904, 2854, 2842, 1678, 1596, 1576, 1517, 1507, 1459, 1452, 1441, 1418, 1334, 1321, 1304, 1260, 1254, 1228, 1221, 1209, 1199, 1177, 1165, 1122, 1108, 1027, 1011, 995, 987, 950, 915, 859, 844, 828, 818, 802, 774, 737.

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 (58cf)



According to the TP10, mesitylene (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.0 equiv) were prepared. The solutions were mixed with an overall 10 mL·min^{-1} 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 (54 mg, 0.30 mmol, 1.0 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 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.

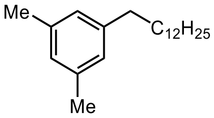
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3347, 3005, 2958, 2947, 2926, 2857, 1605, 1491, 1467, 1442, 1398, 1373, 1350, 1318, 1289, 1240, 1139, 1118, 1104, 1090, 1062, 1049, 1016, 996, 967, 945, 921, 905, 855, 831, 812, 729, 710, 672.

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 (58cg')



According to the TP10, mesitylene (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.0 equiv) were prepared. The solutions were mixed with an overall 10 mL·min^{-1} 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 (89 mg, 0.30 mmol, 1.0 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 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 (vol$^{inj.}$ = 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).

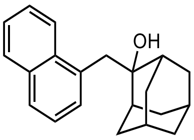
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.1, 137.8 (2C), 127.3, 126.4 (2C), 36.0, 32.1, 31.8, 29.9, 29.9 (2C), 29.8, 29.8, 29.7, 29.6, 29.5 (2C), 22.9, 21.4, 14.3.

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 (58dt)



According to the TP10, a solution of 1-methylnaphthalene (28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 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.

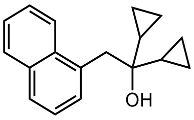
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3562, 2946, 2934, 2901, 2874, 2847, 1594, 1508, 1473, 1461, 1451, 1440, 1396, 1383, 1360, 1351, 1331, 1284, 1272, 1230, 1219, 1168, 1154, 1140, 1126, 1101, 1070, 1041, 1027, 1018, 1002, 986, 944, 929, 893, 864, 857, 807, 782, 742, 726.

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-(naphthalen-1-yl)ethan-1-ol (58dc')



According to the TP10, a solution of 1-methylnaphthalene (28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (33 mg, 0.30 mmol, 1.5 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 = 9:1) afforded the title compound as slightly yellow oil (31 mg, 0.12 mmol, 61% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.30 (dd, *J* = 8.2, 1.2, 1H), 7.86 (dd, *J* = 7.9, 1.7, 1H), 7.77 (d, *J* = 8.1, 1H), 7.55 – 7.40 (m, 4H), 3.43 (s, 2H), 1.01 (s, 1H), 0.85 (tt, *J* = 8.3, 5.6, 2H), 0.50 – 0.35 (m, 6H), 0.28 – 0.20 (m, 2H).

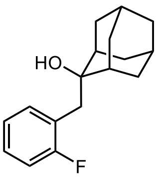
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 134.2, 134.0, 133.6, 129.4, 128.6, 127.2, 125.5, 125.4, 125.4, 125.2, 71.8, 44.4, 19.1 (2C), 1.6 (2C), 0.0 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3562, 3084, 3006, 2926, 2874, 1595, 1510, 1461, 1451, 1396, 1352, 1321, 1284, 1273, 1245, 1230, 1206, 1166, 1154, 1142, 1120, 1102, 1083, 1070, 1039, 1020, 988, 914, 888, 828, 798, 776, 735, 714, 688.

MS (EI, 70 eV): *m/z* (%) = 234 (11), 219 (19), 206 (16), 205 (59), 204 (16), 203 (35), 202 (31), 193 (16), 192 (10), 191 (68), 190 (33), 189 (40), 179 (16), 178 (80), 176 (14), 166 (11), 165 (79), 164 (12), 163 (14), 153 (15), 152 (32), 143 (12), 142 (100), 141 (72), 139 (19), 128 (14), 115 (53), 111 (27), 91 (12), 69 (38).

HRMS (EI): *m/z* calc. for [$C_{18}H_{20}O$]: 252.1514; found 252.1503.

2-(2-Fluorobenzyl)adamantan-2-ol (58et)



According to the TP10, a solution of 1-fluoro-2-methylbenzene (22 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 as slightly yellow solid (35 mg, 0.13 mmol, 67% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.29 – 7.22 (m, 1H), 7.02 (dt, *J* = 7.6, 1.3, 1H), 6.99 – 6.91 (m, 2H), 2.99 (s, 2H), 2.15 (dd, *J* = 12.6, 3.1, 2H), 2.10 – 2.01 (m, 3H), 1.96 – 1.89 (m, 1H), 1.80 (dq, *J* = 11.0, 2.2, 1.8, 3H), 1.69 (dt, *J* = 18.0, 3.3, 4H), 1.54 (dt, *J* = 12.6, 1.7, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.8 (d, *J* = 245.5), 140.1 (d, *J* = 7.3), 129.6 (d, *J* = 8.3), 126.4 (d, *J* = 2.7), 117.6 (d, *J* = 20.6), 113.5 (d, *J* = 20.9), 74.9, 43.8 (d, *J* = 1.8), 39.4, 38.5, 37.0, 34.7, 33.1, 27.6, 27.6, 27.4.

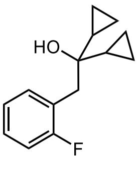
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3479, 2906, 2855, 1720, 1702, 1616, 1586, 1487, 1474, 1443, 1379, 1354, 1332, 1324, 1317, 1292, 1275, 1251, 1202, 1175, 1163, 1141, 1122, 1098, 1079, 1058, 1042, 1018, 1011, 994, 947, 936, 927, 915, 890, 880, 863, 832, 786, 747, 718, 688, 670.

MS (EI, 70 eV): *m/z* (%) = 152 (10), 151 (100), 133 (10), 81 (18).

HRMS (EI): *m/z* calc. for [$C_{17}H_{21}FO$]: 260.1576; found 242.1465 [M – H_2O].

m.p. (°C): 84.2 – 88.9.

1,1-Dicyclopropyl-2-(2-fluorophenyl)ethan-1-ol (58ec')



According to the TP10, a solution of 1-fluoro-2-methylbenzene (22 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, 25 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (33 mg, 0.30 mmol, 1.5 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 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).

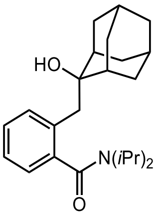
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.9 (d, J = 244.6), 140.8 (d, J = 7.3), 129.6 (d, J = 8.3), 126.9 (d, J = 2.7), 118.1 (d, J = 20.8), 113.5 (d, J = 21.0), 71.6, 48.9 (d, J = 1.7), 18.8 (2C), 1.7 (2C), 0.0 (2C).

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-Hydroxyadamantan-2-yl)methyl)-*N,N*-diisopropylbenzamide (58ft)



According to the TP10, a solution of *N,N*-diisopropyl-2-methylbenzamide (44 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 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 as a white solid (70 mg, 0.19 mmol, 95% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.29 (td, *J* = 7.5, 1.5, 1H), 7.23 – 7.15 (m, 2H), 7.11 (dd, *J* = 7.6, 1.5, 1H), 3.70 (p, *J* = 6.7, 1H), 3.57 – 3.45 (m, 2H), 2.47 (dd, *J* = 12.5, 3.1, 1H), 2.36 (d, *J* = 13.8, 1H), 2.20 (d, *J* = 12.2, 2H), 1.96 – 1.68 (m, 8H), 1.58 (d, *J* = 6.8, 4H), 1.55 (d, *J* = 6.9, 3H), 1.50 – 1.43 (m, 2H), 1.14 (d, *J* = 6.7, 3H), 1.06 (d, *J* = 6.7, 3H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 172.6, 138.1, 136.0, 130.9, 128.4, 126.1, 124.9, 73.4, 51.2, 46.3, 42.1, 40.8, 38.8, 35.0, 34.7, 34.4, 33.8, 32.8, 27.8, 27.6, 21.3, 20.7, 20.6, 20.5.

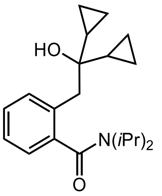
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3357, 2974, 2962, 2940, 2921, 2902, 2854, 1609, 1598, 1490, 1469, 1453, 1442, 1415, 1374, 1346, 1324, 1306, 1298, 1221, 1212, 1204, 1184, 1166, 1156, 1139, 1128, 1116, 1111, 1098, 1084, 1056, 1040, 1030, 996, 930, 918, 758, 732, 700, 669.

MS (EI, 70 eV): *m/z* (%) = 351 (12), 252 (11), 251 (45), 220 (12), 219 (22), 204 (29), 177 (14), 176 (100), 119 (44).

HRMS (EI): *m/z* calc. for [$C_{24}H_{35}NO_2$]: 369.2668; found 351.2565 [M – H_2O].

m.p. (°C): 138.2 – 140.8.

2-(2,2-Dicyclopropyl-2-hydroxyethyl)-*N,N*-diisopropylbenzamide (58fc')



According to the TP10, a solution of *N,N*-diisopropyl-2-methylbenzamide (44 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (33 mg, 0.30 mmol, 1.5 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 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).

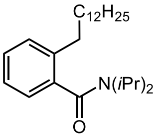
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 170.6, 144.5, 138.8, 134.4, 130.1, 127.5, 126.4, 124.8, 120.4, 51.0, 45.8, 21.0, 20.9, 20.6, 20.4, 14.2, 13.1, 6.2, 5.9, 5.9, 5.4.

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 (58fg')



According to the TP10, a solution of *N,N*-diisopropyl-2-methylbenzamide (44 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (89 mg, 0.30 mmol, 1.5 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 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).

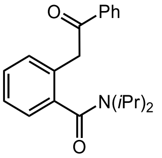
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 170.7, 139.0, 138.3, 129.4, 128.2, 125.8, 125.0, 50.8, 45.8, 33.1, 32.1, 31.2, 30.0, 29.8, 29.8 (2C), 29.8 (2C), 29.6, 29.5, 22.8, 20.9, 20.9, 20.8, 20.6, 14.3.

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 (58fw'')



According to the TP10, a solution of *N,N*-diisopropyl-2-methylbenzamide (44 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 4 mL reactor tube (24 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of *N*-methoxy-*N*-methylbenzamide (50 mg, 0.30 mmol, 1.5 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 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.

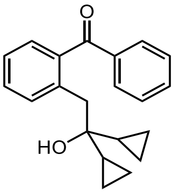
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2993, 2966, 2931, 2916, 2856, 1687, 1619, 1595, 1578, 1490, 1470, 1447, 1438, 1417, 1377, 1364, 1339, 1326, 1262, 1215, 1201, 1185, 1159, 1136, 1110, 1080, 1030, 993, 911, 851, 834, 795, 768, 752, 735, 700, 682, 658.

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 (58gc')



According to the TP10, a solution of phenyl(*o*-tolyl)methanone (39 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.18 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropyl ketone (33 mg, 0.30 mmol, 1.5 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 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).

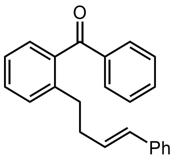
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 199.8, 138.4, 138.4, 138.3, 133.9, 133.4, 130.9 (2C), 130.5, 130.37, 128.4 (2C), 125.4, 70.7, 45.6, 19.7 (2C), 0.6 (2C), 0.3 (2C).

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 (58gx'')



According to the TP10, a solution of phenyl(*o*-tolyl)methanone (39 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.18 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of cinnamyl bromide (59 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (1.0 M in THF, 0.01 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 = 100:0 → 99:1) afforded the title compound 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).

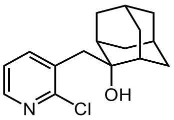
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 198.8, 140.9, 138.7, 137.9, 137.7, 133.3, 130.6, 130.5, 130.4, 130.4 (2C), 129.8, 128.8, 128.6 (4C), 127.0, 126.1 (2C), 125.5, 35.2, 33.3,

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 (58ht)



According to the TP10, a solution of 2-chloro-3-methylpyridine (26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-adamantanone (45 mg, 0.30 mmol, 1.5 equiv) in THF. Stirring was continued for 10 min at −50 °C before *sat. aq.* NH$_4$Cl 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 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.

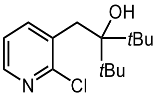
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2915, 2903, 2882, 2851, 1743, 1605, 1595, 1456, 1438, 1419, 1381, 1360, 1350, 1321, 1305, 1290, 1270, 1249, 1236, 1221, 1185, 1156, 1096, 1066, 1059, 1046, 1020, 982, 972, 958, 922, 901, 894, 873, 866, 827, 795, 775, 752, 740.

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 (58hh')



According to the TP10, a solution of 2-chloro-3-methylpyridine (26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 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 (43 mg, 0.30 mmol, 1.5 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 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).

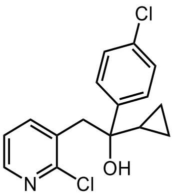
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 2926, 1744, 1602, 1492, 1476, 1458, 1424, 1402, 1392, 1369, 1342, 1294, 1264, 1248, 1220, 1180, 1171, 1044, 943, 921, 892, 782, 732.

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 (58hf)



According to the TP10, a solution of 2-chloro-3-methylpyridine (26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of (4-chlorophenyl)(cyclopropyl)methanone (54 mg, 0.30 mmol, 1.5 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 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).

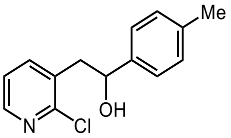
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.2, 146.8, 143.9, 133.8, 133.3, 128.6 (2C), 126.7 (2C), 119.8, 117.0, 88.4, 41.5, 22.3, 1.9, 1.6.

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 (58hm'')



According to the TP10, a solution of 2-chloro-3-methylpyridine (26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 4-methylbenzaldehyde (36 mg, 0.30 mmol, 1.5 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 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).

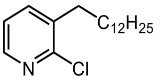
^{13}C-NMR (100 MHz, CDCl$_3$): δ / ppm = 168.2, 146.9, 138.3, 138.1, 133.7, 129.5 (2C), 125.7 (2C), 119.7, 116.9, 81.9, 37.0, 21.3.

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 (58hg')



According to the TP10, a solution of 2-chloro-3-methylpyridine (26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (89 mg, 0.30 mmol, 1.5 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 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.

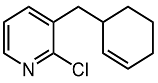
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2914, 2867, 2851, 1746, 1562, 1472, 1456, 1405, 1376, 1219, 1095, 1056, 838, 798, 748, 714, 686.

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 (58hh)



According to the TP10, a solution of 2-chloro-3-methylpyridine (26 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.18 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohex-1-ene (48 mg, 0.30 mmol, 1.5 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 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).

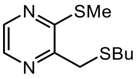
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.6, 147.3, 140.1, 135.2, 130.4, 128.3, 122.5, 39.7, 35.0, 28.8, 25.4, 21.2.

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 (58iz)



According to the TP10, a solution of 2-methyl-3-(methylthio)pyrazine (28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfide (54 mg, 0.30 mmol, 1.5 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 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).

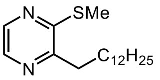
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.4, 151.4, 142.1, 137.3, 34.8, 31.9, 31.4, 22.1, 13.8, 13.1.

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 (58ig')



According to the TP10, a solution of 2-methyl-3-(methylthio)pyrazine (28 mg, 0.20 M, 0.20 mmol) in THF (total volume: 1.0 mL) and a solution of KDA (0.30 M in hexane, 0.30 mmol, 1.5 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 0.03 mL reactor tube (0.1 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dodecyl iodide (89 mg, 0.30 mmol, 1.5 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 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)