Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

der Ludwig-Maximilians-Universität München

The Preparation of Ketones in Continuous Flow using Li- or Mg-Organometallics and Convenient Ester and Amide Acylation Reagents

and

The Preparation of Functionalized Pyridines *via* Pyridyne Intermediates

von

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aus

München, Deutschland

2022

E R K L Ä R U N G

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

Eidesstattliche Erklärung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, 12.04.2022

……..

(Benjamin Lukas Heinz)

Dissertation eingereicht am	24.01.2022
1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Oliver Trapp
Mündliche Prüfung am	31.03.2022

This work was carried out under the guidance of Prof. Dr. Paul Knochel from September 2018 to March 2022 at the Department of Chemistry of the Ludwig-Maximilians-University, Munich.

First, I would like to thank Prof. Dr. Paul Knochel for giving me the great opportunity to carry out my PhD thesis in his group, for his support throughout the past three years and for the guidance in the course of scientific research. I would further like to express my gratitude to Prof. Dr. Oliver Trapp for agreeing to be second reviewer of my thesis, as well as to Prof. Dr. Konstantin Karaghiosoff, Prof. Dr. Franz Bracher, Prof. Dr. Anja Hoffmann-Röder and Prof. Dr. Thomas Carell for their interest in this work and for being members of my defence committee.

I really appreciate the proofreading and careful correction of this manuscript by Johannes Harenberg and Dimitrije Djukanovic.

Additionally, I would like to thank Dr. Benjamin Martin for his great support throughout the industrial collaborations, for always being encouraging and for enabling my visit to Basel. The fruitful discussions about chemistry with Dr. Francesca Mandrelli, Dr. Paolo Filipponi and Dr. Serena Mostarda are also highly appreciated.

Furthermore, I would like to thank all the past and present group members of the Knochel group for all the great moments inside and outside of the lab. Especially, I want to mention all my former and current lab mates of F2.012 for creating a pleasant working atmosphere, Dr. Moritz Balkenhohl, Dr. Maximillian Hofmayer, Dr. Ferdinand Lutter, Dr. Lucie Grokenberger, Prof. Dr. Jie "Jack" Li and Clemence Hamze. Another thank goes to the continuous flow team: Dr. Maximillian Ganiek, Dr. Niels Weidmann and Johannes Harenberg for their support and the great discussions about flow chemistry. I especially would like to thank Dimitrije Djukanovic for the great collaborations over the past three years and Dr. Moritz Balkenhohl for introducing me to the group and supporting me in the beginning of my work.

Next, I want to say thank you to my former students Mohamed Idriess, Lena Samhammer, Nikolas Schneider, Fiona Siemens and Basile Weyl for having invested much time and energy into my research work and their contributions during their internships. I would also like to thank Peter Dowling, Yulia Tsvik, Claudia Ravel and Dr. Vladimir Malakhov for their help in practical matters and organizing everyday life in the lab and the office, as well as the analytical team of the LMU for their invaluable help.

I want to thank my family for always believing in me and supporting me in every possible way. Also, I am deeply grateful for having friends I can always count on and for having great times asides the working life with them.

Finally, I want to thank Lisa for her love, encouragement and support over the last eight years.

Parts of this PhD thesis have been published

A) Communications

1) "Selective Acylation of Aryl- and Heteroarylmagnesium Reagents with Esters in Continuous Flow"
B. Heinz, D. Djukanovic, M. A. Ganiek, B. Martin, B. Schenkel, P. Knochel, *Org. Lett.* **2020**, *22*, 493–496.

2) "Regioselective Difunctionalization of Pyridines *via* 3,4-Pyridynes"
B. Heinz, D. Djukanovic, P. Filipponi, B. Martin, K. Karaghiosoff, P. Knochel, *Chem. Sci.* **2021**, *12*, 6143 –6147.

3) "Continuous Flow Acylation of (Hetero)aryllithiums with Polyfunctional *N*,*N*-Dimethylamides and Tetramethylurea in Toluene"
D. Djukanovic, **B. Heinz**, F. Mandrelli, S. Mostarda, P. Filipponi, B. Martin, P. Knochel, *Chem. Eur. J.* **2021**, *27*, 13977 – 13981.

4) "Regioselective Amination or Alkoxylation of Halogenated Amino-, Thio- or Alkoxypyridines *via* Pyridyne Intermediates"
B. Heinz, D. Djukanovic, F. Siemens, M. Idriess, B. Martin, P. Knochel, *Synthesis* **2021**, *53*, DOI: 10.1055/s-0037-1610786.

B) Reviews

1) "Regioselective Magnesiations and Zincations of Aromatics and Heterocycles Triggered by Lewis Acids"
A. Kremsmair, A. Hess, **B. Heinz**, P. Knochel, *Chem. Eur. J.* **2021**, 27, https://doi.org/10.1002/chem.202103269

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
Bu	butyl
Bz	benzoyl
C	Celsius
ca.	circa
calc.	calculated
cat.	catalytical
CCDC	Cambridge Crystallographic Data Center
Cy	cyclohexane
d	doublet (NMR)
dba	dibenzylideneacetone
DCM	dichloromethane
DMF	dimethylformamide
DMG	direct metalation group
dppe	1,2-bis(diphenylphosphino)ethane
E	electrophile
e.g.	for example
EI	electron ionization
Equiv	equivalents
Et	ethyl
etc.	*et cetera*
g	gram

[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, 11.10.2021.
[2] Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names (Eds.: H. A. Favre, W. H. Powell), RCS, London, 2013.

GC	gas chromatography
h	hour
Het	undefined heteroaryl substituent
Hex	hexyl
HMDS	hexamethyldisilizane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	*iso*
i.d.	inner diameter
IR	infrared
J	coupling constant
KDA	potassium diisopropylamide
kV	kilovolt
LDA	lithium diisopropylamide
m	multiplet (NMR)
m	*meta*
mA	milliampere
Me	methyl
Met	undefined metallic substituent
mg	milligram
min	minute
mL	millilitre
m.p.	melting point
MS	mass spectroscopy
NaDA	sodium diisopropylamide
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PFA	perfluoroalkoxy alkanes
Ph	phenyl
PMDTA	pentamethyldietylenetriamine
ppm	parts per million
Pr	propyl

PTFE	polytetrafluoroethylene
q	quartet (NMR)
R	undefined organic substituent
s	*sec*
s	singlet (NMR)
sat.	saturated
SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t	*tert*
t	triplet (NMR)
t	time
T	temperature
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N´*,*N´*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMU	1,1,3,3-tetramethylurea
TP	typical procedure
vol	volume

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A. Introduction

1. Overview

The rapid growth of the human population in a more and more globalized world is raising huge challenges for the international society. To properly portray this problem, the world population has been doubled within the last forty years and will grow, according to predictions, to around 11 billion people in the year 2100.[3] This population increase, combined with the desire of the modern world for new technologies, advanced pharmaceutical care and a safe food supply[4] slowly drives the limited natural resources to the edge of exhaustion. For example, the Earth Overshoot Day, which marks the date when humanity´s resource consumption for the year exceed the regeneration capacity of the earth, was this year on the 29th of July, while 30 years ago it was in the mid of October.[5] Alongside political and social efforts to overcome these problems, a steady improvement in the field of chemistry is a mandatory task due to the important role of small organic molecules in the development of new and more potent drugs[6] and agrochemicals.[7] As a promising field for the investigation of potential pharmaceutical active candidates, organometallic chemistry offers a broad range of possibilities for various bond formations and the area of application of organometallic reagents ranges from bases and nucleophiles to catalysts.[8] But not only the development of improved organic compounds is of interest, also more efficient, green and sustainable methods for already existing synthetic pathways are a major goal for modern chemists.[9] Therefore, over the last decades, continuous flow technology was moved in the centre of attention as it offers numerous advantages compared to conventional batch chemistry such as advanced temperature, time and stoichiometry control.[10] Especially the use of reactive organometallic species (mostly organolithium- and magnesiums), which often suffers from hardly controllable side reactions and inconvenient reaction conditions, showed to be particularly beneficial in a continuous flow

[3] United Nations, Department of Economic and Social Affairs, Population Division, *World Population Prosepects: The 2019 Revision*, Key Findings, ST/ESA/SER.A/423.
[4] N. Alexandratos, J. Bruinsma, *ESA Working Paper* **2012**, *12-03*.
[5] "Past Earth Overshoot Days", *https://www.overshootday.org/newsroom/past-earth-overshoot-days/*, (accessed 09 November 2021).
[6] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Ed.* **2010**, *87*, 1348.
[7] K. Smith, D. A. Evans, G. A. El-Hiti, *Phil. Trans. R. Soc. B* **2008**, *363*, 623-637;
[8] *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.
[9] (a) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273; (b) E. S. Beach, Z. Cui, P. T. Anastas, *Energy Environ. Sci.* **2009**, *2*, 1038-1049; (c) R. H. Crabtree, *Organometallics* **2011**, *30*, 17-19, (d) W. R. Melchert, B. F. Reis, F. R. P. Rocha, *Anal. Chim. Acta* **2012**, *714*, 8-19.
[10] (a) K. Geyer, J. D. C. Codée, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434-8442; (b) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300-2318; (c) A. R. Bogdan, A. W. Dombrowski, *J. Med. Chem.* **2019**, *62*, 6422-6468.

setup.[11] Therefore, merging organometallic chemistry, which offers lots of synthetic tools towards new organic compounds, with continuous flow chemistry, enabling resource- and energy-saving reaction conditions, is of high interest and should be further investigated.

2. Organometallic Chemistry

Organometallic compounds are classified as chemical compounds containing at least one carbon-metal bond, including alkaline, earth alkaline and transition metals, expanded by metalloids such as boron. The organometallic chemistry made its first steps with Franklands preparation of diethylzinc in 1848[12], but firstly draw attention with the development of organomagnesium reagents by Grignard in 1900[13], a discovery that was awarded with the Nobel Prize twelve years later. In modern times, organometallic reagents have become an indispensable part of the organic chemistry in research and industry.[8,14]

The reactivity of organometallic species is based on the polarization of the C-M bond, which can be described with the Pauling electronegativity difference between the carbon and the corresponding metal (Figure 1). Due to the great electronegativity difference between lithium and carbon, organolithium reagents (and related organosodium[15] and organopotassium[16] reagents) are highly reactive species which offer unique reaction pathways. Though, the high reactivity results in the lack of functional group tolerance and the urgency for cost and energy intensive cooling to low temperatures.[17] On the other hand, organomagnesiums have an increased covalent character leading to a decreased reactivity compared to organoalkali reagents but show a higher thermal stability and a better functional group tolerance. Finally, organozinc species showed to be extraordinary stable and therefore tolerate most of functional groups. As a drawback, these compounds often have to be prepared *via* transmetalation starting

[11] (a) M. Colella, A. Nagaki, R. Luisi, *Chem. Eur. J.* **2020**, *26*, 19-32; (b) M. Power, E. Alcock, G. P. McGlacken, *J. Org. Process Res. Dev.* **2020**, *24*, 1814-1838.
[12] E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263.
[13] V. Grignard, *Compt. Rend. Acad. Sci.* **1900**, *130*, 1322.
[14] (a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414–4435; (b) K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem. Int. Ed*. 2000, *39*, 44–122; (c) *Organometallic Chemistry in Industry Vol 1*, (Ed: T. J. Colacot, C. C. C. Johansson Seechurn), Wiley VCH, Weinheim, **2020**.
[15] (a) J. H. Harenberg, N. Weidmann, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *60*, 731-735. (b) J. H. Harenberg, N. Weidmann, A. J. Wiegand, C. A. Hoefer, R. R. Annapureddy, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 14296-14301.
[16] J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 12321–12325.
[17] P. Stanetty, M. D. Miho1ilovic, *J. Org. Chem.* **1997**, *62*, 1514–1515.

from more reactive organometallic species. Furthermore, due to the low reactivity, external activation either by adding transition metals (e.g. Pd or Cu) or heating is required for a successful reaction outcome.

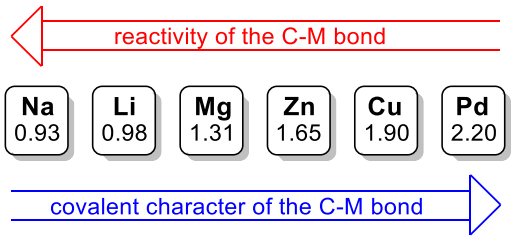
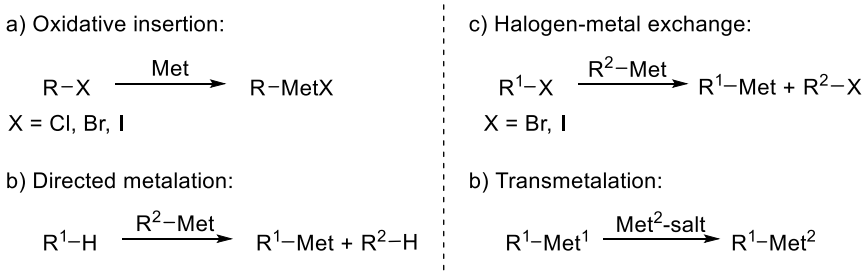


Figure 1: Electronegativity table of selected metals (Pauling scale).

2.1 Preparation of Organometallic Reagents

Inspired by the pioneering work from Frankland[12] and Grignard[13], various methods for carbon metal bond formations were described in the last century. The first general route towards organometallic reagents is the oxidative insertion of a metal into a carbon halogen bond (Scheme 1a).[12,13,18] Second, the abstraction of a proton *via* various metal bases is described as directed metalation, whereby a directed metalation group (DMG) is usually controlling the regioselectivity (Scheme 1b).[19] A common pathway for the preparation of versatile organometallics is the halogen/metal exchange reaction, which is based on the formation of a more stable carbon-metal bond compared to the initial one (Scheme 1c).[20]



Scheme 1: Preparation of organometallic reagents *via* different methods.

[18] (a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445-1453: (b) S. Bernhardt, Z.-L. Shen, P. Knochel, *Chem. Eur. J.* **2012**, *19*, 828-833.
[19] (a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879-933; (b) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376-393; (c) M. Balkenhohl, P. Knochel, *SynOpen* **2018**, *2*, 78-95.
[20] (a) W. F. Bailey, J. J. Patricia, *J. Org. Chem.* **1988**, *352*, 1–46; (b) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. Ahn Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302-4320.

Last, transmetalation reactions between an already existing organometallic species and a metal salt result in more stable (more covalent) carbon-metal bonds (Scheme 1d).[21] All these pathways towards organometallics have been deployed in this thesis and are described in more detail in the following sections.

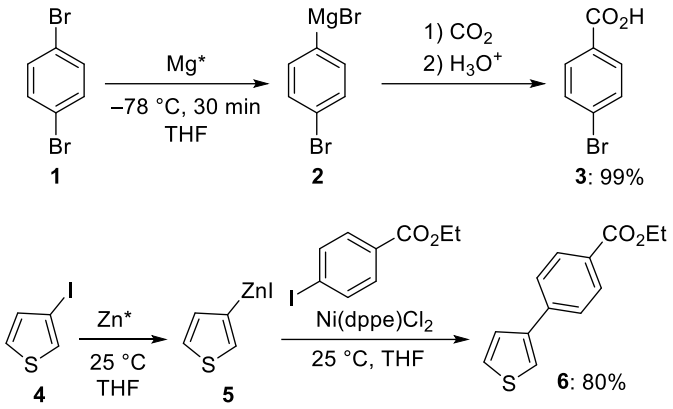
2.1.1 Oxidative Insertion

The oxidative insertion towards various organometallic reagents is usually performed by adding metals into an ethereal solution of organohalides. The most prominent class of organometallic species prepared by oxidative insertion are organomagnesium reagents (Grignard reagents) which were first prepared in 1900.[13] In the following decades, several methods for activating magnesium were developed as Mg metal possesses a passivation layer of MgO on its surface which significantly reduces its reactivity. For example, the addition of iodine[22] or 1,2-dibromoethane[23] in catalytic amounts improved the carbon-magnesium bond formation. A highly effective method was described by R. Rieke, reducing $MgCl_2$ salt with alkali metals in an ethereal solution. Starting from 1,4-dibromobenzene **1**, this highly activated magnesium ("Rieke-Mg") was able to generate 4-bromophenylmagnesium bromide **2** in THF at −78 °C, leading to the acid **3** after treatment with CO_2 (Scheme 1).[24]

With diethylzinc, the first organometallic species was formed in 1848 by oxidative addition of zinc metal to ethyliodide.[12] Due to the low reactivity of the metal and consequent synthetic limitations,[25] various procedures for the activation of zinc were described in the literature including the addition of 1,2-dibromoethane,[26] ultrasound irradiation[27] and treatment with HCl solution.[28] Additionally, an effective method to obtain activated zinc is the reduction of $ZnCl_2$ salt with alkali metals ("Rieke-Zn").[18a,29] Using this method, 3-iodothiophene (**4**) was

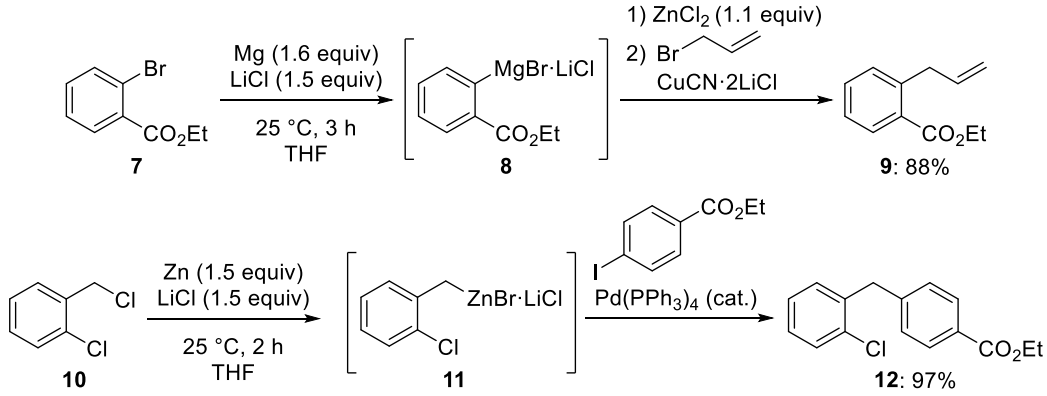
[21] C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, 114, 3983-3985.
[22] H. Gilman N. B. St. John, *Recl. Trav. Chim. Pays-Bas* **1930**, *49*, 717.
[23] E. Pearson, D. Cowan, J. D. Becker, J. Org. Chem. **1959** ,24, 504-509.
[24] (a) R. D. Rieke, P. M. Hudnall, *J. Am. Chem. Soc.* **1972**, *94*, 7178-7179; (b) R. D. Rieke, S. E. Bales, P. M. Hudnall, T. P. Burns, G. S. Poindexter, *Org. Synth.* **1979**, *59*, 85; (c) R. D. Rieke, *Science* **1989**, *246*, 1260–1264; (d) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925-1956.
[25] E. Erdik, *Tetrahedron* **1987**, *43*, 2203-2212.
[26] M. Gaudemar, A. E. Burgi, B. Baccar, *J. Organomet. Chem.* **1986**, *280*, 165.
[27] B. H. Han, P. Boudjouck, *J. Org. Chem.* **1982**, *47*, 5030-5032.
[28] S. Newman, F. J. Arens, *J. Am. Chem. Soc.* **1955**, *77*, 946-947.
[29] R. D. Rieke, P. Hudnall, S. T. Uhm, *J. Chem. Soc. Chem. Commun.* **1973,** 269-270.

transformed to the corresponding Zn-species **5** at ambient temperatures and later arylated *via* Ni-catalyzed Negishi cross-coupling to give the ester **6**.[30]



Scheme 1: Oxidative insertion of activated Mg and Zn into organohalides and subsequent reactions.

In 2006, Knochel and co-workers developed a new method to prepare sensitive organomagnesium and organozinc reagents without prior activation by adding anhydrous LiCl to the reaction. As LiCl increases the solubility of the formed metal species, a constantly clean metal surface is ensured, enabling insertions at ambient temperatures and therefore increasing the functional group tolerance.[31]



Scheme 2: Oxidative insertion of organohalides in the presence of LiCl and subsequent reactions.

[30] E. Negishi, S. Baba, *J. Am. Chem. Soc.* **1976**, *98*, 6729-6731.
[31] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040-6044.

Thus, performing the oxidative magnesium insertion in the presence of LiCl on ethyl 2-bromobenzoate (**7**) led to the magnesium species **8** at 25 °C, tolerating the ester function. Transmetalation and subsequent Cu-catalyzed allylation gave the compound **9** in 88% yield.[32] Furthermore, direct zinc insertion into the benzylic halide **10** at 25 °C furnished, *via* the organozinc reagent **11**, the diarylmethane derivative **12** after Negishi cross-coupling.[33]

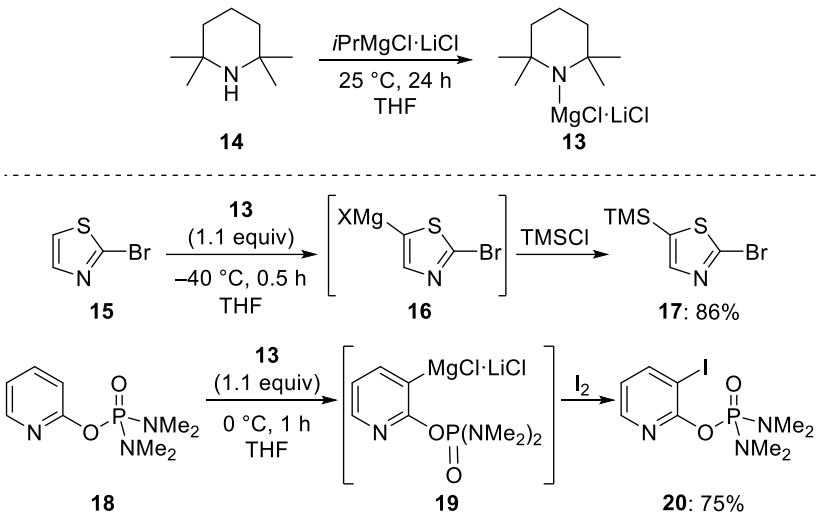
2.1.2 Directed Metalation

The directed metalation describes the deprotonation ("metalation") of substrates with various organometallic bases, forming carbon-metal bonds.[19,34] The most obvious advantage over the previously described methods is to be independent from halogens in the desired positions. But also the atom economy is of benefit in a halogen-free metalation pathway. Anyway, the metalation position is usually determined by so-called directing metalation groups (DMG), providing a strong coordinating effect towards the base. The first directed metalations were described by Gilman[35] and Wittig[36] using strong lithium bases such as *n*-BuLi and PhLi. Later, lithium amide bases such as LDA (lithium diisopropylamide) were developed.[37] Although still frequently used, lithium bases carry several drawbacks such as instability of the lithium compounds, requirement for low temperatures, undesired side reactions and low functional group tolerance due to their high reactivity.

Therefore, Hauser *et al.* investigated the potential application of magnesium amides of type R_2NMgX as metalating agents, increasing the functional group tolerance and the chemoselectivity.[38] Later, Eaton[39] and Mulzer[40] employed sterically hindered 2,2,6,6-tetramethylpiperidyl magnesium bases (TMPMgX) to their directed metalation reaction. Even though these bases were versatile reagents for deprotonations of functionalized substrates, larger excess of the base (and therefore the electrophile) were mandatory due to the low solubility in THF. In 2006, Knochel and co-workers developed the magnesium amide base

[32] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802-6806.
[33] A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107-1110.
[34] P. Knochel, K. P. Cole, *Org. Process Res. Dev.* **2021**, *25*, 2188-2191.
[35] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109-112.
[36] Wittig, G. Fuhrmann, *Ber. Dtsch. Chem. Ges.* 1940, 73, 1197-1218.
[37] M. Hamell, R. Levine, *J. Org. Chem.* **1950**, *15*, 162-168.
[38] C.R. Hauser, G. H. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295-297.
[39] P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018.
[40] W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414-8416.

TMPMgCl·LiCl (**13**) by simple mixing TMPH (**14**) and *i*PrMgCl·LiCl (Scheme 3). With LiCl breaking the aggregates, a well-soluble and kinetically highly reactive base was obtained.[41] These bases were suitable metalating agents for various sensitive substrates such as the brominated thioazole **15**. Adding just 1.1 equiv of **13** led to a complete conversion to the heteroarylmagnesium **16** at –40 °C within 30 min. Quenching with TMSCl gave the functionalized heterocycle **17** in excellent yield.[42] The pyridine **18**, having phosphorodiamidate as DMG in position C2, was regioselectively metalated in position C3 towards the intermediate **19** at 0 °C within 1 h. Quenching with iodine produced the 3-haolgenated pyridine, which was further functionalized.[43]



Scheme 3: Directed metalation of heterocycles using the amide base TMPMgCl·LiCl.

Based on this investigation, a range of LiCl-containing TMP-bases such as TMPZnCl·LiCl,[44] $(TMP)_2Mg·2LiCl$[45] and $(TMP)_2Zn·MgCl_2·2LiCl$[46] were prepared. But also bases containing

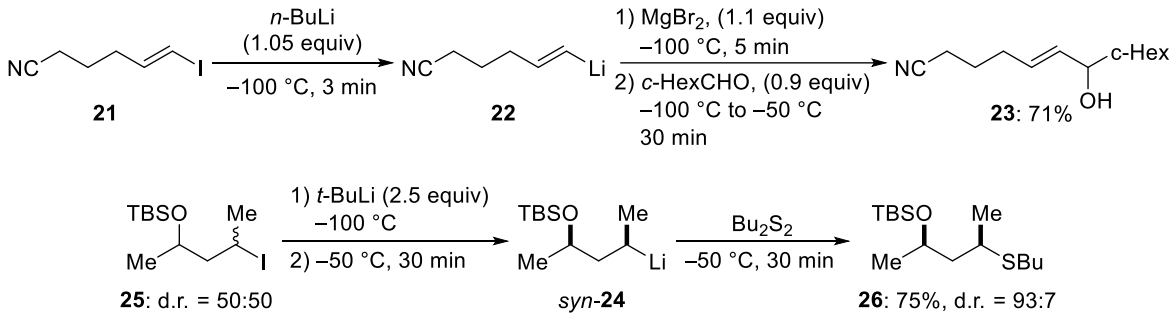
[41] (a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed*. 2006, *45*, 2958-2961; (b) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673-5676; (c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497-2500.
[42] C. Dust, P. Knochel, *J. Org. Chem.* **2011**, *76*, 6972-6978.
[43] M. Balkenhohl, B. Heinz, T. Abegg, *Org. Lett.* **2018**, *20*, 8057-8060.
[44] (a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837-1840; (b) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Comm.* **2009**, *37*, 5615-5617; (c) T. Bresser, M. Mosrin, G. Monzon, *J. Org. Chem.* **2010**, *75*, 4686-4695; (d) S. Duez, S. Bernhard, J. Heppekausen, F. F. Flemming, P. Knochel, *Org. Lett.* **2011**, *13*, 1690-1693; (e) A. Unsinn, M. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128-1131; (f) D. Haas, M. Hofmayer, T. Bresser, P. Knochel, *Chem. Comm.* **2015**, *51*, 6415-6417; (g) M. Balkenhohl, H. Jangra, I. S. Makarov, S.-M. Yang, H. Zipse, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 14992-14999.
[45] (a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684; (b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503-1507; (c) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237-3239; (d) A. Unsinn, C. J. Rohbogner, P. Knochel, *Adv. Syn. & Cat.* **2013**, *355*, 1553-1560.
[46] (a) M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1468-1477; (b) A. Unsinn; P. Knochel, *Chem. Comm.* **2012**, *48*, 2680-2682.

less commonly used metals like $(TMP)_2Mn\cdot 2MgCl_2\cdot 4LiCl$[47] and $(TMP)_3La\cdot 3MgCl_2\cdot 5LiCl$[48] were successfully applied into the synthesis of organic substrates. Due to differences in the reactivity and selectivity of theses bases, a broad range of substrates were successfully metalated in various positions and subsequent functionalized.[49]

2.1.3 Halogen/Metal Exchange

A widely used method for the preparation of organometallic reagents is the halogen/metal exchange. The principle of this new carbon-metal bond generation is based on the formation of the thermodynamically more stable organometallic species compared to the initially added exchange reagent.[50] The stability of the formed organometallic species is highly influenced by the hybridisation of the carbon centre (C(sp) > $C(sp^2_{vinyl})$ > $C(sp^2_{aryl})$ > $C(sp^3_{primary})$ > $C(sp^3_{secondary})$ > $C(sp^3_{tertiary})$) as well as by mesomeric and inductive effects.

Having a highly polarized carbon-metal bond, exchange reactions involving lithium species are usually very fast reactions.[51] Firstly discovered by Wittig[52] and Gilman[53], the halogen/Li exchange is still a frequently used method for rapid formations of organometallic species.[54]

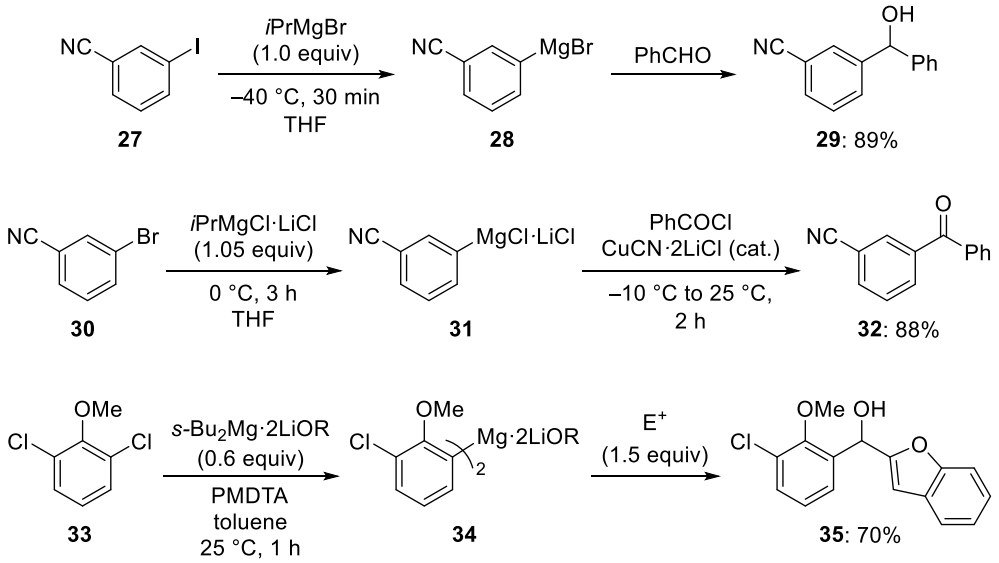


Scheme 4: Selected examples for halogen/Li exchange reactions using *n*-BuLi and *t*-BuLi.

[47] (a) S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256-7260; (b) D. Haas, J. M. Hammann, A. Moyeux, G. Cahiez, P. Knochel, *Synlett* **2015**, *26*, 1515-1519.
[48] S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3304-3307.
[49] M. Balkenhohl, R. Greiner, I. S. Makarov, B. Heinz, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 13046-13050.
[50] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733-738.
[51] (a) W. F. Bailey, J. J. Patricia, T.T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861-1864; (b) I. S. Aidhen, J. R. Ahuja, *Tetrahedron Lett*. **1992**, 33, 5431-5432.
[52] G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903–1912.
[53] H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106-109.
[54] (a) G. Köbrich, P. Buck, *Chem. Ber.* **1970**, *103*, 1412–1419; (b) H. Neumann, D. Seebach, *Tetrahedron Lett.* **1976**, *17*, 4839–4842; (c) J. Skotnitzki, A. Kremsmair, D. Keefer; Y. Gong, R. de Vivie-Riedle, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 320–324.

For example, the commercially available lithium base *n*-butyllithium was added to the functionalized alkenyl iodide **21** at −100 °C leading to the lithium species **22** within 3 min *via* I/Li-exchange. Subsequent transmetalation (for further information, see chapter A.2.1.4) with $MgBr_2$ and reaction with an aldehyde gave the secondary alcohol **23** in 73% yield.[21] Also, a stereoselective synthesis of the secondary alkyllithium species **24**, starting from the racemic alkyl iodide **25**, was feasible by using *t*-BuLi at low temperatures followed by a quench with dibutyl disulfide towards the compound **26** (Scheme 4).[55]

Due to the high reactivity of the lithium reagents, these reactions normally take place at low temperatures down to −100 °C. To avoid these harsh conditions and allow more sensitive substrates, Knochel and coworkers investigated a convenient halogen/magnesium exchange based on the pioneering contributions of Prévost[56] and Villieras[57]. After a first description of a iodine/magnesium exchange using the exchange reagents *i*PrMgBr or *i*Pr_2Mg,[58] the addition of LiCl significantly enhanced the reactivity enabling a bromine/magnesium exchange at ambient temperatures.[59]



Scheme 5: Various halogen/magnesium exchange reactions using different Mg-bases.

The aryl iodide **27**, bearing a cyano group, was converted to the corresponding magnesium species **28** at –40 °C within 30 min and was conveniently quenched with benzaldehyde to

[55] K. Moriya, D. Didier, M. Simon, J. M. Hammann, G. Berionni, K. Karaghiosoff, H. Zipse, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 2754-2757.
[56] C. Prévost, Bull. *Soc. Chim. Fr.* **1931**, *49*, 1372.
[57] J. Villieras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* **1986**, 470.
[58] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701-1703.
[59] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336.

obtain the alcohol **29** in 89% yield.[58] With the so-called "turbo-Grignard" reagent (*i*PrMgCl·LiCl), it was possible to start from the aryl bromide **30** and to obtain the organomagnesium species **31** after 3 h at 0 °C. The ketone **32** was then prepared *via* Cu-catalyzed acylation of the **31**. Recently, a chlorine/magnesium exchange with various electron-rich aryl chlorides, e.g. compound **33**, and the new exchange reagent *s*Bu_2Mg·LiOR in toluene was reported.[60] The reaction of this newly formed diorganomagnesium **34** with an aldehyde produced the alcohol **35** in 70% yield (Scheme 5).

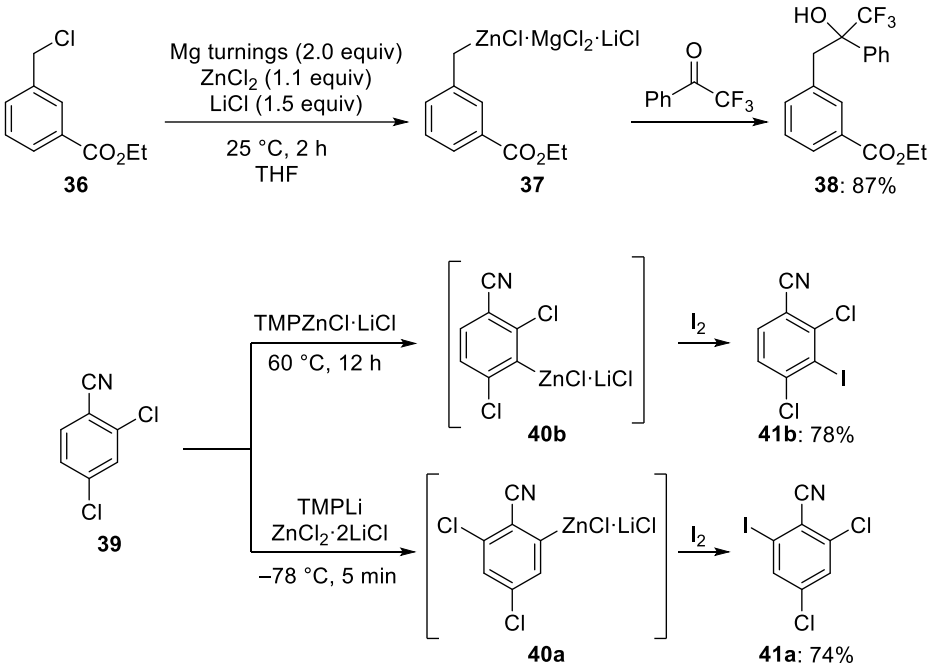
2.1.4 Transmetalation

Transmetalation reactions are usually used to generate comparatively stable organometallic reagents from reactive organometallic intermediates by addition of metal salts. The driving force for this reaction is the formation of a thermodynamically favoured more covalent C-M bond, therefore the cation of the metal salt requires a higher electronegativity than the one in the initial organometallic reagent. The biggest advantage of this method is the formation of relatively stable organometallic species, enabling the use of sensitive scaffolds and tolerating various functional groups.[61] Commonly used metal salts are $MgCl_2$, $ZnCl_2$ and CuCN, often complexed with LiCl. These newly formed magnesium, zinc and copper species are often required for specific functionalizations such as Negishi cross-couplings or Cu-mediated allylations and acylations.[62]

To ensure a fast and complete transmetalation without further decomposition of the reactive species, the *in situ* trapping of these species was extensively investigated. Thus, the preparation of the benzylic organozinc reagent **36** was performed *via* oxidative magniesum insertion into the benzylic chloride **37** in the presence of $ZnCl_2$ salt. It is of note, that the benzylic magnesium reagent was not stable due to uncontrollable homocoupling and reactions with the ester function. The direct *in situ* transmetalation to zinc allowed the preparation of the tertiary alcohol **38** in 87 % at convenient reaction conditions.[63] Deprotonations of arenes and heteroarenes with TMPLi in the presence of various metal salts allowed the use of various functional groups. Even more, the *in situ* transmetalation enabled a new metalation pattern and

[60] D. S. Ziegler, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6701–6704.
[61] (a) *Organometallchemie Vol 6* (Ed.: C. Elschenbroich), Teubner, Wiesbaden, **2008**; (b) S. C. Rasmussen, *ChemTexts* **2020**, *7*, 1-8.
[62] P. Wipf, *Synthesis* **1993**, *6*, 537-557.
[63] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665-4668.

led to a regioselectivity switch from the thermodynamically to the kinetically favoured aryl iodide. While the slow deprotonation of the starting material **39** with the weak base TMPZn·LiCl exclusively showed metalation in position C3 leading to the organozinc species **40a**, the *in situ* approach led to a fast metalation in position C6 and the subsequent fast transmetalation gave the species **40b**. Quenching with iodine gave the expected regioisomers **41a-b** in comparable yields (Scheme 6).[64]



Scheme 6: Examples for *in situ* transmetalations using $ZnCl_2$ allowing new reaction pathways.

[64] 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*, 7928-7932.

3. Continuous Flow Chemistry

3.1 Introduction

As initially mentioned, basic natural resources on earth are becoming increasingly scare. Therefore, the urge for new resource- and energy-saving manufacturing methods arose in the modern research and industrial chemistry.[65] In the 20th century, a novel approach away from conventional batch chemistry has been established by a precise continuous mixing of reagents in microreactors, the so-called "continuous flow chemistry".[66] Numerous advantages can occur from the use of a continuous flow setup compared to a typical batch procedure.

First, the mixing of reagents (in this work only liquid phases were used) can have a huge impact on the reaction conversion and selectivity. Due to the small diameters of the reactors in continuous flow, the mixing of different compounds is usually superior to reactions in flasks leading to an advanced reaction outcome.[67] The large surface to volume ratio of the microreactors allows a precise temperature control, being especially beneficial for exothermic reactions, avoiding overheating of the reaction mixture by efficient heat-transfer.[68] But also practical aspects should be considered, for example the enhanced safety due to minimized contact of the reagents and the easy handling of higher pressures and temperatures.[69] As a consequence of the above mentioned points, a lot of continuous flow procedures offer the opportunity for industrially important upscaling, minimizing the typical problems such as controlling the reaction parameters and subsequent yield loss.[70]

In the following, a general continuous flow setup will be discussed as well as the benefits of continuous flow in the field of organometallic chemistry.

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[65] M. Baumann, T. S. Moody, M. Smyth, S. Wharry, *Org. Process Res. Dev.* **2020**, *24*, 1802-1813.
[66] (a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, 11796-11893; (b) M. Guidi, P. H. Seeberger, K. Gilmore, *Chem. Soc. Rev.* **2020**, *49*, 8910-8932.
[67] (a) S. Schwolow, J. Hollmann, B. Schenkel, T. Röder, *Org. Process Res. Dev.* **2012**, *16*, 1513-1522; (b) J. Reckamp, A. Bindels, S. Duffield, Y. C. Liu, E. Bradford, E. Ricci, F. Susanne, A. Rutter, *Org. Process Res. Dev.* **2017**, *21*, 816-820.
[68] (a) H. Wakami, J.-i. Yoshida, *Org. Process Res. Dev.* **2005**, *9*, 787-791; (b) J.-i. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450-7459; (c) V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem.* **2013**, *6*, 746-789; (d) S. Schwolow, B. Heikenwälder, L. Abahmane, N. Kockmann, T. Röder, *Org. Process Res. Dev.*
[69] (a) H. Lehmann, *Green Chem.* **2017**, *19*, 1449-1453; (b) A. Adeyemi, J. Bergman, J. Branalt, J. Sävmarker, M. Larhed, *Org. Process Res. Dev.* **2017**, *21*, 947-955.
[70] (a) X. Ye, M. D. Johnson, T. Diao, M. H. Yates, S. S. Stahl, *Green Chem.* **2010**, *12*, 1180-1186; (b) M. Damm, T. N. Glasnov, C. O. Kappe, *Org. Process Res. Dev.* **2010**, *14*, 215-224; (c) M. Viviano, T. N. Glasnov, B. Reichart, G. Tekautz, C. O. Kappe, *Org. Process Res. Dev.* **2011**, *15*, 858-870.

3.2 General Continuous Flow Setup

Running a reaction in continuous flow requires careful preparation. The compatibility of the reagents and solvents with the flow apparatus has to be examined, and the setup with its varying residence times, temperatures, flow rates and additional devices has to be planned in advance. A continuous flow setup is made up of many individually connected modular building blocks and therefore can be tailored to the desired reaction protocol.[66b] In the following, a typical 3-pump continuous flow setup will be described (Figure 2).

At first, the reagent solutions, previously prepared in a certain molarity and stored in reservoir flasks, are directly pumped into a mixing device at set flow rates, usually specified as $mL \cdot min^{-1}$. In this work, exclusively peristaltic pumps were used, which compress a flexible tube while rotating, forcing the liquids to move through the tube in the given direction. If the reaction should take place at a specific temperature T^1, the reagents are pumped through so-called precooling (or preheating) loops to preset the desired reaction temperatures. The mixing devices range from simple T- or Y-pieces to advanced micromixing units for rapid mixing times.[71] As the pumps directly determine the flow rates and with it the stoichiometry of the reagents as well as the residence times, the pumping device is of special importance for a successful reaction outcome and should be calibrated regularly. After mixing, the combined stream passes a tube reactor with a certain volume, defining, together with the flow rate, the residence time t^1. The surrounding (cooling bath) of the reactor allows to precisely determine the reaction temperature and the large surface of the reactor ensures excellent heat transfer.

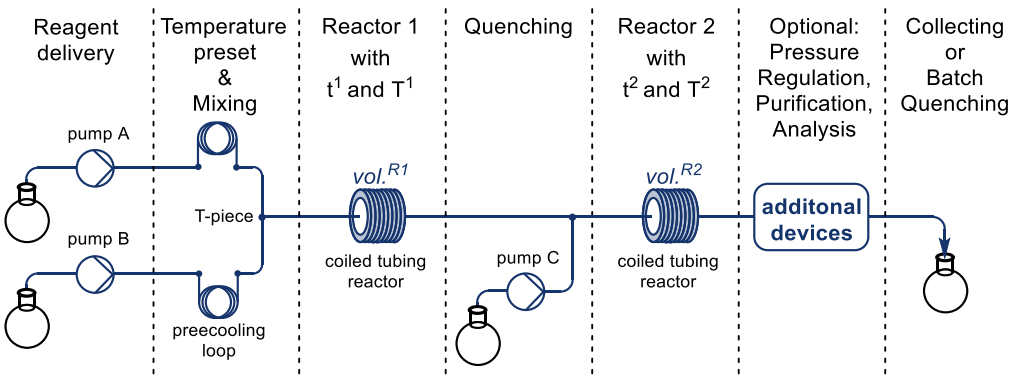


Figure 2: General 3-pump continuous flow setup of a 2-step procedure.

[71] (a) V. Hessel, H. Löwe, F. Schönfeld, *Chem. Eng. Sci.* **2005**, *60*, 2479-2501; (b) A. Ghanem, T. Lemenand, D. D. Valle, H. Peerhossaini, *Chem. Eng. Res. Des.* **2014**, *92*, 205-228.

The resulting reaction intermediate is subsequently quenched with another reagent solution, added *via* a third pump or directly quenched in batch by injecting the reaction stream into a flask containing the quenching reagent. By connecting a back pressure regulator, the pressure can be adjusted to the desired value allowing the use of solvents above their usual boiling points.[66a,72] Several additional devices were developed over the last years, including in-line-analysis of the reaction progress *via* IR- or NMR-monitoring[73] as well as direct purification steps in continuous flow.[74] Expanding this continuous flow procedure by the implementation of additional pumping devices enables to set up longer reaction sequences, which might provide a rapid and efficient synthesis of active pharmaceutical intermediates or natural product building blocks.[75]

3.3 Organometallic Reagents in Continuous Flow

Since the increasing interest in continuous flow methodologies, the merging of organometallic chemistry with this new synthetic approach was extensively investigated. Having the high reactivity and sensibility of (especially alkali)organometallic species in mind, the previously described advantages of continuous flow can have a positive influence on the generation and consumption of a broad range of organometallic reagents.[76]

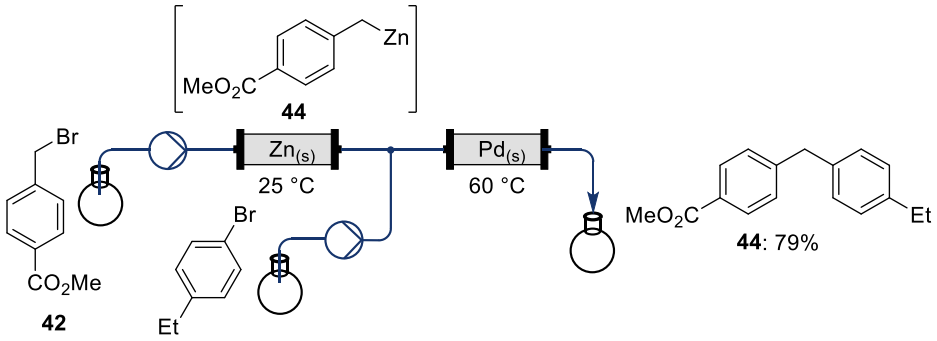
As continuous flow procedures offer the precise control over reaction temperature and stoichiometry of the reagents, the generation of reactive organometallics is often achievable at ambient temperatures, avoiding energy-wasteful batch procedures at low temperatures. Even more, due to excellent time control, "on-demand" generated, highly unstable intermediates can be further reacted in numerous reactions enabling otherwise unreachable synthetic pathways. As only small amounts of reactive intermediate are formed at once and often directly

[72] (a) M. W. Bedore, N. Zaborenko, K. F. Jensen, T. F. Jamison, *Org. Process Res. Dev.* **2010**, *14*, 432-440; (b) N. Zaborenko, M. W. Bedore, T. F. Jamison, K. F. Jensen, *Org. Process Res. Dev.* **2011**, *15*, 131−139.
[73] (a) C. F. Carter, I. R. Baxendale, M. O´Brian, J. B. J. Pavey, S. V. Ley, *Org. Biomol. Chem.* **2009**, *7*, 4594-4597; (b) C. F. Carter, H. Lane, S. V. Ley, I. R. Baxendale, B. Wittkamp, J. G. Goode, N. L. Gaunt, *Org. Process Res. Dev.* **2010**, *14*, 393-404; (c) B. J. Reizman, K. F. Jensen, *Acc. Chem. Res.* **2016**, *49*, 1786-1796; (d) D. C. Fabry, E. Sugiono, M. Rueping, *React. Chem. Eng.* **2016**, *1*, 129-133; (e) M. Goldbach, E. Danieli, J. Perlo, B. Kaptein, V. M. Litvinov, B. Blümich, F. Casanova, A. L. L. Duchateau, *Tetrahedron Lett.* **2016**, *57*, 122-125. (f) M. Hosoya, S. Nishijima, N. Kurose, *Org. Process Res. Dev.* **2020**, *24*, 1095-1103.
[74] (a) A. G. O´Brian, Z. Horváth, F. Lévesque, J. W. Lee, A. Seidel-Morgenstern, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 7028-7030; (b) D. R. Snead, T. F. Jamison, *Chem. Sci.* **2013**, *4*, 2822-2827; (c) D. R. Snead, T. F. Jamison, *Angew. Chem. Int. Ed.* **2015**, *54*, 983-987; (d) N. Weeranoppanant, A. Adamo, *ACS Med. Chem. Lett.* **2020**, *11*, 9-15.
[75] D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675-680.
[76] J. H. Harenberg, N. Weidmann, P. Knochel, *Synlett*, **2020**, *31*, 1880-1887.

consumed, the safe handling was ensured and a scale-up of a broad range of organometallic reactions was accessible by simply prolonging the run-time.[77] The generation of different organometallic species in continuous flow *via* the previously described methods (chapter A.2.1) as well as further applications of the formed intermediates will be discussed in the following.

3.3.1 Oxidative Insertion in Continuous Flow

The application of continuous flow chemistry on oxidative insertions towards organometallic species can be of benefit. As these kind of reaction usually proceeds exothermically, the improved heat-transfer in a flow system helps to keep the oxidative insertion under control. Even more, the freshly formed organometallic reagents is rapidly removed from the metal surface, avoiding potential side-reactions and securing a cleaner formation of the organometallic intermediate. As continuous flow apparatuses are susceptible for clogging when flushed with suspension, the metals are packed as powders into column reactors and the organic halide solution are pumped over the metal surface.



Scheme 7: Preparation of organozinc species *via* oxidative insertion in continuous flow.

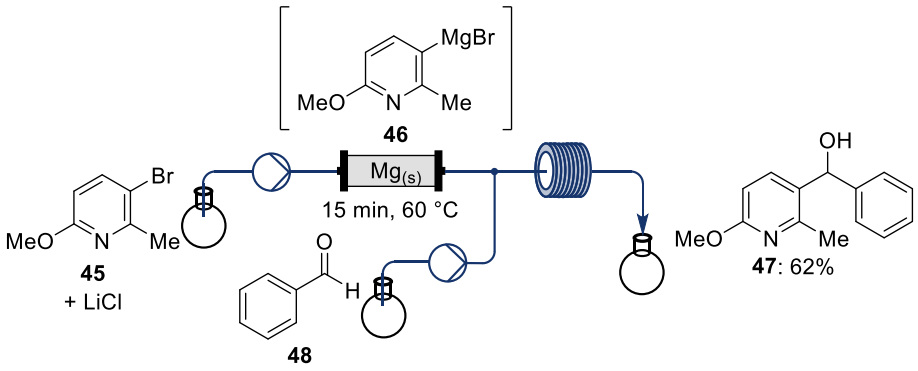
Thus, *Alcázar* and *McQuade* reported the oxidative insertion of Zn into benzyl, allylic or alkyl halides, directly follow by Negishi cross-couplings.[78] Therefore, a column was packed with Zn powder and the metal was activated by flushing with TMSCl and 1,2-dibromoethane followed by washing with THF. Passing a solution of benzylbromide **42** in THF over the column at room temperature furnished the desired organozinc reagent **43** in high yields. In a subsequent

[77] P. Filipponi, B. Guelat, J. Haber, S. Mostarda, R. O'Meadhra, L. Piccioni, J. Polenk, B. Schenkel, S. Schoenebeck, A. Streit, R. Suremann, F. Venturoni, S. Wegmann, *Chimia* **2019**, *73*, 809-816.
[78] N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737-3741.

continuous flow step using aryl halides and a silicat DPP-Pd column, this zinc species underwent Negishi cross-coupling leading to the diphenylmethane derivative **44** in 79% yield (Scheme 7).

Based on this work, organozinc species, prepare *via* in-line oxidative insertion, were used for Reformatsky and Blaise type reactions[79], the preparation of a precursor to Sacubitril[80] and for synthesizing heteroaromatic 1,3-substituted cyclobutyls.[81]

Analogically, *Grignard* reagents were successfully prepared in continuous flow using an activated Mg column (activation according to the Zn procedure). To ensure the solubility of the Grignard solution, the aryl bromide **45** was mixed with LiCl (1.0 equiv) in THF and then passed over the magnesium surface. After 7.5 min at 25 °C, the organomagnesium species **46** was obtained in full conversion. Addition of different electrophiles *via* a second pump furnished a broad range of functionalized (hetero)cycles, e.g. the substituted pyridine **47** after quenching with benzaldehyde (**48**) (Scheme 8).[82]

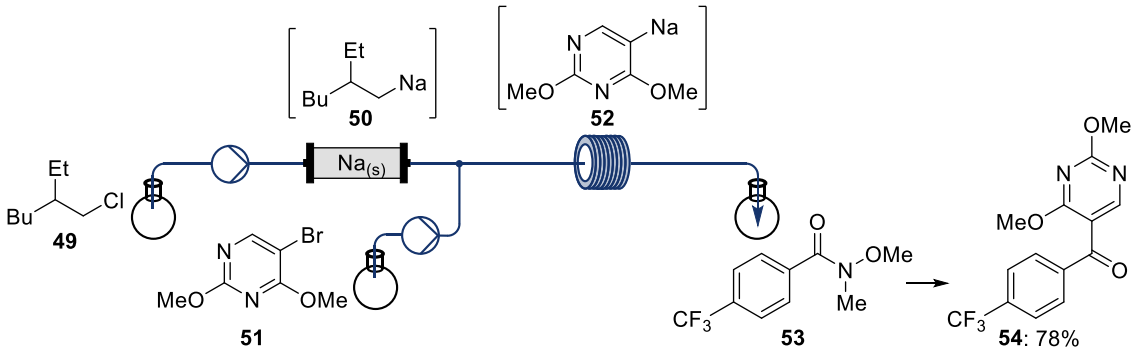


Scheme 8: Preparation of organomagnesium reagents in continuous flow *via* directed metalation and subsequent quench.

Recently, Harenberg *et al.* reported the preparation of a soluble organosodium reagent in continuous flow using a sodium-packed-bed reactor.[15b] Passing 3-(chloromethyl)heptane **49** in hexane over the column at 25 °C, the sodium species **50** was obtained *via* oxidative insertion. This sodium intermediate was subsequently merged with (hetero)aryl bromides such as **51**, furnishing the aryl sodium **52** in continuous flow. Injecting the intermediate **52** into different

[79] L. Huck, M. Berton, A. de la Hoz, A. Díaz-Ortiz, *Green Chem.* **2017**, *19*, 1420-1424.
[80] S.-H. Lau, S. L. Bourne, B. Martin, B. Schenkel, G. Penn, S. V. Ley, *Org. Lett.* **2015**, *17*, 5436-5439.
[81] M. Tissot, N. Body, S. Petit, J. Claessens, C. Genicot, P. Pasau, *Org. Lett.* **2018**, *20*, 8022-8025.
[82] L. Huck, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar, *Org. Lett.* **2017**, *19*, 3747-3750.

electrophiles such as the Weinreb amide **53** led to the functionalized ketone **54** in 78% yield (Scheme 9).

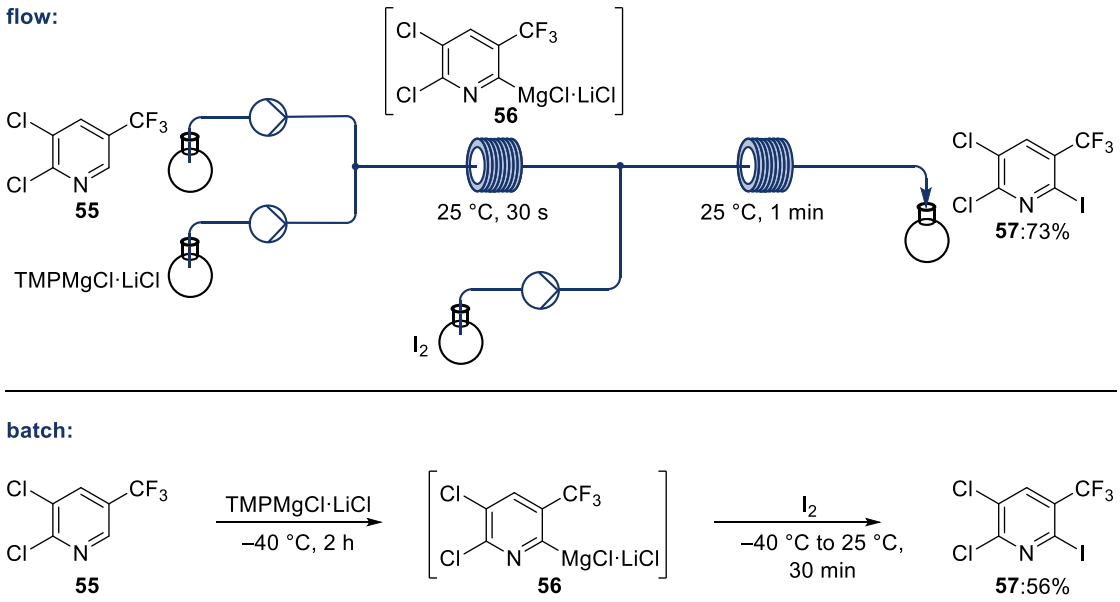


Scheme 9: Preparation of a hexane-soluble sodium reagent **50** for subsequent Br/Na exchanges.

3.3.2 Directed Metalation in Continuous Flow

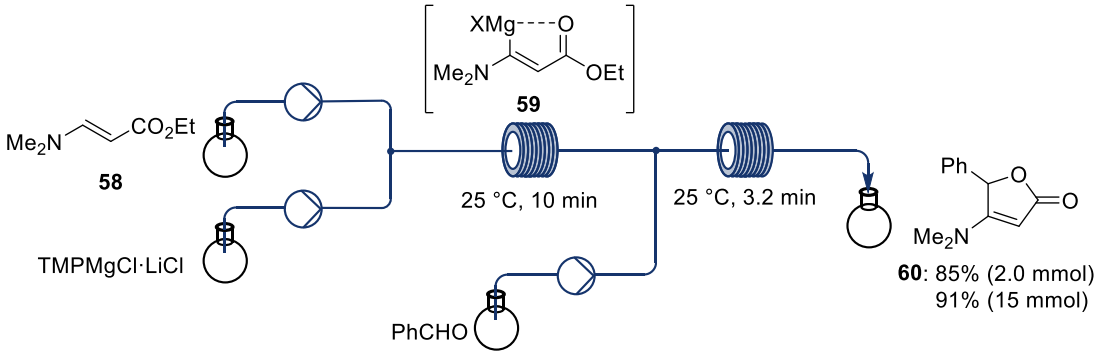
The deprotonation of organic compounds with Li- and Mg-bases showed to be beneficial in a continuous flow set-up avoiding the often required low temperatures and improving the selectivity of the metalation.

Thus, Knochel and coworkers demonstrated the superiority of continuous flow compared to batch procedures by metalating *N*-heterocycles such as the pyridine **55** at ambient temperatures in continuous flow with significantly shortened reaction times.



Scheme 10: Preparation of functionalized pyridines *via* directed metalation; flow/batch comparison.

Mixing the heterocycle with TMPMgCl·LiCl at 25 °C gave the regioselectively magnesiated pyridine **56** within 30 s. The addition of electrophiles such as iodine *via* a third pump furnished the functionalized heterocycle **57** in 73% yield within 1 min at 25 °C. In contrast, performing the reaction sequence in a conventional batch set-up required a temperature of –40 °C and 2 h of metalation time (Scheme 10).[83]

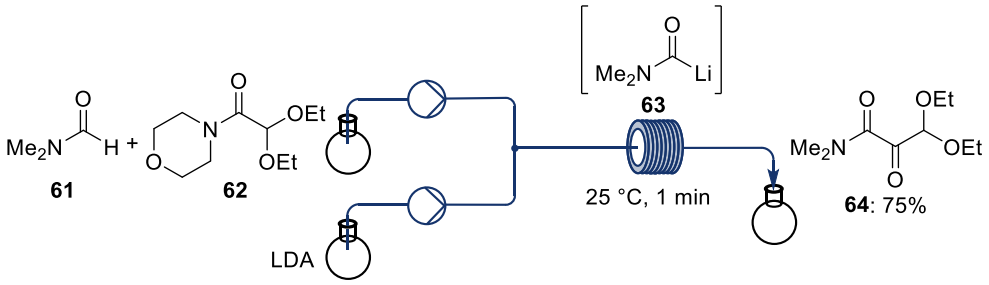


Scheme 11: Metalation of acrylates using TMPMgCl·LiCl and subsequent in-line benzaldehyde quench.

Later, the metalation and subsequent functionalization of acrylates, acrylonitriles and nitroolefins in continuous flow was described.[84] In batch, these metalations usually require low reaction temperatures and suffer from side reactions such as polymerization.[85] In that approach, the bases TMPMgCl·LiCl and TMPZnCl·LiCl were used at convenient reaction conditions. For example, the acrylate **58** was magnesiated with the corresponding TMP-base at 25 °C within 10 min towards the coordinated intermediate **59**. In a second continuous flow step, benzaldehyde was added at 25 °C and the furan-5*H*-one **60** was obtained after a ring-closing reaction. Notably, it was shown that a scale-up was possible, providing an even higher yield on a 15 mmol scale (Scheme 11). Also, direct zincations of (hetero)arenes were achieved by treatment with $(CyN)_2Zn·2LiCl$ at elevated temperatures.[86]

[83] T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933-7937.
[84] M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828-831.
[85] (a) B. A. Feit, U. Melamed, R. R. Schmidt, H. Speer, *Tetrahedron* **1981**, *37*, 2143-2148; (b) D. C. Harrowven, H. S. Poon, *Tetrahedron* **1996**, *52*, 1389-1398.
[86] M. Becker, P. Knochel, *Org. Lett.* **2016**, *18*, 1462-1465.

In a Babier-type reaction (the organometallic species is generated *in situ* in the presence of trapping agents) in continuous flow, the formation of amides and thioamides was described by deprotonation of formamides with LDA (lithium diisopropylamide) in the presence of electrophiles.[87] Due to fast mixing and excellent heat control, these reactions were able to be carried out at 25 °C within ~1 min. In practice, the formamide **61** was premixed with the morpholine-amide **62** and mixed with LDA in a continuous flow apparatus at 25 °C, providing the lithium amide **63**. After a residence time of 60 s, in which the newly formed lithium species was directly quenched, the reaction mixture was poured into *sat. aq.* NH_4Cl solution and the amide **64** was obtained in 75% yield (Scheme 12).

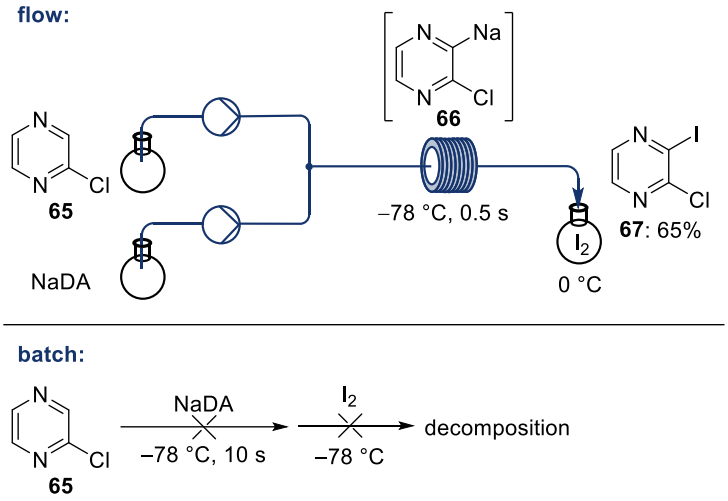


Scheme 12: Metalation of formamides with LDA in the presence of an electrophile.

Recently, the attention of metalations in continuous flow was brought to the highly reactive alkali organometallics NaDA (sodium diisopropylamine)[15a,88] and KDA (potassium diisopropylamine).[89] These amine-soluble bases, generated in batch, were used for a broad range of deprotonations on unstable or highly functionalized systems, exploiting the advantages of continuous flow chemistry such as short reaction times, rapid mixing and superior control over stoichiometry. This was demonstrated for the directed metalation of the sensitive pyrazine substrate **65**. Mixing with NaDA in a microreactor at low temperatures and high flowrates gave, after a short residence time of 0.5 s, the sodiated species **66** in continuous flow. Subsequent iodination in batch produced the desired halogenated pyrazine **67** in a good yield. As these short times are not achievable in a standard batch procedure, the fast addition of NaDA to **65** and quenching with I_2 after 10 s led to complete decomposition of the starting material and no product formation (Scheme 13).[88] Additionally, the successful sodiated of

[87] M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280-10284.
[88] N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748-10751.
[89] J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 12321-12325.

unsaturated nitriles, which are often difficult to deprotonate due to competitive side-reactions,[84,85,90] was described by using the strong sodium bases NaDA and TMPNa in continuous flow.[15a]

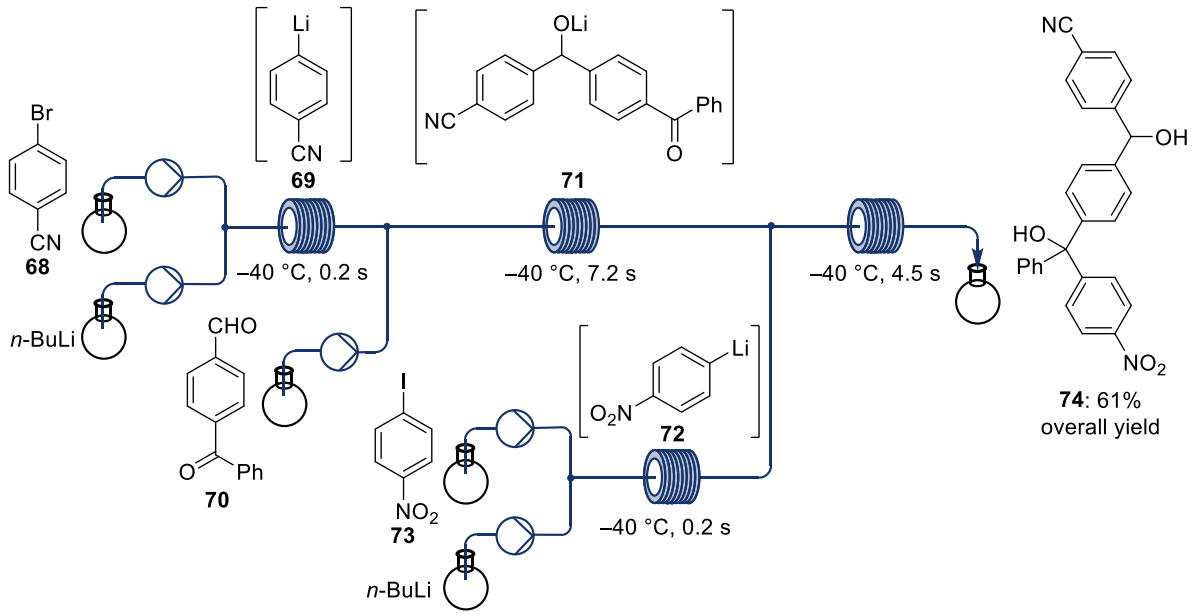


Scheme 13: Deprotonation of the sensitive heterocycle **65** with NaDA and subsequent iodine quench; flow/batch comparison

3.3.3 Halogen/Metal Exchange in Continuous Flow

The halogen/lithium exchange in continuous flow was extensively described in the last decades, as these fast reactions can profit a lot from the rapid mixing and precisely determined short reaction times. Pioneered by Yoshida,[91] the ultrafast[92] preparation of organolithium reagents (in the range of milliseconds) and subsequent quenching with different electrophiles led to novel possibilities for preparing compounds bearing highly sensitive functional groups such as esters, nitriles and nitro groups, in spite of comparatively (to batch) higher temperatures.[76,93]

[90] (a) F. F. Fleming, V. Gudipati, O. W. Steward, *Tetrahedron* **2003**, *59*, 5585-5593; (b) F. F. Fleming, S. Gudipati, J. A. Aitken, *J. Org. Chem.* **2007**, *72*, 6961-6969.
[91] (a) A. Nagaki, Y. Tomida, H. Usutani, H. Kim, N. Takabayashi, T. Nokami, H. Okamoto, J.-I. Yoshida, *Chem. Asian J.* **2007**, *2*, 1513-1523; (b) A. Nagaki, H. Kim, J.-i. Yoshida, *Angew. Chem., Int. Ed*. **2008**, *47*, 7833-7836; (c) A. Nagaki, N. Takabayashi, Y. Tomida, J.-i. Yoshida, *Org. Lett.* **2008**, *10*, 3937-3940.
[92] H. Kim, K. I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691-694.
[93] For reviews on the halogen/Li exchange, see: (a) L. Degennaro, C. Calucci, S. De Angelis, R. Luisi, *J. Flow. Chem.* **2016**, *6*, 136-166; (b) A. Nagaki, *Tetrahedron Lett.* **2019**, *60*, 150923.



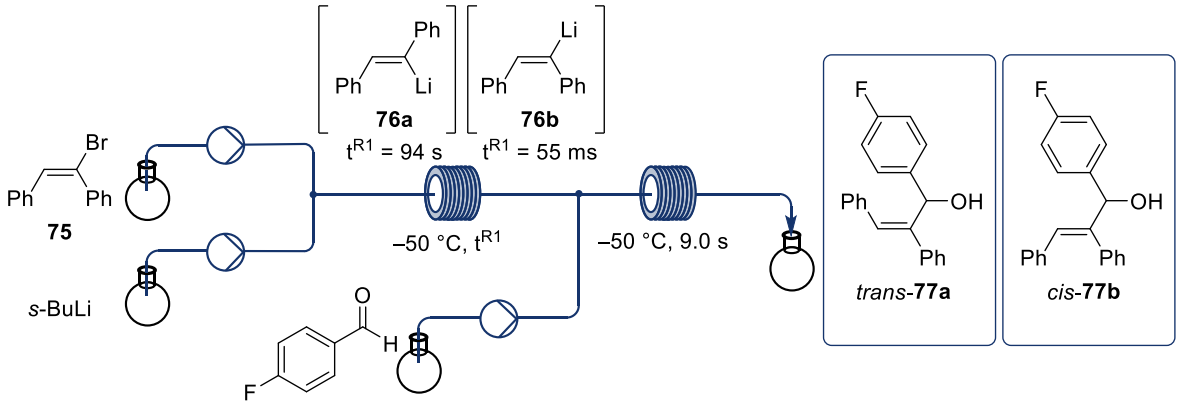
Scheme 14: Chemoselective halogen/Li exchanges in a multi-step continuous flow set-up for the preparation of the highly functionalized compound **74**.

For example, highly functionalized aromatic compounds were obtained in good overall yields by the successive addition of different organolithium reagents prepared in continuous flow *via* halogen/Li exchange. First, the aromatic halide **68**, bearing a cyano group, was mixed with *n*-BuLi at –40 °C furnishing the sensitive lithium reagent **69** within 0.2 s. Subsequent quenching with the aldehyde **70** led to the alkoxide **71**. Next, the organolithium **72** containing a nitro group, was prepared by mixing the corresponding aryl iodide **73** with *n*-BuLi at –40 °C for 0.2 s and subsequently added to the reaction mixture. After 4.5 s of residence time, the highly functionalized aromatic compound **74** was obtained in 61% overall yield (Scheme 14).[94]

Due to the ultrafast mixing and precise control over reaction times in a continuous flow set-up, undesired competitive reactions might be excluded. For example, the anionic Fries rearrangement of *o*-lithiated aryl esters usually occurs in batch and macrobatch reactors but the implementation of novel chip reactors allowed to outpace the rearrangement, leading to direct electrophile trapping after extremely short residence times for the I/Li exchange (3.9-14 ms).[92] Another example for controlling the reaction outcome *via* continuous flow is the functionalization of stilbenes with control over the *cis*-*trans* isomerization. As the *trans*-isomer

[94] A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914-1918.

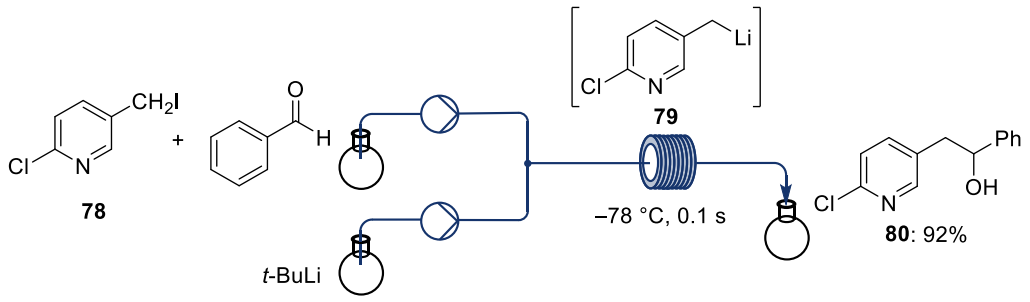
is energetically more stable, the *cis*-isomer is usually easily isomerized and the *trans*-product cannot be prevented. Thus, treating *cis*-bromo stilbene (**75**) with *s*-BuLi at –50 °C for 94 s gave the isomerized lithium species **76a** and subsequent quenching with the aldehyde led selectively to the *trans*-product **77a**. Remarkably, by reducing the residence time for the Br/Li exchange drastically to 55 ms, the isomerization was outpaced and the *cis*-intermediate **76b** was directly quenched furnishing the desired product **77b** in 99% yield (Scheme 15).[95]



Scheme 15: Preparation of functionalized *cis*- and *trans*-stilbenes, controlled *via* residence times in continuous flow.

Also, the generation and consumption of substituted benzylic lithium reagents benefits from the continuous flow technique as these intermediates tend to perform side reactions such as homocouplings under batch conditions.[96] Knochel and coworkers envisioned a Barbier-type continuous flow set-up for the functionalization of benzylic positions, exploiting the extremely fast I/Li exchange with the strong exchange reagent *t*-BuLi.[97] For this approach, a solution of pyridine **78** containing benzaldehyde was prepared and mixed with *t*-BuLi at –78 °C for 0.1 s at high flow rates. The formed benzylic lithium **79** (I/Li exchange is faster than the reaction of *t*-BuLi with benzaldehyde)[51a,98] was directly quenched by the electrophile present in the solution leading to the alcohol **80** in 92% yield (Scheme 16). In batch, only <5 % GC-yield of **80** were observed, demonstrating the high influence of the superior flow mixing.

[95] H.-J. Lee, Y. Yonekura, N. Kim, J.-i. Yoshida, H. Kim, *Org. Lett.* **2021**, *23*, 2904-2910.
[96] (a) H. Gilman, G. L. Schwebke, *J. Org. Chem.* **1962**, *27*, 4259-4261; (b) S. Warren, P. Wyatt, *Tetrahedron Lett.* **1996**, *37*, 5609-5612; (b) L. Kupracz, A Kirschning, *Adv. Synth. Catal.* **2013**, *355*, 3375-3380.
[97] N. Weidmann, J. H. Harenberg, P. Knochel, *Org. Lett.* **2020**, *22*, 5895-5899.
[98] W. F. Bailey, J. J. Patricia, T. T. Nurmi, *Tetrahedron Lett.* **1986**, *27*, 1865-1868.

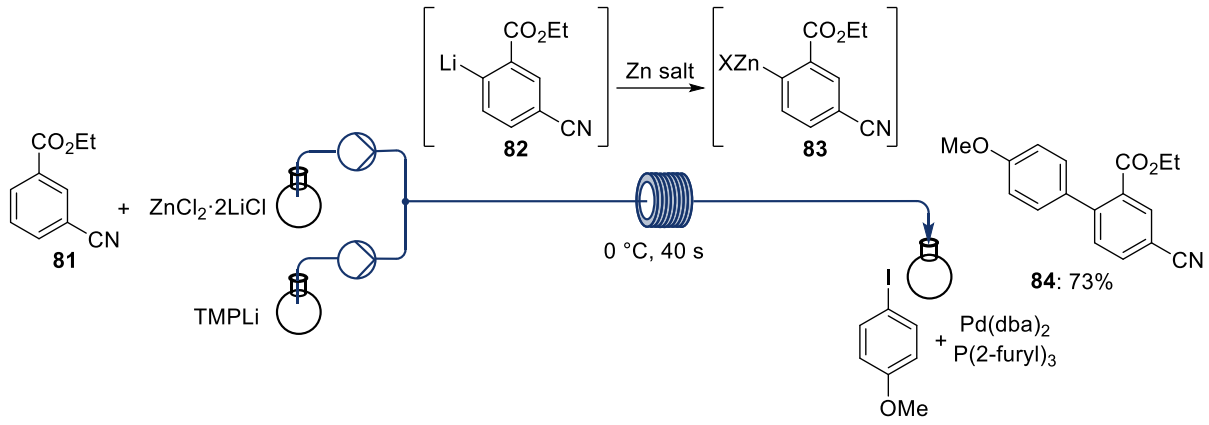


Scheme 16: Preparation and consumption of benzylic lithium species in a Barbier-type continuous flow set-up.

3.3.4 Transmetalation in Continuous Flow

Transmetalations in a continuous flow set-up are mostly carried out by *in-situ* trapping of the more reactive intermediate with Zn or Mg salts. Due to fast mixing, short reaction times and precisely controlled stoichiometry, the otherwise occurring side reactions of the reactive intermediates could be supressed in a flow apparatus. In 2015, the Knochel group described a practical procedure for a Barbier-type transmetalation towards relatively stable Mg, Zn, Cu, and La organometallic species by metalating (hetero)arenes with TMPLi in the presence of the corresponding metal salts.[99] In batch, these reactions required very low temperatures and scaling up was difficult and needed further optimizations. Thus the ethyl benzoate **81** was premixed with $ZnCl_2$ and LiCl in THF. This reaction solution was then pumped into a stream of TMPLi, producing first the aryllithium **82** followed by transmetalation to the more stable Zn species **83** at 0 °C within 40 s. Injecting the intermediate into a solution of aryl halid, $Pd(dba)_2$ and $P(2\text{-furyl})_3$ furnished regioselectively the arylated product **84** in good yield (Scheme 17). Noteworthy, this reaction set-up is just working when the deprotonation is faster than a direct transmetalation reaction of TMPLi with the metal salt. Also unsymmetrical azobenzenes were successfully functionalized by treatment with TMPLi and Barbier-type transmetalation with different metal salts.[100]

[99] M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501-12505.
[100] M. Ketels, D. B. Konrad, K. karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.* **2017**, *19*, 1666-1669.

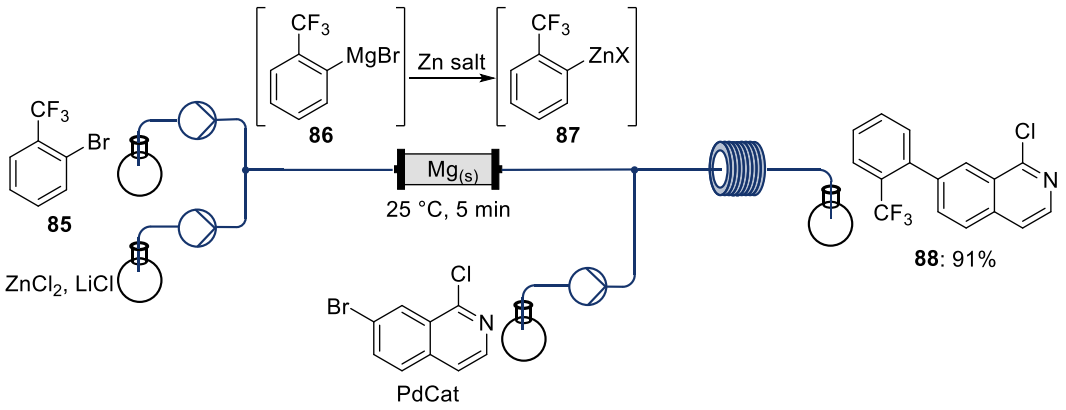


Scheme 17: Preparation of organozinc species *via* directed metalation with TMPLi and subsequent *in situ* transmetalation.

Additionally, a similar procedure was investigated for a *in situ* transmetalation of various lithium species prepared *via* halogen/Li exchange in continuous flow.[101] According to the previously described protocol, a solution of aryl halide and $ZnCl_2$ in THF was prepared and subsequently mixed with *n*-BuLi in continuous flow at 0 °C. As the halogen/Li exchange is a faster reaction than deprotonations, the residence time could be shortened to just 2.5 s and various sensitive functional groups such as NO_2 or N_3 were tolerated.

As previously described (chapter A.3.3.1), organozinc species could be prepared by oxidative insertion in continuous flow by running organic halides over a Zn-packed column. Due to the moderate reactivity of the zinc metal, this method was limited to more reactive halides such as benzyl bromides or secondary alkyl iodides. Hence, a new route towards organozinc species in continuous flow was investigated by first oxidative insertion of Mg into various organic halides followed by transmetalation to zinc.[102] Starting from the bromide **85** and a solution of $ZnCl_2$ and LiCl, the organomagnesium intermediate **86** was prepared *via* insertion in continuous flow and immediately transmetalated to the zinc species **87**. After in-line Negishi cross-coupling, the compound **88** was obtained in 91% yield (Scheme 18).

[101] M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770-12773.
[102] A. Herath, V. Molteni, S. Pan, J. Loren, *Org. Lett.* **2018**, *23*, 7429-7432.



Scheme 18: Preparation of organozinc species by oxidative Mg insertion followed by *in situ* transmetalation to zinc.

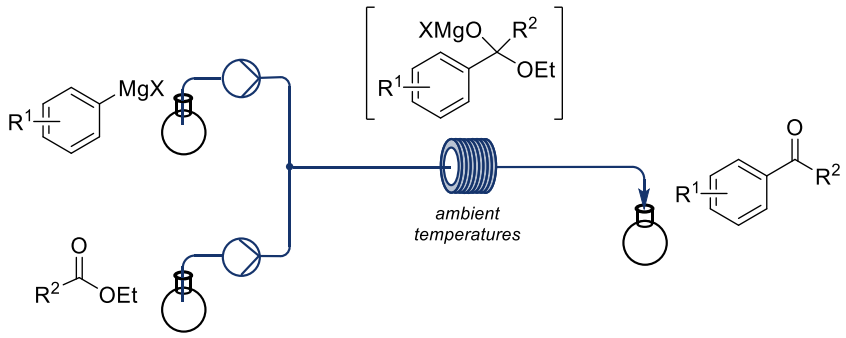
Buchwald and coworkers showed that transmetalation in continuous flow can also be beneficial in a stepwise approach. First, fluorinated arenes were lithiated by mixing with *n*-BuLi in the presence of KO*t*Bu (Schlosser base)[103], taking advantage of the excellent heat-transfer in continuous flow and avoiding temperature hotspots. This species was then transmetalated by adding $ZnCl_2$ to the intermediate in an extra step.[104] The zincation of oxirane was performed in a analogical way by first lithiation and subsequent transmetalation with Zn salt, allowing to perform this reaction at –50 °C (in batch –90 °C) in continuous flow.[105]

[103] M. Schlosser, *Pure & Appl. Chem.* **1988**, *60*, 1627-1634.
[104] S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463-10467.
[105] H. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2017**, *139*, 11590-1594.

4. Objectives

The development of resource and energy-saving synthetic methods is an ongoing task in the modern organic chemistry and will become more important in the future years. Therefore, the methodology of preparing all sorts if compounds in a continuous flow set-up, which is promising to tackle the above mentioned challenges, is of high interest and should be further investigated.

First, the preparation of ketones starting from commercially available esters and readily prepared Grignard reagents in continuous flow should be explored, as these reactions usually suffer from uncontrollable side reactions such as double additions towards tertiary alcohols. Further, very low temperatures are required to obtain an acceptable reaction outcome in batch. In this approach, the addition of Grignard reagents to esters in a continuous flow set-up should proceed at ambient temperatures due to precise temperature and stoichiometry control. As the premature collapse of the tetrahedral intermediate should be avoided, a broad range of synthetically usefull ketones could be obtainable and the formation of tertiary alcohols might be supressed (Scheme 19).[106]

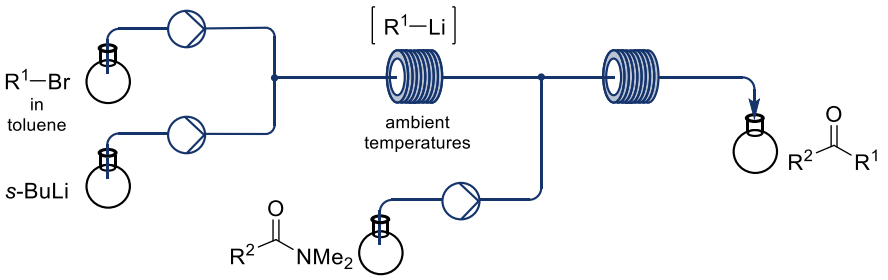


Scheme 19: Continuous flow acylation of Grignard reagents with readily available esters at convenient reaction conditions.

Furthermore, the application of continuous flow for the improved handling of unstable organolithiums in toluene at ambient temperatures and a subsequent ketone formation should be investigated. The aim was to provide a scalable and reproducible process in industrial friendly solvent systems for the convenient preparation of pharmaceutical important building blocks. Thus, the use of the unpolar solvent toluene should avoid the decomposition of the in-situ prepared organolithium species at ambient temperatures. A fast consumption of the "on-

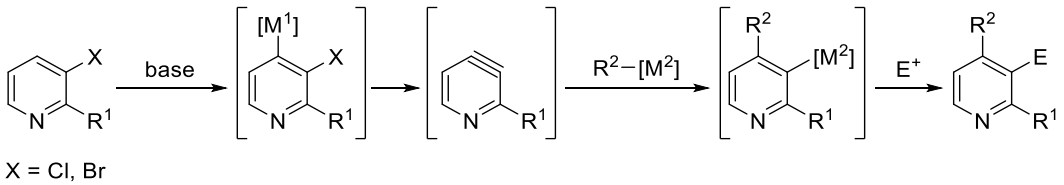
[106] This project was developed in cooperation with D. Djukanovic in synthetic aspects, see: D. Djukanovic, Dissertation, LMU München, **2022**.

demand" prepared lithium species with readily available *N*,*N*-dimethylamides should produce a broad range of ketones, excluding side reactions like enolizations of starting materials and double addition (Scheme 20). The typically used Weinreb amides should be replaced in order to reduce toxicity and costs and enhance the safety aspects of the process.[107]



Scheme 20: Continuous flow acylation of *in situ* prepared organolithiums with readily available *N*,*N*-dimethylamides.

The last project comprises the functionalization of pyridines *via* pyridyne intermediates in batch and continuous flow. Due to the high reactivity of pyridynes and the ensuing drawbacks such as limited scope and lack of regioselectivity, this synthetic field is still relatively unexplored. Also, complex and cost-intensive precursors are typically used for the generation of pyridynes. The aim was to develop a convenient procedure for the regioselective functionalization of readily available pyridines, using commercially available reagents. Even more, quenching the emerging intermediate with various electrophiles should enable the telescoped difunctionalization of the precursor, producing highly functionalized pyridines. Further, this procedure should be transposed to a continuous flow set-up to ensure scalability and reproducibility (Scheme 21).[108]



Scheme 21: Generation of pyridyne intermediates and subsequent difunctionalization.

[107] This project was developed in cooperation with D. Djukanovic in synthetic aspects, see: D. Djukanovic, Dissertation, LMU München, **2022**. This project was developed in cooperation with Dr. B. Martin (Novartis Pharma AG).

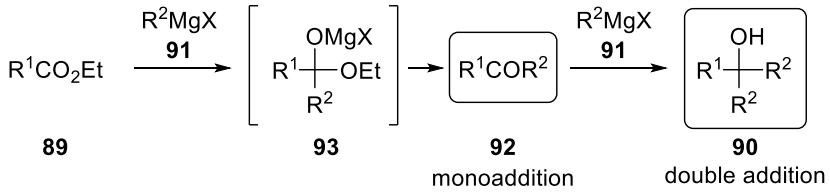
[108] This project was developed in cooperation with D. Djukanovic in synthetic aspects, see: D. Djukanovic, Dissertation, LMU München, **2022**. The measurement of the crystal structures was performed by Prof. Dr. K. Karaghiosoff.

B. RESULTS AND DISCUSSION

1. Selective Acylation of Aryl- and Heteroarylmagnesium Reagents with Esters in Continuous Flow

1.1 Introduction

The selective acylations of Grignard reagents using acid chlorides, Weinreb amides and related activated carbonyl groups are well established and widely used routes towards polyfunctional ketones.[109,110] However, several drawbacks of such acylations can be enumerated: The moderate stability of acid chlorides, the poor commercial availability of activated acyl derivatives as well as the toxicity of Weinreb amides. Therefore, the use of ethyl esters of type **89**, which are readily available and stable under a wide range of conditions, would be highly desirable. Unfortunately, the undesired tertiary alcohol **90** is usually formed during the acylation with organomagnesium reagents of type R^2MgX (**91**) by a subsequent reaction of the more electrophilic produced ketones **92** with the Grignard reagent present in solution (Scheme 22).[111]



Scheme 22: General reaction of organomagnesium reagents with ethyl esters towards ketones or tertiary alcohols.

[109] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815-3818; b) D. E. Bergbreiter, J. M. Killough, *J. Org. Chem.* **1976**, *41*, 2750-2753; c) M. Araki, S. Shigeru, T. Hisashi, M. Teruaki, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777-1780; d) S. Wattanasin, F. G. Kathawala, *Tetrahedron Lett.* **1984**, *25*, 811-814; e) T. Fujisawa, *Chem. Lett*. **1983**, *12*, 1267-1270; f) T. Fujisawa, M. Toshiki, T. Sato, *Tetrahedron Lett.* **1982**, *23*, 5059-5062; g) M. W. Anderson, J. Raymond, J. Saunders, *J. Chem. Soc.* **1982**, *5*, 282-283; h) M. N. Mattson, H. Rapoport, *J. Org. Chem.* **1996**, *61*, 6071-6074; i) D. A. Evans, G. Borg, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2002**, *41*, 3188-3191; j) J. K. Park, W. K. Shin, D. K. An, *Tetrahedron Lett.* **2013**, *54*, 3199-3203; k) C. G. Knudsen, H. Rapoport *J. Org. Chem.* **1983**, 48, 2260-2266.

[110] For transition-metal catalysis on selective preparation of ketones see: a) F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel, *Chem. Sci.* **2019**, *10*, 8241-8245; b) H. Li, Y. Xu, E. Shi, W. Wei, X. Suo, X. Wan, *Chem. Commun.* **2011**, *47*, 7880-7882; c) D. Milstein, J. K. Stille, *J. Org. Chem.* **1979**, *44*, 1613-1618; d) S. Shi, R. Lalancette, R. Szostak, M. Szostak, *Org. Lett.* **2019**, *21*, 1253-1257; e) G. Meng, M. Szostak, *Org. Lett.* **2018**, *20*, 6789-6793; f) G. Li, S. Shi, P. Lei, M. Szostak, *Adv. Synth. Catal.* **2018**, *360*, 1538-1543; g) X. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986-5009; h) J. Schranck, X. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 4827-4831.

[111] F. C. Whitmore, W. S. Forster, *J. Am. Chem. Soc.* **1942**, *64*, 2966-2968.

As the addition of the organomagnesium species **91** to ketones is faster than to esters, the collapse of the tertiary intermediate of type **93** has to be prevented in order to get a selective monoaddition towards the ketone **92**. As continuous flow offers several advantages (see chapter A.3.1) for the performance of organometallic reactions, the generation of the organomagnesium intermediate **93** may be controlled more accurately.[87,88,112] The use of a continuous flow setup may generate and consume the tetrahedral magnesiated hemiacetal of type **93** in a controlled manner due to superior mixing compared to batch and therefore avoid the imminent formation of the tertiary alcohol **90**. For the reason of fast generation and consumption under advanced stoichiometric control, a flow setup could avoid low temperatures which are required in batch reactions for controlling the reaction selectivity.[113]

Recent publications by Yoshida in the field of continuous flow chemistry showed that functionalized ketones can be prepared by the reaction of strongly activated acid chlorides with organolithium reagents using extremely fast micro-mixing[114] and that α-keto-esters were selectively produced by the reaction of lithium organometallics with dialkyl oxalates.[115]

1.2 Optimization of the Acylation of Grignard Reagents with Ethyl Trifluoroacetate

The optimum reaction conditions were investigated by optimizing the preparation of *p*-trifluoromethyl ketone **92a** starting from commercially available ethyl trifluoroacetate (**89a**) and *p*-anisylmagnesium bromide (**91a**).

[112] a) F. G. J. Odille, A. Stenemyr, F. Pontén, *Org. Process Res. Dev.* **2014**, *18*, 1545-1549; b) D. Webb, T. F. Jamison, *Org. Lett.* **2012**, *14*, 568-571; c) T. Fukuyama, H. Chiba, H. Kuroda, T. Takigawa, A. Kayano, K. Tagami, *Org. Process Res. Dev.* **2016**, *20*, 503−509; d) A. Hafner, V. Mancino, M. Meisenbach, B. Schenkel, J. Sedelmeier, *Org. Lett.* **2017**, *19*, 786−789; e) C. Stueckler, P. Hermsen, B. Ritzen, M. Vasiloiu, P. Poechlauer, S. Steinhofer, A. Pelz, C. Zinganell, U. Felfer, S. Boyer, M. Goldbach, A. De Vries, T. Pabst, G. Winkler, V. LaVopa, S. Hecker, C. Schuster, *Org. Process Res. Dev.* **2019**, *23*, 1069-1077; f) D. T. McQuade, H. J. Seeberger, *Org. Chem.* **2013**, *78*, 6384-6389; g) Y. Chen, C. A. Hone, B. Gutmann, C. O. Kappe, *Org. Process Res. Dev.* **2017**, *21*, 1080-1087; h) G. A. Price, A. Hassan, N. Chandrasoma, A. R. Bogdan, S. W. Djuric, M. G. Organ, *Angew. Chem. Int. Ed.* **2017**, *56*, 13347-13350; i) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967-1973; j) 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*, 1221-1228.

[113] a) X. J. Creary, *Org. Chem.* **1987**, *52*, 5026-5030; b) T. Yamazaki, T. Tsukasa, T. Kawasaki-Taskasuka, *Tetrahedron* **2008**, *64*, 2419-2424; c) M. Rambaud, M. Bakasse, G. Duguay, J. Villieras, *Synthesis*, **1988**, *7*, 564-566.

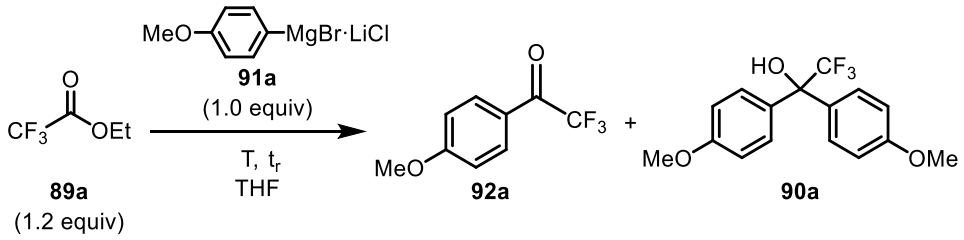
[114] a) A. Nagaki, K. Sasatsuki, S. Ishiuchi, N. Miuchi, M. Takumi, J. Yoshida, *Chem. Eur. J.* **2019**, *25*, 4946-4950; b) S. Moon, S. Jung, U. Bin Kim, W. Kim, *RSC Adv.* **2015**, *2*, 79385.

[115] A. Nagaki, D. Ichinari, J. Yoshida, *Chem. Commun.* **2013**, *49*, 3242-3244.

First, a batch/flow comparison screening was performed. Slow addition of Grignard reagent **91a** (1.0 equiv in THF) to ethyl trifluoroacetate (**89a**, 1.2 equiv in THF) at −78 °C in batch, followed by a reaction time of 2 min, gave the *p*-trifluoromethyl ketone **92a** in 50% calibrated GC-yield as well as 10% of the undesired tertiary alcohol **90a** with only 71% conversion (Table 1, entry 1).[116] A longer reaction time of 180 min enhanced the conversion to 83%, leading to an improved GC-yield of the desired ketone (entry 2). Increasing the reaction temperature to −5 °C with 2 min of reaction time led again to an improved conversion, but the selectivity of the reaction was considerably lowered, showing the limitation of the batch procedure (entry 3).

In contrast, using a commercially available continuous flow setup at −5 °C with a residence time (t_r) of 2 min provided the *p*-trifluoromethyl ketone **92a** in 72% GC-yield and only 8% of the tertiary alcohol **90a**, clearly showing the superiority of the flow technique over a batch protocol at elevated temperatures (entry 4).

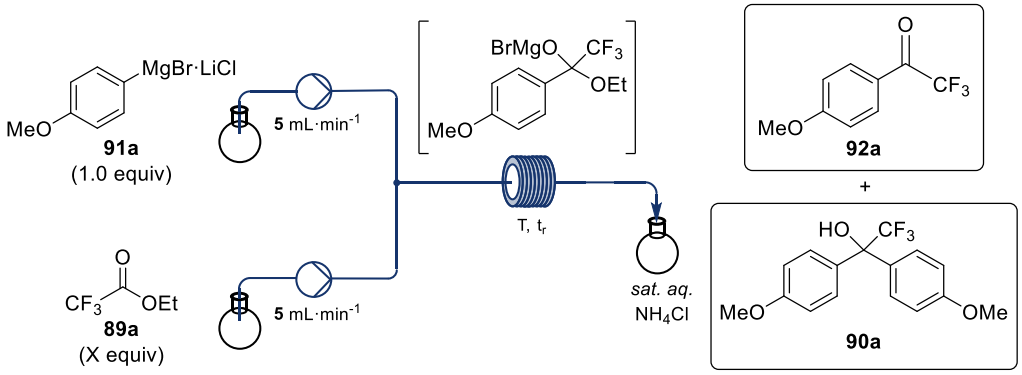
Table 1: Batch/Flow comparison for the formation of *p*-anisyl trifluoromethyl ketone **92a** and the undesired tertiary alcohol **90a**.



entry	setup	T [°C]	t [min]	conversion **91a** [GC-%]	yield **92a** [GC-%]	yield **90a** [GC-%]
1	batch	−78	2	71	50	10
2	batch	−78	180	83	66	9
3	batch	−5	2	92	37	27
4	flow	−5	2	90	72	8

[116] The conversion was determined by measuring the amount of anisole, the hydrolysis product of the Grignard reagent **91a**, after the reaction was quenched with *sat. aq.* NH_4Cl.

Table 2a. Temperature screening for the reaction of ethyl trifluoroacetate (**89a**) with a Grignard reagent.



entry	T [°C]	t_r [min]	equiv of **89a**	conversion **91a** [GC-%]	yield **92a** [GC-%]	yield **90a** [GC-%]
1	–15	2	1.2	75	65	3
2	–10	2	1.2	81	70	6
3	–5	2	1.2	88	72	8
4	0	2	1.2	89	70	12

Several reaction parameters for the continuous flow procedure were optimized. A temperature screening showed, that even small changes of reaction temperature influenced the conversion as well as the selectivity of the acylation. We observed a decreased conversion at –15 °C (Table 2a, entry 1) as well as increased tertiary alcohol formation at 0 °C (entry 4). The best balance between good conversion and suppression of double addition were found at –5 °C (entry 3).

Table 2b. Time screening.

entry	T [°C]	t_r [s]	equiv of **89a**	conversion **91a** [GC-%]	yield **92a** [GC-%]	yield **90a** [GC-%]
1	–5	10	1.2	78	60	6
2	–5	15	1.2	82	64	7
3	–5	20	1.2	85	66	7
4	–5	60	1.2	87	70	8
5	–5	120	1.2	89	72	8

Investigating the residence time (t_r) showed a fast formation of the desired ketone (**92a**) within the first minute (Table 2b, entries 1-4), observing a small improvement by prolonging the residence time to 2 min (entry 5). Further extension of the residence time gave no noteworthy improvements.

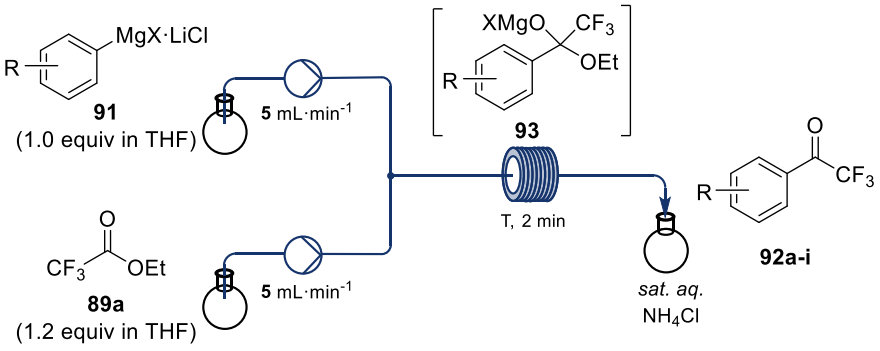
Table 2c. Equivalent screening of ethly trifluoroacetate (**89a**).

entry	T [°C]	t_r [min]	equiv of **89a**	conversion **91a** [GC-%]	yield **92a** [GC-%]	yield **90a** [GC-%]
1	–5	2	1.05	82	67	11
2	–5	2	1.2	89	72	8
3	–5	2	1.5	90	73	7
4	–5	2	2.0	89	74	7
5	–5	2	3.0	90	75	7

Increasing the equivalents of ethyl trifluoroacetate had a positive effect on conversion of **91a** and selectivity of the reaction (Table 2c, entries 1-2) as a higher ester concentration while mixing prevents the double addition due to absence of available Grignard reagent. The superior mixing in continuous flow enabled the use of this nearly stoichiometric amounts of the reactants and increasing the equivalents to 1.5-3.0 equiv gave just negligible improvements (entries 3-5).

1.3 Preparation of Trifluoromethyl Ketones in Continuous Flow

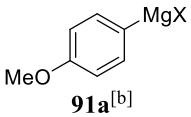
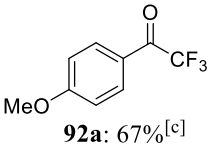
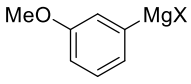
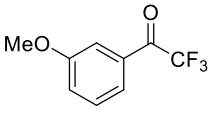
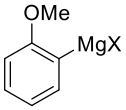
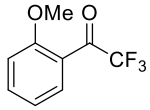
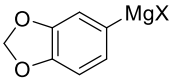
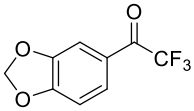
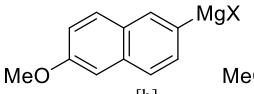
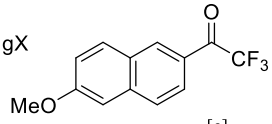
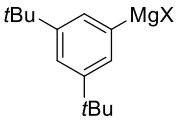
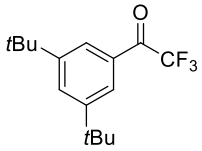
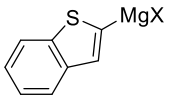
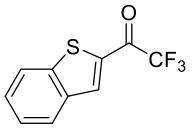
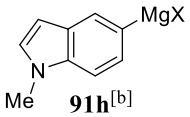
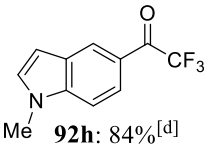
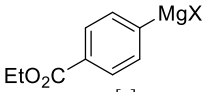
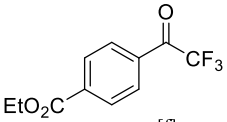
With these optimized conditions in hand, several trifluoromethyl ketones were prepared (Scheme 23).[117] Thus, *p*- and *m*-anisylmagnesium bromide (**91a-b**, 1.0 equiv in THF) were mixed in a T-mixer (0.5 mm i.d.) with ethyl trifluoroacetate (**89a**, 1.2 equiv in THF) and after a residence time (t_r) of 2 min at –5 °C using an overall flowrate of 10 mL·min^{-1}, the anisyl trifluoromethyl ketones **92a-b** were obtained in 65-69% isolated yield (Table 3, entries 1-2). The use of *o*-anisylmagnesium bromide **91c** furnished **92c** in a higher yield of 75%, presumably due to a chelating effect of the methoxy group to a further stabilization of the tetrahedral intermediate of type **93** (entry 3). Other electron-rich Grignard reagents (**91d-f**) were prepared by oxidative insertion and their reactions with **89a** provided several trifluoromethyl ketones **92d-f** in 62-69% yield (entries 4-6). Additionally, the heteroaryl ketone **92g** was prepared in 74% yield by reacting the heteroarylmagnesium bromide **91g** (prepared from 2-bromobenzothiophene *via* magnesium insertion reaction) with the ester at standard flow conditions (entry 7). A temperature screening for the reaction of indolylmagnesium bromide with **89a** resulted in optimum conditions for product formation of this substrate at 0 °C, giving ketone **92h** in 84% yield (entry 8). Finally, the organomagnesium reagent **91i** bearing a sensitive ester group (prepared *via* Br/Mg exchange using *i*PrMgCl·LiCl at –30 °C and stirring for 30 min) provided the polyfunctional ketone **92i** in 71% yield (entry 9). Due to the electron-withdrawing effect of the ester group in position 4 of the organomagnesium reagent, the tetrahedral intermediate **93i** was stabilized and allowed the use of a higher reaction temperature of 15 °C.



Scheme 23: Continuous flow setup for the preparation of trifluoromethyl ketones of type **92**.

[117] For batch procedures for trifluoromethyl ketones formation see: a) K. Funabiki, A. Hayakawa, T. Inuzuka, *Org. Biomol. Chem.* **2018**, *16*, 913-918. b) J. Wiedemann, T. Heiner, G. Mloston, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.* **1998**, *37*, 820-821.

Table 3: Product scope for the acylation of various organometallics of type **91** with ethyl trifluoroacetate (**89a**) in continuous flow.

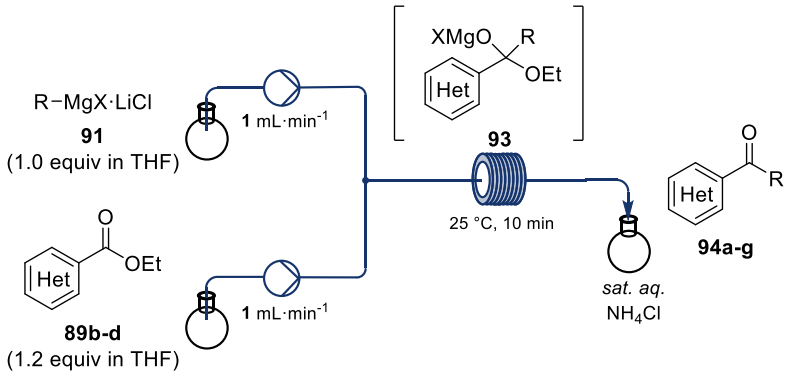
entry	nucleophile	product[a]
1	 **91a**[b]	 **92a**: 67%[c]
2	 **91b**[b]	 **92b**: 65%[c]
3	 **91c**[b]	 **92c**: 75%[c]
4	 **91d**[b]	 **92d**: 62%[c]
5	 **91e**[b]	 **92e**: 69%[c]
6	 **91f**[b]	 **92f**: 64%[c]
7	 **91g**[b]	 **92g**: 74%[c]
8	 **91h**[b]	 **92h**: 84%[d]
9	 **91i**[e]	 **92i**: 71%[f]

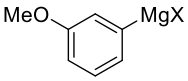
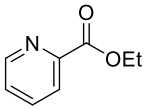
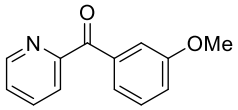
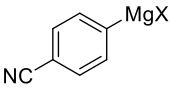
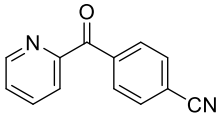
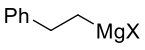
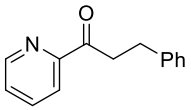
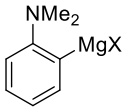
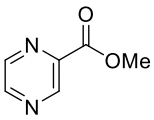
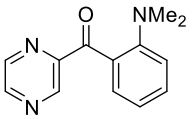
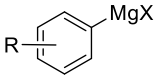
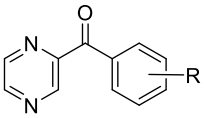
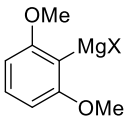
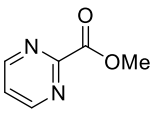
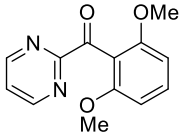
[a] Yield of analytically pure isolated product. [b] Organometallic species was prepared *via* oxidative insertion using Mg turnings and LiCl (1.2 equiv). [c] Reaction temperatur of –5 °C. [d] Reaction temperatuer of 0 °C. [e] Organometallic species was prepared *via* Mg/Br exchange at –30 °C for 30 min using *i*PrMgCl·LiCl (1.2 equiv). [f] Reaction temperature of 15 °C.

1.4 Preparation of Heteroaryl Ketones using *N*-Heterocyclic Esters in Continuous Flow

Noticing the positive impact of the methoxy group in *ortho*-position to the carbonyl group for stabilizing the tetrahedral intermediate of type **93** (see Table 3, entries 1-3), related commercially available esters were examined. First, we investigated the stabilizing coordinating effect of *N*-heterocyclic esters such as ethyl 2-picolinate (**89b**). This heterocycle and related structures (**89c-d**) have proven to be suitable starting materials. Due to the strong coordination of the heteroatom to the tetrahedral intermediate, this reaction proceeded in continuous flow at room temperature without the occurance of double addition (Table 4).

Table 4: Preparation of *N*-heteroaryl ketones of type **94** *via* acylation of Grignard reagents of type **91** with *N*-heterocyclic esters such as **89b-d** in continuous flow.



entry	nucleophile[a]	electrophile	product[b]
1	 **91b**	 **89b**	 **94a**: 75%
2	 **91j**	**89b**	 **94b**: 77%
3	 **91k**	**89b**	 **94c**: 63%[c]
4	 **91l**	 **89c**	 **94d**: 64%
5	 **91m**: R = 3-Cl	**89c**	 **94e**: 51%
6	**91j**: R = 4-CN	**89c**	**94f**: 55%
7	 **91n**	 **89d**	 **94g**: 60%[d]

[a] All Grignard reagents were prepared *via* oxidative insertion using Mg turnings and LiCl (1.2 equiv). [b] Yield of analytically pure isolated product. [c] Reaction temperature of 0 °C. [d] 40 min residence time

Thus, *m*-anisylmagnesium bromide **91b** and ethyl 2-picolinate (**89b**) were mixed in continuous flow (T-mixer: 0.5 mm i.d.) at room temperature (t = 10 min) using an overall flowrate of 2 mL·min^{-1}, providing the 2-pyridyl ketone **94a** in 75% yield (Table 4, entry 1). The use of the electron-poor *p*-cyanophenylmagnesium bromide **91j** furnished the corresponding ketone **94b** in 77% yield (entry 2). For ethyl trifluoroacetate as starting material (chapter B.1.3), alkylmagnesium reagents like **91k** were not suitable for a selective acylation as the tetrahedral intermediate of type **93** was destabilized and large amounts of double addition were obtained. Due to the strong coordinating and electron-withdrawing effects of the heterocycle, the alkylmagnesium bromide **91k** was a feasible substrate for this continuous flow procedure, leading to the alkylpyridyl ketone **94c** in 63% yield (entry 3). Additionally, other commercially available heterocyclic esters like methyl 2-pyrazinecarboxylate (**89c**) and methyl pyrimidine-2-carboxylate (**89d**) were investigated. Several organomagnesium reagents reacted well with the pyrazine ester **89c**, producing the desired heteroaryl ketones **94d-f** in 51-64% yield (entries 4-6). After extending the residence time to 40 min, the pyrimidine ester **89d** and the corresponding Grignard reagent furnished the pyrimidinyl ketone **94g** in 60% yield (entry 7). It is of note, that the use of ethyl nicotinate gave overaddition towards tertiary alcohols leading to the assumption, that the heteroatom was required next to the carbonyl group for a sufficient coordination.

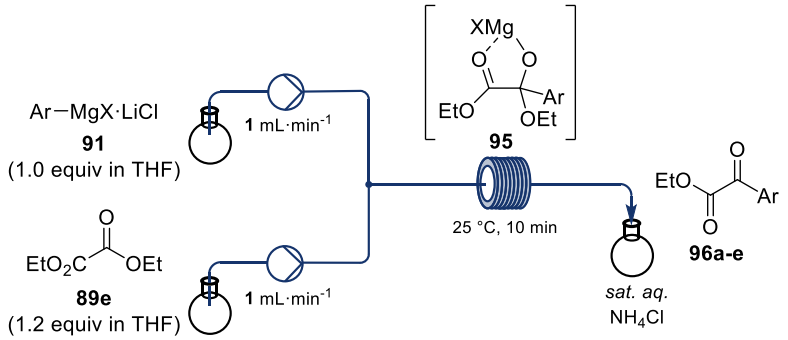
1.5 Preparation of α-Keto Esters using *N*-Heterocyclic Esters in Continuous Flow

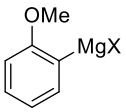
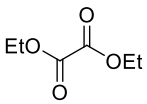
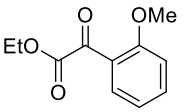
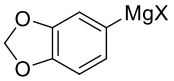
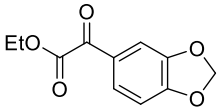
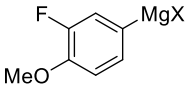
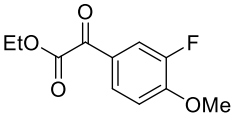
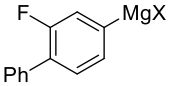
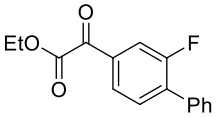
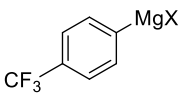
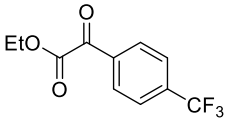
α-Keto esters are valuable building blocks for various types of reactions, for example for the preparation of α-amino acid derivatives[118] and as building blocks for the synthesis of different heterocycles[119]. Employing diethyl oxalate (**89e**) as electrophile to the previously described method in continuous flow provided these desired molecules in excellent yields in the absence of usually used transition metal catalysts.[120] Similar to *N*-heterocyclic esters, it was possible to perform these reactions at room temperature due to a highly stabilized tetrahedral intermediate **95**.

[118] X. Xiao, Y. Xie, C. Su, M. Liu, Y. Shi, *J. Am. Chem. Soc.* **2011**, *133*, 12914-12917.
[119] B. Efthekari-Sis, M. Zirak, *Chem. Rev.* **2015**, *115*, 151-264.
[120] a) F. Babudri, V. Fiandanese, G. Marchese, A. Punzi, *Tetrahedron* **1996**, *52*, 13513-13520; b) Z. Guo, H. Huang, Q. Fu, W. Hu, *Synlett* **2006**, 2486-2488; c) Y. Su, L. Zhang, N. Jiao, *Org. Lett.* **2011**, *13*, 2168-2171.

Thus, the electron-rich organomagnesium reagent **91c** and **91d** were mixed with diethyl oxalate (**89e**) at room temperature for 10 min using an overall flowrate of 2 mL·min^{-1}, providing the desired α-keto esters **96a-b** in 63-83% yield (Table 5, entries 1-2). The fluorine-containing Grignard reagents **91o** and **91p** produced the corresponding esters **96c-d** in 69-79% yield in continuous flow (entries 3-4). Additionally, an electron-poor trifluoromethyl-substituted organomagnesium reagent was successfully applied to this method, affording the expected ester **96e** in 71% yield (entry 5).

Table 5: Preparation of α-keto esters of type **95** *via* acylation of Grignard reagents of type **91** with diethyl oxalate (**89e**) in continuous flow.



Entry	Nucleophile[a]	Electrophile	Product[b]
1	 **91c**	 **89e**	 **96a**: 83%
2	 **91d**	**89e**	 **96b**: 63%
3	 **91o**	**89e**	 **96c**: 69%
4	 **91p**	**89e**	 **96d**: 79%
5	 **91q**	**89e**	 **96e**: 71%

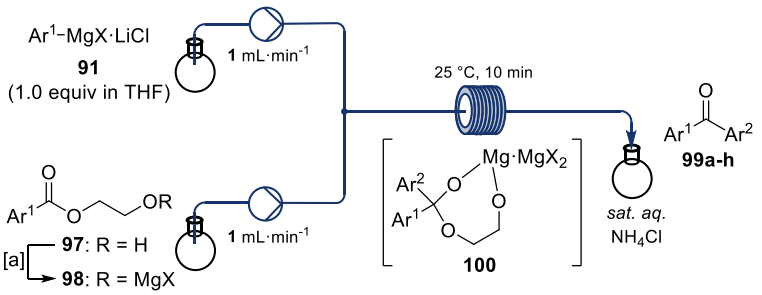
[a] All Grignard reagents were prepared *via* oxidative insertion using Mg turnings and LiCl (1.2 equiv). [b] Yield of analytically pure isolated product.

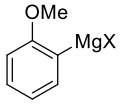
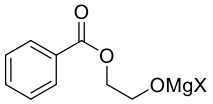
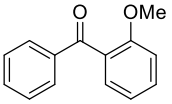
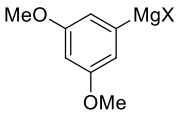
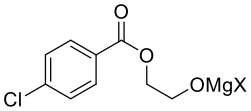
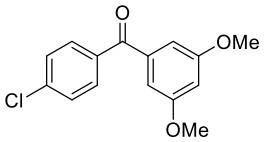
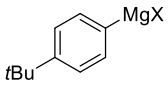
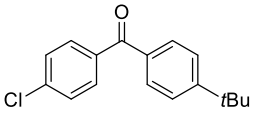
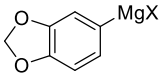
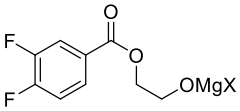
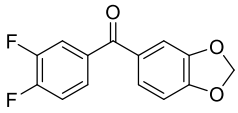
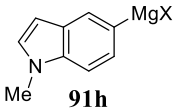
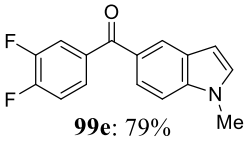
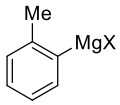
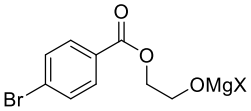
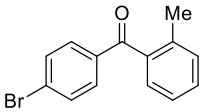
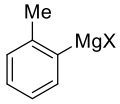
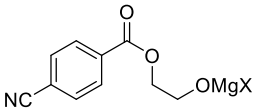
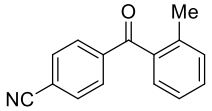
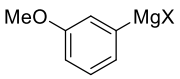
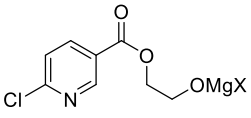
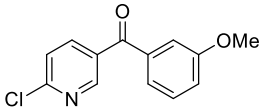
1.6 Preparation of Bis-Aryl Ketones using Aryl Esters bearing an Alkoxy Group

As previously reported (chapter B.1.4 and B.1.5), a coordinating group proved to be beneficial for the stabilization of the tetrahedral intermediate and hence for selective ketone formations. For ethyl (or methyl) esters, this restricts the utility of this method as the coordinating group has to stay in the product. Though, for generalizing the ketone formation, a coordinating group on the ester leaving group would enable the otherwise elusive formation of non-coordinating bis-aryl ketones. It was found, that 2-hydroxyethyl esters of type **97**, bearing an alkoxy group for the desired coordination, were suitable reagents. The alkoxy group was generated by stirring *i*PrMgCl·LiCl (1.05 equiv)[60,121] and the corresponding ethylene glycol monoester at 0 °C in THF for 5 min in batch. The electrophile of type **98**, starting from 3-hydroxy-1-phenylpropan-1-one (**97a**), was mixed with the Grignard reagent **91c** at room temperature using an overall flowrate of 2 mL·min^{-1}, furnishing selectively the bis-aryl ketone **99a** in 78% yield after a residence time of 10 min (Table 6, entry 1). Due to the strong coordinating effect of the alkoxy group in the tetrahedral intermediate of type **100**, this reaction proceeded cleanly towards the selective formation of ketones. For comparison, using the same continuous flow setup for the reaction of simple ethyl benzoate with the organomagnesium reagent **91c** provided large amounts of double addition and just 10% of the desired ketone. Furthermore, other alkoxybenzoates were readily prepared and used for this acylation protocol. The use of halogenated benzoate derivatives like **98b-d** gave the difluroro-substituted ketones **99b-c** in 63-79% yield (entries 2-3), 4-chloroaryl ketones **99d-e** in 62-74% yield (entries 4-5) and a bromo-substituted bis-aryl ketone **99f** in 81% yield (entry 6). The alkoxybenzoates **98e**, bearing a cyano-group in position 4, gave, after reaction with *o*-tolylmagnesium bromide **91s**, the functionalized bis-aryl ketone **99g** in 68% yield (entry 7). To prove the utility of these new electrophiles, the heterocyclic ketone **99h** was prepared in 63% *via* mixing of 3-pyridyl alkoxyester **98f** with a Grignard reagent in continuous flow (entry 8). As previously mentioned (chapter B.1.4), this 3-pyridyl ketones were not possible to obtain using the regular ethyl nicotinate.

[121] F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, *20*, 2288-2289.

Table 6: Preparation of bis-(hetero)aryl ketones of type **99** in continuous flow.



entry	nucleophile[b]	electrophile	product[c]
1	 **91c**	 **98a**	 **99a**: 78%
2	 **91r**	 **98b**	 **99b**: 62%
3	 **91s**	**98b**	 **99c**: 74%
4	 **91d**	 **98c**	 **99d**: 63%
5	 **91h**	**98c**	 **99e**: 79%
6	 **91t**	 **98d**	 **99f**: 81%
7	 **91t**	 **98e**	 **99g**: 68%
8	 **91b**	 **98f**	 **99h**: 63%

[a] Substrates of type **98** were generated by mixing *i*PrMgCl·LiCl (1.05 equiv) and the corresponding glycol monoesters of type **97** at 0 °C in THF for 5 min in batch. [b] All Grignard reagents were prepared *via* oxidative insertion using Mg turnings and LiCl (1.2 equiv). [c] Yield of analytically pure isolated product.

2. Selective Acylation of (Hetero)aryllithiums with Polyfunctional *N,N*-Dimethylamides in Continuous Flow and Addition of Organolithium Reagents to Tetramethylurea

2.1 Introduction

The preparation of highly functionalized alkyl and aryl ketones is one of the most important tasks in pharmaceutical, agrochemical and medicinal chemistry.[122] Therefore, numerous different strategies were intensively investigated over the last decades.[110a,123] One of the most common procedures is the acylation of organometallic reagents with carbonyl derivatives, for example Weinreb amides[109a,124], 2-pyridyl amides[125], thiopyridyl esters[126], morpholine amides[127] and *N,N*-dimethylamides[128].

Nevertheless, due to several drawbacks of these methods (see chapter B.1.1), an acylation reaction with readily available, non-toxic starting materials with convenient reaction conditions (e. g. temperature, time, solvent system, scalability) would be of interest. Recently, the field of continuous flow chemistry enabled new approaches in various synthetic fields.[112,129]

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[122] a) J. Otera, *Modern Carbonyl Chemistry* Wiley-VCH, Weinheim, **2000**. b) P. Vogel in: *Science of Synthesis*, Vol. 26 (Ed. J. Cossy), Thieme, New York, **2005**, pp. 13-18; c) R. Luisi, V. Capriati, *Lithium Compounds in Organic Synthesis*, Wiley-VCH, Weinheim, **2014**; d) V. Pace, W. Holzer, B. Olofsson, *Adv. Synth. Catal*. **2014**, *356*, 3697-3736.

[123] a) M. Giannerini, C. Vila, V. Hornillos, B. L. Feringa, *Chem. Commun.* **2016**, *52*, 1206-1209; b) J. de Jong, D. Heijnen, H. Helbert, B. L. Feringa, *Chem. Commun.* **2019**, *55*, 2908-2911; c) P. Lei, G. Li, Y. Ling, J. An, S. P. Nolan, M. Szostak, *Synthesis* **2021**, *53*, 682-687; d) A. T. Wolters, V. Hornillos, D. Heijnen, M. Giannerini, B. L. Feringa, *ACS Catal.* **2016**, *6*, 2622-2625; e) C. Chen, P. Liu, M. Luo, X. Zeng, *ACS Catal.* **2018**, *8*, 5864-5868; f) R. Ruzi, K. Liu, C. Zhu, J. Xie, *Nat. Commun.* **2020**, *11*, 3312.

[124] G. Li, M. Szostak, *Org. Biomol. Chem*. **2020**, *18*, 3827-3831.

[125] D. L. Comins, J. D. Brown, *Tetrahedron Lett.* **1984**, *25*, 3297-3300.

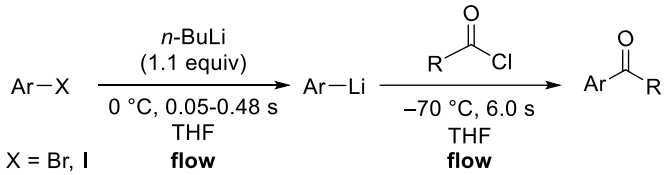
[126] T. Mukaiyama, M. Araki, H. Takei, *J. Am. Chem. Soc.* **1973**, *95*, 4763-4765.

[127] a) R. Martin, P. Romea, C. Tey, F. Urpi, J. Vilarrasa, *Synlett* **1997**, 1414-1416; b) K.-W. Lin, C.-H. Tsai, I.-L. Hsieh, T.-H. Yan, *Org. Lett.* **2008**, *10*, 1927-1930; c) Y.-H. Chen, S. Grassl, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 1108-1111.

[128] a) D. C. Owsley, J. M. Nelke, J. J. Bloomfield, *J. Org. Chem.* **1973**, *38*, 901-903; b) G. A. Olah, G. K. S. Prakash, M. Arvanaghi, *Synthesis* **1984**, 228-230; c) Y. Honda, A. Ori, G. Tsuchihashi, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1027-1036; d) M. Buswell, I. Fleming, U. Ghosh, S. Mack, M. Russell, B. P. Clark, *Org. Biomol. Chem*. **2004**, *2*, 3006-3017; e) S. Collins, Y. Hong, G. J. Hoover, J. R. Veit, *J. Org. Chem.* **1990**, *55*, 3565-3568; h) A. D. Benischke, L. Anthore-Dalion, F. Kohl, P. Knochel, *Chem. Eur. J.* **2018**, *24*, 11103-11109; j) S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti, C. Prandi, *Chem. Eur. J.* **2021**, *27*, 2868-2874.

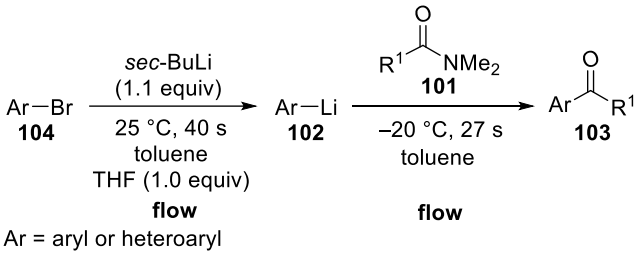
[129] a) M. G. Russell, T. F. Jamison, *Angew. Chem. Int. Ed.* 2019, *58*, 7678-7681; b) W. Shu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2012**, *51*, 5355-5358; c) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; d) C. Battilocchio, F. Bosica, S. M. Roew, B. L. Abreu, E. Godineau, M. Lehmann, S. V. Ley, *Org. Process Res. Dev.* **2017**, *21*, 1588-1594; e) C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4945-4948; f) H. C. De Angelis, L. Degennaro, P. Celestini, R. Luisi, O. Kappe, *J. Flow. Chem.* **2018**, *8*, 109–116; g) X.-J. Wei, I. Abdiaj, C. Sambiagio, C. Li, E. Zysman-Colman, J. Alcazar, T. Noël, *Angew. Chem. Int. Ed.* **2019**, *58*, 13030-13034.

Due to a more accurate control of the reaction temperature, the residence times and the stoichiometry of the reactants, especially the field of organometallic chemistry benefits from a continuous flow setup.[15,89,130] Thus, Yoshida and Nagaki reported a new method towards functionalized ketones, using extremely fast micro-mixing of acyl chlorides with lithium reagents (Scheme 24).[131]



Scheme 24: Ketone preparation *via* extremely fast micro-mixing of lithium reagents with acyl chlorides (Yoshida *et. al.*).

In this work, readily prepared *N*,*N*-dimethylamides[132] of type **101** were used as effective reagents for the acylation of various (hetero)aryllithiums of type **102** in toluene. Implementing a continuous flow setup led to a large range of functionalized ketones of type **103** at convenient temperatures and short residence times (Scheme 25).



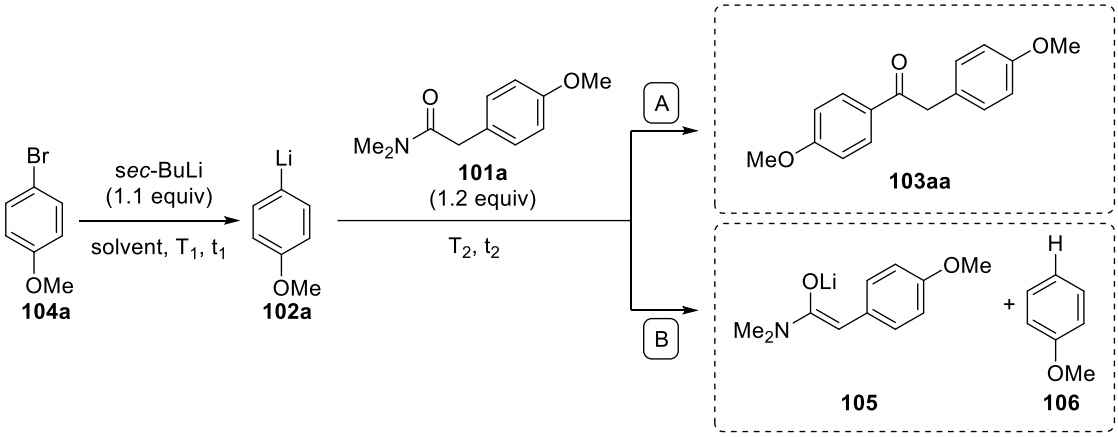
Scheme 25: Acylation of (hetero)aryllithiums of type **102** (prepared *via* Br/Li exchange in continuous flow) with *N*,*N*-dimethylamides of type **101**.

[130] a) M. A. Ganiek, M. V. Ivanova, B. Martin, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 17249-17253; b) B. Heinz, D. Djukanovic, P. Filipponi, B. Martin, K. Karaghiosoff, P. Knochel, *Chem Sci.* **2021**, *12*, 6143-6147.
[131] a) A. Nagaki, K. Sasatsuki, S. Ishiuchi, N. Miuchi, M. Takumi, J.-I. Yoshida, *Chem. Eur. J.* **2019**, *25*, 4946-4950; b) S.-Y. Moon, S.-H. Jung, U. B. Kim, W.-S. Kim, *RSC Adv.* **2015**, *5*, 79385-79390.
[132] For the preparation procedure for *N*,*N*-dimethylamides, see the Experimental Part (chapter C.3.2)

2.2 Optimization of the Reaction Conditions

In preliminary experiments, we investigated the reaction of aryllithium reagents of type **102** with benzylic *N*,*N*-dimethylamides of type **101a**. Thus, we mixed 4-bromoanisole (**104a**) with *sec*-BuLi in different solvents, leading to the organolithium species **102a**. Addition of the benzylic amide **101a** gave two possible reaction pathways: A) The aryllithium could add to the amide, providing selectively the desired benzylic ketone **103aa** after aqueous workup. B) The deprotonation of the amide by the aryllithium led to enolization side-reaction, resulting in the starting material **101a** (after aqueous quench of the lithium enolate **105**) and anisole (**106**) as a result of the deprotonation of the benzylic position (Table 7).

Table 7: Solvent screening for the addition of ArLi **102a** to the benzylic amide **101a**.



entry	setup	solvent	T_1 [°C]	t_1 [min]	T_2 [°C]	t_2 [min]	conv. **104a** [GC-%]	yield **103aa** [GC-%]	yield **105** [GC-%]
1	batch	THF	25	1	–20	5	80	33	40
2[a]	batch	THF	–20	5	–20	5	88	35	38
3	batch	THF	–78	30	–78	30	>99	45	28
4	batch	toluene[b]	25	0.67	–20	5	97	59	18
5	flow	toluene[b]	25	0.67	–20	0.5	>99	60	17
6	flow	toluene[b]	25	2	–40	0.5	>99	59	20

[a] Reaction was quenched with benzaldehyde instead of *sat. aq.* NH_4Cl to prove that **106** is formed during the reaction and not when quenched. [b] 1.0 Equiv of THF was added.

Performing the reaction in THF at –20 °C gave approximately 1:1 mixtures of pathways A:B (Table 7, entries 1-2). However, the ratio was shifted towards the ketone formation at cryogenic temperatures (entry 3). In contrast, using the solvent system toluene:THF (1 equiv) at –20 °C led more selectively to the formation of the desired ketone **103aa** in batch and continuous flow (entries 4-5). Due to the relatively high acidity of the benzylic proton, the enolization reaction could not be completely avoided for this compound in toluene but was still less present than in THF.

With this results in hand, the preparation of the aryllithium **102b** was optimized. The goal was to develop a fast Br/Li exchange at ambient temperatures resulting in a stable aryllithium intermediate. Thus, we explored the Br/Li exchange of 1-bromo-4-methylthiobenzene (**104b**) with *sec*-Buli in THF and toluene by quenching the freshly prepared lithium species **102b** with 4-fluorobenzaldehyde (**107**).

First, **104b** was treated with *sec*-BuLi (1.1 equiv) in THF at 25 °C. Even though a high conversion was observed, only 24-27% of the expected alcohol **108** were obtained after quenching with the electrophile showing the poor stability of the metal species in THF at ambient temperatures (Table 8, entries 1-2). Switching to the less polar solvent toluene[133,134,135] afforded the alcohol **108** in higher yields, but the metal exchange required long reaction times (up to 2 h) leading to sluggish reactions with already decomposed lithium species (entries 3-5). In balance, the addition of 1.0 equiv of THF to the reaction mixture in toluene provided a fast Br/Li exchange with *sec*-BuLi within 1 min at 25 °C, furnishing the desired alcohol **108** in

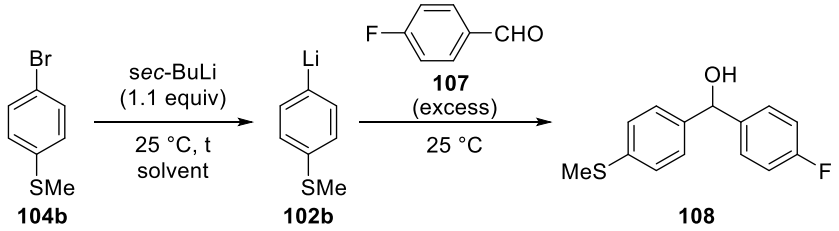
[133] a) M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 12898-12902; b) A. Desaintjean, T. Haupt, L. J. Bole, N. R. Judge, E. Hevia, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *60*, 1513-1518; c) F. H. Lutter, L. Grokenberger, L. A. Perego, D. Broggini, S. Lemaire, S. Wagschal, P. Knochel, *Nature Commun.* **2020**, *11*, 1-8.

[134] a) Solvent Recovery Handbook (Ed.: I. M. Smallwood), Blackwell Science Ltd., Oxford, **2002**; b) M. Sassian, D. Panov, A. Tuulmets, *Appl. Organometal. Chem.* **2002**, *16*, 525-529; c) L. Delhaye, A. Ceccato, P. Jacobs, C. Köttgen, A. Merschaert, *Org. Process Res. Dev.* **2007**, *11*, 160; d) J. Garcia-Alvarez, E. Hevia, V. Capriati, *Eur. J. Org. Chem.* **2015**, *31*, 6779-6799.

[135] For the preparation of various aryllithiums in toluene, see: a) W. J. Trepka, R. J. J. Sonnenfeld, *Organomet. Chem.* **1969**, *16*, 317–320; b) D. W. Slocum, D. Reed, F. Jackson, C. Friesen, *J. Organomet. Chem.* **1996**, *512*, 265–267; c) D. W. Slocum, P. Dietzel, *Tetrahedron Lett.* **1999**, *40*, 1823–1826; d) M. P. R. Spee, J. Boersma, M. D. Meijer, M. Q. Slagt, G. van Koten, J. W. Geus, *J. Org. Chem.* **2001**, *66*, 1647–1656, e) D. W. Slocum, A. Carroll, P. Dietzel, S. Eilerman, J. P. Culver, B. McClure, S. Brown, R. W. Holman, *Tetrahedron Lett.* **2006**, *47*, 865–868; f) D. W. Slocum, D. Kusmic, J. C. Raber, T. K. Reinscheld, P. E. Whitley, *Tetrahedron Lett.* **2010**, *51*, 4793–4796; g) A. Hernan-Gomez, E. Herd, E. Hevia, A. Kennedy, P. Knochel, K. Kozinowski, S. M. Manolikakes R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706–2710; h) Z. Zhou, A. Wakamiya T. Kushida, S. Yamaguchi, *J. Am. Chem. Soc.* **2012**, *134*, 4529–4532; i) J. E. Borger, A. W. Ehlers, M. Lutz, J. C. Slootweg, K. Lammertsma, *Angew. Chem. Int. Ed.* **2014**, *53*, 12836–12839; j) H. Guyon, A. Boussonniere, A.-S.; Castanet, *J. Org. Chem.* **2017**, *82*, 4949–4957; k) N. Ando, H. Soutome, S. Yamaguchi, *Chem. Sci.* **2019**, *10*, 7816–7821; l) T. T. T. Nguyen, H. Guyon, K. P. P. Nguyen, A. Boussonniere, J. Mortier, A.-S. Castanet, *Eur. J. Org. Chem.* **2020**, 3829–3833.

95% calibrated GC-yield (entry 6). Longer reaction times in this solvent mixture led to lower yields due to decomposition of the Li-species **102b** (entries 7-8). Finally, the performance of the reaction at 25 °C in continuous flow led to a quantitative formation of the desired product within 1 min after quenching with the aldehyde **107** (entry 9). Due to the low stability of the lithium species, the "on-demand" preparation in continuous flow was of benefit and enabled otherwise unmanageable scale-ups. Using the less reactive exchange reagent *n*-BuLi led to a slow Br/Li exchange in this solvent mixture, which was incompatible with the low stability of the Li-species.[136]

Table 8: Optimization of the aryllithium generation in different solvent systems.

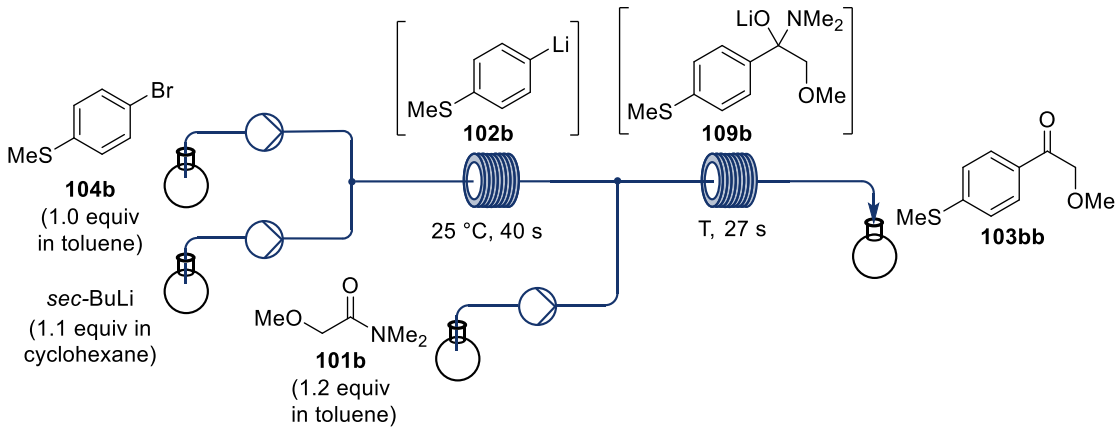


entry	setup	solvent	t_2 [min]	conversion **104b** [GC-%]	yield **108** [GC-%]
1	batch	THF	1	90	24
2	batch	THF	30	93	27
3	batch	toluene	1	18	8
4	batch	toluene	30	75	49
5	batch	toluene	120	94	57
6	batch	toluene[a]	1	96	95
7	batch	toluene[a]	10	98	85
8	batch	toluene[a]	30	>99	60
9	flow	toluene[a]	1	>99	99

[a] 1.0 equiv of THF was added which corresponded to a 50:1 toluene:THF mixture.

[136] For the optimization of aryllithium generation for other aryl bromides, see the Experimental Part (chapter C.3.1)

Table 9: Optimization of the acylation temperature in continuous flow.



entry	T [°C]	conversion **104b** [GC-%]	yield **103bb** [GC-%]
1	25	>99	50
2	0	>99	67
3	–20	>99	82
4	–40	>99	84

Performing the acylation of the aryllithium **102b** with the *N*,*N*-dimethylamide **101b** in continuous flow at 25 °C or 0 °C led only to 50 or 67% yield of the desired ketone **103bb** due to increased enolization side reactions (Table 9, entries 1-2). However, performing the reaction at –20 °C led to an excellent yield (82%, entry 3). Lowering the acylation temperature to –40 °C did not provide a noteworthy advantage (entry 5).

2.3 Preparation of Various Functionalized Ketones starting from Enolizable *N*,*N*-Dimethylamides and Readily Prepared Aryllithiums

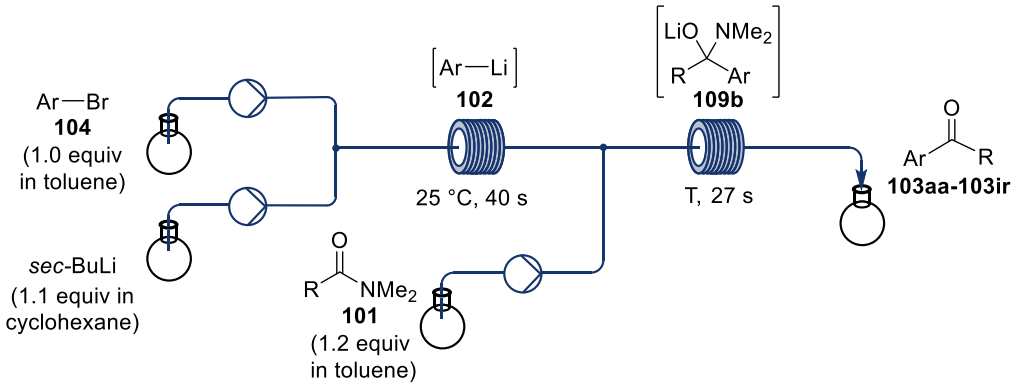
Having the optimized conditions in hand, a broad range of functionalized ketones was prepared using a continuous flow setup. Thus, the aryl bromide **104b** (0.25 M in toluene with 1.0 equiv of THF) was mixed with *sec*-BuLi (1.1 equiv, ~1.35 M in *n*-hexane) at 25 °C for 40 s, producing quantitatively the corresponding aryllithium species **102b**. The reaction stream was precooled to –20 °C for 10 s *via* an interconnected reactor and then mixed with the *N*,*N*-dimethylamide **101b** (1.2 equiv, 0.3 M in toluene). This acylation reaction step was performed at –20 °C for

27 s and afforded, *via* the formation of the tetrahedral intermediate **109b** and subsequent quenching with *sat. aq.* NH_4Cl, the desired ketone **103bb** in 82% yield. Collecting the reaction mixture for a longer time (390 s instead of 30 s) gave a comparable yield with 78%, demonstrating the possibility of scaling up these reactions with unstable intermediates in continuous flow (Table 10, entry 1).

This kind of reactions proved to be general and various ketones were prepared following this procedure. Functionalized aryllithiums like **102c-f** were readily prepared in a first continuous flow step and gave, after acylation with **101b**, the corresponding ketones **103bc-bf** in 75-85% yield (entries 2-5). Furthermore, the heterocyclic lithium species **102g-h** provided the desired ketones **103bg** and **103bh** in 82 and 89% yield (entries 6-7). Also, fluoro-substituted aryl bromides were suitable substrates and generated, after Br/Li exchange and acylation with 2,2-diethoxy-*N*,*N*-dimethylacetamide (**101c**), the ketones **101ci-ck** in 74-78% yield (entries 8-10). The use of α-monofluoro-, difluoro- or monochloro-substituted amides **101d-f** led to the expected ketones **103dh-dk**, **103ea-el** and **103fg** in 48-78% yield (entries 11-18). Interestingly, no enolization was observed despite the presence of protons in the α-position to the amide group. Other *N*,*N*-dimethylamides such as **101g**, **101h** and **101i** containing various functional groups, were prepared and used in the continuous flow procedure, furnishing the aromatic and heterocyclic ketones **103gg-gn**, **103ha** and **103io** in 63-81% isolated yield (entries 19-23). As described earlier (chapter B.2.2), benzylic amides benefited from the use of toluene as solvent (with 1.0 equiv of THF for promoting the exchange) and the aryl benzyl ketones **103aa-ab** were obtained in 51-53% yield (entries 24-25) (ca. 25% of enolization was noticed in the present solvent system, whereas over 70% enolization was found in pure THF). The [1.1.1]-bicyclopentane moiety was also tolerated and gave, by mixing [1.1.1]-bicyclopentane carboxamide **101j** with the aryllithiums **102p** and **102q**, the bicyclopent-1-yl ketones **103jp** and **103jq** in 59-70% isolated yield (entries 26-27).[137] Finally, alkyl lithium species such as *n*-BuLi generated the dialkyl ketone **103i** *via* a 2-pump system in 74% yield (entry 28).

[137] For the synthesis of [1.1.1]-bicyclopentane derivatives using metalorganic chemistry, see: a) J. Kanazawa, K. Maeda, M. Uchiyama, *J. Am. Chem. Soc.* 2017, *139*, 17791–17794; b) I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem. Int. Ed.* 2017, *56*, 12774–12777; c) K. Schwärzer, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* 2020, *59*, 20235–20241; d) M. Kondo, T. Ichikawa, T. Shimokawa, Y. Nagashima, K. Miyamoto, M. Uchiyama, *Angew. Chem. Int. Ed.* 2020, *59*, 1970–1974.

Table 10: A continuous flow acylation of *in situ* generated organolithiums **102** with various amides **101**.



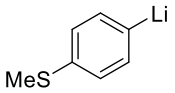
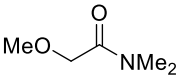
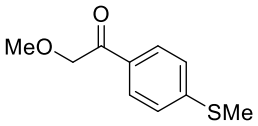
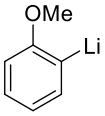
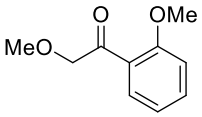
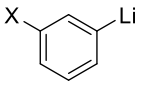
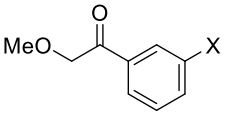
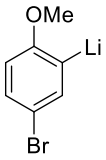
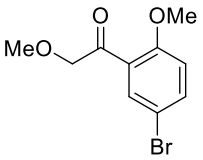
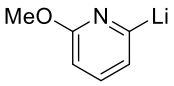
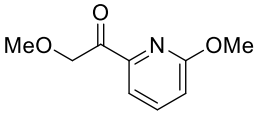
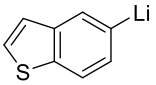
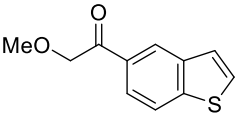
entry	nucleophile	electrophile	product[a]
1	 **102b**	 **101b**	 **103bb**: 82% (0.63 mmol) scale-up: 78% (8.15 mmol)
2	 **102c**	**101b**	 **103bc**: 75%
3	 **102d**: X = Cl	**101b**	 **103bd**: 81%
4	**102e**: X = Br	**101b**	**103be**: 85%
5	 **102f**	**101b**	 **103bf**: 77%
6	 **102g**	**101b**	 **103bg**: 82%
7	 **102h**	**101b**	 **103bh**: 89%

Table 10: continued.

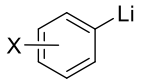
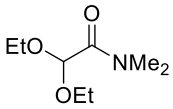
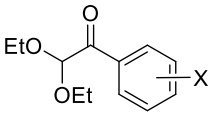
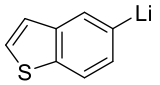
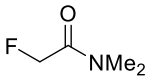
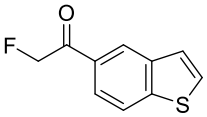
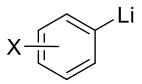
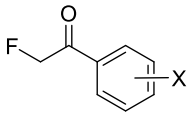
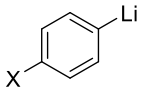
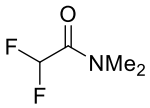
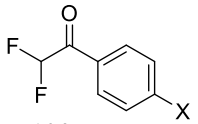
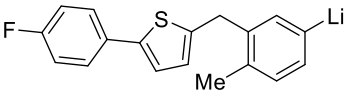
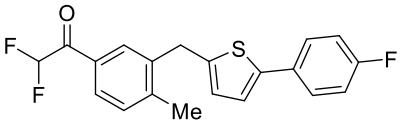
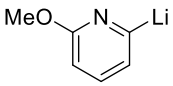
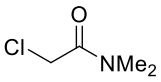
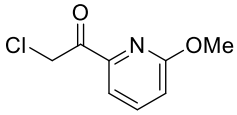
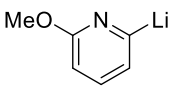
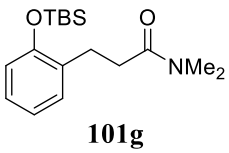
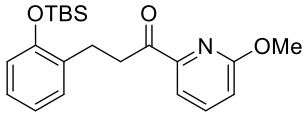
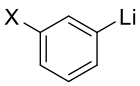
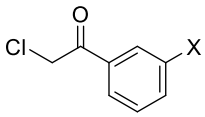
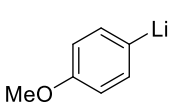
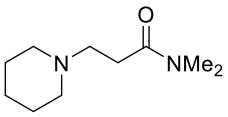
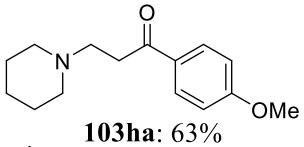
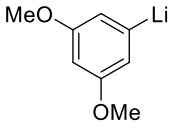
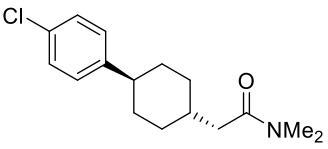
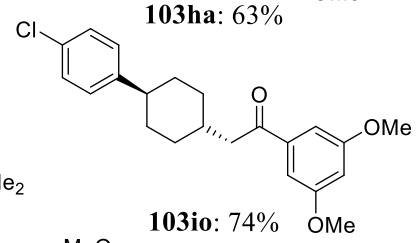
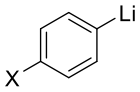
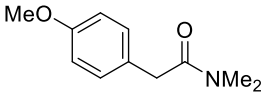
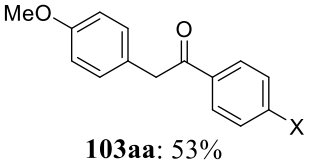
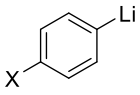
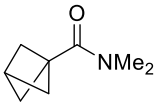
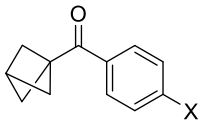
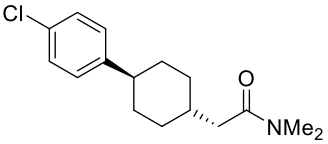
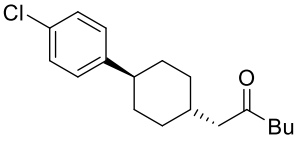
entry	nucleophile	electrophile	product[a]
			
8	**102i**: X = 4-F	**101c**	**103ci**: 74%
9	**102j**: X = 3-CF_3	**101c**	**103cj**: 75%
10	**102k**: X = 4-OCF_3	**101c**	**103ck**: 78%
			
11	**102h**	**101d**	**103dh**: 66%
			
12	**102i**: X = 4-F	**101d**	**103di**: 52%
13	**102j**: X = 3-CF_3	**101d**	**103dj**: 48%
14	**102k**: X = 4-OCF_3	**101d**	**103dk**: 65%
			
15	**102a**: X = OMe	**101e**	**103ea**: 74%
16	**102b**: X = SMe	**101e**	**10eb**: 69%
			
17	**102l**	**101e**	**103el**: 75%
			
18	**102g**	**101f**	**103fg**: 78%
			
19	**102g**	**101g**	**103gg**: 69%
			
20	**102m**: X = $CH(OEt)_2$	**101g**	**103gm**: 81%
21	**102n**: X = F	**101g**	**103gn**: 78%

Table 10: continued.

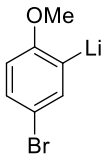
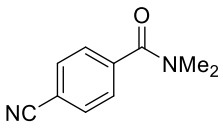
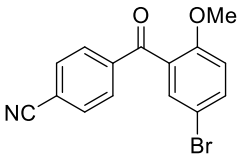
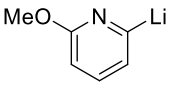
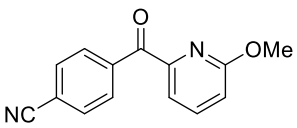
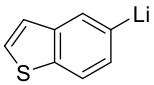
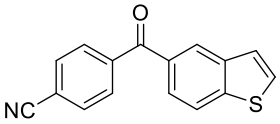
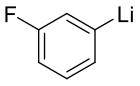
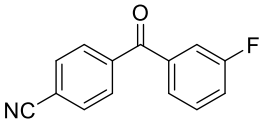
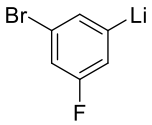
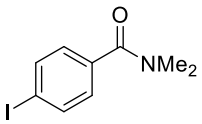
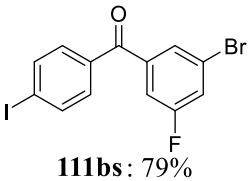
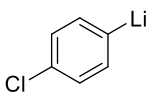
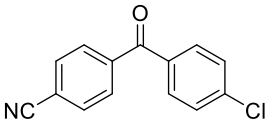
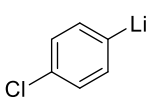
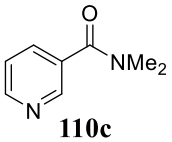
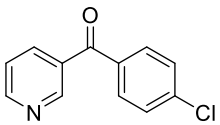
entry	nucleophile	electrophile	product[a]
22	 **102a**	 **101h**	 **103ha**: 63%
23	 **102o**	 **101i**	 **103io**: 74%
24	 **102a**: X = OMe	 **101a**	 **103aa**: 53%
25	**102b**: X = SMe	**101a**	**103ab**: 51%
26	 **102p**: X = OBu	 **101j**	 **103jp**: 59%
27	**102q**: X = Cl	**101j**	**103jq**: 70%
28	*n*-BuLi	 **101i**	 **103i**: 74%

[a] Yield of analytically pure isolated product.

2.4 Preparation of Functionalized Benzophenone Derivatives

Additionally, the preparation of functionalized benzophenone derivatives starting from *N*,*N*-dimethylbenzamides of type **110** was investigated.

Table 11: A continuous flow preparation of functionalized benzophenone derivatives of type **111** using *N*,*N*-dimethylbenzamides of type **110** and *in situ* prepared organolithium species **102**.

entry	nucleophile	electrophile	product[a]
1	 **102f**	 **110a**	 **111af**: 73%
2	 **102g**	**110a**	 **111ag**: 79%
3	 **102h**	**110a**	 **111ah**: 61%
4	 **102r**	**110a**	 **111ar**: 64%
5	 **102s**	 **110b**	 **111bs**: 79%
6	 **102q**	**110b**	 **111bq**: 63%
7	 **102q**	 **110c**	 **111cq**: 58%

[a] Yield of analytically pure isolated product.

Thus, *N*,*N*-dimethyl-4-cyanobenzamide (**110a**) was readily prepared[138] and mixed with the (hetero)aryllithiums **102f-r** in the previously described procedure. Tolerating the sensitive nitrile group, various substituted benzophenones **111af-ar** were prepared in 61-79% isolated yield (Table 11, entries 1-4). Further, no competitive I/Li exchange was observed when using *N*,*N*-dimethyl-4-iodobenzamide (**110b**), leading to the desired iodo-substituted benzophenone derivatives **111bq-bs** in 63-79% yield (entries 5-6). Using the usual reaction sequence in continuous flow, commercially available *N*,*N*-diethylnicotinamide (**110c**) was successfully converted into the corresponding heterocyclic ketone **111cq** in 58% yield (entry 7).

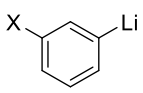
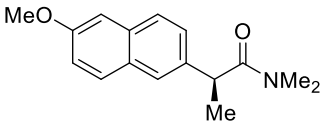
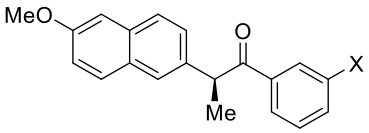
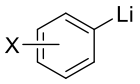
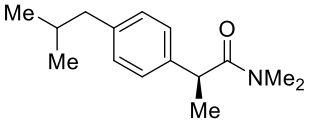
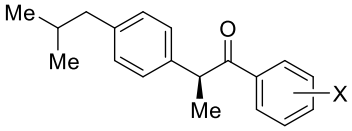
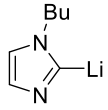
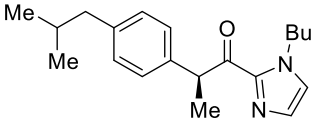
2.5 Preparation of Chiral Naproxen and Ibuprofen Ketone Derivatives

In order to demonstrate the absence of enolization side reactions, racemizable α-chiral ketones were prepared with this new acylation procedure in continuous flow. To show the utility of the procedure, α-chiral ketones derivatives of the non-steroidal anti-inflammatory drugs (NSAIDs) were targeted. Those drug analogues are of interest in the pharmaceutical industry in the pursuit of antivirals[139] and to handle gastrointestinal side-effects such as ulceration.[140]

Thus, the chiral *N*,*N*-dimethylamide derivative of naproxen (**112a**, 99% *ee*) was mixed with various *in situ* prepared aryllithiums of type **102** under standard continuous flow conditions (Table 12) and the chiral ketones **113ad-an** were obtained in 65-88% yield (99% *ee*, entries 1-3).[141] The chiral *N*,*N*-dimethylamide derivative of ibuprofen **112b** was prepared analogously, leading to the α-chiral ketones **113bi-bt** in 75-89% yield with complete retention of chirality (98-99% *ee*, entries 4-6). It is of note, that the lithium species **102t** was prepared by direct metalation instead of Br/Li exchange, mixing a solution of 1-butyl-1*H*-imidazole with TMEDA (1.0 equiv) in toluene and a solution of *sec*-BuLi (1.2 equiv) in cyclohexane in continuous flow at 25 °C with a retention time of 40 s followed by the standard acylation step.

[138] For further information, see the Experimental Section (chapter C.3.1)
[139] S. Dilly, A. F. Fotso, N. Lejal, G. Zedda, M. Chebbo, F. Rahman, S. Companys, H. C. Betrand, J. Vidic, M. Noiray, M.-C. Alessi, B. Tarus, S. Quideau, B. Riteau, A. Slama-Schowk, *J. Med. Chem.* **2018**, *61*, 7202-7217.
[140] M. Amir, H. Kumar, S. A. Javed, *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 577-585.
[141] a) S. Pal, P. Bindu, P. R. Venna, P. K. Dubey, *Lett. Org. Chem.* **2007**, *4*, 292–295; b) K. Kanomata, Y. Toda, Y. Shibata, M. Yamanaka, S. Tsuzuki, I. D. Gridnev, M. Terada, *Chem. Sci.* **2014**, *5*, 3515; c) T. Verheyen, L. van Turnhout, J. K, Vandavasi, E. S. Isbrandt, W. M. De Borggraeve, S. G. Newman, *J. Am. Chem. Soc.* **2019**, *141*, 6869–6874.

Table 12: Preparation of chiral naproxen and ibuprofen ketone derivatives of type **113** by the acylation of (hetero)aryllithiums of type **102** with the corresponding *N*,*N*-dimethylamides **112**.

entry	nucleophile	electrophile	product[a]
			
1	**102e**: X = Br	**112a**	**113ae**: 75%; 99% *ee*
2	**102m**: X = $CH(OEt)_2$	**112a**	**113am**: 65%, 99% *ee*
3	**102r**: X = F	**112a**	**113ar**: 88%, 99% *ee*
			
4	**102i**: X = 4-F	**112b**	**113bi**: 80%; 99% *ee*
5	**102o**: X = 3,5-$(OMe)_2$	**112b**	**113bo**: 75%; 99% *ee*
			
6	**102t**	**112b**	**113bt**: 89%; 98% *ee*

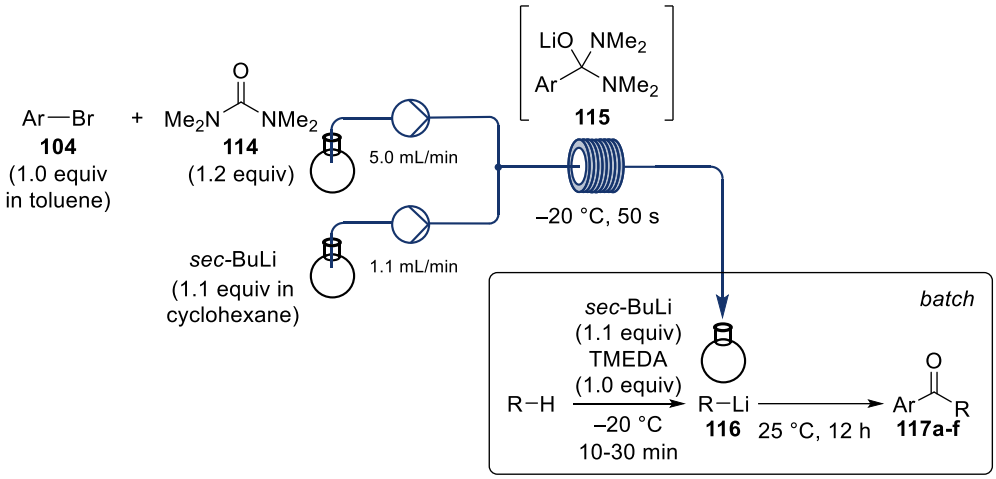
[a] Yield of analytically pure isolated product.

2.6 Preparation of Unsymmetrical Ketones by Stepwise Addition of Organolithium Reagents to Tetramethylurea

Finally, we envisioned that the previously developed acylation method could be extended to a semi-batch telescoped procedure for the preparation of unsymmetrical ketones by stepwise addition of various organolithium reagents to 1,1,3,3-tetramethylurea (**114**, TMU). Recently, Hattan and Jamison described the preparation of unsymmetrical ketones in continuous flow by double addition of organometallic reagents to carbon dioxide.[142] As the save handling of gases requires special flow equipment, the use of liquid TMU as C1 building block could be of benefit. In preliminary experiments[143], it was observed that TMU, in contrast to *N*,*N*-dimethylamides, play a similar activator role for the Br/Li exchange as THF for the fast formation of the lithium species. This discovery enabled the use of a Barbier-type flow reaction setup.

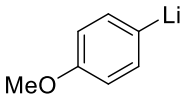
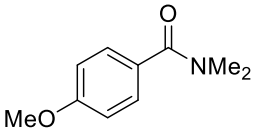
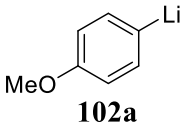
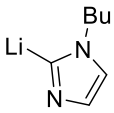
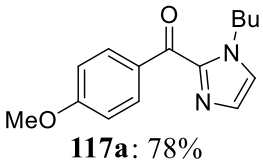
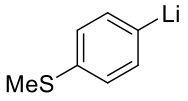
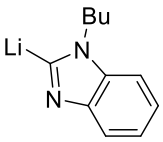
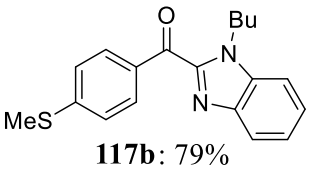
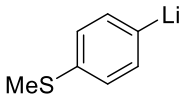
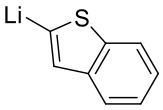
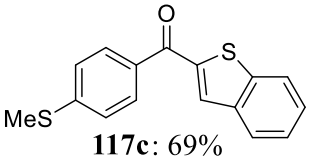
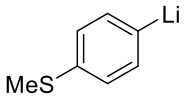
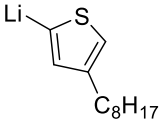
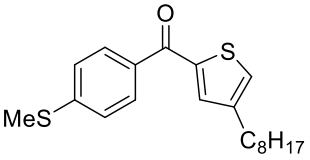
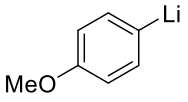
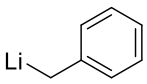
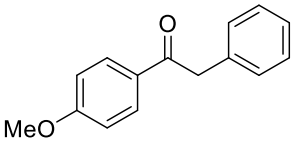
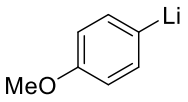
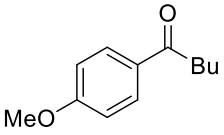
[142] a) J. Wu, X. Yang, Z. He, X. Mao, T. A. Hatton, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *53*, 8416-8420; b) H. Seo, L. V. Nguyen, T. F. Jamison, *Adv. Synth. Catal.* **2018**, *361*, 247-261.
[143] For further information, see the Experimental Part (chapter C.3.1).

Thus, the treatment of a mixture of aryl bromides of type **104** and TMU (**114**) in toluene with *sec*-BuLi at –20 °C for 50 s in continuous flow provided the tetrahedral intermediates of type **115** (Scheme 26). Quenching the reaction mixture with *sat. aq.* NH_4Cl in batch produced the *N*,*N*-dimethylamide **101j** in 83% yield (Table 13, entry 1). However, injecting the reaction stream into a freshly prepared Li-species of type **116** led to the desired unsymmetrical ketones of type **117**. These organolithiums were conveniently prepared in batch *via* directed metalation by adding *sec*-BuLi (1.1 equiv) to a mixture of the starting material and TMEDA (1.0 equiv) in toluene at –20 °C (10-30 min). The addition of the second Li-species took up to 12 h at 25 °C, presumably due to a highly stable intermediate **115**. Using various heterocyclic starting materials for the metalations towards the organolithiums **116a-d**, the highly functionalized bis-(hetero)aryl ketones **117a-d** were prepared in 69-79% yield (entries 2-5). Also, the benzylic lithium species **116e** was a suitable substrate and gave the ketone **117e** in 77% yield (entry 6). Finally, pouring the reaction mixture into commercially available *n*-BuLi gave the unsymmetrical ketone **117f** in 70% yield, demonstrating the applicability of alkyl lithiums (entry 7).



Scheme 26: Continuous flow reaction set-up for the preparation of unsymmetrical ketones of type **117** by the stepwise acylation of TMU (**114**) with different lithium organometallics.

Table 13: Preparation of unsymmetrical ketones of type **117** by the stepwise acylation of TMU with different lithium organometallics.

entry	nucleophile 1	nucleophile 2	product[a]
1	 **102a**	—	 **101j**: 83%
2	 **102a**	 **116a**	 **117a**: 78%
3	 **102b**	 **116b**	 **117b**: 79%
4	 **102b**	 **116c**	 **117c**: 69%
5	 **102b**	 **116d**	 **117d**: 70%
6	 **102a**	 **116e**	 **117e**: 83%
7	 **102a**	*n*-BuLi	 **117f**: 70%

[a] Yield of analytically pure isolated product.

3. Regioselective Double Functionalizations of Pyridines *via* 3,4-Pyridyne Intermediates

3.1 Introduction

Functionalized *N*-heterocycles play a major role in modern pharmaceutical chemistry.[144] Especially pyridines are important building blocks for many biologically and pharmaceutically relevant molecules.[145] As a consequence, numerous synthetic methods for the functionalization of pyridines were developed over the last decades.[146] For the regioselective functionalization of this heterocycle in different positions, the directed metalation with various organometallic reagents (LDA, TMP-bases etc.) played a prominent role.[43,19c,147] An underrepresented synthetic field for the modification of pyridine rings is the use of the highly unsaturated intermediate pyridyne (analogue to arynes).[148] The precursors for pyridyne intermediates are often expensive or challenging to prepare and their further reactions with nucleophiles were of limited scope and complicated by a lack of regioselectivity.[149] In this work, a synthetic approach towards regioselectively double functionalized pyridines *via* pyridyne intermediates, starting from the readily prepared 3-chloro-2-ethoxypyridine (**118**, according to the work of Hegarty[150]) was investigated.

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[144] a) C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer, C. R. Scholz, *J. Am. Chem. Soc.* **1946**, *68*, 1999–2002 b) M. Heravi, V. Zadsirjan, *RSC Adv.* **2020**, *10*, 44247–44311; c) N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu, S. B. Jonnalagadda, *Molecules* **2020**, *25*, 1909; d) A. Mermer, T. Keles, Y. Sirin, *Bioorg. Chem.* **2021**, *114*, 205076.

[145] a) J. N. Newton, D. F. Fischer, R. Sarpong, *Angew. Chem. Int. Ed.* **2013**, *52*, 1726–1730; b) G. Rouquet, D. C Blakemore, S. V. Ley, *Chem. Commun.* **2014**, *50*, 8908–8911; c) L-G. Xie, S. Shaaban, X. Chen, N. Maulide, *Angew. Chem. Int. Ed.* **2016**, *128*, 13056–13059; d) M. Hilton, R. D. Dolweski, A. McNally *J. Am. Chem. Soc.* **2016**, *138*, 13806-13809.

[146] a) L. C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021; b) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451–5455; c) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642–2713; d) Q. Chen, X. Mollat du Jourdin, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 4958–4961. e) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754–5757; f) A. K. Steib, S. Fernandez, O. M. Kuzmina, M. Corpet, C. Gosmini, P. Knochel, *Synlett* **2015**, *26*, 1049–1054.

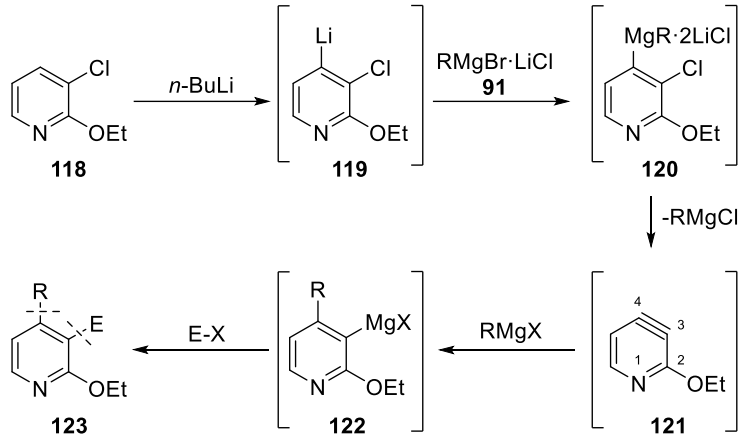
[147] a) D. L. Comins, M. O. Killpack, *J. Org. Chem.* **1990**, *55*, 69–73; b) P. Gros, Y. Fort, G. Queguiner, P. Caubère, *Tetrahedron Lett.* **1995**, *36*, 4791–4794; c) M. Balkenhohl, C. François, D. S. Roman, P. Quinio, P. Knochel, *Org. Lett.* **2017**, *19*, 536–539; d) A. B. Bellan, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 1838–1941.

[148] a) G. W. Gribble, M. G. Saulnier, *Heterocycles* **1993**, *35*, 151–169; b) W. Lin, L. Chen, P. Knochel, *Tetrahedron* **2007**, *63*, 2787–2797; c) A. E. Goetz, S. M. Bronner, J. D. Cisneros, J. M. Melamed, R. S. Paton, K. N. Houk, N. K. Garg, *Angew. Chem. Int. Ed.* **2012**, *51*, 2758–2762; d) A. E. Goetz, N. K. Garg, *J. Org. Chem.* **2014**, *79*, 846–851; e) J. M. Medina, M. K. Jackl, R. B. Susick, N. K. Garg, *Tetrahedron* **2016**, *72*, 3629–3634.

[149] a) M. Tsukazaki, V. Snieckus, *Heterocycles* **1992**, *33*, 533–536; b) K. Vinter-Pasquier, B. Jamart-Grégoire, P. Caubère, *Heterocycles* **1997**, *45*, 2113–2119.

[150] S. J. Connon, A. F. Hegarty, *J. Chem Soc., Perkin Trans. 1* **2000**, 1245–1249.

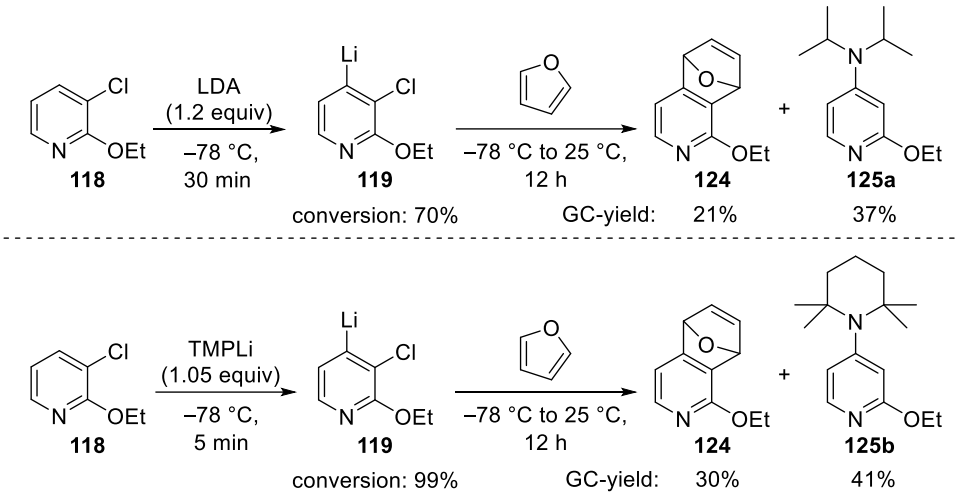
Thus, we envisioned the following reaction sequence: A regioselective lithiation of the pyridine **118** with a Li-base will afford the 4-lithiated pyridine **119**. Adding a Grignard reagent of type **91** will produce, after transmetalation, the mixed diorganomagnesiums of type **120**. By heating, the elimination should be triggered leading to the 3,4-pyridyne intermediate **121**. A regioselective addition of organomagnesium reagents should afford the 3-magnesiated pyridines of type **122** and, after quenching with various electrophiles, produce the desired difunctionalized pyridines of type **123** (Scheme 27).



Scheme 27: General reaction sequence towards difunctionalized pyridines of type **123** starting from 3-chloro-2-ethoxypyridine (**118**) *via* the 3,4-pyridyne intermediate **121**.

3.2 Optimization of the Reaction Conditions

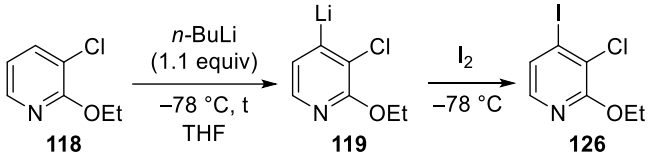
In preliminary experiments, the starting material 3-chloro-2-ethoxypyridine (**118**) was metalated with the commonly used amide bases LDA and TMPLi at −78 °C. Having a stable lithium species **119** at these low temperatures, furan was added and the mixture was slowly warmed to 25 °C over 12 h. Apart from the expected [4+2] cycloaddition product **124**, the 4-aminated pyridines **125a** and **125b** were also observed in larger amounts, displaying the addition of the corresponding lithium amides to the *in-situ* formed pyridyne intermediate (Scheme 28).



Scheme 28: Preliminary experiments using the amide bases LDA and TMPLi for the formation of pyridyne intermediates.

In order to avoid these side reaction, the commercially available organolithium reagent *n*-buthyllithium was successfully apllied as metalating agent and the reaction time was optimized (Table 14).[151]

Table 14: Optimization of the reaction time for the lithiation of 3-chloro-2-ethoxypyridine (**118**) with *n*-BuLi.



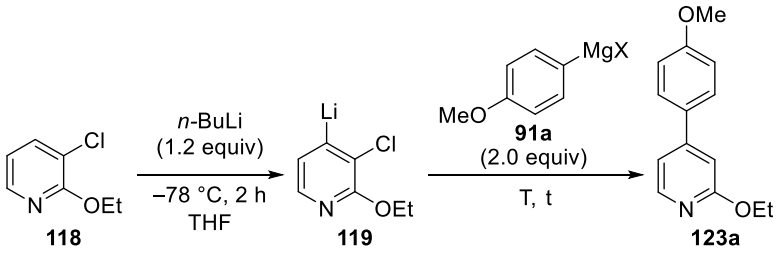
entry	t [min]	conversion **118** [GC-%]	yield **126** [GC-%]
1	15	53	53
2	30	64	60
3	60	78	70
4	120	93	81
5	300	94	81

[151] a) S. Choppin, P. Gros, Y. Fort, *Eur. J. Org. Chem.* **2001**, *2001*, 603–606; b) J. S. Dhau, A. Singh, Y. Kasetti, S. Bhatia, P. V. Bharatam, P. Brandão, V. Félix, K. N. Singh, *Tetrahedron* **2013**, *69*, 10284–10291.

By quenching the reaction mixture with iodine it was shown, that the lithiation of the pyridine **118** at −78 °C was complete after 2 h (entry 4) furnishing the 4-iodinated heterocycle **126**. Shorter reaction time led to incomplete conversions (entries 1-3). Longer times did not further improve the reaction outcome (entry 5). Higher temperatures led to immediate pyridyne formation and uncontrollable side reactions such as polymerization and oligomerization.

After addition of organomagnesium reagents of type **91** and subsequent transmetalation at −78 °C for 30 min, significantly more stable mixed diorganomagnesiums of type **120** were produced. To promote the elimination towards the pyridyne intermediate **121**, a temperature optimization screening was performed (Table 15). Aqueous quenching after 12 h at 25 °C showed that 38% of the starting material **118** were still present and the desired product **123a** was obtained in only 25% calibrated GC-yield (entry 1). Heating to 50 °C led to a faster elimination, but the reaction outcome was still not satisfactory (entries 2-3). Further increasing of the reaction temperature to 75 °C in a sealed tube led to a complete conversion of the starting material and a reaction time of 1-2 h gave the best results. Those conditions were used as standard procedure (entries 4-6).

Table 15: Optimization of the reaction temperature and time for the elimination towards the pyridyne intermediate **121** and the subsequent formation of the 4-arylated pyridine **123a**.



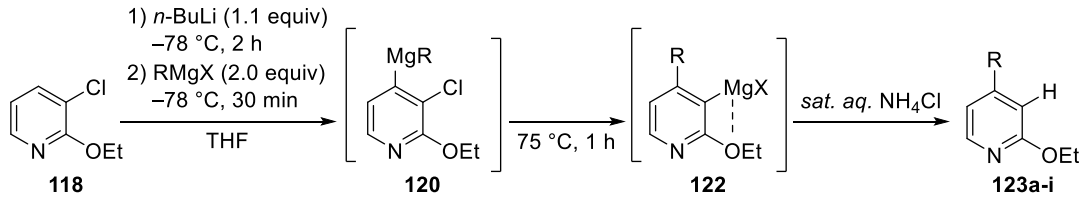
entry	t [h]	T [°C]	conversion **118** [GC-%]	yield **123a** [GC-%]
1	12	25	62	25
2	1	50	84	32
3	12	50	99	53
4	0.5	75	95	59
5	2	75	99	67
6	12	75	99	60

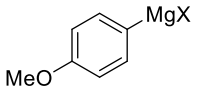
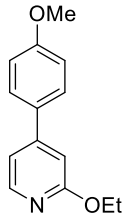
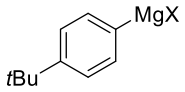
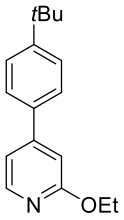
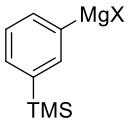
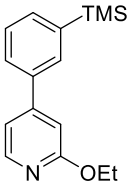
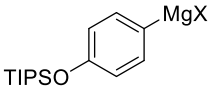
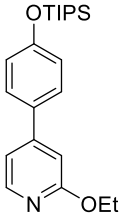
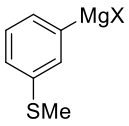
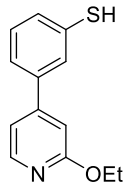
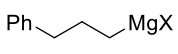
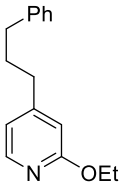
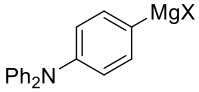
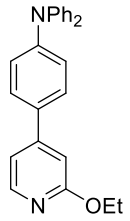
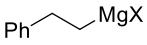
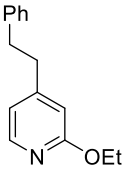
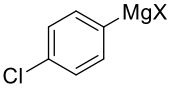
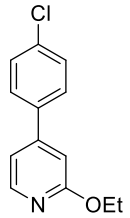
3.3 Preparation of 4-Arylated Pyridines *via* 3,4-Pyridyne Intermediates

Following the optimizations, 3-chloro-2-ethoxypyridine **118** was treated with *n*-BuLi (1.1 equiv) at −78 °C for 2 h for a regioselective lithiation in position C4. Addition of 4-anisylmagnesium bromide **91a**[152] at −78 °C furnished the diorganomagnesium reagent **120** after 30 min of stirring. The elimination of this relatively stable species to the desired pyridyne was achieved at 75 °C within 1-2 h. In order to suppress typical aryne side reactions (oligomerization, polymerization etc.) and to obtain acceptable yields, 2.0 equiv of the organomagnesium reagent **91a** were required. After cooling the reaction mixture to 25 °C and subsequent aqueous workup, the regioselectively formed 4-arylated pyridine **123a** was obtained in 64% isolated yield (Table 16, entry 1). The regioselectivity can be explained by the coordination of the magnesium to the ethoxy group in position C2 as well as with sterically hindrance. The gap between conversion and isolated yield can be explained by unintentional side reactions like polymerization of the *in-situ* formed pyridyne intermediate (99% conversion to 64% isolated yield).[153] Other arylmagnesium reagents of type **91** were suitable substrates as well and were added regioselectively to position C4, producing the functionalized pyridines **123b-g** in 41-61% yield (entries 2-7). Interestingly, by using 3-methylthiophenylmagnesium bromide, a free thiol group was observed in the isolated product **123c** leading to the assumption, that the methylthio group was metalated during the reaction resulting in a magnesium cabenoid which was not stable at 75 °C. Furthermore, the use of 5.0 equiv of alkylmagnesium halides led to the 4-alkylated pyridines **123h-i** in 56-59% yield (entries 8-9).

[152] The organomagnesium reagent was prepared *via* oxidative insertion using magnesium turnings and LiCl.
[153] a) W. E. Bachmann, H. T. Clarke, *J. Org. Chem. Rev.* **1927**, *49*, 2089–2098; b) L. S. Chen, G. J. Chen, C. Tamborski, *J. Org. Chem.* **1980**, *193*, 283–292; c) M. Fossatelli, L. Brandsma, *Synthesis* **1992**, 756.

Table 16: Preparation of 4-arylated pyridines of type **123** *via* regioselective addition of organomagnesium reagents to pyridyne intermediates.



entry	nucleophile	product[a]	entry	nucleophile	product[a]
1	 **91a**[b]	 **123a**: 64%	6	 **91s**[b]	 **123f**: 43%
2	 **91u**[b]	 **123b**: 56%	7	 **91x**[b]	 **123g**: 41%
3	 **91v**[b]	 **123c**: 51%	8	 **91y**[b,c]	 **123h**: 58%
4	 **91w**[b]	 **123d**: 61%	9	 **91k**[b,c]	 **123i**: 56%
5	 **91m**[b]	 **123e**: 51%			

[a] Yield of analytically pure isolated product, [b] Organomagnesium reagent was prepared *via* oxidative insertion using Mg turnings and LiCl (1.2 equiv), [c] 5.0 equiv of RMgX was used.

3.4 Difunctionalization of 3-Chloro-2-Ethoxypyridine

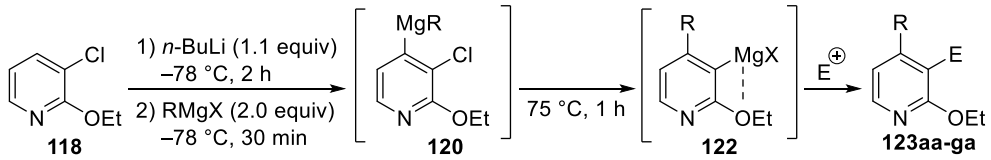
Following the same reaction procedure as previously described (see chapter B.3.3), the newly generated 3-magnesiated 2-ethoxypyridine **122** was trapped with various electrophiles to produce highly functionalized pyridines of type **123**. Thus, starting from 3-chloro-2-ethoxypyridine, *n*-BuLi and *p*-anisylmagnesium bromide **91a**, the intermediate of type **122** was generated after heating to 75 °C. This magnesium reagent was subsequently quenched with TMSCl (2.5 equiv) after cooling the reaction mixture to 25 °C, leading to the 2,3,4-trisubstituted pyridine **123aa** in 53% overall yield (0.5 mmol scale). A similar yield (54%) was achieved by scaling the reaction up to 5.0 mmol (Table 17, entry 1). The bromination with $(CCl_2Br)_2$ led to the 3-halogenated pyridine **123ab** in 57% yield and adding *S*-methyl methanesulfonothioate gave the thiolated pyridine **123ac** in 43% yield (entries 2-3). Different aldehydes were suitable substrates for direct quenching the magnesium species, furnishing the secondary alcohols **123ad** and **123ae** in 57-60% yield over two steps (entries 4-5). Additionally, adding CuCN·2LiCl in catalytic amounts enabled the allylation of the intermediate **122a** leading to the pyridine **123af** in 56% yield (entry 6). Similarly, a copper(I)-mediated acylation with 4-chlorobenzoyl chloride gave the bis-aryl ketone **123ag** in 58% yield (entry 7). Transmetalation with a $ZnCl_2$ solution in THF (1 M, 1.1 equiv), followed by the addition of $Pd(OAc)_2$ (5.0 mol%), SPhos[154] (10 mol%) and ethyl 3-bromobenzoate afforded the 3,4-bis-arylated pyridine **123ah** in 56% *via* Negishi cross-coupling (entry 8).[155] Furthermore, electrophilic aminations with $Cu(OTf)_2$ and *N*-hydroxylamino benzoates produced the 3-aminated pyridines **123ai** and **123aj** in 47-54% yield (entries 9-10).[127c,156]

Using 3-(trimethylsilyl)phenylmagnesium bromide for the generation of **122b**, cross-coupling reactions with functionalized aryl bromides were performed as previously described to get the pyridines **123ba** and **123bb** in 53-55% yield (entries 11-12). Another cross-coupling with 4-iodobenzotrifluoride led to the pyridine **123ca** in 53% yield (entry 13). Direct quenching of the magnesium species **122d** with $(CCl_2Br)_2$ or DMF furnished the pyridines **123da** and **123db** in 49-52% yield (entries 14-15). Iodolysis of the magnesium species **122e** gave the bis-halogenated compound **123ea** in 50% yield (entry 16). Further functionalizations of the

[154] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; b) R.A. Altmann, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115–3121.
[155] a) G. Manolikakes, C. M. Hernandez, M. A. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422–8436. b) L. Melzig, A. Metzger, P. Knochel, *J. Org. Chem.* **2010**, *75*, 2131–2133.
[156] a) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc*. **2004**, *126*, 5680–5681; b) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2006**, *71*, 219–224.

reagents **122f-g** by Cu(I)-catalyzed acylation or direct quenching with benzaldehyde afforded the highly functionalized 4-alkylated pyridines **123fa-ga** in 49-55% yield (entries 17-18).

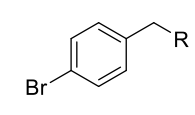
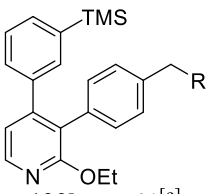
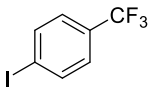
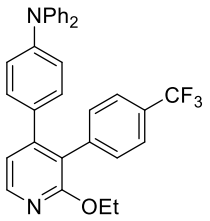
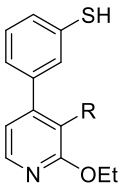
Table 17: Preparation of 3,4-difunctionalized pyridines of type **123** by quenching the *in-situ* formed 3-pyridylmagnesium reagent **122** with various electrophiles.

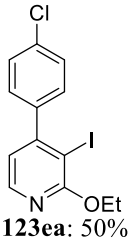
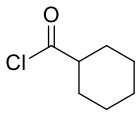
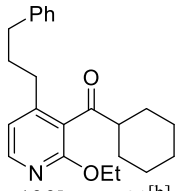
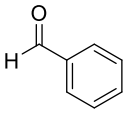
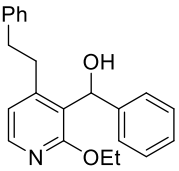


118 **120** **122** **123aa-ga**

entry	electrophile	product[a]	entry	electrophile	product[a]
1	TMSCl	**123aa**: 53% (0.5 mmol) 54% (5.0 mmol)	6	+ CuCN·2LiCl (10 mol%)	**123af**: 56%[b]
2	$(CCl_2Br)_2$	**123ab**: 57%	7	+ CuCN·2LiCl (1.0 equiv)	**123ag**: 58%[b]
3	$Me-S(=O)_2-SMe$	**123ac**: 43%	8	$Pd(OAc)_2$ (5,0 mol%) SPhos (10 mol%)	**123ah**: 53%[c]
4		**123ad**: 60%	9	$Cu(OTf)_2$ (10 mol%)	**123ai**: 54%[d]
5		**123ae**: 57%	10	$Cu(OTf)_2$ (10 mol%)	**123aj**: 47%[d]

Table 17: continued.

entry	electrophile	product[a]
	 Pd(OAc)$_2$ (5,0 mol%) SPhos (10 mol%)	
11	R = CO_2Et	**123ba**: 55%[c]
12	R = CN	**123bb**: 53%[c]
	 Pd(OAc)$_2$ (5,0 mol%) SPhos (10 mol%)	
13		**123ca**: 57%[c]
		
14	$(CCl_2Br)_2$	**123da**: R = Br; 43%
15	DMF	**123db**: R = CHO; 49%

entry	electrophile	product[a]
	I_2	
16		**123ea**: 50%
	 + CuCN·2LiCl (1.0 equiv)	
17		**123ha**: 55%[b]
		
18		**123ia**: 53%

[a] yield of analytically pure isolated product, [b] The Cu-salt was added at 0 °C, 10 min; [c] $ZnCl_2$ (2.0 equiv) was added at 0 °C, 10 min, then the mixture of aryl halide, Pd-salt and ligand was added; [d] $ZnCl_2$ (1.0 equiv) was added at 0 °C, 10 min, then *N*-hydroxylamino benzoate (2.0 equiv) and $Cu(OTf)_2$ (10 mol%) at 0 °C to 25 °C, 12 h.

To confirm the regioselectivity, a single crystal X-ray diffraction measurement was done. Single crystals of compound **123aa**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM solution and a dimer of the proposed structure was obtained (Figure 3).

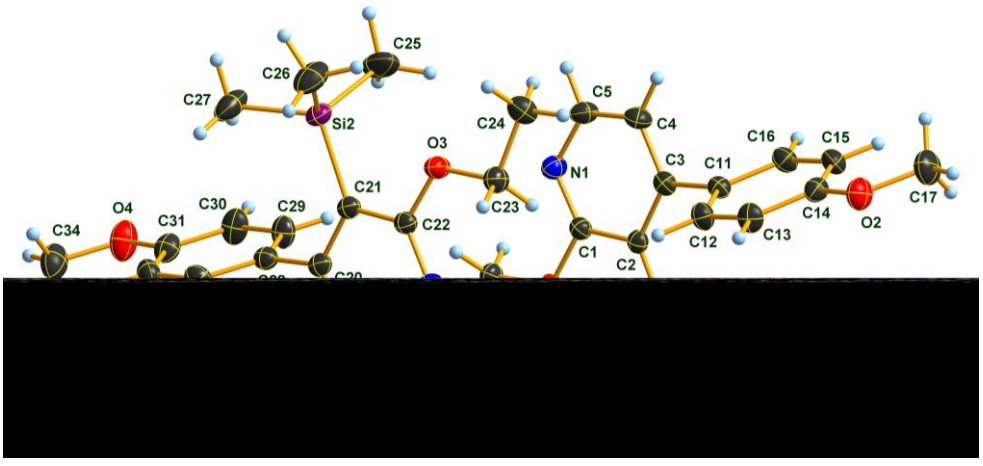
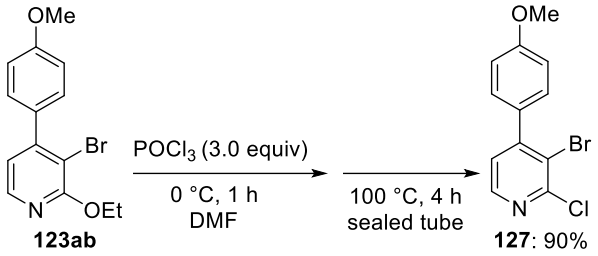


Figure 3: Molecular structure of the dimer of compound **123aa** in the crystal.

The trisubstituted compound **123ab** was further derivatized by treating the newly prepared pyridine with $POCl_3$ in DMF at 100 °C in a sealed tube. After 4 h of heating, the 2,3-dihalogenated pyridine **127** was obtained in 90% yield. With this reaction, it was demonstrated that the ethoxy group, which was required for successful pyridyne chemistry, could be substituted for further functionalizations (Scheme 29).

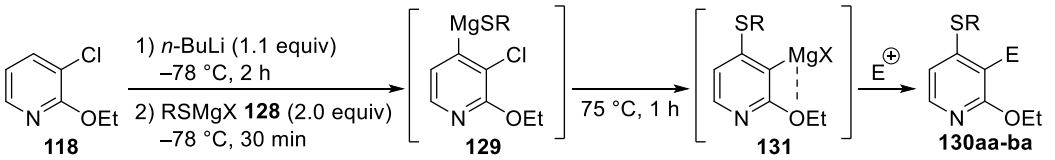


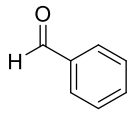
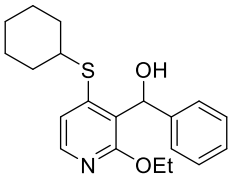
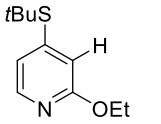
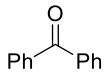
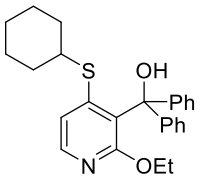
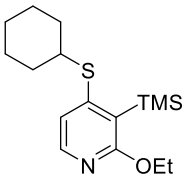
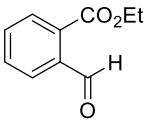
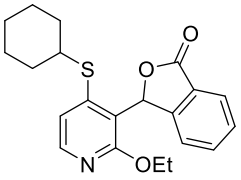
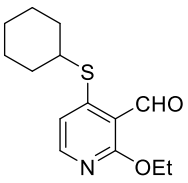
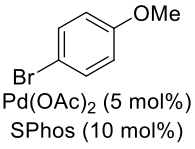
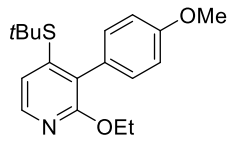
Scheme 29: Chlorination of the trisubstituted pyridine **123ab** using $POCl_3$ in DMF.

3.5 Preparation of 4-Thiolated Pyridines *via* Pyridyne Intermediates

Other organomagnesium reagents were investigated, and magnesium thiolates of type **128** were found to be excellent reagents for the regioselective addition to the pyridyne in position C4. Thus, magnesium thiolates of type **128** were prepared by stirring the corresponding thiol with *i*-PrMgCl·LiCl (1.1 equiv) at 0 °C for 15 min. After adding the organomagnesium (generating bisorganomagnesiums of type **129**), applying the standard conditions towards the pyridyne intermediate (heating to 75 °C for 1 h in a sealed tube) and subsequent aqueous workup, the 4-aminated pyridines of **130a** and **130b** were obtained in 69-72% yield (Table 18, entries 1-2). Quenching with electrophiles such as TMSCl, DMF, benzaldehyde or benzophenone gave the expected highly functionalized pyridines **130aa-ad** in 50-71% isolated yield (entries 3-6). A ring closing reaction towards the phthalide **130ae** (71% yield) took place after treating the pyridylmagnesium reagent **131a** with ethyl 2-formylbenzoate (entry 7). Additionally, a Negishi cross-coupling reaction gave, after transmetalation with $ZnCl_2$, the 3-arylated pyridine **130ba** in 67% isolated yield (entry 8).

Table 18: Preparation of 4-aminated pyridines of type **131** by quenching pyridylmagnesium intermediates of type **130** with various electrophiles.



entry	electrophile	product[a]	entry	electrophile	product[a]
1	*sat. aq.* NH_4Cl	**130a**: 72%	5		 **130ac**: 71%
2	*sat. aq.* NH_4Cl	 **130b**: 69%	6		 **130ad**: 67%
3	TMSCl	 **130aa**: 71%	7		 **130ae**: 71%
4	DMF	 **130ab**: 50%	8	 $Pd(OAc)_2$ (5 mol%) SPhos (10 mol%)	 **130ba**: 67%[b]

[a] Yield of analytically pure isolated product; [b] $ZnCl_2$ (2.0 equiv) was added at 0 °C, 10 min, then the mixture of aryl halide, Pd-salt and ligand was added.

3.6 Continuous Flow Setup for the Preparation of Difunctionalized Pyridines

Continuous flow chemistry offers a lot of advantages for organometallic reaction sequences including several steps, such as better reproducibility, fast and superior temperature control as well as the option for convenient scale ups for industrial applications.[112,157] Thus, after intensive investigations, it was found that the continuous flow setup was not applicable for the reaction

[157] a) Z. He, T. F. Jamison, *Angew. Chem. Int. Ed*. **2014**, *53*, 3353–3357; b) A. Nagaki, D. Ichinari, J. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 12245–12248; c) A. Khadra, M. G. Organ, *J. Flow Chem.* **2016**, *6*, 293–296; e) J. Schwan, M. Kleoff, B. Hartmayer, P. Heretsch, M. Christmann, *Org. Lett.* **2018**, *20*, 7661–7664; f) Z. Tan, Z. Li, G. Jin, C. Yu, *Org. Process Res. Dev.* **2019**, *23*, 31–37.

starting from 3-chloro-2-ethoxypyridine (**118**) due to long reaction times and pressure limitations.[158] However, the arylation of the similar starting material 2-*iso*propylthio-3-chloropyridine (**132**) was examined. In batch, the reaction with *n*-BuLi (1.1 equiv, –60 °C, 10 min) gave quantitatively the 4-lithiated species **133**. Addition of *p*-anisylmagnesium bromide (**91a**) at –60 °C, followed by heating to 75 °C for 1 h, provided the 4-arylated pyridine **134a** in 56% yield (Table 19). This reaction sequence was converted into a continuous flow setup as followed: A solution of the 2,3-disubstituted pyridine **132** (0.10 M in THF) was mixed with *n*-BuLi (0.11 M in cyclohexane) at a flowrate of 1 mL·min^{-1} at –60 °C with a residence time of 5 min to give the aryllithium species **133**. A solution of Grignard reagent (**91a**, 0.3 M in THF) was added *via* a third pump with a flowrate of 2 mL·min^{-1} at –60 °C and after a residence time of 5 min for transmetalation, providing the bisarylmagnesium **136a**, the reaction stream was passed through a reactor at 75 °C (10 min residence time). Injecting the 3-pyridylmagnesium bromide **135a** directly into the electrophile at 25 °C provided various functionalized pyridines of type **134** (Table 15, entry 1). Quenching the mixture with an aqueous solution of NH_4Cl gave the pyridine **134a** in 57% isolated yield. Iodolysis furnished the 2,3,4-trisubstituted pyridine **134aa** in 53% yield and the use of TMSCl gave the desired product **134ab** in 51% isolated yield (entries 2-3). Variations of organomagnesium bromides and electrophiles led to the pyridines **134ba-bb** and **134ca** in 49-51% yield (entries 4-6). To confirm the regioselectivity, a single crystal X-ray diffraction measurement was done for compound **134aa** (Figure 4).

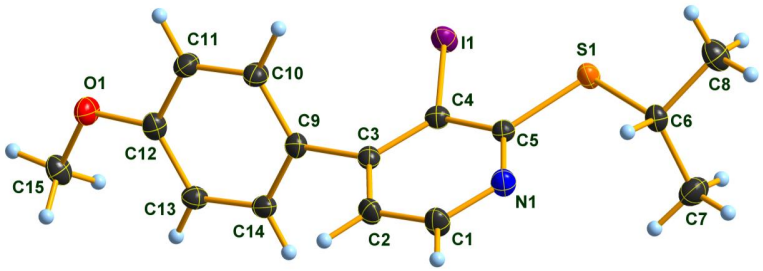
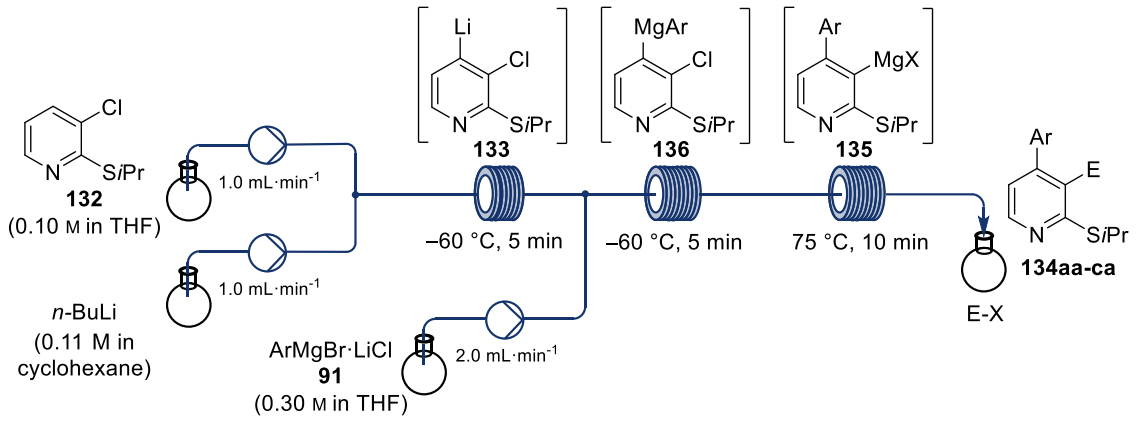
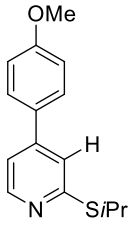
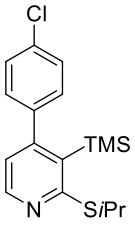
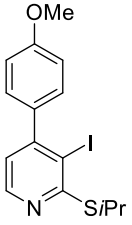
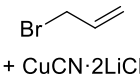
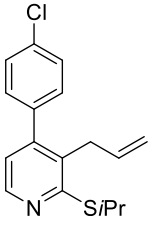
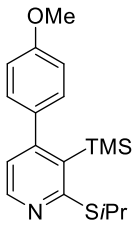
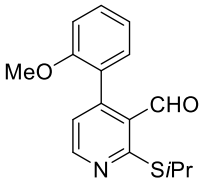


Figure 4: Molecular structure of compound **134aa** in the crystal.

[158] For a detailed continuous flow/batch comparison, see the Experimental Chapter (C.4.1).

Table 19: Difunctionalization of 2-*iso*propylthio-3-chloropyridine (**132**) in a continuous flow setup.



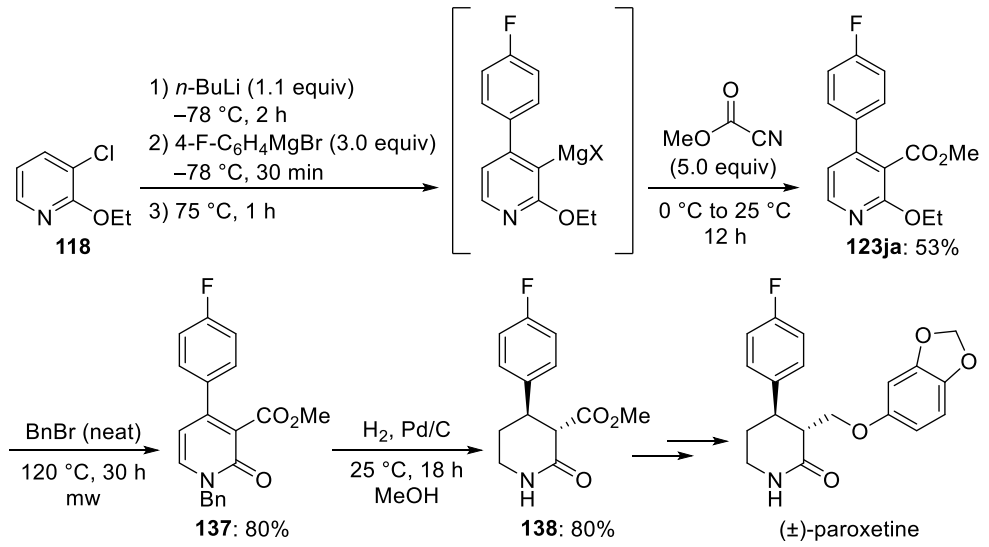
entry	electrophile	product[a]	entry	electrophile	product[a]
1	*sat. aq.* NH_4Cl	 **134a**: 57%	4	TMSCl	 **134ba**: 50%
2	I_2	 **134aa**: 53%	5	 + CuCN·2LiCl (10 mol%)	 **134bb**: 49%
3	TMSCl	 **134ab**: 51%	6	DMF	 **134ca**: 51%

[a] Yield of analytically pure isolated product.

3.6 Preparation of a Key Intermediate in the Synthesis of (±)-Paroxetine

To demonstrate the value of this newly developed method for the regioselective difunctionalization of pyridines *via* pyridyne intermediates, a key intermediate towards the

antidepressant paroxetine was prepared.[159] Thus, 3-chloro-2-ethoxypyridine (**118**) was treated with *n*-BuLi and the Grignard reagent **91z** in the known procedure leading to the 2,3,4-trisubstituted pyridine **123ja** in 53% yield on a 5 mmol scale. Heating a mixture of the pyridine and neat benzyl bromide at 120 °C for 30 h produced the *N*-benzylated pyridone **137** in 80% yield.[160] Finally, treatment with H_2 gas and Pd/C led to selective hydrogenation of the pyridone and afforded the piperidone **138** in 50% yield (Scheme 30).[161]



Scheme 30: Synthesis route towards the piperidone **138**, a key intermediate for the preparation of (±)-paroxetine.

[159] a) C. De Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente, V. Zanirato, *Tetrahedron: Asymmetry* **2008**, *19*, 131–155; b) S. Ötvös, M. Pericàs, C. O. Kappe, *Chem. Sci.* **2019**, *10*, 11141–11146; c) S. Jara, S. Sarkar, S. A. Morris, *Tetrahedron* **2020**, *76*, 131215.
[160] W. R. Bowman, C. F. Bridge, *Synth. Comm.* **1999**, *29*, 4051–4059.
[161] a) S. Maris, N. Castagnoli, *J. Org. Chem.* **1996**, *61*, 1, 309–313; b) J. Wysocki, C. Schlepphorst, F. Glorius, *Synlett* **2015**, *26*, 1557–1562; c) B. Zacharie, S. D. Abbott, C. B. Baigent, C. Doyle, R. S. Yalagala, Eur. *J. Org. Chem.* **2018**, *46*, 6486–6493; d) Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander, F. Glorius, *Nat. Chem.* **2019**, *11*, 264–270.

4. Regioselective Amination of 2,3- and 3,5-Difunctionalized Pyridines using KHMDS *via* Pyridyne Intermediates

4.1 Introduction

Aminated *N*-heterocycles play an important role in modern pharmaceutical industry, whereby aminopyridines are of special interest.[162,163] Thus, various methods for the regioselective amination of pyridines are described in the literature, especially the regioselective metalation using various organometallic reagents.[19c,43,44d,147,151] Due to previously described reasons (see chapter B.3.1), pyridyne chemistry is still a rarely used method for the selective functionalization of heterocycles,[148,149,150,164] while the amination of non-hetero arenes *via* aryne intermediates, is more commonly known.[165]

To fill this synthetic gap, a new method towards regioselectively aminated pyridines was described in this work. As shown in chapter B.3.2, TMPLi and LDA were unsuitable metalating agents for the deprotonation of 3-chloro-2-ethoxypyridine due to their tendency to react unintentionally with the pyridyne intermediate. Still, these results showed that the regioselective amination *via* pyridyne intermediates was accomplishable using simple starting materials such as 3-halo-2-alkoxypyridines and related structures (2-thio, 2-amino etc.).

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[162] a) T. Eicher, S. Hauptmann, A. Speicher, *The Chemistry of Heterocycles* 2nd Ed. Wiley-VHC, Weinheim, **2003**; b) J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, *Modern Heterocyclic Chemistry* 1st Ed. Wiley-VHC, Weinheim, **2011**.

[163] a) T. Sato, K. Suemaru, K. Matsunaga, S. Hamaoka, Y. Gomita, R. Oishi, *Jpn. J. Pharmacol.* **1996**, *71*, 81–84; b) P. R. Graves, J. J. Kwiek, P. Fadden, R. Ray, K. Hardeman, A. M. Coley, M. Foley, T. A. Haystead, J. Mol. Pharmacol. **2002**, 62, 1364–1372; c) S. Harish, K. Bhuvana, G. Bengalorkar, T. Kumar, J. *Anaesthesiol. Clin. Pharmacol.* **2012**, *28*, 172–177.

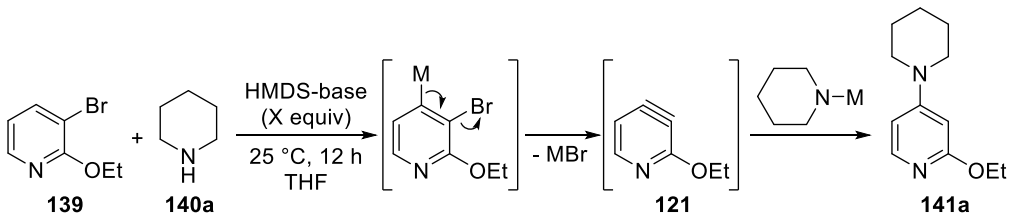
[164] a) M. Mallet, G. Quenguiner, *Tetrahedron* **1982**, *38*, 3035-3042; b) A. A. Cant, G. H. V. Bertrand, J. L. Henderson, L. Roberts, M. F. Greaney, *Angew. Chem. Int. Ed.* **2009**, *48*, 5199-5202.

[165] a) E. R. Biehl, S. M. Smith, P. C. Reeves, *J. Org. Chem.* **1971**, *36*, 1841-1842; b) H. Y. Xin, E. R. Biehl, *J. Org. Chem.* **1983**, *48*, 4397-4399; c) E. R. Biehl, A. Razzuk, M. V. Jovanovic, S. P. Khanapure, *J. Org. Chem.* **1986**, *51*, 5157-5160; d) A. Razuk, E. R. Biehl, *J. Org. Chem.* **1987**, *52*, 2619-2622; e) W. Lin, I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 4258-4261; f) J. M. Medina, J. L. Mackey, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 15798–15805; g) J.-A. Garcia-Lopez, M. Cetin, M. F. Greaney, *Angw. Chem. Int. Ed.* **2015**, *54*, 2156-2159; h) J.-A. Garcia-Lopez, M. Cetin, M. F. Greaney, *Org. Lett.* **2015**, *17*, 2649-2651; i) S. Ghorai, D. Lee, *Synlett* **2020**, *31*, 750-771; j) S. Cho, Q. Wang, *Org. Lett.* **2020**, *22*, 1670-1674.

4.2 Preparation of 4-Aminated Pyridines Starting from 2,3-Disubstituted Pyridines and KHMDS

To avoid the addition of the metalating agents to the pyridyne, the highly sterically hindered HMDS-bases were investigated. Thus, 3-bromo-2-ethoxypyridine (**139**) was treated with various bases derived from HMDS (Li, Na, K) at 25 °C for 12 h in the presence of piperidine (**140a**). It was found, that LiHMDS was too weak to metalate the heterocycle in position C4 at room temperature (Table 20, entry 1). In contrast, the stronger base NaHMDS (2.2 equiv) gave 90% conversion of **139** after 12 h at 25 °C, leading to 2-ethoxy-4-*N*-piperidylpyridine (**141a**) in 82% calibrated GC-yield (entry 2). A complete conversion (>99%) was achieved using KHMDS (2.2 equiv), increasing the yield of **141a** to 90% (entry 3). Screening the amount of base led to the result, that the use of just 1.2 equiv of KHMDS decreased the conversion and the yield of the desired product significantly (entry 4). Increasing the amount of base to 3.0 equiv did not improve the yield further (entry 5).

Table 20: Optimization of the metalation of the pyridine **139** with HMDS-bases and subsequent amination *via* pyridyne formation.



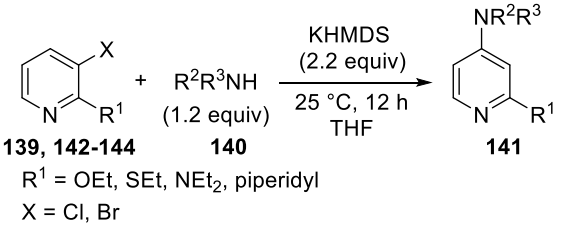
entry	base	equiv of base	conversion **139** [GC-%]	yield **141a** [GC-%]
1	LiHMDS	2.2	3	-
2	NaHMDS	2.2	90	82
3	KHMDS	2.2	99	90
4	KHMDS	1.2	73	69
5	KHMDS	3.0	99	91

With these optimized conditions in hand, various amines were successfully applied in the reaction procedure, resulting in a broad range of 4-aminated pyridines of type **141** (Table 21). Thus, 3-bromo-2-ethoxypyridine (**139**) was mixed with piperidine (**140a**, 1.2 equiv) in THF (2 mL/mmol of pyridine). After the addition of KHMDS at 25 °C and stirring for 12 h, the desired 4-piperidylpyridine **141a** was isolated in 90% yield (entry 1). Interestingly, changing the starting material to 3-chloro-2-ethoxypyridine (**118**) gave a significantly decreased yield of just 57%. In order to show the beneficial effect of a substituent such as an ethoxy group in position C2, the reaction of simple 3-bromopyridine with KHMDS and piperidine under standard conditions was examined. Due to a lower stability of the pyridyne intermediate, only 32% of 4-(piperidin-1-yl)pyridine was obtained, demonstrating the importance of an electron-donating C2-substitutent with a coordinating effect.

Submitting the secondary cyclic amine **140b** to the reaction protocol provided the functionalized pyridine **141b** in 70% yield. The reaction of other secondary amines like **140c-d** with the 2-ethoxypyridine **139** led to the 4-aminated pyridines **141c** and **141d** in 72-85% yield (entries 3-4). Furthermore, primary amines such as **140e** and **140f** were suitable substrates and furnished the secondary amines **141e-f** in 56-64% yield (entries 5-6).

Finally, it was demonstrated that the ethoxy group in position C2 was replaceable by thiol and amino groups. Starting from 2-ethylthio-3-chloropyridine (**142**) and piperidine under standard reaction conditions, the desired pyridine **141g** was obtained in 74% yield (entry 7). Additionally, the 2-aminated starting materials **143** and **144** provided the desired 2,4-aminated pyridines **141h** and**141i** in 67-83% yield after the treatment with piperidine (**140a**) and KHMDS (entries 8-9).

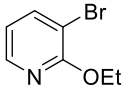
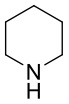
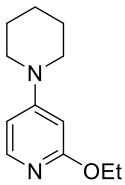
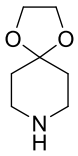
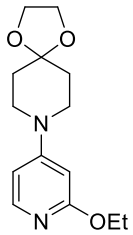
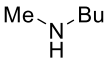
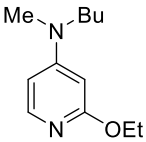
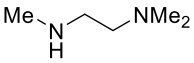
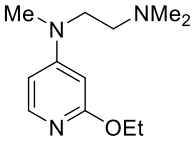
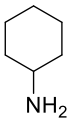
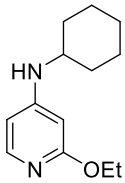
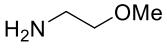
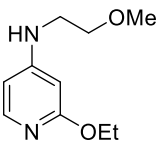
Table 21: Preparation of 4-aminated pyridines of type **141** *via* regioselective addition of potassium amides to pyridyne intermediates.



139, 142-144 **140** **141**

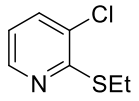
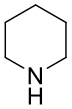
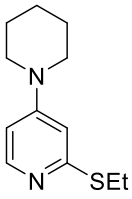
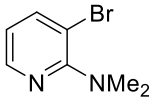
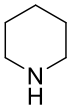
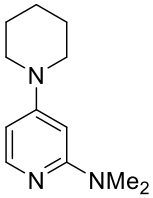
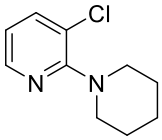
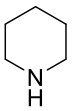
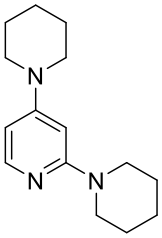
R^1 = OEt, SEt, NEt_2, piperidyl

X = Cl, Br

entry	starting material	amine	product[a]
1	 **139**	 **140a**	 **141a**: 90%
2	 **139**	**140b**	 **141b**: 70%
3	 **139**	**140c**	 **141c**: 85%
4	 **139**	**140d**	 **141d**: 72%
5	 **139**	**140e**	 **141e**: 64%
6	 **139**	**140f**	 **141f**: 64%

[a] Yield of analytically pure isolated product.

Table 21: continued.

entry	starting material	amine	product[a]
7	 **142**	 **140a**	 **141g**: 74%
8	 **143**	 **140a**	 **141h**: 67%
9	 **144**	 **140a**	 **141i**: 74%

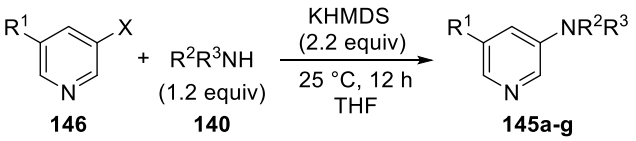
[a] yield of analytically pure isolated product.

4.3 Preparation of 5-Aminated Pyridines Starting from 3,5-Disubstituted Pyridines and KHMDS

In order to extend this amination procedure, another substitution pattern of pyridine starting materials was investigated. Starting from 3-halopyridines bearing either and alkoxy, a thio or an amino group in position C5, the standard procedure using amine **140a** (1.2 equiv) and KHMDS (2.0 equiv) at 25 °C for 12 h furnished 5-aminated pyridines of type **145** with a good regioselectivity (Table 22). Again, the coordinating and electron donating effects of the substituents increased the stability of the *in situ* formed pyridyne and determined the regioselectivity of the addition. Thus, the 5-alkoxy-3-halopyridines **146a** and **146b** were mixed with different amines of type **140**, leading to the desired aminopyridines **145a-d** in 60-77% yield (entries 1-4). The thiolated starting material **146c** gave, after treatment with piperidine and KHMDS, the 3,5-difunctionalized heterocycle **145e** in 62% yield (entry 5) and the diaminated product **145f** was prepared in 62% isolated yield according to the procedure (entry

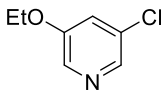
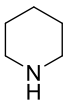
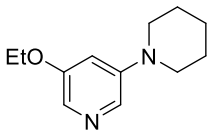
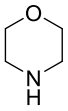
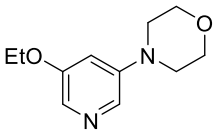
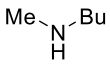
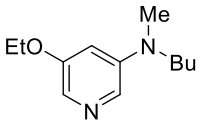
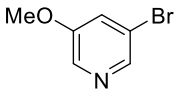
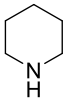
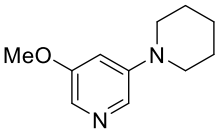
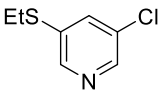
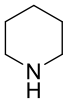
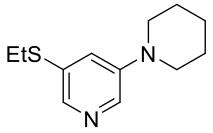
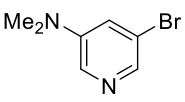
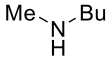
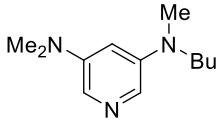
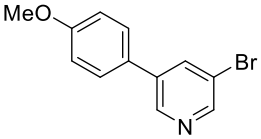
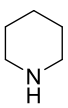
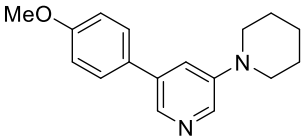
6). Last, we examined the reaction of the starting material **146e**, bearing an aryl substituent in position C5. Interestingly, the desired 5-aminated pyridine **145g** was obtained in 68% yield with a high regioselectivity in the absence of a coordinating effect, leading to the assumption, that steric effects determined the selective addition of the amine in this case (entry 7).

Table 22: Preparation of 5-aminated pyridines of type **145**.



146 **140** **145a-g**

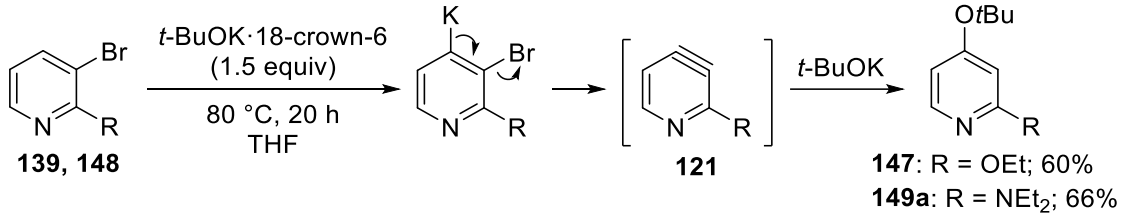
R^1 = OEt, OMe, SEt, NMe_2, aryl
X = Cl, Br

entry	starting material	amine	product[a]
1	 **146a**	 **140a**	 **145a**: 69%
2	**146a**	 **140g**	 **145b**: 77%
3	**146a**	 **140c**	 **145c**: 64%
4	 **146b**	 **140a**	 **145d**: 60%
5	 **146c**	 **140a**	 **145e**: 62%
6	 **146d**	 **140c**	 **145f**: 90%
7	 **146e**	 **140a**	 **145g**: 68%

[a] Yield of analytically pure isolated product.

4.4 Preparation of 3-Alkoxylated Pyridines Starting from 2,3-Disubstituted Pyridines and *t*-BuOK with 18-Crown-6

As regioselective aminations of pyridyne intermediates showed to work out excellent, investigations towards the addition of alcohols, provided as potassium alkoxides, were made. Tilley and co-workers recently described the formation of arynes using *t*-BuOK in the presence of 18-crown-6.[166] Thus, *t*-BuOK (1.5 equiv) and 18-crown-6 (1.5 equiv) were mixed to form the base *t*-BuOK·18-crown-6. Addition to 3-bromo-2-ethoxypyridine (**139**) led, after stirring at 25 °C for 20 h, to the 4-alkoxylated pyridine **147** in 60% yield. Similarly, 3-bromo-2-diethylaminopyridine (**148**) gave the desired transition metal free C-O bond formation towards the pyridine **149a** in 66 % yield (Scheme 31).



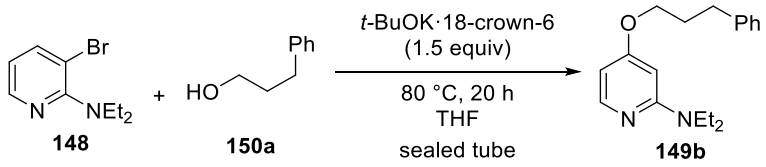
Scheme 31: Preparation of 4-alkoxylated pyridines such as **147** and **149** *via* regioselective addition of *t*-BuOK to pyridynes of type **121**.

To extend the reaction scope to other 4-alkoxylated pyridines, various alkyl alcohols of type **150** were added to the base *t*-BuOK·18-crown-6 to generate the corresponding alkoxides. Then, these mixtures were slowly added to 3-bromo-2-ethoxypyridine (**139**). However, only small amounts of the desired product were obtained. Instead, GC-MS analysis revealed 3-bromo-2-cyclohexyloxypyridine as main product as the ethoxy group in position C2 was substituted by the alkoxide. To overcome this problem, the more robust diethylamino pyridine **148** was tested under similar conditions. Coupling of alkoxides other than *tert*-butoxide at room temperature did not prove feasible, as the reaction proceeded very slow probably due to a lower concentration of the deprotonating agent *t*-BuOK in the mixture, as it gets consumed during the generation of the alkoxides. Nevertheless, heating to 80 °C for 20 h in a sealed tube gave a good conversion and various 4-alkoxylated pyridines of type **149** were obtained. Unfortunately, the addition of *t*-BuOK to the pyridyne intermediate, leading to the previously described

[166] Y. Dong, M. I. Lipschutz, T. D. Tilley, *Org. Lett.* **2016**, *18*, 1530–1533.

product **149a**, was observed in small amounts as a side reaction. To suppress this competitive reaction, an equivalent screening of the alcohol **150a** was performed. The best results were obtained using 3.0 equiv of the alcohol, avoiding the side reaction (Table 23, entries 1-2). Smaller amounts of the alcohol (1.5 equiv) led to a decreased GC-yield (entries 3-4), whereas 5.0 equivalents did not show to be beneficial (entries 5-6).

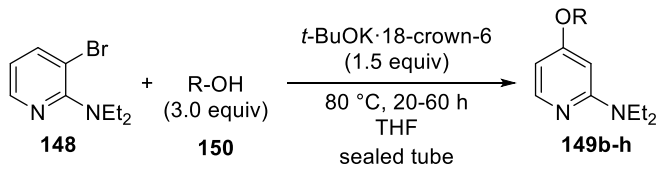
Table 23: Optimization of the equivalents of alcohol **150a**.

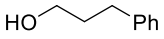
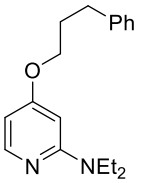
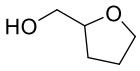
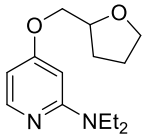
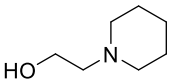
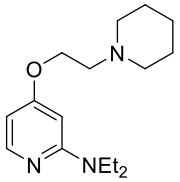
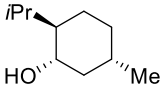
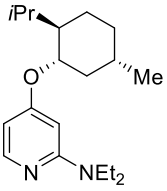
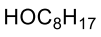
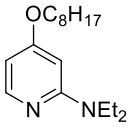
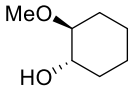
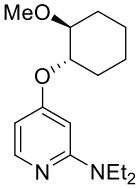
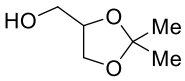
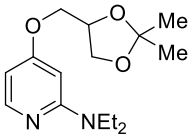


entry	equivalents of alcohol **150a**	T [h]	conversion **148** [GC-%]	Yield **149b** [GC-%]
1	3.0	1	66	40
2	3.0	20	96	66
3	1.5	1	75	38
4	1.5	20	98	53
5	5.0	1	41	21
6	5.0	20	77	56

Following these optimizations, a range of pyridine ethers were prepared (Table 24). Using the primary alcohols **150a-e**, bearing different function groups like amines or ethers, furnished the desired 4-alkoxylated 2-diethylaminopyridines **149b-f** in 61-81% yield (entries 1-5). (+)-Menthol (**150f**) and the chiral secondary alcohol **150g** were suitable substrates for this kind of reaction and provided the 2,4-difunctionalized pyridines **149g-h** in 68-71% yield (entries 6-7).

Table 24: Preparation of 4-aminated pyridines of type **149** *via* regioselective addition of potassium alkoxides to pyridyne intermediates.



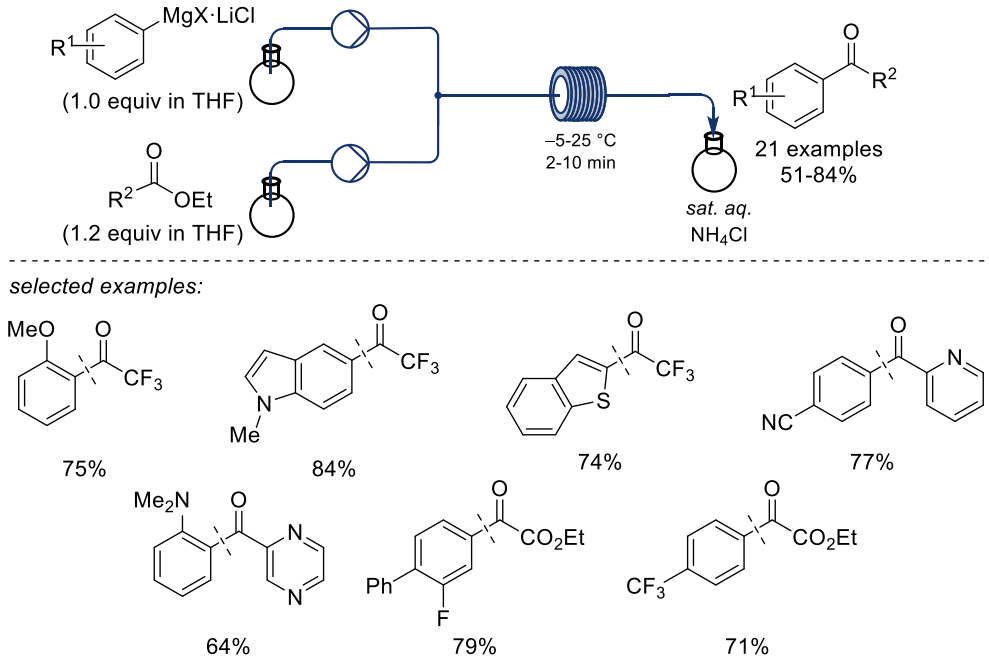
entry	alcohol	product[a]	entry	alcohol	product[a]
1	 **150a**	 **149b**: 61%	5	 **150e**	 **149f**: 81%
2	 **150b**	 **149c**: 65%	6	 **150f**	 **149g**: 68%
3	 **150c**	 **149d**: 77%	7	 **150g**	 **149h**: 71%
4	 **150d**	 **149e**: 62%			

[a] Yield of analytically pure isolated product.

5. Summary

5.1 Preparation of Ketones in Continuous Flow

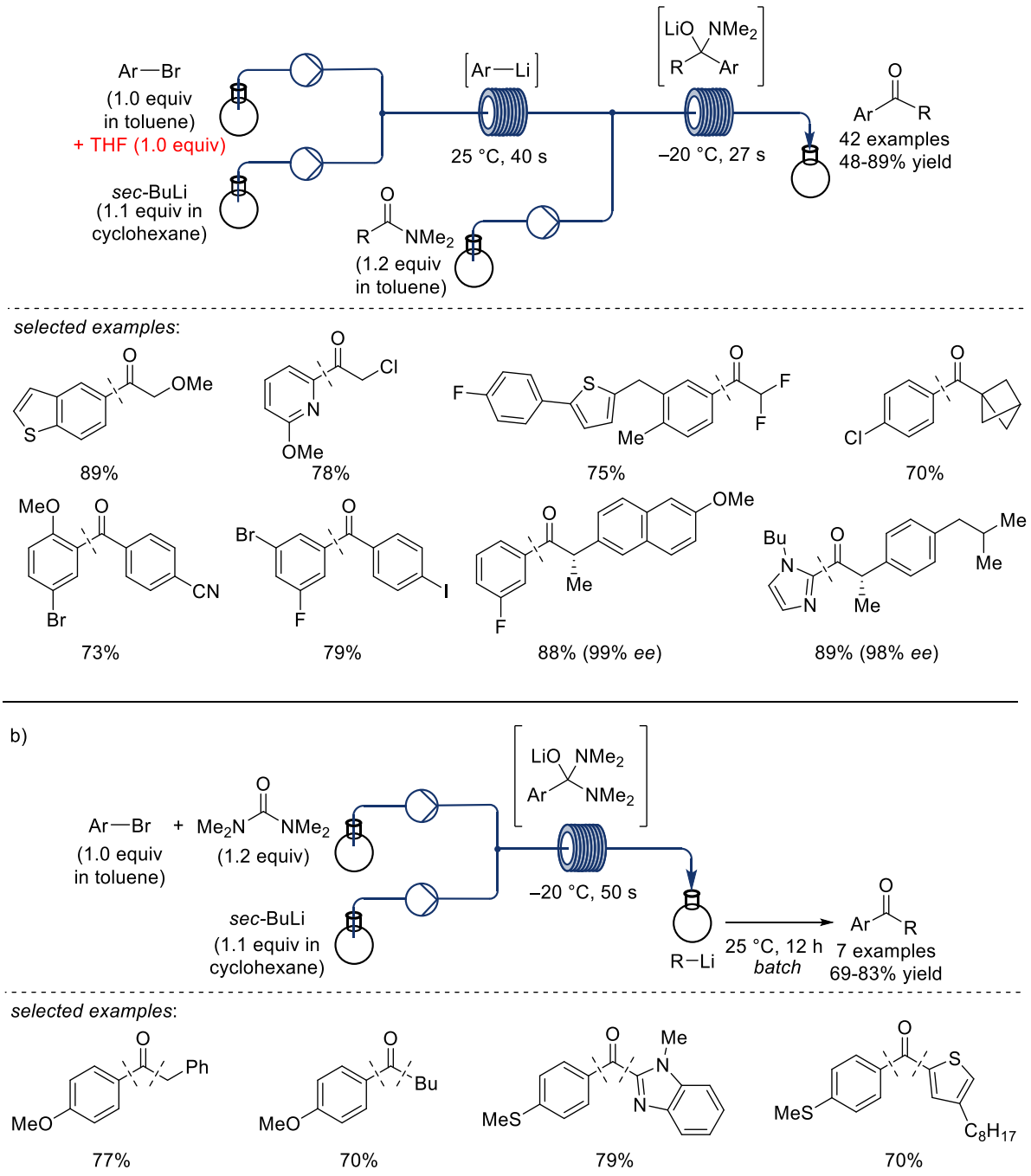
In this thesis, the preparation of ketones starting from Li- or Mg-organometallics and convenient acylation reagents was investigated with special attention to the shift of laboratory synthesis to potential industrial production. The use of a continuous flow setup offers a lot of benefits towards the handling of organometallic reagents, for example the precise control over temperature, reaction time and stoichiometry. Furthermore, continuous flow chemistry offers a high reproducibility and enables otherwise unachievable scale-ups. These benefits were exploited to conveniently generate various functionalized ketones starting from readily available esters or amides by treatment with different organometallic reagents.



Scheme 32: Selective acylation of various organomagnesium reagents with commercially available esters in continuous flow.

First, a selective acylation of Grignard reagents with commercially available esters was achieved (Scheme 32). Due to unstable tetrahedral intermediates and subsequent double additions to the generated ketones, these reactions were usually performed at very low temperatures in batch or by the use of stabilizing derivatives such as Weinreb amides. In continuous flow, the superior mixing and stoichiometric control of the reaction enabled higher reaction temperatures (–5 °C) for the selective acylation of organomagnesium reagents with

ethyl trifluoroacetate within just 2 min of reaction time. Diethyl oxalate and *N*-heterocyclic esters also proved to be suitable substrates for this procedure, producing various functionalized ketones at 25 °C in continuous flow. Furthermore, various bis-aryl ketones were produced in continuous flow starting from magnesiated ester derivatives of 2-hydroxyethyl esters, stabilizing the tetrahedral intermediate.



Scheme 33: Selective acylation of organolithiums reagents with *N*,*N*-dimethylamides in continuous flow.

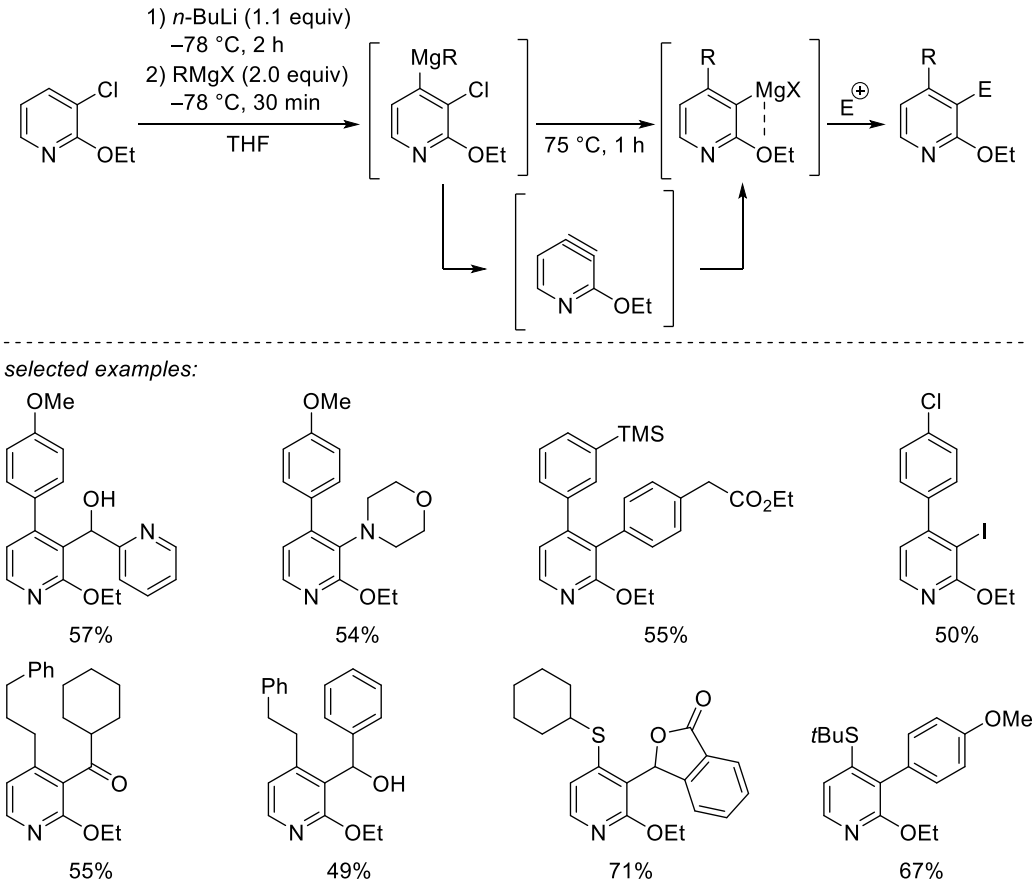
Second, a convenient acylation of organolithiums with readily available and functionalized *N*,*N*-dimethylamides in continuous flow was reported (Scheme 33). The lithium species was prepared *via* Br/Li-exchange in toluene (with 1.0 equiv of THF). This solvent system in continuous flow enabled a fast exchange (40 s) using *sec*-BuLi at 25 °C, temperatures which were unreachable in the commonly used solvent THF. Due to the instability of the aryllithiums over time, continuous flow showed to be beneficial for the "on-demand" preparation of these species. Subsequently, these lithium reagents were mixed at −20 °C with various *N*,*N*-dimethylamides, bearing sensitive groups and enolizable positions. After a residence time of 27 s, a broad range of ketones was obtained in excellent yields. Using these methods, α-chiral ketones derived from naproxen and ibuprofen were prepared with complete retention of chirality (99% *ee*). Additionally, a semi-batch telescoped preparation of unsymmetrical ketones was performed using TMU (tetramethylurea) as C1-building block. In a Barbier-type reaction in continuous flow, a solution of TMU and aryl bromides in toluene was mixed with *sec*-Buli at −20 °C for 50 s, leading to a first acylation. Injecting this mixture into another lithium species, prepared in batch, furnished a range of highly functionalized ketones.

5.2 Regioselective Functionalizations of Pyridines *via* Pyridyne Intermediates

The regioselective functionalization of *N*-heterocycles such as pyridine is an important synthetic task in pharmaceutical chemistry and related fields. Although various methods have been developed over the last decades, modification of pyridines *via* pyridyne intermediates is underrepresented even though it offers great possibilities. Due to elaborated precursors, which often have to be prepared over several steps, the lack of regioselectivity and a limited product scope, this chemistry is still mostly unattractive for industrial application. In this thesis, regioselective functionalizations of pyridines were investigated with the aim to overcome those problems and to develop new reaction protocols towards pyridyne intermediates using readily available starting materials and convenient reaction conditions.

Thus, a new reaction sequence towards 2,3,4-trifunctionalized pyridines *via* pyridynes was developed (Scheme 34). Starting from readily prepared 3-chloro-2-ethoxypyridine, a regioselective metalation in position C4 was achieved at −78 °C. After addition of organomagnesium reagents and subsequent transmetalation, a stable diorganomagnesium species was obtained. Heating to 75 °C triggered the elimination reaction towards a pyridyne

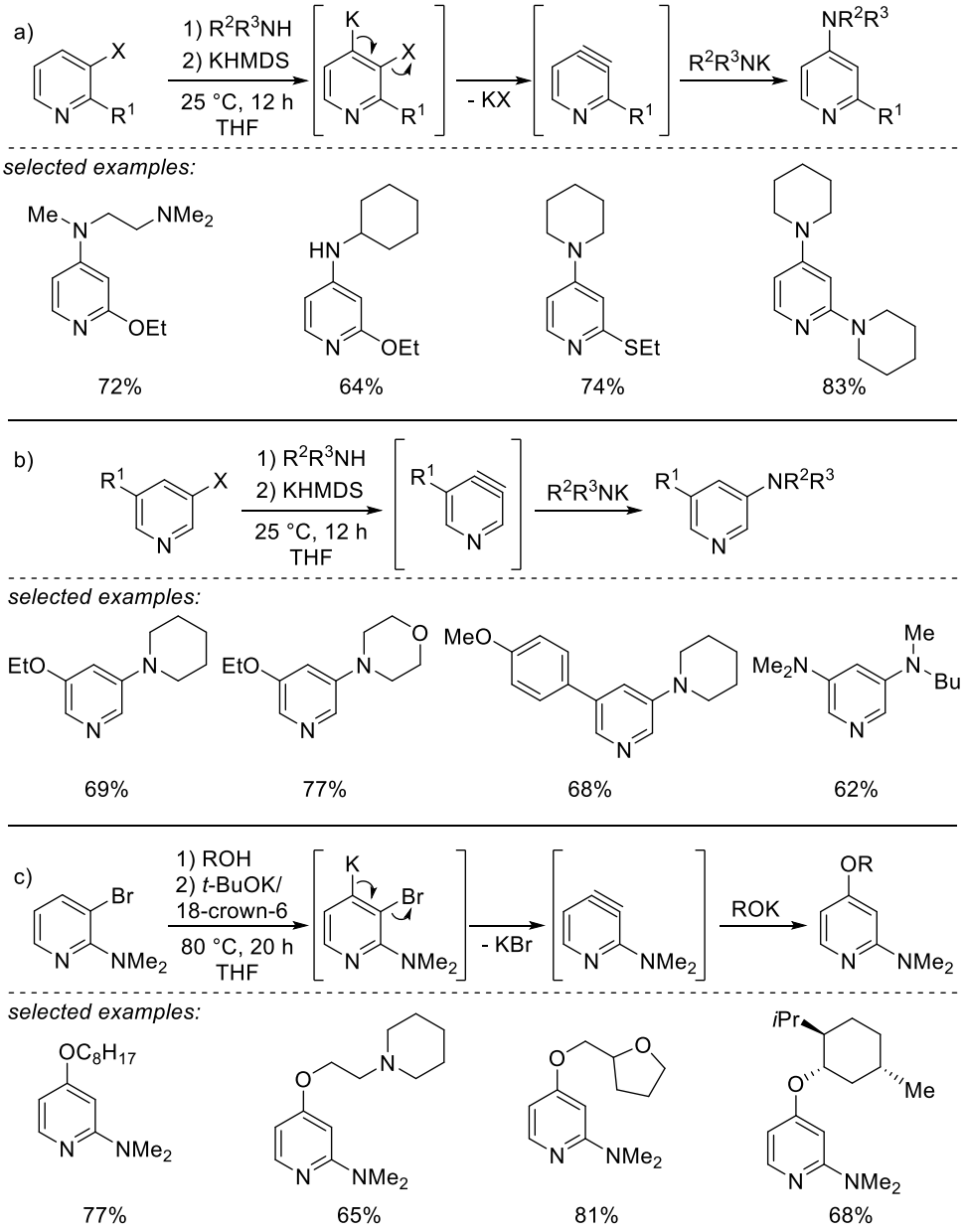
intermediate, immediately followed by regioselective addition of the organomagnesium reagents present in the solution. Quenching this newly prepared 3-magnesiated pyridines with various electrophiles led regioselectively to a 3,4-difunctionalization of the starting heterocycle. This multi-step procedure was transposed into a continuous flow setup.



Scheme 34: Regioselective difunctionalization of pyridines *via* pyridyne intermediates.

Finally, a new and convenient procedure for the regioselective amination and alkoxylation of pyridines *via* pyridyne intermediates was investigated. Treating 3-halo-2-alkoxypyridines (or related structures) with the strong but sterically hindered base KHMDS at 25 °C in the presence of differenct amines provided, after metalation and subsequent formation of the 3,4 pyridyne intermediate, regioselectively 2,4-disubstituted pyridines (Scheme 35). Also, the 3,5-substitution pattern could be addressed using this method, conveniently producing 5-aminated pyridines. Additionally, 4-alkoxylated pyridines were prepared by treatment of 3-bromo-2-

diethylaminopyridine with a *t*-BuOK·18-crown-6 mixture in the presence of primary or secondary alcohols.



Scheme 35: Regioselective amination and alkoxylation of pyridines *via* pyridyne intermediates.

C. EXPERIMENTAL PART

1. General Information

Batch reactions involving moisture sensitive reagents were carried out under argon or nitrogen atmosphere in glassware dried with a heat gun (650 °C) under high vacuum (<1 mbar). Syringes which were used to transfer anhydrous solvents or reagents were purged thrice with argon or nitrogen prior to use. Indicated yields are isolated yields of compounds estimated to be >95% pure as determined by 1H-NMR (25 °C) and capillary GC analyses. Unless otherwise indicated, all reagents were obtained from commercial sources. Undecane or tetradecane were used as internal standards.

Flow reactions were carried out with solutions of the reactants in dry solvents (toluene, THF, *n*-hexane). Flame dried glassware was used for the reagent solutions and kept under an argon atmosphere during the reactions. Undecane or tetradecane were used as internal standards. For all flow reactions a Vapourtec E-series Integrated Flow Chemistry System with 3rd Pump Kit, Organometallic Kit and Collection Valve Kit was used. Reactions were performed in coiled tube reactors. Coiled reactors (1.0, 2.0, 4.0, 5.0, 10.0 or 20.0 mL) were made from PFA or PTFE Teflon (i.d. = 0.8 mm, o.d. = 1.6 mm or i.d. = 1.6 mm, o.d. = 3.2 mm) and T-pieces (i.d. = 0.5 mm). Prior to performing reactions, the system was dried by flushing it with methanol, followed by THF or toluene (blue tubing) or *n*-hexane (red tubing) (flowrate of all pumps: 1.00 mL·min^{-1}; run-time: 30 min). After usage, the flow system was flushed in the following order: 1) THF, toluene or *n*-hexane (depending on the solvent systems used for the reaction); 2) methanol (5 min); 3) water (30 min, flowrate of all pumps: 1.00 mL·min^{-1})

1.1 Solvents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

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

***n*-Hexane** was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Toluene was purchased from Acros Organics (anhydrous, 99.85%).

Solvents for column chromatography were distilled on a rotary evaporator prior to use.

1.2 Reagents

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

***i*PrMgCl·LiCl** solution in THF was obtained from Albemarle and the concentration was determined by titration against I_2.[167]

CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a Schlenk flask under vacuum at 140 °C for 5 h. After cooling, dry THF (80 mL) was added and stirring continued until the salts were dissolved.[168]

$ZnCl_2$ solution (1.00 M) was prepared by drying $ZnCl_2$ (200 mmol, 27.3 g) in a Schlenk flask under vacuum at 140 °C for 5 h. After cooling, dry THF (200 mL) was added and stirring continued until the salt was dissolved.

***n*-BuLi** solution in hexane was obtained from Albemarle and the concentration was determined by titration agains 1,10-phenantroline in THF with dry *iso*propanol at 0 °C.[169]

***sec*-BuLi** solution in hexane was obtained from Albemarle and the concentration was determined by titration agains 1,10-phenantroline in THF with dry *iso*propanol at –40 °C.[64]

TMPH was distilled prior to use and stored under argon.

TMPLi solution in THF was prepared by slow addition of *n*-BuLi (4.0 mL, 10 mmol, 2.5 M in hexane) to a solution of TMPH (1.7 mL, 10 mmol) in THF (10 mL) at –40 °C and stirred for 30 min at this temperature. The solution was warmed to 0 °C before use. The concentration was determined by titration against *N*-benzylbenzamide in THF.[170]

[167] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336.
[168] P. Knochel.; M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390-2392.
[169] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[170] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281-283.

1.3 Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from MERCK.

Thin layer chromatography was performed using SiO2 pre-coated aluminum plates (Merck 60, F-254). The chromatograms were examined under 254 nm UV irradiation and/or by staining the TLC plate with a KMnO4 solution followed by heating with a heat gun.

HPLC was performed on an Agilent Technologies 1200 Series using a Chromolit® SemiPrep RP-18e 100-10 mm column. The HPLC was run with a gradient of acetonitrile/water.

1.4 Analytical Data

^{1}H-NMR and **^{13}C-NMR** spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as values in ppm relative to tetramethylsilane. $CDCl_3$ peaks were set to 7.26 ppm in ^{1}H-NMR and 77.16 ppm in ^{13}C-NMR experiments. The following abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), hept (heptet) as well as m (multiplet).

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an ionization energy of 70 eV. For coupled gas chromatography/mass spectrometry, a HEWLETT-PACKARD HP 6890/MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10-20%.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSamplIR II Diamond ATR sensor was used. The main absorption peaks are reported in cm^{-1}.

Melting points (m.p.) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected.

Single crystall X-ray diffraction studies: Single crystals, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into

perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-Kα radiation (λ = 0.71071 Å). Data collection and data reduction were performed with the CrysAlisPro software.[171] Absorption correction using the multiscan method6 was applied. The structures were solved with SHELXS-97,[172] refined with SHELXL-97[173] and finally checked using PLATON.[174] Details for data collection and structure refinement are summarized in the corresponding tables.

Optical rotation values were recorded on a *Perkin Elmer* 241 *or Anton Paar MCP* 500 polarimeter. The specific rotation is calculated as follows:

$$[\propto]_D^{20} = \frac{[\propto] \cdot 100}{c \cdot d}$$

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

[171] Program package 'CrysAlisPro 1.171.40.81a (Rigaku OD, 2020)'.
[172] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Goettingen, Germany.
[173] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[174] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

2. Selective Acylation of Aryl- and Heteroarylmagnesium Reagents with Esters in Continuous Flow

2.1 Typical Procedures

Typical Procedure 1: Preparation of organomagnesium reagents via Mg-insertion.

LiCl (509 mg, 12.0 mmol, 1.2 equiv) was flame dried and cooled to room temperature *in vacuo*. Then, magnesium turnings (288 mg, 12.0 mmol, 1.2 equiv) and THF (10 mL) were added and the reaction mixture was cooled to 0 °C. The organic halide (10.0 mmol, 1.0 equiv) was added dropwise and the reaction was stirred at 0 °C for 1-3 h. Upon completion of the insertion, the concentration was determined by titration against iodine in THF.

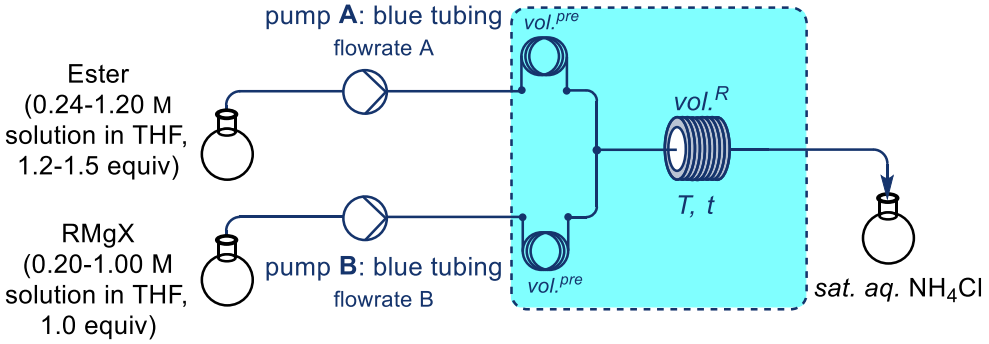
Typical Procedure 2: Preparation of organomagnesium reagents *via* I/Mg exchange.

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the substituted aryl iodide (10.0 mmol, 1.0 equiv) and dry THF (10 mL). The reaction mixture was cooled to the appropriate temperature before *i*PrMgCl·LiCl (11.0 mmol, 1.1 equiv) was added dropwise. The progress of the iodine/magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with *aq. sat.* NH_4Cl solution. Upon completion of the exchange, concentration was determined by titration against iodine in THF.

Typical Procedure 3: Preparation of glycol esters of type **97** and subsequent formation of Mg-alkoxides of type **98**.

Acyl chloride (25.0 mmol, 1.0 equiv) was added slowly to a stirring solution of ethylene glycol (4.20 mL, 75.0 mmol, 3.0 equiv) and pyridine (2.25 mL, 27.5 mmol, 1.1 equiv) in 25 mL of anhydrous dichloromethane at 0 °C. After stirring for an additional 24 h at room temperature, the reaction was diluted with ethyl acetate (200 mL), washed with water (3 x 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification over silica with the appropriate eluent afforded the monoacylated ethylene glycol derivatives of type **97**. A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the monoacylated ethylene glycol (5.00 mmol, 1.0 equiv) and dry THF (16 mL). The reaction mixture was cooled to 0 °C, before *i*PrMgCl·LiCl (5.00 mmol, 1.0 equiv) was added dropwise. The reaction mixture was stirred for additional 5 min prior to use.

Typical Procedure 4: Preparation of ketones of type **92**, **94**, **96** and **99** starting from esters and organomagnesium reagents in flow.



Scheme 36: Flow chemistry setup for preparation of ketones starting from Grignard reagents and esters.

An organomagnesium reagent in THF (0.20 – 1.00 M, 1.0 equiv) and a solution of ester in THF (0.24 – 1.20 M, 1.2 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 1.0 – 5.0 mL·min^{-1} and flowrate B = flowrate A. After passing a PTFE tubing (vol^{pre} = 2.0 mL, T = –5 °C to 25 °C, residence time: 24 – 120 s) for precooling, the solutions were mixed in a T-mixer[175] (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (vol^{R} = 20 mL; residence time: t = 2 – 10 min, T = –5 °C to 25 °C) and was subsequently injected in a flask containing a stirred *sat. aq.* NH_4Cl solution for quenching. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash column chromatographical purification with suited *iso*hexane:EtOAc mixtures afforded the pure products.

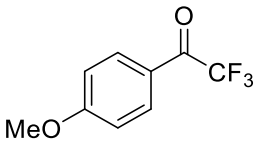
Batch Comparison Experiments

An argon-flushed, flame dried flask was charged with ethyl trifluoroacetate (**89a**) (0.07 mL, 0.60 mmol, 1.2 equiv) and THF (1.2 mL). After cooling the solutions to the desired temperature, (4-methoxyphenyl)magnesium bromide (0,51 mL, 0.98 M, 1.0 equiv, 0.50 mmol) was added dropwise over 1 min to the stirred reaction mixture. The reaction was quenched after the appropriate time by adding sat. aq. NH_4Cl.

[175] The use of a Y-mixer (i.d. = 0.5 mm) led to the same results.

2.2 Preparation of Compounds

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethan-1-one (92a)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (1.18 M, 0.40 mmol, 1.2 equiv) and (4-methoxyphenyl)magnesium bromide (**91a**) (0.98 M, 0.33 mmol, 1.0 equiv), prepared via **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 2 min, T = –5 °C). Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (isohexane:ethyl acetate = 9.5:0.5) to give **92a** (45.0 mg, 0.22 mmol, 67%) as a colourless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 (dq, *J* = 9.2, 1.1 Hz, 2H), 7.00 (d, *J* = 9.1 Hz, 2H), 3.91 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 178.9 (q, *J* = 34.5 Hz), 165.4, 132.8, 122.8, 118.4 (q, *J* = 291.5 Hz), 114.4, 55.7.

The spectra matched those of the literature.[176]

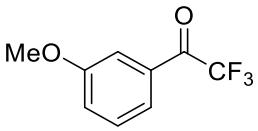
Upscale Experiment for Compound 92a

(4-Methoxyphenyl)magnesium bromide (**91a**) (0.50 M, 2.00 mmol, 1.0 equiv), prepared *via* **TP1** and a solution of ethyl trifluoroacetate (**89a**) in THF (0.60 M, 2.40 mmol, 1.2 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 5.0 mL·min^{-1} and flowrate B = flowrate A (suction time = 48 s). After passing a PTFE tubing (vol^{pre} = 2.0 mL, T = –5 °C, residence time: 24 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} = 20 mL; residence time: t = 2 min, T = –5 °C) and was subsequently injected in a flask containing a stirred *sat. aq.* NH_4Cl solution for quenching at 25 °C. The aqueous phase was extracted with Et_2O and the combined organic phases were dried over Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash column chromatographical

[176] T. Konno, T. Takehana, M. Mishima, T. Ishihara, *J. Org. Chem.* **2006**, *71*, 3545-3550.

purification (*iso*hexane:ethyl acetate = 9.5:0.5) afforded the pure product **92a** (270 mg, 1.32 mmol, 66%) as a colourless solid.

2,2,2-Trifluoro-1-(3-methoxyphenyl)ethan-1-one (92b)

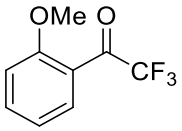


Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (1.12 M, 1.80 mmol, 1.2 equiv) and (3-methoxyphenyl)magnesium bromide (**91b**) (0.93 M, 1.50 mmol, 1.0 equiv), prepared via **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 2 min, T = –5 °C). Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give **92b** (201 mg, 0.98 mmol, 65%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.68 (dq, *J* = 7.8, 1.4 Hz, 1H), 7.59 (t, *J* = 2.2 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.23 (m, 1H), 3.90 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 180.4 (q, *J* = 35.0 Hz), 160.0, 131.1, 130.1, 122.7 (q, *J* = 2.7 Hz), 122.3, 116.6 (d, *J* = 291.3 Hz), 114.0 (q, *J* = 1.8 Hz), 55.5.

The spectra matched those of the literature.[71]

2,2,2-Trifluoro-1-(2-methoxyphenyl)ethan-1-one (92c)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (1.20 M, 0.40 mmol, 1.2 equiv) and (2-methoxyphenyl)magnesium bromide (**91c**) (1.00 M, 0.33 mmol, 1.0 equiv), prepared via **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 2 min, T = –5 °C). Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give **92c** (51.0 mg, 0.25 mmol, 75%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.67 (d, *J* = 7.8, 1.9, 0.6 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.07 – 7.01 (m, 2H), 3.91 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 183.0 (q, *J* = 36.6 Hz), 159.8, 135.9, 131.3, 121.7, 120.7, 116.2 (q, *J* = 291.0 Hz), 112.1, 55.9.

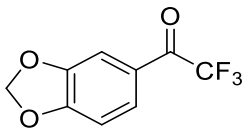
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –74.16.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2949, 2845, 2355, 1709, 1600, 1489, 1278, 1145, 1114, 1020, 930, 753, 657.

MS (EI, 70 eV): m/z (%) = 204 (10), 135 (100), 92 (11), 77 (16).

HRMS (EI): m/z calc. for [$C_9H_7F_3O_2$]: 204.0398; found 204.0392.

1-(Benzo[d][1,3]dioxol-5-yl)-2,2,2-trifluoroethan-1-one (92d)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (0.60 M, 0.45 mmol, 1.2 equiv) and benzo[d][1,3]dioxol-5-ylmagnesium bromide (**91d**) (0.50 M, 0.37 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^R = 20 mL, residence time: t = 2 min, T = –5 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give **92d** (50.0 mg, 0.23 mmol, 62%) as a colourless oil.

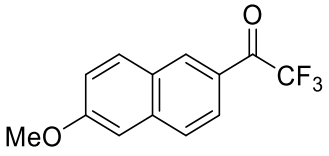
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.72 – 7.66 (m, 1H), 7.47 (s, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.10 (s, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 178.6 (q, *J* = 34.8 Hz), 154.0, 148.6, 127.6, 124.4, 116.81 (q, *J* = 291.2 Hz), 109.2, 108.5, 102.5.

The spectra matched those of the literature. [177]

2,2,2-Trifluoro-1-(6-methoxynaphthalen-2-yl)ethan-1-one (92e)

[177] C. B. Kelly, M. A. Mercadante, T. H. Hamlin, M. H. Fletcher, N. E. Leadbeater, J. Org. Chem. 2012, 77, 8131-8141.



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (1.20 M, 0.48 mmol, 1.2 equiv) and (6-methoxynaphthalen-2-yl)magnesium (**91e**) (1.00 M, 0.40 mmol, 1.0 equiv), prepared via **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min-1, VolR = 20 mL, residence time: t = 2 min, T = –5 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give **92e** (67.0 mg, 0.27 mmol, 69%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.53 (t, *J* = 1.9 Hz, 1H), 8.04 (ddd, *J* = 8.8, 1.9, 0.8 Hz, 1H), 7.89 (dd, *J* = 8.9, 0.7 Hz, 1H), 7.83 – 7.80 (m, 1H), 7.25 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.17 (d, *J* = 2.5 Hz, 1H), 3.97 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 180.1 (q, *J* = 34.6 Hz), 161.1, 138.5, 133.0, 131.9, 127.7, 127.5, 125.1, 125.1, 120.4, 117.0 (q, *J* = 291.5 Hz), 105.9, 55.5.

^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –70.6.

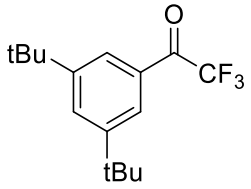
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 3015, 2940, 1697, 1618, 1481, 1400 1266, 1194, 1140, 1028, 900, 749.

MS (EI, 70 eV): *m/z* (%) = 254 (35), 186 (13), 185 (100), 157 (38), 142 (25), 114 (16).

HRMS (EI): *m/z* calc. for [$C_{13}H_9F_3O_2$]: 254.0555; found 254.0584.

M.p. (°C): 69-70.

1-(3,5-Di-tert-butylphenyl)-2,2,2-trifluoroethan-1-one (92f)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (0.89 M, 1.78 mmol, 1.2 equiv) and (3,5-di-tert-butylphenyl)magnesium bromide (**91f**) (0.74 M, 1.48 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^R = 20 mL, residence time: t = 2 min, T = –5 °C). Thereafter, the reaction mixture was quenched with

NH_4Cl. After workup, the crude product was purified via column chromatography (pentane + 1% triethylamine) to give **92f** (272 mg, 0.95 mmol, 64%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 (dd, *J* = 1.9, 1.1 Hz, 2H), 7.81 (t, *J* = 1.9 Hz, 1H), 1.38 (s, 18H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 181.0 (q, *J* = 34.3 Hz), 151.9, 130.0, 129.6, 124.4, 116.9 (q, *J* = 291.7 Hz), 35.1, 31.2.

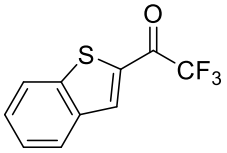
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –71.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2965, 2356, 1718, 1594, 1478, 1366, 1200, 1178, 1140, 996, 839, 709.

MS (EI, 70 eV): *m/z* (%) = 272 (16), 271 (100), 243 (21).

HRMS (EI): *m/z* calc. for [$C_{16}H_{21}F_3O$]: 286.1544; found 286.1537.

1-(Benzo[b]thiophen-2-yl)-2,2,2-trifluoroethan-1-one (92g)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (0.6 M, 0.60 mmol, 1.2 equiv) and benzo[b]thiophen-2-ylmagnesium bromide (**91g**) (0.50 M, 0.50 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^R = 20 mL, residence time: t = 2 min, T = –5 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.9:0.1) to give **92g** (170 mg, 0.74 mmol, 74%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.24 (dt, *J* = 2.4, 1.2 Hz, 1H), 7.98 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.92 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.57 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.48 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 175.3 (q, *J* = 37.0 Hz), 143.6, 138.8, 135.6, 134.3, 129.2, 127.1, 125.8, 122.9, 116.4 (q, *J* = 290.4 Hz).

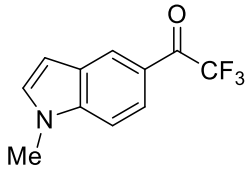
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –71.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1682, 1595, 1508, 1345, 1250, 1225, 1189, 1139, 882, 842, 760, 744, 718.

MS (EI, 70 eV): *m/z* (%) = 230 (38), 162 (10), 161 (100), 133 (24), 89 (23).

HRMS (EI): *m/z* calc. for [$C_9H_5F_3OS$]: 230.0006; found 230.0013.
m.p. (°C): 50-51.

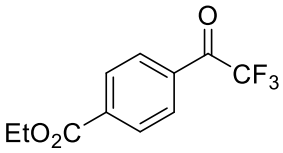
2,2,2-Trifluoro-1-(1-methyl-1H-indol-5-yl)ethan-1-one (92h)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (0.27 M, 0.27 mmol, 1.2 equiv) and (1-methyl-1*H*-indol-5-yl)magnesium bromide (**91h**) (0.22 M, 0.22 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 2 min, T = –5 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **92h** (42 mg, 0.19 mmol, 84%) as a red solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 – 8.41 (m, 1H), 7.99 (m, 1H), 7.42 (dt, *J* = 8.8, 0.8 Hz, 1H), 7.19 (d, *J* = 3.2 Hz, 1H), 6.69 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.87 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 180.4 (q, *J* = 33.8 Hz), 140.2, 131.3, 128.1, 125.8, 123.3, 121.8, 117.3 (q, *J* = 291.8 Hz), 109.9, 103.9, 33.1.
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –71.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2360, 1696, 1606, 1218, 1192, 1138, 1099, 962, 752, 718.
MS (EI, 70 eV): *m/z* (%) = 227 (47), 159 (11), 158 (100), 130 (45), 128 (21), 103 (15), 77 (12).
HRMS (EI): *m/z* calc. for [$C_{11}H_8F_3NO$]: 227.0558; found 227.0550.
m.p. (°C): 55-56.

Ethyl 4-(2,2,2-trifluoroacetyl)benzoate (92i)

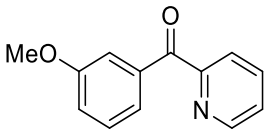


Following **TP4**, precooled solutions of ethyl trifluoroacetate (**89a**) (0.6 M, 1.50 mmol, 1.2 equiv) and (4-(ethoxycarbonyl)phenyl)magnesium chloride (**91i**) (0.50 M, 1.25 mmol, 1.0

equiv), prepared *via* **TP2** (–30 °C, 30 min), were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 2 min, T = 15 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (pentane/Et_2O = 7.0:3:0) to give **92i** (218 mg, 0.89 mmol, 71%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 – 8.18 (m, 2H), 8.13 (dq, *J* = 7.7, 1.0 Hz, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 180.2 (q, *J* = 35.7 Hz), 165.1, 136.3, 132.9, 130.1, 130.0 (d, *J* = 7.3 Hz), 116.5 (q, *J* = 291.0 Hz), 61.8, 14.2.
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –71.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2985, 2358, 1721, 1276, 1205, 1181, 1145, 1106, 1021, 941, 730, 696.
MS (EI, 70 eV): *m/z* (%) = 246 (25), 201 (64), 178 (11), 177 (100), 173 (14), 149 (77), 123 (16), 104 (11).
HRMS (EI): *m/z* calc. for [$C_{11}H_9F_3O_3$]: 246.0504; found 246.0497.

(3-Methoxyphenyl)(pyridin-2-yl)methanone (94a)



Following **TP4**, solutions of ethyl 2-picolinate **89b** (0.60 M, 0.60 mmol, 1.2 equiv) and (3-methoxyphenyl)magnesium bromide (**91b**) (0.50 M, 0.50 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 2 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.9:0.1) to give **94a** (170 mg, 0.74 mmol, 75%) as a pink liquid.

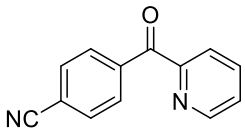
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.69 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.99 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.45 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.12 (ddd, *J* = 8.3, 2.7, 1.1 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.7, 159.4, 155.1, 148.6, 137.5, 137.1, 129.2, 126.2, 124.6, 123.9, 119.5, 115.1, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2835, 1661, 1595, 1578, 1484, 1431, 1304, 1282, 1248, 1141, 1041, 994, 954, 829, 745, 706

MS (EI, 70 eV): *m/z* (%) = 213 (31), 212 (65), 198 (17), 186 (11), 185 (84), 184 (100), 182 (21), 170 (22), 156 (12), 155 (16), 154 (14), 135 (67), 107 (31), 77 (26)

HRMS (EI): *m/z* calc. for [$C_{13}H_{11}NO_2$]: 213.0790; found 213.0782.

4-Picolinoylbenzonitrile (94b)



Following **TP4**, solutions of ethyl 2-picolinate **89b** (0.23 M, 0.23 mmol, 1.2 equiv) and (4-cyanophenyl)magnesium chloride (**91j**) (0.19 M, 0.19 mmol, 1.0 equiv), prepared *via* **TP2** (–30 °C, 30 min), were mixed in continuous flow (flowrate A = 1 $mL \cdot min^{-1}$, vol^R = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **94b** (30 mg, 0.15 mmol, 77%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.72 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.21 – 8.25 (m, 2H), 8.12 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.91 (td, *J* = 7.8, 1.8 Hz, 1H), 7.83 – 7.75 (m, 2H), 7.58 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.2, 153.8, 148.7, 139.9, 137.4, 131.9, 131.4, 127.0, 124.8, 118.2, 115.8.

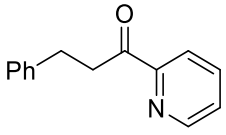
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 1730, 1669, 1584, 1437, 1407, 1309, 1285, 1244, 1157, 996, 938, 856, 804, 749, 705, 680.

MS (EI, 70 eV): *m/z* (%) = 207 (56), 181 (13), 180 (100), 179 (70), 130 (20), 130 (23).

HRMS (EI): *m/z* calc. for [$C_{13}H_7N_2O$]: 207.0564; found 207.0551 (M^+-H).

m.p. (°C): 116-117.

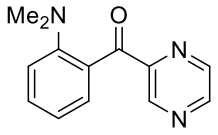
3-Phenyl-1-(pyridin-2-yl)propan-1-one (94c)



Following **TP4**, solutions of ethyl 2-picolinate **89b** (0.27 M, 0.27 mmol, 1.5 equiv) and phenethylmagnesium bromide (**91k**) (0.18 M, 0.18 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 0 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 8.0:2.0) to give **94c** (24 mg, 0.12 mmol, 63%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.67 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.05 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 7.28 (d, *J* = 4.4 Hz, 4H), 7.23 – 7.17 (m, 1H), 3.58 (dd, *J* = 8.3, 7.2 Hz, 2H), 3.08 (dd, *J* = 8.2, 7.2 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 201.0, 153.3, 149.0, 141.4, 136.9, 128.5, 128.4, 127.1, 126.0, 121.8, 39.4, 29.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2926, 1697, 1583, 1454, 1437, 1363, 1305, 1212, 995, 980.
MS (EI, 70 eV): *m/z* (%) = 211 (17), 184 (10), 183 (73), 183 (12), 182 (89), 91 (14), 79 (100), 78 (18).
HRMS (EI): *m/z* calc. for [$C_{14}H_{13}NO$]: 211.0997; found 211.0990.

(2-(Dimethylamino)phenyl)(pyrazin-2-yl)methanone (94d)



Following **TP4**, solutions of methyl pyrazine-2-carboxylate **89c** (0.32 M, 0.32 mmol, 1.5 equiv) and (2-(dimethylamino)phenyl)magnesium bromide (**91l**) (0.21 M, 0.21 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 7.0:3.0) to give **94d** (30 mg, 0.13 mmol, 64%) as an orange oil.

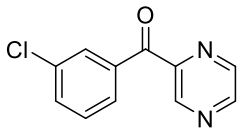
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.04 (d, *J* = 1.5 Hz, 1H), 8.68 (d, *J* = 2.5 Hz, 1H), 8.62 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.06 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.01 (td, *J* = 7.4, 1.0 Hz, 1H), 2.62 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.6, 153.0, 150.7, 146.4, 145.2, 143.6, 133.0, 131.2, 128.7, 120.3, 117.5, 43.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2865, 2360, 1663, 1596, 1496, 1454, 1430, 1306, 1268, 1156, 1050, 1017, 953, 933, 921, 752.

MS (EI, 70 eV): *m/z* (%) = 210 (35), 209 (100), 195 (14), 156 (13), 148 (14), 130 (14), 120 (13), 118 (11), 104 (22), 94 (10), 91 (19), 77 (21).

HRMS (EI): *m/z* calc. for [$C_{13}H_{13}N_3O$]: 227.1059; found 227.1053.

(3-Chlorophenyl)(pyrazin-2-yl)methanone (94e)



Following **TP4**, solutions of methyl pyrazine-2-carboxylate **89c** (0.9 M, 1.08 mmol, 1.2 equiv) and (3-chlorophenyl)magnesium bromide (**91m**) (0.75 M, 0.75 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 10 mL·min^{-1}, vol^R = 20 mL, residence time: t = 2 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 8.0:2.0) to give **94e** (210 mg, 0.13 mmol, 51%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.27 (d, *J* = 1.5 Hz, 1H), 8.80 (d, *J* = 2.5 Hz, 1H), 8.69 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.10 (t, *J* = 1.9 Hz, 1H), 8.05 – 7.93 (m, 1H), 7.69 – 7.55 (m, 1H), 7.45 (t, *J* = 7.9 Hz, 1H).

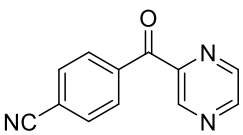
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.8, 149.2, 147.2, 146.2, 142.9, 137.0, 134.5, 133.4, 130.8, 129.7, 129.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 1662, 1566, 1421, 1401, 1293, 1267, 1154, 1016, 949, 762, 703.

MS (EI, 70 eV): *m/z* (%) = 218 (15), 183 (25), 141 (32), 139 (100), 111 (18), 75 (23).

HRMS (EI): *m/z* calc. for [$C_{11}H_7ClN_2O$]: 218.0247; found 218.0238.

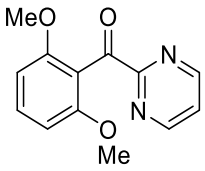
4-(Pyrazine-2-carbonyl)benzonitrile (94f)



Following **TP4**, solutions of pyrazine-2-carboxylate **89c** (0.27 M, 0.27 mmol, 1.5 equiv) and (4-cyanophenyl)magnesium chloride (**91j**) (0.19 M, 0.19 mmol, 1.0 equiv), prepared *via* **TP2** (–30 °C, 30 min), were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **94f** (21.0 mg, 0.10 mmol, 55%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.34 (d, *J* = 1.5 Hz, 1H), 8.84 (d, *J* = 2.5 Hz, 1H), 8.69 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.23 – 8.21 (m, 2H), 7.82 – 7.80 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.8, 148.6, 147.6, 146.3, 142.9, 138.9, 132.1, 131.3, 118.0, 116.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2064, 2360, 2234, 1673, 1406, 1302, 1153, 1019, 934, 770.
MS (EI, 70 eV): *m/z* (%) = 209 (27), 181 (41), 130 (35), 130 (100), 102 (10).
HRMS (EI): *m/z* calc. for [$C_{12}H_7N_3O$]: 209.0589; found 209.0582.
M.p. (°C): 127-128.

(2,6-Dimethoxyphenyl)(pyrimidin-2-yl)methanone (94g)



Following **TP4**, solutions of methyl pyrimidine-2-carboxylate **89d** (0.27 M, 0.27 mmol, 1.5 equiv) and (2,6-dimethoxyphenyl)magnesium bromide (**91n**) (0.18 M, 0.18 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 40 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 8.0:2.0) to give **94g** (51 mg, 0.21 mmol, 60%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.91 (d, *J* = 4.8 Hz, 2H), 7.62 – 7.33 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 3.69 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm =192.6, 161.9, 158.8, 157.6, 132.2, 122.3, 117.3, 104.2, 56.0.

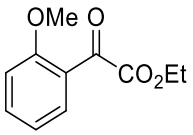
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2845, 1705, 1590, 1473, 1434, 1407, 1306, 1286, 1250, 1104, 943, 784, 759, 740, 702

MS (EI, 70 eV): *m/z* (%) = 244 (), 213 (46), 165 (100), 150 (25), 122 (15), 107 (23)

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}N_2O_3$]: 244.0848; found 244.0844.

M.p. (°C): 127-128.

Ethyl 2-(2-methoxyphenyl)-2-oxoacetate (96a)



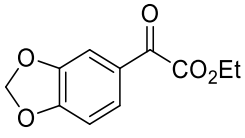
Following **TP4**, solutions of diethyl oxalate (**89e**) (0.53 M, 1.32 mmol, 1.2 equiv) and (2-methoxyphenyl)magnesium bromide (**91c**) (0.44 M, 1.10 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^R = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **96a** (190 mg, 0.91 mmol, 83%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.80 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.00 (tt, *J* = 7.3, 0.9 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 4.35 – 4.30 (m, 2H), 3.80 (t, *J* = 0.8 Hz, 3H), 1.32 (tt, *J* = 7.2, 0.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 186.6, 165.3, 160.3, 136.4, 130.6, 122.7, 121.3, 112.1, 61.8, 56.0, 14.1.

The spectra matched those of the literature.[178]

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-oxoacetate (96b)



Following **TP4**, solutions of diethyl oxalate (**89e**) (0.60 M, 0.60 mmol, 1.2 equiv) and benzo[d][1,3]dioxol-5-ylmagnesium bromide (**91d**) (0.50 M, 0.50 mmol, 1.0 equiv), prepared

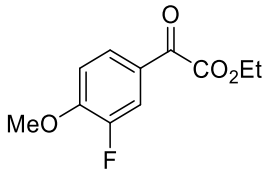
[178] Y. Kumar, Y. Jaiswal, A. Kumar, *J. Org. Chem.* **2016**, *81*,12247-12257.

via **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) to give **96b** (70.0 mg, 0.31 mmol, 63%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 (dt, *J* = 8.2, 1.8 Hz, 1H), 7.47 (t, *J* = 1.8 Hz, 1H), 6.89 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.08 (d, *J* = 1.8 Hz, 2H), 4.42 (qd, *J* = 7.1, 1.7 Hz, 2H), 1.41 (td, *J* = 7.2, 1.8 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 184.6, 164.0, 153.5, 148.5, 127.9, 127.2, 108.7, 108.3, 102.2, 62.3, 14.1.

The spectra matched those of the literature.[71]

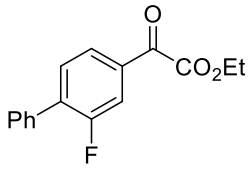
Ethyl 2-(3-fluoro-4-methoxyphenyl)-2-oxoacetate (96c)



Following **TP4**, solutions of diethyl oxalate (**89e**) (0.32 M, 0.32 mmol, 1.4 equiv) and (3-fluoro-4-methoxyphenyl)magnesium bromide (**91o**) (0.23 M, 0.23 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **96c** (36.0 mg, 0.16 mmol, 69%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 (ddd, *J* = 8.6, 2.1, 1.1 Hz, 1H), 7.78 (dd, *J* = 11.5, 2.1 Hz, 1H), 7.03 (t, *J* = 8.3 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 183.9, 163.4, 153.4 (d, *J* = 32.0 Hz), 150.8, 128.3, 125.7, 117.2 (d, *J* = 19.5 Hz), 112.6, 62.4, 56.4, 14.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 2941, 2360, 1731, 1679, 1608, 1516, 1439, 1284, 1253, 1221, 1161, 1118, 1015, 896, 762.
MS (EI, 70 eV): *m/z* (%) = 153 (100).
HRMS (EI): *m/z* calc. for [$C_{11}H_{11}FO_4$]: 226.0641; found 226.0643.

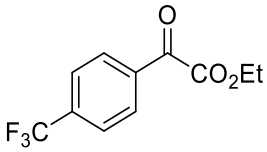
Ethyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetate (96d)



Following **TP4**, solutions of diethyl oxalate (**89e**) (0.30 M, 0.30 mmol, 1.5 equiv) and (2-fluoro-[1,1'-biphenyl]-4-yl)magnesium bromide (**91p**) (0.20 M, 0.20 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **96d** (45.0 mg, 0.17 mmol, 79%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92 – 7.82 (m, 2H), 7.63 – 7.56 (m, 3H), 7.52 – 7.38 (m, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 184.6, 163.1, 160.9, 158.4, 135.8 (d, *J* = 13.7 Hz), 134.3 (d, *J* = 1.5 Hz), 133.1 (d, *J* = 7.0 Hz), 131.3 (d, *J* = 3.5 Hz), 129.1 (d, *J* = 3.2 Hz), 128.7, 126.3 (d, *J* = 3.5 Hz), 117.5 (d, *J* = 24.9 Hz), 62.6, 14.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3452, 2984, 1731, 1687, 1612, 1408, 1300, 1248, 1215, 1154, 1132, 1121, 1025, 1010, 892, 765, 720, 696.
MS (EI, 70 eV): *m/z* (%) = 200 (11), 199 (100), 171 (18), 170 (47).
HRMS (EI): *m/z* calc. for [$C_{16}H_{13}O_3F$]: 272.0849; found 272.0837.

Ethyl 2-oxo-2-(4-(trifluoromethyl)phenyl)acetate (96e)

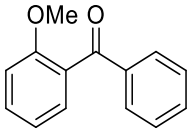


Following **TP4**, solutions of diethyl oxalate (**89e**) (0.30 M, 0.30 mmol, 1.2 equiv) and (4-(trifluoromethyl)phenyl)magnesium bromide (**91q**) (0.24 M, 0.24 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with

NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 8.0:2.0) to give **96e** (41.0 mg, 0.17 mmol, 71%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 – 8.15 (m, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = δ 185.0, 162.8, 135.9 (q, *J* = 32.9 Hz), 135.3 (d, *J* = 1.3 Hz), 130.4, 125.9, 62.8, 14.1.
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = -63.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2987, 1735, 1697, 1412, 1323, 1203, 1166, 1125, 1112, 1065, 1013, 981, 847.
MS (EI, 70 eV): *m/z* (%) = 173 (100), 145 (35).
HRMS (EI): *m/z* calc. for [$C_{11}H_9O_3F_3$]: 246.0504; found 246.0489.

(2-Methoxyphenyl)(phenyl)methanone (99a)



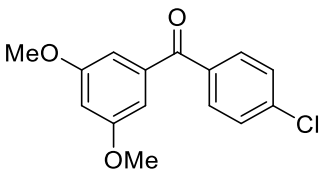
Following **TP4**, solutions of alkoxide **98a** (0.60 M, 0.60 mmol, 1.2 equiv), prepared *via* **TP3**, and (2-methoxyphenyl)magnesium bromide (**91c**) (0.48 M, 0.48 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^R = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **99a** (80.0 mg, 0.38 mmol, 78%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 – 7.80 (m, 2H), 7.58 – 7.53 (m, 1H), 7.50 – 7.41 (m, 3H), 7.36 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.07 – 6.98 (m, 2H), 3.73 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.5, 157.4, 137.8, 132.9, 131.9, 129.8, 129.6, 128.9, 128.2, 120.5, 111.5, 55.6.

The spectra matched those of the literature.[179]

[179] H. Neumann, A. Brennführer, M. Beller, *Chem. Eur. J.*, **2008**, *14*, 3645-3652.

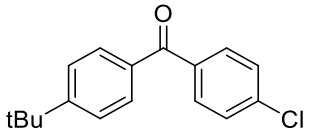
(4-Chlorophenyl)(3,5-dimethoxyphenyl)methanone (99b)



Following **TP4**, solutions of alkoxide **98b** (0.84 M, 0.84 mmol, 1.2 equiv), prepared *via* **TP3**, and (3,5-dimethoxyphenyl)magnesium bromide (**91r**) (0.70 M, 0.70 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give **99b** (120 mg, 0.43 mmol, 62%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.76 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 2.3 Hz, 2H), 6.68 (t, *J* = 2.3 Hz, 1H), 3.83 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.1, 160.6, 139.1, 138.9, 135.8, 131.4, 128.6, 107.8, 104.9, 55.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 2839, 2362, 1659, 1587, 1455, 1425, 1352, 1324, 1300, 1205, 1156, 1090, 1065, 990, 842, 812, 759.
MS (EI, 70 eV): *m/z* (%) = 278 (32), 277 (16), 276 (100), 241 (26), 226 (15), 165 (85), 140 (28), 139 (13), 139 (85), 137 (31), 122 (15), 111 (12).
HRMS (EI): *m/z* calc. for [$C_{15}H_{13}O_3Cl$]: 276.0553; found 276.0545.

(4-(Tert-butyl)phenyl)(4-chlorophenyl)methanone (99c)

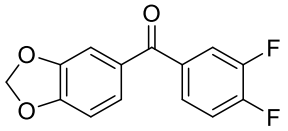


Following **TP4**, solutions of alkoxide **98b** (0.60 M, 0.60 mmol, 1.2 equiv), prepared *via* **TP3**, and (4-(tert-butyl)phenyl)magnesium bromide (**91s**) (0.45 M, 0.45 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **99c** (91.0 mg, 0.33 mmol, 74%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 – 7.74 (m, 2H), 7.74 – 7.72 (m, 2H), 7.52 – 7.49 (m, 2H), 7.47 – 7.44 (m, 2H), 1.37 (d, *J* = 1.0 Hz, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.2, 156.5, 138.6, 136.2, 134.4, 131.4, 130.0, 128.5, 125.4, 35.1, 31.1.

The spectra matched those of the literature.[180]

Benzo[d][1,3]dioxol-5-yl(3,4-difluorophenyl)methanone (99d)

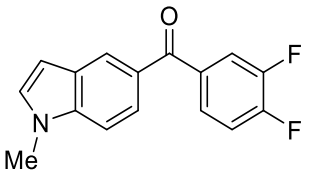


Following **TP4**, solutions of alkoxide **98c** (0.27 M, 0.27 mmol, 1.2 equiv), prepared *via* **TP3**, and benzo[d][1,3]dioxol-5-ylmagnesium bromide (**91d**) (0.23 M, 0.23 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **99d** (38.0 mg, 0.14 mmol, 63%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.56 (ddd, *J* = 10.5, 7.7, 2.1 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.28 – 7.25 (m, 2H), 7.26 – 7.19 (m, 1H), 6.82 (dd, *J* = 7.8, 0.6 Hz, 1H), 6.02 (s, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.4, 151.9, 151.5 (qd, *J* = 251.3, 35.6, 12.9 Hz), 148.16, 134.94 (d, *J* = 3.9 Hz), 131.14, 126.72, 126.70 – 126.59 (m), 119.19, 117.12, 109.73, 107.86, 102.02.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1656, 1603, 1515, 1442, 1305, 1291, 1249, 1110, 1040, 904, 724.
MS (EI, 70 eV): *m/z* (%) = 262 (41), 149 (100), 141 (48), 121 (18),
HRMS (EI): *m/z* calc. for [$C_{14}H_8F_2O_3$]: 262.0442; found 262.0435.
M.p. (°C): 77-78.

[180] H. Li, Y. Xu, E. Shi, W. Wei, X. Suo, X. Wan, *Chem. Commun.* **2011**, *47*, 7880-7882.

(3,4-Difluorophenyl)(1-methyl-1H-indol-5-yl)methanone (99e)



Following **TP4**, solutions of alkoxide **98c** (0.33 M, 0.33 mmol, 1.5 equiv), prepared *via* **TP3**, and (1-methyl-1H-indol-5-yl)magnesium bromide (**91h**) (0.22 M, 0.22 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **99e** (47.0 mg, 0.17 mmol, 79%) as a red solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.77 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.59 (dddd, *J* = 8.5, 4.4, 2.1, 1.3 Hz, 1H), 7.40 (dt, *J* = 8.7, 0.8 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.16 (d, *J* = 3.2 Hz, 1H), 6.60 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.86 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 194.6, 154.5 – 148.3 (m), 139.1, 136.0 (t, *J* = 4.1 Hz), 130.7, 128.4, 127.7, 126.8 (dd, *J* = 7.1, 3.7 Hz), 125.2, 123.6, 119.2 (dd, *J* = 18.0, 1.5 Hz), 117.0 (d, *J* = 17.7 Hz), 109.3, 103.1, 33.1.

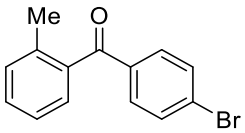
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2360, 1647, 1600, 1511, 1422, 1341, 1313, 1279, 1172, 1108, 1089,773, 742, 732.

MS (EI, 70 eV): *m/z* (%) = 272 (10), 217 (64), 159 (10), 158 (100), 130 (25).

HRMS (EI): *m/z* calc. for [$C_{16}H_{11}F_2NO$]: 271.0809; found 271.0804.

M.p. (°C): 104-105.

(4-Bromophenyl)(o-tolyl)methanone (99f)

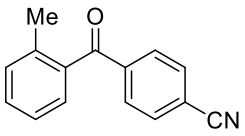


Following **TP4**, solutions of alkoxide **98d** (0.33 M, 0.33 mmol, 1.2 equiv), prepared *via* **TP3**, and *o*-tolylmagnesium bromide (**91t**) (0.27 M, 0.27 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the

crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.9:0.1) to give **99f** (60.0 mg, 0.22 mmol, 81%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.68 – 7.65 (m, 2H), 7.61 – 7.59 (m, 2H), 7.40 (td, *J* = 7.3, 1.9 Hz, 1H), 7.31 – 7.25 (m, 3H), 2.33 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 197.5, 138.0, 136.8, 136.5, 131.8, 131.6, 131.2, 130.5, 128.5, 128.4, 125.3, 20.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 2926, 2362, 1665, 1584, 1480, 1454, 1395, 1265, 1068, 1011, 924, 845, 743.
MS (EI, 70 eV): *m/z* (%) = 196 (16), 195 (100), 194 (36), 177 (24), 165 (14), 91 (13).
HRMS (EI): *m/z* calc. for [$C_{14}H_{10}OBr$]: 272.9921; found 272.9909 (M^+-H).

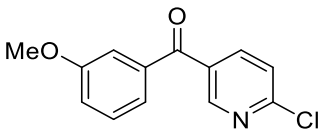
4-(2-Methylbenzoyl)benzonitrile (99g)



Following **TP4**, solutions of alkoxide **98e** (0.33 M, 0.33 mmol, 1.2 equiv), prepared *via* **TP3**, and *o*-tolylmagnesium bromide (**91t**) (0.27 M, 0.27 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^R = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give **99g** (40.0 mg, 0.18 mmol, 68%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 – 7.86 (m, 2H), 7.79 – 7.74 (m, 2H), 7.44 (ddd, *J* = 7.6, 6.3, 2.4 Hz, 1H), 7.33 (dq, *J* = 7.1, 0.7 Hz, 1H), 7.29 – 7.26 (m, 2H), 2.36 (d, *J* = 0.7 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.9, 141.2, 137.5, 137.0, 132.3, 131.5, 131.2, 130.4, 129.0, 125.5, 118.0, 116.2, 20.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2065, 2937, 1665, 1405, 1310, 1294, 1264, 927, 857, 749.
MS (EI, 70 eV): *m/z* (%) = 221 (26), 220 (100), 203 (11), 119 (10), 91 (15).
HRMS (EI): *m/z* calc. for [$C_{15}H_{11}NO$]: 221.0841; found 221.0835.

(6-Chloropyridin-3-yl)(3-methoxyphenyl)methanone (99h)



Following **TP4**, solutions of alkoxide **98f** (0.35 M, 0.35 mmol, 1.5 equiv), prepared *via* **TP3**, and (3-methoxyphenyl)magnesium (**91b**) (0.23 M, 0.23 mmol, 1.0 equiv), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, vol^{R} = 20 mL, residence time: t = 10 min, T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*iso*hexane:ethyl acetate = 9.0:1.0) to give **99h** (37.0 mg, 0.15 mmol, 63%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.77 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.09 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.48 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.5, 0.4 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.18 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 3.87 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.4, 159.9, 155.0, 151.2, 139.8, 137.7, 132.0, 129.7, 124.3, 122.7, 119.9, 114.1, 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2837, 1662, 1579, 1485, 1450, 1427, 1359, 1280, 1240, 1104, 759.

MS (EI, 70 eV): *m/z* (%) = 249 (23), 247 (69), 246 (34), 218 (33), 216 (50), 212 (61), 139 (38), 135 (100), 111 (39), 107 (45), 77 (28).

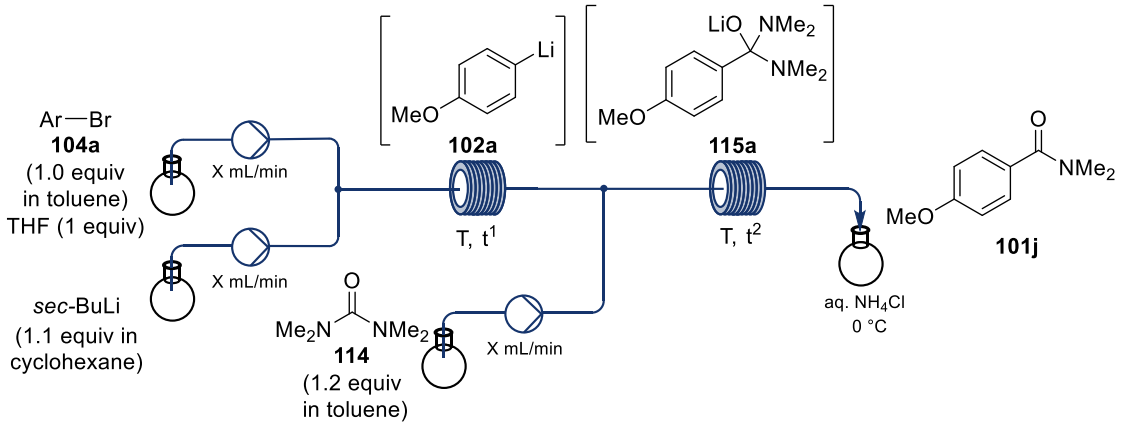
HRMS (EI): *m/z* calc. for [$C_{13}H_{10}O_2NCl$]: 247.0400; found 247.0394.

3. Selective Acylation of (Hetero)aryllithiums with Polyfunctional *N,N*-Dimethylamides in Continuous Flow and Addition of Organolithium Reagents to Tetramethylurea

3.1 Screening Tables

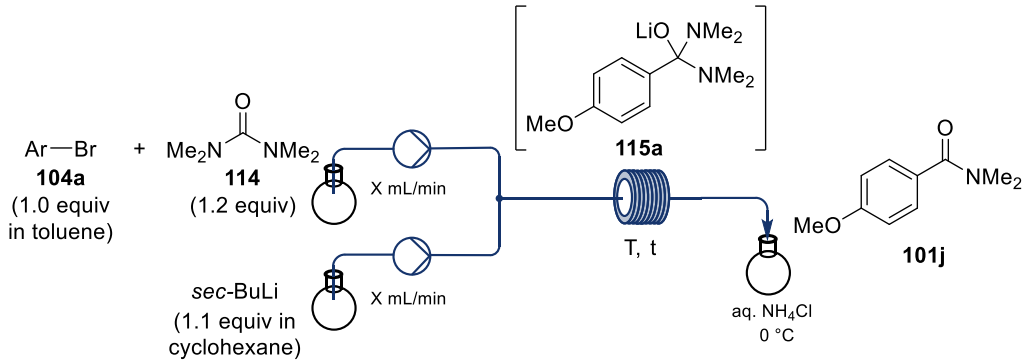
Tetramethylurea in a Barbier-type Reaction vs a Stepwise Reaction in Continuous Flow

Table 25: Screening for stepwise acylations in continuous flow starting from aryl bromide **104a** in toluene with 1.0 equiv of THF, *sec*-BuLi and tetramethylurea **114**.



entry	T [°C]	t^1 [s]	t^2 [s]	flowrate **X** A+B+C	conversion **104a** [GC-%]	yield **101j** [GC-%]
1	25	50	27	5+1+5	92	75
2	25	50	100	8+1.6+8	95	77
3	25	50	27	5+1.1+5.1	97	79
4	25	50	27	5+1.2+5.2	99	82

Table 26: Screening for Barbier-type acylations in continuous flow starting from aryl bromide **104a** in toluene, tetramethylurea **114** and *sec*-BuLi.

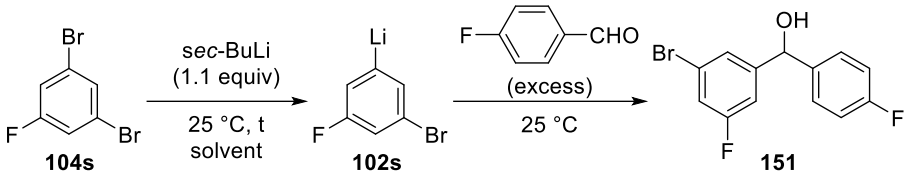


entry	T [°C]	t[1] [s]	flowrate **X** A+B	conversion **104a** [GC-%]	yield **101j** [GC-%]
1	25	50	5+1	75	41
2	25	25	10+2	78	52
3	0	25	10+2	87	73
4	–10	25	10+2	93	81
5	–20	25	10+2	96	83
6	–30	25	10+2	99	82

Optimization of Br/Li Exchange using *sec*-BuLi in different Solvent Systems

In this screening, the instability of the aryllithium species at 25 °C in THF was demonstrated. Even though a high conversion was achieved after 10 min, the expected alcohol **151** was not detected on GC (Table 27, entries 1-2). In the solvent system toluene/THF (1.0 equiv), the lithium species decomposed over 10 min, yielding to only 5% of the desired product after quenching with 4-fluorobenzaldehyde (entries 3-4). Though, after 1 min residence time in continuous flow, full conversion and quantitative amounts of the product **151** were obtained, demonstrating the advantages of continuous flow for the “on-demand” preparation of these species (entry 5).

Table 27: Optimization of the Br/Li exchange at 25 °C in different solvent system for a challenging aryl bromide.



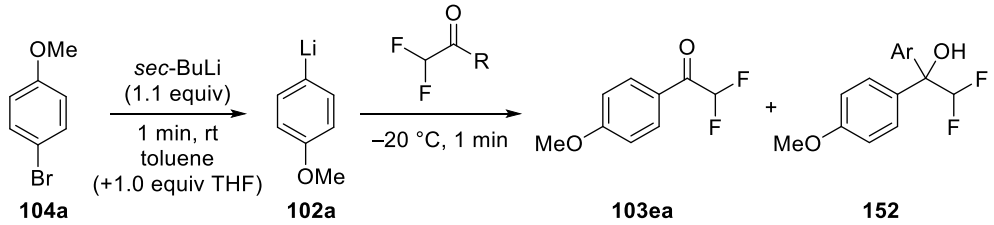
entry	setup	solvent	t_2 [min]	conversion **104s** [GC-%]	yield **151** [GC-%]
1	batch	THF	10	93	-
2	batch	THF	60	94	-
3	batch	toluene[a]	10	99	5
4	batch	toluene[a]	60	99	-
5	flow	toluene[a]	1	99	98

[a] 1.0 equiv of THF was added.

Comparison of different Amides and Esters for the Acylation of Aryllithiums in Batch

In this screening, different amides were compared towards their reactivity with the aryllithium **102a** at the standard conditions in batch (Table 28). It was observed, that each of the amides gave a similar reaction outcome with a complete conversion and ~80% yield while completely excluding the double addition side reaction (entries 1-3). Having a convenient preparation procedure for *N*,*N*-dimethylamides in hand and being the most atom economic compound, these amides showed to be the ideal starting material for this newly developed ketone preparation procedure. The ethyl ester led, as expected, to a larger amount of double addition, lowering the yield of the ketone significantly (entry 4).

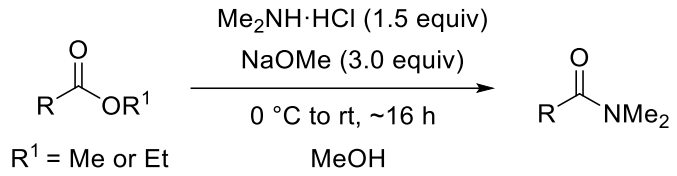
Table 28: Comparison experiments for different amides and esters for the acylation of the aryllithium **102a**.



entry	R	conversion **104a** [GC-%]	yield **103ea** [GC-%]	double addition **152** [GC-%]
1	NMe_2	99	79	-
2	NEt_2	99	78	-
3	morpholino	99	81	-
4	OEt	97	43	14

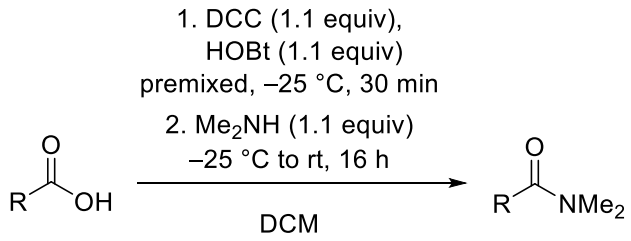
3.2 Typical Procedures

Typical Procedure 5A: Preparation of *N,N*-dimethylamides starting from the corresponding methyl or ethyl carboxylates.



To a 1 M solution of ethyl or methyl ester in MeOH was added Me2NH·HCl (1.5 equiv). Then, 30% NaOMe in MeOH (3.0 equiv) was added at 0 °C while stirring. After full conversion to the corresponding *N,N*-dimethylamide (checked via GC or TCL analysis), the reaction mixture was quenched with *sat. aq.* NH_4Cl. Methanol was removed under vacuo (300 mbar) and water was added under stirring until a clear solution was obtained. After extraction with the indicated solvent (depending on the volatility of the compound), the combined organic layers were dried with $MgSO_4$ and evaporated to give the crude dimethylamide. The crude compounds were either directly used or purified *via* distillation under reduced pressure or column chromatography.

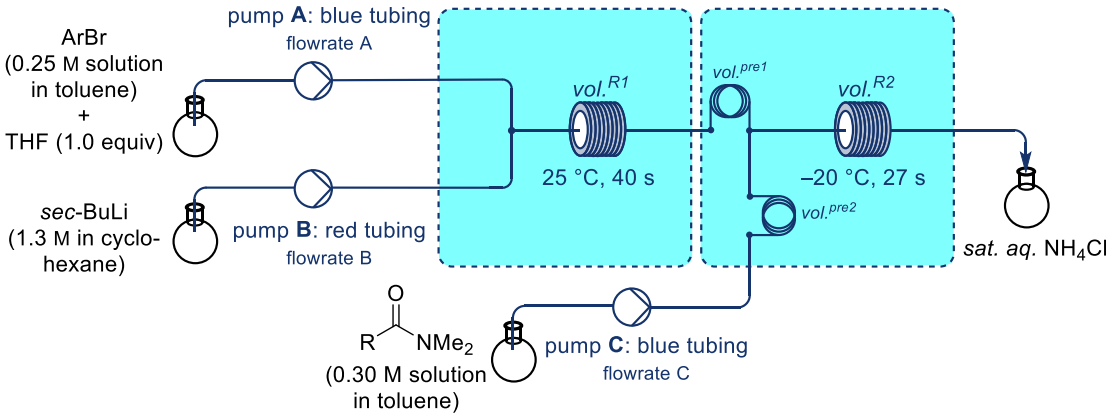
Typical Procedure 5B: Preparation of *N,N*-dimethylamides starting from the corresponding carboxylic acids.



To DCC (dicyclohexylcarbodiimide, 1.1 equiv), dissolved in 60 ml of dry DCM, was added HOBt (hydroxybenzotriazole, 1.1 equiv) in one portion at 25 °C. In a separate flask, carboxylic acid (0.5 M, 1.1 equiv) was dissolved or suspended in dry DCM and cooled to –25 °C. The solution of DCC/HOBt was cannulated over 15 min into the solution of carboxylic acid. After stirring for 30 min at –25 °C, Me_2NH (2 M in THF, 1.1 equiv) was added dropwise. The suspension was allowed to warm to 25 °C and stirred for 16 h. The reaction mixture was filtered over sinter to remove *N,N'*-dicyclohexylurea and the DCM layer was washed with 10% *aq.*

Na_2CO_3 (3 x 30 mL). The combined aqueous layers were washed with DCM. After drying, filtrating and concentrating the organic layers, flash column purification gave pure *N*,*N*-dimethylamides.

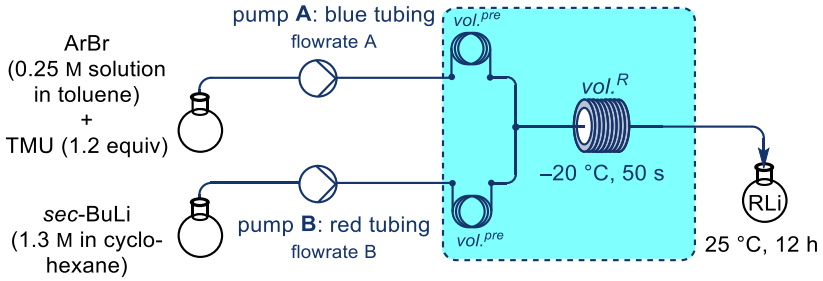
Typical Procedure 6: A continuous flow acylation of *in situ* generated aryllithiums with various *N*,*N*-dimethylamides.



Scheme 37: Flow chemistry setup for preparation of ketones starting from lithium species, prepared via Br/Li exchange in flow, and *N*,*N*-dimethylamides.

A solution of aryl bromide (0.25 M, 1.0 equiv) and THF (1.0 equiv) in toluene and a solution of *sec*-BuLi in cyclohexane (1.3 M, 1.2 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 5.0 mL·min^{-1} and flowrate B = 1.15 mL·min^{-1}. The solutions were mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm) and the combined stream passed a PTFE reactor tube (i.d = 0.8 mm, vol^{R1} = 4 mL; residence time: t = 40 s, T = 25 °C), followed by a PTFE reactor tube (i.d = 0.8 mm, vol^{pre1} = 1 mL; residence time: t = 10 s, T = –20 °C) for precooling the reaction mixture. A *N*,*N*-dimethylamide solution (0.3 M, 1.2 equiv) in toluene was added *via* a third pump (flowrate C = 5.0 mL·min^{-1}, i.d = 0.8 mm, vol^{pre2} = 2.0 mL, residence time: t = 24 s, T = –20 °C). The combined stream passed a PTFE reactors tube (i.d = 1.6 mm, vol^{R2} = 5 mL; residence time: t = 27 s, T = –20 °C) and the reaction mixture was subsequently quenched with *sat. aq.* NH_4Cl at 0 °C. After extraction with EtOAc or DCM, the combined organic phases were dried over Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash column chromatography purification with *n*-pentane:EtOAc mixtures afforded the pure products.

Typical Procedure 7: One-pot preparation of unsymmetrical ketones by two successive acylation reactions on TMU with various lithium organometallics.



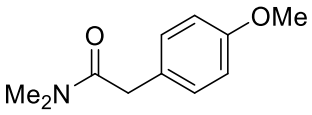
Scheme 38: Flow chemistry setup for preparation of unsymmetrical ketones starting from TMU, aryl bromides and *sec*-BuLi in a Barbier-type reaction.

A solution of aryl bromide (0.25 M, 1.0 equiv) and 1,1,3,3-tetramethylurea (TMU**,** 1.2 equiv) in toluene and a solution of *sec*-BuLi in cyclohexane (1.5 M, 1.2 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 5.0 mL·min^{-1} and flowrate B =1 mL·min^{-1}. The single streams passed a PTFE reactor tube (i.d = 0.8 mm, vol_{pre} = 2 mL; residence time: t = 20 s, T = –20 °C) for precooling the solutions and were subsequently mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (i.d = 0.8 mm, vol_R = 5 mL; residence time: t = 50 s, T = –20 °C). Then, the combined stream was poured into a flask at 25 °C, containing 1.5 equiv of aryllithiums which were prepared in batch *via* direct metalation of the corresponding starting materials in toluene plus TMEDA (1.0 equiv) with *sec*-BuLi (1.2 equiv) at –20 °C for 30 min. After stirring at 25 °C for 12 h, the reaction mixture was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash column chromatography purification with *iso*hexane(or pentane):EtOAc mixtures afforded the pure products.

3.3 Preparation of Compounds

3.3.1 Preparation of *N,N*-Dimethylamides

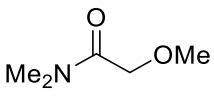
2-(4-Methoxyphenyl)-*N,N*-dimethylacetamide (101a)



Following **TP5A**, methyl 2-(4-methoxyphenyl)acetate (16.0 mL, 100 mmol) was mixed with $Me_2NH{\cdot}HCl$ (12.2 g, 150 mmol) and NaOMe (60.0 mL, 300 mmol) in methanol (200 mL). Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 8:2) to give 2-(4-methoxyphenyl)-*N,N*-dimethylacetamide (**101a**) (15.1 g, 78.1 mmol, 78% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.22 – 7.15 (m, 2H), 6.90 – 6.83 (m, 2H), 3.80 (s, 3H), 3.67 (s, 2H), 2.99 (d, *J* = 14.4 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.4, 158.4, 129.8 (2C), 127.1, 114.1 (2C), 55.3, 40.1, 37.7, 35.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2934, 1633, 1611, 1511, 1393, 1244, 1177, 1126, 1030, 793.
MS (EI, 70 eV): *m/z* (%) = 193 (29), 148 (12), 121 (100), 72 (11).
HRMS (EI): *m/z* calc. for $[C_{11}H_{15}O_2N]$: 193.1103; found 193.1097.

2-Methoxy-*N,N*-dimethylacetamide (101b)



Following **TP5A**, methyl 2-methoxyacetate (20.8 g, 200 mmol) was mixed with $Me_2NH{\cdot}HCl$ (24.4 g, 300 mmol) and NaOMe (113 mL, 600 mmol) in methanol. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup (extraction with DCM), the crude product was purified *via* fractional distillation (0.1 mbar, 64 °C) to give 2-methoxy-*N,N*-dimethylacetamide (**101b**) (19.4 g, 166 mmol, 83% yield) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.06 (s, 2H), 3.40 (s, 3H), 2.94 (d, *J* = 13.6 Hz, 6H).

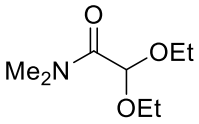
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.1, 71.5, 59.1, 36.2, 35.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3500, 2930, 2822, 1641, 1505, 1452, 1415, 1401, 1346, 1263, 1199, 1110, 1012, 927.

MS (EI, 70 eV): *m/z* (%) = 87 (96), 72 (100), 45 (23).

HRMS (EI): *m/z* calc. for [$C_5H_{12}O_2N$]: 118.0868; found 118.0863 [M+H].

2,2-Diethoxy-*N,N*-dimethylacetamide (101c)



Following **TP5A**, methyl 2,2-diethoxyacetate (32.4g, 200 mmol) was mixed with $Me_2NH{\cdot}HCl$ (24.4 g, 300 mmol) and NaOMe (113 mL, 600 mmol) in methanol. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup (extraction with DCM), the crude product was purified *via* fractional distillation (0.3 mbar, 100 °C) to give 2,2-diethoxy-*N,N*-dimethylacetamide (**101c**) (19.1 mg, 108 mmol, 54% yield) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.97 (s, 1H), 3.72 (dq, *J* = 9.6, 7.1 Hz, 2H), 3.58 (dq, *J* = 9.5, 7.0 Hz, 2H), 3.13 (s, 3H), 2.94 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 6H).

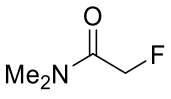
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.5, 101.1, 63.2 (2C), 36.4, 35.8, 15.1 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976, 2932, 2891, 2882, 1650, 1418, 1401, 1373, 1325, 1152, 1104, 1058, 1027, 985, 681.

MS (EI, 70 eV): *m/z* (%) = 130 (15), 103 (100), 102 (62), 75 (84), 74 (24), 72 (28), 47 (77).

HRMS (EI): *m/z* calc. for [$C_8H_{18}O_3N$]: 176.1287; found 16.1281 [M+H].

2-Fluoro-*N,N*-dimethylacetamide (101d)



Following **TP5A**, ethyl 2-fluoroacetate (10.6 g, 100 mmol) was mixed with $Me_2NH{\cdot}HCl$ (12.2 g, 150 mmol) and 30% NaOMe (56.6 mL, 300 mmol) in methanol. Thereafter, the reaction mixture was quenched with 50 ml of *sat. aq.* NH_4Cl. After workup (extraction with

Et_2O), the crude product was purified *via* column chromatography (pure ethyl acetate) to give 2-fluoro-*N*,*N*-dimethylacetamide (**101d**) (8.20 g, 78.0 mmol, 78% yield) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.95 (d, *J* = 47.2 Hz, 2H), 2.95 (dd, *J* = 2.7, 1.3 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.8 (d, *J* = 18.4 Hz), 79.7 (d, *J* = 178.7 Hz), 35.8 (d, *J* = 4.6 Hz), 35.6.

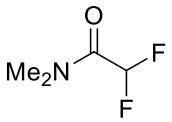
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –225.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3481, 2944, 1650, 1645, 1505, 1447, 1425, 1405, 1357, 1263, 1058, 1011, 806.

MS (EI, 70 eV): *m/z* (%) = 105 (53), 72 (100), 44 (9).

HRMS (EI): *m/z* calc. for [C_4H_8ONF]: 105.0590; found 105.0585.

2,2-Difluoro-*N*,*N*-dimethylacetamide (101e)



Following **TP5A**, ethyl 2-fluoroacetate (24.8 g, 200 mmol) was mixed with $Me_2NH{\cdot}HCl$ (24.5 g, 300 mmol) and 30% NaOMe (113 mL, 600 mmol) in methanol. Thereafter, the reaction mixture was quenched with 100 ml of *sat. aq.* NH_4Cl. After concentration (1 h at 280 mbar, 40 °C), salts were dissolved with distilled water and the product was extracted with Et_2O. After drying with $MgSO_4$, solvents were evaporated (atmospheric pressure, 40 °C, then 200 mbar, 40 °C, 15 min) to give 2,2-difluoro-*N*,*N*-dimethylacetamide (**101e**) (21.3 g, 173 mmol, 87% yield) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.09 (t, *J* = 53.7 Hz, 1H), 3.12 (t, *J* = 1.6 Hz, 3H), 2.99 (t, *J* = 1.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.1 (t, *J* = 25.0 Hz), 110.4 (t, *J* = 253.5 Hz), 36.0, 35.9 (t, *J* = 4.4 Hz).

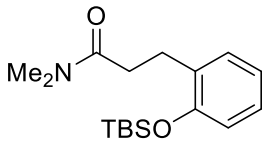
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –121.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1671, 1668, 1105, 1049, 863.

MS (EI, 70 eV): *m/z* (%) = 123 (31), 72 (100).

HRMS (EI): *m/z* calc. for [$C_4H_7ONF_2$]: 123.0496; 123.0491.

3-(2-((*Tert*-butyldimethylsilyl)oxy)phenyl)-*N*,*N*-dimethylpropanamide (101g)

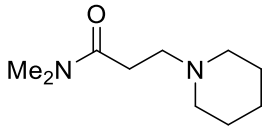


Following **TP5A**, dihydrocoumarine (7.40 g, 50.0 mmol) was mixed with $Me_2NH{\cdot}HCl$ (6.10 g, 75.0 mmol) and NaOMe (28.3 mL, 150 mmol) in methanol. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup (extraction with DCM), the crude product 3-(2-hydroxyphenyl)-*N*,*N*-dimethylpropanamide was directly used for the protection step.

To a solution of 3-(2-hydroxyphenyl)-*N*,*N*-dimethylpropanamide in THF (100 mL) was added TBDMSCl (7.50 g, 50.0 mmol) and Et_3N (8.40 mL, 60 mmol). The reaction mixture was stirred for 24 h at 25 °C. Then, the mixture was extracted with EtOAc, dried over $MgSO_4$ and filtrated. After removing the solvents in *vacuo*, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 8:2) to give 3-(2-((*tert*-butyldimethylsilyl)oxy)-phenyl)-*N*,*N*-dimethylpropanamide (**101g**) (10.3 g, 33.5 mmol, 67% overall yield) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.20 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 6.90 (td, *J* = 7.4, 1.2 Hz, 1H), 6.81 (dd, *J* = 8.1, 1.2 Hz, 1H), 2.99 – 2.90 (m, 8H), 2.64 – 2.58 (m, 2H), 1.03 (s, 9H), 0.27 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.4, 153.5, 131.8, 130.3, 127.0, 121.0, 118.2, 36.9, 35.2, 33.2, 26.6, 25.6 (3C), 18.1, -4.3 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2928, 2857, 1649, 1490, 1471, 1462, 1452, 1409, 1395, 1250, 1138, 1103, 921, 837, 824, 809, 779, 755.
MS (EI, 70 eV): *m/z* (%) = 251 (39), 250 (100), 102 (17), 73 (14).
HRMS (EI): *m/z* calc. for $[C_{17}H_{28}O_2NSi]^+$: 306.1884; found 306.1888 $[M\text{-}H]^+$.

***N*,*N*-Dimethyl-3-(piperidin-1-yl)propanamide (101h)**

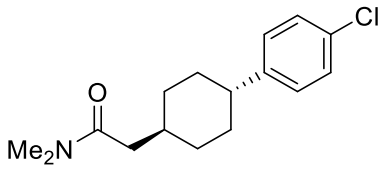


Following **TP5A**, ethyl 3-(piperidin-1-yl)propanoate (18.5 g, 100 mmol) was mixed with $Me_2NH{\cdot}HCl$ (12.2 g, 150 mmol) and NaOMe (60.0 mL, 300 mmol) in methanol. Thereafter,

the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup (extraction with DCM), the crude product was purified *via* column chromatography (pentane:ethyl acetate =3:7) to give *N*,*N*-dimethyl-3-(piperidin-1-yl)propanamide (**101h**) (13.1 g, 71.1 mmol, 71% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 2.98 (s, 3H), 2.90 (s, 3H), 2.68 – 2.61 (m, 2H), 2.53 – 2.47 (m, 2H), 2.38 (t, *J* = 5.3 Hz, 4H), 1.59 – 1.50 (m, 4H), 1.40 (ddt, *J* = 7.9, 4.5, 2.6 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.0, 54.8, 54.6 (2C), 37.2, 35.3, 31.2, 26.0 (2C), 24.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3475, 2931, 2853, 2797, 1629, 1497, 1443, 1398, 1393, 1263, 1149, 1116, 1042, 992.
MS (EI, 70 eV): *m/z* (%) = 98 (100), 96 (20), 84 (58), 70 (21).
HRMS (EI): *m/z* calc. for [$C_{10}H_{20}ON_2$]: 184.1576; found 184.1569.

2-((1*r*,4*r*)-4-(4-Chlorophenyl)cyclohexyl)-*N*,*N*-dimethylacetamide (101i)



Following **TP5A**, methyl 2-(4-(4-chlorophenyl)cyclohexyl)acetate (13.3 g, 50.0 mmol) was mixed with $Me_2NH{\cdot}HCl$ (8.10 g, 100 mmol) and NaOMe (30.0 mL, 150 mmol) in methanol (100 mL). Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 7:3) to give 2-((1*r*,4*r*)-4-(4-chlorophenyl)cyclohexyl)-*N*,*N*-dimethylacetamide (**101i**) (7.80 g, 28.0 mmol, 56% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.21 (m, 2H), 7.13 – 7.09 (m, 2H), 3.02 (s, 3H), 2.95 (s, 3H), 2.43 (tt, *J* = 12.2, 3.4 Hz, 1H), 2.25 (d, *J* = 6.4 Hz, 2H), 1.97 – 1.81 (m, 5H), 1.53 – 1.41 (m, 2H), 1.19 – 1.07 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.3, 145.9, 131.4, 128.4 (2C), 128.2 (2C), 43.7, 40.5, 37.6, 35.4, 34.5, 34.0 (2C), 33.5 (2C).

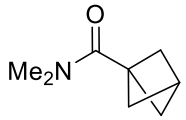
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2846, 1637, 1490, 1446, 1408, 1394, 1150, 1127, 1089, 1012, 820.

MS (EI, 70 eV): *m/z* (%) = 279 (12), 125 (10), 87 (100), 72 (11), 44 (21).

HRMS (EI): *m/z* calc. for [$C_{16}H_{22}ONCl$]: 279.1390; found 279.1387.

m.p: 93.3-93.7 °C.

N,N-Dimethylbicyclo[1.1.1]pentane-1-carboxamide (101j)



Bicyclo[1.1.1]pentane-1-carboxylic acid[181] (2.24 g, 20.0 mmol) was mixed with CDI (carbonyldiimidazole, 4.86 g, 35.0 mmol, 1.5 equiv) in DCM (50 mL). After stirring for 30 min at 25 °C and degassing the reaction mixture with N_2, Me_2NH (2 M in THF, 40.0 mL, 80.0 mmol, 4.0 equiv) was added. After 16 h of stirring, the reaction mixture was quenched with H_2O and extracted with DCM. After workup, the crude product was purified *via* column chromatography (DCM:MeOH = 9.8:0.2) to give *N,N*-dimethylbicyclo[1.1.1]pentane-1-carboxamide (**101j**) (2.50 g, 18.0 mmol, 90% yield) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.05 (s, 3H), 2.86 (s, 3H), 2.42 (s, 1H), 2.12 (s, 6H).

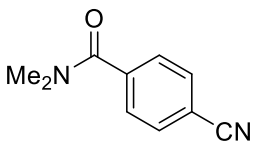
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.4, 52.6 (3C), 45.2, 37.3, 35.9, 28.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2971, 2916, 2878, 1613, 1513, 1497, 1393, 1211, 1103, 674.

MS (EI, 70 eV): *m/z* (%) = 138 (73), 124 (59), 94 (70), 72 (97), 67 (100), 66 (52), 65 (57).

HRMS (EI): *m/z* calc. for $[C_9H_{12}ON]^+$: 138.0913; found 138.0913 [M-H^+].

4-Cyano-*N,N*-dimethylbenzamide (110a)

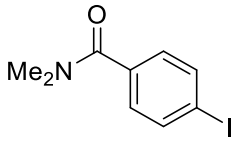


[181] a) K. Mondanaro, W. P. Dailey, *Org. Synth.* **1998**, *75*, 98. b) M. T. Hossain, J. W. Timberlake, *J. Org. Chem.* **2001**, *66*, 6282-6285. c) I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12774-12777.

4-Cyanobenzoic acid (11.2 g, 75.8 mmol) was mixed with CDI (13.5 g, 83.4 mmol) in DCM (100 mL). After stirring for 30 min at 25 °C, Me_2NH (2 M in THF, 40.0 mL, 84.0 mmol) was added. After 16 h of stirring, the reaction mixture was quenched with H_2O and extracted with DCM. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give 4-cyano-*N*,*N*-dimethylbenzamide (**110a**) (11.2 g, 71.0 mmol, 85% yield) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.75 – 7.65 (m, 2H), 7.55 – 7.45 (m, 2H), 3.10 (s, 3H), 2.93 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.5, 140.7, 132.3 (2C), 127.8 (2C), 118.2, 113.3, 39.3, 35.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2934, 2229, 1628, 1512, 1490, 1396, 1266, 1080, 850, 761.
MS (EI, 70 eV): *m/z* (%) = 173 (67), 130 (100), 102 (54), 44 (18), 43 (21).
HRMS (EI): *m/z* calc. for [$C_{10}H_9ON_2$]: 173.0709; found 173.0711.
m.p: 88.3-89.1 °C.

4-Iodo-N,N-dimethylbenzamide (110b)



Following **TP5A**, ethyl 4-iodobenzoate (19.3 g, 70 mmol) was mixed with $Me_2NH{\cdot}HCl$ (8.60 g, 105 mmol) and NaOMe (40 mL, 210 mmol) in methanol. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 8:2) to give 4-iodo-*N*,*N*-dimethylbenzamide (**110b**) (14.9 g, 54.2 mmol, 77% yield) as a white solid.

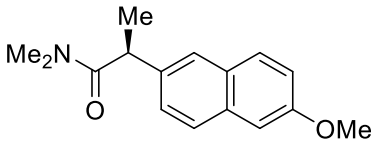
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71 (d, *J* = 8.4 Hz, 2H), 7.17 – 7.07 (m, 2H), 2.99 (d, *J* = 49.7 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.6, 137.5 (2C), 135.7, 128.9 (2C), 95.7, 39.5, 35.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 1622, 1584, 1475, 1393, 1264, 1080, 1006, 831, 751.

MS (EI, 70 eV): *m/z* (%) = 274 (80), 230 (100), 202 (24), 76 (11).

HRMS (EI): *m/z* calc. for $[C_9H_9ONI]^+$: 273.9723; found 273.9729 $[M-H]^+$.

m.p: 105.4-106.3 °C.

(*S*)-2-(6-Methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (112a)



Following **TP5B**, ethyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (4.60 g, 20.0 mmol) was mixed with DCC (4.50 g, 22.0 mmol), HOBt (2.97 g, 22.0 mmol) and Me_2NH (2 M in THF, 11.0 mL, 22.0 mmol). After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 8.5:1.5) to give (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (**112a**) (4.50 g, 17,6 mmol, 88% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.67 (dd, *J* = 8.6, 6.8 Hz, 2H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.36 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.14 – 7.06 (m, 2H), 3.97 (q, *J* = 6.8 Hz, 1H), 3.86 (s, 3H), 2.89 (d, *J* = 32.6 Hz, 6H), 1.49 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.7, 157.5, 137.0, 133.4, 129.1, 129.0, 127.4, 126.2, 125.5, 118.9, 105.5, 55.2, 43.1, 37.1, 35.8, 20.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 1640, 1604, 1504, 1484, 1391, 1264, 1228, 1213, 1031, 854.

MS (EI, 70 eV): *m/z* (%) = 257 (11), 186 (12), 185 (100), 170 (27), 153 (12), 141 (14).

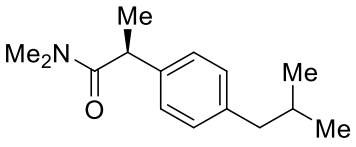
HRMS (EI): *m/z* calc. for $[C_{16}H_{19}O_2N]$: 257.1408; found 257.1416.

m.p: 86.8-87.1 °C.

Optical rotation: $[\propto]_D^{20}$ = 111 (c = 1.02, $CHCl_3$).

Chiral HPLC: >99% *ee*, OD-H column, heptane:*i*-PrOH = 99:1, 1.5 mL/min, 30 °C.

(*S*)-2-(4-*Iso*butylphenyl)-*N*,*N*-dimethylpropanamide (112b)

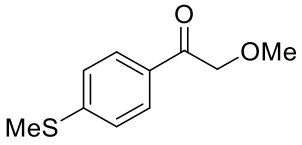


Following **TP5B**, (*S*)-2-(4-*iso*butylphenyl)propanoic acid (5.00 g, 24.2 mmol) was mixed with DCC (5.50 g, 26.6 mmol), HOBt (3.60 g, 26.6 mmol) and Me_2NH (2 M in THF, 15.0 mL, 26.6 mmol). After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 8:2 to 7:3) to give (*S*)-2-(4-*iso*butylphenyl)-N,N-dimethylpropanamide (**112b**) (5.13 g, 22.0 mmol, 91% yield) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.15 (d, *J* = 8.1 Hz, 2H), 7.10 – 7.05 (m, 2H), 3.84 (q, *J* = 6.9 Hz, 1H), 2.94 (s, 3H), 2.88 (s, 3H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.83 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H), 0.88 (dd, *J* = 6.6, 0.9 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 174.0, 140.2, 139.2, 129.6 (2C), 127.1 (2C), 45.1, 43.0, 37.3, 36.0, 30.3, 22.5, 20.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2927, 1642, 1509, 1464, 1393, 1146, 1060, 848.
MS (EI, 70 eV): *m/z* (%) = 233 (21), 161 (100), 119 (15), 117 (14), 72 (53).
HRMS (EI): *m/z* calc. for [$C_{15}H_{23}ON$]: 233.1780; found 233.1771.
Optical rotation: $[\propto]_D^{20}$ = 87 (c = 1.09, $CHCl_3$).
Chiral HPLC: >99% *ee*, OD-H column, heptane:*i*-PrOH = 99:1, 1.5 mL/min, 30 °C.

3.3.2 Preparation of Products

2-Methoxy-1-(4-(methylthio)phenyl)ethan-1-one (103bb)



Following **TP6**, solutions of 4-bromothioanisole (**104b**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**101b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **103bb** (101 mg, mmol, 82%) as a colourless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.89 – 7.82 (m, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 4.65 (s, 2H), 3.50 (s, 3H), 2.52 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.4, 146.7, 131.3, 128.5 (2C), 125.2 (2C), 75.4, 59.6, 14.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2990, 2924, 2832, 1683, 1588, 1235, 1190, 1131, 1095, 981, 976, 920, 815.

MS (EI, 70 eV): *m/z* (%) = 166 (15), 151 (100), 123 (11).

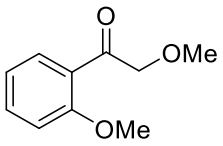
HRMS (EI): *m/z* calc. for [$C_{10}H_{12}O_2S$]:196.0558; found 196.0553.

m.p: 61.1-61.9 °C.

Scale Up of 2-Methoxy-1-(4-(methylthio)phenyl)ethan-1-one (103bb)

Following **TP6**, solutions of 4-bromothioanisole (**104b**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**101b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 6.5 min, corresponding to 8.125 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **103bb** (1.25 g, 6.37 mmol, 78%) as a colourless solid.

2-Methoxy-1-(2-methoxyphenyl)ethan-1-one (103bc)



Following **TP6**, solutions of 2-bromoanisole (**104c**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**101b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **103bc** (85.0 mg, 0.47 mmol, 75%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.43 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1H), 6.96 (ddd, *J* = 8.0, 7.3, 1.0 Hz, 1H), 6.90 (dd, *J* = 8.4, 1.0 Hz, 1H), 4.58 (s, 2H), 3.85 (s, 3H), 3.43 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 197.6, 159.3, 134.5, 130.8, 125.4, 121.0, 111.6, 79.2, 59.4, 55.6.

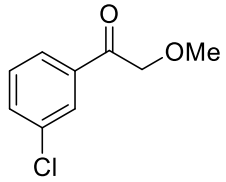
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2942, 1681, 1597, 1484, 1466, 1437, 1286, 1243, 1193, 1182, 1163, 1129, 1108, 1022, 757.

MS (EI, 70 eV): *m/z* (%) = 136 (9), 135 (100), 77 (16).

HRMS (EI): *m/z* calc. for [$C_{10}H_{12}O_3$]: 180.0768; found 180.0781.

m.p: 102.1-102.8 °C.

2-Methoxy-1-(2-methoxyphenyl)ethan-1-one (103bd)



Following **TP6**, solutions of 1-bromo-3-chlorobenzene (**104d**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**101b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromid. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **103bd** (94.0 mg, 0.51 mmol, 82%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 (ddd, *J* = 2.1, 1.6, 0.5 Hz, 1H), 7.81 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.55 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.44 – 7.37 (m, 1H), 4.66 (s, 2H), 3.50 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.2, 136.4, 135.2, 133.6, 130.2, 128.2, 126.1, 75.5, 59.6.

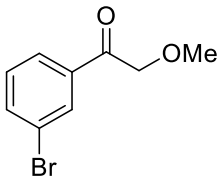
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2824, 1703, 1571, 1424, 1418, 1223, 1196, 1131, 789, 724, 681.

MS (EI, 70 eV): *m/z* (%) = 156 (11), 154 (32), 141 (33), 139 (100), 111 (21), 75 (11).

HRMS (EI): *m/z* calc. for [$C_{10}H_{12}O_2Cl$]: 184.0291; found 184.0286.

m.p: 45.7-46.2 °C.

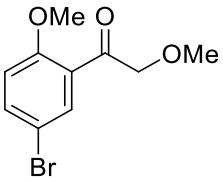
2-Methoxy-1-(2-methoxyphenyl)ethan-1-one (103be)



Following **TP6**, solutions of 1,3-dibromobenzene (**104e**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**101b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **103be** (121 mg, 0.53 mmol, 85%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (t, *J* = 1.9 Hz, 1H), 7.85 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 7.70 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.38 – 7.31 (m, 1H), 4.66 (s, 2H), 3.50 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.1, 136.6, 131.1, 130.4, 126.6, 123.2, 75.4, 59.6, 29.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 1704, 1566, 1422, 1220, 1196, 1130, 705, 681.
MS (EI, 70 eV): *m/z* (%) = 200 (36), 184 (100), 183 (80), 157 (44), 155 (45), 76 (28).
HRMS (EI): *m/z* calc. for [$C_9H_9O_2Br$]: 227.9686; found 227.9779.

1-(5-Bromo-2-methoxyphenyl)-2-methoxyethan-1-one (103bf)



Following **TP6**, solutions of 2,4-dibromo-1-methoxybenzene (**104f**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**101b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **103bf** (124 mg, 0.48 mmol, 77%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (d, *J* = 2.6 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.86 (d, *J* = 8.9 Hz, 1H), 4.60 (s, 2H), 3.91 (s, 3H), 3.48 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.3, 158.3, 136.9, 133.4, 126.9, 113.7, 113.6, 79.1, 59.5, 56.0.

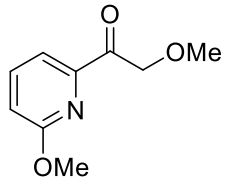
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 2822, 1684, 1588, 1479, 1463, 1439, 1395, 1269, 1247, 1177, 1138, 1116, 1016, 988, 928, 810, 661.

MS (EI, 70 eV): *m/z* (%) = 215 (99), 213 (100), 172 (17), 170 (18).

HRMS (EI): *m/z* calc. for [$C_{10}H_{11}O_3Br$]: 257.9892; found 257.9883.

m.p: 65.0-65.6 °C.

2-Methoxy-1-(6-methoxypyridin-2-yl)ethan-1-one (103bg)



Following **TP6**, solutions of 2-bromo-6-methoxypyridine (**104g**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**101b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **103bg** (93.0 mg, 0.51 mmol, 82%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71 (dd, *J* = 8.1, 7.3 Hz, 1H), 7.65 (dd, *J* = 7.3, 1.1 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.99 (s, 2H), 3.95 (s, 3H), 3.53 (s, 3H).

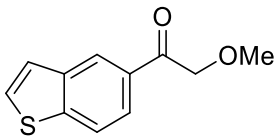
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.9, 163.4, 149.5, 139.4, 116.1, 115.1, 75.3, 59.6, 53.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2823, 1713, 1590, 1468, 1431, 1325, 1275, 1230, 1200, 1131, 1049, 1037, 986, 809.

MS (EI, 70 eV): *m/z* (%) = 166 (100), 152 (12), 108 (55), 93 (19).

HRMS (EI): *m/z* calc. for [$C_9H_{11}O_3N$]: 181.0739; found 181.0732.

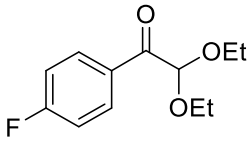
1-(Benzo[*b*]thiophen-5-yl)-2-methoxyethan-1-one (103bh)



Following **TP6**, solutions of 5-bromobenzo[*b*]thiophene (**104h**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**101b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **103bh** (134 mg, 0.55 mmol, 89%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.42 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.97 – 7.86 (m, 2H), 7.56 – 7.50 (m, 1H), 7.43 (dd, *J* = 5.5, 0.7 Hz, 1H), 4.78 (s, 2H), 3.53 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.1, 144.8, 139.5, 131.4, 128.1, 124.7, 124.0, 123.0, 122.9, 75.6, 59.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3087, 2926, 2820, 1688, 1594, 1319, 1240, 1201, 1171, 1154, 1122, 1087, 1050, 817, 779, 755, 697.
MS (EI, 70 eV): *m/z* (%) = 176 (17), 162 (10), 161 (28), 161 (100), 133 (18), 89 (16).
HRMS (EI): *m/z* calc. for [$C_{11}H_{10}O_2S$]: 206.0402; found 206.0393.
m.p: 77.3-77.9 °C.

2,2-Diethoxy-1-(4-fluorophenyl)ethan-1-one (103ci)

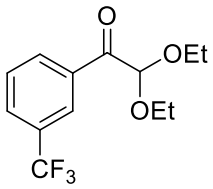


Following **TP6**, solutions of 1-bromo-4-fluorobenzene (**104i**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2,2-diethoxy-*N*,*N*-dimethylacetamide (**101c**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column

chromatography (pentane:ethyl acetate= 9.8:0.2) to give **103ci** (104 mg, 0.46 mmol, 74%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.30 – 8.14 (m, 2H), 7.18 – 7.07 (m, 2H), 5.19 (s, 1H), 3.79 (dq, *J* = 9.6, 7.1 Hz, 2H), 3.65 (dq, *J* = 9.6, 7.0 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.8, 166.1 (d, *J* = 255.4 Hz), 132.8 (d, *J* = 9.3 Hz, 2C), 130.1 (d, *J* = 3.0 Hz), 115.6 (d, *J* = 21.8 Hz, 2C), 103.3, 63.6 (2C), 15.3 (2C).
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = δ -104.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 1695, 1684, 1599, 1235, 1158, 1058, 904, 846, 725, 724, 685.
MS (EI, 70 eV): *m/z* (%) = 153 (49), 123 (44), 123 (100), 103 (50), 97 (72), 95 (34), 75 (77).
HRMS (EI): *m/z* calc. for $[C_{10}H_{10}O_2F]^+$: 181. 0659; found 181.0659 [M-OEt].

2,2-Diethoxy-1-(3-(trifluoromethyl)phenyl)ethan-1-one (103cj)



Following **TP6**, solutions of 1-bromo-3-(trifluoromethyl)benzene (**104j**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2,2-diethoxy-*N*,*N*-dimethylacetamide (**101c**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq*. NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **103cj** (130 mg, 0.47 mmol, 75%) as a colourless oil.

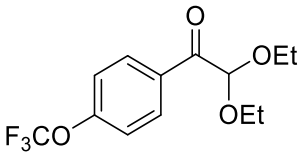
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 1H NMR (400 MHz, Chloroform-d) δ 8.46 – 8.42 (m, 1H), 8.39 – 8.35 (m, 1H), 7.86 – 7.78 (m, 1H), 7.63 – 7.53 (m, 1H), 5.19 (s, 1H), 3.80 (dq, *J* = 9.6, 7.1 Hz, 2H), 3.65 (dq, *J* = 9.5, 7.0 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.1, 134.2, 133.3, 131.1 (q, *J* = 32.8 Hz), 129.9 (q, *J* = 3.6 Hz), 129.1, 127.0 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.5 Hz), 103.4, 63.9 (2C), 29.9, 15.3 (2C).
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –62.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2927, 1698, 1332, 1262, 1168, 1124, 1096, 1071, 1057, 1002, 693.

MS (EI, 70 eV): *m/z* (%) = 190 (10), 173 (100), 145 (32), 47 (11).

HRMS (EI): *m/z* calc. for $[C_{13}H_{14}O_3F_3]^+$: 275.0890; found 275.0888 [M-H].

2,2-Diethoxy-1-(4-(trifluoromethoxy)phenyl)ethan-1-one (103ck)



Following **TP6**, solutions of 1-bromo-4-(trifluoromethoxy)benzene (**104k**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2,2-diethoxy-*N*,*N*-dimethylacetamide (**101c**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **103ck** (143 mg, 0.49 mmol, 78%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.31 – 8.17 (m, 2H), 7.35 – 7.15 (m, 2H), 5.16 (s, 1H), 3.77 (dq, *J* = 9.5, 7.1 Hz, 2H), 3.63 (dq, *J* = 9.5, 7.0 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.8, 132.2 (4C), 131.9, 120.2, 103.5, 63.8 (2C), 15.3 (2C).

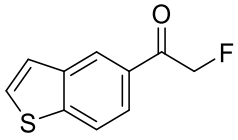
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = -57.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2873, 1692, 1254, 1208, 1162, 1128, 1111, 1057, 1017, 736, 704.

MS (EI, 70 eV): *m/z* (%) = 219 (34), 189 (100), 163 (38), 123 (28), 103 (43), 95 (26), 77 (31), 75 (61), 47 (39).

HRMS (EI): *m/z* calc. for $[C_{11}H_{10}O_3F_3]^+$: 247.0577; found 247.0579 [M-OEt].

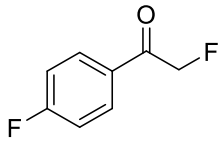
1-(Benzo[*b*]thiophen-5-yl)-2-fluoroethan-1-one (103dh)



Following **TP6**, solutions of 5-bromobenzo[*b*]thiophene (**104h**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-fluoro-*N*,*N*-dimethylacetamide (**101d**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **103dh** (80.0 mg, 0.41 mmol, 66%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.37 (d, *J* = 1.7 Hz, 1H), 7.97 (dt, *J* = 8.5, 0.8 Hz, 1H), 7.86 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.56 (dd, *J* = 5.5, 0.5 Hz, 1H), 7.44 (dd, *J* = 5.5, 0.8 Hz, 1H), 5.60 (d, *J* = 47.0 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.3 (d, *J* = 15.5 Hz), 145.2, 139.4, 130.2, 128.4, 124.6, 123.7 (d, *J* = 3.1 Hz), 123.0, 122.75 (d, *J* = 2.4 Hz), 83.7 (d, *J* = 182.5 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3084, 2941, 1694, 1594, 1547, 1439, 1383, 1321, 1244, 1232, 1178, 1096, 1080, 1047, 1004, 994, 977, 897, 811, 776, 752, 717, 694, 683.
MS (EI, 70 eV): *m/z* (%) = 194 (26), 162 (10), 161 (31), 161 (100), 133 (22), 89 (20).
HRMS (EI): *m/z* calc. for [$C_{10}H_7OFS$]: 194.0195; found 194.0202.
m.p: 87.9-88.5 °C.

2-Fluoro-1-(4-fluorophenyl)ethan-1-one (103di)



Following **TP6**, solutions of 1-bromo-4-fluorobenzene (**104i**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-fluoro-*N*,*N*-dimethylacetamide (**101d**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.6:0.4) to give **103di** (51.0 mg, 0.33 mmol, 52%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 – 7.89 (m, 2H), 7.21 – 7.14 (m, 2H), 5.48 (d, *J* = 46.9 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.2 (d, *J* = 15.9 Hz), 166.4 (d, *J* = 256.6 Hz), 130.9 (dd, *J* = 9.5, 3.1 Hz, 2C), 130.4 (d, *J* = 3.1 Hz), 116.3 (d, *J* = 22.0 Hz, 2C), 83.7 (d, *J* = 183.2 Hz).

^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –102.8, –229.39 (t, *J* = 46.9 Hz).

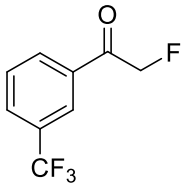
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 1698, 1683, 1593, 1507, 1407, 1231, 1163, 1158, 1102, 1081, 975, 832.

MS (EI, 70 eV): *m/z* (%) = 123 (100), 95 (49), 75 (17), 57 (20).

HRMS (EI): *m/z* calc. for [$C_8H_6OF_2$]: 156.0387; found 156.0378.

m.p: 50.9-51.4 °C.

2-Fluoro-1-(3-(trifluoromethyl)phenyl)ethan-1-one (103dj)



Following **TP6**, solutions of 1-bromo-3-(trifluoromethyl)benzene (**104j**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-fluoro-*N*,*N*-dimethylacetamide (**101d**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.6:0.4) to give **103dj** (62.0 mg, 0.30 mmol, 48%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 – 8.17 (m, 1H), 8.15 – 8.09 (m, 1H), 7.91 (dddd, *J* = 7.8, 1.8, 1.2, 0.6 Hz, 1H), 7.68 (tt, *J* = 7.9, 0.7 Hz, 1H), 5.55 (d, *J* = 46.8 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.6 (d, *J* = 16.4 Hz), 134.3, 131.6 (q, *J* = 33.3 Hz), 131.2 (t, *J* = 2.3 Hz), 130.5 (q, *J* = 3.6 Hz), 129.7, 125.1 – 124.9 (m), 123.5 (q, *J* = 272.5 Hz), 83.7 (d, *J* = 184.2 Hz).

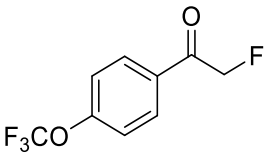
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –63.0, –229.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2849, 1713, 1615, 1436, 1328, 1265, 1218, 1167, 1122, 1097, 1089, 1070, 1042, 1001, 981, 802, 765, 692, 681.

MS (EI, 70 eV): *m/z* (%) = 187 (11), 173 (100), 145 (58), 125 (10).

HRMS (EI): *m/z* calc. for [$C_9H_7OF_4$]: 207.0424; found 207.0433 [M+H].

2-Fluoro-1-(4-(trifluoromethoxy)phenyl)ethan-1-one (103dk)



Following **TP6**, solutions of 1-bromo-4-(trifluoromethoxy)benzene (**104k**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-fluoro-*N*,*N*-dimethylacetamide (**101d**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.6:0.4) to give **103dk** (90.0 mg, 0.41 mmol, 65%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 – 7.91 (m, 2H), 7.32 (dp, *J* = 8.0, 1.1 Hz, 2H), 5.49 (d, *J* = 46.9 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.4 (d, *J* = 16.3 Hz), 153.4 (t, *J* = 1.8 Hz), 132.1, 130.3 (d, *J* = 3.1 Hz, 2C), 120.8 (2C), 117.8 (q, *J* = 259.3 Hz), 83.8 (d, *J* = 183.7 Hz).

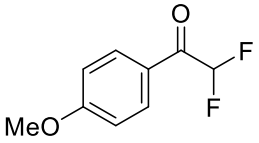
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –57.6, –229.4 (t, *J* = 46.9 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2934, 1708, 1605, 1253, 1205, 1159, 1110, 1091, 973, 854, 840, 824, 814.

MS (EI, 70 eV): *m/z* (%) = 189 (100), 123 (13), 95 (12).

HRMS (EI): *m/z* calc. for [$C_9H_6O_2F_4$]: 222.0304; found 222.0299.

2,2-Difluoro-1-(4-methoxyphenyl)ethan-1-one (103ea)



Following **TP6**, solutions of 4-bromoanisole (**104a**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2,2-difluoro-*N*,*N*-dimethylacetamide (**101e**) (0.3 M,

1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **103ea** (86.0 mg, 0.46 mmol, 74%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (dt, *J* = 9.1, 1.0 Hz, 2H), 7.04 – 6.91 (m, 2H), 6.25 (t, *J* = 53.7 Hz, 1H), 3.90 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 186.0 (t, *J* = 25.0 Hz), 164.0, 132.1 (t, *J* = 2.4 Hz, 2C), 124.4 (2C), 114.3, 111.5 (t, *J* = 253.7 Hz), 55.6.

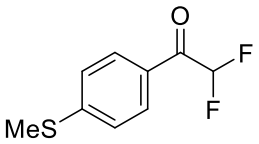
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = -121.4 (d, *J* = 53.6 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1692, 1595, 1572, 1513, 1310, 1250, 1176, 1129, 1119, 1053, 1022, 976, 871.

MS (EI, 70 eV): *m/z* (%) = 135 (100), 77 (17).

HRMS (EI): *m/z* calc. for [$C_9H_8O_2F_2$]: 186.0492; found 186.0489.

2,2-Difluoro-1-(4-(methylthio)phenyl)ethan-1-one (103eb)



Following **TP6**, solutions of 4-bromothioanisole (**104b**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2,2-difluoro-*N*,*N*-dimethylacetamide (**101e**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **103eb** (87.0 mg, 0.43 mmol, 69%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.96 (dt, *J* = 8.8, 1.0 Hz, 2H), 7.32 – 7.28 (m, 2H), 6.25 (t, *J* = 53.6 Hz, 1H), 2.53 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 186.7 (t, *J* = 25.3 Hz), 149.1, 130.0 (t, *J* = 2.4 Hz), 127.6 (t, *J* = 1.9 Hz), 125.1, 111.5 (t, *J* = 253.8 Hz), 14.6.

^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = □121.5.

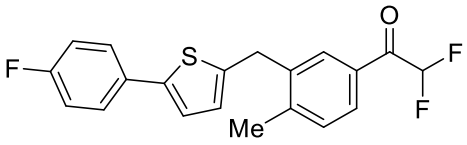
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1692, 1587, 1575, 1553, 1256, 1142, 1093, 1071, 1049, 978, 969, 964, 956, 870, 815, 747, 672.

MS (EI, 70 eV): *m/z* (%) = 202 (15), 151 (100), 123 (12).

HRMS (EI): *m/z* calc. for [$C_9H_8OF_2S$]: 202.0257; found 202.0264.

m.p: 100.6-101.6 °C.

2,2-Difluoro-1-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)ethan-1-one (103el)



Following **TP6**, solutions of 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (**104l**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2,2-difluoro-*N*,*N*-dimethylacetamide (**101e**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **103dl** (169 mg, 0.47 mmol, 75%) as a green solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 (d, *J* = 1.9 Hz, 1H), 7.90 (dq, *J* = 7.9, 1.4 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.06 – 7.00 (m, 3H), 6.67 (dt, *J* = 3.6, 1.1 Hz, 1H), 6.28 (t, *J* = 53.6 Hz, 1H), 4.20 (d, *J* = 1.1 Hz, 2H), 2.42 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 187.2 (t, *J* = 25.1 Hz), 163.4, 161.0, 144.9, 141.9 (d, *J* = 8.0 Hz), 139.3, 131.2, 130.6 (q, *J* = 2.4, 2.0 Hz), 129.9 – 129.8 (m), 128.4 (t, *J* = 2.6 Hz), 127.2 (d, *J* = 7.9 Hz, 2C), 126.3, 122.8 (d, *J* = 1.3 Hz), 115.8 (d, *J* = 21.7 Hz, 2C), 111.2 (t, *J* = 253.7 Hz), 34.1, 20.0.

^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –114.8 to –114.9 (m), –121.8 (d, *J* = 53.7 Hz).

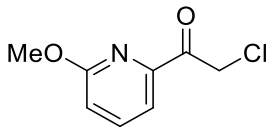
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1705, 1704, 1699, 1694, 1605, 1508, 1231, 1159, 1098, 1057, 833, 809, 802.

MS (EI, 70 eV): *m/z* (%) = 360 (84), 309 (48), 233 (20), 191 (59), 178 (100), 131 (50).

HRMS (EI): *m/z* calc. for [$C_{20}H_{15}OSF_3$]: 360.0796; found 360.0792.

m.p: 58.8-59.4 °C.

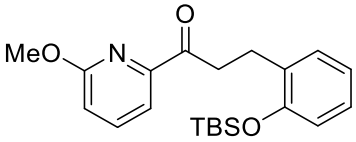
2-Chloro-1-(6-methoxypyridin-2-yl)ethan-1-one (103fg)



Following **TP6**, solutions of 2-bromo-6-methoxypyridine (**104g**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-chloro-*N*,*N*-dimethylacetamide (**101f**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **103fg** (90.0 mg, 0.49 mmol, 78%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.79 – 7.69 (m, 2H), 6.99 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.07 (s, 2H), 3.98 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.0, 163.5, 149.1, 139.5, 116.6, 115.9, 53.7, 47.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 1709, 1601, 1589, 1470, 1430, 1380, 1346, 1285, 1209, 1187, 1155, 1041, 1010, 986, 808, 781, 735, 729.
MS (EI, 70 eV): *m/z* (%) = 187 (20), 185 (65), 136 (57), 126 (22), 108 (100), 93 (20).
HRMS (EI): *m/z* calc. for [$C_8H_8O_2ClN$]: 185.0244; found 185.0238.
m.p: 82.1-82.9 °C.

3-(2-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-(6-methoxypyridin-2-yl)propan-1-one (103gg)



Following **TP6**, solutions of 2-bromo-6-methoxypyridine (**104g**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 3-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-*N*,*N*-dimethylpropanamide (**101g**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **103gf** (161 mg, 0.43 mmol, 69%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.67 (dd, *J* = 8.1, 7.3 Hz, 1H), 7.62 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.21 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.08 (td, *J* = 7.7, 1.8 Hz, 1H), 6.91 – 6.86 (m, 2H), 6.79 (dd, *J* = 8.1, 1.2 Hz, 1H), 3.93 (s, 3H), 3.48 (dd, *J* = 8.3, 7.0 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H), 0.98 (s, 9H), 0.23 (s, 6H).

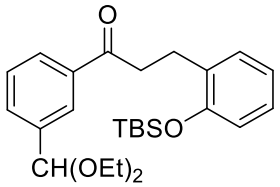
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 201.3, 163.4, 153.9, 151.1, 139.2, 132.3, 130.6, 127.2, 121.2, 118.5, 115.3, 115.0, 53.6, 38.2, 25.9, 25.3 (3C), 18.3, -4.0 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2928, 2857, 1698, 1589, 1490, 1467, 1453, 1250, 1027, 921, 837, 824, 811, 808, 778, 755, 731.

MS (EI, 70 eV): *m/z* (%) = 315 (31), 314 (58), 208 (100), 109 (13).

HRMS (EI): *m/z* calc. for $[C_{21}H_{28}O_3NSi]^+$: 370.1833; found 370.1823 $[M-H]^+$.

3-(2-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-(3-(diethoxymethyl)phenyl)propan-1-one (103gm)



Following **TP6**, solutions of 1-bromo-3-(diethoxymethyl)benzene (**104m**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 3-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-*N*,*N*-dimethylpropanamide (**101g**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **103gm** (225 mg, 0.51 mmol, 81%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 (dd, *J* = 2.1, 1.3 Hz, 1H), 7.91 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.68 (dq, *J* = 7.7, 0.9 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.21 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.10 (td, *J* = 7.9, 1.8 Hz, 1H), 6.90 (td, *J* = 7.4, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.53 (s, 1H), 3.66 – 3.51 (m, 4H), 3.30 (dd, *J* = 8.6, 6.9 Hz, 2H), 3.05 (dd, *J* = 8.5, 6.9 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 6H), 0.99 (s, 9H), 0.26 (d, *J* = 0.8 Hz, 6H).

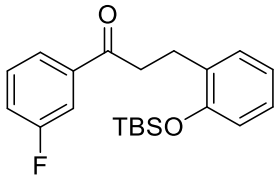
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.6, 153.9, 139.9, 137.2, 131.9, 131.3, 130.6, 128.6, 128.0, 127.3, 126.5, 121.3, 118.6, 101.2, 61.3 (2C), 39.0, 25.9 (3C), 25.6, 18.3, 15.3 (2C), -4.0 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 2858, 1687, 1490, 1453, 1251, 1156, 1103, 1052, 919, 837, 824, 810, 779, 755.

MS (EI, 70 eV): *m/z* (%) = 386 (46), 385 (100), 311 (22), 177 (12), 165 (11).

HRMS (EI): *m/z* calc. for $[C_{25}H_{35}O_4Si]^+$: 427.2299; found 427.2302 $[M\text{-}CH_3]^+$.

3-(2-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-(3-fluorophenyl)propan-1-one (103gn)



Following **TP6**, solutions of 1-bromo-3-fluorobenzene (**104n**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 3-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-*N*,*N*-dimethylpropanamide (**101g**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **103gn** (176 mg, 0.49 mmol, 78%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.72 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.63 (ddd, *J* = 9.5, 2.7, 1.6 Hz, 1H), 7.42 (td, *J* = 8.0, 5.5 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.20 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.11 (td, *J* = 7.7, 1.8 Hz, 1H), 6.90 (td, *J* = 7.4, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.26 (dd, *J* = 8.6, 6.9 Hz, 2H), 3.04 (dd, *J* = 8.5, 6.9 Hz, 2H), 0.99 (s, 9H), 0.26 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 198.3 (d, *J* = 2.1 Hz), 162.8 (d, *J* = 247.8 Hz), 153.7, 139.1 (d, *J* = 6.0 Hz), 131.5, 130.4, 130.2 (d, *J* = 7.6 Hz), 127.3, 123.7 (d, *J* = 3.0 Hz), 121.2, 119.9 (d, *J* = 21.5 Hz), 118.5, 114.7 (d, *J* = 22.2 Hz), 39.0 (d, *J* = 0.6 Hz), 25.7 (3C), 25.5, 18.2, □4.1 (2C).

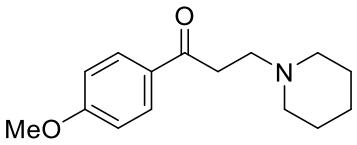
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –112.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2930, 2858, 1690, 1589, 1490, 1453, 1442, 1250, 1239, 918, 835, 806, 779, 755, 732, 680.

MS (EI, 70 eV): *m/z* (%) = 302 (20), 301 (100), 177 (13), 151 (13), 109 (12), 75 (23).

HRMS (EI): *m/z* calc. for $[C_{20}H_{24}O_2FSi]^+$: 343.1524; found 343.1522 $[M\text{-}CH_3]^+$.

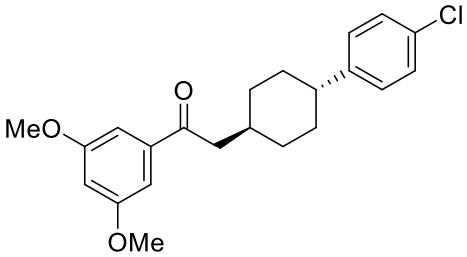
1-(4-Methoxyphenyl)-3-(piperidin-1-yl)propan-1-one (103ha)



Following **TP6**, solutions of 4-bromoanisole (**104a**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and *N*,*N*-dimethyl-3-(piperidin-1-yl)propanamide (**101h**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 4:6) to give **103ha** (94.0 mg, 0.39 mmol, 63%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.16 (dd, *J* = 8.3, 6.8 Hz, 2H), 2.81 (dd, *J* = 8.2, 6.8 Hz, 2H), 2.48 (s, 4H), 1.60 (p, *J* = 5.7 Hz, 4H), 1.44 (q, *J* = 5.7 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 197.8, 163.6, 130.4 (2C), 130.1, 113.8 (2C), 55.6 (2C), 54.6, 54.1, 35.8, 25.8 (2C), 24.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 2841, 1672, 1598, 1575, 1509, 1304, 1256, 1241, 1208, 1167, 1154, 1109, 1028, 977, 836.
MS (EI, 70 eV): *m/z* (%) = 162 (16), 135 (63), 98 (100), 97 (45), 92 (12), 84 (15), 77 (15).
HRMS (EI): *m/z* calc. for [$C_{15}H_{21}O_2N$]: 247.1572; found 247.1570.
m.p: 68.1-68.5 °C.

2-((1*r*,4*r*)-4-(4-Chlorophenyl)cyclohexyl)-1-(3,5-dimethoxyphenyl)ethan-1-one (103io)

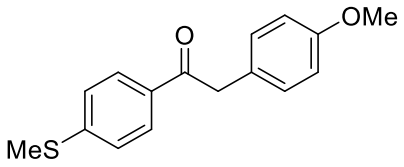


Following **TP6**, solutions of 1-bromo-3,5-dimethoxybenzene (**104o**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-((1*r*,4*r*)-4-(4-chlorophenyl)-cyclohexyl)-*N*,*N*-dimethylacetamide (**101i**) (0.3 M, 1.2 equiv) in toluene were mixed in

continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **103io** (172 mg, 0.46 mmol, 74%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 – 7.09 (m, 4H), 6.66 (t, *J* = 2.3 Hz, 1H), 3.85 (s, 6H), 2.46 (tt, *J* = 12.0, 3.4 Hz, 1H), 2.04 (ddt, *J* = 11.7, 7.0, 4.4 Hz, 1H), 1.97 – 1.83 (m, 4H), 1.48 (qd, *J* = 13.6, 13.0, 3.8 Hz, 2H), 1.27 – 1.11 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.7, 161.0, 145.9, 139.5, 131.6, 128.5 (2C), 128.3 (2C), 106.2 (2C), 105.2, 55.7 (2C), 46.1, 43.7, 34.1 (2C), 33.6 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920, 2843, 1686, 1682, 1601, 1591, 1492, 1454, 1447, 1424, 1356, 1314, 1296, 1204, 1153, 1089, 1065, 1028, 1013, 909, 846, 829, 730, 719, 715, 679.
MS (EI, 70 eV): *m/z* (%) = 207 (49), 192 (31), 190 (100), 165 (40), 152 (99), 138 (37).
HRMS (EI): *m/z* calc. for [$C_{22}H_{25}O_3Cl$]: 372.1492; found 372.1487.
m.p: 85.3-85.8 °C.

2-(4-Methoxyphenyl)-1-(4-(methylthio)phenyl)ethan-1-one (103aa)



Following **TP6**, solutions of 4-bromothioanisole (**104a**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-(4-methoxyphenyl)-*N*,*N*-dimethylacetamide (**101a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **103aa** (87.0 mg, 0.32 mmol, 51%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.96 – 7.87 (m, 2H), 7.26 – 7.24 (m, 2H), 7.20 – 7.12 (m, 2H), 6.91 – 6.80 (m, 2H), 4.17 (s, 2H), 3.78 (s, 3H), 2.51 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 197.1, 158.7, 146.1, 133.1, 130.5 (2C), 129.2 (2C), 126.8, 125.2 (2C), 114.3 (2C), 55.4, 44.7, 14.9.

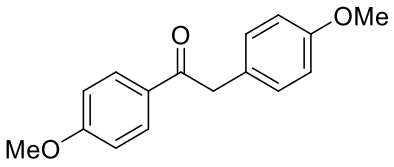
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2833, 2364, 1681, 1586, 1518, 1250, 1034, 824, 813, 795, 668.

MS (EI, 70 eV): *m/z* (%) = 151 (100), 121 (12).

HRMS (EI): *m/z* calc. for [$C_{16}H_{16}O_2S$]: 272.0871; found 272.0865.

m.p: 111.8-112.2 °C.

1,2-Bis(4-methoxyphenyl)ethan-1-one (103ab)



Following **TP6**, solutions of 4-bromoanisole (**104b**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 2-(4-methoxyphenyl)-*N*,*N*-dimethylacetamide (**101a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.2:0.8) to give **103ab** (84.0 mg, 0.33 mmol, 53%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02 – 7.96 (m, 2H), 7.20 – 7.15 (m, 2H), 6.95 – 6.90 (m, 2H), 6.88 – 6.83 (m, 2H), 4.17 (s, 2H), 3.86 (s, 3H), 3.78 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.7, 163.6, 158.6, 131.1 (2C), 130.5 (2C), 129.8, 127.1, 114.2 (2C), 113.9 (2C), 55.6, 55.4, 44.5.

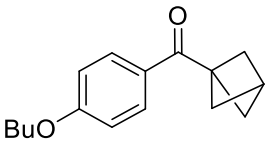
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2904, 2836, 1679, 1601, 1578, 1514, 1257, 1249, 1228, 1202, 1174, 1031, 994, 828, 807.

MS (EI, 70 eV): *m/z* (%) = 135 (100), 77 (10).

HRMS (EI): *m/z* calc. for [$C_{16}H_{16}O_3$]: 256.1099; found 256.1093.

m.p: 129.6-131.0 °C.

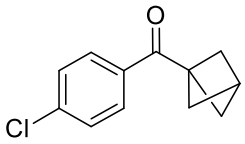
Bicyclo[1.1.1]pentan-1-yl(4-butoxyphenyl)methanone (103jp)



Following **TP6**, solutions of 1-bromo-4-butoxybenzene (**104p**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and *N*,*N*-dimethylbicyclo[1.1.1]pentane-1-carboxamide (**101j**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **103jp** (91.0 mg, 0.37 mmol, 59%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.55 (s, 1H), 2.30 (s, 6H), 1.78 (ddt, *J* = 8.9, 7.8, 6.4 Hz, 2H), 1.55 – 1.45 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.9, 163.0, 131.4, 129.4, 114.2, 68.0, 53.5 (3C), 49.5, 31.3, 28.5, 19.3, 13.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 2874, 1655, 1597, 1572, 1508, 1420, 1309, 1252, 1214, 1162, 1135, 984, 969, 884, 843, 793.
MS (EI, 70 eV): *m/z* (%) = 244 (16), 177 (48), 171 (17), 121 (100), 93 (13), 65 (16), 41 (15).
HRMS (EI): *m/z* calc. for [$C_{16}H_{20}O_2$]: 244.1463; found 244.1460.

Bicyclo[1.1.1]pentan-1-yl(4-butoxyphenyl)methanone (103jr)

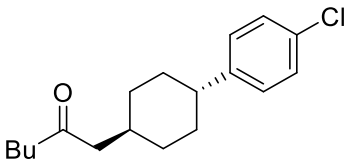


Following **TP6**, solutions of 1-bromo-3-chlorobenzene (**104r**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and *N*,*N*-dimethylbicyclo[1.1.1]pentane-1-carboxamide (**101j**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column

chromatography (pentane:ethyl acetate= 9.8:0.2) to give **103jr** (90.0 mg, 0.44 mmol, 70%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 – 7.91 (m, 2H), 7.45 – 7.37 (m, 2H), 2.57 (d, *J* = 0.9 Hz, 1H), 2.31 (d, *J* = 0.7 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.2, 139.4, 134.9, 130.5, 128.9, 53.5 (3C), 49.4, 28.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979, 2878, 1663, 1586, 1569, 1487, 1400, 1314, 1295, 1212, 1170, 1089, 1014, 985, 882, 854, 842, 789, 726.
MS (EI, 70 eV): *m/z* (%) = 171 (15), 141 (27), 139 (100), 111 (34), 75 (18), 42 (17).
HRMS (EI): *m/z* calc. for $[C_{12}H_{10}OCl]^+$: 205.0415; found 205.0432 [M-H$^+$].

1-((1*r*,4*r*)-4-(4-Chlorophenyl)cyclohexyl)hexan-2-one (103i)



A solution of 2-((1*r*,4*r*)-4-(4-chlorophenyl)-cyclohexyl)-*N*,*N*-dimethylacetamide (**101i,** 0.30 M, 1.0 equiv) and THF (1.0 equiv) in toluene and a solution of *n*-BuLi in *n*-hexane (0.25 M, 1.2 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 5.0 mL·min^{-1} and flowrate B = 5.0 mL·min^{-1}. The solutions passed a PTFE reactor tube (i.d = 0.8 mm, Vol_{R1} = 2 mL; residence time: t = 24 sec, T = –20 °C) for precooling the reaction mixture, and then mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (i.d = 0.8 mm, Vol_{R1} = 5 mL; residence time: t = 30 sec, T = –20 °C) and the reaction mixture was subsequently quenched with *sat. aq.* NH_4Cl at 0 °C for 30 s corresponding to 0.625 mmol of *n*-BuLi. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **103i** (146 mg, 0.50 mmol, 80%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.21 (m, 2H), 7.14 – 7.09 (m, 2H), 2.48 – 2.36 (m, 3H), 2.32 (d, *J* = 6.7 Hz, 2H), 1.95 – 1.77 (m, 5H), 1.61 – 1.39 (m, 4H), 1.37 – 1.24 (m, 2H), 1.16 – 1.02 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 211.1, 145.9, 131.6, 128.5, 128.3, 50.3, 43.7, 43.4, 34.0, 33.5, 33.4, 26.0, 22.5, 14.0.

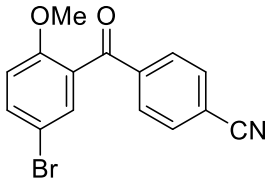
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2871, 2849, 1698, 1491, 1406, 1380, 1355, 1128, 1089, 1046, 1012, 960, 823.

MS (EI, 70 eV): *m/z* (%) = 192 (33), 191 (13), 155 (49), 140 (11), 138 (33), 127 (11), 125 (35), 115 (10).

HRMS (EI): *m/z* calc. for [$C_{18}H_{25}OCl$]: 292.1594; found 292.1586.

m.p: 44.5-45.9 °C.

4-(5-Bromo-2-methoxybenzoyl)benzonitrile (111af)



Following **TP6**, solutions of 2,4-dibromo-1-methoxybenzene (**104f**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 4-cyano-*N*,*N*-dimethylbenzamide (**110a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **111af** (144 mg, 0.46 mmol, 73%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.86 – 7.82 (m, 2H), 7.75 – 7.71 (m, 2H), 7.60 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.52 (d, *J* = 2.5 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.67 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.5, 156.7, 140.8, 135.7, 132.6, 132.3 (2C), 129.9 (2C), 129.2, 118.2, 116.3, 113.5, 113.3, 55.9.

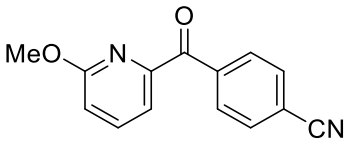
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2935, 2840, 2229, 1672, 1590, 1480, 1460, 1408, 1391, 1293, 1289, 1259, 1235, 1182, 1121, 1020, 949, 937, 859, 818, 770, 675.

MS (EI, 70 eV): *m/z* (%) = 315 (19), 219 (32), 214 (95), 212 (100), 200 (41), 199 (43), 172 (48), 170 (48), 130 (65).

HRMS (EI): *m/z* calc. for [$C_{15}H_{10}O_2NBr$]: 314.9895; found 314.9886.

m.p: 113.6-115.2 °C.

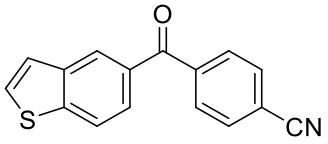
4-(6-Methoxypicolinoyl)benzonitrile (111ag)



Following **TP6**, solutions of 2-bromo-6-methoxypyridine (**104g**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 4-cyano-*N*,*N*-dimethylbenzamide (**110a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **111ag** (118 mg, 0.49 mmol, 79%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.32 – 8.15 (m, 2H), 7.87 – 7.66 (m, 4H), 7.00 (dd, *J* = 8.2, 1.0 Hz, 1H), 3.88 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.8, 163.1, 151.0, 140.5, 139.6, 131.7 (2C), 131.3 (2C), 118.4, 118.3, 115.7, 115.5, 53.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2991, 2949, 2230, 1662, 1590, 1464, 1336, 1290, 1267, 1151, 1031, 989, 974, 868, 851, 814, 762.
MS (EI, 70 eV): *m/z* (%) = 237 (43), 210 (67), 209 (57), 195 (29), 179 (44), 130 (100), 93 (39), 79 (35).
HRMS (EI): *m/z* calc. for [$C_{14}H_{10}O_2N_2$]: 238.0742; found 238.0743.
m.p: 127.1-127.8 °C.

4-(Benzo[*b*]thiophene-5-carbonyl)benzonitrile (111ah)



Following **TP6**, solutions of 5-bromobenzo[*b*]thiophene (**104h**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 4-cyano-*N*,*N*-dimethylbenzamide (**110a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column

chromatography (pentane:ethyl acetate= 9.5:0.5) to give **111ah** (100 mg, 0.38 mmol, 61%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (d, *J* = 1.7 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.91 – 7.86 (m, 2H), 7.80 (dd, *J* = 8.3, 1.6 Hz, 3H), 7.57 (d, *J* = 5.4 Hz, 1H), 7.42 (d, *J* = 5.5 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.1, 144.7, 141.8, 139.3, 132.8, 132.3 (2C), 130.3 (2C), 128.5, 126.5, 125.1, 124.6, 122.9, 118.2, 115.6.

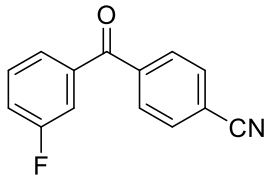
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 2229, 1651, 1592, 1402, 1325, 1289, 1274, 1251, 1198, 1088, 1048, 979, 956, 853, 817, 758, 728, 712, 691.

MS (EI, 70 eV): *m/z* (%) = 263 (25), 161 (100), 133 (15), 89 (20).

HRMS (EI): *m/z* calc. for [$C_{16}H_9ONS$]: 263.0405; found 263.0398.

m.p: 157.0-158.0 °C.

4-(3-Fluorobenzoyl)benzonitrile (111ar)



Following **TP6**, solutions of 1-bromo-3-fluorobenzene (**104r**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 4-cyano-*N*,*N*-dimethylbenzamide (**110a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromid. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **111ar** (90.0 mg, 0.40 mmol, 64%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 – 7.88 (m, 2H), 7.85 – 7.81 (m, 2H), 7.59 – 7.49 (m, 3H), 7.37 (tdd, *J* = 8.2, 2.6, 1.3 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.8 (d, *J* = 2.2 Hz), 162.8 (d, *J* = 249.2 Hz), 140.7, 138.5 (d, *J* = 6.5 Hz), 132.4 (2C), 130.5 (d, *J* = 7.8 Hz), 130.3 (2C), 126.01(d, *J* = 3.1 Hz), 120.6 (d, *J* = 21.4 Hz), 118.0, 116.9 (d, *J* = 22.6 Hz), 116.2.

^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –111.0.

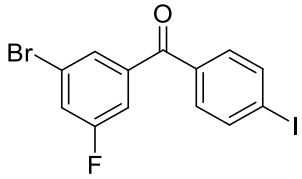
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3069, 2232, 1664, 1585, 1482, 1440, 1404, 1311, 1294, 1277, 1272, 1208, 857, 839, 758, 710.

MS (EI, 70 eV): *m/z* (%) = 225 (30), 130 (65), 123 (100), 95 (19), 75 (23).

HRMS (EI): *m/z* calc. for [$C_{14}H_8ONF$]: 225.0590; found 225.0582.

m.p: 92.4-93.3 °C.

(3-Bromo-5-fluorophenyl)(4-iodophenyl)methanone (111bs)



Following **TP6**, solutions of 1,3-dibromo-5-fluorobenzene (**104s**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 4-iodo-*N*,*N*-dimethylbenzamide (**110b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **111bs** (201 mg, 0.49 mmol, 79%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 – 7.85 (m, 2H), 7.67 (t, *J* = 1.7 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.40 (ddd, *J* = 8.5, 2.4, 1.4 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.0 (d, *J* = 2.1 Hz), 162.4 (d, *J* = 253.7 Hz), 140.3 (d, *J* = 6.7 Hz), 138.1 (2C), 135.7, 131.4 (2C), 128.8 (d, *J* = 3.3 Hz), 123.2 (d, *J* = 24.5 Hz), 123.0, 115.8 (d, *J* = 22.5 Hz), 101.3.

^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –108.9.

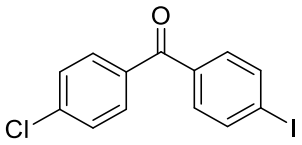
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 1661, 1575, 1557, 1427, 1390, 1304, 1278, 1214, 1179, 1001, 989, 864, 835, 766, 750, 658.

MS (EI, 70 eV): *m/z* (%) = 406 (13), 404 (13), 230 (100), 202 (19).

HRMS (EI): *m/z* calc. for [$C_{13}H_7OBrFI$]: 403.8709, found 403.8706.

m.p: 80.5-81.1 °C.

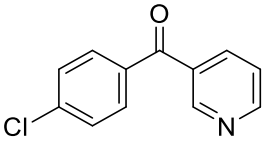
(4-Chlorophenyl)(4-iodophenyl)methanone (111bq)



Following **TP6**, solutions of 1-bromo-4-chlorobenzene (**104q**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and 4-iodo-*N*,*N*-dimethylbenzamide (**110b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **111bq** (134 mg, 0.39 mmol, 63%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.87 – 7.83 (m, 2H), 7.75 – 7.69 (m, 2H), 7.51 – 7.44 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 194.7, 139.3, 137.8 (2C), 136.6, 135.5, 131.5 (2C), 131.4 (2C), 128.9 (2C), 100.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1643, 1580, 1391, 1306, 1302, 1287, 1282, 1093, 1058, 1015, 1008, 926, 905, 853, 825, 748, 730, 665.
MS (EI, 70 eV): *m/z* (%) = 341 (44), 306 (25), 230 (100), 215 (20), 140 (25), 138 (77).
HRMS (EI): *m/z* calc. for [$C_{13}H_8OClI$]: 341.9308; found 341.9303.
m.p: 169.0-170.0 °C.

(4-Chlorophenyl)(4-iodophenyl)methanone (111cq)



Following **TP6**, solutions of 1-bromo-4-chlorobenzene (**104q**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and *N*,*N*-diethylnicotinamide (**110c**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 7:3) to give **111cq** (79.0 mg, 0.36 mmol, 58%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.96 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.82 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.09 (ddd, *J* = 7.9, 2.2, 1.7 Hz, 1H), 7.84 – 7.69 (m, 2H), 7.51 – 7.47 (m, 2H), 7.45 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.7, 153.2, 150.9, 139.9, 137.2, 135.1, 133.0, 131.5 (2C), 129.1 (2C), 123.6.

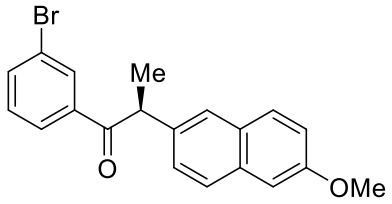
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3050, 1644, 1581, 1570, 1484, 1418, 1401, 1337, 1299, 1282, 1149, 1093, 1024, 1011, 935, 923, 850, 845, 819, 745, 711, 678.

MS (EI, 70 eV): *m/z* (%) = 183 (13), 182 (100), 141 (11), 139 (34).

HRMS (EI): *m/z* calc. for $[C_{12}H_7ONCl]^+$: 216.0211; found 216.0211 $[M-H]^+$.

m.p: 91.0-91.2 °C.

(*S*)-1-(3-Bromophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (113ae)



Following **TP6**, solutions of 1,3-bromobenzene (**104e**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (**112a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **113ae** (173 mg, 0.47 mmol, 75%, 99% *ee*) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (t, *J* = 1.8 Hz, 1H), 7.87 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.69 (t, *J* = 9.1 Hz, 2H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.55 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.37 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.14 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 4.74 (q, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 1.61 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.1, 157.9, 138.4, 136.1, 135.7, 133.7, 131.9, 130.1, 129.3, 129.3, 127.9, 127.4, 126.4, 126.4, 123.0, 119.3, 105.7, 55.4, 48.2, 19.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2973, 2931, 1682, 1603, 1483, 1391, 1265, 1224, 1201, 1172, 1162, 1030, 907, 852, 730, 728, 673.

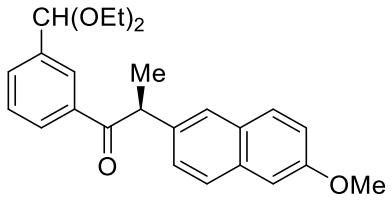
MS (EI, 70 eV): *m/z* (%) = 185 (100), 170 (24), 153 (10), 141 (12).

HRMS (EI): *m/z* calc. for [$C_{20}H_{17}O_2Br$]: 368.0412; found 368.0406.

Optical rotation: $[\alpha]_D^{20}$ = 125 (c 1.09, $CHCl_3$).

Chiral HPLC: 99% *ee*, OD-H column, heptane:*i*-PrOH = 95:5, 1.0 mL/min, 30 °C.

(*S*)-1-(3-(diethoxymethyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (113am)



Following **TP6**, solutions of 1-bromo-3-(diethoxymethyl)benzene (**104m**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (**112a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **113am** (159 mg, 0.41 mmol, 65%, 99% *ee*) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (t, *J* = 1.8 Hz, 1H), 7.95 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.71 – 7.63 (m, 3H), 7.58 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.16 – 7.02 (m, 2H), 5.48 (s, 1H), 4.84 (q, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 3.49 (ddtt, *J* = 18.6, 14.1, 9.4, 7.0 Hz, 4H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.19 (td, *J* = 7.1, 2.5 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 200.2, 157.6, 139.5, 136.7, 136.4, 133.5, 131.1, 129.2, 129.2, 128.7, 128.4, 127.6, 127.2, 126.4, 126.3, 119.0, 105.6, 100.8, 61.1, 60.9, 55.2, 47.9, 19.4 (2C), 15.1 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2973, 2931, 1681, 1604, 1263, 1170, 1162, 1113, 1052, 1031, 907, 852, 727.

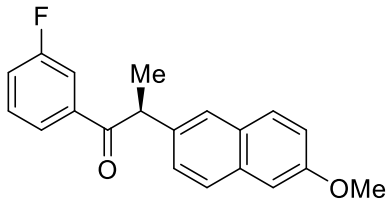
MS (EI, 70 eV): *m/z* (%) = 207 (11), 185 (100), 183 (17), 170 (24), 153 (13).

HRMS (EI): *m/z* calc. for [$C_{25}H_{28}O_4$]: 392.1988, found 392.1984.

Optical rotation: $[\alpha]_D^{20}$ = 158 (c 0.99, $CHCl_3$).

Chiral HPLC: 99% *ee*, OD-H column, heptane:*i*-PrOH = 98:2, 1.0 mL/min, 30 °C.

(*S*)-1-(3-Fluorophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (113ar)



Following **TP6**, solutions of 1-bromo-3-fluorobenzene (**104r**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (**112a**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **113ar** (170 mg, 0.55 mmol, 88%, 99% *ee*) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.75 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1H), 7.72 – 7.62 (m, 4H), 7.40 – 7.28 (m, 2H), 7.17 – 7.07 (m, 3H), 4.74 (q, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 1.61 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.1, 162.7 (d, *J* = 247.6 Hz), 157.7, 138.7 (d, *J* = 6.1 Hz), 136.1, 133.5, 130.1 (d, *J* = 7.6 Hz), 129.2, 129.2, 127.8, 126.3, 126.2, 124.5 (d, *J* = 3.0 Hz), 119.7 (d, *J* = 21.5 Hz), 119.1, 115.5 (d, *J* = 22.4 Hz), 105.6, 55.3, 48.2, 19.4.

^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –108.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2973, 2934, 1682, 1604, 1587, 1483, 1439, 1391, 1260, 1246, 1226, 1211, 1173, 1162, 1151, 1030, 924, 907, 889, 886, 852, 815, 806, 803, 768, 751, 727, 673.

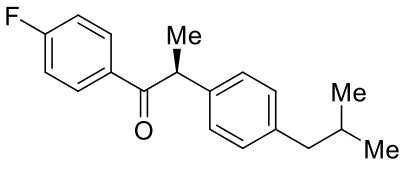
MS (EI, 70 eV): *m/z* (%) = 185 (100), 170 (42), 154 (14), 153 (21), 141 (16).

HRMS (EI): *m/z* calc. for [$C_{20}H_{17}O_2F$]: 308.1213; found 308.1204.

Optical rotation: $[\propto]_D^{20}$ = 96 (c 1.00, $CHCl_3$).

Chiral HPLC: 99% *ee*, OD-H column, heptane:*i*-PrOH = 99.5:0.5, 1.0 mL/min, 30 °C.

(2*S*)-1-(4-Fluorophenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one (113bi)



Following **TP6**, solutions of 1-bromo-4-fluorobenzene (**104i**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(4-*iso*butylphenyl)-*N*,*N*-dimethylpropanamide (**112b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **113bi** (150 mg, 0.50 mmol, 80%, 99% *ee*) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 – 7.87 (m, 2H), 7.19 – 7.13 (m, 2H), 7.10 – 7.00 (m, 4H), 4.60 (q, *J* = 6.8 Hz, 1H), 2.41 (d, *J* = 7.2 Hz, 2H), 1.81 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 198.2, 165.4 (d, *J* = 254.5 Hz), 140.5, 138.5, 132.9 (d, *J* = 3.0 Hz), 131.4 (d, *J* = 9.2 Hz, 2C), 129.8 (2C), 127.4 (2C), 115.5 (d, *J* = 21.9 Hz, 2C), 47.6, 45.0, 30.1, 22.4 (d, *J* = 1.3 Hz), 19.5.

^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –105.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2929, 2926, 1682, 1596, 1505, 1224, 1155, 1006, 953, 847, 836, 819, 802, 788, 779.

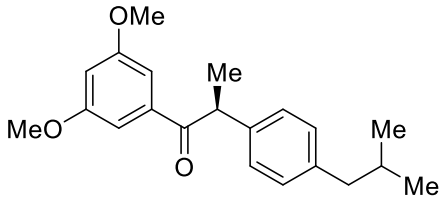
MS (EI, 70 eV): *m/z* (%) = 162 (13), 161 (100), 123 (57), 119 (20), 117 (14), 105 (13), 91 (11).

HRMS (EI): *m/z* calc. for [$C_{19}H_{21}OF$]: 284.1576; found 284.1571.

Optical rotation: $[\propto]_D^{20}$ = 106 (c 1.05, $CHCl_3$).

Chiral HPLC: 99% *ee*, OD-H column, heptane:*i*-PrOH = 99.5:0.5, 1.0 mL/min, 30 °C.

(2*S*)-1-(3,5-Dimethoxyphenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one (113bo)

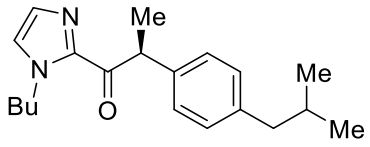


Following **TP6**, solutions of 1-bromo-3,5-dimethoxybenzene (**104o**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *sec*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(4-*iso*butylphenyl)-*N*,*N*-dimethylpropanamide (**112b**) (0.3 M, 1.2 equiv) in toluene were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via*

column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **113bo** (160 mg, 0.47 mmol, 75%, 99% *ee*) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.20 – 7.15 (m, 2H), 7.12 – 7.04 (m, 4H), 6.56 (t, *J* = 2.3 Hz, 1H), 4.59 (q, *J* = 6.8 Hz, 1H), 3.77 (s, 6H), 2.40 (d, *J* = 7.2 Hz, 2H), 1.81 (hept, *J* = 6.8 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), 0.87 (dd, *J* = 6.6, 1.3 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 200.3, 160.8, 140.5, 138.8, 138.7, 129.9 (2C), 127.5 (2C), 106.8 (2C), 105.3, 55.6 (2C), 47.8, 45.1, 30.3, 22.5, 19.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2930, 1682, 1601, 1592, 1457, 1425, 1354, 1346, 1308, 1293, 1205, 1196, 1155, 1069, 1017, 854.
MS (EI, 70 eV): *m/z* (%) = 165 (100), 137 (24), 122 (10).
HRMS (EI): *m/z* calc. for [$C_{21}H_{26}O_3$]: 326.1877; found 326.1882.
Optical rotation: $[\propto]_D^{20}$ = 84 (c 1.12, $CHCl_3$).
Chiral HPLC: 99% *ee*, OD-H column, heptane:*i*-PrOH = 95:5, 1.0 mL/min, 30 °C.

(*S*)-1-(1-butyl-1H-imidazol-2-yl)-2-(4-isobutylphenyl)propan-1-one (113bt)



A solution of 1-butyl-1*H*-imidazole (0.25 M, 1.0 equiv) and TMEDA (1.0 equiv) in toluene and a solution of *sec*-BuLi in cyclohexane (1.3 M, 1.2 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 5.0 mL·min^{-1} and flowrate B = 1.15 mL·min^{-1}. The solutions were mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm) and the combined stream passed a PTFE reactor tube (i.d = 0.8 mm, Vol_{R1} = 4 mL; residence time: t = 40 s, T = 25 °C), followed by a PTFE reactor tube (i.d = 0.8 mm, Vol_{R1} = 1 mL; residence time: t = 10 sec, T = –20 °C) for precooling the reaction mixture. A (*S*)-2-(4-*iso*butylphenyl)-*N*,*N*-dimethylpropanamide (**112b**) solution (0.3 M, 1.2 equiv) in toluene was added *via* a third pump (flowrate C = 5.0 mL·min^{-1}, i.d = 0.8 mm Vol_{pre} = 2.0 mL, T_{pre} = –20 °C, residence $time_{pre:}$ t = 24 s). The combined stream passed a PTFE reactors tube (i.d = 1.6 mm, Vol_{R2} = 5 mL; residence time: t = 27 s, T = –20 °C) and the reaction mixture was subsequently quenched with *sat. aq.* NH_4Cl at 0 °C. After extraction with EtOAc, the combined organic phases were dried over Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, the crude product was

purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **113bt** (174 mg, 0.56 mmol, 89%, 98% *ee*) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.36 – 7.31 (m, 2H), 7.16 (d, *J* = 1.0 Hz, 1H), 7.12 – 7.02 (m, 3H), 5.29 (q, *J* = 7.1 Hz, 1H), 4.34 (t, *J* = 7.3 Hz, 2H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.84 (dp, *J* = 13.6, 6.8 Hz, 1H), 1.76 – 1.62 (m, 2H), 1.55 (d, *J* = 7.1 Hz, 3H), 1.33 – 1.22 (m, 2H), 0.94 – 0.86 (m, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.5, 142.4, 140.3, 138.1, 129.4 (2C), 129.3, 128.1 (2C), 126.3, 48.6, 46.6, 45.2, 33.2, 30.3, 22.5, 19.8, 18.2, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2929, 1674, 1464, 1404, 1382, 955, 911.

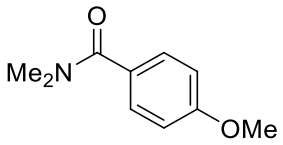
MS (EI, 70 eV): *m/z* (%) = 311 (100), 295 (52), 283 (24), 255 (31), 161 (42), 151 (50), 123 (35), 117 (52), 91 (27).

HRMS (EI): *m/z* calc. for [$C_{20}H_{28}ON_2$]: 312.2197; found 312.2202.

Optical rotation: $[\propto]_D^{20}$ = 39 (c 0.99, $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, heptane:*i*-PrOH = 99:1, 1.0 mL/min, 30 °C.

4-Methoxy-*N*,*N*-dimethylbenzamide (101j)



Following **TP7**, solutions of 4-bromoanisole (**104a**) (0.25 M, 1.0 equiv) plus tetramethylurea **114** (0.3 M, 1.2 equiv) in toluene and *sec*-BuLi (1.4 M, 1.2 equiv) were mixed in continuous flow. After reaching a steady state, the combined stream was collected into *sat. aq.* NH_4Cl for 30 s, corresponding to 0.625 mmol of the bromide. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **101j** (93.0 mg, 0.52 mmol, 83%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 3.08 (s, 6H).

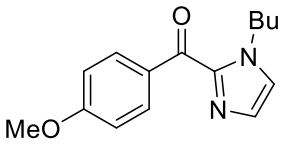
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.7, 160.8, 129.3 (2C), 128.4, 113.7 (2C), 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3469, 2933, 2839, 1605, 1490, 1440, 1389, 1300, 1246, 1172, 1082, 1024, 840, 764.

MS (EI, 70 eV): *m/z* (%) = 178 (42), 135 (100), 77 (14).

HRMS (EI): *m/z* calc. for [$C_{10}H_{13}O_2N$]: 179.0946; found 179.0939.

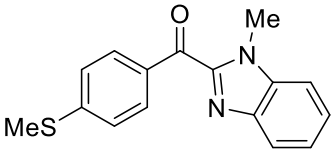
(1-Butyl-1*H*-imidazol-2-yl)(4-methoxyphenyl)methanone (117a)



Following **TP7**, solutions of 4-bromoanisole (**104a**) (0.25 M, 1.0 equiv) plus tetramethylurea **114** (0.3 M, 1.2 equiv) in toluene and *sec*-BuLi (1.4 M, 1.2 equiv) were mixed in continuous flow. After reaching a steady state, the combined stream was was poured into an organolithiums species for 30 s (corresponding to 0.625 mmol bromide), which was prepared in batch starting from 1-butyl-1H-imidazole (1.00 mmol, 1.6 equiv) plus TMEDA (1.00 mmol, 1.6 equiv) in toluene and *sec*-BuLi (1.4 M, 1.1 mmol, 1.8 equiv) at –20 °C. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **117a** (126 mg, 0.49 mmol, 78%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.31 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 1.0 Hz, 1H), 7.12 (d, *J* = 1.0 Hz, 1H), 6.98 – 6.93 (m, 2H), 4.55 – 4.28 (m, 2H), 3.88 (s, 3H), 1.91 – 1.74 (m, 2H), 1.47 – 1.29 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 183.0, 163.5, 143.1, 133.4 (2C), 130.5, 129.1, 125.3, 113.6 (2C), 55.6, 48.7, 33.5, 20.0, 13.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2932, 1636, 1596, 1461, 1420, 1396, 1381, 1309, 1251, 1180, 1159, 1144, 1029, 929, 903, 843, 776.
MS (EI, 70 eV): *m/z* (%) = 257 (57), 229 (44), 173 (32), 135 (70), 123 (24), 121 (100), 77 (34).
HRMS (EI): *m/z* calc. for [$C_{15}H_{18}O_2N_2$]: 258.1368; found 258.1363.

(1-Methyl-1H-benzo[*d*]imidazol-2-yl)(4-(methylthio)phenyl)methanone (117b)

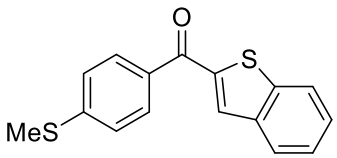


Following **TP7**, solutions of 4-bromothioanisole (**104b**) (0.25 M, 1.0 equiv) plus tetramethylurea **114** (0.3 M, 1.2 equiv) in toluene and *sec*-BuLi (1.4 M, 1.2 equiv) were mixed

in continuous flow. After reaching a steady state, the combined stream was poured into an organolithiums species for 30 s (corresponding to 0.625 mmol bromide), which was prepared in batch starting from 1-methyl-1H-benzo[*d*]imidazole (1.00 mmol, 1.6 equiv) plus TMEDA (1.00 mmol, 1.6 equiv) in toluene and *sec*-BuLi (1.4 M, 1.1 mmol, 1.8 equiv) at –20 °C. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.2:0.8) to give **117b** (138 mg, 0.49 mmol, 79%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.36 – 8.26 (m, 2H), 7.92 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.41 – 7.32 (m, 3H), 4.15 (s, 3H), 2.55 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 185.3, 147.0, 147.0, 142.0, 136.7, 133.2, 131.8 (2C), 125.7, 125.0 (2C), 123.7, 122.1, 110.5, 32.4, 14.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2919, 1641, 1585, 1477, 1456, 1400, 1390, 1335, 1266, 1234, 1186, 1091, 943, 897, 767, 743.
MS (EI, 70 eV): *m/z* (%) = 281 (100), 238 (23), 207 (14), 206 (16), 151 (14).
HRMS (EI): *m/z* calc. for $[C_{16}H_{13}ON_2S]^+$: 281.0743; found 281.0743 $[M\text{-}H]^+$.

Benzo[*b*]thiophen-2-yl(4-(methylthio)phenyl)methanone (117c)

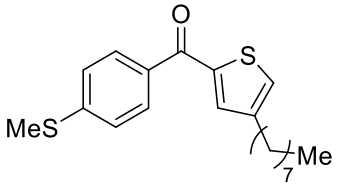


Following **TP7**, solutions of 4-bromothioanisole (**104b**) (0.25 M, 1.0 equiv) plus tetramethylurea **114** (0.3 M, 1.2 equiv) in toluene and *sec*-BuLi (1.4 M, 1.2 equiv) were mixed in continuous flow. After reaching a steady state, the combined stream was poured into an organolithiums species for 30 s (corresponding to 0.625 mmol bromide), which was prepared in batch starting from benzo[*b*]thiophene (1.00 mmol, 1.6 equiv) plus TMEDA (1.00 mmol, 1.6 equiv) in toluene and *sec*-BuLi (1.4 M, 1.1 mmol, 1.8 equiv) at –20 °C. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **117c** (123 mg, 0.43 mmol, 69%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 – 7.84 (m, 5H), 7.52 – 7.40 (m, 2H), 7.39 – 7.33 (m, 2H), 2.57 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 188.7, 145.6, 143.3, 142.7, 139.2, 134.1, 131.7, 130.0 (2C), 127.5, 126.1, 125.3 (2C), 125.2, 123.1, 15.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 2917, 1621, 1589, 1513, 1296, 754, 742, 727, 723.
MS (EI, 70 eV): *m/z* (%) = 284 (77), 281 (38), 237 (40), 225 (26), 207 (100), 161 (28), 151 (54).
HRMS (EI): *m/z* calc. for [$C_{16}H_{12}OS_2$]: 284.0330; found 283.0324.
m.p: 124.6-126.0 °C.

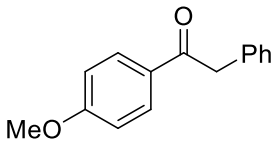
(4-(Methylthio)phenyl)(4-octylthiophen-2-yl)methanone (117d)



Following **TP7**, solutions of 4-bromothioanisole (**104b**) (0.25 M, 1.0 equiv) plus tetramethylurea **114** (0.3 M, 1.2 equiv) in toluene and *sec*-BuLi (1.4 M, 1.2 equiv) were mixed in continuous flow. After reaching a steady state, the combined stream was poured into an organolithiums species for 30 s (corresponding to 0.625 mmol bromide), which was prepared in batch starting from 3-octylthiophene (1.00 mmol, 1.6 equiv) plus TMEDA (1.00 mmol, 1.6 equiv) in toluene and *sec*-BuLi (1.4 M, 1.1 mmol, 1.8 equiv) at –20 °C. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **117d** (170 mg, 0.44 mmol, 70%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.81 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 1.4 Hz, 1H), 7.34 – 7.29 (m, 3H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.55 (s, 3H), 1.62 (p, *J* = 7.4 Hz, 2H), 1.29 (d, *J* = 14.3 Hz, 10H), 0.92 – 0.80 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 187.3, 144.9, 144.5, 143.2, 135.6, 134.6, 129.9 (2C), 129.3, 125.2 (2C), 32.0, 30.6, 30.5, 29.5, 29.4, 29.4, 22.8, 15.1, 14.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2853, 1629, 1589, 1418, 1290, 1185, 1087, 855.
MS (EI, 70 eV): *m/z* (%) = 346 (16), 248 (41), 247 (14), 151 (100).
HRMS (EI): *m/z* calc. for [$C_{20}H_{26}OS_2$]: 346.1425; found 346.1420.

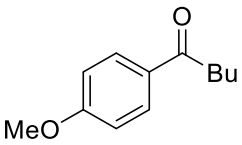
1-(4-Methoxyphenyl)-2-phenylethan-1-one (117e)



Following **TP7**, solutions of 4-bromoanisole (**104a**) (0.25 M, 1.0 equiv) plus tetramethylurea **114** (0.3 M, 1.2 equiv) in toluene and *sec*-BuLi (1.4 M, 1.2 equiv) were mixed in continuous flow. After reaching a steady state, the combined stream was was poured into an organolithiums species for 30 s (corresponding to 0.625 mmol bromide), which was prepared in batch starting from toluene plus TMEDA (1.00 mmol, 1.6 equiv) and *sec*-BuLi (1.4 M, 1.1 mmol, 1.8 equiv) at –20 °C. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **117e** (109 mg, 0.48 mmol, 77%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 – 7.96 (m, 2H), 7.39 – 7.22 (m, 5H), 6.99 – 6.90 (m, 2H), 4.25 (s, 2H), 3.87 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.3, 163.6, 135.1, 131.0 (2C), 129.7, 129.5 (2C), 128.7 (2C), 126.9, 113.9 (2C), 55.6, 45.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2932, 2838, 1676, 1670, 1667, 1598, 1574, 1509, 1257, 1223, 1167, 1029, 990, 828, 727, 705, 696.
MS (EI, 70 eV): *m/z* (%) = 135 (100), 77 (23).
HRMS (EI): *m/z* calc. for [$C_{15}H_{14}O_2$]: 226.0994; found 226.0984.
m.p: 71.3-71.8 °C.

1-(4-Methoxyphenyl)pentan-1-one (117f)



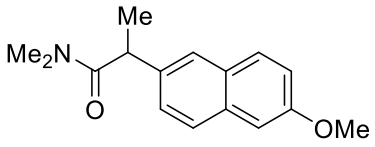
Following **TP7**, solutions of 4-bromoanisole (**104a**) (0.25 M, 1.0 equiv) plus tetramethylurea **114** (0.3 M, 1.2 equiv) in toluene and *sec*-BuLi (1.4 M, 1.2 equiv) were mixed in continuous flow. After reaching a steady state, the combined stream was poured into a *n*-BuLi solution (1.7 M, 1.0 mmol, 1.6 equiv) for 30 s (corresponding to 0.625 mmol bromide). After workup,

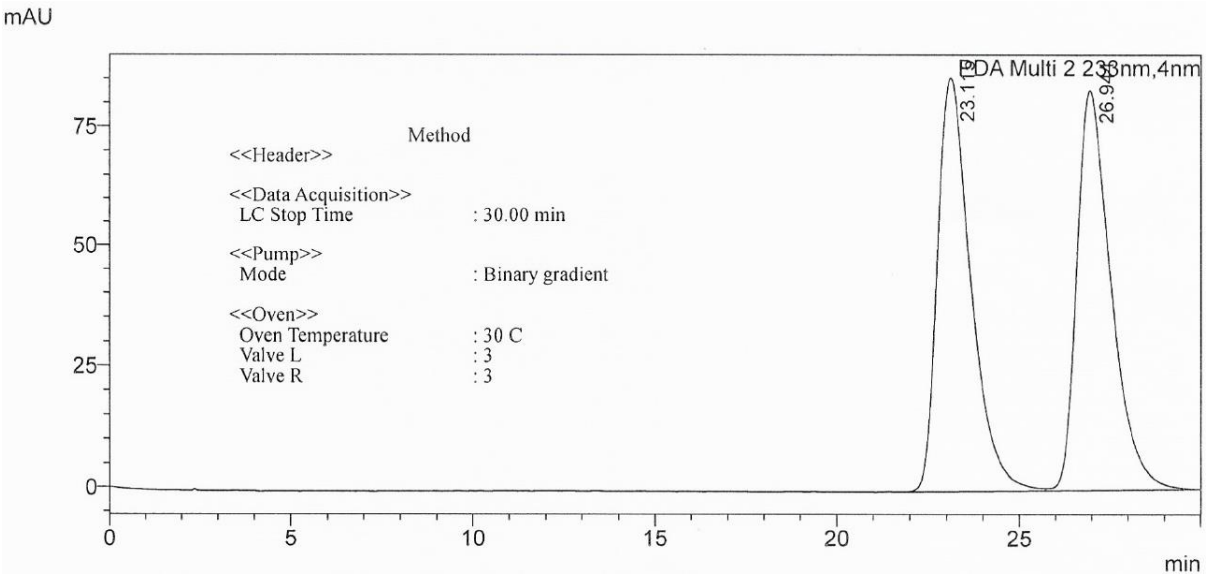
the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **117f** (84.0 mg, 0.44 mmol, 70%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 – 7.85 (m, 2H), 6.98 – 6.85 (m, 2H), 3.86 (s, 3H), 3.03 – 2.82 (m, 2H), 1.76 – 1.64 (m, 2H), 1.47 – 1.32 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.3, 163.3, 130.3 (2C), 113.7 (2C), 55.5, 38.0, 26.8, 22.6, 14.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2932, 1674, 1599, 1509, 1460, 1417, 1307, 1254, 1211, 1168, 1029, 839.
MS (EI, 70 eV): *m/z* (%) = 150 (48), 135 (100).
HRMS (EI): *m/z* calc. for [$C_{12}H_{16}O_2$]: 192.1150; found 192.1145.

3.4 Chiral HPLC Analysis

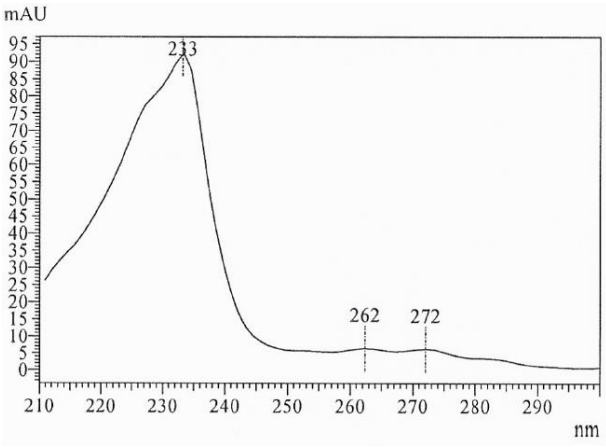
(*R/S*)-2-(6-Methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide

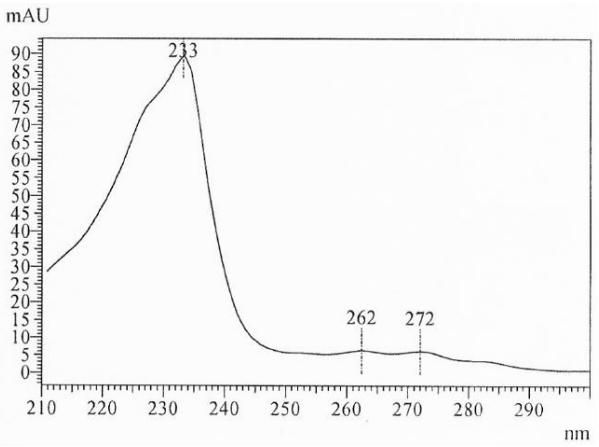




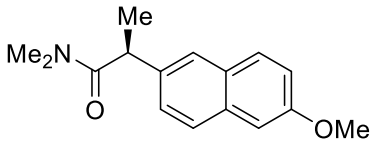
PDA Ch2 233nm

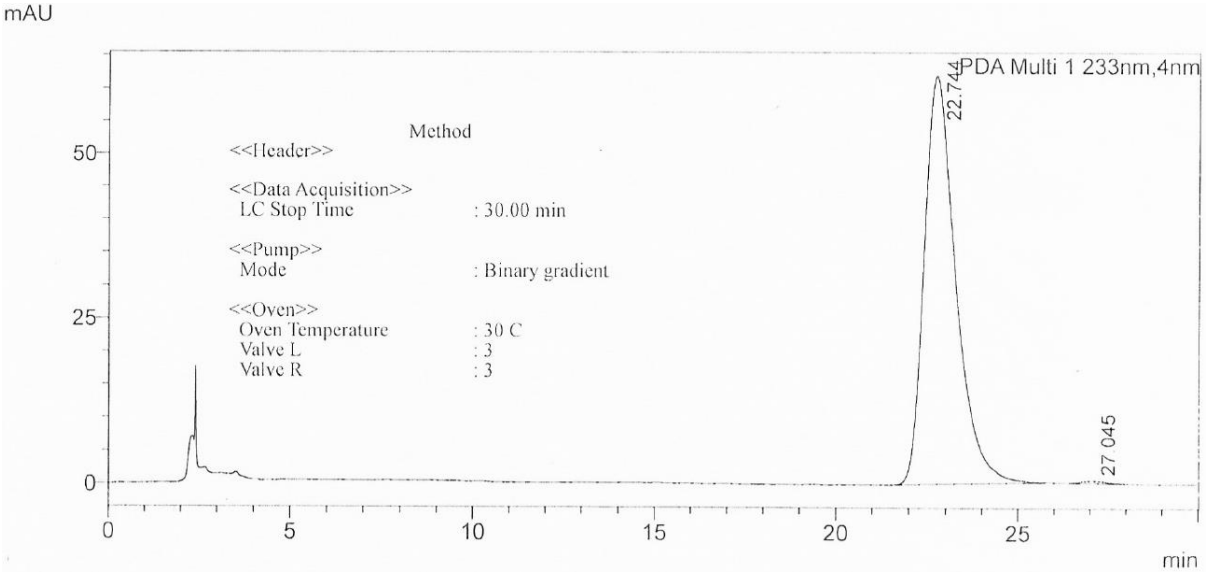
Peak#	Ret. Time	Area	Height	Area%
1	23.115	5446727	85898	49.990
2	26.944	5448902	83150	50.010
Total		10895629	169048	100.000





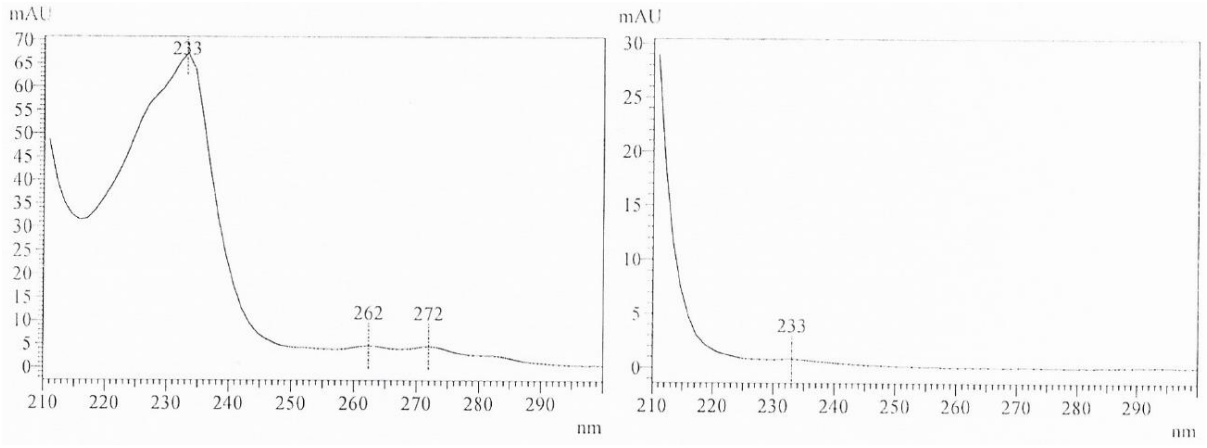
(*S*)-2-(6-Methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (112a)



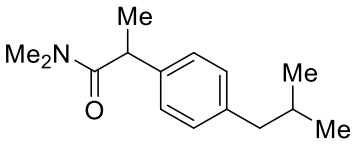


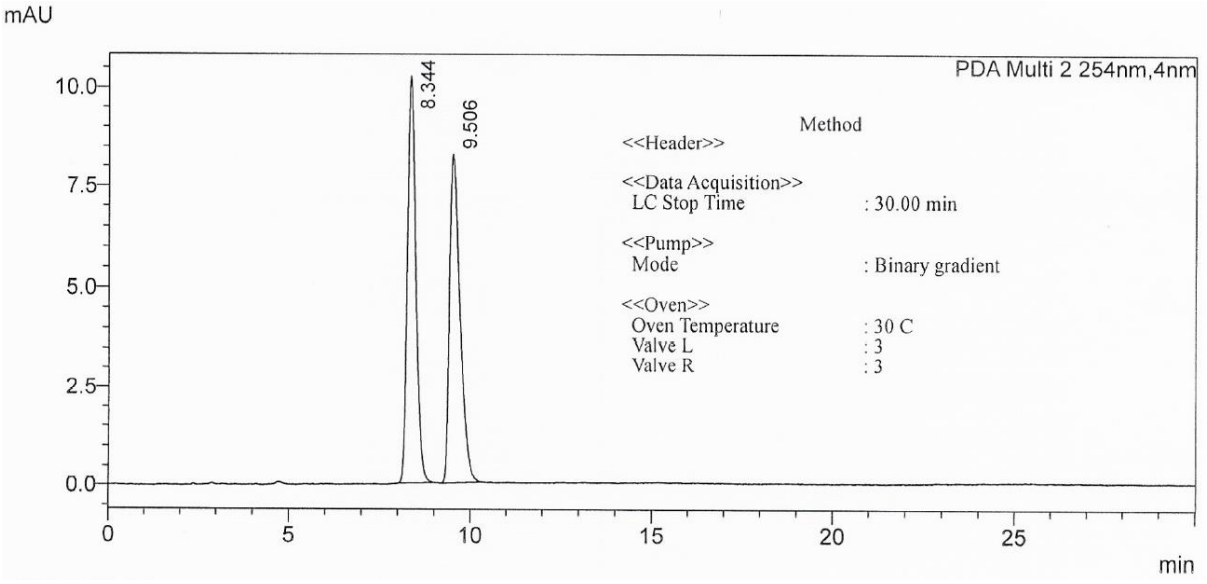
PDA Ch1 233nm

Peak#	Ret. Time	Area	Height	Area%
1	22.744	3706565	61766	99.513
2	27.045	18158	355	0.487
Total		3724723	62121	100.000



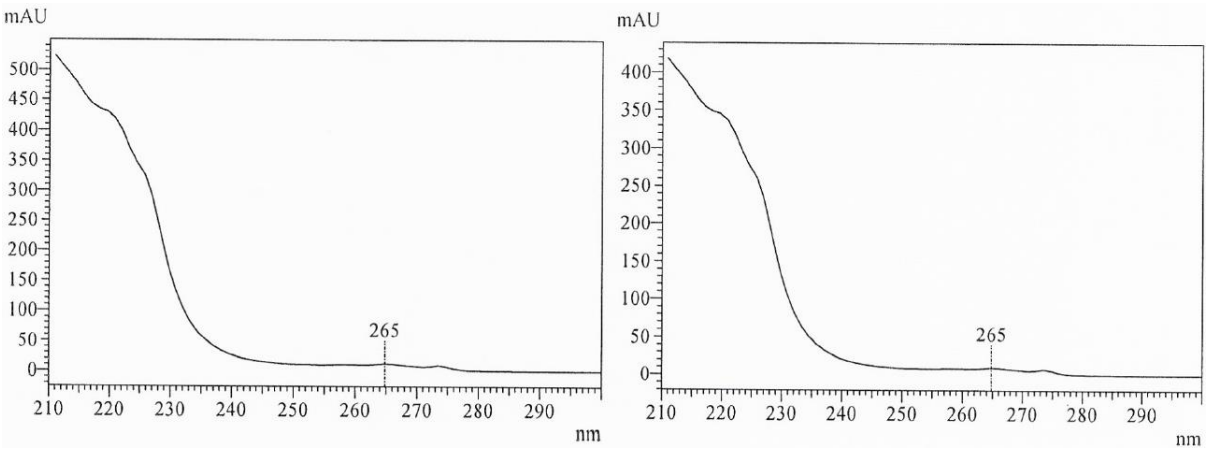
(*R/S*)-2-(4-*Iso*butylphenyl)-*N*,*N*-dimethylpropanamide



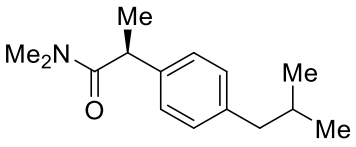


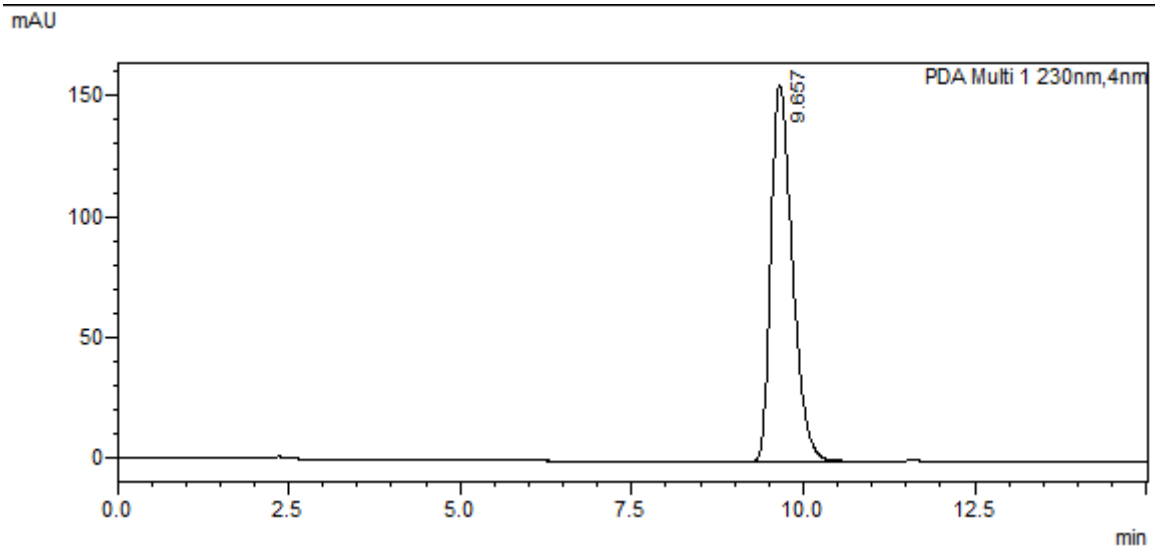
PDA Ch2 254nm

Peak#	Ret. Time	Area	Height	Area%
1	8.344	166570	10232	49.768
2	9.506	168125	8248	50.232
Total		334695	18480	100.000



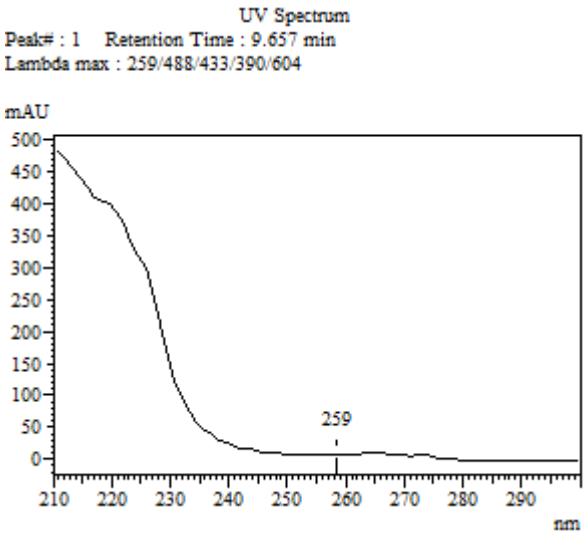
(*S*)-2-(4-*Iso*butylphenyl)-*N*,*N*-dimethylpropanamide (112b)



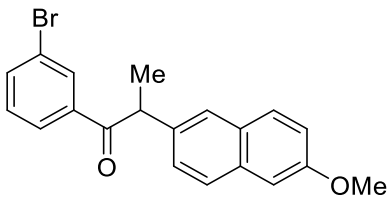


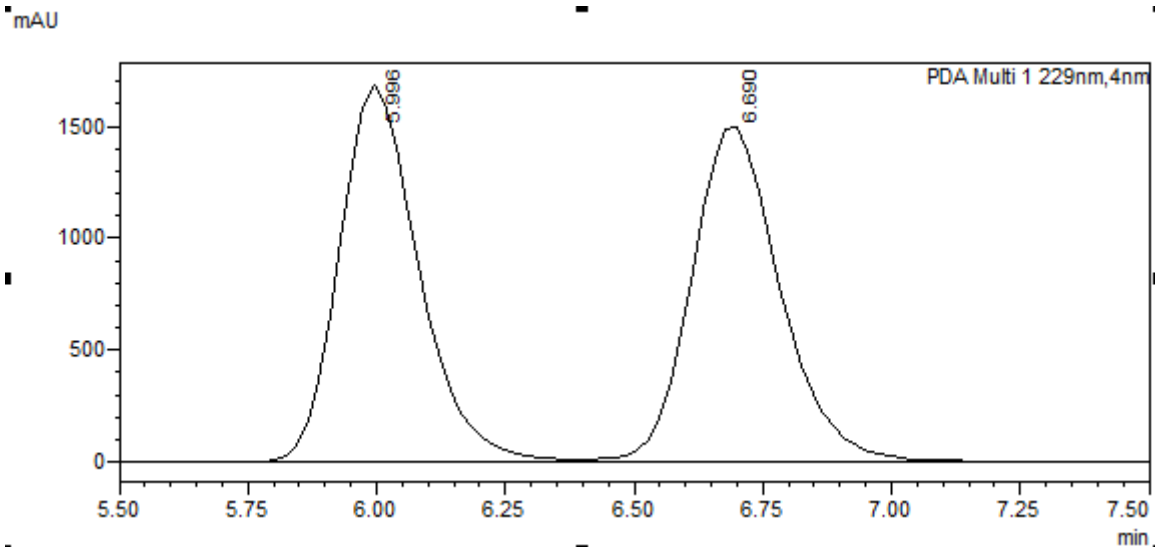
PDA Ch1 230nm

Peak#	Ret. Time	Area	Height	Area%
1	9.657	3409172	156051	100.000
Total		3409172	156051	100.000



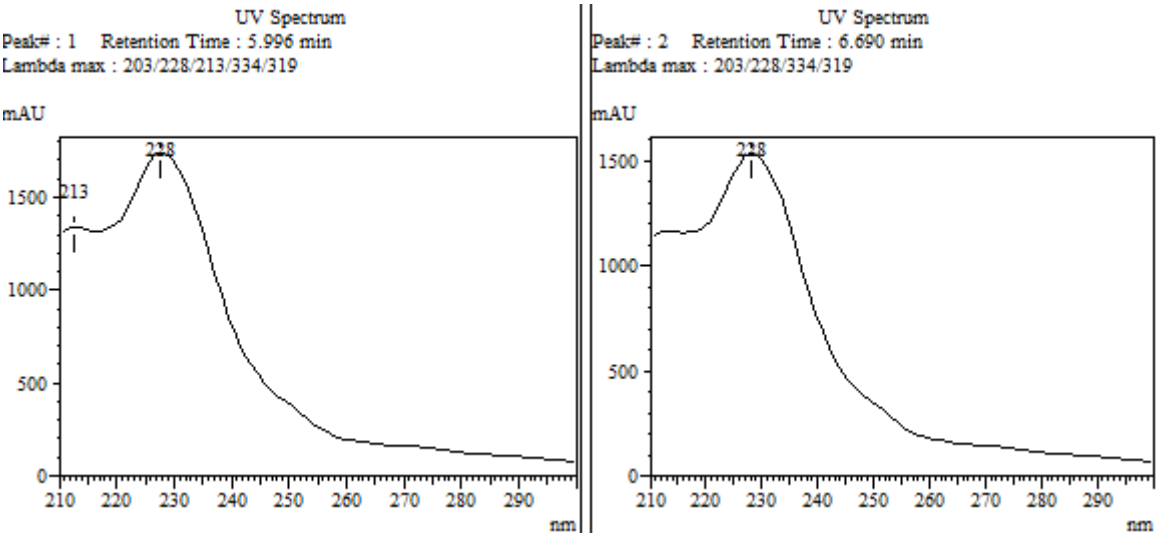
(*R/S*)-1-(3-Bromophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one



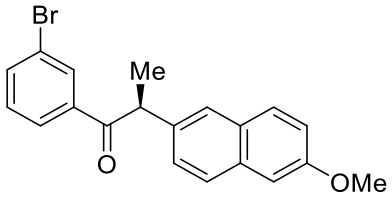


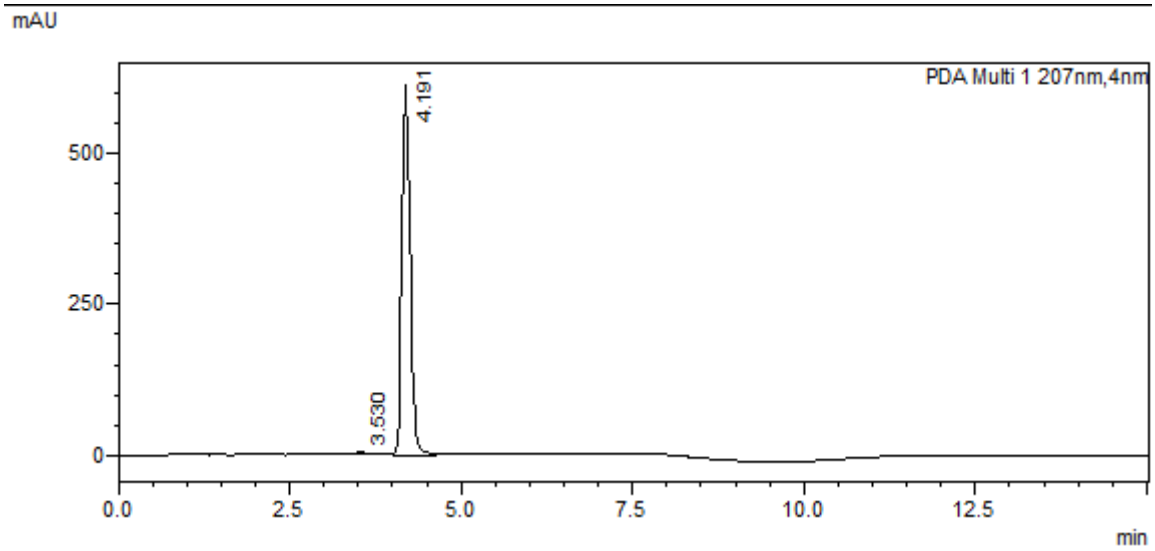
PDA Ch1 229nm

Peak#	Ret. Time	Area	Height	Area%
1	5.996	18093980	1685217	50.016
2	6.690	18082376	1495748	49.984
Total		36176356	3180965	100.000



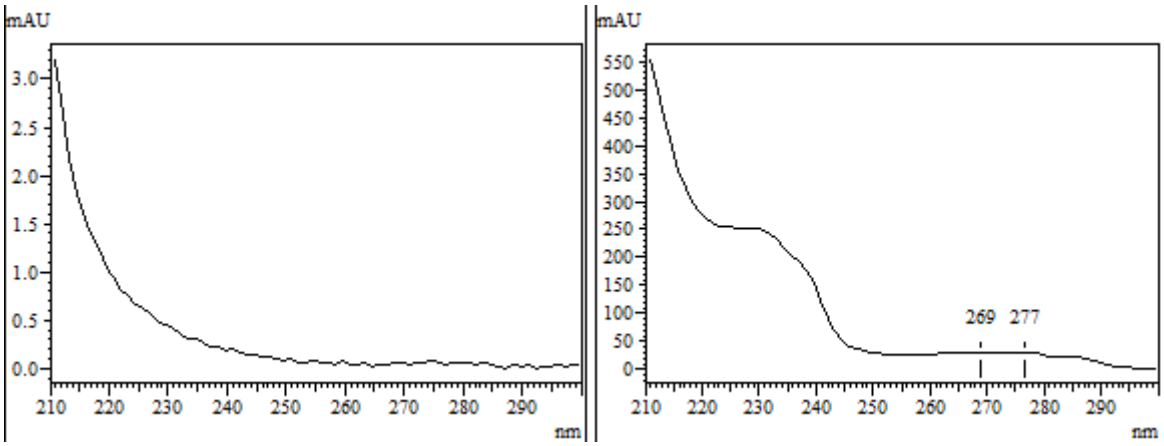
(*S*)-1-(3-Bromophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (113ae)



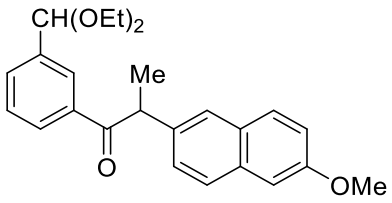


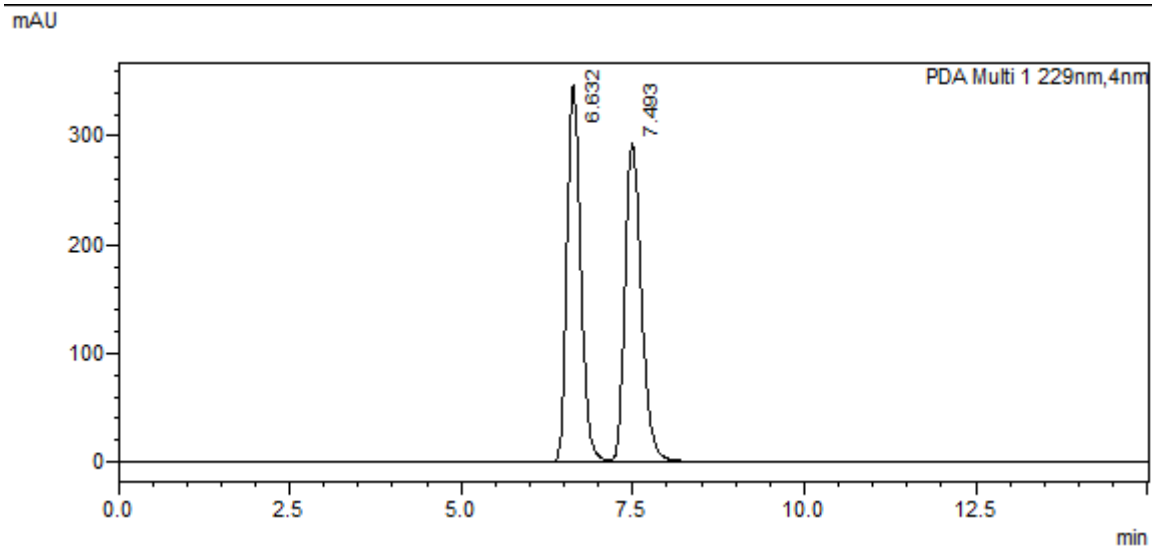
PDACh1 207nm

Peak#	Ret. Time	Area	Height	Area%
1	3.530	32158	4156	0.622
2	4.191	5135829	613076	99.378
Total		5167987	617232	100.000



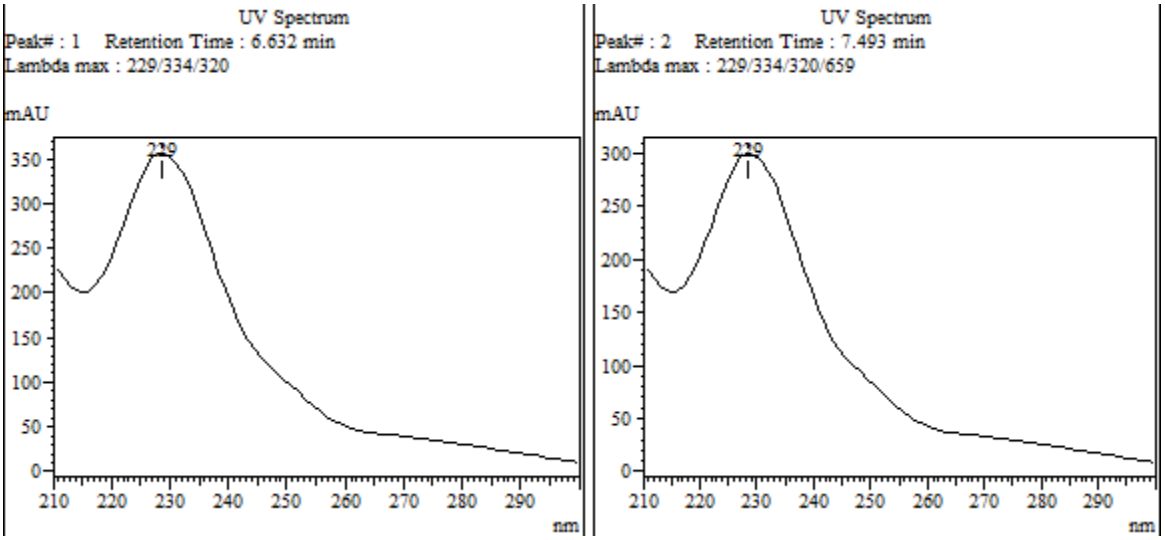
(*R/S*)-1-(3-(Diethoxymethyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one



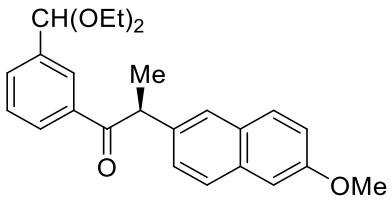


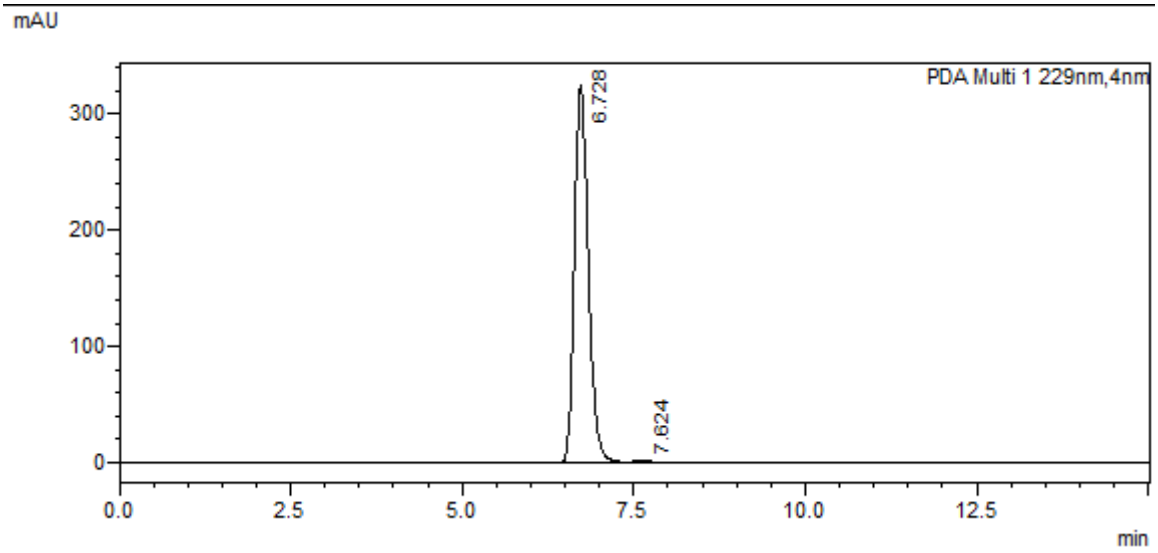
PDA Ch1 229nm

Peak#	Ret. Time	Area	Height	Area%
1	6.632	4870437	347024	49.932
2	7.493	4883779	292491	50.068
Total		9754217	639515	100.000



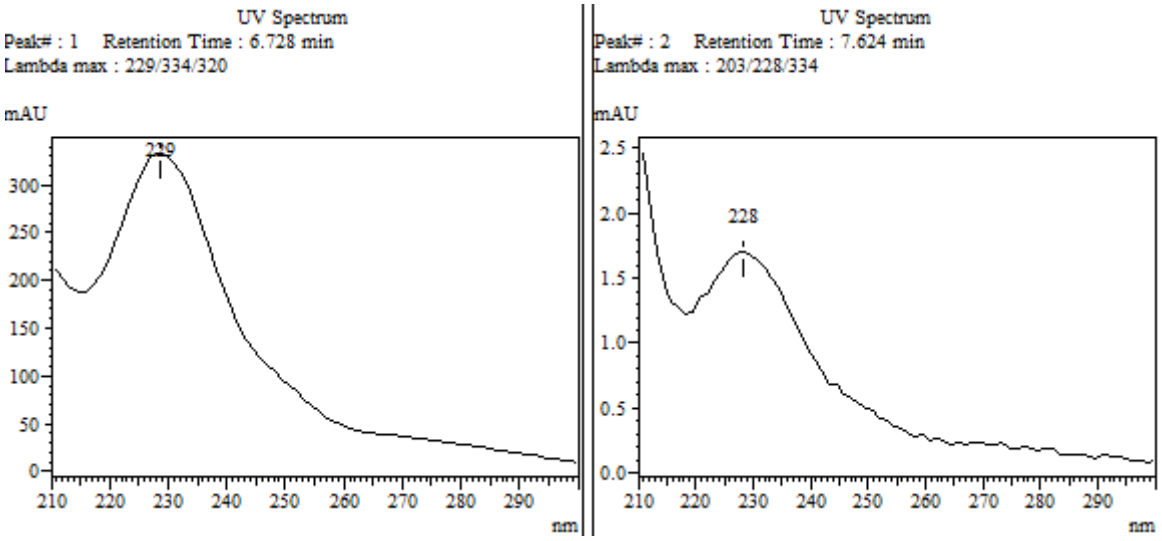
(*S*)-1-(3-(Diethoxymethyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (113am)



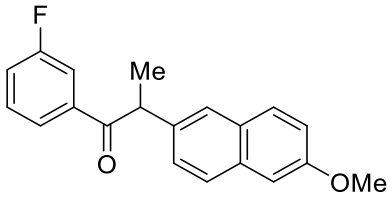


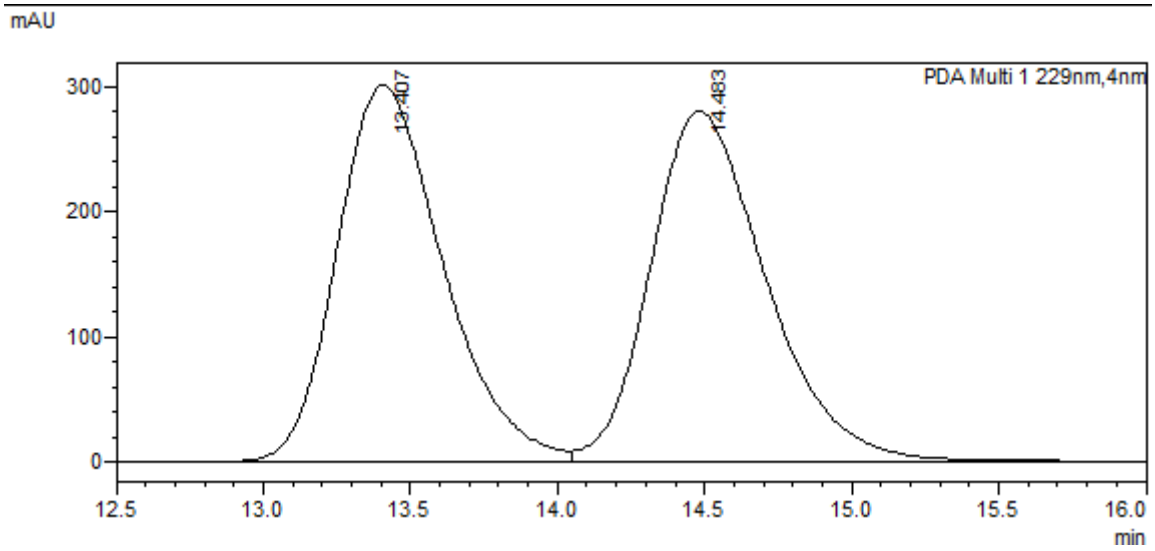
PDA Ch1 229nm

Peak#	Ret. Time	Area	Height	Area%
1	6.728	4593107	324655	99.517
2	7.624	22304	1345	0.483
Total		4615410	326000	100.000



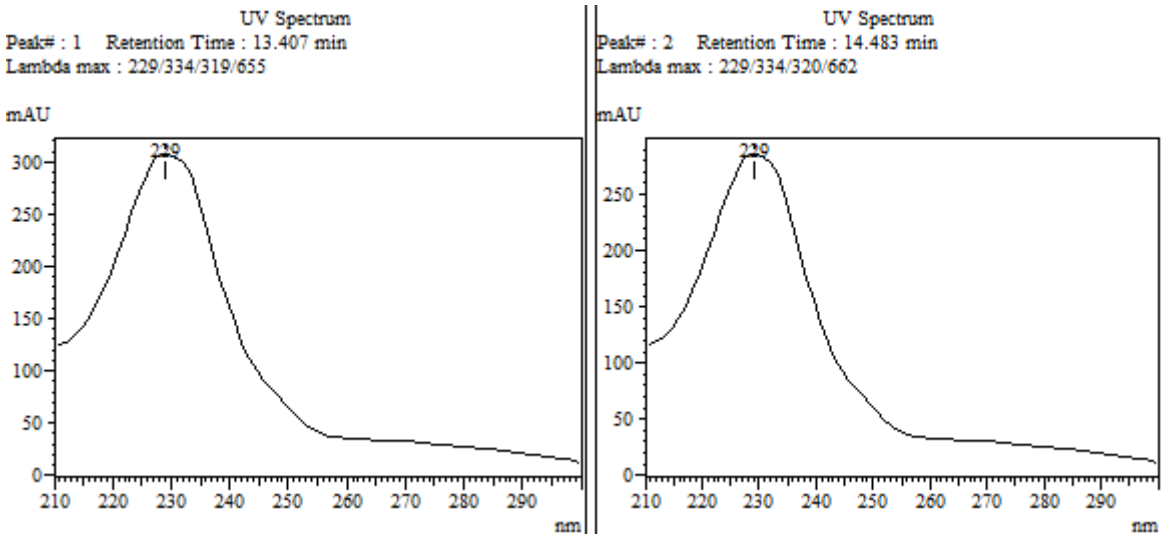
(*R*/*S*)-1-(3-Fluorophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one



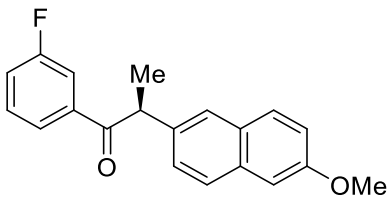


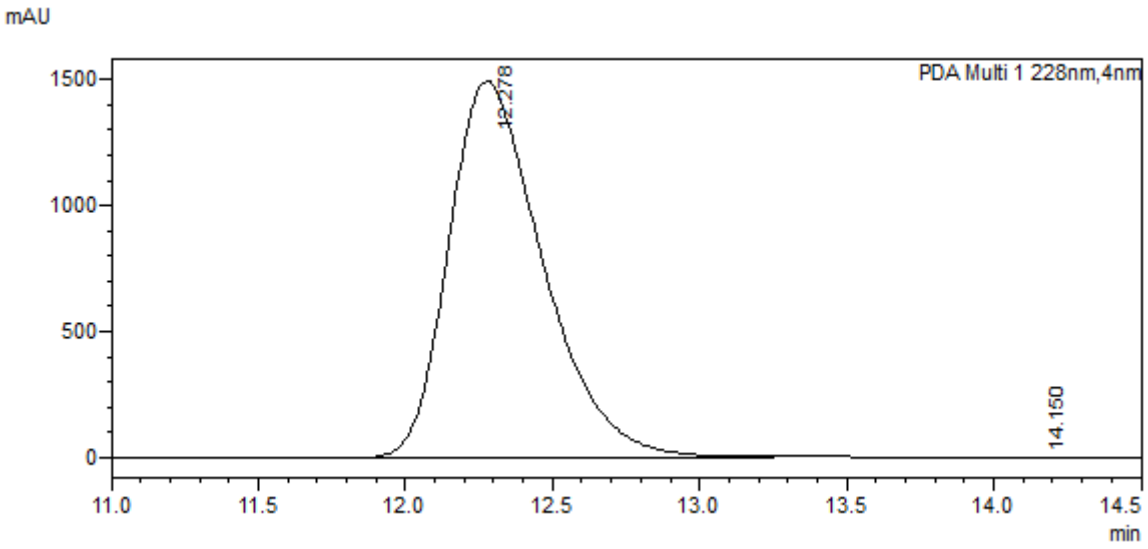
PDA Ch1 229nm

Peak#	Ret. Time	Area	Height	Area%
1	13.407	7540672	300842	49.567
2	14.483	7672267	279782	50.433
Total		15212940	580625	100.000



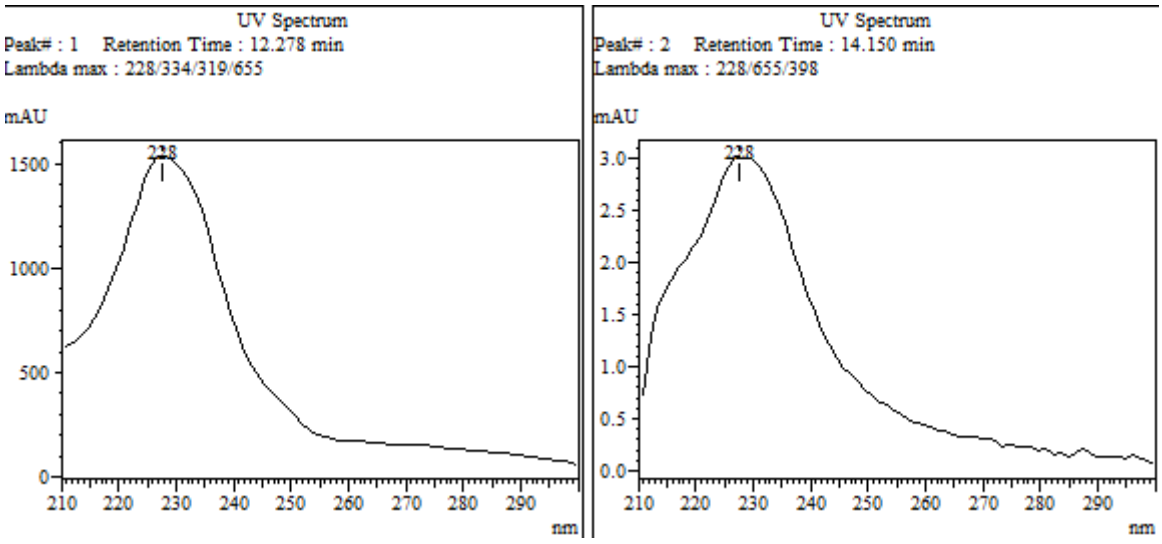
(*S*)-1-(3-Fluorophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (113ar)



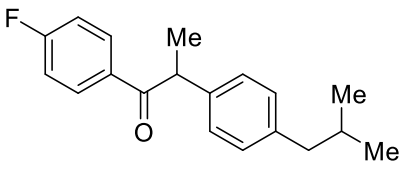


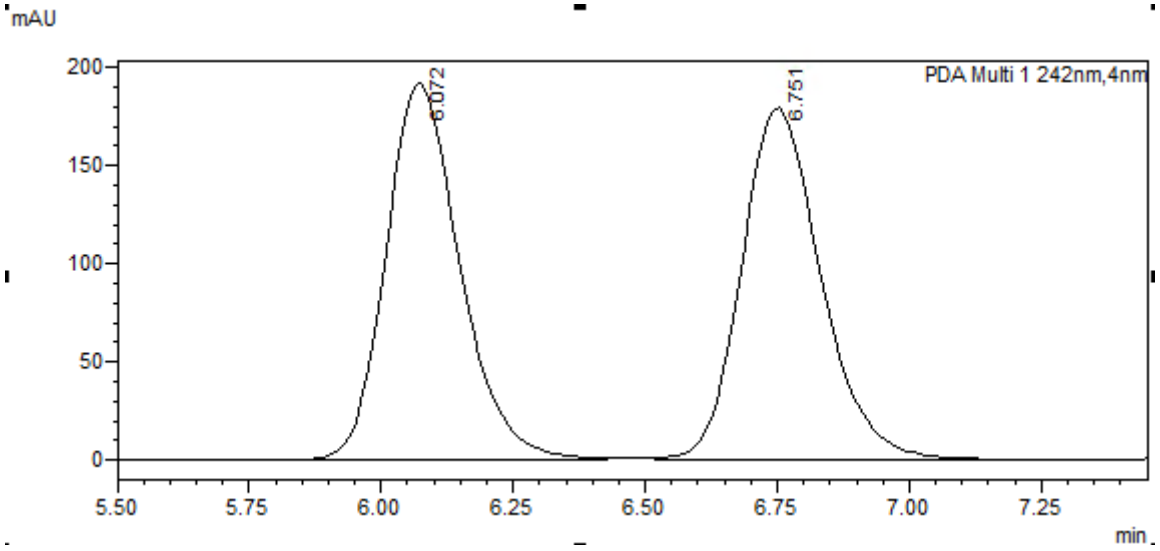
PDA Ch1 228nm

Peak#	Ret. Time	Area	Height	Area%
1	12.278	33481637	1494172	99.733
2	14.150	89620	2669	0.267
Total		33571257	1496841	100.000



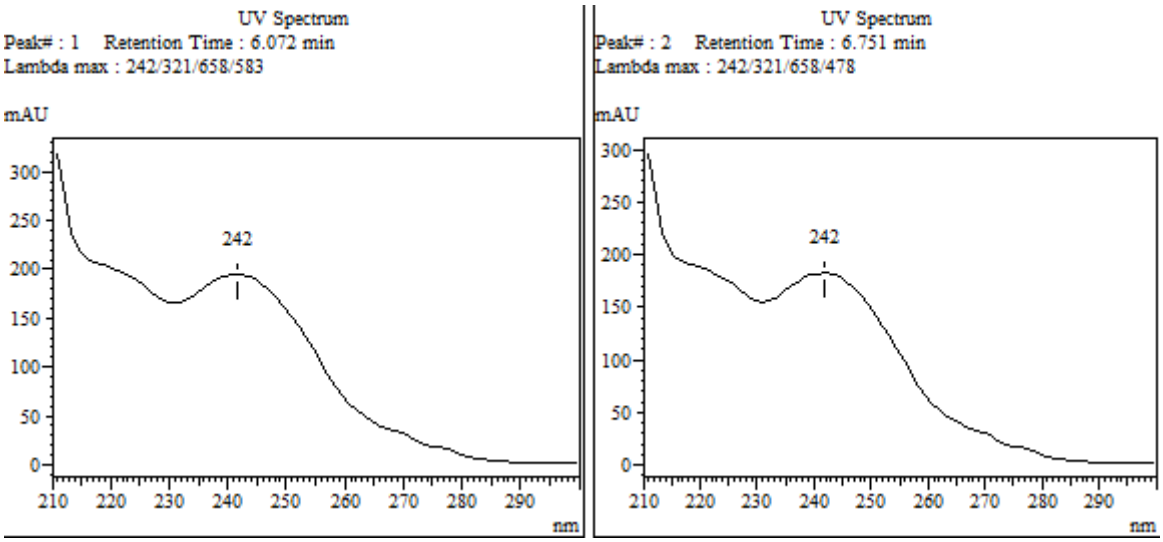
(*R/S*)-1-(4-Fluorophenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one



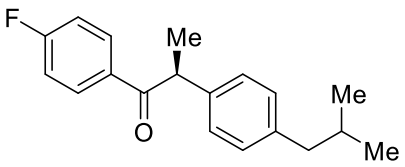


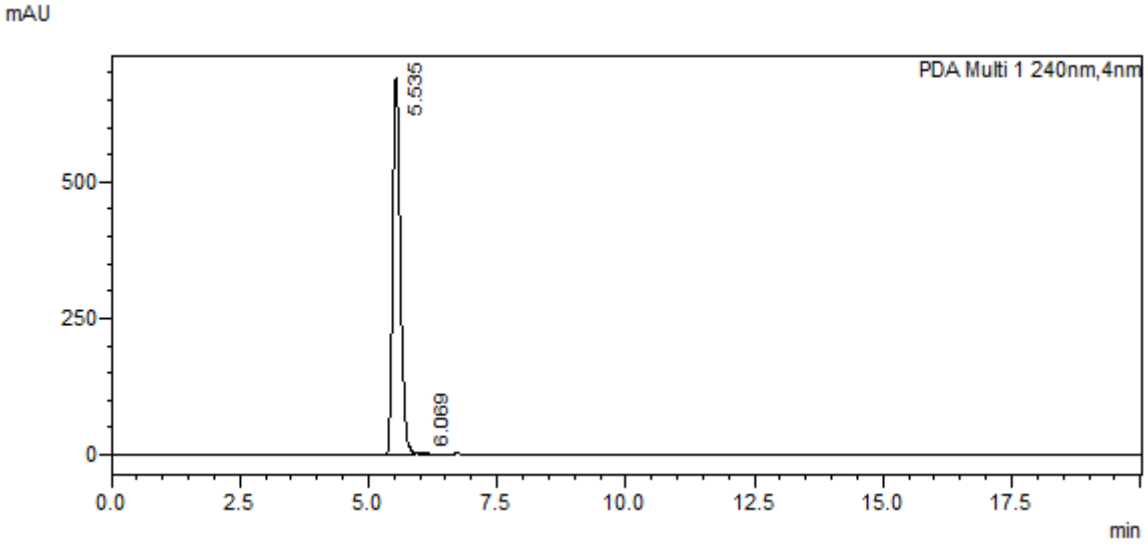
PDA Ch1 242nm

Peak#	Ret. Time	Area	Height	Area%
1	6.072	1880990	192205	49.908
2	6.751	1887911	179719	50.092
Total		3768901	371925	100.000



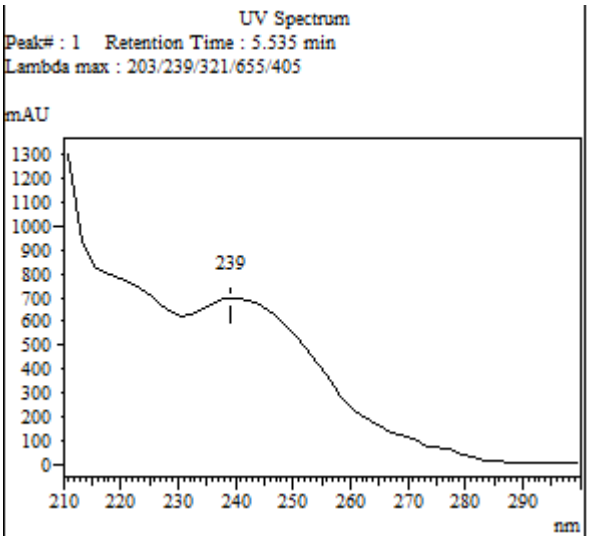
(*S*)-1-(4-Fluorophenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one (113bi)

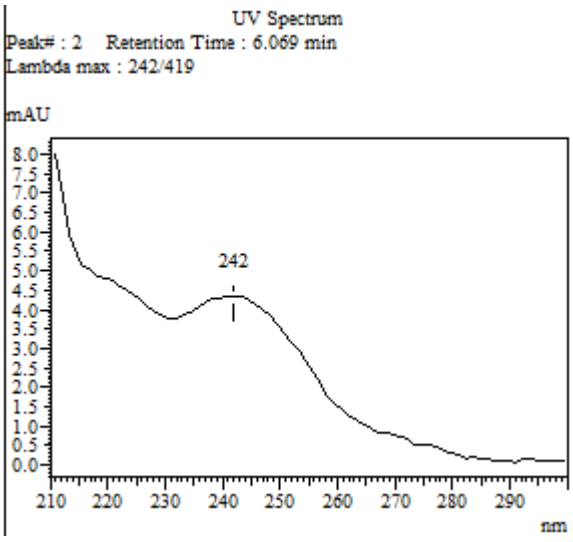




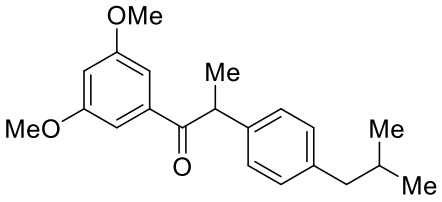
PDA Ch1 240nm

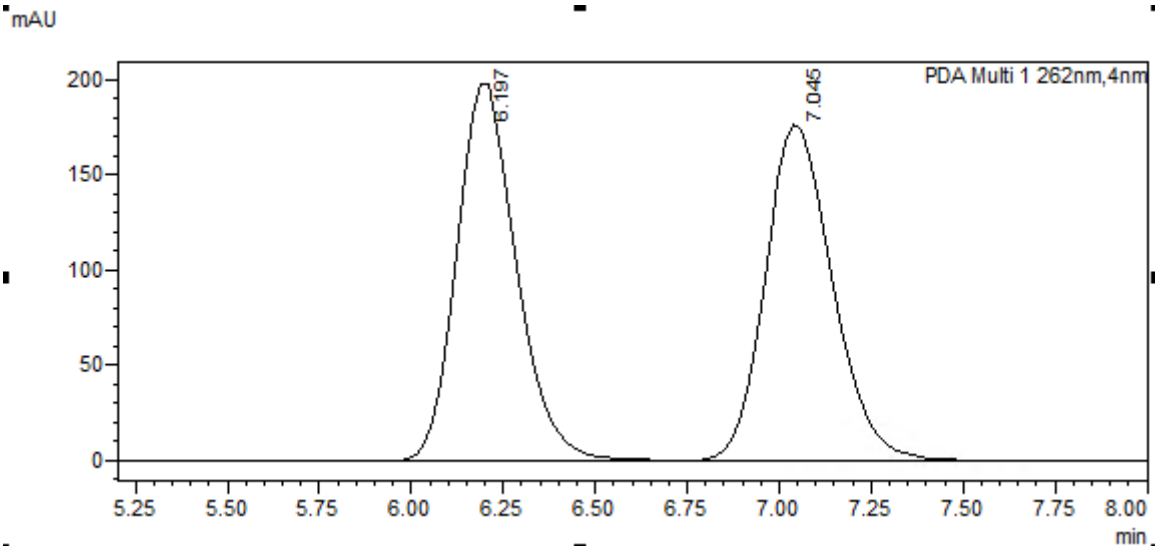
Peak#	Ret. Time	Area	Height	Area%
1	5.535	7226041	690405	99.335
2	6.069	48347	4292	0.665
Total		7274388	694696	100.000





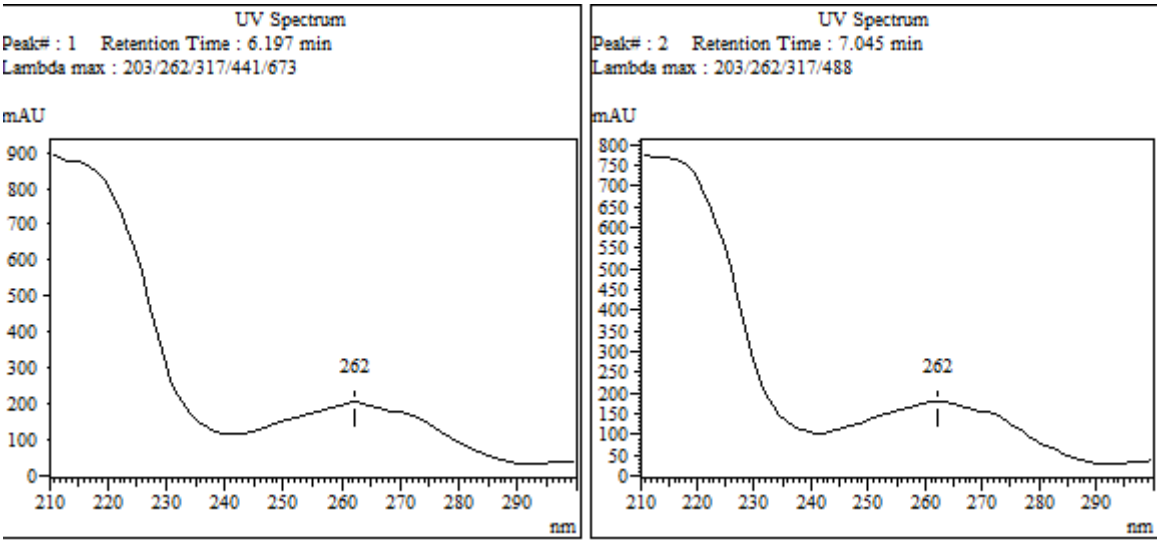
(*R*/*S*)-1-(3,5-Dimethoxyphenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one



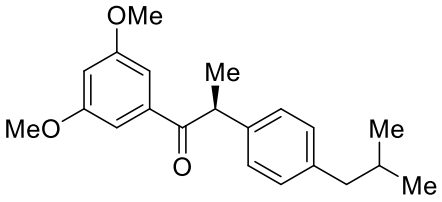


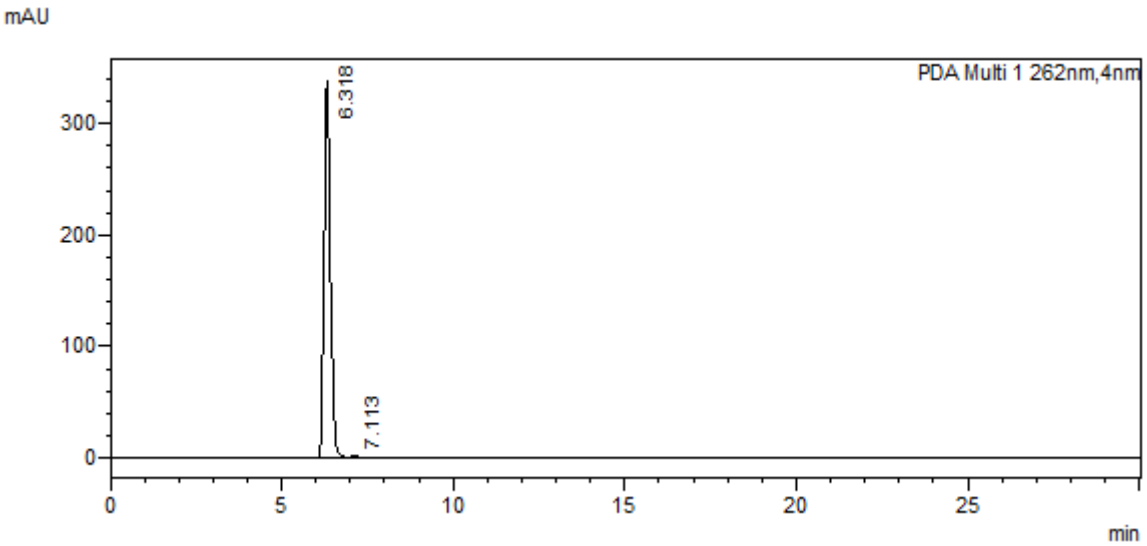
PDA Ch1 262nm

Peak#	Ret. Time	Area	Height	Area%
1	6.197	2242498	198179	49.966
2	7.045	2245589	176629	50.034
Total		4488087	374807	100.000



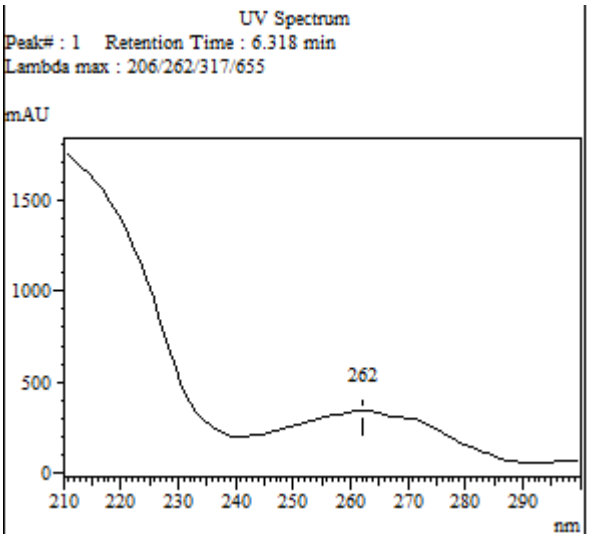
(*S*)-1-(3,5-Dimethoxyphenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one (113bo)

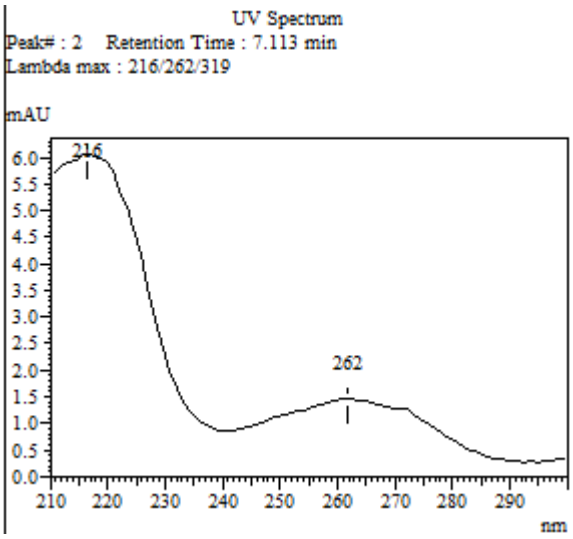




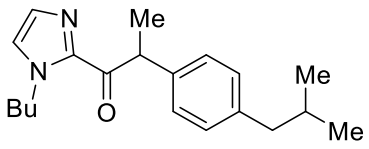
PDA Ch1 262nm

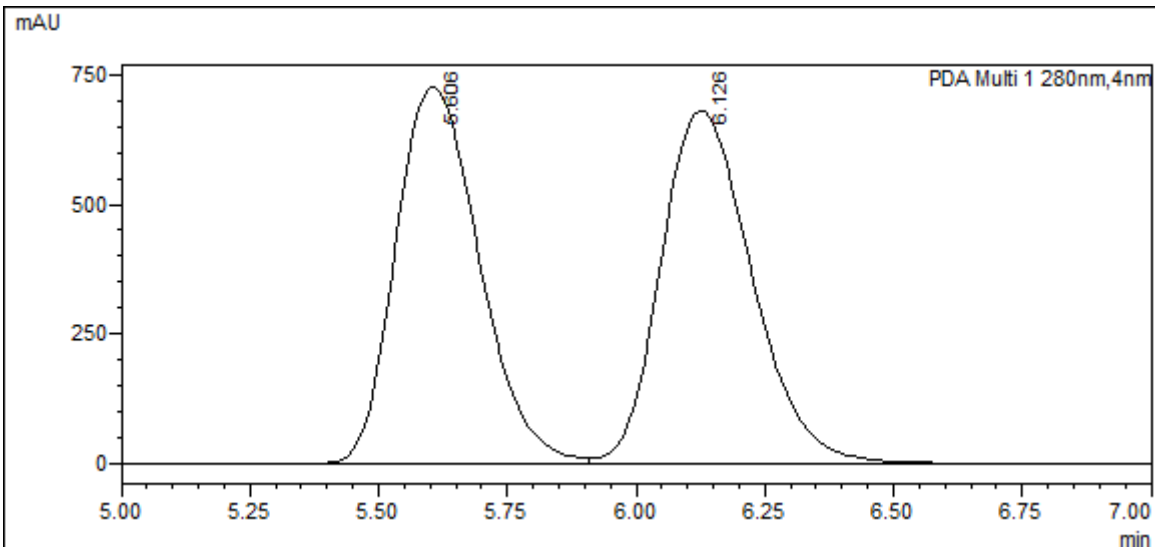
Peak#	Ret. Time	Area	Height	Area%
1	6.318	4360137	338124	99.585
2	7.113	18160	1282	0.415
Total		4378297	339406	100.000





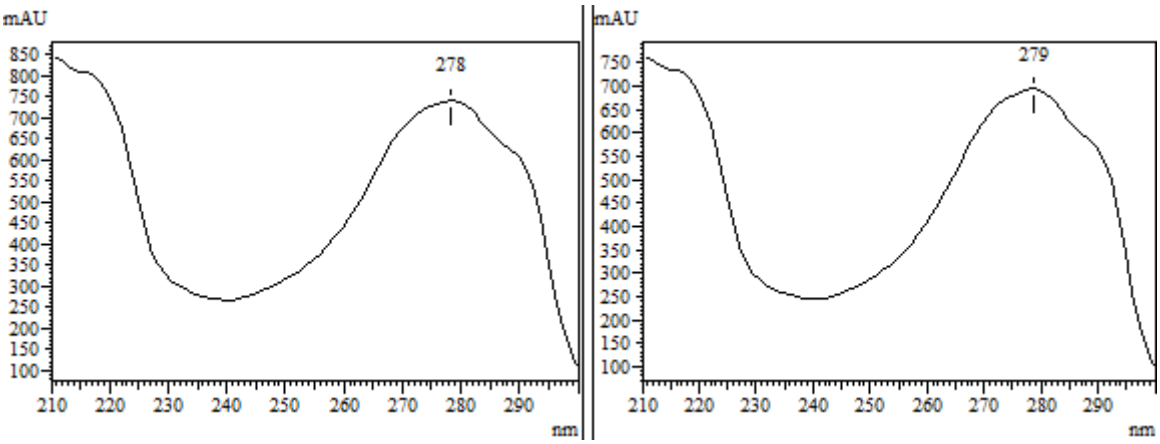
(*R/S*)-1-(1-butyl-1H-imidazol-2-yl)-2-(4-isobutylphenyl)propan-1-one



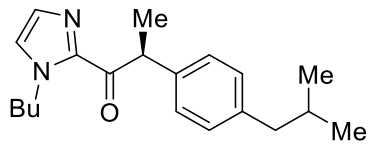


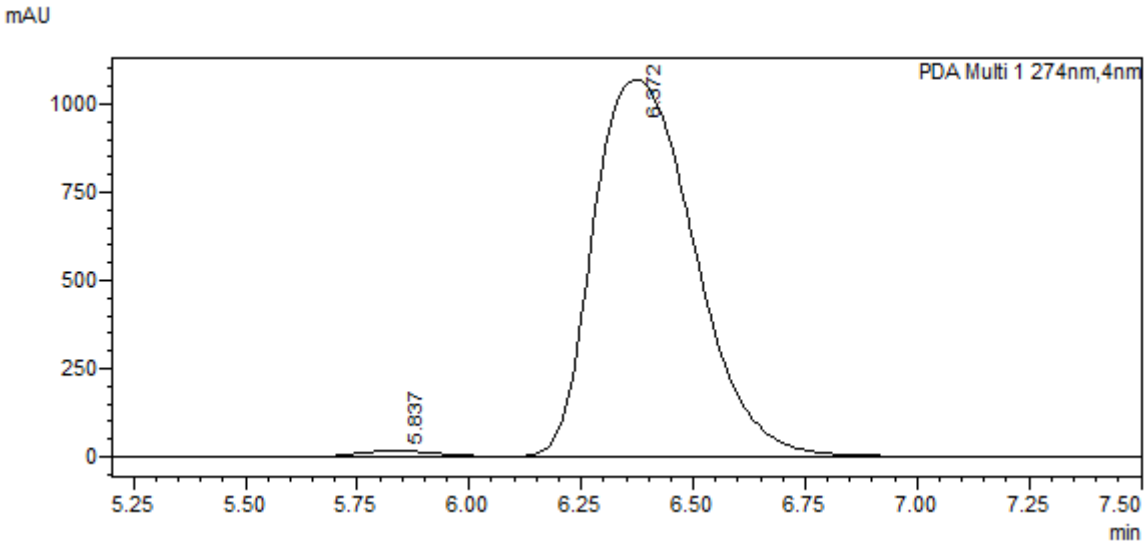
PDA Ch1 280nm

Peak#	Ret. Time	Area	Height	Area%
1	5.606	8267332	726798	49.442
2	6.126	8454054	680959	50.558
Total		16721385	1407757	100.000



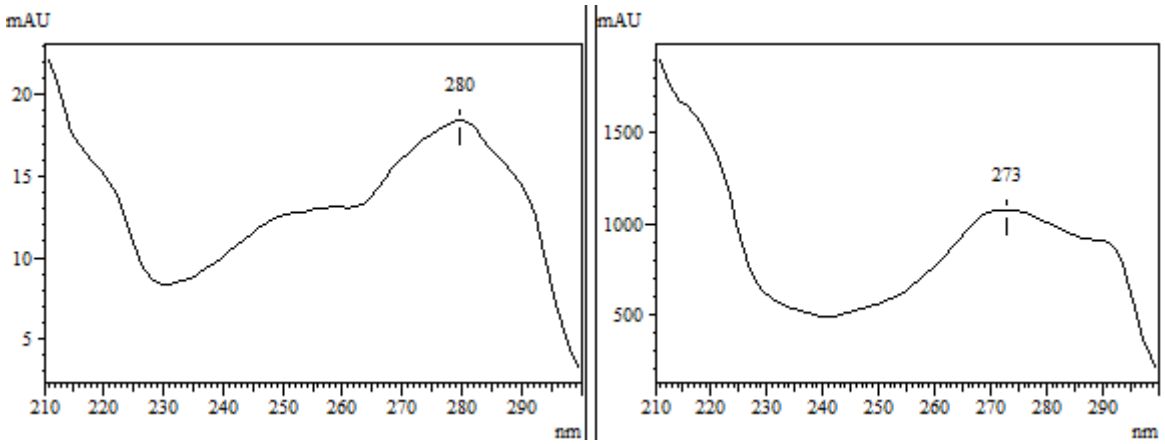
(*S*)-1-(1-butyl-1H-imidazol-2-yl)-2-(4-isobutylphenyl)propan-1-one (113bt)





PDA Ch1 274nm

Peak#	Ret. Time	Area	Height	Area%
1	5.837	210373	16982	1.237
2	6.372	16802645	1068054	98.763
Total		17013018	1085036	100.000



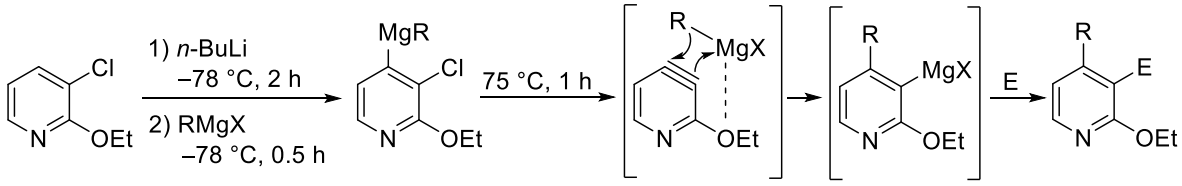
4. Regioselective Double Functionalizations of Pyridines *via* 3,4-Pyridyne Intermediates

4.1 Typical Procedures

Typical Procedure 8: Preparation of organomagnesium reagents *via* Mg-insertion.

LiCl (509 mg, 12.0 mmol, 1.2 equiv) was flame dried and cooled to room temperature *in vacuo*. Then, magnesium turnings (288 mg, 12.0 mmol, 1.2 equiv) and THF (10 mL) were added and the reaction mixture was cooled to 0 °C. The organic bromide (10.0 mmol, 1.0 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 1-3 h. Upon complete conversion, the concentration of the organomagnesium reagent **3** was determined by titration against iodine in THF.[182]

Typical Procedure 9: Preparation of 2,3,4-trifunctionalized pyridines *via* 3,4-pyridyne intermediates.

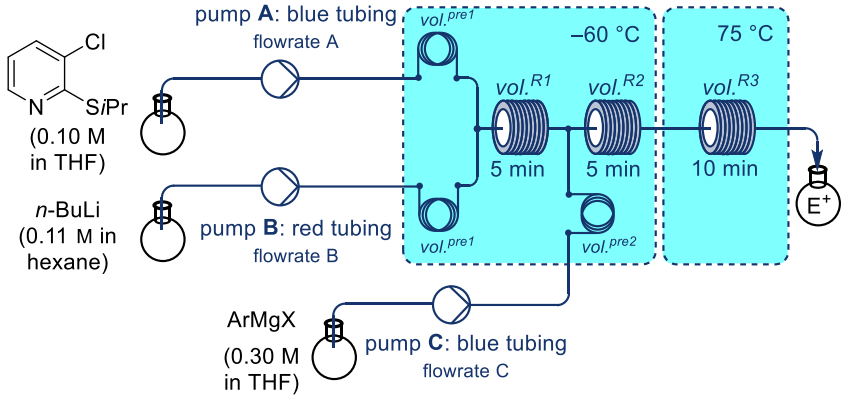


n-Buthyllithium (1.1 equiv, 2.6 M) was slowly added to a stirred solution of 3-chloro-2-ethoxypyridine (1.0 equiv) in THF (2 mL/mmol of 3-chloro-2-ethoxypyridine) at –78 °C in a sealed tube. After stirring for 2 h, the representative organomagnesium reagent (2.0-5.0 equiv) was slowly added at –78 °C. The solution was allowed to warm to 25 °C after 30 min of stirring at –78 °C. Then, the reaction mixture was heated to 75 °C for 1 h, followed by quenching with the representative electrophile (2.1-2.5 equiv) at 0 °C. The reaction mixture was then stirred at 25 °C until completion. After quenching with *sat. aq.* NH_4Cl, the aqueous phase was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4 and filtrated. After

[182] F. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed*. **2008**, *47*, 6802-6806.

removal of the solvent *in vacuo*, flash column chromatography purification with *iso*hexane (or pentane):EtOAc mixtures afforded the pure products.

Typical Procedure 10: Preparation of 2,3,4-trifunctionalized pyridines *via* 3,4-pyridyne intermediates in continuous flow.

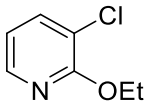


Scheme 39: Flow chemistry setup for preparation highly functionalized ketones.

A solution of pyridine in THF (0.10 M, 1.0 equiv) and a solution of *n*-BuLi in *n*-hexane (0.11 M, 1.1 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 1.0 mL·min^{-1} and flowrate B = flowrate A. After passing a PTFE tubing (vol^{pre1} = 2.0 mL, T = –60 °C, residence time: 2 min) 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$_{R1}$ = 10 mL; residence time: t = 5 min, T = –60 °C) and a organomagnesium reagent (0.3 M, 6.0 equiv), prepared *via* **TP1**, was added *via* a third pump (flowrate C = 2.0 mL·min^{-1}, vol^{pre2} = 2.0 mL, T = –60 °C, residence time: 1 min). The combined stream passed a PTFE reactors tube (vol$_{R2}$ = 20 mL; residence time: t = 5 min, T = –60 °C) and was afterwards heated in another PTFE reactors tube (vol$_{R3}$ = 40 mL; residence time: t = 10 min, T = 75 °C). The reaction mixture was subsequently injected in a flask at 0 °C, containing an electrophile for quenching (7.0 equiv). The reaction mixture was then stirred at 25 °C until completion. After quenching with *sat. aq.* NH_4Cl, the aqueous phase was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash column chromatography purification with *iso*hexane (or pentane):EtOAc mixtures afforded the pure product.

4.2 Preparation of Compounds

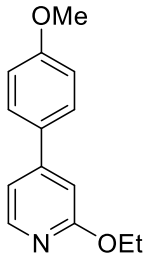
3-Chloro-2-ethoxypyridine (118)



Sodium metal (ca. 6 g) was added to dry ethanol (200 mL) at 0 °C. The resulting suspension was stirred until the sodium was dissolved or the hydrogen liberation ceased. 2,3-Dichloropyridine (14.9 g, 100 mmol) was added and the resulting mixture was refluxed for 12 h. After cooling to 25 °C, the reaction mixture was quenched with *sat. aq.* NH_4Cl. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash column chromatography purification (isohexane:ethyl acetate = 9.7:0.3) afforded the 3-chloro-2-ethoxypyridine (**118**) (13.4 g, 85.0 mmol, 85% yield) as an colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.72 (dd, *J* = 7.6, 4.9 Hz, 1H), 4.36 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.2, 144.7, 138.3, 118.3, 117.2, 62.8, 14.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 1583, 1472, 1448, 1431, 1383, 1362, 1352, 1317, 1302, 1281, 1254, 1246, 1129, 1105, 1092, 1072, 1045, 1027, 929, 910, 784, 753, 713, 696.
MS (EI, 70 eV): *m/z* (%) = 144 (33), 142 (100), 130 (14), 129 (42), 113 (19), 103 (15), 101 (46).
HRMS (EI): *m/z* calc. for [C_7H_8ClNO]: 157.0294; found 157.0288.

2-Ethoxy-4-(4-methoxyphenyl)pyridine (123a)

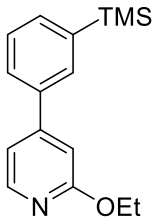


Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (**91a**) (1.02 mL, 1.00 mmol),

prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give 2-ethoxy-4-(4-methoxyphenyl)pyridine (**123a**) (73.0 mg, 0.32 mmol, 64% yield) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.05 (dd, *J* = 5.4, 1.6 Hz, 1H), 7.01 – 6.95 (m, 2H), 6.90 (dd, *J* = 1.6, 0.7 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.8, 160.5, 150.7, 147.3, 130.7, 128.2, 114.9, 114.5, 107.9, 61.8, 55.5, 14.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2977, 1605, 1582, 1544, 1518, 1473, 1441, 1425, 1405, 1379, 1350, 1327, 1288, 1246, 1205, 1180, 1056, 1027, 838, 818.
MS (EI, 70 eV): *m/z* (%) = 215 (14), 214 (100), 201 (35), 200 (28), 185 (16), 170 (15), 158 (18).
HRMS (EI): *m/z* calc. for [$C_{14}H_{14}NO_2$]: 228.1019; found 228.1018 [M^+-H].
m.p.: 33.5-34.6 °C.

2-Ethoxy-4-(3-(trimethylsilyl)phenyl)pyridine (123b)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (3-(trimethylsilyl)phenyl)magnesium bromide (**91u**) (1.06 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 2-ethoxy-4-(3-(trimethylsilyl)phenyl)pyridine (**123b**) (76.0 mg, 0.28 mmol, 56% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.74 (dt, *J* = 1.8, 0.7 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.95 (dd, *J* = 1.6, 0.7 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 0.31 (s, 9H).

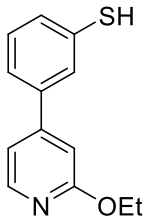
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.6, 151.9, 147.2, 141.7, 137.7, 134.1, 131.9, 128.5, 127.6, 115.5, 108.9, 62.1, 14.9, -1.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 1615, 1603, 1589, 1546, 1470, 1422, 1376, 1348, 1326, 1248, 1206, 1119, 1060, 1039, 990, 951, 862, 836, 791, 779, 752, 704, 694.

MS (EI, 70 eV): *m/z* (%) = 270 (2), 257 (14), 256 (100), 228 (46).

HRMS (EI): *m/z* calc. for [$C_{16}H_{20}ONSi$]: 270.1308; found 270.1309 [M^+-H].

3-(2-Ethoxypyridin-4-yl)benzenethiol (123c)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (3-(methylthio)phenyl)magnesium bromide (**91v**) (1.00 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 3-(2-ethoxypyridin-4-yl)benzenethiol (**123c**) (60.0 mg, 0.26 mmol, 51% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92 (d, *J* = 5.6 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.47 – 7.37 (m, 3H), 6.60 (dd, *J* = 5.6, 1.7 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

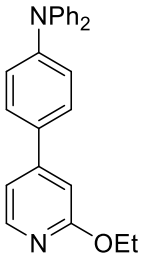
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.9, 145.9, 135.3, 129.9, 129.7, 129.4, 114.6, 107.2, 62.2, 14.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 1586, 1580, 1559, 1542, 1475, 1457, 1440, 1412, 1378, 1347, 1312, 1280, 1221, 1091, 1082, 1043, 1024, 986, 949, 806, 749, 690.

MS (EI, 70 eV): *m/z* (%) = 217 (13), 216 (100), 202 (57), 187 (20), 186 (31).

HRMS (EI): *m/z* calc. for [$C_{13}H_{13}ONS$]: 231.0718; found 231.0714.

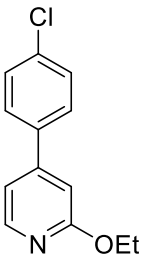
4-(2-Ethoxypyridin-4-yl)-*N*,*N*-diphenylaniline (123d)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-(diphenylamino)phenyl)magnesium bromide (**91w**) (1.08 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give 4-(2-ethoxypyridin-4-yl)-*N*,*N*-diphenylaniline (**123d**) (112 mg, 0.31 mmol, 61% yield) as a red oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.18 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.35 – 7.27 (m, 4H), 7.19 – 7.14 (m, 5H), 7.14 – 7.07 (m, 4H), 6.94 (dd, *J* = 1.6, 0.7 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.7, 150.7, 149.0, 147.4, 147.2, 131.3, 129.5, 127.7, 125.1, 123.6, 123.0, 114.7, 107.7, 62.0, 14.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 1603, 1589, 1542, 1515, 1486, 1471, 1451, 1425, 1406, 1380, 1350, 1325, 1274, 1251, 1206, 1180, 1056, 1035, 942, 840, 815, 754, 732, 696.
MS (EI, 70 eV): *m/z* (%) = 267 (27), 366 (100), 351 (25), 338 (25).
HRMS (EI): *m/z* calc. for [$C_{25}H_{22}ON_2$]: 366.1732; found 366.1723.

4-(4-Chlorophenyl)-2-ethoxypyridine (123e)

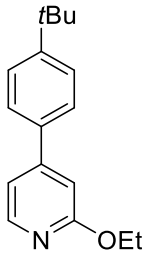


Following **TP9**, 3-chloro-2-ethoxypyridine (1**18**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-chlorophenyl)magnesium bromide (**91m**) (1.04 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched

with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 4-(4-chlorophenyl)-2-ethoxypyridine (**123e**) (60.0 mg, 0.26 mmol, 51% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.46 – 7.40 (m, 2H), 7.04 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.89 (dd, *J* = 1.6, 0.7 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.8, 150.1, 147.5, 136.9, 135.3, 129.3, 128.4, 115.0, 108.6, 62.1, 14.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 1608, 1575, 1545, 1502, 1472, 1423, 1380, 1350, 1327, 1250, 1207, 1093, 1057, 1034, 1014, 992, 904, 874, 838, 814, 725, 674.
MS (EI, 70 eV): *m/z* (%) = 220 (32), 219 (12), 218 (100), 205 (31), 204 (21), 189 (28), 177 (23), 154 (22), 115 (15).
HRMS (EI): *m/z* calc. for [$C_{12}H_9ONCl$]: 218.0367; found 218.0367 [M^+-CH_3].
m.p.: 40.4-41.2 °C.

4-(4-(*Tert*-butyl)phenyl)-2-ethoxypyridine (123f)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-(*tert*-butyl)phenyl)magnesium bromide (**91s**) (1.11 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give 4-(4-(*tert*-butyl)phenyl)-2-ethoxypyridine (**123f**) (55.0 mg, 0.22 mmol, 43% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.18 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.52 – 7.45 (m, 2H), 7.10 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.95 (dd, *J* = 1.6, 0.7 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H), 1.36 (s, 9H).

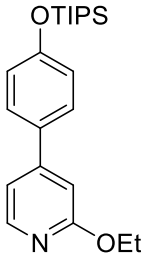
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.7, 152.4, 151.2, 147.2, 135.4, 126.8, 126.1, 115.2, 108.4, 62.0, 34.8, 31.4, 14.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 1605, 1543, 1476, 1421, 1379, 1328, 1208, 1056, 1036, 817.

MS (EI, 70 eV): *m/z* (%) = 241 (18), 240 (100), 227 (11), 212 (41), 211 (11), 184 (13).

HRMS (EI): *m/z* calc. for [$C_{17}H_{20}ON$]: 254.1539; found 254.1538 [M^+-H].

2-Ethoxy-4-(4-((tri*iso*propylsilyl)oxy)phenyl)pyridine (123g)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-((tri*iso*propylsilyl)oxy)phenyl)magnesium bromide (**91x**) (1.04 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give 2-ethoxy-4(4((tri*iso*propylsilyl)oxy)phenyl)pyridine (**123g**) (76.0 mg, 0.21 mmol, 41% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 5.4 Hz, 1H), 7.57 – 7.44 (m, 2H), 7.07 (dd, *J* = 5.5, 1.6 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.91 (d, *J* = 1.6 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.34 – 1.22 (m, 3H), 1.12 (d, *J* = 7.3 Hz, 18H).

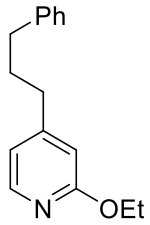
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.5, 157.4, 151.2, 146.8, 130.8, 130.7, 128.2, 120.5, 114.9, 107.9, 62.2, 18.0, 14.9, 12.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2943, 2865, 1604, 1543, 1515, 1471, 1423, 1379, 1326, 1272, 1265, 1249, 1204, 1174, 1056, 1035, 910, 882, 841, 817, 761, 684.

MS (EI, 70 eV): *m/z* (%) = 371 (9), 328 (43), 300 (38), 290 (26), 273 (15), 272 (100), 258 (35), 228 (10).

HRMS (EI): *m/z* calc. for [$C_{22}H_{33}O_2NSi$]: 371.2281; found 371.2271.

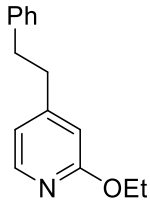
2-Ethoxy-4-(3-phenylpropyl)pyridine (123h)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (3-phenylpropyl)magnesium bromide (**91y**) (2.55 mL, 2.50 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give 2-ethoxy-4-(3-phenylpropyl)pyridine (**123h**) (70.0 mg, 0.29 mmol, 58% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 (d, *J* = 5.3 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 6.69 (dd, *J* = 5.3, 1.5 Hz, 1H), 6.55 (dd, *J* = 1.5, 0.8 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.61 (dt, *J* = 24.8, 7.7 Hz, 4H), 2.00 – 1.82 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.2, 154.5, 146.4, 141.8, 128.5, 128.5, 126.1, 117.5, 110.6, 61.9, 35.4, 34.7, 31.7, 14.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 2934, 1610, 1558, 1496, 1478, 1453, 1420, 1381, 1351, 1318, 1288, 1158, 1050, 749, 699 (m).
MS (EI, 70 eV): *m/z* (%) = 227 (16), 226 (100), 196 (12), 134 (12), 109 (28).
HRMS (EI): *m/z* calc. for [$C_{16}H_{19}ON$]: 241.1467; found 241.1465.

2-Ethoxy-4-phenethylpyridine (123i)

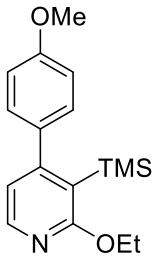


Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and phenethylmagnesium bromide (**91k**) (2.61 mL, 2.50 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography

(*iso*hexane:ethyl acetate = 9.8:0.2) to give 2-ethoxy-4-phenethylpyridine (**123i**) (64.0 mg, 0.28 mmol, 56% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (dd, *J* = 5.3, 1.1 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.27 – 7.19 (m, 3H), 6.71 (dd, *J* = 5.4, 1.4 Hz, 1H), 6.59 (s, 1H), 4.38 (tdd, *J* = 7.4, 6.9, 1.2 Hz, 2H), 2.98 – 2.87 (m, 4H), 1.52 – 1.37 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.1, 153.1, 146.4, 140.8, 128.3, 128.2, 126.0, 117.1, 110.2, 61.3, 36.8, 36.2, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2975, 2927, 1609, 1558, 1496, 1480, 1453, 1440, 1422, 1381, 1319, 1291, 1159, 1050, 814, 698 (m).
MS (EI, 70 eV): *m/z* (%) = 213 (15), 212 (100), 198 (30), 183 (14), 182 (14), 91 (35).
HRMS (EI): *m/z* calc. for [$C_{14}H_{14}ON$]: 212.1070; found 212.1069 [M^+-CH_3].

2-Ethoxy-4-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (123aa)



Following **TP2**, 3-chloro-2-ethoxypyridine (**118**, 790 mg, 5.00 mmol), *n*-butyllithium (2.10 mL, 5.50 mmol) and (4-methoxyphenyl)magnesium bromide (10.1 mL, 10.0 mmol), prepared *via* **TP1**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with TMSCl (1.59 mL, 12.5 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 2-ethoxy-4-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (**123aa**) (814 mg, 2.7 mmol, 54% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 5.2 Hz, 1H), 7.19 – 7.11 (m, 2H), 6.95 – 6.88 (m, 2H), 6.70 (d, *J* = 5.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H), -0.01 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.9, 159.9, 159.5, 146.4, 135.3, 129.9, 119.6, 119.3, 113.4, 61.8, 55.4, 14.8, 1.1.

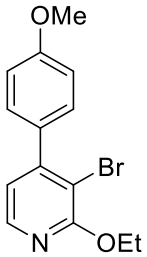
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 2953, 1611, 1574, 1528, 1515, 1462, 1448, 1441, 1373, 1331, 1319, 1290, 1269, 1245, 1174, 1112, 1030, 843, 825, 761, 755.

MS (EI, 70 eV): *m/z* (%) = 301 (26), 300 (12), 283 (20), 256 (15), 242 (22), 241 (100), 239 (11), 225 (26).

HRMS (EI): *m/z* calc. for [$C_{17}H_{23}O_2NSi$]: 301.1498; found 301.1488.

m.p.: 43.1.5-45.2 °C.

3-Bromo-2-ethoxy-4-(4-methoxyphenyl)pyridine (123ab)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with 1,2-dibromo-tetrachloroethane (407 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 3-bromo-2-ethoxy-4-(4-methoxyphenyl)pyridine (**123ab**) (88.0 mg, 0.29 mmol, 57% yield) as a brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 5.1 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.00 – 6.95 (m, 2H), 6.82 (d, *J* = 5.1 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.6, 159.9, 152.3, 144.7, 131.5, 130.3, 119.2, 113.7, 107.5, 63.4, 55.5, 14.7.

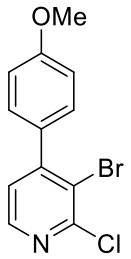
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2853, 1561, 1519, 1448, 1358, 1262, 1150, 1087, 809, 792 (s).

MS (EI, 70 eV): *m/z* (%) = 307 (16), 293 (96), 292 (100), 281 (45), 279 (46), 236 (20), 184 (55), 169 (33), 141 (24).

HRMS (EI): *m/z* calc. for [$C_{14}H_{14}O_2NBr$]: 307.0208; found 307.0200.

m.p.: 46.8-47.6 °C.

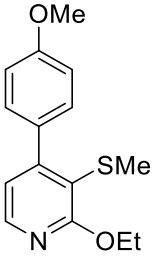
3-Bromo-2-chloro-4-(4-methoxyphenyl)pyridine (127)



The pyridine **123ab** (308 mg, 1.00 mmol, 1.0 equiv) was dissolved in dry DMF (11.6 mL, 15.0 mmol, 15 equiv). The mixture was cooled to 0 °C, $POCl_3$ (0.28 mL, 3.00 mmol, 3.0 equiv) was added dropwise and the solution was stirred for 1 h at that temperature. After sealing the reaction flask, the reaction mixture was heated to 100 °C and stirred for 4 h. After cooling to 0 °C, it was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give 3-bromo-2-chloro-4-(4-methoxyphenyl)pyridine (**127**) (269 mg, 0.90 mmol, 90% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.24 (d, *J* = 4.8 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.09 (d, *J* = 4.9 Hz, 1H), 6.96 – 6.88 (m, 2H), 3.80 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3, 153.6, 152.4, 147.3, 131.1, 130.2, 124.6, 120.9, 113.9, 55.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2362, 2358, 2339, 1608, 1570, 1515, 1506, 1434, 1346, 1297, 1248, 1180, 1063, 1030, 827, 668 (m).
MS (EI, 70 eV): *m/z* (%) = 300 (24), 299 (100), 297 (77), 175 (21), 140 (39), 113 (23).
HRMS (EI): *m/z* calc. for [$C_{12}H_9ONBrCl$]: 296.9556; found 296.9553.
m.p.: 145.2-146.5 °C.

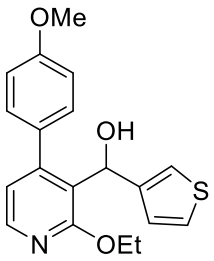
2-Ethoxy-4-(4-methoxyphenyl)-3-(methylthio)pyridine (123ac)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *S*-methyl-thiomethanesulfonate (158 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.6:0.4) to give 2-ethoxy-4-(4-methoxyphenyl)-3-(methylthio)pyridine (**123ac**) (59.0 mg, 0.22 mmol, 43% yield) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 5.1 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.83 (d, *J* = 5.2 Hz, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.26 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.8, 160.0, 154.9, 145.1, 132.1, 130.9, 119.1, 118.2, 113.9, 63.1, 55.7, 18.4, 15.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 2926, 1609, 1577, 1515, 1453, 1441, 1416, 1402, 1376, 1350, 1337, 1324, 1292, 1273, 1248, 1177, 1137, 1114, 1028, 1010, 947, 839, 822 (m).
MS (EI, 70 eV): *m/z* (%) = 275 (40), 261 (15), 260 (100), 246 (20), 232 (12), 227 (13), 226 (18), 214 (33), 196 (12).
HRMS (EI): *m/z* calc. for [$C_{15}H_{18}O_2NS$]: 275.0980; found 275.0974.

(2-Ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)(thiophen-3-yl)methanol (123ad)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with freshly purified thiophene-3-carbaldehyde (140 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.0:2.0) to give (2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)(thiophen-3-yl)methanol (**123ad**) (102 mg, 0.30 mmol, 60% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.10 (d, *J* = 5.2 Hz, 1H), 7.25 – 7.20 (m, 3H), 6.96 (dt, *J* = 2.9, 1.3 Hz, 1H), 6.94 – 6.90 (m, 3H), 6.86 (d, *J* = 5.2 Hz, 1H), 5.84 (d, *J* = 11.0 Hz, 1H), 4.40 (qd, *J* = 7.0, 2.6 Hz, 2H), 4.15 (d, *J* = 11.9 Hz, 1H), 3.83 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H).

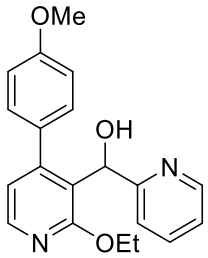
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.8, 159.8, 150.6, 145.9, 145.2, 130.6, 130.0, 126.7, 125.5, 122.6, 120.8, 119.2, 114.1, 68.5, 62.4, 55.5, 14.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3547, 2976, 2835, 1609, 1592, 1578, 1550, 1514, 1463, 1441, 1420, 1405, 1379, 1349, 1324, 1293, 1246, 1227, 1208, 1178, 1148, 1125, 1110, 1089, 1026, 953, 841, 826, 788, 738, 729.

MS (EI, 70 eV): *m/z* (%) = 341 (28), 295 (24), 256 (27), 228 (100), 212 (48), 207 (21), 111 (47), 110 (26).

HRMS (EI): *m/z* calc. for [$C_{19}H_{19}O_3NS$]: 341.1086; found 341.1079.

(2-Ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)(pyridin-2-yl)methanol (123ae)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with freshly purified picolinaldehyde (134 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 7.0:3.0) to give (2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)(pyridin-2-yl)methanol (**123ae**) (96.0 mg, 0.29 mmol, 57% yield) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.52 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.08 (d, *J* = 5.3 Hz, 1H), 7.58 (td, *J* = 7.7, 1.7 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.16 – 7.09 (m, 2H), 6.98 – 6.94 (m, 2H), 6.87 (d, *J* = 5.3 Hz, 1H), 5.91 (s, 1H), 5.02 (s, 1H), 3.84 (s, 2H), 0.95 (td, *J* = 7.0, 0.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.0, 162.0, 159.8, 152.2, 147.6, 145.7, 136.4, 131.0, 130.5, 122.3, 121.7, 120.1, 118.9, 114.0, 69.9, 61.7, 55.5, 14.3.

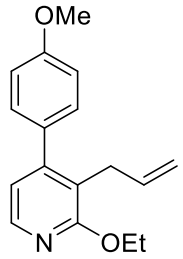
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2364, 2355, 2342, 1609, 1591, 1558, 1539, 1516, 1506, 1472, 1464, 1456, 1436, 1424, 1419, 1249, 1030, 668 (s).

MS (EI, 70 eV): *m/z* (%) = 291 (86), 263 (22), 240 (43), 214 (50), 212 (98), 201 (27), 200 (28), 169 (39), 80 (32), 78 (100)

HRMS (EI): *m/z* calc. for [$C_{20}H_{20}O_3N_2$]: 336.1474; found 336.1470.

m.p.: 100.5-102.2 °C.

3-Allyl-2-ethoxy-4-(4-methoxyphenyl)pyridine (123af)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with CuCN·2LiCl (0.05 mL, 0.05 mmol) and allyl bromide (0.11 mL, 1.25 mmol) at 0 °C. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.6:0.4) to give 3-allyl-2-ethoxy-4-(4-methoxyphenyl)pyridine (**123af**) (75.0 mg, 0.28 mmol, 56% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 5.2 Hz, 1H), 7.31 – 7.23 (m, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 5.2 Hz, 1H), 5.99 (ddt, *J* = 17.2, 10.1, 6.0 Hz, 1H), 5.01 (dq, *J* = 10.1, 1.6 Hz, 1H), 4.91 (dt, *J* = 17.2, 1.8 Hz, 1H), 4.44 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 3.32 (dt, *J* = 6.0, 1.7 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

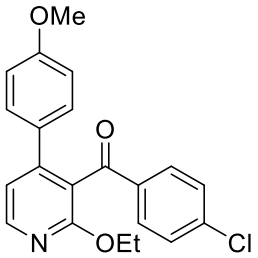
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.5, 159.4, 151.3, 143.8, 136.8, 131.9, 130.0, 120.1, 118.6, 115.2, 113.7, 61.9, 55.4, 31.4, 14.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2927, 2836, 1609, 1588, 1530, 1514, 1459, 1440, 1417, 1368, 1305, 1290, 1248, 1180, 1129, 1114, 1097, 1050, 1028, 986, 915, 841, 817, 770, 696.

MS (EI, 70 eV): *m/z* (%) = 254 (34), 240 (100), 226 (86), 225 (52), 225 (28), 224 (86), 222 (44), 214 (50), 208 (25), 196 (37).

HRMS (EI): *m/z* calc. for [$C_{17}H_{19}O_2N$]: 269.1416; found 269.1410.

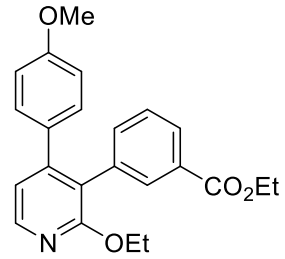
(4-Chlorophenyl)(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)methanone (123ag)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with CuCN·2LiCl (0.50 mL, 0.50 mmol) and 4-chlorobenzoyl chloride (219 mg, 1.25 mmol) at 0 °C. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give (4-chlorophenyl)(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)methanone (**123ag**) (107 mg, 0.29 mmol, 58% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.25 (d, *J* = 5.4 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.34 – 7.30 (m, 2H), 7.24 – 7.18 (m, 2H), 6.97 (d, *J* = 5.3 Hz, 1H), 6.82 – 6.75 (m, 2H), 4.35 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 3H), 1.19 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm 194.8, 160.9, 160.1, 150.3, 147.6, 139.8, 135.9, 130.7, 129.9, 129.8, 128.9, 121.1, 117.9, 114.2, 62.5, 55.3, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1674, 1609, 1585, 1547, 1517, 1463, 1420, 1378, 1327, 1298, 1272, 1252, 1180, 1128, 1091, 1027, 925, 823, 732 (m).
MS (EI, 70 eV): *m/z* (%) = 367 (5), 323 (33), 312 (15), 310 (47), 308 (19), 288 (24), 280 (15), 228 (100), 213 (22), 210 (17), 185 (18), 139 (15).
HRMS (EI): *m/z* calc. for [$C_{21}H_{18}O_3NCl$]: 367.0975; found 367.0971.

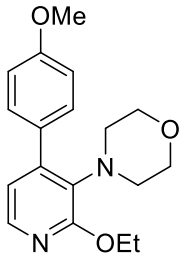
Ethyl 3-(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)benzoate (123ah)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with a solution of $ZnCl_2$ (1.00 mL, 1.00 mmol) in THF at 0 °C. Then, a mixture of ethyl 3-bromobenzoate (286 mg, 1.25 mmol), $Pd(OAc)_2$ (5 mol%) and SPhos (10 mol%) was added. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give ethyl 3-(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)benzoate (**123ah**) (106 mg, 0.28 mmol, 56% yield) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 (d, *J* = 5.3 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.30 – 7.21 (m, 3H), 7.01 – 6.94 (m, 3H), 6.74 – 6.68 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.4, 161.2, 158.8, 150.1, 145.5, 135.7, 135.4, 132.3, 130.9, 130.4, 129.7, 127.7, 127.5, 121.5, 118.3, 113.3, 61.8, 60.6, 55.0, 14.4, 14.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 1718, 1700, 1609, 1587, 1546, 1515, 1464, 1457, 1441, 1418, 1404, 1378, 1367, 1347, 1323, 1296, 1248, 1216, 1178, 1132, 1110, 1082, 1031, 823, 754.
MS (EI, 70 eV): *m/z* (%) = 377 (30), 362 (61), 360 (100), 348 (52), 332 (42), 330 (47), 320 (30), 316 (74), 304 (55), 302 (88), 276 (25), 204 (34).
HRMS (EI): *m/z* calc. for [$C_{23}H_{23}O_4N$]: 377.1627; found 377.1624.

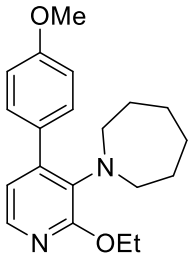
4-(2-Ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)morpholine (123ai)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with a solution of $ZnCl_2$ (0.50 mL, 0.50 mmol) in THF at 0 °C. Then, a solution of *N*-morpholino benzoate (259 mg, 1.25 mmol) was added, followed by a solution of $Cu(OTf)_2$ (10 mol%) in THF. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.3:0.7) to give 4-(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)morpholine (**123ai**) (85.0 mg, 0.27 mmol, 54% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 (d, *J* = 5.1 Hz, 1H), 7.42 – 7.35 (m, 2H), 6.97 – 6.92 (m, 2H), 6.79 (d, *J* = 5.2 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 3.59 (t, *J* = 4.6 Hz, 4H), 2.97 (t, *J* = 4.2 Hz, 4H), 1.45 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.9, 159.3, 148.1, 141.8, 131.6, 130.8, 130.4, 118.8, 113.3, 67.4, 62.0, 55.3, 50.3, 14.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2849, 1608, 1585, 1513, 1464, 1450, 1440, 1424, 1408, 1380, 1350, 1325, 1290, 1261, 1244, 1205, 1175, 1127, 1110, 1028, 952, 925, 844, 820 (s).
MS (EI, 70 eV): *m/z* (%) = 315 (20), 314 (99), 313 (25), 255 (77), 241 (31), 227 (100), 214 (18), 184 (21).
HRMS (EI): *m/z* calc. for [$C_{18}H_{22}O_3N_2$]: 314.1630; found 314.1625.
m.p.: 77.0-78.6 °C.

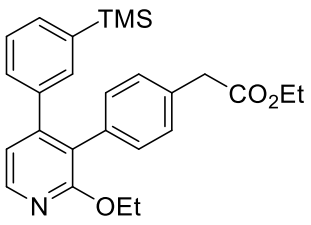
1-(2-Ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)azepane (123aj)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (1.02 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with a solution of $ZnCl_2$ (0.50 mL, 0.50 mmol) in THF at 0 °C. Then, a solution of *N*-azepan-1-yl benzoate (274 mg, 1.25 mmol) was added, followed by a solution of $Cu(OTf)_2$ (10 mol%) in THF. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.3:0.7) to give 1-(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)azepane (**123aj**) (77.0 mg, 0.24 mmol, 47% yield) as an orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.86 (d, *J* = 5.2 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.00 – 6.89 (m, 2H), 6.78 (d, *J* = 5.2 Hz, 1H), 4.42 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 2.94 (t, *J* = 4.8 Hz, 4H), 1.51 (d, *J* = 1.8 Hz, 8H), 1.44 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.3, 159.2, 147.8, 141.1, 135.1, 131.7, 130.4, 118.7, 113.4, 61.8, 55.4, 54.2, 30.1, 27.8, 15.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 1609, 1514, 1464, 1440, 1423, 1379, 1326, 1292, 1246, 1175, 1128, 1031, 819 (m).
MS (EI, 70 eV): *m/z* (%) = 326 (96), 297 (100), 269 (81), 255 (46), 241 (57), 227 (100), 214 (43).
HRMS (EI): *m/z* calc. for [$C_{20}H_{26}O_2N_2$]: 326.1994; found 326.1990.
m.p.: 81.2-82.6 °C.

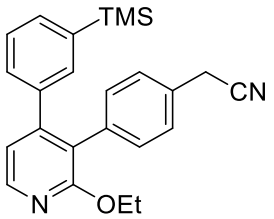
Ethyl 2-(4-(2-ethoxy-4-(3-(trimethylsilyl)phenyl)pyridin-3-yl)phenyl)acetate (123ba)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (3-(trimethylsilyl)phenyl)magnesium bromide (1.06 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with a solution of $ZnCl_2$ (1.00 mL, 1.00 mmol) in THF at 0 °C. Then, a mixture of ethyl 2-(4-bromophenyl)acetate (304 mg, 1.25 mmol), $Pd(OAc)_2$ (5 mol%) and SPhos (10 mol%) was added. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give ethyl 2-(4-(2-ethoxy-4-(3-(trimethylsilyl)phenyl)-pyridin-3-yl)phenyl)acetate (**123ba**) (119 mg, 0.28 mmol, 55% yield) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm 8.17 (d, *J* = 5.2 Hz, 1H), 7.34 (dt, *J* = 7.2, 1.3 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.20 (dt, *J* = 7.6, 1.7 Hz, 1H), 7.16 – 7.12 (m, 2H), 7.10 – 7.04 (m, 3H), 6.98 (d, *J* = 5.2 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.07 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.6, 161.6, 150.9, 145.5, 140.0, 138.4, 135.0, 134.3, 132.6, 132.3, 131.4, 129.6, 128.6, 127.6, 122.7, 118.6, 62.2, 60.9, 41.3, 14.7, 14.3, -1.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979, 2955, 1736, 1584, 1573, 1547, 1467, 1462, 1419, 1408, 1377, 1346, 1322, 1271, 1262, 1248, 1151, 1138, 1116, 1036, 1002, 863, 838, 795, 754, 707, 695.
MS (EI, 70 eV): *m/z* (%) = 434 (35), 433 (100), 432 (43), 418 (70), 416 (39), 404 (36), 346 (41), 316 (54), 73 (46).
HRMS (EI): *m/z* calc. for [$C_{26}H_{31}O_3NSi$]: 433. 2073; found 433.2069.

2-(4-(2-Ethoxy-4-(3-(trimethylsilyl)phenyl)pyridin-3-yl)phenyl)acetonitrile (123bb)

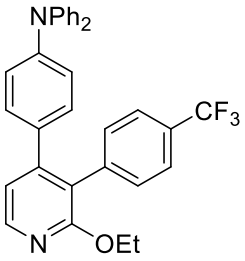


Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (3-(trimethylsilyl)phenyl)magnesium bromide (1.06 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with a solution of $ZnCl_2$ (1.00 mL, 1.00 mmol) in THF at 0 °C. Then, a mixture of 2-(4-bromophenyl)acetonitrile (245 mg, 1.25 mmol), $Pd(OAc)_2$ (5 mol%) and SPhos (10

mol%) was added. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 2-(4-(2-ethoxy-4-(3-(trimethylsilyl)phenyl)pyridin-3-yl)phenyl)acetonitrile (**123bb**) (102 mg, 0.27 mmol, 53% yield) as an orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.25 (d, *J* = 5.2 Hz, 1H), 7.41 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.34 – 7.23 (m, 3H), 7.22 – 7.17 (m, 1H), 7.16 – 7.12 (m, 2H), 7.09 (dd, *J* = 2.0, 1.1 Hz, 1H), 7.05 (d, *J* = 5.2 Hz, 1H), 4.46 (q, *J* = 7.0 Hz, 2H), 3.65 (s, 2H), 1.37 (t, *J* = 7.0 Hz, 3H), 0.13 (d, *J* = 0.6 Hz, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.4, 151.1, 145.9, 140.2, 138.1, 136.7, 134.9, 132.5, 131.1, 130.9, 129.6, 129.3, 128.6, 127.7, 126.3, 122.1, 118.5, 117.8, 62.3, 23.6, 14.7, -1.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 1584, 1547, 1413, 1378, 1347, 1322, 1276, 1263, 1249, 1138, 1117, 1040, 863, 838, 794, 754, 708 (m).
MS (EI, 70 eV): *m/z* (%) = 386 (6), 372 (33), 371 (100), 343 (16).
HRMS (EI): *m/z* calc. for [$C_{24}H_{26}ON_2Si$]: 386.1814; found 386.1805.
m.p.: 73.8-75.3 °C.

4-(2-Ethoxy-3-(4-(trifluoromethyl)phenyl)pyridin-4-yl)-*N*,*N*-diphenylaniline (123ca)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-(diphenylamino)phenyl)magnesium bromide (1.08 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with a solution of $ZnCl_2$ (1.00 mL, 1.00 mmol) in THF at 0 °C. Then, a mixture of 1-bromo-4-(trifluoromethyl)benzene (245 mg, 1.25 mmol), $Pd(OAc)_2$ (5 mol%) and SPhos (10 mol%) was added. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 4-(2-ethoxy-3-(4-(trifluoromethyl)phenyl)pyridin-4-yl)-*N*,*N*-diphenylaniline (**123ca**) (136 mg, 0.27 mmol, 53% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.18 (d, *J* = 5.3 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.25 (dt, *J* = 8.8, 7.3 Hz, 6H), 7.07 – 6.97 (m, 7H), 6.86 (s, 4H), 4.39 (q, *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H).

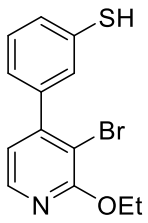
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.3, 150.8, 147.5, 147.4, 146.2, 139.8, 132.2, 131.7, 130.3, 129.4, 124.8, 124.5, 124.2, 123.4, 122.4, 121.5, 118.3, 62.3, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976, 2929, 1588, 1511, 1494, 1487, 1324, 1292, 1273, 1164, 1126, 1105, 1068, 697 (m).

MS (EI, 70 eV): *m/z* (%) = 367 (28), 366 (100), 352 (23), 351 (87), 339 (16), 338 (62), 337 (22), 167 (16).

HRMS (EI): *m/z* calc. for [$C_{32}H_{25}ON_2F_3$]: 510.1919; found 510. 1915.

3-(3-Bromo-2-ethoxypyridin-4-yl)benzenethiol (123da)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (3-(methylthio)phenyl)magnesium bromide (1.00 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with 1,2-dibromotetrachloroethane (407 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give 3-(3-bromo-2-ethoxypyridin-4-yl)benzenethiol (**123da**) (81.0 mg, 0.26 mmol, 52% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 (dq, *J* = 14.3, 8.8, 7.3 Hz, 1H), 7.55 (ddd, *J* = 37.8, 18.9, 8.2 Hz, 2H), 7.32 (td, *J* = 12.0, 5.7 Hz, 1H), 6.64 (p, *J* = 7.9, 7.1 Hz, 1H), 6.43 – 6.32 (m, 1H), 4.34 (dp, *J* = 21.2, 6.9 Hz, 2H), 1.77 (s, 1H), 1.37 (tq, *J* = 9.9, 5.6, 4.2 Hz, 3H).

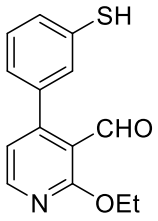
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.4, 150.9, 146.8, 137.3, 133.4, 132.6, 132.4, 131.2, 123.4, 115.1, 108.1, 62.0, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 1584, 1574, 1562, 1542, 1459, 1411, 1378, 1347, 1312, 1280, 1222, 1084, 1070, 1042, 986, 949, 851, 806, 780, 757, 681 (m).

MS (EI, 70 eV): *m/z* (%) = 310 (62), 308 (64), 282 (100), 280 (99), 201 (86), 154 (81), 127 (82).

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}ONBrS$]: 308.9823; found 308.9818.

2-Ethoxy-4-(3-mercaptophenyl)nicotinaldehyde (123db)



Following **TP2**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (3-(methylthio)phenyl)magnesium bromide (1.00 mL, 1.00 mmol), prepared *via* **TP1**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with DMF (excess) and heated to 75 °C for 1 h. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give 2-ethoxy-4-(3-mercaptophenyl)-nicotinaldehyde (**123db**) (64.0 mg, 0.25 mmol, 49% yield) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm 10.01 (s, 1H), 8.02 (t, *J* = 1.8 Hz, 1H), 7.95 (d, *J* = 5.5 Hz, 1H), 7.92 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.77 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 6.61 (dd, *J* = 5.5, 1.6 Hz, 1H), 6.34 (d, *J* = 1.6 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

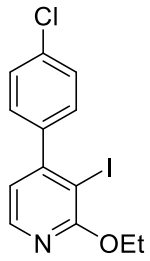
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.2, 164.4, 150.6, 146.9, 140.3, 137.8, 135.7, 132.2, 130.6, 130.3, 115.2, 108.3, 62.1, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979, 1699, 1583, 1543, 1469, 1460, 1412, 1378, 1348, 1312, 1280, 1222, 1197, 1086, 1042, 986, 950, 865, 795, 731, 684 (m).

MS (EI, 70 eV): *m/z* (%) = 245 (14), 244 (100), 230 (35), 214 (10), 202 (29), 186 (16), 184 (12).

HRMS (EI): *m/z* calc. for [$C_{14}H_{13}O_2NS$]: 259.0667; found 259.0671.

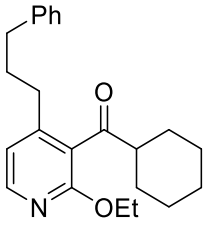
4-(4-Chlorophenyl)-2-ethoxy-3-iodopyridine (123ea)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-chlorophenyl)magnesium bromide (1.04 mL, 1.00 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with iodine (318 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 4-(4-chlorophenyl)-2-ethoxy-3-iodopyridine (**123ea**) (90.0 mg, 0.25 mmol, 50% yield) as an orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 5.0 Hz, 1H), 7.49 – 7.35 (m, 2H), 7.32 – 7.17 (m, 2H), 6.76 (d, *J* = 5.0 Hz, 1H), 4.45 (q, *J* = 7.0 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.6, 156.2, 146.3, 140.8, 134.7, 130.2, 128.6, 118.3, 84.9, 63.7, 14.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 1598, 1579, 1522, 1492, 1467, 1450, 1413, 1397, 1377, 1338, 1321, 1277, 1264, 1131, 1102, 1088, 1034, 1016, 1005, 948, 817 (s).
MS (EI, 70 eV): *m/z* (%) = 359 (57), 346 (30), 344 (100), 330 (55), 188 (51), 149 (34), 141 (27), 140 (32), 113 (29).
HRMS (EI): *m/z* calc. for [$C_{13}H_{11}ONClI$]: 358.9574; found 358.9572.
m.p.: 76.8-78.2 °C.

Cyclohexyl(2-ethoxy-4-(3-phenylpropyl)pyridin-3-yl)methanone (123ha)

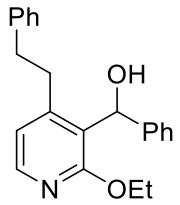


Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (3-phenylpropyl)magnesium bromide (2.55 mL, 2.50 mmol), prepared *via*

TP8, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with CuCN·2LiCl (2.50 mL, 2.50 mmol) and cyclohexanecarbonyl chloride (219 mg, 2.75 mmol) at 0 °C. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give cyclohexyl(2-ethoxy-4-(3-phenylpropyl)-pyridine-3-yl) methanone (**123ha**) (97.0 mg, 0.28 mmol, 55% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02 (d, *J* = 5.3 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.22 – 7.14 (m, 3H), 6.74 (d, *J* = 5.3 Hz, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 2.83 (tt, *J* = 11.4, 3.4 Hz, 1H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.51 – 2.41 (m, 2H), 1.90 (m, 4H), 1.82 – 1.73 (m, 2H), 1.70 – 1.64 (m, 1H), 1.59 (s, 2H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.26 – 1.17 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 209.4, 160.5, 151.3, 146.8, 141.8, 128.5, 126.0, 124.4, 117.8, 62.2, 51.4, 35.8, 32.4, 32.3, 28.4, 26.0, 26.0, 14.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 1610, 1558, 1496, 1478, 1453, 1420, 1381, 1319, 1288, 1159, 1051, 748, 733, 699 (m).
MS (EI, 70 eV): *m/z* (%) = 269 (14), 168 (75), 240 (19), 163 (10), 162 (100), 134 (73), 91 (15).
HRMS (EI): *m/z* calc. for [$C_{23}H_{30}O_2N$]: 352.2271; found 352.2266 [$M+H^+$]

(2-Ethoxy-4-phenethylpyridin-3-yl)(phenyl)methanol (123ia)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and phenethylmagnesium bromide (2.61 mL, 2.50 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with benzaldehyde (0.28 mL mg, 2.75 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.4:0.6) to give (2-ethoxy-4-phenethylpyridin-3-yl)(phenyl)methanol (**123ia**) (82.0 mg, 0.25 mmol, 49% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01 (d, *J* = 5.2 Hz, 1H), 7.33 – 7.27 (m, 5H), 7.26 – 7.17 (m, 3H), 7.16 – 7.11 (m, 2H), 6.77 (d, *J* = 5.3 Hz, 1H), 6.12 (d, *J* = 10.7 Hz, 1H), 4.40 – 4.25 (m, 2H), 3.99 (d, *J* = 10.9 Hz, 1H), 3.09 – 2.90 (m, 2H), 2.89 – 2.81 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 3H).

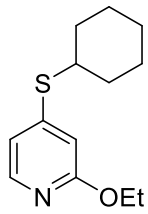
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5, 145.3, 143.6, 140.8, 128.7, 128.5, 128.3, 127.1, 126.4, 125.8, 123.5, 119.0, 69.7, 62.5, 36.8, 34.7, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3026, 2978, 1595, 1564, 1416, 1381, 1333, 1316, 1058, 1035, 1024, 904, 727, 698.

MS (EI, 70 eV): *m/z* (%) = 304 (12), 286 (33), 226 (28), 211 (14), 210 (100), 208 (25), 196 (14), 178 (12), 148 (11), 91 (25).

HRMS (EI): *m/z* calc. for [$C_{22}H_{23}O_2N$]: 333.1729; found 333.1723.

4-(Cyclohexylthio)-2-ethoxypyridine (130a)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and magnesium cyclohexanethiolate (1.00 mL, 1.00 mmol), prepared *via* addition of *i*PrMgCl·LiCl (1.05 equiv) to cyclohexanethiol at 0 °C, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.9:0.1) to give 4-(cyclohexylthio)-2-ethoxypyridine (**130a**) (85.0 mg, 0.36 mmol, 72% yield) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 (dd, *J* = 5.5, 0.7 Hz, 1H), 6.99 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.81 (dd, *J* = 5.4, 1.8 Hz, 1H), 3.31 (tt, *J* = 10.2, 3.7 Hz, 1H), 3.15 (q, *J* = 7.3 Hz, 2H), 2.09 – 1.99 (m, 2H), 1.85 – 1.74 (m, 2H), 1.70 – 1.60 (m, 1H), 1.50 – 1.23 (m, 8H).

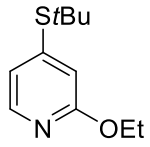
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.4, 148.7, 119.4, 118.0, 43.6, 33.0, 26.0, 25.7, 24.7, 14.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2852, 1583, 1538, 1460, 1449, 1409, 1376, 1346, 1310, 1280, 1263, 1220, 1087, 1042, 997, 986, 949, 931, 842, 803 (m).

MS (EI, 70 eV): *m/z* (%) = 222 (76), 209 (13), 140 (100), 128 (44), 127 (62), 111 (13), 99 (16).

HRMS (EI): *m/z* calc. for [$C_{13}H_{20}ONS$]: 238.1260; found 238.1259 [$M+H^+$]

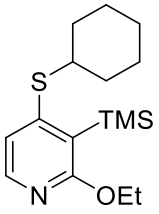
4-(*Tert*-butylthio)-2-ethoxypyridine (130b)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and magnesium 2-methylpropane-2-thiolate (1.00 mL, 1.00 mmol), prepared *via* addition of *i*PrMgCl·LiCl (1.05 equiv) to 2-methylpropane-2-thiol at 0 °C, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.9:0.1) to give 4-(*tert*-butylthio)-2-ethoxypyridine (**130b**) (73.0 mg, 0.35 mmol, 69% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 8.05 (d, *J* = 5.3 Hz, 1H), 6.93 (dd, *J* = 5.3, 1.5 Hz, 1H), 6.86 (d, *J* = 1.4 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.38 (d, *J* = 9.0 Hz, 12H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.9, 146.2, 122.7, 116.8, 62.2, 47.1, 31.4, 14.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974, 2963, 1583, 1540, 1471, 1461, 1407, 1377, 1364, 1345, 1311, 1273, 1218, 1164, 1043 (s).
MS (EI, 70 eV): *m/z* (%) = 155 (55), 140 (58), 127 (100), 57 (19).
HRMS (EI): *m/z* calc. for [$C_{11}H_{17}ONS$]: 211.2031; found 211.2023.

4-(Cyclohexylthio)-2-ethoxy-3-(trimethylsilyl)pyridine (130aa)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and magnesium cyclohexanethiolate (1.00 mL, 1.00 mmol), prepared *via* addition of *i*PrMgCl·LiCl (1.05 equiv) to cyclohexanethiol at 0 °C, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with TMSCl (0.16 mL, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give 4-(cyclohexylthio)-2-ethoxy-3-(trimethylsilyl)pyridine (**130aa**) (110 mg, 0.36 mmol, 71% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (d, *J* = 5.5 Hz, 1H), 6.83 – 6.70 (m, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.27 (tt, *J* = 10.3, 3.6 Hz, 1H), 2.08 – 1.98 (m, 2H), 1.83 – 1.74 (m, 2H), 1.69 – 1.60 (m, 1H), 1.46 – 1.22 (m, 7H), 0.38 (s, 9H).

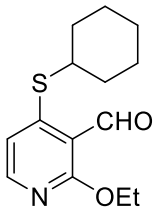
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.5, 157.4, 146.5, 119.3, 115.5, 61.9, 45.2, 33.2, 26.2, 25.9, 14.7, 2.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 2900, 2854, 1558, 1524, 1448, 1427, 1372, 1328, 1290, 1262, 1245, 1048, 1035, 997, 953, 842, 800, 782, 762, 750, 736, 693, 686.

MS (EI, 70 eV): *m/z* (%) = 294 (25), 228 (30), 227 (71), 226 (27), 212 (98), 184 (39), 168 (100), 83 (20), 73 (31), 55 (49), 41 (31).

HRMS (EI): *m/z* calc. for [$C_{16}H_{27}ONSSi$]: 309.1583; found 309.1575.

4-(Cyclohexylthio)-2-ethoxynicotinaldehyde (130ab)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and magnesium cyclohexanethiolate (1.00 mL, 1.00 mmol), prepared *via* addition of *i*PrMgCl·LiCl (1.05 equiv) to cyclohexanethiol at 0 °C, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with DMF (excess) and heated to 75 °C for 1 h. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 4-(cyclohexylthio)-2-ethoxynicotinaldehyde (**130ab**) (66.0 mg, 0.25 mmol, 50% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.51 (d, *J* = 0.7 Hz, 1H), 8.06 (d, *J* = 5.8 Hz, 1H), 6.87 (d, *J* = 5.8 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.29 (tt, *J* = 10.7, 3.6 Hz, 1H), 2.09 (dd, *J* = 10.4, 4.8 Hz, 2H), 1.84 (dt, *J* = 12.8, 3.7 Hz, 2H), 1.74 – 1.65 (m, 1H), 1.54 – 1.37 (m, 7H).

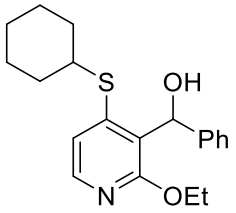
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 189.4, 165.7, 157.7, 148.2, 115.0, 113.4, 64.1, 43.0, 32.6, 26.2, 25.7, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 1670, 1571, 1530, 1447, 1376, 1339, 1297, 1274, 1038 (s).

MS (EI, 70 eV): *m/z* (%) = 250 (47), 236 (80), 232 (27), 204 (27), 182 (52), 156 (22), 154 (100), 139 (23), 127 (64), 111 (21).

HRMS (EI): *m/z* calc. for [$C_{14}H_{18}O_2NS$]: 264.1053; found 264.1052 [M^+-H]

(4-(Cyclohexylthio)-2-ethoxypyridin-3-yl)(phenyl)methanol (130ac)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and magnesium cyclohexanethiolate (1.00 mL, 1.00 mmol), prepared *via* addition of *i*PrMgCl·LiCl (1.05 equiv) to cyclohexanethiol at 0 °C, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with benzaldehyde (0.13 mL, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give (4-(cyclohexylthio)-2-ethoxypyridin-3-yl)(phenyl)methanol (**130ac**) (121 mg, 0.36 mmol, 71% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (d, *J* = 5.5 Hz, 1H), 7.32 (dq, *J* = 6.6, 1.3 Hz, 2H), 7.29 – 7.23 (m, 2H), 7.22 – 7.16 (m, 1H), 6.88 (d, *J* = 5.6 Hz, 1H), 6.31 (d, *J* = 10.9 Hz, 1H), 4.30 (dtq, *J* = 17.5, 10.4, 7.1 Hz, 3H), 3.28 (tt, *J* = 10.5, 3.7 Hz, 1H), 2.02 (tt, *J* = 11.8, 4.0 Hz, 2H), 1.82 – 1.71 (m, 2H), 1.65 – 1.56 (m, 1H), 1.47 – 1.24 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 3H).

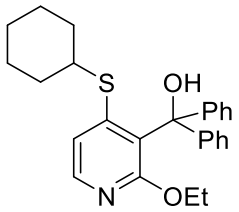
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.2, 147.8, 144.9, 143.3, 128.1, 126.9, 125.6, 124.1, 116.7, 70.5, 62.3, 45.5, 33.1, 26.0, 25.7, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2852, 1575, 1541, 1448, 1406, 1378, 1346, 1331, 1306, 1261, 1221, 1203, 1181, 1168, 1034, 1023, 997, 958, 941, 909, 863, 815, 802, 732, 696 (s).

MS (EI, 70 eV): *m/z* (%) = 260 (29), 232 (17), 214 (27), 182 (23), 154 (100), 115 (11), 77 (24).

HRMS (EI): *m/z* calc. for [$C_{20}H_{25}O_2NS$]: 343.1606; found 343.1593.

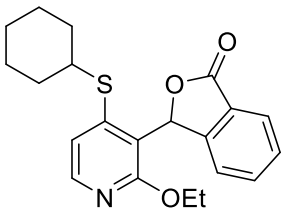
(4-(Cyclohexylthio)-2-ethoxypyridin-3-yl)diphenylmethanol (130ad)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and magnesium cyclohexanethiolate (1.00 mL, 1.00 mmol), prepared *via* addition of *i*PrMgCl·LiCl (1.05 equiv) to cyclohexanethiol at 0 °C, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with benzophenone (228 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.6:0.4) to give (4-(cyclohexylthio)-2-ethoxypyridin-3-yl)diphenylmethanol (**130ad**) (141 mg, 0.34 mmol, 67% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.88 (d, *J* = 5.5 Hz, 1H), 7.31 – 7.16 (m, 10H), 6.85 (d, *J* = 5.5 Hz, 1H), 6.07 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.94 (dp, *J* = 10.5, 3.8, 2.9 Hz, 1H), 1.77 (dd, *J* = 9.6, 5.2 Hz, 2H), 1.62 (dq, *J* = 10.3, 3.1, 2.6 Hz, 2H), 1.54 – 1.45 (m, 1H), 1.19 – 1.05 (m, 5H), 0.88 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5, 149.0, 146.3, 144.1, 129.2, 128.1, 127.8, 127.4, 118.4, 81.9, 62.4, 46.3, 32.6, 25.9, 25.7, 14.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2852, 1568, 1531, 1492, 1445, 1405, 1377, 1335, 1294, 1271, 1262, 1248, 1034, 1012, 956, 922, 905, 886, 759, 732, 698, 655.
MS (EI, 70 eV): *m/z* (%) = 290 (100), 242 (88), 214 (75), 202 (43), 198 (31), 165 (55), 91 (31).
HRMS (EI): *m/z* calc. for [$C_{26}H_{27}ONS$]: 401.1802; found 401.1803 [M^+-H_2O]

3-(4-Cyclohexylthio)-2-ethoxypyridin-3-yl)isobenzofuran-1(3*H*)-one (130ae)

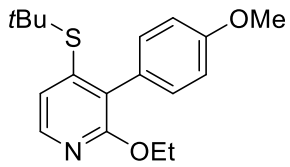


Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and magnesium cyclohexanethiolate (1.00 mL, 1.00 mmol), prepared *via*

addition of *i*PrMgCl·LiCl (1.05 equiv) to cyclohexanethiol at 0 °C, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with ethyl 2-formylbenzoate (223 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.4:0.6) to give 3-(4-cyclohexylthio)-2-ethoxypyridin-3-yl) isobenzofuran-1(3*H*)-one (**130ad**) (131 mg, 0.36 mmol, 71% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 8.00 – 7.97 (m, 1H), 7.95 – 7.90 (m, 1H), 7.58 (tt, *J* = 7.7, 1.5 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.22 (dq, *J* = 7.5, 1.0 Hz, 1H), 7.17 (s, 1H), 6.93 (d, *J* = 5.5 Hz, 1H), 4.15 – 3.91 (m, 2H), 3.42 – 3.22 (m, 1H), 2.04 (t, *J* = 17.3 Hz, 2H), 1.80 (t, *J* = 14.6 Hz, 2H), 1.65 (d, *J* = 11.9 Hz, 1H), 1.57 – 1.25 (m, 5H), 0.90 (d, *J* = 8.6 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.4, 162.3, 149.7, 149.5, 146.9, 133.7, 128.8, 127.7, 125.1, 121.7, 117.3, 62.1, 46.6, 33.2, 33.2, 26.0, 25.9, 25.7, 13.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2853, 1762, 1573, 1545, 1465, 1450, 1417, 1381, 1328, 1308, 1284, 1263, 1207, 1091, 1057, 1039, 1013, 997, 964, 816, 744, 723, 687.
MS (EI, 70 eV): *m/z* (%) = 351 (15), 243 (15), 242 (100), 226 (11), 214 (50), 165 (20).
HRMS (EI): *m/z* calc. for [$C_{21}H_{23}O_3NS$]: 369.1399; found 369.1393.

4-(*Tert*-butylthio)-2-ethoxy-3-(4-methoxyphenyl)pyridine (130ba)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and magnesium 2-methylpropane-2-thiolate (1.00 mL, 1.00 mmol), prepared *via* addition of *i*PrMgCl·LiCl (1.05 equiv) to 2-methylpropane-2-thiol at 0 °C, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with a solution of $ZnCl_2$ (1.00 mL, 1.00 mmol) in THF at 0 °C. Then, a mixture of 1-bromo-4-methoxybenzene (234 mg, 1.25 mmol), $Pd(OAc)_2$ (5 mol%) and SPhos (10 mol%) was added. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 4-(*tert*-butylthio)-2-ethoxy-3-(4-methoxyphenyl)pyridine (**130ba**) (106 mg, 0.34 mmol, 67% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm 8.02 (d, *J* = 5.4 Hz, 1H), 7.19 – 7.16 (m, 2H), 7.15 (d, *J* = 5.4 Hz, 1H), 6.94 – 6.91 (m, 2H), 4.34 (q, *J* = 7.0 Hz, 2H), 3.85 (d, *J* = 1.3 Hz, 3H), 1.33 – 1.20 (m, 12H).

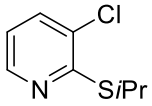
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.6, 158.8, 143.9, 132.2, 127.8, 127.6, 121.9, 113.1, 62.4, 55.3, 47.8, 31.4, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974, 2961, 1611, 1565, 1541, 1511, 1465, 1456, 1441, 1415, 1407, 1377, 1364, 1345, 1291, 1269, 1245, 1226, 1175, 1161, 1041, 996, 828 (m).

MS (EI, 70 eV): *m/z* (%) = 261 (27), 260 (23), 246 (36), 232 (100), 228 (15), 214 (24).

HRMS (EI): *m/z* calc. for [$C_{18}H_{23}O_2NS$]: 317.1442; found 317.1442.

3-Chloro-2-(isopropylthio)pyridine (132)



Sodium 2-propanethiolate (3.53 g, 36.0 mmol, 1.2 equiv) was added to a solution of 2,3-dichloropyridine (4.44 g, 30 mmol, 1.0 equiv) in DMF (120 mL) at 0 °C. After stirring the reaction for 12 h at 25 °C, the mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, flash column chromatography purification (isohexane:ethyl acetate = 9.8:0.2) afforded the pure product **132** (5.24 g, 27.9 mmol, 93% yield) as an colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.34 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.93 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.05 (p, *J* = 6.8 Hz, 1H), 1.43 (d, *J* = 6.8 Hz, 6H).

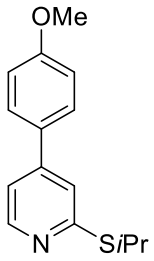
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.0, 147.1, 135.9, 129.2, 119.5, 35.2, 23.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2926, 1566, 1461, 1454, 1432, 1386, 1365, 1242, 1145, 1126, 1055, 1037, 1028, 785, 762, 729, 656 (m).

MS (EI, 70 eV): *m/z* (%) = 187 (19), 172 (15), 156 (27), 154 (82), 152 (12), 147 (33), 145 (100), 110 (73).

HRMS (EI): *m/z* calc. for [$C_8H_{10}ClNS$]: 187.0222; found 187.0216.

2-(Isopropylthio)-4-(4-methoxyphenyl)pyridine (134a)



Flow procedure: A solution of 3-chloro-2-(isopropylthio)pyridine (**132**) in THF (0.10 M, 1.0 equiv, pump A), *n*-butyllithium in *n*-hexane (0.11 M, 1.1 equiv, pump B) and (4-methoxyphenyl)magnesium bromide in THF (0.3 M, 6.0 equiv, pump C) were prepared. According to **TP10**, the reaction was run in continuous flow (suction-time pump A = 30 min) and afterwards injected into a flask containing *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give 2-(isopropylthio)-4-(4-methoxyphenyl) pyridine (**134a**) (444 mg, 1.71 mmol, 57% yield) as a yellow solid.

Batch procedure: Following **TP9**, 3-chloro-2-(isopropylthio)pyridine (**132**, 94.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-methoxyphenyl)magnesium bromide (3.12 mL, 3.0 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give 2-(isopropylthio)-4-(4-methoxyphenyl)pyridine (**134a**) (73.0 mg, 0.28 mmol, 56% yield) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm 8.45 (dd, *J* = 5.3, 0.8 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.35 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.17 (dd, *J* = 5.3, 1.7 Hz, 1H), 7.01 – 6.96 (m, 2H), 4.06 (p, *J* = 6.8 Hz, 1H), 3.86 (s, 3H), 1.43 (d, *J* = 6.8 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.7, 159.9, 149.7, 148.3, 130.2, 128.3, 120.2, 117.5, 114.7, 55.5, 35.5, 23.4.

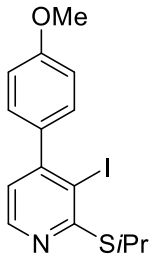
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 2928, 1610, 1590, 1531, 1516, 1460, 1441, 1367, 1291, 1251, 1181, 1130, 1114, 1054, 1029, 820 (s).

MS (EI, 70 eV): *m/z* (%) = 244 (32), 227 (16), 226 (100), 217 (32), 185 (28), 173 (21), 170 (14), 158 (18).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}ONS$]: 259.1031; found 259.1027.

m.p.: 74.9-76.5 °C.

3-Iodo-2-(isopropylthio)-4-(4-methoxyphenyl)pyridine (134aa)



A solution of 3-chloro-2-(isopropylthio)pyridine (**132**) in THF (0.10 M, 1.0 equiv, pump A), *n*-butyllithium in *n*-hexane (0.11 M, 1.1 equiv, pump B) and (4-methoxyphenyl)magnesium bromide in THF (0.3 M, 6.0 equiv, pump C) were prepared. According to **TP10**, the reaction was run in continuous flow (suction-time pump A = 5 min) and afterwards injected into a flask containing iodine (889 mg, 3.5 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 3-iodo-2-(isopropylthio)-4-(4-methoxyphenyl)pyridine (**134aa**) (100 mg, 0.27 mmol, 53% yield) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.36 (d, *J* = 4.9 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.01 – 6.96 (m, 2H), 6.88 (d, *J* = 4.8 Hz, 1H), 3.98 (p, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 1.48 (d, *J* = 6.9 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.6, 159.8, 154.7, 148.1, 135.0, 130.1, 120.3, 113.7, 99.0, 55.4, 38.4, 22.9.

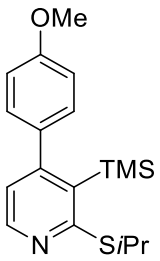
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2925, 1609, 1562, 1514, 1462, 1428, 1412, 1325, 1304, 1287, 1247, 1194, 1176, 1156, 1109, 1063, 1054, 1031, 1000, 824, 767.

MS (EI, 70 eV): *m/z* (%) = 344 (11), 259 (18), 258 (100), 216 (14), 184 (19), 173 (15).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}ONIS$]: 387.9997; found 387.9989.

m.p.: 57.2-59.4 °C.

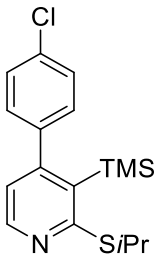
2-(Isopropylthio)-4-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (134ab)



A solution of 3-chloro-2-(isopropylthio)pyridine (**132**) in THF (0.10 M, 1.0 equiv, pump A), *n*-butyllithium in *n*-hexane (0.11 M, 1.1 equiv, pump B) and (4-methoxyphenyl)magnesium bromide in THF (0.3 M, 6.0 equiv, pump C) were prepared. According to **TP10**, the reaction was run in continuous flow (suction-time pump A = 5 min) and afterwards injected into a flask containing TMSCl (0.44 mL, 3.5 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give 2-(isopropylthio)-4-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (**134ab**) (85.0 mg, 0.26 mmol, 51% yield) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm 8.35 (d, *J* = 4.9 Hz, 1H), 7.23 – 7.12 (m, 2H), 6.98 – 6.89 (m, 2H), 6.83 (d, *J* = 4.9 Hz, 1H), 4.21 (p, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 6H), 0.12 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.8, 159.7, 157.8, 147.9, 135.8, 132.3, 130.1, 121.5, 113.6, 55.4, 36.8, 23.3, 2.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 1608, 1556, 1512, 1462, 1442, 1422, 1409, 1319, 1304, 1283, 1244, 1172, 1154, 1107, 1058, 1032, 841, 824, 783, 772, 758, 752, 734, 693, 684.
MS (EI, 70 eV): *m/z* (%) = 316 (18), 288 (21), 174 (55), 257 (29), 256 (100), 226 (16).
HRMS (EI): *m/z* calc. for [$C_{18}H_{25}NSSi$]: 331.1426; 331.1419.
m.p.: 55.4-56.4 °C.

4-(4-Chlorophenyl)-2-(isopropylthio)-3-(trimethylsilyl)pyridine (134ba)



A solution of 3-chloro-2-(isopropylthio)pyridine (**132**) in THF (0.10 M, 1.0 equiv, pump A), *n*-butyllithium in *n*-hexane (0.11 M, 1.1 equiv, pump B) and (4-chlorophenyl)magnesium bromide in THF (0.3 M, 6.0 equiv, pump C) were prepared. According to **TP10**, the reaction was run in continuous flow (suction-time pump A = 5 min) and afterwards injected into a flask containing TMSCl (0.44 mL, 3.5 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give 4-(4-chlorophenyl)-2-

(isopropylthio)-3-(trimethylsilyl)pyridine (**134ba**) (84.0 mg, 0.25 mmol, 50% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.35 (d, *J* = 5.0 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.18 – 7.12 (m, 2H), 6.78 (d, *J* = 5.0 Hz, 1H), 4.21 (p, *J* = 6.9 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 6H), 0.08 (s, 9H).

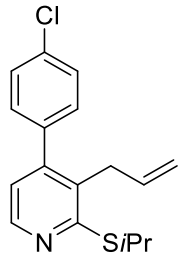
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.2, 156.6, 148.1, 141.6, 134.2, 132.0, 130.2, 128.4, 121.1, 36.9, 23.3, 2.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 1597, 1572, 1533, 1492, 1449, 1433, 1362, 1184, 1164, 1155, 1092, 1056, 1015, 927, 916, 834, 820, 792.

MS (EI, 70 eV): *m/z* (%) = 320 (28), 292 (33), 280 (24), 278 (61), 262 (35), 260 (100), 226 (25).

HRMS (EI): *m/z* calc. for [$C_{17}H_{21}ClNSSi$]: 334.0847; found 334.0847 [M^+-H].

3-Allyl-4-(4-chlorophenyl)-2-(isopropylthio)pyridine (134bb)



A solution of 3-chloro-2-(isopropylthio)pyridine (**132**) in THF (0.10 M, 1.0 equiv, pump A), *n*-butyllithium in *n*-hexane (0.11 M, 1.1 equiv, pump B) and (4-chlorophenyl)magnesium bromide in THF (0.3 M, 6.0 equiv, pump C) were prepared. According to **TP10**, the reaction was run in continuous flow (suction-time pump A = 5 min) and afterwards injected into a flask containing CuCN·2LiCl (0.05 mL, 0.05 mmol) and allyl bromide (0.30 mL, 3.5 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give 3-allyl-4-(4-chlorophenyl)-2-(isopropylthio)pyridine (**134bb**) (74.0 mg, 0.25 mmol, 49% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.36 (d, *J* = 5.0 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.29 – 7.17 (m, 2H), 6.85 (d, *J* = 5.0 Hz, 1H), 5.88 (ddt, *J* = 17.2, 10.2, 5.6 Hz, 1H), 5.05 (dq, *J* = 10.2, 1.7 Hz, 1H), 4.81 (dq, *J* = 17.2, 1.8 Hz, 1H), 4.14 (p, *J* = 6.8 Hz, 1H), 3.33 (dt, *J* = 5.7, 1.9 Hz, 2H), 1.42 (d, *J* = 6.8 Hz, 6H).

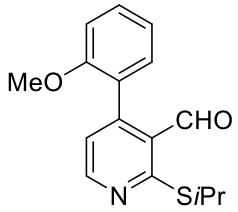
^{13}C-NMR (101 MHz, $CDCl_3$): 159.9, 149.2, 146.5, 137.7, 135.0, 134.4, 130.4, 130.0, 128.6, 120.7, 116.6, 35.7, 33.8, 23.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 1555, 1520, 1486, 1422, 1318, 1250, 1174, 1091, 1052, 1015, 904, 846, 823, 802, 726.

MS (EI, 70 eV): *m/z* (%) = 262 (37), 260 (100), 248 (15), 246 (42), 228 (44), 191 (15).

HRMS (EI): *m/z* calc. for [$C_{17}H_{17}ClNS$]: 302.08765; found 302.08764 [M^+-H].

2-(Isopropylthio)-4-(2-methoxyphenyl)nicotinaldehyde (134ca)



A solution of 3-chloro-2-(isopropylthio)pyridine (**132**) in THF (0.10 M, 1.0 equiv, pump A), *n*-butyllithium in *n*-hexane (0.11 M, 1.1 equiv, pump B) and (2-methoxyphenyl)magnesium bromide in THF (0.3 M, 6.0 equiv, pump C) were prepared. According to **TP10**, the reaction was run in continuous flow (suction-time pump A = 5 min) and afterwards injected into a flask containing DMF (excess) and heated to 75 °C for 1 h. After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give 2-(isopropylthio)-4-(2-methoxyphenyl) nicotinaldehyde (**134ca**) (73.0 mg, 0.26 mmol, 51% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.84 (s, 1H), 8.60 (d, *J* = 5.0 Hz, 1H), 7.44 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 6.98 – 6.95 (m, 2H), 4.23 (h, *J* = 6.8 Hz, 1H), 3.74 (s, 3H), 1.44 (d, *J* = 6.9 Hz, 6H).

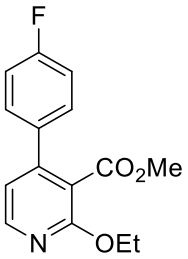
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.7, 161.8, 156.3, 152.1, 151.9, 131.1, 130.8, 125.8, 125.1, 121.2, 121.1, 110.9, 55.6, 34.2, 23.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 1686, 1599, 1581, 1558, 1538, 1492, 1462, 1436, 1396, 1359, 1301, 1274, 1242, 1197, 1185, 1124, 1061, 1023, 864, 814, 755, 691 (m).

MS (EI, 70 eV): *m/z* (%) = 256 (81), 229 (67), 226 (100), 217 (57), 214 (34), 201 (41), 184 (40), 154 (43), 143 (30).

HRMS (EI): *m/z* calc. for [$C_{16}H_{17}NO_2S$]: 287.0980; found 287.0977.

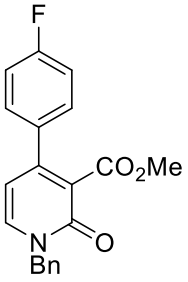
Methyl 2-ethoxy-4-(4-fluorophenyl)nicotinate (123ja)



Following **TP9**, 3-chloro-2-ethoxypyridine (**118**, 790 mg, 5.00 mmol), *n*-butyllithium (2.10 mL, 5.50 mmol) and (4-fluorophenyl)magnesium bromide (16.2 mL, 15.0 mmol), prepared *via* **TP8**, were mixed in a sealed tube. Thereafter, the reaction mixture was quenched with methyl cyanoformate (2.00 mL, 25.0 mmol). After workup, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give methyl 2-ethoxy-4-(4-fluorophenyl)nicotinate (**123ja**) (73.0 mg, 0.27 mmol, 53% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (d, *J* = 5.3 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.17 – 7.06 (m, 2H), 6.87 (d, *J* = 5.3 Hz, 1H), 4.46 (q, *J* = 7.0 Hz, 2H), 3.70 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.45, 163.23 (d, *J* = 248.8 Hz), 160.70, 148.99, 147.84, 134.04 (d, *J* = 3.4 Hz), 129.83 (d, *J* = 8.4 Hz), 117.32, 116.75, 115.90 (d, *J* = 21.7 Hz), 62.83, 52.53, 14.68.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2951, 1734, 1607, 1589, 1555, 1514, 1468, 1434, 1421, 1380, 1349, 1328, 1290, 1273, 1227, 1161, 1140, 1117, 1099, 1069, 1032, 824, 733 (m).
MS (EI, 70 eV): *m/z* (%) = 260 (34), 228 (32), 216 (100), 173 (34), 172 (38),133 (20).
HRMS (EI): *m/z* calc. for [$C_{15}H_{14}O_3NF$]: 275.0958; found 275.0947.

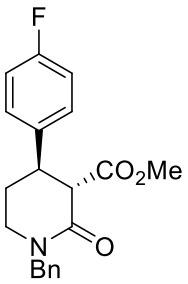
Methyl 1-benzyl-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (137)



Methyl 2-ethoxy-4-(4-fluorophenyl)nicotinate (**123ja**, 358 mg, 1.30 mmol) and neat benzylbromide (2.6 mL, ~0.5 M) were added into a sealed tube. The reaction mixture was heated to 120 °C for 30 h in a microwave setup. The crude product was directly purified *via* column chromatography (*iso*hexane:ethyl acetate = 6.0:4.0) to give methyl 1-benzyl-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**137**) (351 mg, 1.04 mmol, 80% yield) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 – 7.31 (m, 8H), 7.13 – 7.06 (m, 2H), 6.19 (d, *J* = 7.1 Hz, 1H), 5.17 (s, 2H), 3.72 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.9, 163.3 (d, *J* = 249.7 Hz), 159.6, 149.7, 137.5, 135.6, 133.3 (d, *J* = 3.4 Hz), 129.4 (d, *J* = 8.4 Hz), 129.1, 128.7, 128.4, 124.1, 115.9 (d, *J* = 21.7 Hz), 107.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2359, 1733, 1647, 1602, 1599, 1592, 1538, 1533, 1521, 1512, 1456, 1371, 1256, 1239, 1228, 1163, 1127, 1090, 703.
MS (EI, 70 eV): *m/z* (%) = 305 (100), 277 (53), 276 (71), 248 (35), 91 (65).
HRMS (EI): *m/z* calc. for [$C_{20}H_{16}O_3NF$]: 337.1114; found 337.1104.

Methyl 1-benzyl-4-(4-fluorophenyl)-2-oxopiperidine-3-carboxylate (138)



(±)-trans

Methyl 1-benzyl-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**137**, 348 mg, 1.00 mmol) and MeOH (30 mL) were added into a flask. Then, 5% Pd/C (2.13 g, 1.0 mmol) was added while stirring and the solution was saturated with hydrogen gas. Under hydrogen-atmosphere (balloon filled with H_2), the reaction mixture was stirred for 16 h at 23 °C. The suspension was filtered and the residue was washed with MeOH several times. After removal of MeOH, the crude product was purified *via* column chromatography (pure ethyl acetate) to give methyl 1-benzyl-4-(4-fluorophenyl)-2-oxopiperidine-3-carboxylate (**138**) (176 mg, 0.50 mmol, 50% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.28 (m, 5H), 7.15 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.03 – 6.96 (m, 2H), 4.81 (d, *J* = 14.5 Hz, 1H), 4.47 (d, *J* = 14.5 Hz, 1H), 3.64 (s, 3H), 3.61 – 3.56 (m, 1H), 3.48 – 3.35 (m, 2H), 3.29 (ddd, *J* = 12.3, 5.4, 3.0 Hz, 1H), 2.09 – 1.91 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.6, 165.8, 162.1 (d, *J* = 245.8 Hz), 137.2 (d, *J* = 3.3 Hz), 136.7, 128.9, 128.4 (d, *J* = 8.0 Hz), 128.4, 127.8, 115.9 (d, *J* = 21.4 Hz), 56.8, 52.5, 50.5, 46.3, 41.9, 29.5 (d, *J* = 0.9 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3207, 2952, 1738, 1666, 1605, 1511, 1491, 1464, 1457, 1435, 1424, 1342, 1304, 1267, 1223, 1210, 1195, 1161, 1121, 1032, 834, 782, 731.

MS (EI, 70 eV): *m/z* (%) = 341 (23), 283 (26), 282 (36), 149 (46), 132 (46), 118 (44), 91 (100).

HRMS (EI): *m/z* calc. for [$C_{20}H_{20}O_3NF$]: 341.1427; found 341.1420.

m.p.: 158.8-160.5.

4.3 Single Crystal X-ray Diffraction Studies

Single crystals of compound 123aa, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation ($\lambda = 0.71071$ Å).

Data collection and data reduction were performed with the CrysAlisPro software. Absorption correction using the multiscan method was applied. The structures were solved with SHELXS-97, refined with SHELXL-97 and finally checked using PLATON. Details for data collection and structure refinement are summarized in the corresponding tables.

CCDC-2057614 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 29: Details for X-ray data collection and structure refinement for compound **123aa**.

	123aa
Empirical formula	$C_{17}H_{23}NO_2Si$
Formula mass	301.45
T[K]	123(2)
Crystal size [mm]	0.45 × 0.41 × 0.29
Crystal description	colourless block
Crystal system	orthorhombic
Space group	*Pna*21
a [Å]	30.9518(6)

b [Å]	6.9485(2)
c [Å]	15.9226(3)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	3424.45(14)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.169
μ [mm^{-1}]	0.141
F(000)	1296
Θ range [°]	2.56 – 25.24
Index ranges	$-43 \leq h \leq 44$
	$-9 \leq k \leq 9$
	$-22 \leq l \leq 22$
Reflns. collected	65322
Reflns. obsd.	8971
Reflns. unique	10423
	(R_{int} = 0.0437)
R_1, wR_2 (2σ data)	0.0406, 0.0934
R_1, wR_2 (all data)	0.0513, 0.0995
GOOF on F^2	1.024
Peak/hole [e Å^{-3}]	0.341 / -0.164

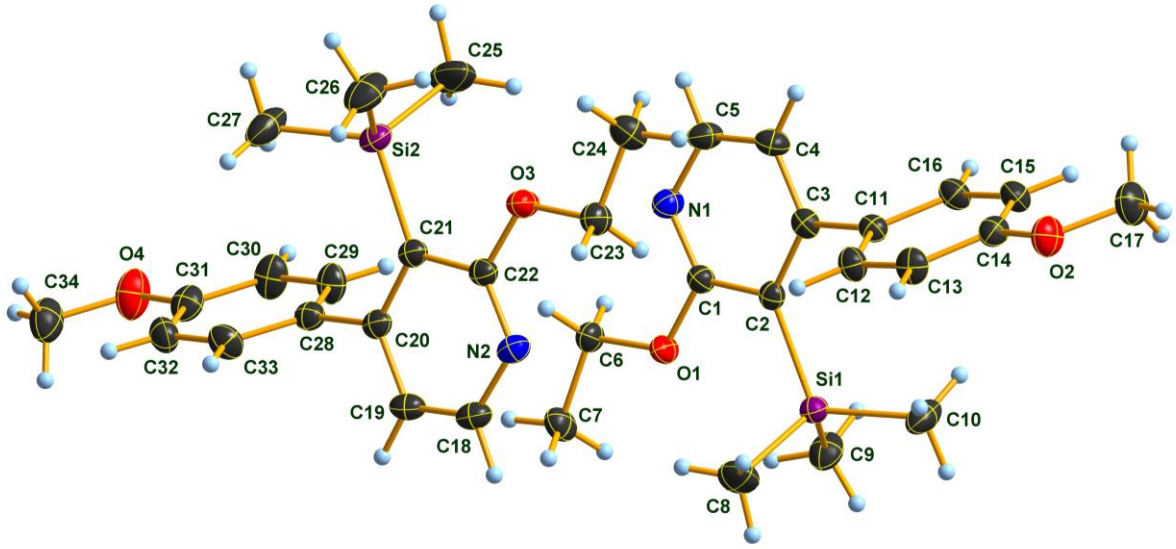


Figure 5: Molecular structure of compound **123aa** in the crystal. DIAMOND[183] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 30: Selected bond lengths (Å) of compound **123aa**.

Si1 – C8	1.865(3)	C32 – C31	1.381(4)
Si1 – C9	1.866(3)	C32 – C33	1.391(4)
Si1 – C10	1.872(3)	C31 – C30	1.396(4)
Si1 – C2	1.903(3)	C28 – C33	1.388(3)
Si2 – C25	1.854(3)	C24 – C23	1.507(3)
Si2 – C26	1.872(3)	O3 – C23	1.443(3)
Si2 – C27	1.872(3)	C22 – C21	1.422(3)
Si2 – C21	1.895(3)	O2 – C17	1.422(3)
O1 – C1	1.353(3)	C2 – C3	1.397(3)
O1 – C6	1.442(3)	C2 – C1	1.420(3)
N1 – C1	1.322(3)	C29 – C30	1.375(4)

[183] DIAMOND, Crystal Impact GbR., Version 3.2i.

N1 – C5	1.340(3)	C29 – C28	1.392(3)
N2 – C22	1.323(3)	C4 – C5	1.378(3)
N2 – C18	1.347(3)	C4 – C3	1.401(4)
C14 – O2	1.364(3)	C3 – C11	1.491(3)
C14 – C15	1.390(4)	C19 – C18	1.370(3)
C14 – C13	1.395(3)	O4 – C31	1.370(3)
C20 – C21	1.397(3)	O4 – C34	1.417(4)
C20 – C19	1.407(4)	C16 – C15	1.390(3)
C20 – C28	1.488(3)	C16 – C11	1.391(3)
C12 – C13	1.384(3)	C7 – C6	1.501(3)
C12 – C11	1.397(3)	O3 – C22	1.351(3)

Table 31: Selected bond angles (°) of compound **123aa**.

C8 – Si1 – C9	111.2(1)	C12 – C13 – C14	120.1(2)
C8 – Si1 – C10	109.0(1)	O1 – C6 – C7	106.7(2)
C9 – Si1 – C10	105.4(1)	C28 – C33 – C32	121.4(2)
C8 – Si1 – C2	109.3(1)	C29 – C30 – C31	119.9(2)
C9 – Si1 – C2	109.1(1)	O3 – C23 – C24	106.5(2)
C10 – Si1 – C2	112.7(1)	N1 – C5 – C4	123.5(2)
C25 – Si2 – C26	111.9(2)	C5 – C4 – C3	119.1(2)
C25 – Si2 – C27	108.7(2)	C2 – C3 – C4	119.5(2)
C26 – Si2 – C27	105.0(1)	C2 – C3 – C11	123.0(2)
C25 – Si2 – C21	108.7(1)	C4 – C3 – C11	117.3(2)

C26 – Si2 – C21	109.7(1)	C18 – C19 – C20	119.3(2)
C27 – Si2 – C21	113.0(1)	N1 – C1 – O1	118.3(2)
C1 – O1 – C6	117.8(2)	N1 – C1 – C2	126.5(2)
C1 – N1 – C5	116.3(2)	O1 – C1 – C2	115.3(2)
C22 – N2 – C18	116.3(2)	C31 – O4 – C34	117.2(2)
O2 – C14 – C15	125.0(2)	C15 – C16 – C11	121.0(2)
O2 – C14 – C13	115.2(2)	C16 – C15 – C14	119.7(2)
C15 – C14 – C13	119.7(2)	N2 – C18 – C19	123.4(2)
C21 – C20 – C19	119.7(2)	C31 – C32 – C33	119.4(2)
C21 – C20 – C28	122.4(2)	C16 – C11 – C12	118.7(2)
C19 – C20 – C28	117.9(2)	C16 – C11 – C3	122.1(2)
C13 – C12 – C11	120.7(2)	C12 – C11 – C3	119.1(2)
C22 – O3 – C23	117.9(2)	O4 – C31 – C32	125.0(2)
N2 – C22 – O3	118.2(2)	O4 – C31 – C30	115.1(2)
N2 – C22 – C21	126.6(2)	C32 – C31 – C30	119.9(2)
O3 – C22 – C21	115.3(2)	C33 – C28 – C29	118.2(2)
C14 – O2 – C17	117.6(2)	C33 – C28 – C20	122.2(2)
C3 – C2 – C1	114.9(2)	C29 – C28 – C20	119.6(2)
C3 – C2 – Si1	127.6(2)	C20 – C21 – C22	114.6(2)
C1 – C2 – Si1	117.4(2)	C20 – C21 – Si2	127.4(2)
C30 – C29 – C28	121.2(2)	C22 – C21 – Si2	118.0(2)

Table 32: Selected torsion angles (°) of compound **123aa**.

C18 – N2 – C22 – O3	-178.3(2)	C11 – C16 – C15 – C14	-1.3(4)
C18 – N2 – C22 – C21	1.0(3)	O2 – C14 – C15 – C16	-179.6(2)
C23 – O3 – C22 – N2	0.9(3)	C13 – C14 – C15 – C16	1.5(4)
C23 – O3 – C22 – C21	-178.5(2)	C22 – N2 – C18 – C19	1.8(3)
C15 – C14 – O2 – C17	-0.2(4)	C20 – C19 – C18 – N2	-1.5(4)
C13 – C14 – O2 – C17	178.8(2)	C15 – C16 – C11 – C12	0.6(3)
C19 – C20 – C21 – C22	4.0(3)	C15 – C16 – C11 – C3	177.2(2)
C28 – C20 – C21 – C22	-172.6(2)	C13 – C12 – C11 – C16	-0.1(3)
C19 – C20 – C21 – Si2	-173.5(2)	C13 – C12 – C11 – C3	-176.8(2)
C28 – C20 – C21 – Si2	9.9(3)	C2 – C3 – C11 – C16	115.5(2)
N2 – C22 – C21 – C20	-3.9(3)	C4 – C3 – C11 – C16	-68.2(3)
O3 – C22 – C21 – C20	175.4(2)	C2 – C3 – C11 – C12	-68.0(3)
N2 – C22 – C21 – Si2	173.8(2)	C4 – C3 – C11 – C12	108.4(2)
O3 – C22 – C21 – Si2	-6.9(3)	C34 – O4 – C31 – C32	-0.6(4)
C25 – Si2 – C21 – C20	-106.9(2)	C34 – O4 – C31 – C30	-179.9(3)
C26 – Si2 – C21 – C20	130.6(2)	C33 – C32 – C31 – O4	179.1(2)
C27 – Si2 – C21 – C20	13.8(2)	C33 – C32 – C31 – C30	-1.6(4)
C25 – Si2 – C21 – C22	75.7(2)	C30 – C29 – C28 – C33	0.3(4)
C26 – Si2 – C21 – C22	-46.8(2)	C30 – C29 – C28 – C20	178.6(2)
C27 – Si2 – C21 – C22	-163.6(2)	C21 – C20 – C28 – C33	-111.0(3)
C1 – C2 – C3 – C4	-3.9(3)	C19 – C20 – C28 – C33	72.3(3)
Si1 – C2 – C3 – C4	171.9(2)	C21 – C20 – C28 – C29	70.8(3)

C1 – C2 – C3 – C11	172.3(2)	C19 – C20 – C28 – C29	-105.9(3)
Si1 – C2 – C3 – C11	-11.8(3)	C11 – C12 – C13 – C14	0.3(4)
C5 – C4 – C3 – C2	2.1(3)	O2 – C14 – C13 – C12	180.0(2)
C5 – C4 – C3 – C11	-174.4(2)	C15 – C14 – C13 – C12	-1.0(4)
C21 – C20 – C19 – C18	-1.7(3)	C1 – O1 – C6 – C7	-177.9(2)
C28 – C20 – C19 – C18	175.1(2)	C29 – C28 – C33 – C32	-0.8(4)
C5 – N1 – C1 – O1	178.4(2)	C20 – C28 – C33 – C32	-179.1(2)
C5 – N1 – C1 – C2	-0.7(3)	C31 – C32 – C33 – C28	1.5(4)
C6 – O1 – C1 – N1	-1.0(3)	C28 – C29 – C30 – C31	-0.5(4)
C6 – O1 – C1 – C2	178.1(2)	O4 – C31 – C30 – C29	-179.5(2)
C3 – C2 – C1 – N1	3.4(3)	C32 – C31 – C30 – C29	1.1(4)
Si1 – C2 – C1 – N1	-172.9(2)	C22 – O3 – C23 – C24	178.0(2)
C3 – C2 – C1 – O1	-175.7(2)	C1 – N1 – C5 – C4	-1.6(4)
Si1 – C2 – C1 – O1	8.0(3)	C3 – C4 – C5 – N1	0.9(4)

Single crystals of compound 134a, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation ($\lambda = 0.71071$ Å).

Data collection and data reduction were performed with the CrysAlisPro software. Absorption correction using the multiscan method was applied. The structures were solved with SHELXS-97, refined with SHELXL-97 and finally checked using PLATON. Details for data collection and structure refinement are summarized in Table 33.

CCDC-2057612 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 33: Details for X-ray data collection and structure refinement for compound **134a**.

	134a
Empirical formula	$C_{15}H_{17}NOS$
Formula mass	259.35
T[K]	123(2)
Crystal size [mm]	0.40 × 0.20 × 0.02
Crystal description	colourless platelet
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	8.8398(4)
b [Å]	22.2474(13)

c [Å]	7.0250(5)
α [°]	90.0
β [°]	105.163(6)
γ [°]	90.0
V [Å^3]	1333.46(14)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.292
μ [mm^{-1}]	0.230
F(000)	552
Θ range [°]	2.39 – 25.24
Index ranges	$-11 \leq h \leq 11$
	$-29 \leq k \leq 29$
	$-9 \leq l \leq 9$
Reflns. collected	23262
Reflns. obsd.	2627
Reflns. unique	3298
	(R_{int} = 0.0710)
R_1, wR_2 (2σ data)	0.0513, 0.1161
R_1, wR_2 (all data)	0.0685, 0.1248
GOOF on F^2	1.061
Peak/hole [e Å^{-3}]	0.389 / -0.299

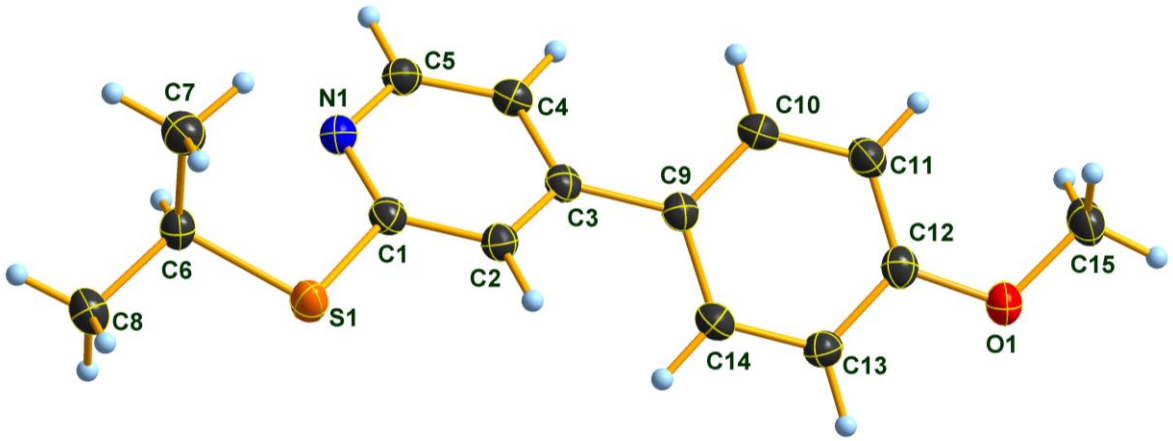


Figure 6: Molecular structure of compound **134a** in the crystal. DIAMOND[79] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 34: Selected bond lengths (Å) of compound **134a**.

S1 – C1	1.771(2)	C14 – C13	1.384(3)
S1 – C6	1.827(2)	C13 – C12	1.398(3)
C5 – N1	1.347(2)	C2 – C1	1.402(3)
C5 – C4	1.383(3)	C12 – O1	1.369(2)
N1 – C1	1.337(2)	C15 – O1	1.430(2)
C6 – C7	1.522(3)	C3 – C2	1.394(3)
C6 – C8	1.525(3)	C3 – C4	1.397(3)
C9 – C10	1.396(2)	C11 – C10	1.385(3)
C9 – C14	1.403(3)	C11 – C12	1.393(3)
C9 – C3	1.485(3)		

Table 35: Selected bond angles (°) of compound **134a**.

C1 – S1 – C6	102.6(1)	C3 – C2 – C1	119.1(2)
N1 – C5 – C4	124.3(2)	O1 – C12 – C11	125.0(2)
C1 – N1 – C5	116.5(2)	O1 – C12 – C13	115.3(2)
C7 – C6 – C8	112.7(2)	C11 – C12 – C13	119.8(2)
C7 – C6 – S1	111.3(1)	N1 – C1 – C2	123.5(2)
C8 – C6 – S1	107.9(1)	N1 – C1 – S1	119.5(1)
C10 – C9 – C14	117.9(2)	C2 – C1 – S1	117.0(1)
C10 – C9 – C3	121.4(2)	C12 – O1 – C15	117.0(2)
C14 – C9 – C3	120.7(2)	C5 – C4 – C3	119.0(2)
C2 – C3 – C4	117.5(2)	C11 – C10 – C9	121.6(2)
C2 – C3 – C9	121.4(2)	C13 – C14 – C9	121.2(2)
C4 – C3 – C9	121.1(2)	C14 – C13 – C12	119.9(2)
C10 – C11 – C12	119.6(2)		

Table 36: Selected torsion angles (°) of compound **134a**.

C4 – C5 – N1 – C1	1.0(3)	C9 – C14 – C13 – C12	0.8(3)
C1 – S1 – C6 – C7	-79.4(2)	C4 – C3 – C2 – C1	2.6(3)
C1 – S1 – C6 – C8	156.5(1)	C9 – C3 – C2 – C1	-176.3(2)
C10 – C9 – C3 – C2	-146.1(2)	C10 – C11 – C12 – O1	178.2(2)
C14 – C9 – C3 – C2	35.2(3)	C10 – C11 – C12 – C13	-1.5(3)
C10 – C9 – C3 – C4	35.0(3)	C14 – C13 – C12 – O1	-179.2(2)

C14 – C9 – C3 – C4	-143.7(2)	C14 – C13 – C12 – C11	0.5(3)
N1 – C5 – C4 – C3	-0.5(3)	C5 – N1 – C1 – C2	0.4(3)
C2 – C3 – C4 – C5	-1.4(3)	C5 – N1 – C1 – S1	-176.5(1)
C9 – C3 – C4 – C5	177.6(2)	C3 – C2 – C1 – N1	-2.2(3)
C12 – C11 – C10 – C9	1.2(3)	C3 – C2 – C1 – S1	174.8(1)
C14 – C9 – C10 – C11	0.1(3)	C6 – S1 – C1 – N1	-10.6(2)
C3 – C9 – C10 – C11	-178.7(2)	C6 – S1 – C1 – C2	172.3(1)
C10 – C9 – C14 – C13	-1.1(3)	C11 – C12 – O1 – C15	2.7(3)
C3 – C9 – C14 – C13	177.7(2)	C13 – C12 – O1 – C15	-177.6(2)

Single crystals of compound **134aa**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation ($\lambda = 0.71071$ Å).

Data collection and data reduction were performed with the CrysAlisPro software. Absorption correction using the multiscan method was applied. The structures were solved with SHELXS-97, refined with SHELXL-97 and finally checked using PLATON. Details for data collection and structure refinement are summarized in Table 37.

CCDC-2057613 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 37: Details for X-ray data collection and structure refinement for compound **134aa**.

	134aa
Empirical formula	$C_{15}H_{16}INOS$
Formula mass	385.25
T[K]	123(2)
Crystal size [mm]	0.20 × 0.05 × 0.03
Crystal description	colourless rod
Crystal system	monoclinic
Space group	*P*21
a [Å]	8.5870(3)

b [Å]	6.1553(2)
c [Å]	14.6215(5)
α [°]	90.0
β [°]	99.114(3)
γ [°]	90.0
V [Å^3]	763.07(5)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.677
μ [mm^{-1}]	2.227
F(000)	380
Θ range [°]	2.40 – 25.24
Index ranges	$-12 \leq h \leq 12$
	$-8 \leq k \leq 8$
	$-20 \leq l \leq 20$
Reflns. collected	14968
Reflns. obsd.	4430
Reflns. unique	4640
	(R_{int} = 0.0254)
R_1, wR_2 (2σ data)	0.0206, 0.0430
R_1, wR_2 (all data)	0.0225, 0.0439
GOOF on F^2	1.029
Peak/hole [e Å^{-3}]	0.819 / -0.251

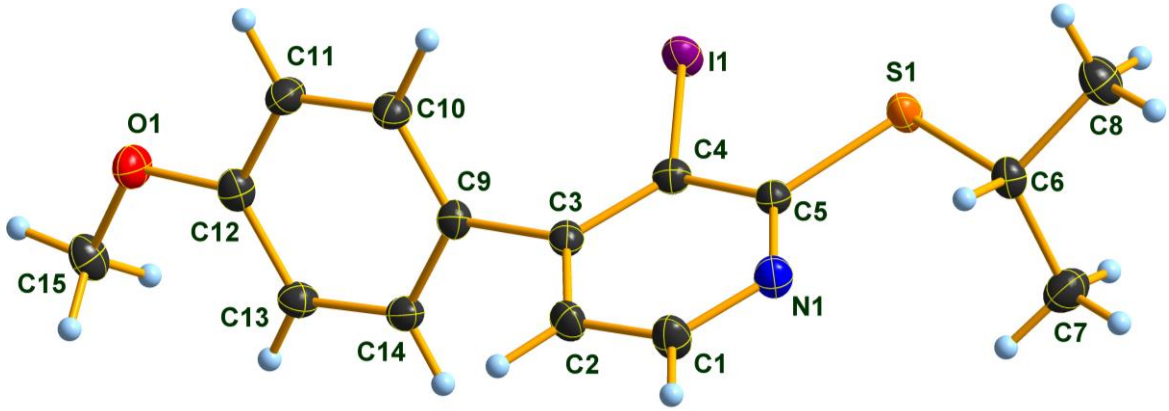


Figure 7: Molecular structure of compound **134aa** in the crystal. DIAMOND[79] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 38: Selected bond lengths (Å) of compound **134aa**.

I1 – C4	2.107(3)	C12 – C11	1.401(4)
S1 – C5	1.769(3)	N1 – C5	1.336(4)
S1 – C6	1.830(3)	N1 – C1	1.344(4)
C7 – C6	1.520(4)	O1 – C15	1.437(3)
C9 – C14	1.393(4)	C4 – C5	1.409(4)
C9 – C10	1.400(4)	C10 – C11	1.380(4)
C9 – C3	1.486(4)	C6 – C8	1.526(4)
C13 – C14	1.391(4)	C3 – C2	1.401(4)
C13 – C12	1.409(6)	C2 – C1	1.382(5)
C3 – C4	1.395(4)	C12 – O1	1.354(5)

Table 39: Selected bond angles (°) of compound **134aa**.

C5 – S1 – C6	102.3(1)	C11 – C10 – C9	120.6(3)
C14 – C9 – C10	118.7(3)	C7 – C6 – C8	112.5(3)
C14 – C9 – C3	120.1(3)	C7 – C6 – S1	110.6(2)
C10 – C9 – C3	121.1(3)	C8 – C6 – S1	107.4(2)
C14 – C13 – C12	119.6(3)	N1 – C5 – C4	122.0(3)
C4 – C3 – C2	116.9(3)	N1 – C5 – S1	118.6(2)
C4 – C3 – C9	123.8(3)	C4 – C5 – S1	119.3(2)
C2 – C3 – C9	119.3(3)	N1 – C1 – C2	123.8(3)
C1 – C2 – C3	119.4(3)	C10 – C11 – C12	120.9(3)
O1 – C12 – C11	116.8(4)	C13 – C14 – C9	121.4(3)
O1 – C12 – C13	124.5(3)	C3 – C4 – C5	120.1(3)
C11 – C12 – C13	118.8(3)	C3 – C4 – I1	120.2(2)
C5 – N1 – C1	117.8(3)	C5 – C4 – I1	119.6(2)
C12 – O1 – C15	116.9(3)		

Table 40: Selected torsion angles (°) of compound **134aa**.

C14 – C9 – C3 – C4	117.4(3)	C14 – C9 – C10 – C11	-0.6(5)
C10 – C9 – C3 – C4	-66.2(4)	C3 – C9 – C10 – C11	-177.1(3)
C14 – C9 – C3 – C2	-63.8(4)	C5 – S1 – C6 – C7	83.5(2)
C10 – C9 – C3 – C2	112.7(4)	C5 – S1 – C6 – C8	-153.3(2)
C4 – C3 – C2 – C1	-0.3(6)	C1 – N1 – C5 – C4	-0.3(4)

C9 – C3 – C2 – C1	-179.2(4)	C1 – N1 – C5 – S1	177.7(2)
C14 – C13 – C12 – O1	179.5(3)	C3 – C4 – C5 – N1	0.8(4)
C14 – C13 – C12 – C11	1.0(5)	I1 – C4 – C5 – N1	-176.5(2)
C11 – C12 – O1 – C15	172.7(3)	C3 – C4 – C5 – S1	-177.2(2)
C13 – C12 – O1 – C15	-5.8(4)	I1 – C4 – C5 – S1	5.5(3)
C12 – C13 – C14 – C9	-1.6(5)	C6 – S1 – C5 – N1	4.6(3)
C10 – C9 – C14 – C13	1.4(4)	C6 – S1 – C5 – C4	-177.4(2)
C3 – C9 – C14 – C13	177.9(3)	C5 – N1 – C1 – C2	-0.5(5)
C2 – C3 – C4 – C5	-0.4(4)	C3 – C2 – C1 – N1	0.8(7)
C9 – C3 – C4 – C5	178.4(2)	C9 – C10 – C11 – C12	0.1(5)
C2 – C3 – C4 – I1	176.8(3)	O1 – C12 – C11 – C10	-178.8(3)
C9 – C3 – C4 – I1	-4.3(3)	C13 – C12 – C11 – C10	-0.3(5)

5. Regioselective Amination of 2,3- and 3,5-Difunctionalized Pyridines using KHMDS via Pyridyne Intermediates

5.1 Typical Procedures

Typical Procedure 11: Amination of 2,3- and 3,5-disubstituted pyridines using KHMDS.

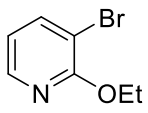
The pyridine starting material was dissolved in THF (2 mL/mmol pyridine derivative) and the amine (1.2 equiv) was added while stirring. A KHMDS (2.2 equiv) solution in THF (1.0 M) was added dropwise at room temperature. After completion (checked *via* GC-analysis of a reaction aliquot), the reaction mixture was quenched with *sat. aq.* NH_4Cl solution, extracted with ethyl acetate and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The product was purified by flash column chromatography using appropriate solvent mixtures.

Typical Procedure 12: Alkoxylation of 3-bromo-2-diethylaminopyridine using *t*-BuOK·18-crown-6.

18-Crown-6 (1.5 equiv) and the respective alcohol (3.0 equiv) were dissolved in THF (1 mL/mmol of alcohol). A *t*-BuOK solution in THF (1.5 equiv, 1.0 M) was added dropwise. After stirring for 15 min, the mixture was added dropwise to a solution of the pyridine derivative in THF (1.0 equiv, 2 mL/mmol pyridine derivative) in a sealed tube. The reaction was stirred at 80 °C until completion. The mixture was cooled to room temperature, quenched with *sat. aq.* NH_4Cl solution, extracted with ethyl acetate and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The product was purified by flash column chromatography using appropriate solvent mixtures.

5.2 Preparation of Compounds

3-Bromo-2-ethoxypyridine (139)

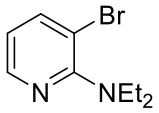


Sodium (2.40 g, 105 mmol) was slowly dissolved in dry EtOH (100 mL) while stirring. Then, 2,3-dibromopyridine (7.11 g, 30.0 mmol) was added and the reaction mixture was refluxed for 12 h. After quenching with *sat. aq.* NH_4Cl, extraction with EtOAc and drying over sodium

sulfate, the crude product was purified by flash chromatography (*n*-pentane:ethyl acetate = 9:1) to give **139** (5.15 g, 25.5 mmol, 85%) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.79 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.74 (dd, *J* = 7.6, 4.9 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.9, 145.6, 141.7, 117.6, 107.3, 63.0, 14.7.
IR (Diamond-ATR, neat): 2978, 1581, 1471, 1444, 1429, 1381, 1351 1314, 1297, 1251, 1243, 1068, 1035, 1019, 928, 781, 750, 690.
MS (EI, 70 eV): m/z (%) = 188 (98), 186 (100), 175 (34), 153 (35), 159 (19), 157 (19), 147 (57), 145 (59), 78 (37).
HRMS (EI) m/z for C_6H_5BrNO (185.9555): 185.9548 [M-CH_3].
The starting materials **142**, **146b** and **146c** were prepared according to this procedure.

3-Bromo-*N*,*N*-diethylpyridin-2-amine (148)



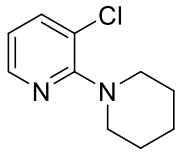
2-Amino-3-bromopyridine (3.29 g, 19.0 mmol) was dissolved in DMF (50 mL). NaH (60% suspension in mineral oil, 3.81 g, 95.0 mmol, 5.0 equiv) was added at 0 °C and the reaction mixture was stirred for 15 min. EtI (7.64 mL, 95.0 mmol, 5.0 equiv) was added slowly at 0 °C and the reaction mixture was then heated to 120 °C while stirring, using a reflux condenser. After 18 h, the solution was cooled to room temperature and then quenched with water (80 mL). The reaction mixture was extracted with EtOAc, washed with water and brine and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. Flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 99.75:0.25:1) of the crude product gave **148** (3.72 g, 16.2 mmol, 85%) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 8.19 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.75 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.67 (dd, *J* = 7.7, 4.7 Hz, 1H), 3.37 (q, *J* = 7.0 Hz, 4H), 1.14 (t, *J* = 7.0 Hz, 6H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 159.4, 146.1, 141.9, 116.8, 111.1, 45.0, 13.3.
IR (Diamond-ATR, neat): 2968, 2930, 2868, 1574, 1539, 1475, 1458, 1427, 1376, 1356, 1332, 1300, 1264, 1244, 1172, 1158, 1111, 1069, 1029, 1009, 780, 745.
MS (EI, 70 eV): m/z (%) = 215 (48), 213 (50), 201 (97), 199 (100), 187 (53), 187 (72), 185 (56), 185 (72), 119 (55).

HRMS (EI) m/z for $C_9H_{13}N_2Br$ (228.0262): 228.0254.

The starting materials **146a** and **146d** were prepared according to this procedure.

3-Chloro-2-(piperidin-1-yl)pyridine (144)



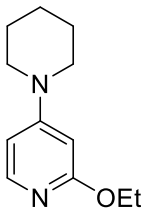
2,3-Dichloropyridine (2.96 g, 20 mmol), piperidine (6.00 mL, 60 mmol, 3.0 equiv) and toluene (20 mL) were mixed. Then, the reaction mixture was refluxed at 120 °C for 16 h in a sealed tube. After cooling, the mixture was quenched with water, extracted with DCM and dried over Na_2SO_4. After filtration, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 8:2) to give **144** (2.99 g, 15.2 mmol, 76%) as a yellow liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 8.16 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.78 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.34 – 3.19 (m, 4H), 1.80 – 1.65 (m, 4H), 1.61 (td, *J* = 7.0, 3.6 Hz, 2H).

^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 159.5, 145.7, 138.7, 123.0, 117.4, 50.5 (2C), 26.0 (2C), 24.5.

The spectra match those in the literature.[184]

2-Ethoxy-4-(piperidin-1-yl)pyridine (141a)



Pyridine **141a** was prepared *via* **TP11** using 3-bromo-2-ethoxypyridine (**139**, 202 mg, 1.00 mmol), piperidine (0.12 mL, 1.20 mmol) and KHMDS (2.20 mL, 2.20 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 9:1) to give **141a** (186 mg, 0.90 mmol, 90%) as a yellow oil.

[184] Koley, M.; Wimmer, L.; Schnürch, M.; Mihovilovic, M. D. *Eur. J. Org. Chem.* **2011**, *10*, 1972-1979.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.83 (d, *J* = 6.2 Hz, 1H), 6.36 (dd, *J* = 6.2, 2.3 Hz, 1H), 6.03 (d, *J* = 2.3 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.28 (dd, *J* = 5.8, 3.2 Hz, 4H), 1.61 (dq, *J* = 5.4, 3.3, 2.4 Hz, 6H), 1.36 (t, *J* = 7.1 Hz, 3H).

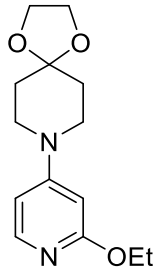
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 165.8, 157.7, 147.1, 104.3, 93.0, 61.4, 47.7, 25.2, 24.5, 15.0.

IR (Diamond-ATR, neat): 2933, 1602, 1539, 1498, 1490, 1456, 1451, 1436, 1382, 1312, 1287, 1223, 1200, 1125, 1054, 987.

MS (EI, 70 eV): m/z (%) = 192 (12), 191 (100), 178 (31), 177 (20), 163 (15).

HRMS (EI) m/z for $C_{12}H_{17}N_2O^+$ (205.1335): 205.1333 $[M-H]^+$.

8-(2-Ethoxypyridin-4-yl)-1,4-dioxa-8-azaspiro[4.5]decane (141b)



Pyridine **141b** was prepared *via* **TP11** using 3-bromo-2-ethoxypyridine (**139**, 101 mg, 0.50 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (87.0 mg, 0.60 mmol,) and KHMDS (1.10 mL, 1.10 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 7:3) to give **141b** (93.0 mg, 0.35 mmol, 70%) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.84 (d, *J* = 6.1 Hz, 1H), 6.37 (dd, *J* = 6.2, 2.4 Hz, 1H), 6.04 (d, *J* = 2.3 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 4H), 3.47 – 3.37 (m, 4H), 1.79 – 1.69 (m, 4H), 1.35 (t, *J* = 7.1 Hz, 3H).

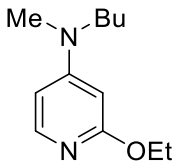
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 165.8, 156.8, 147.3, 107.2, 104.3, 93.4, 64.5 (2C), 61.5, 44.9 (2C), 34.1 (2C), 14.9.

IR (Diamond-ATR, neat): 2975, 2935, 2885, 1599, 1539, 1495, 1489, 1464, 1436, 1382, 1363, 1313, 1289, 1187, 1142, 1093, 1050, 1035, 983, 959, 945, 921, 821, 796, 733.

MS (EI, 70 eV): m/z (%) = 250 (13), 249 (100), 236 (37), 220 (13), 177 (13), 150 (17), 149 (17), 135 (28), 121 (10).

HRMS (EI) m/z for $C_{14}H_{20}N_2O_3$ (264.1474): 264.1472.

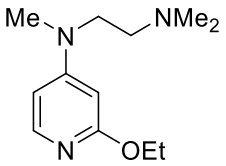
***N*-Butyl-2-ethoxy-*N*-methylpyridin-4-amine (141c)**



Pyridine **141c** was prepared *via* **TP11** using 3-bromo-2-ethoxypyridine (**139**, 101 mg, 0.50 mmol), *N*-methylbutan-1-amine (52.0 mg, 0.60 mmol) and KHMDS (1.10 mL, 1.10 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 9:1) to give **141c** (90.0 mg, 0.43 mmol, 85%) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.85 – 7.63 (m, 1H), 6.14 (dd, *J* = 6.2, 2.4 Hz, 1H), 5.79 (d, *J* = 2.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.29 – 3.18 (m, 2H), 2.86 (s, 3H), 1.53 – 1.44 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.29 – 1.23 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 165.5, 156.0, 146.7, 102.4, 90.7, 61.3, 51.6, 37.7, 29.0, 20.2, 14.9, 14.0.
IR (Diamond-ATR, neat): 2957, 2926, 1606, 1558, 1539, 1516, 1506, 1456, 1440, 1436, 1253, 1193, 1054.
MS (EI, 70 eV): m/z (%) = 193 (52), 180 (25), 166 (10), 165 (100), 138 (12), 137 (69), 122 (11), 94 (17).
HRMS (EI) m/z for $C_{12}H_{20}N_2O$ (208.1576): 208.1568.

***N*^{1}-(2-Ethoxypyridin-4-yl)-*N*^{1},*N*^{2},*N*^{2}-trimethylethane-1,2-diamine (141d)**



Pyridine **141d** was prepared *via* **TP11** using 3-bromo-2-ethoxypyridine (**139**, 202 mg, 1.00 mmol), *N*^{1},*N*^{1},*N*^{2}-trimethylethane-1,2-diamine (0.16 mL, 1.20 mmol) and KHMDS (2.20 mL, 2.20 mmol). After workup, the crude product was purified *via* flash chromatography (DCM:methanol = 9:1) to give **141d** (160 mg, 0.72 mmol, 72%) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.78 (d, *J* = 6.1 Hz, 1H), 6.19 (dd, *J* = 6.2, 2.4 Hz, 1H), 5.83 (d, *J* = 2.3 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.45 – 3.34 (m, 2H), 2.92 (s, 3H), 2.48 – 2.34 (m, 2H), 2.25 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H).

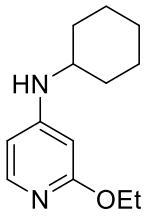
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 165.6, 156.0, 147.0, 102.4, 90.9, 61.3, 56.0, 50.1, 45.9 (2C), 38.0, 14.9.

IR (Diamond-ATR, neat): 3387, 2976, 2939, 2821, 2778, 1603, 1539, 1507, 1471, 1464, 1456, 1440, 1382, 1319, 1283, 1247, 1226, 1174, 1164, 1114, 1104, 1094, 1049, 1000, 814.

MS (EI, 70 eV): m/z (%) = 165 (51), 153 (34), 149 (11), 137 (45), 122 (10), 94 (23), 58 (100).

HRMS (EI) m/z for $C_{12}H_{21}N_3O$ (223.1685): 223.1679.

N-Cyclohexyl-2-ethoxypyridin-4-amine (141e)



Pyridine **8e** was prepared *via* **TP11** using 3-bromo-2-ethoxypyridine (**139**, 202 mg, 1.00 mmol), cyclohexylamine (0.17 mL, 1.20 mmol) and KHMDS (2.20 mL, 2.20 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 9:1) to give **141e** (141 mg, 0.64 mmol, 64%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.73 (d, *J* = 5.9 Hz, 1H), 6.07 (dd, *J* = 5.9, 2.1 Hz, 1H), 5.81 (d, *J* = 2.1 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.99 (d, *J* = 7.8 Hz, 1H), 3.24 (ddt, *J* = 10.4, 6.6, 3.8 Hz, 1H), 2.01 (dt, *J* = 13.1, 3.8 Hz, 2H), 1.79 – 1.70 (m, 2H), 1.69 – 1.59 (m, 1H), 1.41 – 1.29 (m, 5H), 1.26 – 1.08 (m, 3H).

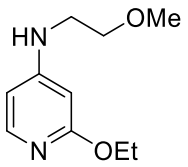
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 165.6, 154.9, 146.8, 104.7, 91.0, 61.4, 51.0, 33.1, 25.8, 25.0, 15.0.

IR (Diamond-ATR, neat): 3262, 2977, 2927, 2852, 1606, 1575, 1569, 1512, 1472, 1436, 1381, 1363, 1344, 1274, 1237, 1198, 1182, 1097, 1049, 983, 819.

MS (EI, 70 eV): m/z (%) = 206 (13), 205 (100), 192 (28), 177 (15), 149 (45), 131 (15), 123 (48), 111 (29).

HRMS (EI) m/z for $C_{13}H_{19}N_2O^+$ (219.1492): 219.1492 $[M-H]^+$.

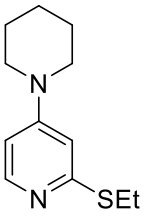
2-Ethoxy-*N*-(2-methoxyethyl)pyridin-4-amine (8f)



Pyridine **141f** was prepared *via* **TP11** using 3-bromo-2-ethoxypyridine (**139**, 202 mg, 1.00 mmol), 2-methoxyethan-1-amine (0.11 mL, 1.20 mmol) and KHMDS (2.20 mL, 2.20 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 9:1) to give **141f** (109 mg, 0.56 mmol, 56%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.79 (d, *J* = 5.8 Hz, 1H), 6.16 (dd, *J* = 5.9, 2.1 Hz, 1H), 5.86 (d, *J* = 2.1 Hz, 1H), 4.46 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.60 (dd, *J* = 5.7, 4.8 Hz, 2H), 3.41 (s, 3H), 3.31 (q, *J* = 5.3 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 165.5, 155.8, 146.9, 104.7, 91.2, 70.6, 61.5, 59.0, 42.4, 15.0.
IR (Diamond-ATR, neat): 3345, 2978, 2928, 2888, 1606, 1575, 1569, 1520, 1517, 1471, 1464, 1456, 1447, 1436, 1382, 1343, 1192, 1119, 1097, 1050, 983, 818.
MS (EI, 70 eV): m/z (%) = 181 (100), 168 (32), 151 (89), 138 (11), 123 (73), 122 (17), 110 (16), 94 (34).
HRMS (EI) m/z for $C_{10}H_{17}N_2O_2^+$ (197.1285): 197.1275 [$M+H^+$].

2-(Ethylthio)-4-(piperidin-1-yl)pyridine (141g)



Pyridine **141g** was prepared *via* **TP11** using 3-chloro-2-(ethylthio)pyridine (**142**, 218 mg, 1.00 mmol), piperidine (0.12 mL, 1.20 mmol) and KHMDS (2.20 mL, 2.20 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane: ethyl acetate = 7:3) to give **141g** (158 mg, 0.72 mmol, 72%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 8.04 (dd, *J* = 6.1, 0.5 Hz, 1H), 6.51 (d, *J* = 2.5 Hz, 1H), 6.37 (dd, *J* = 6.1, 2.5 Hz, 1H), 3.28 – 3.21 (m, 4H), 3.10 (q, *J* = 7.4 Hz, 2H), 1.61 – 1.54 (m, 6H), 1.31 (t, *J* = 7.4 Hz, 3H).

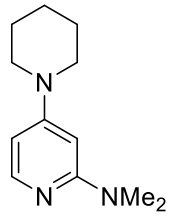
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 159.3, 154.9, 149.5, 105.7, 105.7, 47.3 (2C), 25.1 (2C), 24.5, 24.3, 14.9.

IR (Diamond-ATR, neat): 2930, 2854, 1583, 1525, 1487, 1249, 1097, 982, 946.

MS (EI, 70 eV): m/z (%) = 222 (34), 221 (12), 297 (35), 194 (16), 193 (16), 190 (13), 189 (100), 162 (19).

HRMS (EI) m/z for $C_{12}H_{18}N_2S$ (222.1191): 222.1185.

N,*N*-Diethyl-4-(piperidin-1-yl)pyridin-2-amine (141h)



Pyridine **141g** was prepared *via* **TP11** using 3-bromo-*N*,*N*-diethylpyridin-2-amine (**143**, 229 mg, 1.00 mmol), piperidine (0.12 mL, 1.20 mmol) and KHMDS (2.20 mL, 2.20 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 9:1) to give **141h** (158 mg, 0.67 mmol, 67%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.87 (d, *J* = 6.4 Hz, 1H), 6.13 (dd, *J* = 6.5, 2.3 Hz, 1H), 5.72 (d, *J* = 2.3 Hz, 1H), 3.51 (q, *J* = 7.1 Hz, 4H), 3.30 (d, *J* = 4.9 Hz, 4H), 1.64 (d, *J* = 3.5 Hz, 6H), 1.19 (t, *J* = 7.1 Hz, 6H).

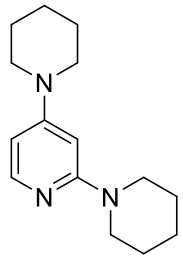
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 157.5, 157.2, 146.3, 99.6, 88.5, 48.0 (2C), 43.0, 25.3 (2C), 24.4, 13.1.

IR (Diamond-ATR, neat): 3396, 2971, 2928, 2854, 1652, 1647, 1635, 1591, 1538, 1533, 1498, 1476, 1472, 1464, 1456, 1447, 1442, 1436, 1373, 1357, 1316, 1229, 1124, 1078, 1021, 797.

MS (EI, 70 eV): m/z (%) = 205 (13), 204 (100), 190 (21), 190 (11).

HRMS (EI) m/z for $C_{14}H_{23}N_3$ (233.1892): 233.1887.

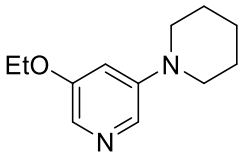
1,1'-(Pyridine-2,4-diyl)dipiperidine (141i)



Pyridine **141i** was prepared *via* **TP11** using 3-chloro-2-(piperidin-1-yl)pyridine (**144**, 120 mg, 0.50 mmol), piperidine (0.06 mL, 0.60 mmol) and KHMDS (1.10 mL, 1.10 mmol). After workup, the crude product was purified *via* flash chromatography (DCM:methanol = 9:1) to give **141i** (105 mg, 0.42 mmol, 83%) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.86 (d, *J* = 6.3 Hz, 1H), 6.14 (dd, *J* = 6.3, 2.2 Hz, 1H), 5.90 (d, *J* = 2.2 Hz, 1H), 3.46 (t, *J* = 5.0 Hz, 4H), 3.28 (t, *J* = 4.6 Hz, 4H), 1.61 (d, *J* = 2.7 Hz, 12H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 159.8, 157.2, 146.0, 100.7, 90.4, 47.8 (2C), 47.2 (2C), 25.6 (2C), 25.3 (2C), 24.6, 24.4.
IR (Diamond-ATR, neat): 3390, 2928, 2851, 1645, 1627, 1623, 1591, 1533, 1505, 1496, 1456, 1441, 1387, 1308, 1231, 1213, 1123, 1021, 976, 853, 799.
MS (EI, 70 eV): m/z (%) = 245 (37), 244 (13), 217 (14), 216 (100), 202 (26), 190 (18), 189 (37), 162 (80), 161 (20).
HRMS (EI) m/z for $C_{15}H_{23}N_3$ (245.1892): 245.1887.

3-Ethoxy-5-(piperidin-1-yl)pyridine (145a)



Pyridine **145a** was prepared *via* **TP11** using 3-bromo-5-ethoxypyridine (**146a**, 202 mg, 1.00 mmol), piperidine (0.12 mL, 1.20 mmol) and KHMDS (2.20 mL, 2.20 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 6:4) to give **145a** (144 mg, 0.69 mmol, 69%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.92 (dd, *J* = 2.6, 1.1 Hz, 1H), 7.74 (dd, *J* = 2.4, 1.1 Hz, 1H), 6.68 (t, *J* = 2.4 Hz, 1H), 4.04 (qd, *J* = 7.0, 1.2 Hz, 2H), 3.21 – 3.14 (m, 4H), 1.72 – 1.64 (m, 4H), 1.62 – 1.55 (m, 2H), 1.40 (td, *J* = 7.0, 1.1 Hz, 3H).

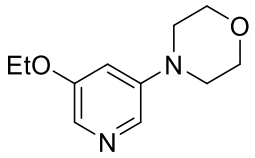
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 155.6, 148.7, 131.9, 127.2, 109.1, 63.9, 50.0, 25.6, 24.2, 14.9.

IR (Diamond-ATR, neat): 2977, 2931, 2853, 2798, 1580, 1465, 1440, 1383, 1277, 1259, 1224, 1194, 1158, 1127, 1052, 1030, 859, 844, 704.

MS (EI, 70 eV): m/z (%) = 206 (50), 205 (100), 177 (44), 122 (11).

HRMS (EI) m/z for $C_{12}H_{18}N_2O$ (206.1419): 206.1415.

4-(5-Ethoxypyridin-3-yl)morpholine (145b)



Pyridine **145b** was prepared *via* **TP11** using 3-bromo-5-ethoxypyridine (**146a**, 81.0 mg, 0.40 mmol), morpholine (0.05 mL, 0.50 mmol) and KHMDS (0.88 mL, 0.88 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 1:1) to give **145b** (64.0 mg, 0.31 mmol, 77%) as a yellow liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.94 (d, *J* = 2.5 Hz, 1H), 7.83 (d, *J* = 2.4 Hz, 1H), 6.68 (t, *J* = 2.5 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.90 – 3.80 (m, 4H), 3.22 – 3.11 (m, 4H), 1.42 (t, *J* = 7.0 Hz, 3H).

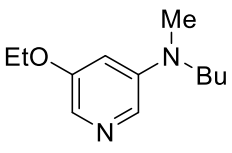
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 155.7, 148.1, 131.1, 128.2, 108.8, 66.8 (2C), 64.1, 48.8 (2C), 15.0.

IR (Diamond-ATR, neat): 2976, 2855, 1584, 1446, 1395, 1380, 1350, 1270, 1248, 1199, 1153, 1120, 1049, 1011, 1002, 869, 845, 704.

MS (EI, 70 eV): m/z (%) = 208 (87), 193 (22), 150 (55), 122 (100), 121 (21), 95 (20).

HRMS (EI) m/z for $C_{11}H_{16}N_2O_2$ (208.1212): 208.1202.

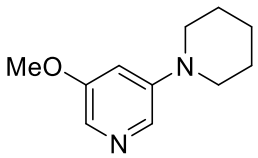
***N*-Butyl-5-ethoxy-*N*-methylpyridin-3-amine (145c)**



Pyridine **145c** was prepared *via* **TP11** using 3-bromo-5-ethoxypyridine (**146a**, 81.0 mg, 0.40 mmol), *N*-methylbutan-1amine (0.06 mL, 0.50 mmol) and KHMDS (0.88 mL, 0.88 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 8:2) to give **145c** (53.0 mg, 0.25 mmol, 64%) as a colourless liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.72 (d, *J* = 2.6 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 6.42 (t, *J* = 2.5 Hz, 1H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.32 – 3.22 (m, 2H), 2.89 (s, 3H), 1.56 – 1.48 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H), 1.35 – 1.27 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 155.8, 146.3, 128.1, 124.1, 105.1, 63.9, 52.3, 38.2, 28.8, 20.4, 15.0, 14.0.
MS (EI, 70 eV): m/z (%) = 166 (9), 165 (100), 137 (61).
HRMS (EI) m/z for $C_{12}H_{21}N_2O^+$ (209.1648): 209.1600 [M+H$^+$].

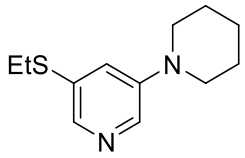
3-Methoxy-5-(piperidin-1-yl)pyridine (145d)



Pyridine **145d** was prepared *via* **TP11** using 3-bromo-5-methoxypyridine (**146b**, 188 mg, 1.00 mmol), piperidine (0.12 mL, 1.20 mmol) and KHMDS (2.20 mL, 2.20 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 8:2) to give **145d** (111 mg, 0.58 mmol, 58%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 8.04 – 7.91 (m, 1H), 7.77 (d, *J* = 2.3 Hz, 1H), 6.70 (t, *J* = 2.4 Hz, 1H), 3.83 (s, 3H), 3.27 – 3.06 (m, 4H), 1.76 – 1.51 (m, 6H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 156.3, 148.8, 131.8, 126.6, 108.5, 55.7, 50.0 (2C), 25.6 (2C), 24.2.
IR (Diamond-ATR, neat): 2933, 2850, 1580, 1476, 1472, 1449, 1436, 1426, 1384, 1349, 1277, 1260, 1253, 1228, 1202, 1180, 1159, 1127, 1054, 1025, 1009, 971, 840, 703.
MS (EI, 70 eV): m/z (%) = 192 (45), 163 (13), 191 (100), 151 (9), 136 (11), 108 (9).
HRMS (EI) m/z for $C_{11}H_{15}N_2O^+$ (191.1179): 191.1179 [M-H$^-$].

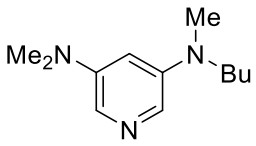
3-(Ethylthio)-5-(piperidin-1-yl)pyridine (145e)



Pyridine **145e** was prepared *via* **TP11** using 3-bromo-5-(ethylthio)pyridine (**146c**, 109 mg, 0.50 mmol), piperidine (0.06 mL, 0.60 mmol) and KHMDS (1.10 mL, 1.10 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 1:1) to give **145e** (69.0 mg, 0.31 mmol, 62%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 8.09 (d, *J* = 2.7 Hz, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.11 (dd, *J* = 2.7, 1.8 Hz, 1H), 3.19 – 3.13 (m, 4H), 2.91 (q, *J* = 7.3 Hz, 2H), 1.71 – 1.63 (m, 4H), 1.61 – 1.53 (m, 2H), 1.28 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 147.5, 139.9, 136.4, 133.1, 123.5, 49.7 (2C), 28.0, 25.5 (2C), 24.1, 14.6.
IR (Diamond-ATR, neat): 2927, 2851, 2809, 1564, 1539, 1464, 1441, 1423, 1419, 1374, 1345, 1277, 1260, 1244, 1216, 1171, 1129, 1111, 1024, 1006, 944, 854, 702.
MS (EI, 70 eV): m/z (%) = 222 (60), 221 (100), 194 (11), 193 (25), 192 (10), 161 (21).
HRMS (EI) m/z for $C_{12}H_{18}N_2S$ (222.1191): 222.1179.

***N*^{3}-Butyl-*N*^{3},*N*^{5},*N*^{5}-trimethylpyridine-3,5-diamine (145f)**



Pyridine **145f** was prepared *via* **TP11** using 3-bromo-5-dimethylaminopyridine (**146d**, 101 mg, 0.50 mmol), *N*-methylbutan-1amine (0.07 mL, 0.60 mmol) and KHMDS (1.10 mL, 1.10 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate = 1:1) to give **145f** (62.0 mg, 0.30 mmol, 62%) as a yellow liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.54 (d, *J* = 2.5 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 6.24 (t, *J* = 2.5 Hz, 1H), 3.36 – 3.26 (m, 2H), 2.95 (d, *J* = 8.3 Hz, 9H), 1.61 – 1.51 (m, 2H), 1.34 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

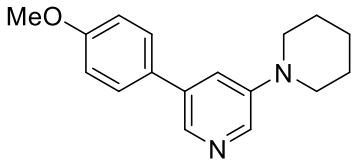
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 147.1, 145.8, 122.7, 122.2, 102.4, 52.3, 40.3 (2C), 38.2, 28.8, 20.3, 14.0.

IR (Diamond-ATR, neat): 2955, 2926, 2871, 1584, 1480, 1463, 1443, 1379, 1353, 1329, 1277, 1242, 1225, 1154, 819, 704.

MS (EI, 70 eV): m/z (%) = 148 (9), 149 (15), 164 (100), 165 (9), 207 (31).

HRMS (EI) m/z for $C_{12}H_{21}N_3$ (207.1735): 207.1730.

3-(4-Methoxyphenyl)-5-(piperidin-1-yl)pyridine (145g)



Pyridine **145g** was prepared *via* **TP11** using 3-bromo-5-(4-methoxyphenyl)pyridine (**146e**, 132 mg, 0.50 mmol), piperidine (0.06 mL, 0.60 mmol) and KHMDS (1.10 mL, 1.10 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine= 6:4:0.1) to give **145g** (91.0 mg, 0.34 mmol, 68%) as a yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 8.24 (d, *J* = 2.3 Hz, 2H), 7.52 – 7.47 (m, 2H), 7.30 (dd, *J* = 2.7, 2.0 Hz, 1H), 7.01 – 6.96 (m, 2H), 3.84 (d, *J* = 1.1 Hz, 3H), 3.27 – 3.22 (m, 4H), 1.76 – 1.69 (m, 4H), 1.66 – 1.57 (m, 2H).

^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 159.7, 147.8, 138.5, 137.2, 136.3, 131.1, 128.4, 120.9 (2C), 114.5 (2C), 55.5, 50.1, 25.7, 24.2.

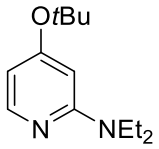
IR (Diamond-ATR, neat): 2933, 2851, 2835, 2806, 1609, 1582, 1514, 1463, 1450, 1437, 1406, 1352, 1284, 1247, 1230, 1180, 1130, 1119, 1033, 1025, 937, 829, 711.

MS (EI, 70 eV): m/z (%) = 268 (39), 267 (77), 225 (37), 212 (47), 207 (54), 197 (33), 193 (27), 169 (33), 141 (36), 140 (29), 115 (47), 75 (23), 73 (100).

HRMS (EI) m/z for $C_{17}H_{20}N_2O$ (268.1576): 268.1577.

m.p.: 100-102 °C.

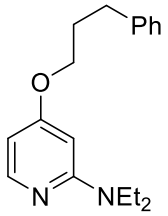
4-(*Tert* -butoxy)-*N,N*-diethylpyridin-2-amine (149a)



Pyridine **149a** was prepared *via* **TP12** using 3-bromo-*N,N*-diethylpyridin-2-amine (**148**, 114 mg, 0.50 mmol), 18-crown-6 (198 mg, 0.75 mmol) and *t*-BuOK (0.75 mL, 0.75 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 9.8:0.2:0.1) to give **149a** (73.0 mg, 0.33 mmol, 66%) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.97 (d, *J* = 5.7 Hz, 1H), 6.19 (dd, *J* = 5.8, 2.0 Hz, 1H), 6.00 (d, *J* = 2.0 Hz, 1H), 3.47 (q, *J* = 7.1 Hz, 4H), 1.43 (s, 9H), 1.17 (t, *J* = 7.0 Hz, 6H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 164.1, 159.4, 148.8, 105.9, 97.9, 79.0, 42.6 (2C), 29.2 (3C), 13.2 (2C).
IR (Diamond-ATR, neat): 2973, 2929, 1590, 1545, 1493, 1475, 1458, 1444, 1430, 1391, 1366, 1359, 1347, 1297, 1273, 1260, 1240, 1219, 1199, 1171, 1143, 1086, 1078, 1034, 991, 968, 893, 855, 819, 781, 676.
MS (EI, 70 eV): m/z (%) = 222 (11), 165 (18), 151 (27), 137 (100), 123 (25), 123 (17).
HRMS (EI) m/z for $C_{13}H_{22}N_2O$ (222.1732): 222.1724.

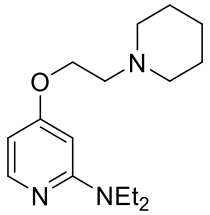
***N,N*-Diethyl-4-(3-phenylpropoxy)pyridin-2-amine (149b)**



Pyridine **149b** was prepared *via* **TP12** using 3-bromo-*N,N*-diethylpyridin-2-amine (**148**, 114 mg, 0.50 mmol), 18-crown-6 (198 mg, 0.75 mmol), 3-phenylpropanol (204 mg, 1.50 mmol) and *t*-BuOK (0.75 mL, 0.75 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **149b** (87.0 mg, 0.31 mmol, 61%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 5.8 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 6.12 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.49 (q, *J* = 7.0 Hz, 4H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.10 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 6H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 166.6, 159.5, 149.4, 141.5, 128.7 (2C), 128.6 (2C), 126.1, 99.5, 90.5, 66.5, 42.6 (2C), 32.2, 30.8, 13.1 (2C).
IR (Diamond-ATR, neat): 3024, 2969, 2928, 2871, 1599, 1559, 1496, 1467, 1454, 1431, 1374, 1360, 1297, 1271, 1222, 1200, 1148, 1079, 1038, 809, 746, 700.
MS (EI, 70 eV): m/z (%) = 284 (10), 256 (11), 255 (62), 241 (35), 165 (23), 151 (19), 137 (100), 123 (14), 91 (18).
HRMS (EI) m/z for $C_{18}H_{24}N_2O$ (284.1889): 284.1876.

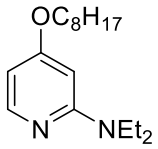
***N*,*N*-Diethyl-4-(2-(piperidin-1-yl)ethoxy)pyridin-2-amine (149c)**



Pyridine **149c** was prepared *via* **TP12** using 3-bromo-*N*,*N*-diethylpyridin-2-amine (**148**, 114 mg, 0.50 mmol), 18-crown-6 (198 mg, 0.75 mmol), 1-(2-hydroxyethyl)piperidine (194 mg, 1.50 mmol) and *t*-BuOK (0.75 mL, 0.75 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 7:3:0.1) to give **149c** (90.0 mg, 0.32 mmol, 65%) as a pink oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm =7.97 (d, *J* = 5.8 Hz, 1H), 6.12 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 4.10 (t, *J* = 6.2 Hz, 2H), 3.47 (q, *J* = 7.1 Hz, 4H), 2.76 (t, *J* = 6.1 Hz, 2H), 2.55 – 2.45 (m, 4H), 1.66 – 1.55 (m, 4H), 1.49 – 1.39 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 6H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 166.3, 159.5, 149.3, 99.6, 90.5, 65.4, 57.8 (2C), 55.2, 42.6 (2C), 25.9 (2C), 24.2, 13.1 (2C).
IR (Diamond-ATR, neat): 2967, 2930, 2853, 2782, 1599, 1560, 1497, 1466, 1455, 1443, 1432, 1374, 1360, 1302, 1272, 1222, 1201, 1149, 1083, 1047, 1038, 808, 780.
MS (EI, 70 eV): m/z (%) = 167 (7), 112 (20), 111 (29.39), 98 (100), 96 (11), 70 (10).
HRMS (EI) m/z for $C_{16}H_{28}N_3O^+$ (278.2227): 278.2183 [M+H$^+$].

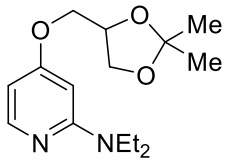
***N*,*N*-Diethyl-4-(octyloxy)pyridin-2-amine (149d)**



Pyridine **149d** was prepared *via* **TP12** using 3-bromo-*N*,*N*-diethylpyridin-2-amine (**148**, 114 mg, 0.50 mmol), 18-crown-6 (198 mg, 0.75 mmol), 1-octanol (195 mg, 1.50 mmol) and *t*-BuOK (0.75 mL, 0.75 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **149d** (106 mg, 0.39 mmol, 77%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm =7.98 (d, *J* = 5.8 Hz, 1H), 6.12 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 1.82 – 1.70 (m, 2H), 1.47 – 1.39 (m, 2H), 1.35 – 1.23 (m, 8H), 1.17 (t, *J* = 7.1 Hz, 6H), 0.88 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 166.7, 159.5, 149.3, 99.5, 90.5, 67.6, 42.6 (2C), 31.9, 29.5, 29.4, 29.2, 26.1, 22.8, 14.2, 13.1 (2C).
IR (Diamond-ATR, neat): 2956, 2927, 2869, 2855, 1599, 1559, 1497, 1467,1446, 1433, 1375, 1360, 1271, 1222, 1200, 1148, 1079, 1037, 907, 820, 809, 728.
MS (EI, 70 eV): m/z (%) = 249 (46), 235 (11), 165 (17), 137 (100), 123 (10).
HRMS (EI) m/z for $C_{17}H_{30}N_2O$ (278.2358): 278.2351.

4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)-*N*,*N*-diethylpyridin-2-amine (149e)



Pyridine **149e** was prepared *via* **TP12** using 3-bromo-*N*,*N*-diethylpyridin-2-amine (**148**, 114 mg, 0.50 mmol), 18-crown-6 (198 mg, 0.75 mmol), 2,2-dimethyl-1,3-dioxolane-4-methanol (198 mg, 1.50 mmol) and *t*-BuOK (0.75 mL, 0.75 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **149e** (87.0 mg, 0.31 mmol, 62%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.99 (d, *J* = 5.8 Hz, 1H), 6.13 (dd, *J* = 5.8, 2.2 Hz, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 4.46 (qn, *J* = 5.9 Hz, 1H), 4.19 – 4.13 (m, 1H), 4.09 – 4.02 (m, 1H),

3.97 – 3.84 (m, 2H), 3.48 (q, *J* = 7.0 Hz, 4H), 1.46 (s, 3H), 1.40 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 6H).

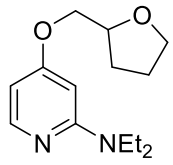
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 166.1, 159.5, 149.5, 110.0, 99.2, 90.6, 73.9, 68.4, 67.0, 42.7 (2C), 26.9, 25.4, 13.1 (2C).

IR (Diamond-ATR, neat): 2972, 2931, 2872, 1600, 1559, 1498, 1455, 1432, 1371, 1360, 1296, 1270, 1261, 1221, 1150, 1081, 1056, 841, 818, 809.

MS (EI, 70 eV): m/z (%) = 265 (11), 251 (24), 237 (19), 165 (20), 151 (26), 137 (100), 123 (12), 123 (14).

HRMS (EI) m/z for $C_{15}H_{24}N_2O_3$ (280.1787): 280.1775.

N,N-Diethyl-4-((tetrahydrofuran-2-yl)methoxy)pyridin-2-amine (149f)



Pyridine **149f** was prepared *via* **TP12** using 3-bromo-*N*,*N*-diethylpyridin-2-amine (**148**, 114 mg, 0.50 mmol), 18-crown-6 (198 mg, 0.75 mmol), 2-(tetrahydrofuryl)methanol (153 mg, 1.50 mmol) and *t*-BuOK (0.75 mL, 0.75 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **149f** (101 mg, 0.40 mmol, 81%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 5.8 Hz, 1H), 6.14 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.96 (d, *J* = 2.1 Hz, 1H), 4.29 – 4.21 (m, 1H), 4.00 – 3.90 (m, 3H), 3.87 – 3.78 (m, 1H), 3.48 (q, *J* = 7.1 Hz, 4H), 2.13 – 2.02 (m, 1H), 2.01 – 1.88 (m, 2H), 1.80 – 1.68 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 6H).

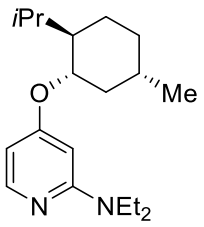
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 166.4, 159.5, 149.4, 99.3, 90.7, 77.0, 69.9, 68.7, 42.6 (2C), 28.4, 25.8, 13.1 (2C).

IR (Diamond-ATR, neat): 2968, 2927, 2868, 1598, 1557, 1497, 1450, 1431, 1374, 1359, 1298, 1271, 1222, 1200, 1149, 1079, 1039, 817, 808, 781.

MS (EI, 70 eV): m/z (%) = 250 (15), 221 (35), 207 (20), 165 (17), 151 (22), 137 (100), 123 (15).

HRMS (EI) m/z for $C_{14}H_{22}N_2O_2$ (250.1681): 250.1676.

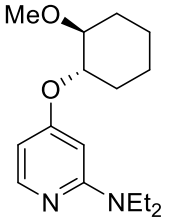
_N,N_-Diethyl-4-(((1_S_,2_R_,5_S_)-2-isopropyl-5-methylcyclohexyl)oxy)pyridin-2-amine (149g)



Pyridine **149g** was prepared *via* **TP12** using 3-bromo-*N*,*N*-diethylpyridin-2-amine (**148**, 114 mg, 0.50 mmol), 18-crown-6 (198 mg, 0.75 mmol), (+)-menthol (234 mg, 1.50 mmol) and *t*-BuOK (0.75 mL, 0.75 mmol). After workup, the crude product was purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **149g** (103 mg, 0.34 mmol, 68%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 6.0 Hz, 1H), 6.14 (dd, *J* = 6.0, 2.1 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 4.08 (td, *J* = 10.6, 4.2 Hz, 1H), 3.49 (q, *J* = 7.1 Hz, 4H), 2.17 – 2.06 (m, 2H), 1.75 – 1.66 (m, 2H), 1.54 – 1.41 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 6H), 1.11 – 0.98 (m, 3H), 0.91 (m, 6H), 0.75 (d, *J* = 7.0 Hz, 3H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 166.3, 159.0, 148.6, 99.7, 91.8, 47.9 (2C), 42.8 (2C), 40.4, 34.5, 31.5, 26.2, 23.8, 22.2, 20.8, 16.7, 13.1 (2C).
IR (Diamond-ATR, neat): 2954, 2925, 2868, 1643, 1596, 1548, 1495, 1471, 1456, 1431, 1373, 1360, 1297, 1271, 1237, 1220, 1200, 1145, 1097, 1040, 1015, 818.
MS (EI, 70 eV): m/z (%) = 165 (17), 151 (18), 137 (100), 123 (20), 123 (10).
HRMS (EI) m/z for $C_{19}H_{32}N_2O$ (304.2515): 304.2508.

_N,N_-Diethyl-4-(((1_S_,2_S_)-2-methoxycyclohexyl)oxy)pyridin-2-amine (149h)



Pyridine **149h** was prepared *via* **TP12** using 3-bromo-*N*,*N*-diethylpyridin-2-amine (**148**, 114 mg, 0.50 mmol), 18-crown-6 (198 mg, 0.75 mmol), (1S,2S)-2-methoxycyclohexan-1-ol (195 mg, 1.50 mmol) and *t*-BuOK (0.75 mL, 0.75 mmol). After workup, the crude product was

purified *via* flash chromatography (*n*-pentane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **149h** (98.0 mg, 0.35 mmol, 71%) as a greenish oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ / ppm = 7.97 (d, *J* = 5.8 Hz, 1H), 6.16 (dd, *J* = 5.9, 2.1 Hz, 1H), 5.97 (d, *J* = 2.1 Hz, 1H), 4.22 (ddd, *J* = 9.1, 7.3, 4.1 Hz, 1H), 3.48 (q, *J* = 7.1 Hz, 4H), 3.42 (s, 3H), 3.31 (ddd, *J* = 9.1, 7.3, 4.2 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.74 – 1.66 (m, 2H), 1.35 – 1.23 (m, 4H), 1.17 (t, *J* = 7.1 Hz, 6H).
^{13}C-NMR (101MHz, $CDCl_3$): δ / ppm = 165.9, 159.5, 149.3, 100.2, 92.0, 80.9, 78.4, 57.8, 42.6 (2C), 29.4, 29.2, 23.1 (2C), 13.2 (2C).
IR (Diamond-ATR, neat): 2967, 2929, 2863, 1596, 1555, 1550, 1495, 1472, 1457, 1446, 1431, 1374, 1359, 1271, 1220, 1199, 1149, 1103, 1087, 1052, 1037, 1000, 983, 817, 810.
MS (EI, 70 eV): m/z (%) = 249 (14), 165 (12), 151 (18), 137 (100), 123 (11), 123 (13), 81 (10).
HRMS (EI) m/z for $C_{16}H_{26}N_2O_2$ (278.1994): 278.1986.