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Synthesis of Polyfunctional Amides, Ketones and Pyridines Using Organometallic Reagents in Continuous Flow and Batch

von

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aus

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Erklärung

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

Eidesstattliche Erklärung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

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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.

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.

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.

4. "Preparation of Functionalized Amides using Dicarbamoylzincs"
   D. Djukanovic, M. A. Ganiek, K. Nishi, K. Karaghiosoff, K. Mashima, P. Knochel, *Angew. Chem. Int. Ed.* **2022**, e202205440; *Angew. Chem.* **2022**, e202205440.

I dedicate this thesis to my mother, Marijana Đukanović

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
CCDC	cambridge crystallographic data centre
CIPE	complex induced proximity effect
CFU	continuous flow unit
conc.	concentrated
Cy	cyclohexyl
d	doublet (NMR)
dba	dibenzylideneacetone
DCM	dichloromethane
DMF	dimethylformamide
DMG	directed metalation group
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
E	electrophile
e.g.	for example (lat. *exempli gratia*)
EI	electron ionisation
equiv	equivalents
Et	ethyl
etc.	and so no (lat. *et cetera*)
g	gram
GC	gas chromatography
h	hour
Het	undefined heteroaryl substituent
h	hour
hex	hexyl
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i	*iso*
i. d.	internal diameter
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
m	multiplet (NMR)
M	metal

[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.

m	*meta*
Me	methyl
Met	undefined metallic substituent
mL	milliliter
mm	millimeter
mmol	millimole
mol%	mole percent
m.p.	melting point
NaDA	sodium diisopropylamide
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
Ph	phenyl
PMDTA	pentamethyldiethylenetriamine
ppm	parts per milion
Pr	propyl
PTFE	polytetrafluoroethylene
q	quartet (NMR)
R	undefined organic substituent
s	singlet (NMR)
s	*sec*
s	second
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-tetramethylpiperidyl
TMS	trimethylsilyl
TMU	tetramethylurea
TP	typical procedure
vol%	volume percent

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A. INTRODUCTION

1. Overview

In an ever-growing world, fast progress is expected. Same expectations exist in chemistry, an exact creation science *par excellence*. While the very beginning of chemistry can be seen in the recognition of the necessity that the world must have its "elements" by the Greek philosophers, the official origins of organic chemistry for humankind started in 1828 with the Wöhler synthesis of urea.[3] Since then, the slow but steady progress exemplified by the introduction of organic solvents and first equipment grew this field of science. As our knowledge of the matter became more and more solid with paradigms such as atom, chirality and three-dimensional structure of molecules, we have ventured into complex molecules such as vitamins and proteins with the question if we can also reproduce these creations of nature. Technologies like IR, UV/VIS and NMR spectroscopy improved our understanding of the structure of organic molecules and enabled faster characterisation of the products. At the same time, synthetic efforts have become more and more ambitious.

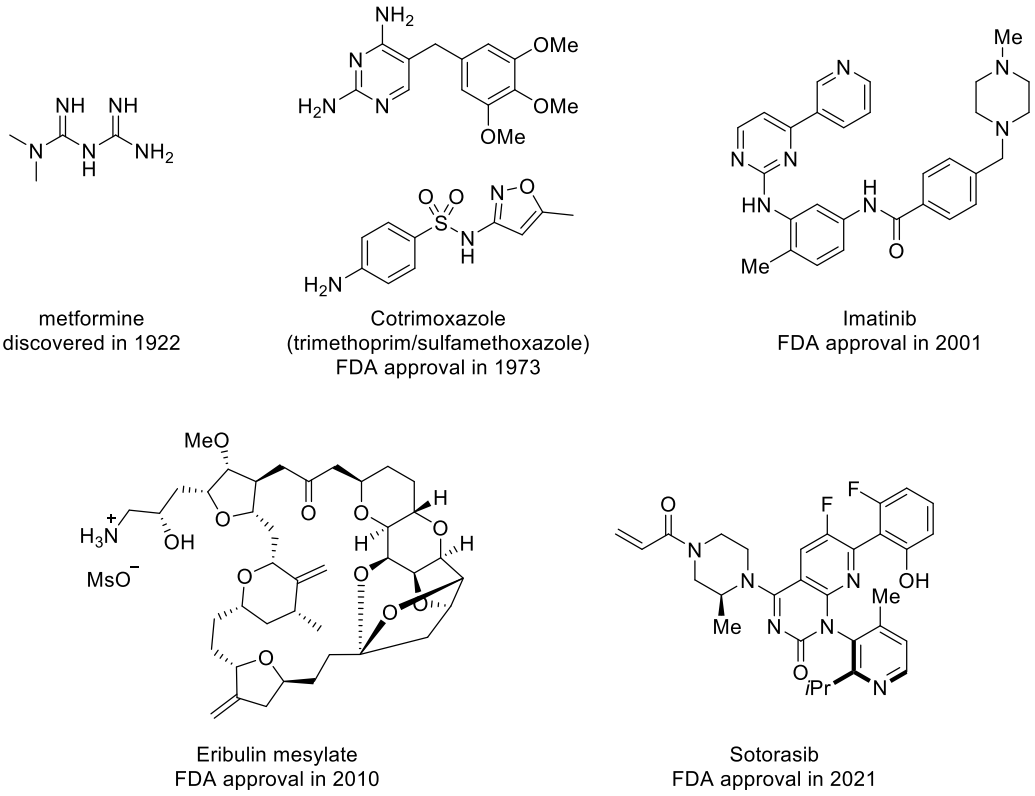
The power of organic synthesis is in its methods to make new molecules, which have yet to gain purpose. Excellence in making a simple oxygen-phosphorus bond has revolutionized biosciences as various oligonucleotides became available.[4] On the other hand, research in amide bond formation resulted in several Nobel Prizes.[5] Today, more than 25% of commercial APIs contain amide bonds. Nevertheless, due to their high diversity, the formation of C-C bonds is still the main challenge in organic chemistry.

Relatively recently, progress in cross-coupling reactions has significantly influenced medicinal chemistry. Scheme 1 highlights state of the art of synthetic methods throughout the last 100 years through the structural complexity of synthetic medicines. From a simple condensation reaction in the synthesis of metformin, over the introduction of heterocycles (see Cotrimoxazole: Scheme 1), the sp^2-rich scaffold such as the one of imatinib show the dominance of cross-coupling methodologies in drug discovery. Nowadays, a venture into more complex, stereochemically rich molecules gained popularity. Complexity is rather embraced than rejected. The development of eribulin mesylate, a totally synthetic analogue of natural product Halihondrin B, is arguably the peak of organic chemistry.[6] Stereoselective synthesis is still very challenging. For example, in the synthesis of sotorasib, atropoisomers posed a big challenge.

Well into 21st century our goals are now focused on the economy of the reaction rather than its feasibility. To respond to the new demands one must revisit and re-evaluate forgotten methods, apply new technologies and ultimately develop new methods or discover new reactivities. One of the "sustainable" technologies is continuous flow chemistry which uses tubings or channels instead of flasks as reaction vessels. Flow chemistry setups often provide better control of reaction parameters,

[3] F. Wöhler, *Annalen der Physik und Chemie* **1828**, *88*, 253.
[4] The Nobel prize in chemistry 1993. to Karry B. Mullis and Michael Smith "for contributions to the developments of methods within DNA-based chemistry".
[5] The Nobel prize in chemistry 1955. to Vincent du Vigneaud "for his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone"; The Nobel prize in chemistry 1958. to Frederick Sanger "for his work on the structure of proteins, especially that of insulin"; The Nobel prize in chemistry 1972. to Christian B. Anfinsen "for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation" and to Stanford Moore and William H. Stein "for their contribution to the understanding of the connection between chemical structure and catalytic activity of the active centre of the ribonuclease molecule"; The Nobel prize in chemistry 1984. to Robert Bruce Merrifield "for his development of methodology for the chemical synthesis on a solid matrix"; The Nobel prize in chemistry 2018. to Frances H. Arnold "for the directed evolution of enzymes" and to George P. Smith and Sir Gregory P. Winter "for the phage display of peptides and antibodies".
[6] A. Bauer, Story of Eribulin Mesylate: Development of the Longest Drug Synthesis in *Synthesis of Heterocycles in Contemporary Medicinal Chemistry*, *Topics in Heterocyclic Chemistry*, Vol. 44 (Eds.: Z. Časar), Springer, Cham, **2016**, pp. 209-270.

opening new process windows unachievable in batch, better reproducibility and, sometimes, new selectivities.



Scheme 1. The structure of synthetic APIs over the last 100 years is highly dependent on the available methods for their preparation.

New imperatives in chemistry emerged with the impact of the rise of the human population being increasingly more clear. Negative trends with respect to available resources (oil, food and water) and therefore energy have played a major role in shifting the focus toward sustainability. Sustainability became the main goal of the industry.[7] Being one of the leading pollutants in the world, the chemical industry has planned a carbon neutral policy.[8] Twelve principles of green chemistry have been set as the leading principles for desired sustainable chemical reactions and processes.[9]

[7] a) Sustainability Guidelines for the chemical industry in Germany: https://www.chemiehoch3.de/fileadmin/user_upload/Home/Presse/Publikationen/chemiehoch3-publikationene-leitlinie-chemische-industrie-eng.pdf; b) Positions and Criteria of the Federal Environmental Agency: https://www.Umweltbundesamt.de/sites/default/files/medien/publikationen/long/3798.pdf.

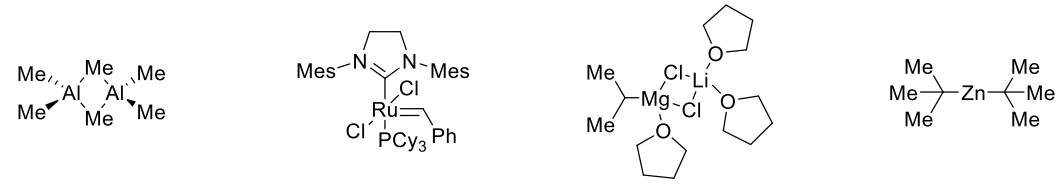
[8] a) L. Chen, G. Msigwa, M. Yang, A. I. Osman, S. Fawzy, D. W. Rooney, R.-S. Yap, *Environ. Chem. Lett.* **2022**, https://doi.org/10.1007/s10311-022-01435-8; b) Y. Zhang, C.-L. Pan, H.-T. Liao, *Front. Environ. Sci.* **2021**, *9*, 1.

[9] a) P. T. Anastas, J. C. Warner, Green Chemistry: Theory and Practice, *Oxford University Press: New York*, **1998**; b) G. T. Whiteker, *Org. Process Res. Dev.* **2019**, *23*, 2109.

2. Organometallic Chemistry

2.1 Overview

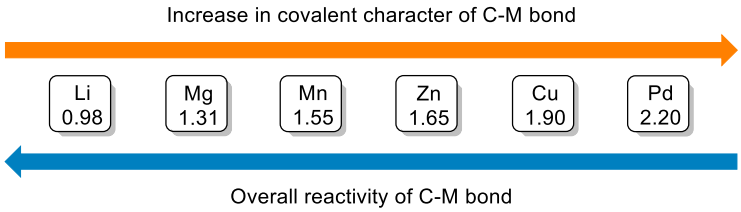
Organometallic compounds are molecules containing at least one carbon-metal bond. Commonly present in the literature are organometallics containing lithium, magnesium, manganese, zinc, copper, aluminium, and indium as these can be prepared in various ways. Those metalorganyls are generally stable in a suitable solvent. In a broader sense, organic compounds of metalloids such as boron and silicon are also considered organometallics (Scheme 2).



trimethylaluminium | Grubbs catalyst (II generation) | *i*-PrMgCl·LiCl | bis(*t*-butyl)zinc

Scheme 2. Examples of organometallic compounds.

Overall reactivity of stoichiometric organometallic reagents can be estimated with the polarization of the C-M bond (covalent or ionic bond character). This parameter is directly dependent on the electronegativity of the metal (Scheme 3). Metals with low electronegativity (such as Li and Mg) form C-M bonds with a low covalent bond character and are in general highly reactive species. Thus, they can react with a broad range of electrophiles. On the other, hand organozinc and organocopper compounds tolerate a lot of functionalities due to their more covalent C-M bond character.



Scheme 3. Pauling electronegativity scale correlates with the reactivity of organometallic compounds.

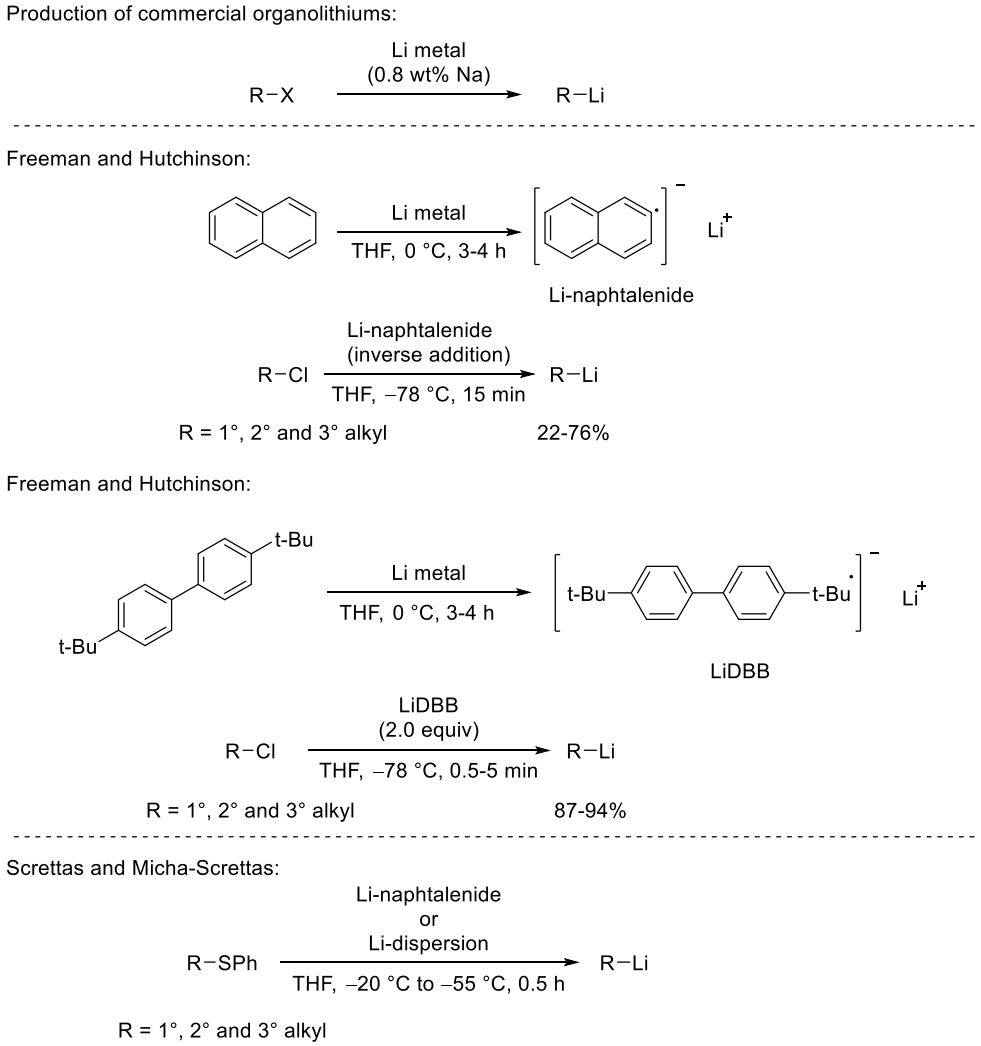
There are four general methods for the preparation of organometallic reagents:

1. Oxidative insertion
2. Halogen/Metal exchange
3. Directed metalation
4. Transmetalation

In the following pages these general methods will be discussed in the context of the preparation of organolithium, organomagnesium and organozinc species. Some exemplars will be given to depict the nature and reactivity of the reagents.

2.2 Preparation and Reactions of Organolithium Reagents

Organolithium reagents are characterised by high reactivity due to the highly ionic C-Li bond. Therefore, they react with a broad range of electrophiles, generally have low functional group tolerance and require low temperatures. The stability of some organolithiums in common ethereal solvents has been studied.[10] Commercial alkyllithiums are produced by the insertion of lithium metal (> 2.0 equiv) into alkyl chlorides or bromides.[11]

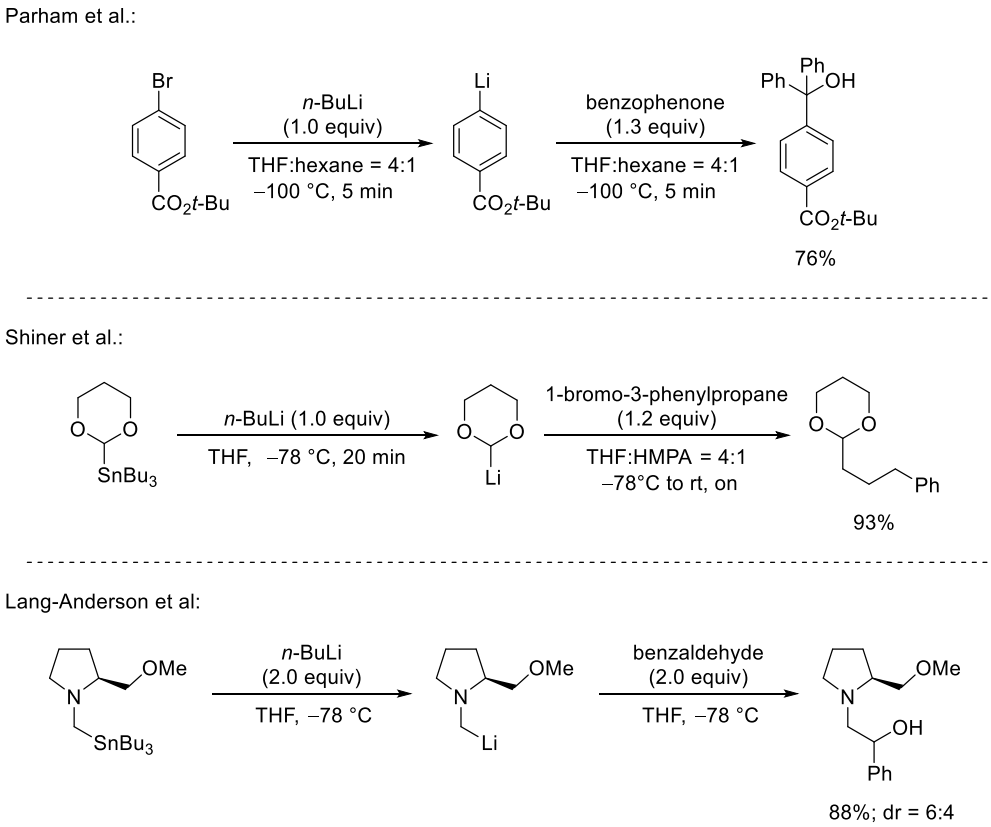


Scheme 4. Insertion of Li metal into C-X bond.

[10] P. Stanetty, M. D. Mihovilovic, *J. Org. Chem.* **1997**, *62*, 1514.
[11] T. L. Rathman, J. A. Schwindeman, *Org. Process Res. Dev.* **2014**, *18*, 1192.

Usually a small amount of sodium metal enhances the rate of the reaction and reduces the cost of the process.[12] Soluble lithium reagents such as Li-naphatalenide or LiDBB (ca. 0.2 M in THF) can be used for the preparation of alkyllithiums from alkyl chlorides in THF.[13] Screttas *et al.* prepared alkyllithiums from phenyl sulphides by using Li-naphtalenide or lithium dispersion (Scheme 4).[14]

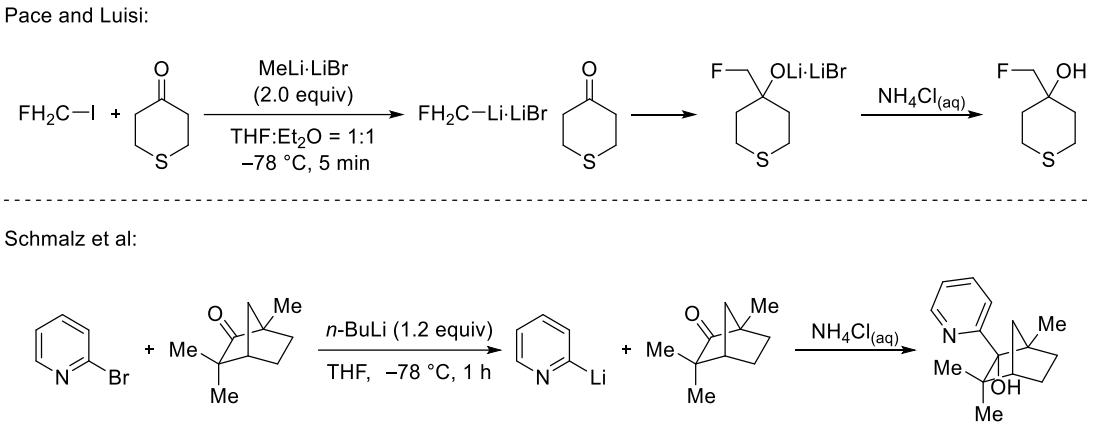
Halogen/lithium exchange reactions[15] are routinely used for the preparation of aryllithium reagents (Scheme 5). The halogen/lithium exchange is an equilibrium process where the most stable organolithium is formed.[16]



Scheme 5. Examples of halogen/lithium exchange and tin/lithium exchange.

Thus, alkinyllithiums (sp hybridised) are easily formed, followed by alkenyl and aryllithiums (sp^2-hybridised). Tertiary alkyllithiums are not suitable for preparation *via* halogen/lithium exchange while secondary and primary alkyllithiums are more favoured.

[12] C. Kamienski, D. Esmay, *J. Org. Chem.* **1960**, *25*, 1807.
[13] a) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 1924; b) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1983**, *48*, 4705.
[14] a) C. G. Screttas, M. Micha-Screttas, *J. Org. Chem.* **1978**, *43*, 1064; b) C. G. Screttas, M. Micha-Screttas, *J. Org. Chem.* **1979**, *44*, 713.
[15] a) c) G. Wittig, U. Pockels, H. Dröge, *Ber. dtsch. Chem. Ges.* **1938**, *71*, 1903; b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106; c) R. G. Jones, H. Gilman, *Org.React.* **2004**, *6*, 339.
[16] H. J. S. Winkler, H. Winkler, *J. Am. Chem. Soc.* **1966**, *88*, 964.



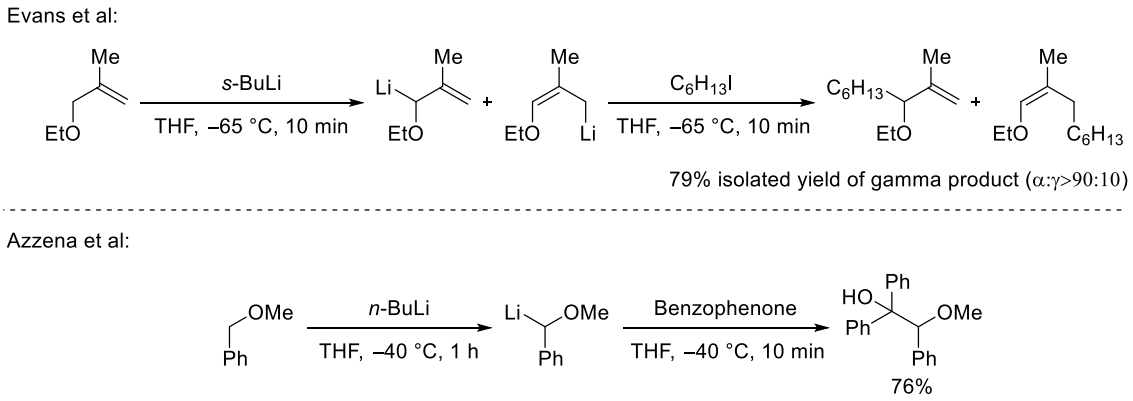
Scheme 6. Application of Barbier conditions for the reactions of unstable organolithium reagents.

The I/Li exchange is among the fastest reactions in the world and can even outcompete the deprotonation of methanol.[17] Therefore, I/Li and Br/Li exchange reactions can be performed in the presence of electrophiles.[18] These so-called Barbier conditions have been particularly beneficial in the case of unstable Li-species such as lithium carbenoids (Scheme 6).[19] So far, the mechanistic findings support intermediary iodo ate complex for I/Li exchange reaction, but the mechanism of the Br/Li exchange is still not conclusive.[20] The results of mechanistic investigations suggest both radical and non-radical pathways depending on the nature of organic bromide (1°/2° alkyl or aryl).[21] For non-stable halogen derivatives, the Sn/Li exchange can serve as a complementary method (Scheme 5).[22] Interestingly, the I/Li exchange can be performed stereoretentively. In a series of publications, the Knochel group showed that this highly sensitive reaction takes place to give chiral 2° alkyllithiums.[23] Chiral organolithiums have previously been known on strained ring systems such as cyclopropanes and epoxides.[24,25]

Lastly, metalation reactions are an important way of generating organolithium reagents. Alkyllithiums (Scheme 7 and 8) and lithium amides (Scheme 9) can both be used as metalating agents. *n*-BuLi is very often used with or without amine additives (TMEDA or PMDTA) in ethereal solvents for metalation of

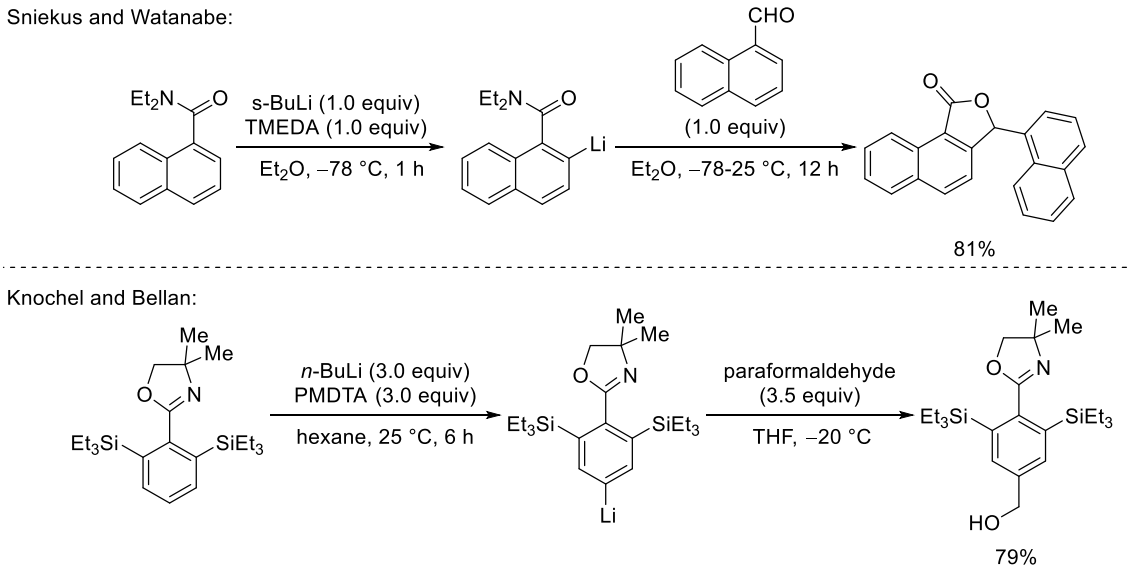
[17] a) W. B. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861; b) W. F. Bailey, J. J. Patricia, *J. Organometall. Chem.* **1988**, *352*, 1.
[18] a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187; b) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704; c) W. E. Parham, C. K. Bradscher, *Acc. Chem. Res.* **1982**, *15*, 300; d) S. Goto, J. Velder, S. El Sheikh, Y. Sakamoto, M. Mitani, S. Elmas, A. Adler, A. Becker, J.-M. Neudörfl, J. Lex, H.-G. Schmalz, *Synlett*, **2008**, *9*, 1361; e) C. Blomberg, *The Barbier Reaction and Related One-Step Processes*, Springer Berlin, Heidelberg, **2012**.
[19] G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degenarro, V. Pace, R. Luisi, *J. Am. Chem. Soc.* **2017**, *139*, 13648.
[20] W. B. Farnham, J. C. Calabrese, *J. Am. Chem. Soc.* **1986**, *108*, 2449.
[21] a) M. Newcomb, W. G. Williams, E. L. Crumpacker, *Tetrahedron Lett.* **1985**, *26*, 1183; b) E. C. Ashby, T. N. Pham, B. Park, *Tetrahedron Lett.* **1985**, *26*, 4691; c) E. C. Ashby, T. N. Pham, *J. Org. Chem.* **1987**, *52*, 1291.
[22] a) P. Lesimple, J.-M. Beau, P. J. Sinaÿ, *Carbohydr. Res.* **1987**, *171*, 289; b) R. Angelaud, Y. Landais, L. Parra-Rapado, *Tetrahedron Lett.* **1997**, *38*, 8845; c) I. Coldham, S. Holman, M. M. S. Lang-Anderson, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1481; d) C. S. Shiner, T. Tsunoda, B. A. Goodman, S. Ingham, S.-H. Lee, P. E. Vorndamm, *J. Am. Chem. Soc.* **1989**, *111*, 1381.
[23] a) G. Dagousset, K. Moriya, R. Mose, G. Berionni, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, 53, 1425; b) V. Morozova, K. Moriya, P. Mayer, P. Knochel, *Chem. Eur. J.* **2016**, *22*, 9962; c) K. Moriya, D. Didier, M. Simon, J. M. Hammann, G. Berionni, K. Karaghiosoff, H. Zipse, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 2754.
[24] K. Tanaka, K. Minami, I. Funaki, H. Suzuki, *Tetrahedron Lett.* **1990**, *31*, 2727.
[25] F. M. Perna, A. Salomone, M. Dammacco, S. Florio, V. Capriati, *Chem. Eur. J.* **2011**, *17*, 8216.

various arenes, allylic and benzylic systems.[26] The aggregation state of organolithiums plays a big role in these reactions.[27]



Scheme 7. Preparation of allylic and benzylic organolithiums by metalation.

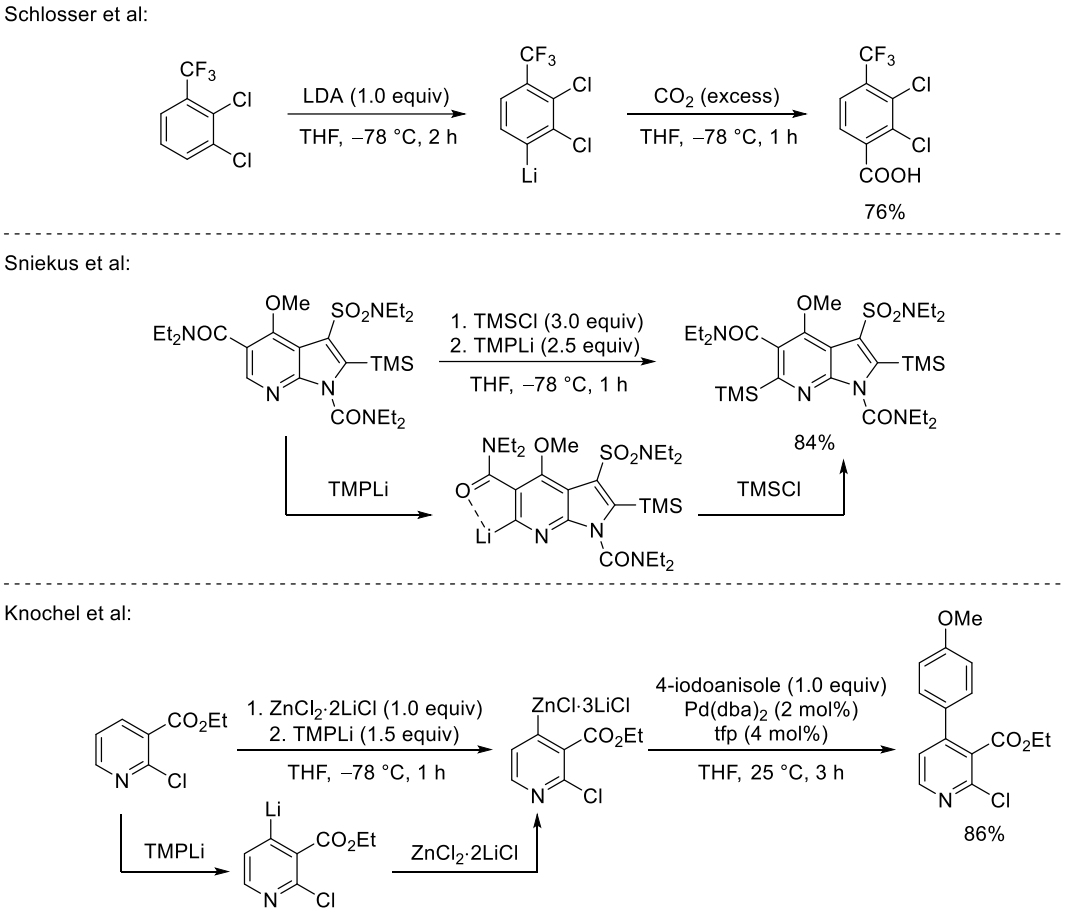
Moreover, directing groups introduced by Sniekus *et al*. are often necessary for these metalations to proceed.[28] A variation of directing group-free metalation was done by the Knochel group (Scheme 8).[28d] In the lack of coordinating groups the metalation proceeds in the least sterically hindered position.



Scheme 8. Metalation of arenes with and without directing group.

[26] a) D. A. Evans, G. C. Andrews, B. Buckwalter, *J. Am. Chem. Soc.* **1974**, *96*, 5560; b) U. Azzena, L. Pilo, A. Sechi, *Tetrahedron* **1998**, *54*, 12389; c) D. Seyferth, R. E. Mammarella, H. A. Klein, *J. Organomet. Chem.* **1980**, *194*, 1; d) U. Azzena, L. Pisano, S. Mocci, *J. Organomet. Chem.* **2009**, *694*, 3619.
[27] H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130.
[28] a) M. Watanabe, V. Sniekus, *J. Am. Chem. Soc.* **1980**, *102*, 1457; b) V. Sniekus, *Chem. Rev.* **1990**, *90*, 879; c) C. Metallinos, S. Nerdinger, V. Snieckus, *Org. Lett.* **1999**, **1**, 1183; d) A. B. Bellan, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 1838.

The thermodynamically less powerful lithium amide bases (LDA and TMPLi) are however kinetically superior.[29] Additionally, lithium amide bases show better functional group tolerance compared to alkyllithiums (Scheme 9). Interestingly, TMPLi can even be used in the presence of $ZnCl_2$, $MgCl_2$, CuCN·2LiCl and La·3LiCl.[30] Such highly kinetic metalations often give distinct regioselectivity compared to TMPMgCl·LiCl and TMPZnCl·LiCl.



Scheme 9. Metalations using Li-amide bases.

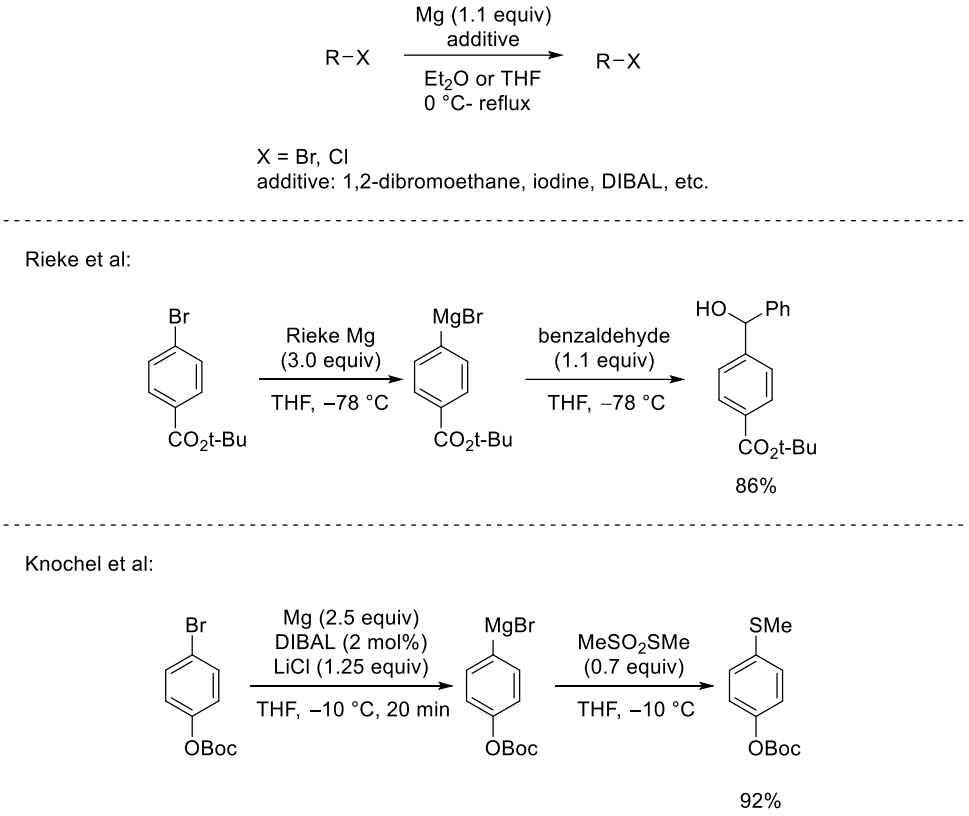
2.3 Preparation and Reactions of Organomagnesium Reagents

Organomagnesium reagents are usually prepared by oxidative addition of Mg metal into organic halides in THF or diethyl ether. The exothermic profile of Mg insertion can be a safety problem for large-scale synthesis. Also, the surface of Mg metal is usually covered with an inert layer consisting of MgO and $Mg(OH)_2$. To ensure reproducible reaction times, activation of the magnesium surface[31] can be done

[29] a) E. Masson, E. Marzi, F. Cottet, C. Bobbio, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 4393; b) C. Schneider, E. David, A. A. Toutov, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 2722.
[30] A. Frischmutt, M. Fernandez, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.
[31] a) C. E. Teerlinck, W. J. Bowyer, *J. Org. Chem.* **1996**, *61*, 1059; b) K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis, A. Sexton, *J. Org. Chem.* **1991**, *56*, 698; c) S. V. Ley, C. M. R. Low, *Ultrasound in synthesis*, Springer, Berlin, Heidelberg, **1989**, pp. 33-38.

with 1,2-dibromoethane,[32] iodine[33] or DIBAL[34] (especially suited for large-scale processes). Oxidative insertion of Mg metal into organic bromides proceeds smoothly at room temperature but organic chlorides normally require heating.

Knochel *et al*. have shown that LiCl facilitates the insertion of magnesium into various highly functionalized aromatic and heteroaromatic halides (Scheme 10).[35] According to the studies, LiCl helps the solubilisation of the metal bound organometallic species, thus ensuring a free metal surface and progress of the reaction.[36] Highly reactive Rieke magnesium, obtained by the reduction of magnesium salt with Li naphtalenide, can also be used for Grignard reagents possessing sensitive functionalities.[37]

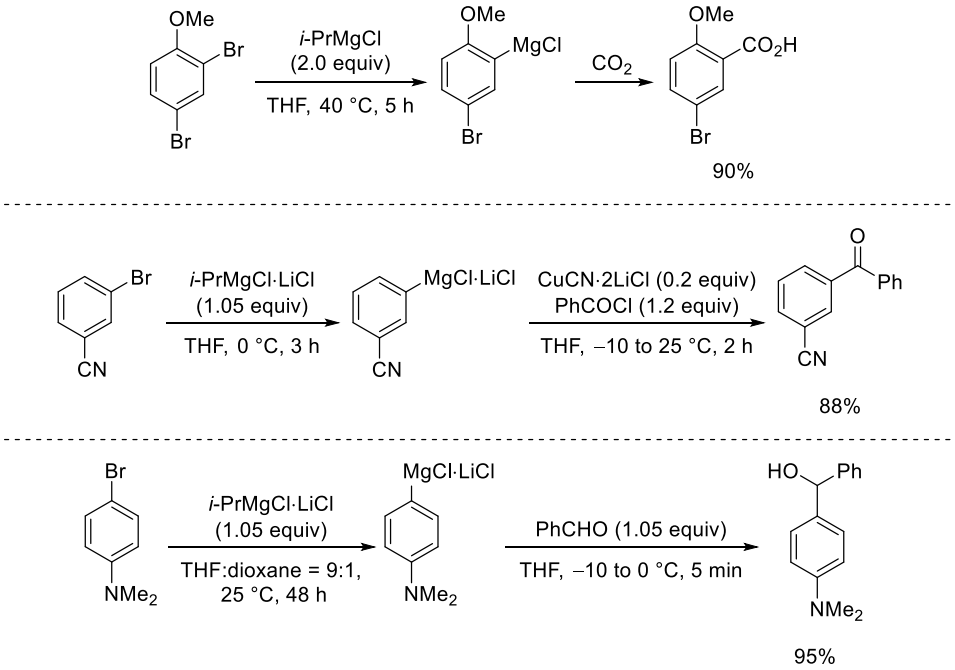


Scheme 10. Magnesium insertion into organic halides.

Halogen/magnesium exchange can be very useful when direct insertion of Mg metal fails. Also, it is not highly exothermic, has no induction period and is homogeneous. The halogen/magnesium exchange reaction is an equilibrium process resulting in the more stable organometallics (C(sp)>vinyl C(sp^2)>aryl C(sp^2)> primary C(sp^3)>secondary C(sp^3)). Iodides react the fastest followed by bromides while chlorides are inert, except for very electron deficient systems such as 1-chloro-2,3,4,5,6-

[32] A. S.-Y. Lee, Y.-T. Chang, S.-F. Chu, K.-W. Tsao, *Tetrahedron Lett.* **2006**, *47*, 7085.
[33] H. Gilman, R. H. Kirby, *Recl. Trav. Chim. Pays-Bas* **1935**, *21*, 577.
[34] U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.
[35] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[36] a) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156; b) C. Feng, Q. T. Easter, S. A. Blum, *Organometallics* **2017**, *36*, 2389.
[37] a) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; b) J.-S. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.

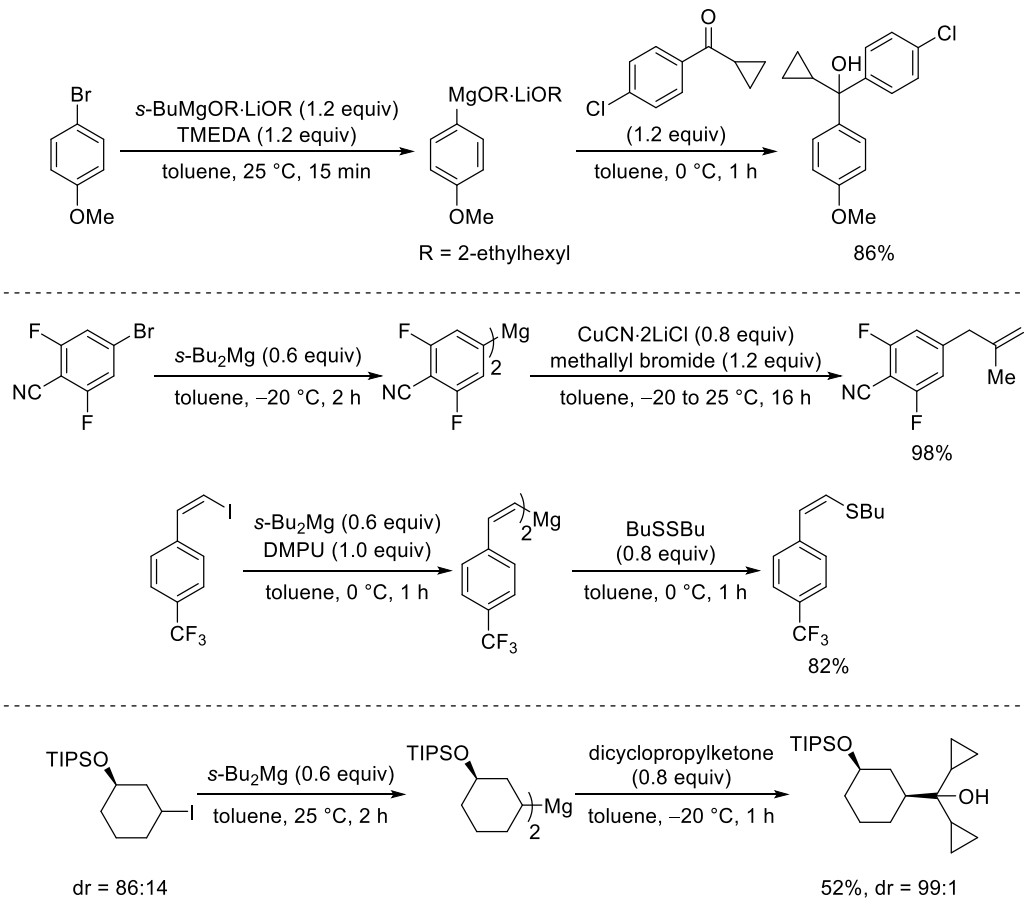
pentaflurobenzene or tetrachlorothiophene.[38] Although mild alternatives such as MesMgBr or PhMgCl have also been used, secondary alkylmagnesium reagents are the best exchange reagents.[39] For example, *i*-PrMgCl and *i*-PrMgBr react with aryl iodides even at very low temperatures.[40] Since only very reactive electrophiles such as aldehydes react with organomagnesiums below 0 °C, halogen/magnesium exchange reactions tolerate a broad range of functional groups including amide, ester, nitrile and even nitro groups (Scheme 11).



Scheme 11. Halogen/magnesium exchange with and without LiCl.

LiCl is found to greatly accelerate the halogen/magnesium exchange, therefore, broadening the scope of organic halides to electron-rich aryl bromides (Scheme 11).[41] The "turbo" reactivity of *i*-PrMgCl·LiCl is due to its monomeric magnesiate-like structure.[42] For more challenging, very electron rich aryl bromides such as 4-bromo-*N*,*N*-dimethylaniline, dialkylmagnesium reagents *i*-Pr_2Mg·LiCl or *s*-Bu_2Mg·LiCl (the addition of 10 vol% dioxane precipitates $MgCl_2$ and produces *i*-Pr_2Mg) are more suitable.[43] More recently, alkoxide-promoted Br/Mg and Cl/Mg exchange reactions in toluene have been reported (Scheme 12).[44] A new reagent consisting of $Mg(OR)_2$ (R = 2-ethylhexyl) and *s*-BuLi produced Mg reagents in toluene in very short reaction times (15 min to 1 h).

[38] a) C. Tamborski, G. J. Moore, *J. Organometal. Chem.* **1971**, *26*, 153; b) M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618.
[39] a) P. Knochel, W. Dohle, N. Gommerman, F. K. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) H. Nishiyama, K. Isaka, K. Itoh, K. Ohno, H. Nagase, K. Matsumoto, H. Yoshiwara, *J. Org. Chem.***1992**, *57*, 407.
[40] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.
[41] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[42] a) F. Blasberg, M. Bolte, M. Wagner, H.-W. Lerner, *Organometallics* **2012**, *31*, 1001; b) C. Schnegelsberg, S. Bachman, M. Kolter, T. Auth, M. John, D. Stalke, K. Koszinowski, *Chem. Eur. J.* **2016**, *22*, 7752;.
[43] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.
[44] D. S. Ziegler, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6701.

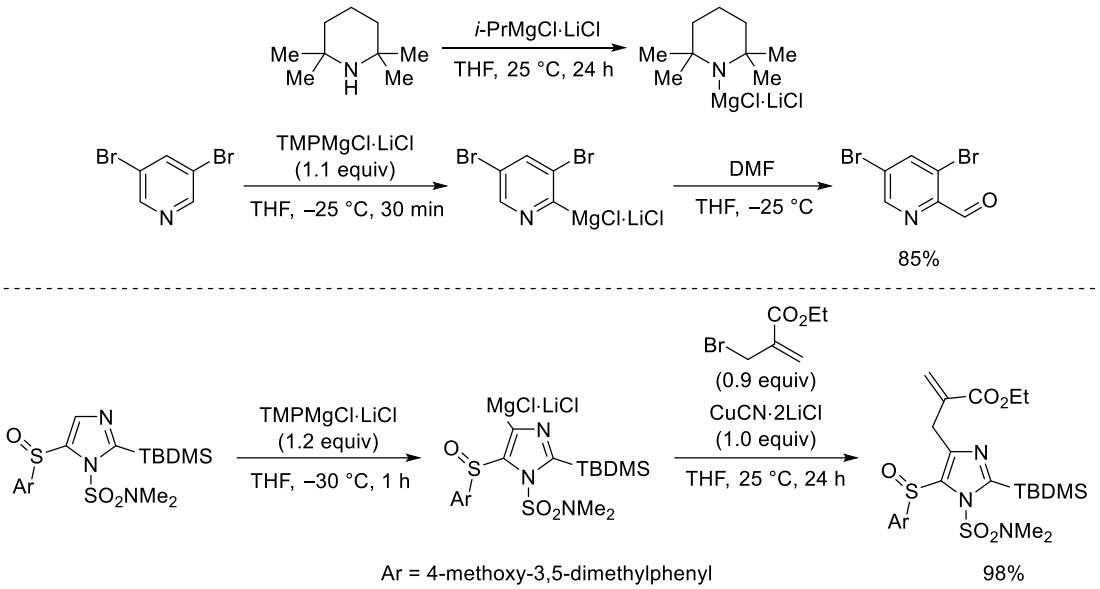


Scheme 12. Halogen/magnesium exchange in toluene.

New selectivities and a strong influence of coordination have been observed.[45] The structure of these reagents has been studied by the Hevia group.[46] To obtain additive-free diorganomagnesium reagents in toluene *s*-Bu_2Mg may be used in I/Mg exchange reactions on both aryl and alkyl iodides.[47] Aryl bromides were exchanged just if they contained strongly electron-withdrawing groups. Vinyl iodides required DMPU as the additive.

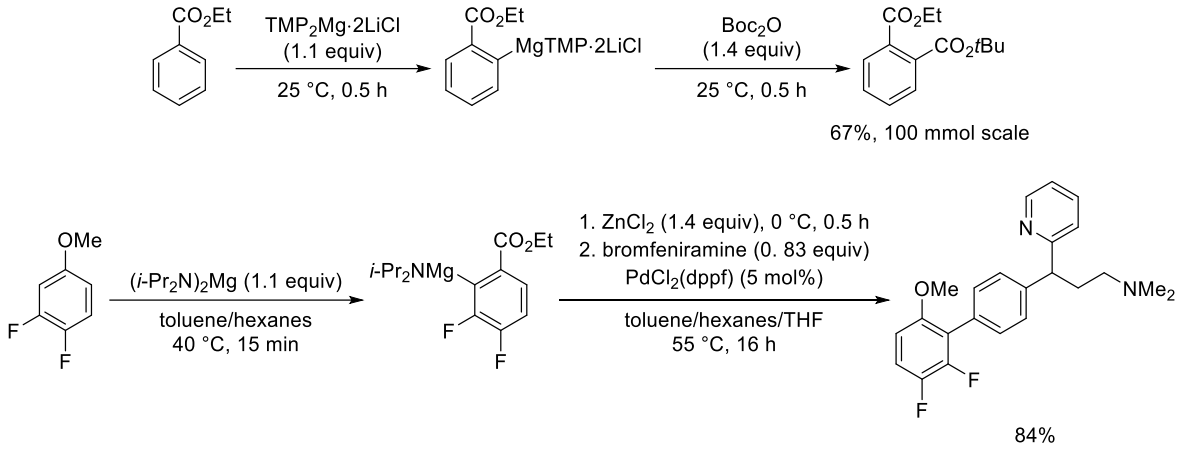
Directed magnesiation is achieved with magnesium amides. Solubility problems in THF associated with reagents of type R_2NMgCl and $(R_2N)_2Mg$ have been solved by the addition of LiCl. Thus, highly soluble mixed Mg/Li amides TMPMgCl·LiCl (Scheme 13) and TMP_2Mg·2LiCl (Scheme 14) have been used for the metalation of sensitive substrates containing ester, nitrile or ketone functionalities.[48] TMPMgCl·LiCl is a stable reagent while TMP_2Mg·2LiCl decays over a few days. New magnesium bases in hydrocarbon solvents such as hexane and toluene have been developed and used in metalations of various arene and heteroarene substrates.[49]

[45] A. Desaintjean, T. Haupt, L. J. Bole, N. R. Judge, E. Hevia, P. Knochel *Angew. Chem. Int. Ed.* **2021**, *60*, 1513.
[46] a) L. J. Bole, N. R. Judge, E. Hevia, *Angew. Chem. Int. Ed.* **2021**, *60*, 7626; b) L. J. Bole, E. Hevia, *Nat. Synth.* **2022**, *1*, 195.
[47] a) A. Desaintjean, F. Danton, P. Knochel, *Synthesis* **2021**, *53*, 4461; b) A. S. Sunagatulina, F. H. Lutter, P. Knochel *Angew. Chem. Int. Ed.* **2022**, *61*, e20211662.
[48] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503.
[49] a) A. Hess, N. Alandini, Y. C. Guersoy, P. Knochel, *Angew. Chem. Int. Ed.* **2022**, *61*, e202206176; b) A. Hess, N. Alandini, H. C. Guelen, J. P. Prohaska, P. Knochel, *Chem. Commun.* **2022**, DOI: 10.1039/D2CC03856K.



Scheme 13. Metalations with TMPMgCl·LiCl.

Moreover, it is important to emphasise that TMPMgCl·LiCl is compatible with strong Lewis acids such as $BF_3{\cdot}OEt_2$ at low temperatures (–40 °C). Such frustrated Lewis pairs often show different regioselectivities and activities towards challenging substrates compared to TMPMgCl·LiCl (Scheme 15).[50]

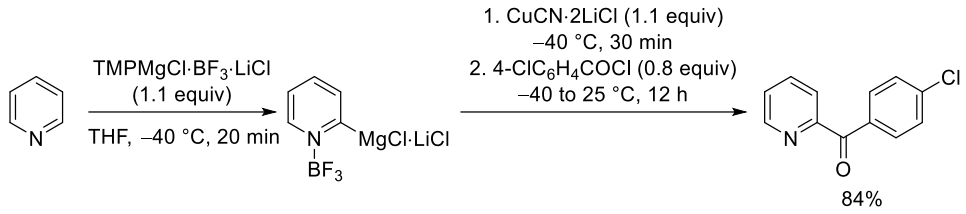


Scheme 14. $TMP_2Mg{\cdot}2LiCl$ and $(i\text{-}Pr_2N)_2Mg$ mediated metalations.

Since their discovery, these reagents have been used to metalate many complex heterocycles.[51]

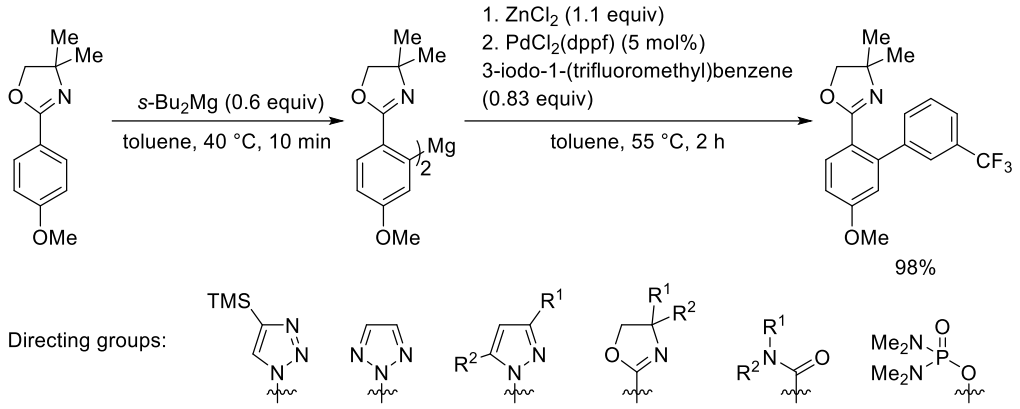
[50] a) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451; b) M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, 13, 2306.

[51] a) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497; b) N. Boudet, S. R. Dubbaka, P. Knochel, *Org. Lett.* **2008**, *10*, 1715; c) C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326; d) C. Sämann, E. Coya, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *53*, 1430; e) J. Nafe, S. Herbert, F. Auras, K. Karaghiosoff, T. Bein, P. Knochel, *Chem. Eur. J.* **2015**, *21*, 1102; f) M. Balkenhohl, R. Greiner, Ilya S. Makarov, B. Heinz, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 13046; g) M. Balkenhohl, B. Salgues, T. Hirai, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2018**, *20*, 3114.



Scheme 15. $BF_3 \cdot OEt_2$ promoted metalation of pyridine.

Alkylmagnesium reagents are seldomly used for metalations due to their high nucleophilicity, but recently Knochel *et al*. reported the metalation reactions of activated heterocyclic substrates with *s*-Bu_2Mg in toluene (Scheme 16).[52]



Scheme 16. Metalations with *s*-Bu_2Mg in toluene.

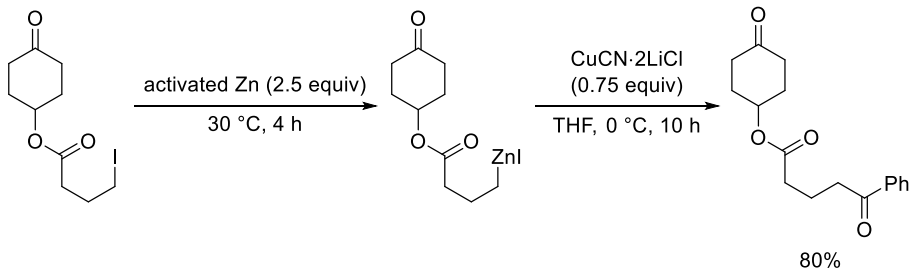
2.4 Preparation and Reactions of Organozinc Reagents

Since the preparation of diethylzinc in 1848 by E. Frankland zinc reagents have found numerous applications in organic synthesis. Except for zinc carbenoids (Simmons-Smith[53] and Furukawa[54] reagents) and zinc enolates (Reformatsky reagents) their potential has been recognised only recently with the emergence of cross-coupling reactions. Due to the high covalent character of the C-Zn bond (ca. 85%), organozinc reagents are inert to electrophiles such as nitriles, esters, ketones and, in some cases, aldehydes. However, the presence of low-lying p-orbitals at the Zn centre allows smooth transmetalation reactions with various transition metal complexes. Indeed, most applications of organozinc reagents require reactivity enhancement by transition metal salts rather than a direct reaction of organozinc with electrophiles.

Direct insertion of Zn metal into organic halides is the method of choice for the preparation of primary organozinc halides. Those reactions are conducted in polar organic solvent (THF, DMF, acetonitrile, DMSO) usually at a slightly elevated temperature. The most commonly used is Zn dust, activated by

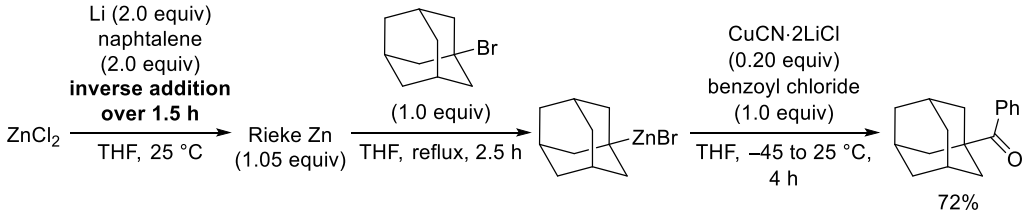
[52] a) F. H. Lutter, L. Grokenberger, L. A. Perego, D. Broggini, S. Lemaire, S. Wagschal, P. Knochel, *Nat. Commun.* **2020**, *11*, 4443; b) A. Hess, J. P. Prohaska, S. B. Doerrich, F. Trauner, F. H. Lutter, S. Lemaire, S. Wagschal, K. Karaghiosoff, P. Knochel, *Chem. Science.* **2021**, *12*, 8424; c) A. Hess, H. C. Guelen, N. Alandini, A. Mourati, Y. C. Guersoy, P. Knochel *Chem. Eur. J.* **2022**, *28*, e202103700.
[53] A. B. Charette, A. Beauchemin, *Org. React.* **2004**, *58*, 1.
[54] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53.

the addition of a small amount of 1,2-dibromoethane and chlorotrimethylsilane.[55] Zn foil can be used in preparation of benzylic zinc reagents.[56] Without any additives, Zn dust reacts with secondary alkyl iodides at room temperature and with primary at 30-50 °C (Scheme 17).[57]



Scheme 17. Insertion of Zn dust into functionalized alkyl iodide.

Highly activated Rieke zinc reacts with alkyl bromides at room temperature and with aryl bromides under THF reflux (Scheme 18).[58]



Scheme 18. Insertion of Rieke zinc into 1-bromoadamantane.

Knochel *et al.* have found that commercial Zn dust in the presence of LiCl in THF can be used for the insertion into a broad range of alkyl bromides and aryl iodides in excellent yields and with broad functional group compatibility (Scheme 19).[59] The scope of this procedure is expanded to alkenyl bromides, benzylic and allylic chlorides.[60] Mechanistic investigations showed that LiCl enables solubilisation of metal-bound zinc species, thus keeping the surface clean, which is essential for insertion reactions.[35] In fact, Blum *et al.* have shown that the supernatant of Rieke zinc dictates its reactivity.[61] For example, when Rieke zinc is obtained by reduction of $ZnCl_2$ with Li source the

[55] a) E. Erdik, *Tetrahedron* **1987**, *43*, 2203; b) G. Picotin, P. Miginiac, *J. Org. Chem.* **1987**, *52*, 4796; c) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; d) S. Achyutha Rao, P. Knochel, *J. Am. Chem. Soc.* **1991**, *113*, 5735; e) M. C. P. Yeh, H. G. Chen, P. Knochel *Org. Synth.* **1992**, *70*, 195; f) G. Casotti, A. Iuliano, A. Carpita, *Eur. J. Org. Chem.* **2019**, 1021.

[56] S. C. Berk, M. C. P. Yeh, N. Jeong, P. Knochel, *Organometallics* **1990**, *9*, 3053.

[57] a) P. Knochel, R. Singer, *Chem. Rev.* **1993**, *93*, 2117; b) A. Fürstner, R. Singer, P. Knochel, *Tetrahedron Lett.* **1994**, *35*, 1047.

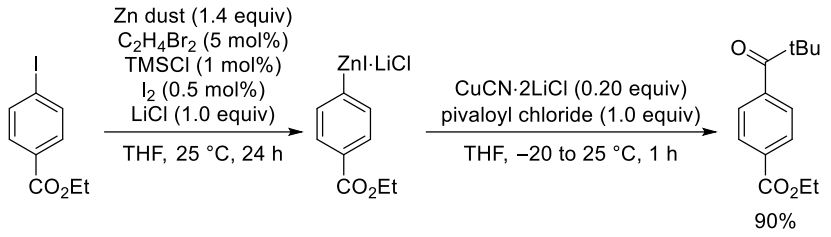
[58] a) R. D. Rieke, P. M. Hudnall, S. T. Uhm, *J. Chem. Soc., Chem. Commun.* **1973**, 269; b) R. D. Rieke, *Science*, **1989**, *246*, 1260; c) L. Zhu, R. D. Rieke *Tetrahedron Lett.* **1991**, *32*, 2865; d) R. D. Rieke, M. S. Sell, H. Xiong, *J. Am. Chem. Soc.* **1995**, *117*, 5429; e) R. D. Rieke S.-H. Kim, X. Wu *J. Org. Chem.* **1997**, *62*, 6921; f) A. Guijarro, R. D. Rieke, *Angew. Chem. Int. Ed.* **1998**, *37*, 1679.

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

[60] a) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376; b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; c) C. Sämann, M. A. Schade, S. Yamada, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 9495.

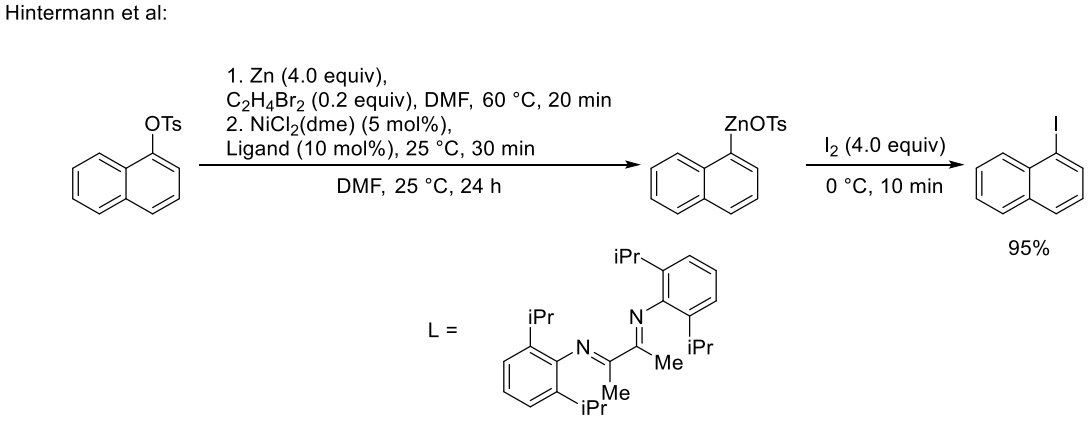
[61] E. M. Hanada, T. K. S. Tagawa, M. Kawada, S. A. Blum, *J. Am. Chem. Soc.* **2022**, *144*, 12081.

supernatant contains LiCl. When the reduction is done with Na source the supernatant contains NaCl. The Rieke zinc with LiCl showed significantly higher activity.



Scheme 19. Insertion of zinc dust into aryl iodides enhanced by LiCl.

It is also worth pointing out that insertion in many (hetero)aryl bromides with electron deficient groups proceeds smoothly but reactions with electron rich aryl bromides are more challenging. Transition metal salts such as $CoBr_2$ or $NiCl_2$ are able to catalyse such reactions (Scheme 20).[62]



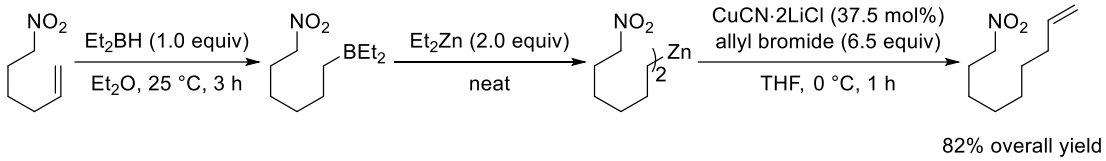
Scheme 20. Ni-catalyzed insertion of zinc dust into aryl tosylates.

The presence of very acidic protons is generally not tolerated but moderately acidic protons of primary and secondary amines and even amides are.[63]

The halogen/zinc exchange is an excellent way to prepare diorganozinc reagents. Halogen/Metal exchange reactions are reversible. The desired reaction outcome can be achieved by a careful choice of the exchange reagent. In general, the more stabilized organometallic will be favoured over the unstabilized. For example, diethylzinc reacts directly with higher homologues of alkyl iodides. The shift in equilibrium can be explained by the evaporation of ethyl iodide from the reaction mixture. Also, the C-Zn bond in diethylzinc is much more reactive and less strong than the C-Zn bond in higher alkylzinc derivatives.[64] Same as direct insertion of Zn metal, the I/Zn exchange can be catalyzed using transition

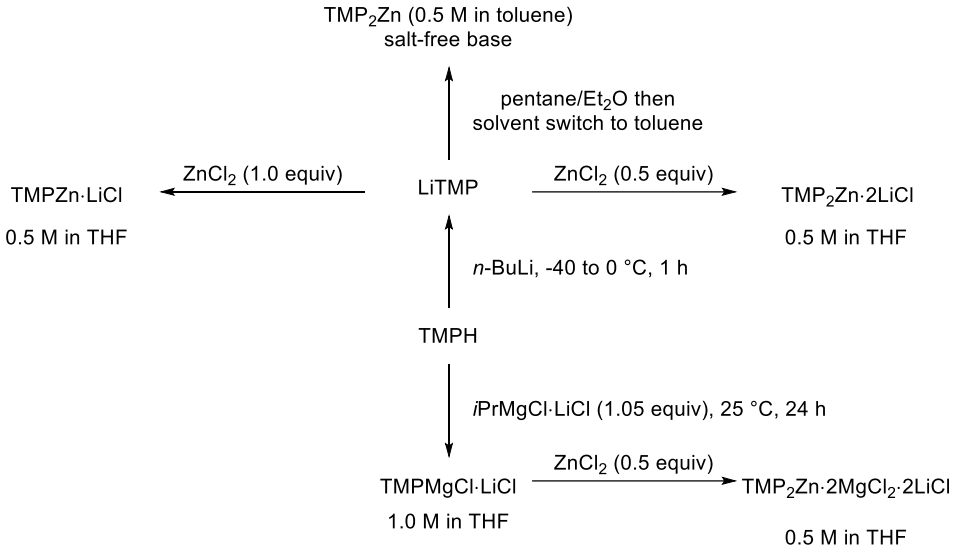
[62] a) H. Fillon, C. Gosmini, J. Périchon, *J. Am. Chem. Soc.* **2003**, *125*, 3867; b) M.-Y. Jin, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 1972; c) P. Klein, V. D. Lecher, T. Schimmel, L. Hintermann, *Chem. Eur. J.* **2020**, *26*, 176.
[63] a) C. S. Dexter, R. F. W. Jackson, J. Elliott, *J. Org. Chem.* **1999**, *64*, 7579; b) H.-S. Jung, S.-H. Kim, *Tetrahedron Lett.* **2015**, *56*, 1004.
[64] M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956.

metals such as Cu, Ni or Pd.[65] Knochel *et al.* have reported nucleophilic catalysis of I/Zn exchange using Li(acac) to obtain diorganozinc reagents with remarkable functional group tolerance.[66] Another way to synthesise highly functionalized diorganozincs is the boron/zinc exchange (Scheme 21).[67] This circumvents the preparation of halogenated derivatives. Additionally, various borons are available by hydroboration of alkenes. More recently, Knochel and coworkers reported the I/Zn exchanges in toluene using alkoxide additives.[68]



Scheme 21. Boron-zinc exchange for the preparation of dialkylzincs.

Another approach to obtain organozinc reagents is by directed metalation. Knochel and co-workers developed TMP-derived Zn-bases for metalations of sensitive substrates (Scheme 22). These amide bases are obtained by transmetalation of TMPLi or TMPMgCl·LiCl with $ZnCl_2$ (0.5 or 1.0 equiv).

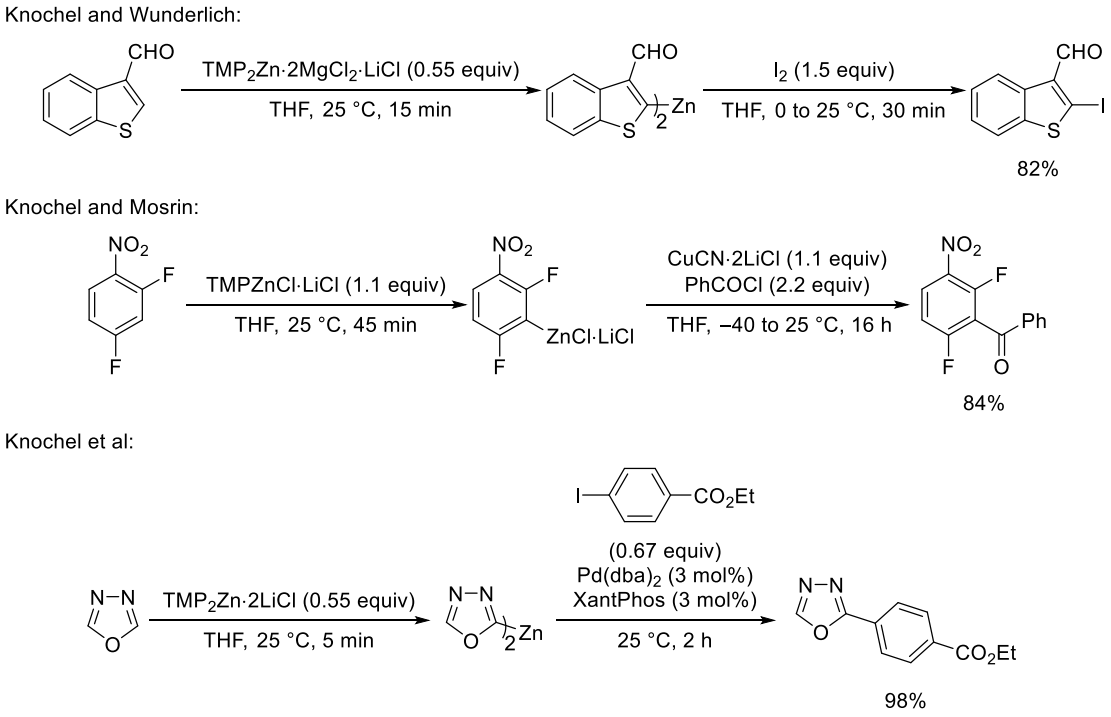


Scheme 22. Various TMPZn bases derived from TMPLi and TMPMgCl·LiCl.

[65] a) M. J. Rozema, C. Eisenberg, H. Lütjens, K. Belyk, *Tetrahedron Lett.* **1993**, *34*, 3115; b) I. Klement, P. Knochel, K. Chau, G. Cahiez, *Tetrahedron Lett.* **1994**, *35*, 1177.
[66] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[67] a) L. I. Zakharkin, O. Y. Okhlobystin, *Z. Obsc. Khim.* **1960**, *30*, 2134 (in English, **1960**, 2109), *Chem. Abstr.* **1961**, *55*, 9319a; b) K.-H. Thiele, G. Engelhardt, J. Köhler, M. Arnstedt, *J. Organomet. Chem.* **1967**, *9*, 385; c) W. Oppolzer, R. N. Radinov, *Tetrahedron Lett.* **1988**, *29*, 5645; d) M. Srebnik *Tetrahedron Lett.* **1991**, *32*, 2449; e) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1992**, *75*, 170; f) W. Oppolzer, R. N. Radinov, *J. Am. Chem. Soc.* **1993**, *115*, 1593; g) W. Oppolzer, R. N. Radinov, J. de Brabander, *Tetrahedron Lett.* **1995**, *36*, 2607; h) F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229.
[68] 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; b) F. Sanchez, A. Desaintjean, F. Danton, P. Knochel, *Synthesis*, **2021**, *53*, 4662.

The role of LiCl in these mixed metal amides is to improve solubility. Generally, $MgCl_2$-free bases such as TMPZnCl·LiCl or TMP_2Zn·2LiCl are milder than those containing $MgCl_2$.[69],[70]For example, using TMPZnCl·LiCl sensitive nitro and aldehyde functionalities are tolerated and no sub-ambient temperatures are necessary (Scheme 23). Remarkably, high temperatures and/or microwave irradiation can be used for unreactive substrates.[71] Due to the homogenous nature of the metalation reactions, scale-up procedures have been developed.[72]

$TMPZn(tBu)_2$ is a zincate base developed by Kondo and coworkers and was one of the first TMPZn bases.[73] Many similar zincate bases have been used for deprotonative metalation of arene substrates.[74] In contrast to bimetallic or trimetallic TMPZn bases, salt-free TMP_2Zn in toluene has been used mostly for enolization reactions.[75]



Scheme 23. Zincations using various TMPZn bases.

Transmetalation of polar organometallics such as organolithiums and organomagnesiums with Zn salts (typically $ZnCl_2$ or $ZnBr_2$) leads to more covalent organozincs. The reaction scope and functional group tolerance are dependent on the availability of starting organometallics. Interestingly, *in situ*

[69] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; K. Schwärzer, C. P. Tüllmann, S. Graßl, B. Gorski, C. E. Brocklehurst, P. Knochel, *Org. Lett.* **2020**, *22*, 1899.
[70] S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.
[71] a) S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; b) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.
[72] a) T. Bresser, G. Monzon, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 1299; b) L. Klier, D. S. Ziegler, R. Rahimoff, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2017**, *21*, 660.
[73] Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539.
[74] R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.
[75] a) M. L. Hlavinka, J. R. Hagadorn, *Organometallics*, **2007**, *26*, 4105; b) Y. Chen, D. Huang, Y. Zhao, T. R. Newhouse, *Angew. Chem. Int. Ed.* **2017**, *56*, 8258; c) D. Huang, Y. Zhao, T. R. Newhouse, *Org. Lett.* **2018**, *20*, 684; d) D. Huang, D. Olivieri, Y. Sun, P. Zhang, T. R. Newhouse, *J. Am. Chem. Soc.* **2019**, *141*, 16249; e) P. Zhang, D. Huang, T. R. Newhouse, *J. Am. Chem. Soc.* **2020**, *142*, 1757.

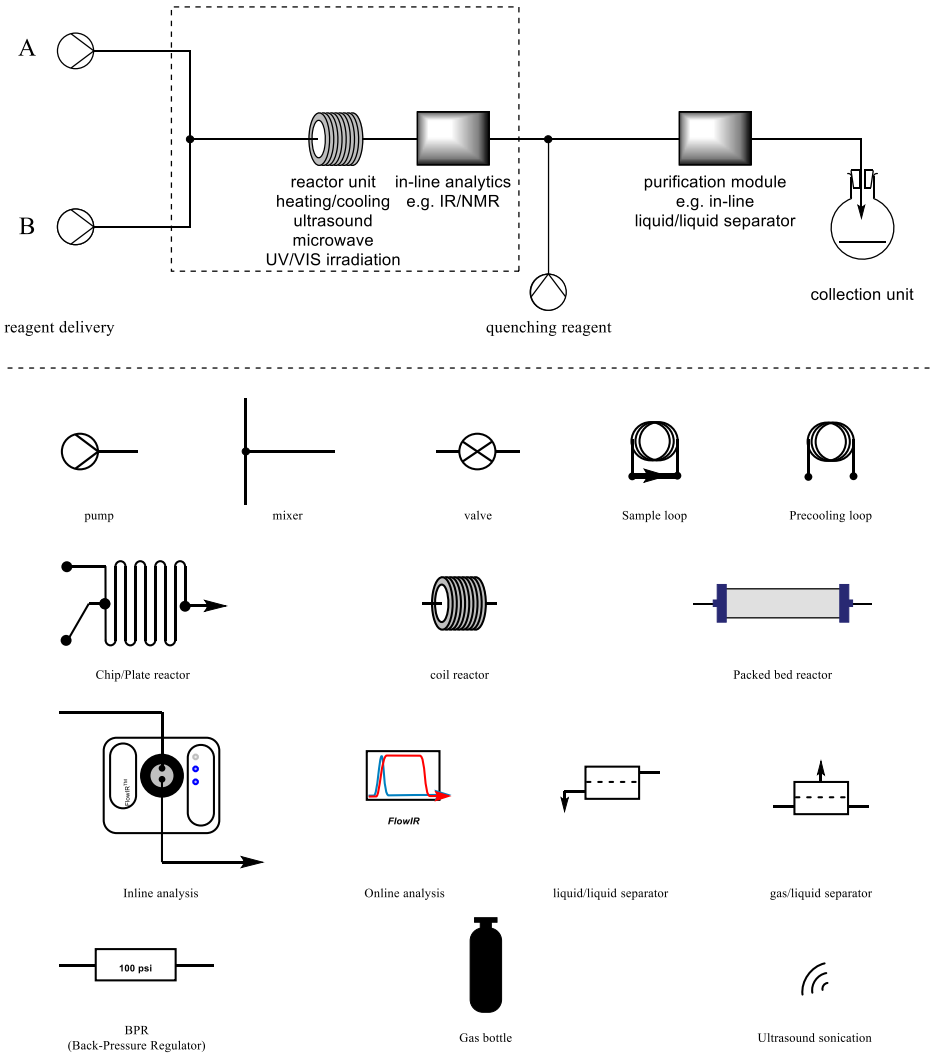
transmetalations, where parent organometallic is generated in the presence of Zn salt, are also possible.[29,76] Transmetalation of organomagnesium reagents with $ZnCl_2$ furnishes organozinc reagents containing magnesium salts. It was shown that such organozinc reagents react faster with aldehydes and even ketones than ordinary $MgCl_2$-free organozincs.[77] The preparation of salt-free organozincs is also important for catalytic asymmetric addition reactions. The addition of $Zn(OMe)_2$ to solutions of Grignard reagents in diethyl ether causes the precipitation of Mg-salts and simultaneous transfer of organic residues to Zn centre (transmetalation).[78]

[76] a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; c) A. Unsinn, S. H. Wunderlich, P. Knochel, *Adv. Synth. Catal.* **2013**, *355*, 989.
[77] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.
[78] A. Cote, A. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 2771.

3. Continuous Flow Chemistry

3.1 Introduction

Flow chemistry is a relatively new enabling technology which uses a modular setup comprised of pumps, mixers and tubings or channels to perform chemical reactions. A common flow setup is shown in Scheme 24. Typically, solutions of reagents are pumped using various pumps into tubings and combined *via* a mixer. After the mixer follows a reactor in which the reaction mixture spends a certain amount of time referred to as residence time. Quenching units, pressure regulators, purification modulus and analytical tools are optional. Depending on the requirement of the process they can be integrated into the setup.



Scheme 24. Graphical representation of continuous flow setup and diagram legend.

There are several advantages of continuous flow chemistry over its batch counterpart. First, as a relatively small amount of reagents is reacting at one point in time it improves the safety of the process. Generally, flow systems are closed systems where exposure of the operator to chemicals is minimised and occurs only during the preparation of reagent solutions. Excellent mixing improves mass transfer significantly in comparison with normal batch chemistry.

The small dimensions of reactors and therefore high surface-to-volume ratios enable an excellent heat transfer. This results in precise control of reaction temperature and easy handling of exothermic reactions. Also, heating solvents above their boiling point can be achieved with backpressure regulators. By increasing the pressure in the system the boiling point also increases which enables to use of solvents above the boiling point at the atmospheric pressure. Such use of high temperatures and pressures ("novel process windows") can reduce reaction times to mere seconds and improve the overall productivity of the system (process intensification).

Finally, the continuous flow has given new paradigms such as "on-demand" synthesis and continuous manufacturing. Although flow equipment is expensive for common laboratories, the cost/benefit ratio shifts with respect to pilot and manufacturing scale batch equipment. Because of easily switchable modules, continuous flow equipment actually saves space and time in industry settings. Moreover, the scale of production can be significantly varied by simply changing the collection time. This gives new flexibilities to production facilities which can now respond to the demands of the market in a timely manner and avoid product shortages.

3.2 Principles of Continuous Flow Chemistry

To understand continuous flow chemistry some of the basic principles of microfluidics as well as reaction setup will be discussed.

The degree to which mixing is influencing a reaction is a major question of whether the reaction should be run in continuous flow. Batch and flow reactions exhibit different mixing mechanisms.

The Reynolds number (Re) depends on flow rates (Q), hydraulic diameter (D_H), channel width (A) and viscosity of the liquids (ν) (Equation 1). There are three flow regimes: laminar, transitional and turbulent. Low Re (< 100) shows truly laminar flow, 100 < Re < 2500 is transient flow and Re > 2500 is turbulent. In batch, a mixing in small area next to the stirring bar is turbulent, while in the bulk of solution laminar/transitional mixing dominates. The main mechanism for mixing in the laminar regime is diffusion.

$$Re = \frac{Q D_H}{\nu A}$$

Equation 1. Reynolds number.

In the tube, reactor diffusion times are inherently smaller and therefore mixing is achieved faster than in batch. For comparison, a molecule inside a cell (ca. 10 μm) can diffuse from one side to the other in 5 ms, while the diffusion of a molecule from a centre of the flask to the wall will take hours.

The real significance of the mixing is seen in the Damköhler number (Da), a ratio of the rate of reaction and the rate of mass transfer in laminar flow (Equation 2). For reactions where Da < 1 homogeneity can be achieved before a reaction occurs (kinetic controlled reactions). Reactions where Da > 1 are faster than mass transfer (diffusion controlled reactions), which causes concentration gradients within the system. These concentration gradients are generally detrimental and lead to side products.

$$D_a = \frac{rate\ of\ reaction}{rate\ of\ diffusion}$$

Equation 2. Damköhler number.

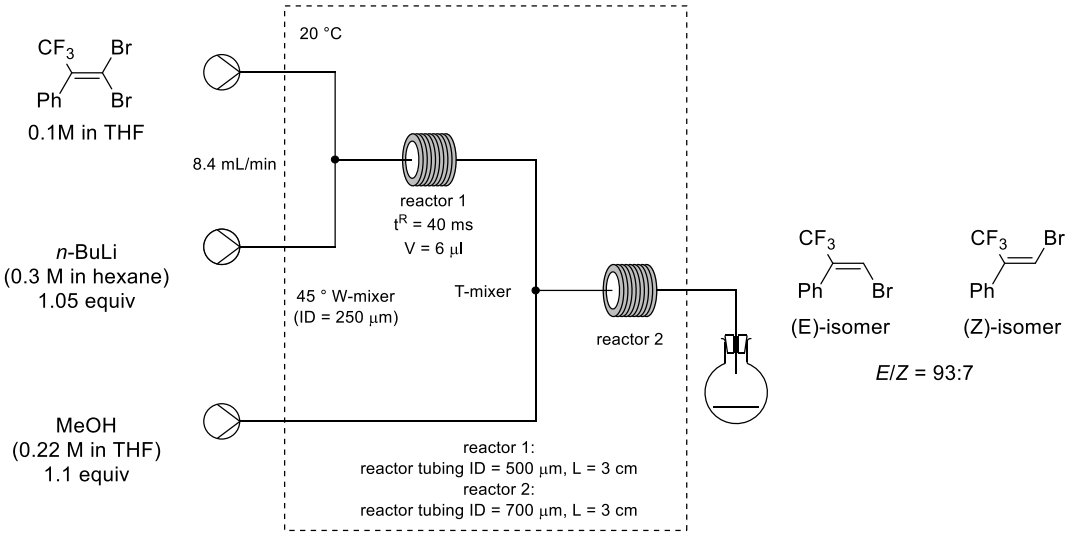
Roberge and co-workers have classified reactions into three types where a continuous flow process would be advantageous based on their kinetics:[79]

- Type A reactions occur in less than 1 s are very sensitive and often require special mixers to obtain the best possible results
- Type B reactions occur between 1 s and 10 min can have flow benefits but mixing is not crucial
- Type C reactions have reaction times > 10 min and these reaction can benefit from a continuous flow process only with increased safety or process intensification

3.3 Mixers in Continuous Flow Setup

From a practical aspect, flow regime and mixing are determined by the diameter of the tubing, type of mixer, flow rates and heterogeneity of reaction. For single phase reaction, the simplest way to achieve good mixing is a small internal diameter T-mixer in combination with high flow rates.

Legros and co-workers have studied the Br/Li exchange of gem-dibromoalkene and the performance of micromixers with different angles between the channels (Scheme 25).[80a,b] All mixers showed higher conversions and better selectivity (Fritsch-Buttemberg-Wiechell rearrangement as side reaction) with higher flow rates. However, the E/Z ratio varied significantly. Fine tuning of the angle between the channels θ led to high E selectivity for θ = 45° (W-shaped mixer). According to the authors control of aggregation state of *n*-BuLi indirectly by control of the mixing of hexane (*n*-BuLi solution) and THF (substrate solution).



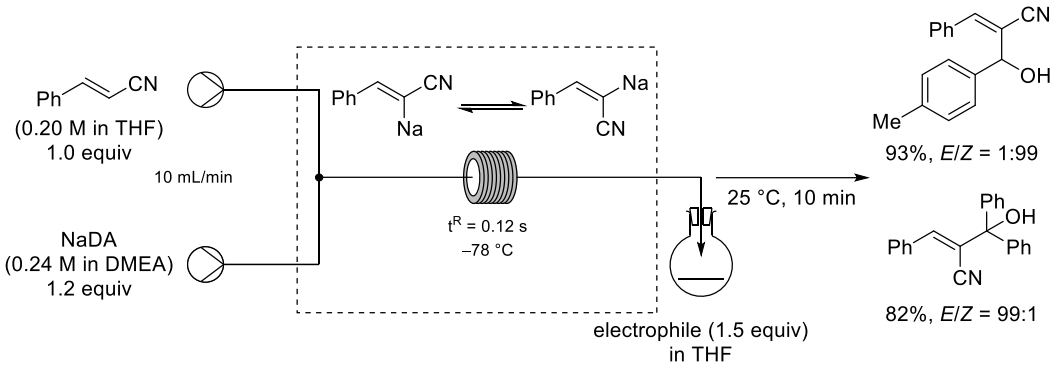
Scheme 25. Influence of micromixer shape (angle between streams) on the selectivity of the Br/Li exchange.

Similar geometry switch of alkenyl metals was observed by Knochel *et al*. (Scheme 26) as well as by Yoshida and Kim (Scheme 27).[80c,d]

Interestingly, Knochel *et al.* fount that depending on the bulk of electrophile, both *E* and *Z* acrylonitriles could be obtained (Scheme 26). Thus, when the 4-methylbenzaldehyde quench was performed, the

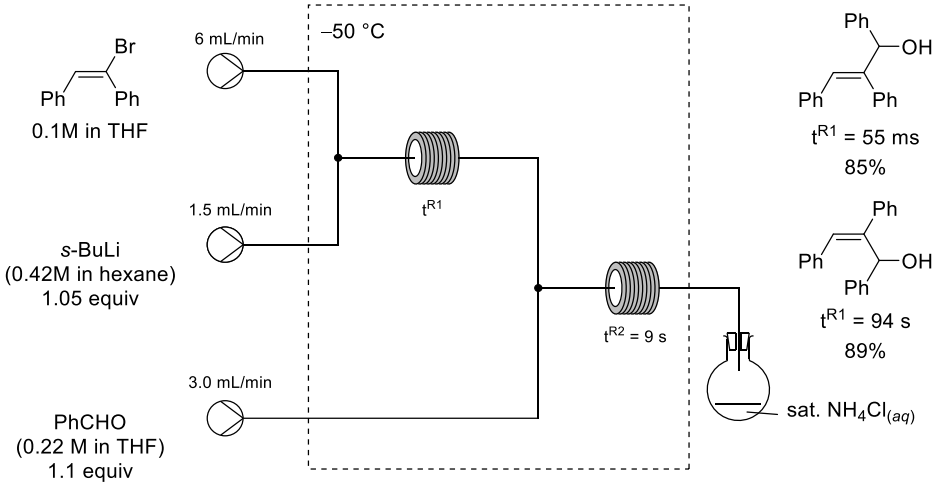
[79] D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, *Chem. Eng. Technol.* **2005**, *28*, 318.
[80] a) B. Picard, K. Pérez, T. Lebleu, D. Vuluga, F. Burel, D. C. Harrowven, I. Chataigner, J. Maddaluno, J. Legros, *J. Flow Chem.* **2020**, *10*, 139; b) K. Pérez, B. Picard. D. Vuluga, F. Burel, R. Hreiz, L. Falk, J.-M. Commenge, A. Nagaki, J.-I. Yoshida, I. Chataigner, J. Maddaluno, J. Legros, *Org. Process Res. Dev.* **2020**, *24*, 787; c) H.-J. Lee, Y. Yonekura, N. Kim, J.-I. Yoshida, H. Kim, *Org. Lett.* **2021**, *23*, 2904; d) J. H. Harenberg, N. Weidmann, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 731.

reaction furnished just the *Z* isomer. On the other hand when benzophenone was used as an electrophile, only the *E* isomer could be found. The structures were confirmed by X-Ray diffraction studies.[80d]



Scheme 26. Geometric fluidity of 2-sodiated acrylonitriles in continuous flow.

In the study by Yoshida and Kim (Scheme 27), Br/Li exchange of (*E*)-(1-bromoethene-1,2-diyl)dibenzene led to lithiostilbenes. When very short residence time (t^R = 55 ms) was used the geometry of double bond was preserved. In contrast, longer residence time (t^R = 94 s) for Br/Li exchange led to complete isomerisation of double bond.[80c]



Scheme 27. Preparation of (*E*)- and (*Z*)-Lithiostyrene in a continuous flow by Br/Li exchange.

In comparison with a simple T-mixer, more efficient alternatives include split-and-recombine mixers (SAR)[81] and multilamination mixers (Figure 1). On the industrial and lab scale, static mixers are most commonly included. They generate turbulence and intense lamellae arrangements by using the energy of the moving fluid itself. Active mixing is used typically when solids are formed during the reaction. Instead of mechanical agitation, submerging the mixing or reactor unit into a ultrasonic bath is also helpful especially in cases when precipitate slowly forms in the reactor.

[81] a) V. Victorov, R. Mahmud, C. Visconte, *Micromachines* **2015**, *6*, 1166; b) R. A. Taheri, V. Goodarzi, A. Allahverdi, *Micromachines* **2019**, *10*, 786; c) T. Frey, R. Schlütemann, S. Schwarz, P. Biessley, M. Hoffman, M. Grünewald, M. Schlüter, *J. Flow Chem.* **2021**, *11*, 599.

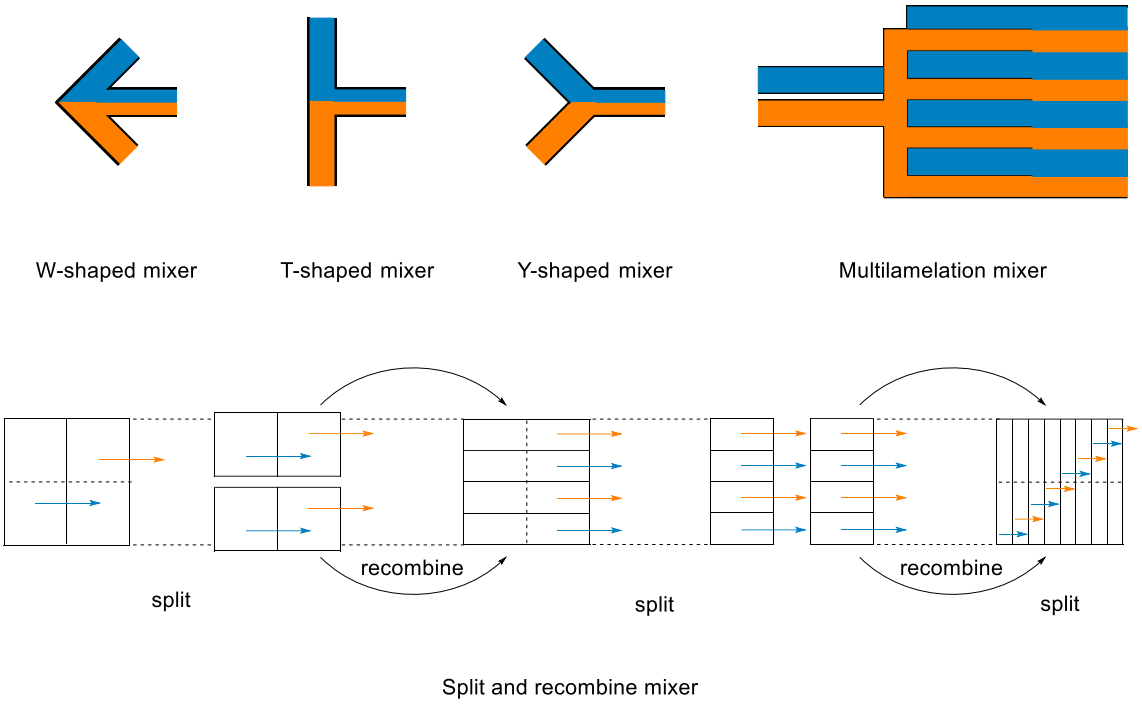


Figure 1. Graphical representation of flow mixers including W, T and Y-shaped mixers, split and recombine and multilamelation mixers.

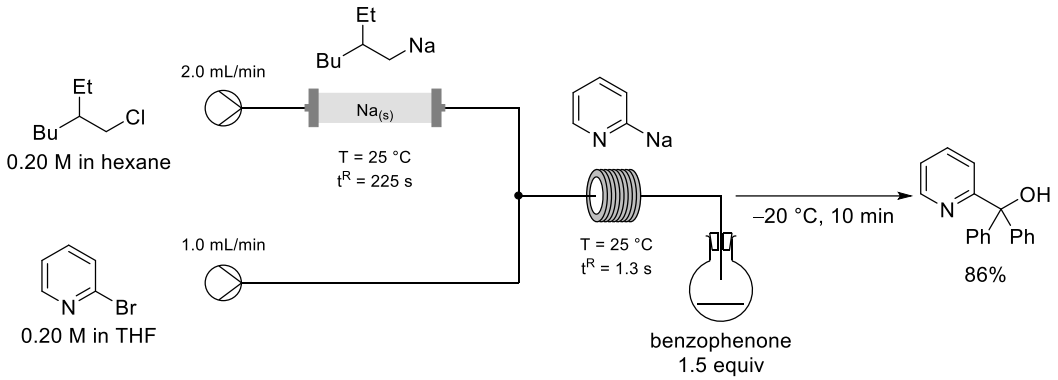
3.4 Reactors in Continuous Flow Setup

The reactor unit is the heart of every flow system. The reactors can be chip, coil and packed bed reactors (Figure 2). The nature of the transformation and reaction conditions determine the material and other features (e.g. photochemical reactors include a light source). Chip reactors offer the best heat transfer characteristics but have low throughput, are expensive and clog easily. They can be made out of glass, silicon or stainless steel.

Figure 2. Pictures of chip (picture taken by Peter Dowling), coil and packed-bed reactors (picture taken by Johannes H. Harenberg).

Coil reactors are most widely used. They are made out of inert fluoropolymers (PTFE, PFA, FEP) or stainless steel and are available in the form of tubing of various internal diameters.

Finally, packed-bed reactors represent a solid (powder or particles) in between two filters through which the reaction solution is passed. The solids can be stoichiometric reagents or immobilized catalysts. Stoichiometric reagents in packed-bed reactors are of limited use since they get spent over time, which directly influences the conversion and pressure in the system. Nevertheless, on a laboratory scale they have shown practical for on-demand preparation of organometallics *via* direct metal insertion.[82] The authors claim that such a way of preparing organometallics is advantageous as better purity is obtained in comparison with batch and commercially available reagents. In Scheme 28 is the exemplified insertion of sodium metal (particle size: <0.1 mm, activated by stirring in hexane) into 2-ethylhexylchloride (0.20 M in hexane).[82f] 2-Ethylhexylsodium in hexane is a clear yellow solution, stable for only a couple of hours at room temperature. Thus, continuous flow operation is very beneficial for the on-demand production of 2-ethylhexylsodium. This reagent was suitable for Br/Na exchange and metalations of heterocycles. Preparation of benzylsodium regents in the presence of TMEDA was also accomplished.[82g] Benzylic sodiums were excellent for epoxide opening and Wurtz-type coupling.



Scheme 28. Insertion of metal sodium into 2-ethylhexyl chloride using packed-bed reactor and subsequent Br/Na exchange.

Catalytic heterogeneous reactions in flow on the other hand are very desirable. A local high concentration of catalyst can drive the reaction very fast to completion and side reactions are minimized due to the fast removal of the product from the reactor zone. Nevertheless, problems such as catalyst leaching can occur. In packed-bed microreactors, high resistance for the flow of the liquid is typical if high flow rates are applied, particularly in combination with long columns. This causes a pressure drop, i.e. changes in flow rates and stoichiometry of the downstream reactions. In packed-bed reactors determination of residence time is more complicated than in chip/coil reactors. This is because the volume of the packed-bed reactor is unknown. Therefore it is a better option to measure the residence time (by applying the solution of the dye) than to calculate it. Biochemical transformations in continuous flow are done with immobilized enzymes.[83] Although there are no safety concerns and mixing has no influence, the main benefit of enzymatic reactions in a continuous flow setup is process intensification. When immobilized properly, enzymes are more stable and less sensitive to high

[82] a) N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737; b) A. Hafner, S. V. Ley, *Synlett* **2015**, *26*, 1470; c) I. Abdiaj, C. R. Horn, J. Alcázar, *J. Org. Chem.* **2019**, *84*, 4748; d); f) L. Huck, M. Berton, A. de la Hoz, A. Diaz-Ortiz, J. Alcázar, *Green Chem.* **2017**, *19*, 1420; e) E. Watanabe, Y. Chen, O. May, S. V. Ley, *Chem. Eur. J.* **2020**, *26*, 186; f) J. H. Harenberg, N. Weidmann, A. J. Wiegand, C. A. Hoefer, R. R. Annapureddy, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 14296; g) J. H. Harenberg, R. R. Annapurreddy, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2022**, *61*, e202203807.

[83] a) R. Yuryev, S. Strompen, A. Liese *Beilstein J. Org. Chem.* **2011**, *7*, 1449; b) J. Britton, S. Majumdar, G. A. Weiss, *Chem. Soc. Rev.* **2018**, *47***,** 5891; c) E. Laurenti, A. dos Santos Vianna, *Biocatalysis* **2016**, *1*, 148; d) P. de Santis, L.-E. Meyer, S. Kara, *React. Chem. Eng.* **2020**, *5*, 2155; e) A. I. Benítez-Mateos, M. L. Contente, D. R. Padrosa, F. Paradisi, *React. Chem. Eng.* **2021**, *6*, 599; f) M. Santi, L. Sancineto, V. Nascimento, J. B. Azeredo, E. V. M. Orozco, L. H. Andrade, H. Gröger, C. Santi, *Int. J. Mol. Sci.* **2021**, *22*, 990.

concentrations of reagents and higher temperatures. Microwave irradiation can also be used for process intensification purposes. In batch, low penetration of microwave irradiation is limiting its use on a bigger scale.[84]

3.5 Analytical and Purification Modules in Continuous Flow Setup

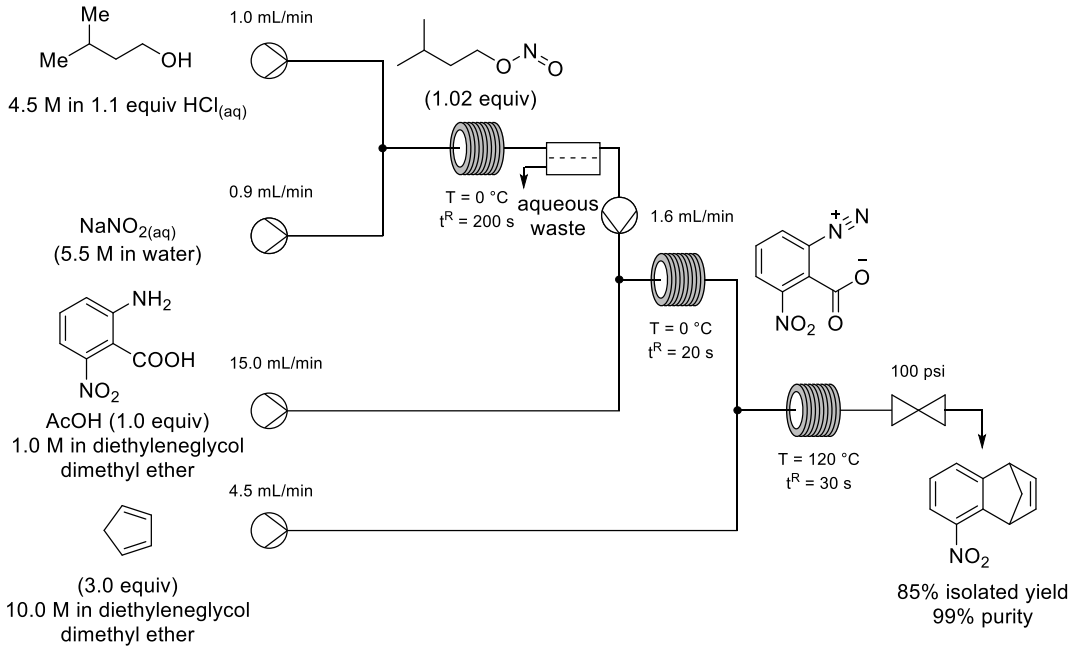
Flow chemistry setup can employ additional analytical tools.[85] Three types of analytical tools can be distinguished: offline, online and inline. Offline analytics means manual sampling and measuring on the device (GC, NMR, …) not directly connected to the flow setup. In general, this approach is sufficient for early-stage optimization of synthetic projects. However, if extensive optimization is pursued or there is a quality control purpose or there are toxic intermediates in the reaction then online and inline analytics is advantageous. Online analytics means automated sampling from the reaction stream directly to the analytical instrument (e.g. HPLC, UPLC). Non-destructive analytical tools such as FTIR, Raman, UV/Vis or NMR spectroscopy can be integrated into a flow-through cell and correspond to what is called inline analytics.[86] Such analysis gives information on the state of the reaction mixture basically at the moment of the measurement which produces "real-time" data. The inline analysis is especially beneficial in the case of reactions such as transmetalations. Transmetalation reactions are hard to follow since the change happens in the C-Met bond and not in the backbone of the molecule. For example, both ArMgCl and ArZnCl species will give the same product (Ar-H) after hydrolysis. The difference is in the *reactivity* of the two organometallics and in their spectroscopic characteristics. Only recently were IR and Raman spectroscopies applied for the tracking of transmetalation progress of RMgCl to RMnCl and RZnCl species.[87] Continuous flow reactors can be coupled with other modules such as sampling devices,[88] extraction devices[89] (e.g. liquid/liquid separator) and distillation modules.[90] Furthermore, automated systems for late-stage optimisations have been developed.[91]

3.6 Handling Hazardous Reagents in Continuous Flow

In scheme 29 a continuous flow preparation and use of diazonium carboxylate in aryne [4+2] cycloadditions are shown.[92] The authors have started from stable, non-toxic compounds. The diazotization reagent, amyl nitrite, was also prepared and purified in continuous flow and reacted with 6-nitroanthranilic acid to give the diazonium carboxylate, an explosive and impact-sensitive compound. Then, cyclopentadiene was introduced into the reaction and this mixture was heated at 120 °C for 30 s to give the final cycloadduct in excellent yield and purity superior to the batch process. Reactors were made from stainless steel (SS316L; 2 mm internal diameter) compatible with 100 psi back-pressure.

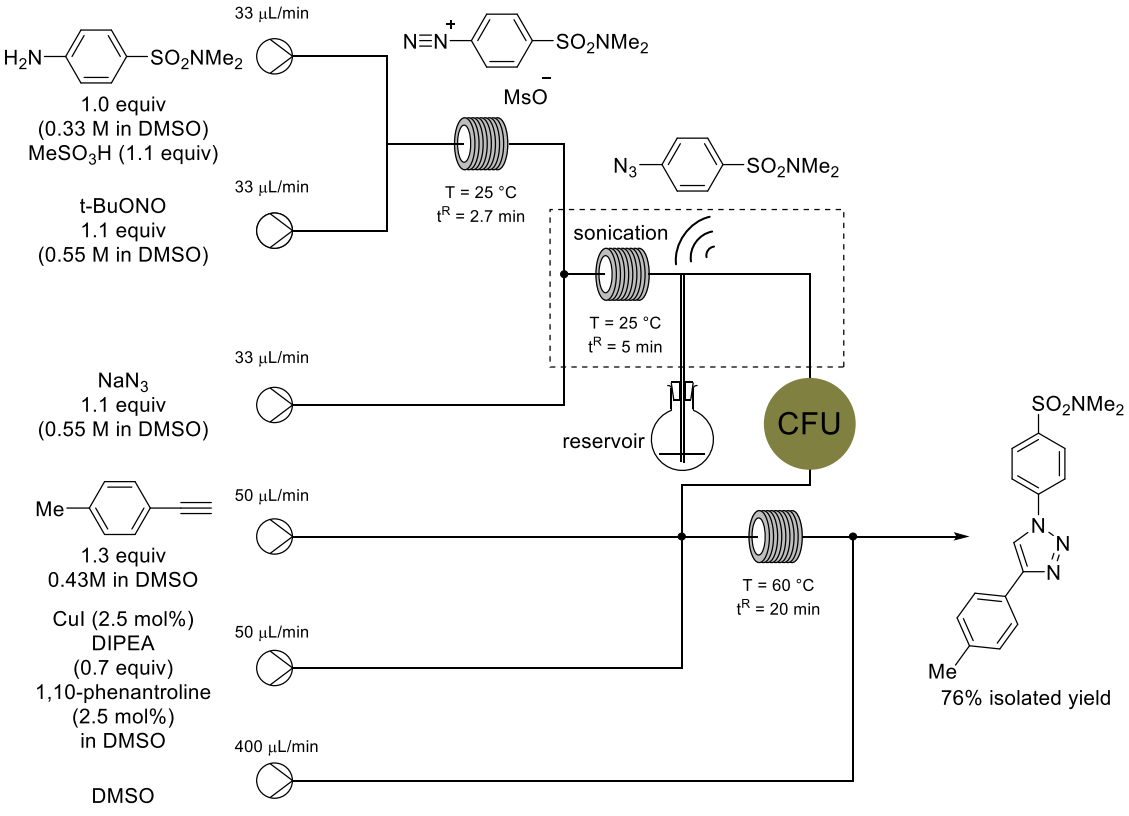
[84] R. Morschhäuser, M. Krull, C. Kayser, C. Boberski, R. Blerbaum, P. A. Püschner, T. N. Glasnov, O. C. Kappe, *Green Process Synth.* **2012**, *1*, 281.
[85] M. Rodriguez-Zubiri, F.-X. Felpin, *Org. Process Res. Dev.* **2022**, *26*, 1766.
[86] K. Sommerville, M. Tilley, G. Li, D. Mallik, M. G. Organ, *Org. Process Res.Dev.* **2014**, *18*, 1315.
[87] a) T. C. Malig, A. Kumar, K. L. Kurita, *Org. Process Res. Dev.* **2022**, *26*, 1514; b) W. Tong, G. Zhou, J. H. Waldman, *Org. Process Res. Dev.* **2022**, *26*, 1184.
[88] J. S. Kwak, W. Zhang, D. Tsoy, H. N. Hunter, D. Malik, M. G. Organ, *Org. Process Res. Dev.* **2017**, *21*, 1051.
[89] C. Day, A. Saldarriaga, M. Tilley, H. Hunter, M. G. Organ, D. J. Wilson, *Org. Process Res. Dev.* **2016**, *20*, 1738.
[90] a) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Chem. Commun.* **2010**, *46*, 2450; b) R. L. Hartman, H. R. Sahoo, B. C. Yen, K. F. Jensen, *Lab Chip* **2009**, *9*, 1843; c) M. Baumann, *React. Chem. Eng.* **2019**, *4*, 368.
[91] a) B. J. Reizman, Y.-M. Wang, S. L. Buchwald, K. F. Jensen, *React. Chem. Eng.* **2016**, *1*, 658; b) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967.
[92] Z. Tan, Z. Li, G. Jin, C. Yu, *Org. Process Res. Dev.* **2019**, *23*, 31.

Due to the release of nitrogen and carbon dioxide, high pressure was necessary to maintain constant residence time and homogeneity of the reaction mixture.



Scheme 29. On-demand production and use of hazardous diazonium carboxylate for the aryne cycloaddition in the synthesis of 5-nitro-1,4-dihydro-1,4-methanonaphtalene.

In another study Organ and coworkers have prepared N^1-triazoles from anilines using a telescoped procedure involving diazotization, azidation and [3+2] cycloaddition (Scheme 30).[91b] Diazonium mesylate was produced by treating ammonium salt with tert-butyl nitrite for 2.7 min at 25 °C.

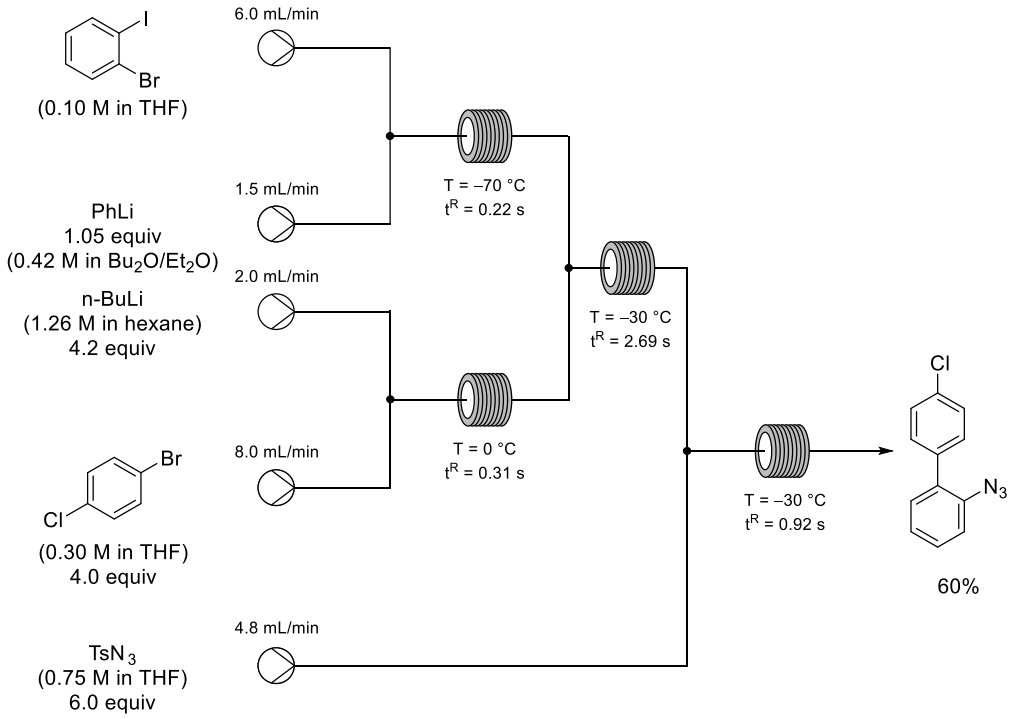


Scheme 30. Synthesis of N^1-aryltriazoles from anilines through hazardous diazonium and azido intermediates.

Then, a DMSO solution of NaN_3 was mixed with a stream of the diazonium salt solution and sonicated for 5 min at 25 °C. The segmented reaction stream was collected in a reservoir to remove the nitrogen gas. A solution of azide was then redirected to Cu-catalyzed cycloaddition (20 min at 60 °C). A dilution pump with DMSO had to be added to prevent clogging. The process was controlled by customised software in a completely automated continuous flow unit (CFU).

3.7 Handling Unstable Intermediates in Continuous Flow

Continuous flow chemistry does not change the kinetics of the reaction but just eliminates concentration gradients which can be detrimental in the case of very fast reactions. This is showcased in Yoshida`s three-component coupling *via* benzyne intermediates (Scheme 31).[93b] Precise generation of 2-bromophenyllithium in continuous flow setup was done within 0.22 seconds at −70 °C. Despite the excellent time and temperature control, the aryne-mediated reaction still required 4.0 equivalents of 4-chlorophenyllithium as the nucleophile. Also, the yields reported (50-73%) match the previous batch reports.[93a] Therefore, flow chemistry is not changing the kinetics or thermodynamics of the reaction in any way but just enables better control of the reaction parameters, reproducibility and handling of unstable reaction intermediates.

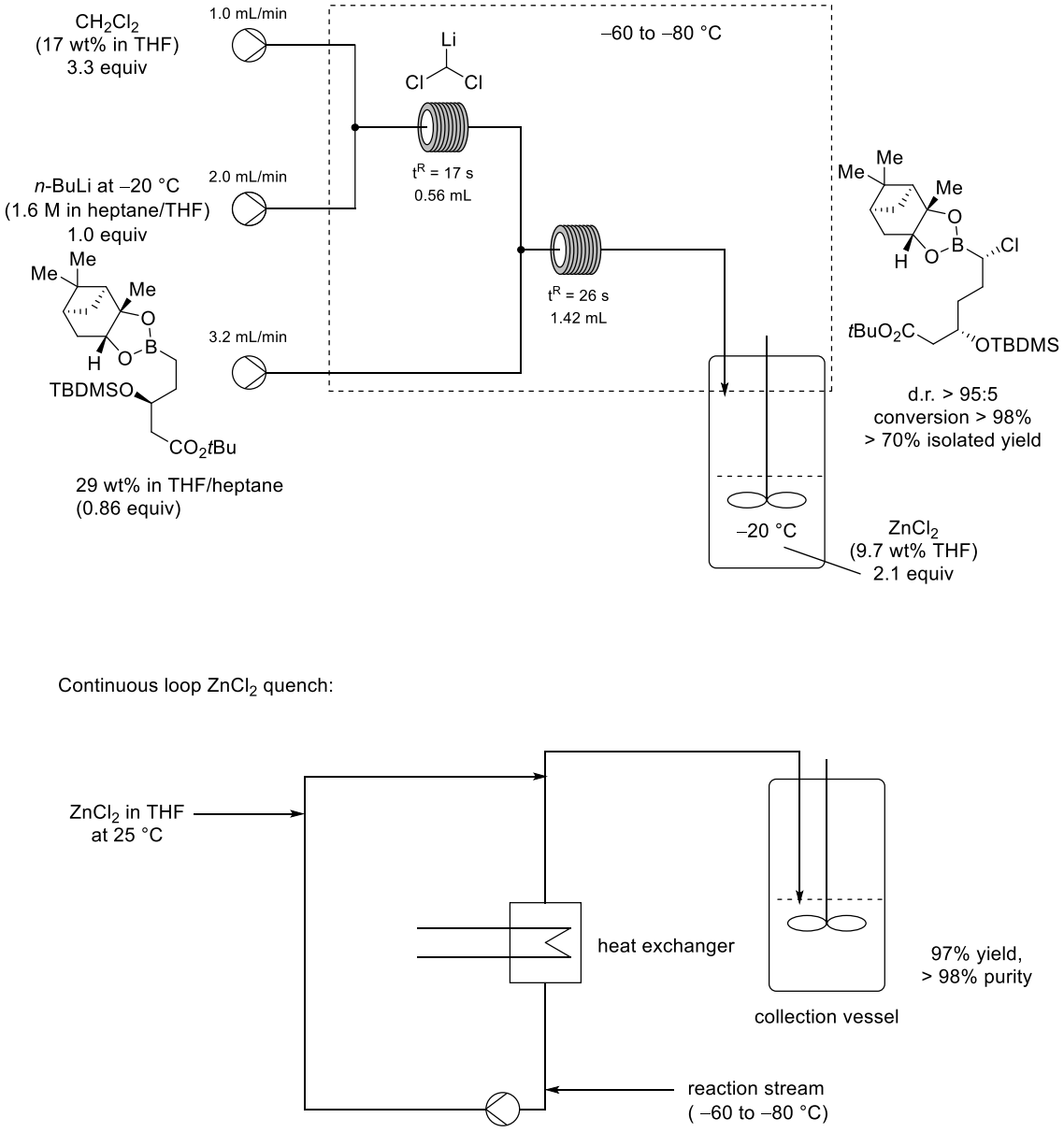


Scheme 31. Three-component aryne coupling in continuous flow.

Another example of unstable species is metal carbenoids.[94] Lithium carbenoids, in particular, pose a serious experimental challenge due to high instability (< 1 s at rt). Thus, continuous flow technologies present an excellent platform for the use of carbenoids. Scheme 32 highlights a large scale

[93] a) F. Leroux, M. Schlosser, *Angew. Chem. Int. Ed.* **2002**, *41*, 4272; b) A. Nagaki, D. Ichinari, J.-I. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 12245.
[94] V. H. Gessner, *Chem. Commun.* **2016**, *52*, 12011.

diastereoselective Matteson homologation applied in the synthesis of vaborbactam.[95] Dichloromethyllithium is generated at –60 °C from dichloromethane and *n*-BuLi within 17 s. The stream of dichloromethyllithium is mixed with a solution of chiral boronic ester. The lithium boronate was obtained. This sensitive intermediate was poured into a solution of $ZnCl_2$ which enhances the diastereoselectivity of the rearrangement. The reaction mixture was slowly warmed up. In order to remove the bottleneck of cooling the batch reactor to –20 °C (time intensive and expensive process), a continuous loop with a heat exchanger was applied (bottom part of Scheme 32). Thus, a solution of $ZnCl_2$ in THF at 25 °C was mixed with the cool reaction stream containing the boronate adduct.



Scheme 32. Big scale Matteson homologation in continuous flow.

The product solution exits *via* an overflow device and consumed $ZnCl_2$ is constantly replenished. The temperature is controlled by a sensor and maintained by a heat exchanger. Remarkably, the continuous

[95] a) 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; b) A. Hafner, V. Mancino, M. Meisenbach, B. Schenkel, J. Sedelmeier, *Org. Lett.* **2017**, *19*, 786.

loop setup gave the product in high diastereomeric purity at temperatures even higher than 0 °C. This approach avoided any batch operations and led to a fully continuous process.

3.8 Practical Aspects of Continuous Flow Chemistry

Continuous flow chemistry merits come as a result of a series of screenings and in-depth optimisation of the reaction conditions and of the reaction setup. Reactions which are trivial in a flask can be complicated to perform in continuous flow. In fact, while continuous flow processes might offer benefits over their batch counterparts, their optimisation can be costly and time-consuming. In the following paragraphs, some of the most common difficulties in flow experimentation will be mentioned.

The preparation of a continuous flow experiment starts by checking the compatibility of the reagents and solvents with the equipment (Figure 3). Secondly, solutions of the reagents in the desired concentrations are prepared and their stability and solubility at different temperatures are checked. Then the reaction is run in batch and inspected for any precipitate, side products and conversion. Once homogeneity of the reaction mixture and starting solutions has been investigated, parameters (residence time, flow rates and reaction temperature) are chosen for the first screenings. From then, tailoring the reaction setup is necessary. Once the reactors are appropriately connected, junctions are checked for leaking by running the solvent through the reactors.

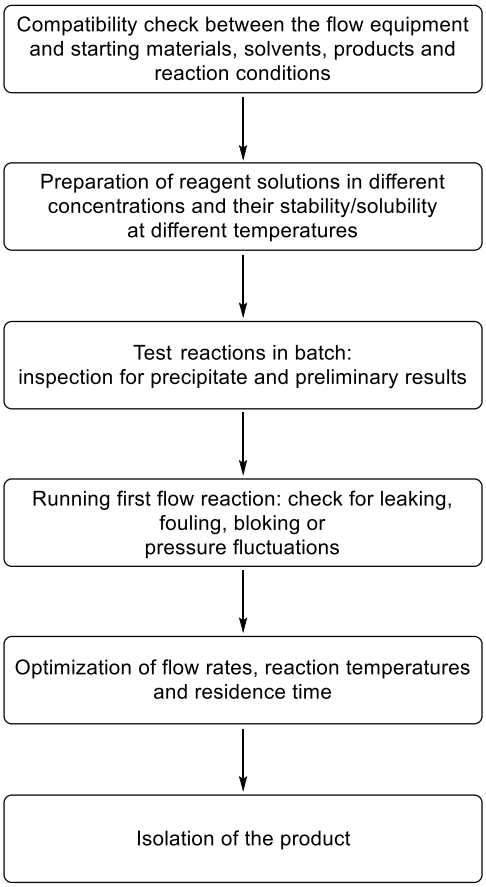


Figure 3. Workflow diagram on running the chemical reaction in continuous flow.

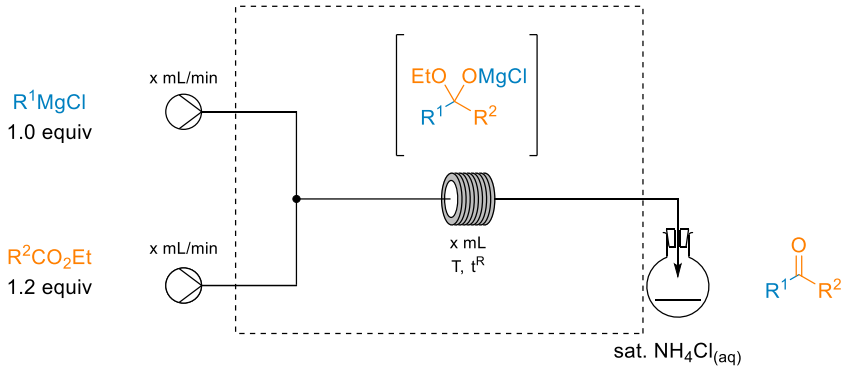
When the proper connection of the junctions is ensured the reactions can be performed. The choice of flow rates will dictate the residence time but will also influence mixing. For example, high flow rates and therefore shorter residence times can give better conversion than lower flow rates (higher residence times). Thus, every optimization of a continuous flow reaction must include careful screening of flow rates. To determine the influence of residence time on the conversion and yield one must change the reactor volume (best to change length without changing diameter) under constant flow rates. Although residence times can be calculated from a flow rate and reactor volume deviations from ideal plug flow can occur. The high viscosity of the solution, for instance at lower temperatures, can result in "stretching" of the reagent stream (so-called residence time distribution). Also, high pressure in the system can lead to stalling, which can as well lead to wrong stoichiometry in the following processes. In long reactors or more commonly packed-bed reactors resistance can be high for fluid movement. This causes higher pressures at the beginning of the reactor than at its end. Such pressure drops can influence flow rates in different parts of the reactor again leading to the wrong stoichiometry downstream. Due to this reason, reactions should always be run in a steady state. Inline analytics can be of great help for the control of imprecise residence times. A steady state is a stable state of the flow process which has constant parameters. Therefore, running a reaction in a steady state is of great importance if a multistep process is to be done as it guarantees constant and reproducible results.

Yield for a continuous flow process can be reported as the yield of a steady state (collection done for a certain time in a steady state) or an overall yield (entire reaction mixture collected). Yield can be reported as productivity (amount of product per time) or space-time yield (amount of product per volume per time).

4. Objectives

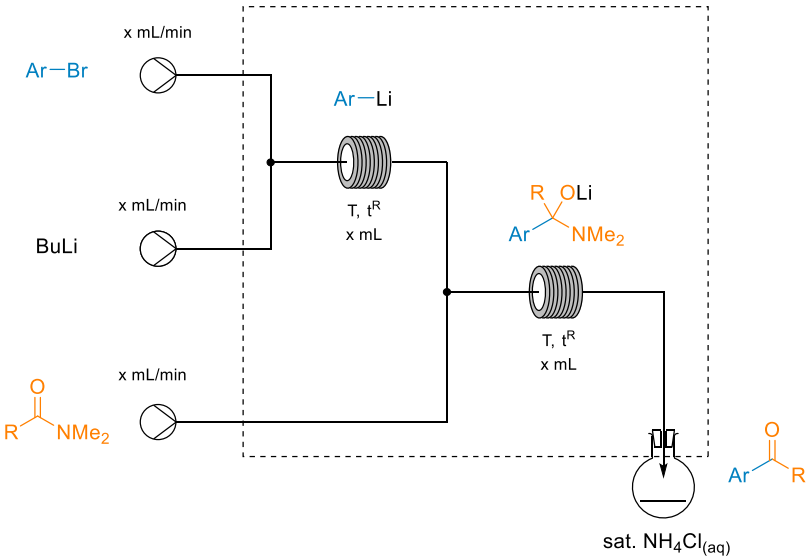
The aim of this thesis is the development of novel organometallic reagents and protocols for the synthesis of various functionalized ketones, pyridines and amides.

In the first project, reactions of ester electrophiles with organomagnesium reagents were to be studied in a continuous flow setup (Scheme 33). Although very cheap and abundant, esters usually suffer from double addition side reactions leading to tertiary alcohols when reacted with Grignard reagents. Additionally, low temperatures are commonly used in the batch. To tackle both problems we argued that precise control of residence time and temperature using continuous flow equipment should be highly beneficial. The stability of the tetrahedral intermediate should be crucial for the success of the reaction.[96]



Scheme 33. Continuous flow acylation of Grignard reagents with commercially available methyl or ethyl esters.

Next, an environmentally friendly alternative to Weinreb amides should be pursued. Although Weinreb amides are excellent reagents for acylation, their toxicity and potential explosive properties make them often unsuitable for large-scale applications.

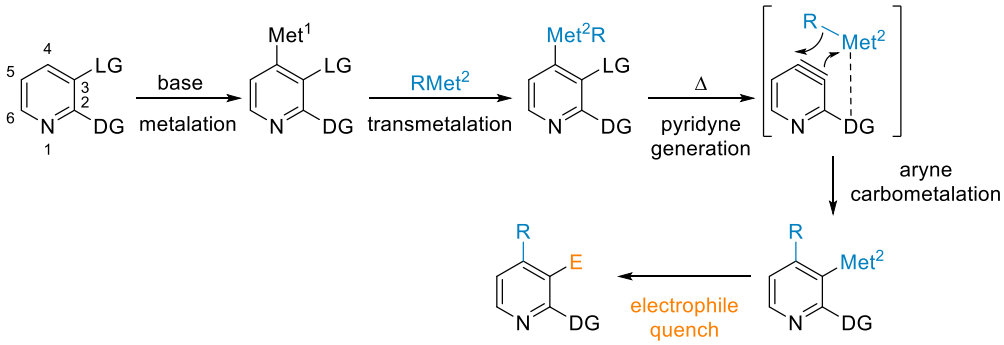


Scheme 34. Continuous flow acylation of organolithium reagents with *N*,*N*-dimethylamides in toluene.

[96] This project was developed in cooperation with Dr. Benjamin Heinz; see B. L. Heinz, Dissertation, LMU München.

Thus, the new atom-economical and environmentally benign reagents such as *N*,*N*-dimethylamides are desired. As organometallic nucleophiles organolithium reagents should be chosen, as amide functionality is normally tolerated by organozincs and organomagnesiums. Finally, hydrocarbon solvent such as toluene should be selected as the solvent of choice as it is more suitable for large-scale applications than THF. Again, the use of continuous flow technology should be beneficial in the "on-demand" preparation of unstable organolithiums (Scheme 34) and for performing reactions at convenient temperatures (≥ -20 °C).[97]

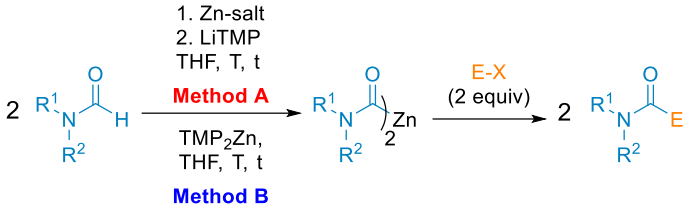
The synthesis of functionalized pyridines can be done *via* transition metal-catalyzed cross-coupling or *via* transition metal-free approaches. One of such ways is the coupling *via* aryne intermediates. The 3,4-pyridynes, nitrogen analogues of benzynes, are underexplored in synthetic literature. So far, the approaches to 3,4-pyridynes have employed very complex precursors made through multistep sequences. The aim of this work would be to develop a selective reaction of organometallic reagents with 3,4-pyridynes starting from inexpensive, readily available materials. From an atom economy perspective, an ideal pyridyne precursor would feature a leaving group (LG) which enables metalation in the ortho position. Such a functionalization would avoid the use of complex 3,4-disubstituted pyridyne precursors. Additonally, in position C2 a directing group (DG) should control the regioselectivity of the carbometalation step but also tune the reactivity of the pyridyne. The reaction of pyridyne with an organometallic reagent should lead to a new stable organometallic species which could be quenched with various electrophiles (Scheme 35). Furthermore, a continuous flow procedure should be developed for the purpose of potential scale-up.[98]



Scheme 35. Difunctionalization of pyridines using organometallic reagents *via* pyridyne intermediates.

Finally, a synthesis of amides using carbamoylzinc reagents was envisioned. The most common reagents for nucleophilic carbamoylation are carbamoyllithiums but they suffer from low stability which limits their use. Thus, the goal of this work was to prepare new carbamoylzinc reagents, which presumably have much higher stability. They would be used for remote installation of amide moiety. Catalytic cross-coupling reactions with a variety of organic halides would be of particular interest. Metalation of bench stable and readily available formamides should be examined because the zinc insertion proceeds at elevated temperatures (potentially incompatible with the limited stability of carbamoylmetal reagents) and the I/Zn exchange requires unstable carbamoyl iodides as precursors. Regarding metalation, two approaches should be investigated. In the first, *in situ* trapping of carbamoyllithium with Zn-salt should be pursued (Scheme 36, Method A). Finally, a direct approach to carbamoylzincs by metalation using various TMPZn bases was also envisioned as it would likely result in a broad functional group tolerance (Scheme 36, Method B).

[97] This project was developed in cooperation with Dr. Benjamin Heinz; see B. L. Heinz, Dissertation, LMU München.
[98] This project was developed in cooperation with Dr. Benjamin Heinz; see B. L. Heinz, Dissertation, LMU München.

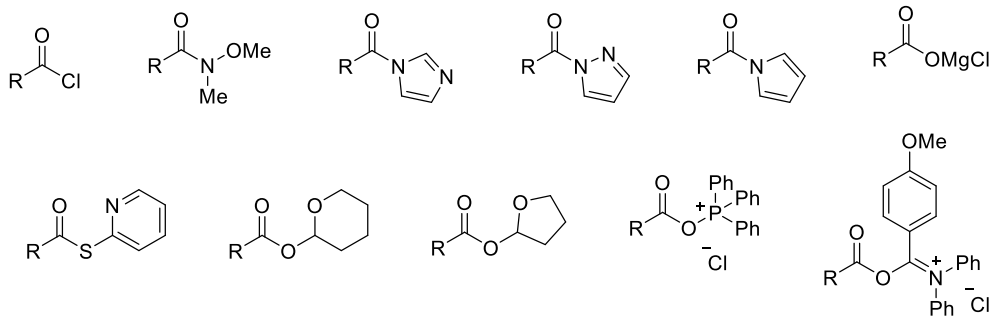


Scheme 36. Preparation and reactions of dicarbamoylzinc reagents.

B. RESULTS AND DISCUSSION

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

The preparation of ketones can be accomplished in many ways. While oxidation of secondary alcohol[99] is very common, such approaches are often non-step economic, cost- and waste-intensive. Instead, ketone synthesis by acylation is a more attractive option. The synthesis of ketones using organometallic reagents and activated carboxylic acid derivatives such as acid chlorides, Weinreb amides and other derivatives (Scheme 37) is well established.[100]



Scheme 37. Commonly used acylation reagents.[101]

As a main drawback these acylation reagents are often not commercially available but moderate moisture stability (acid chlorides) and toxicity (Weinreb amides) can also be listed. On the other side methyl or ethyl esters are ubiquitous, cheap and non-toxic precoursors. However, their reaction with e.g. organomagnesium reagents is often complicated by a favoured side reaction of the ketone product **4** with the Grignard reagent **2**, giving the undesired tertiary alcohol **5** (Scheme 38). The general chemical problem could be attenuated with the use of continuous flow chemistry.This enabling technology has already offered many advantages in handling organometallic reagents, especially in the case of selectivity problems.[93b,102] In the case mentioned above the precise residence time control and good

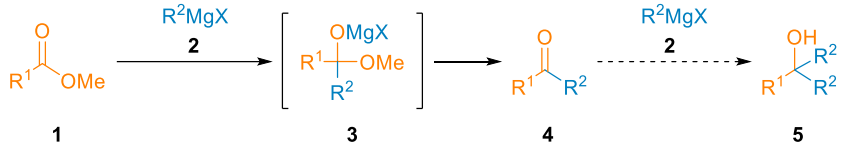
[99] a) R. V. Oppenauer, *Recl. Trav. Chim. Pays-Bas* ***1937,*** *56*, 137; b) K. Bowden, I. M. Heibron, E. R. H. Jones, B. C. L. Weedon, *J. Chem. Soc.* **1946**, 39; c) G. I. Poos, G. E. Arth, R. E. Beyler, L. H. Sharett, *J. Am. Chem. Soc.* **1953**, *75*, 422; d) R. H. Cornforth, J. W. Cornforth, G. Popjak, *Tetrahedron* **1962**, *18*, 1351; e) K. E. Pfitzner, J. G. Moffatt, *J. Am. Chem. Soc.* **1963**, *85*, 3027; f) E. J. Corey, J. W. Suggs, *Tetrahedron*, **1975**, *16*, 2647; g) K. Omura, D. Swern, *Tetrahedron*, **1978**, *34*, 1651; h) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277; i) S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, Synthesis **1994**, *7*, 639; j) S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, D. H. B. Ripin, *Chem. Rev.* **2006**, *106*, 2943; k) J. M. Bobbitt, C. Bruckner, N. Merbouh, *Org. React.* **2009**, *74*, 103; l) C. Parmeggiani, F. Cardona, *Green Chem.* **2012**, *14*, 547.

[100] a) M. Araki, S. Shigeru, T. Hisashi, M. Teruaki, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777; b) D. E. Bergbreiter, J. M. Killough, *J. Org. Chem.* **1976**, *41*, 2750; c) S. Nahm; S. M. Weinreb, *Tetrahedron. Lett.* **1981**, *22*, 3815; d) T. Fujisawa, M. Toshiki, T. Sato, *Tetrahedron. Lett.* **1982**, *23*, 5059; e) M. W. Anderson, J. Raymond, J. Saunders, *J. Chem. Soc.* **1982**, *5*, 282; f) T. Fujisawa, *Chem. Lett.* **1983**, *12*, 1267; g) C. G. Knudsen, H. Rapoport, *J. Org. Chem.* **1983**, *48*, 2260; h) S. Wattanasin, F. G. Kathawala, *Tetrahedron Lett.* **1984**, *25*, 811; i) M. N. Mattson, H. Rapoport, *J. Org. Chem.* **1996**, *61*, 6071; j) J. K. Park, W. K. Shin, D. K. An, *Tetrahedron. Lett.* **2013**, *54*, 3199.

[101] a) C. Kashima, I. Kita, K. Takahashi, A. Hosomi, *J. Heterocycl. Chem.* **1995**, *32*, 25; b) R. K. Dieter, *Tetrahedron* **1999**, *55*, 4177; c) D. A. Evans, G. Borg, K. A. Scheindt, *Angew. Chem. Int. Ed.* **2002**, *41*, 3188; d) G. Meng, R. Szostak, M. Szostak, *Org. Lett.* **2017**, *19*, 3596; e) K. Colas, A. C. V. D. dos Santos, A. Mendoza, *Org. Lett.* **2019**, *21*, 7908; f) F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel, *Chem. Sci.* **2019**, *10*, 8241; g) G. Meng, J. Zhang, M. Szostak, *Chem. Rev.* **2021**, *121*, 12746; h) K. Colas, A. C. V. D. dos Santos, S. V. Kohlhepp, A. Mendoza, *Chem. Eur. J.* **2022**, *28*, e20210405.

[102] a) D. Webb, T. F. Jamison, *Org. Lett.* **2012**, *14*, 568; b) D. T. McQuade, H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384; c) F. G. J. Odille, A. Stenemyr, F. Pontén, *Org. Process Res. Dev.* **2014**, *18*, 1545; d) 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; e) T. Fukuyama; H. Chiba, H. Kuroda, T. Takigawa, A. Kayano, K. Tagami, *Org. Process Res. Dev*. **2016**, *20*, 503; f) G. A. Price, A. Hassan, N. Chandrasoma, A. R. Bogdan, S. W. Djuric, M. G. Organ, *Angew. Chem. Int. Ed.* **2017**, *56*, 13347; g) M. A. Ganiek, M. R.

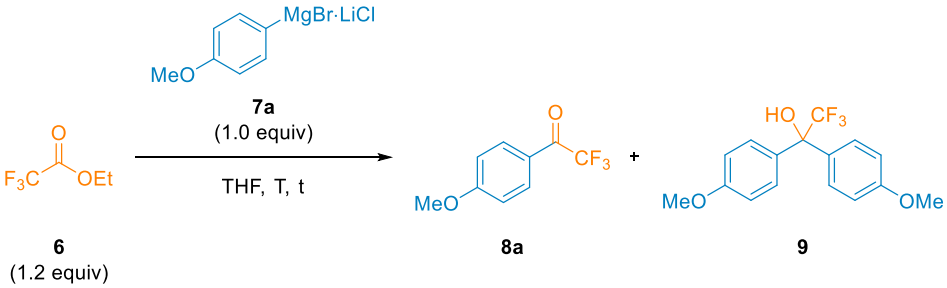
mixing can help in selective consumption of organomagnesium reagent **2** before the collapse of tetrahedral intermediate **3**. Also, the use of low temperatures typical for batch chemistry could be avoided.[103]



Scheme 38. The reaction of Grignard reagents with esters.

Herein, we report selective acylation using various esters at convenient temperatures (–5 to 25 °C). First, we investigated the reaction of ethyl trifluoroacetate (**6**) with 4-MeOC$_6$H$_4$MgCl·LiCl (**7a**). Dropwise addition of Grignard reagent to a solution of ethyl trifluoroacetate (**6**) in THF cooled to –78 °C resulted in 71% conversion (50% calibrated GC yield) after 2 minutes under batch conditions (Table 1). Prolonging the reaction time to 3 h increased the conversion to 83% and the yield to 66%. Performing the reaction in batch conditions at –5 °C improved the conversion to 92% but resulted in a significant amount of tertiary alcohol (27%). Then, the reaction was investigated in a commercial flow setup. Optimisation of reaction temperature, residence time, flow rates and stoichiometry resulted in 90% conversion and 72% calibrated GC yield with only 8% tertiary alcohol. The amount of double addition product was comparable with the one obtained in the batch experiment at –78 °C.

Table 1. Comparison of batch and continuous flow setup for the acylation of 4-methoxyphenylmagnesium bromide (**7a**) with ethyl trifluoroacetate (**6**).



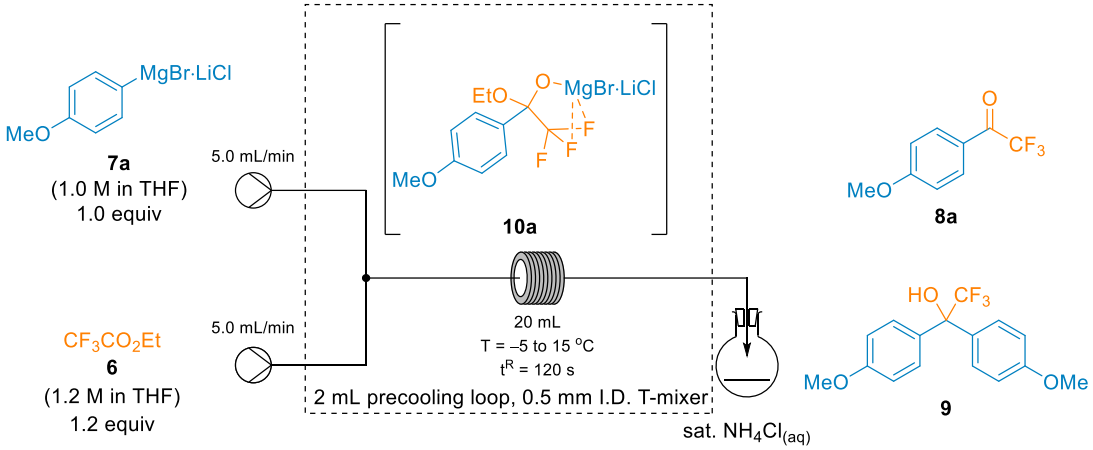
Entry	Setup	T [°C]	t [min]	Conversion **7a** [GC-%]	Yield **8a** [GC-%]	Yield **9** [GC-%]
1	Batch	–78	2	71	50	10
2	Batch	–78	180	83	66	9
3	Batch	–5	2	92	37	27
4	Flow	–5	2	90	72	8

Reaction parameters, namely reaction temperature, residence time, ester equivalents and flow rates, were optimised. The temperature screening (Table 2) showed that even small change of the reaction temperature can strongly influence the reaction outcome. The optimum was found at –5 °C. At –15 °C lower conversion was observed, while already at 0 °C, a significant amount of tertiary alcohol could be observed.

Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280; h) Y. Chen, C. A. Hone, B. Gutmann, C. O. Kappe, *Org. Process Res. Dev.* **2017**, *21*, 1080; i) N. Weidmann, M. Ketels, P. Knochel, *Angew.Chem. Int. Ed.* **2018**, *57*, 10748.

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

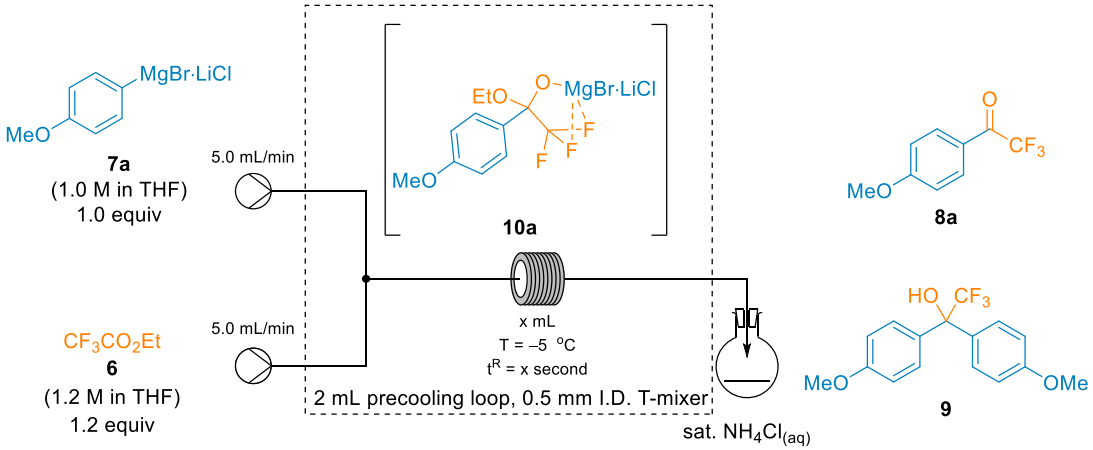
Table 2. Temperature screening of the reaction of ethyl trifluoroacetate (**6**) and 4-methoxyphenylmagnesium bromide (**7a**) in continuous flow.



Entry	T [°C]	t^R [s]	Equiv of **6**	Conversion **7a** [GC-%]	Yield **8a** [GC-%]	Yield **9** [GC-%]
1	–15	120	1.2	75	65	3
2	–10	120	1.2	81	70	6
3	–5	120	1.2	88	72	8
4	0	120	1.2	89	70	12

Investigation of the residence time (Table 3) was done at –5 °C using a constant flow rate of 10 mL/min. While significant product formation was observed within 1 min, only gradual improvements could be made by increasing the residence time to 2 min. Further prolongation of the residence time gave no improvements.

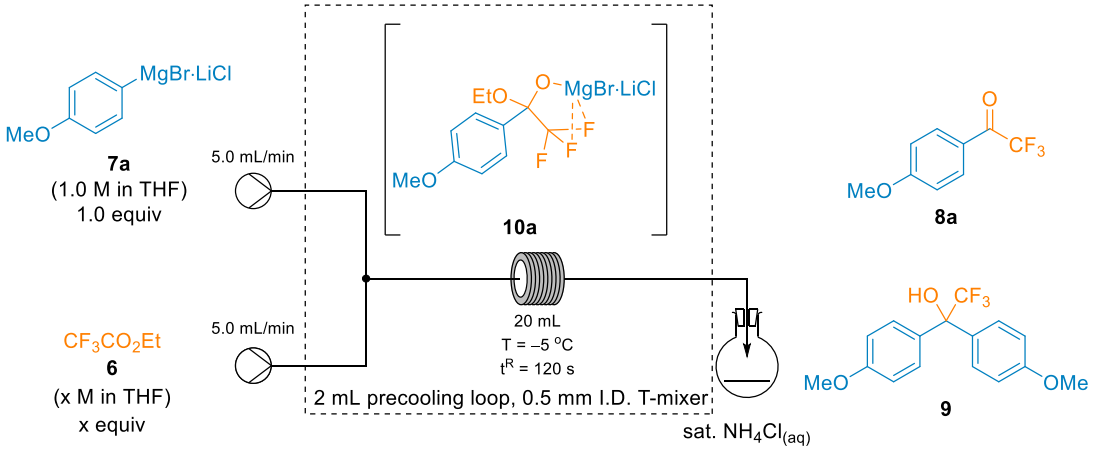
Table 3. Residence time screening of the reaction of ethyl trifluoroacetate (**6**) and 4-methoxyphenylmagnesium bromide (**7a**) in continuous flow.



Entry	T [°C]	t^R [s]	Equiv **6**	Conversion **7a** [GC-%]	Yield **8a** [GC-%]	Yield **9** [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

Based on the screening of ethyl trifluoroacetate (**6**) equivalents it was clear that continuous flow equipment enabled the use of near stoichiometric amounts of reactants (Table 4). The increase from 1.2 to 1.5 equiv of **6** resulted in only incremental improvement of the ketone **8a** yield (72% to 74%).

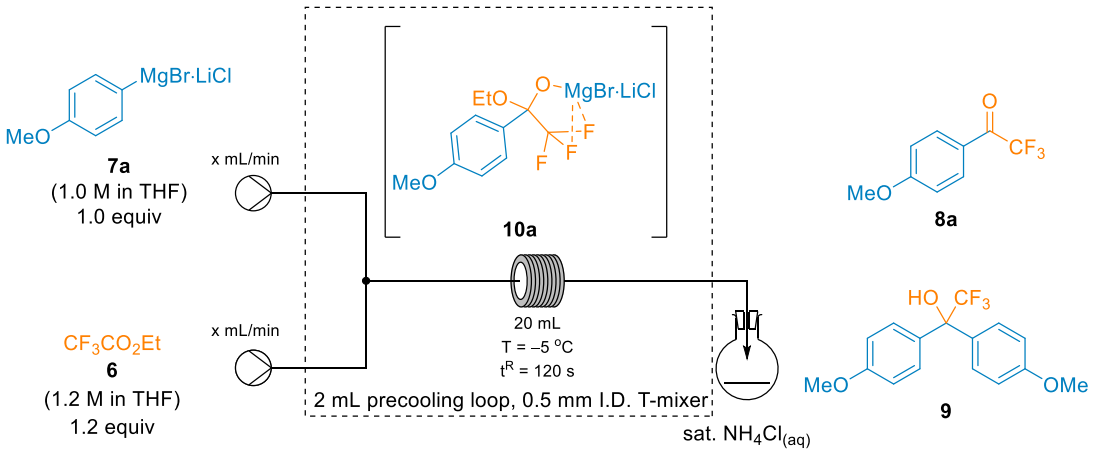
Table 4. Screening of equivalents of ethyl trifluoroacetate (**6**).



Entry	T [°C]	t^R [s]	Equiv **6**	Conversion **7a** [GC-%]	Yield **8a** [GC-%]	Yield **9** [GC-%]
1	–5	120	1.05	82	67	11
2	–5	120	1.2	89	72	8
3	–5	120	1.5	90	73	7
4	–5	120	2.0	89	74	7
5	–5	120	3.0	91	75	7

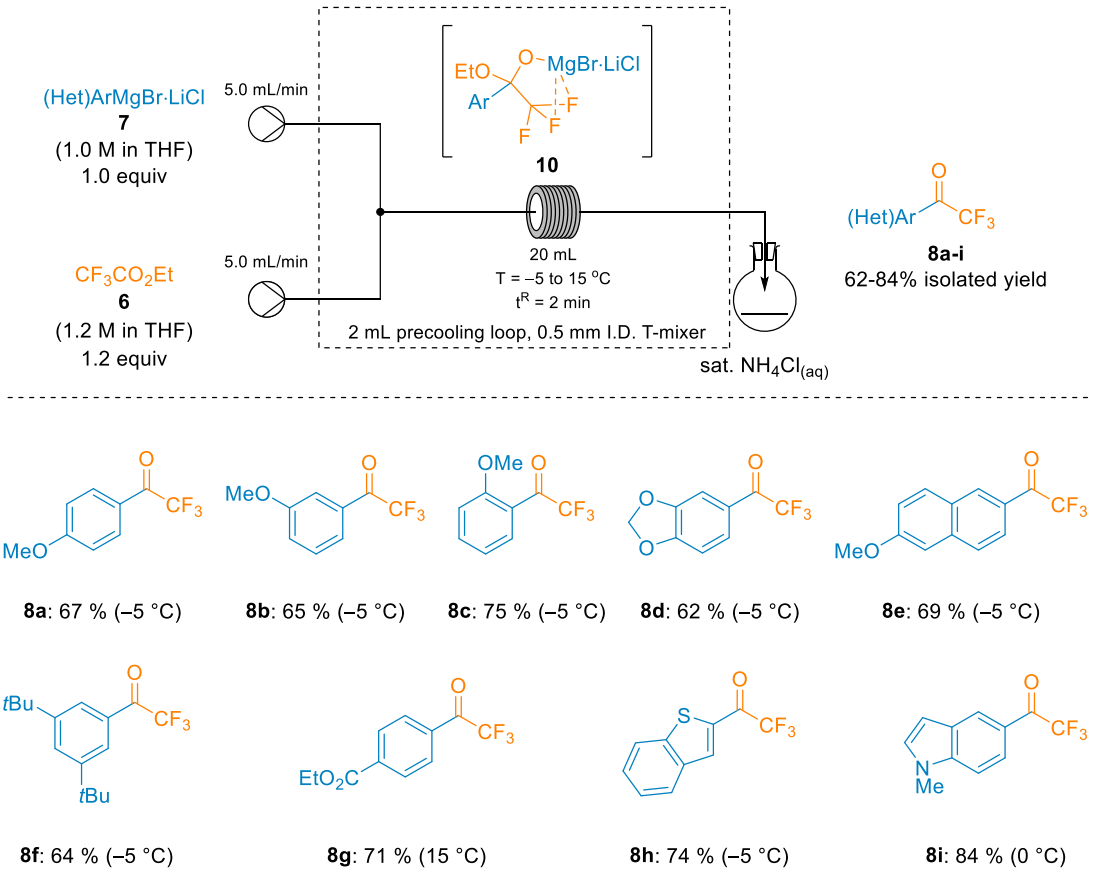
Lastly, the optimisation of the flow rates was done (Table 5). As expected, fast flow rates resulted in better selectivity for **8a** over **9**. However, an increase from 10 mL/min to 20 mL/min overall flow rate gave no improvement. In fact, some problems related to pressure were observed. Thus 10 mL/min total flow rate was selected as the optimal flow rate.

Table 5. Flow rate optimization for the reaction of ethyl trifluoroacetate (**6**) and 4-methoxyphenylmagnesium bromide (**7a**) in continuous flow.



Entry	Flowrate x [mL/min]	T [°C]	t^R [min]	Yield **8a** [GC-%]	Yield **9** [GC-%]
1	1	–5	2	56	13
2	2.5	–5	2	65	10
3	5	–5	2	72	8
4	10	–5	2	72	8

With these optimised conditions at hand, we explored the scope of our new procedure (Scheme 39). Thus, the reaction of 4-$MeOC_6H_4MgBr{\cdot}LiCl$ (**7a**) and 3-$MeOC_6H_4MgBr{\cdot}LiCl$ (**7b**) with ethyl trifluoroacetate (**6**) at –5 °C with an overall flow rate of 10 mL/min (residence time of 2 min) gave the expected trifluoromethyl ketones[104] **8a** and **8b** in 65-67% isolated yield. Interestingly, the reaction of 2-$MeOC_6H_4MgCl{\cdot}LiCl$ gave the ketone **8c** in 75% yield. The higher yield might be explained due to the coordination effect of the methoxy group. This coordination likely stabilises the tetrahedral intermediate which in turn results in a lower amount of double addition side product. Grignard reagents with electron-donating groups gave similar results and ketones **8d-f** have been obtained in 62-69% yield. Furthermore, an organomagnesium reagent **7g** bearing a sensitive ester group could also be utilised despite its instability. Thus, polyfunctional ketone **8g** was prepared in 71% isolated yield. Stabilization of the tetrahedral intermediate by an electron-withdrawing group was the reason why relatively high temperatures (15 °C) were tolerated. An organomagnesium reagent **7h** prepared from 2-bromobenzothiophene *via* Mg-insertion furnished the heteroaryl ketone **8h** in 74% yield. The reaction of an indolyl organomagnesium **7i** reagent was performed at 0 °C and gave the ketone **8i** in 84% yield.

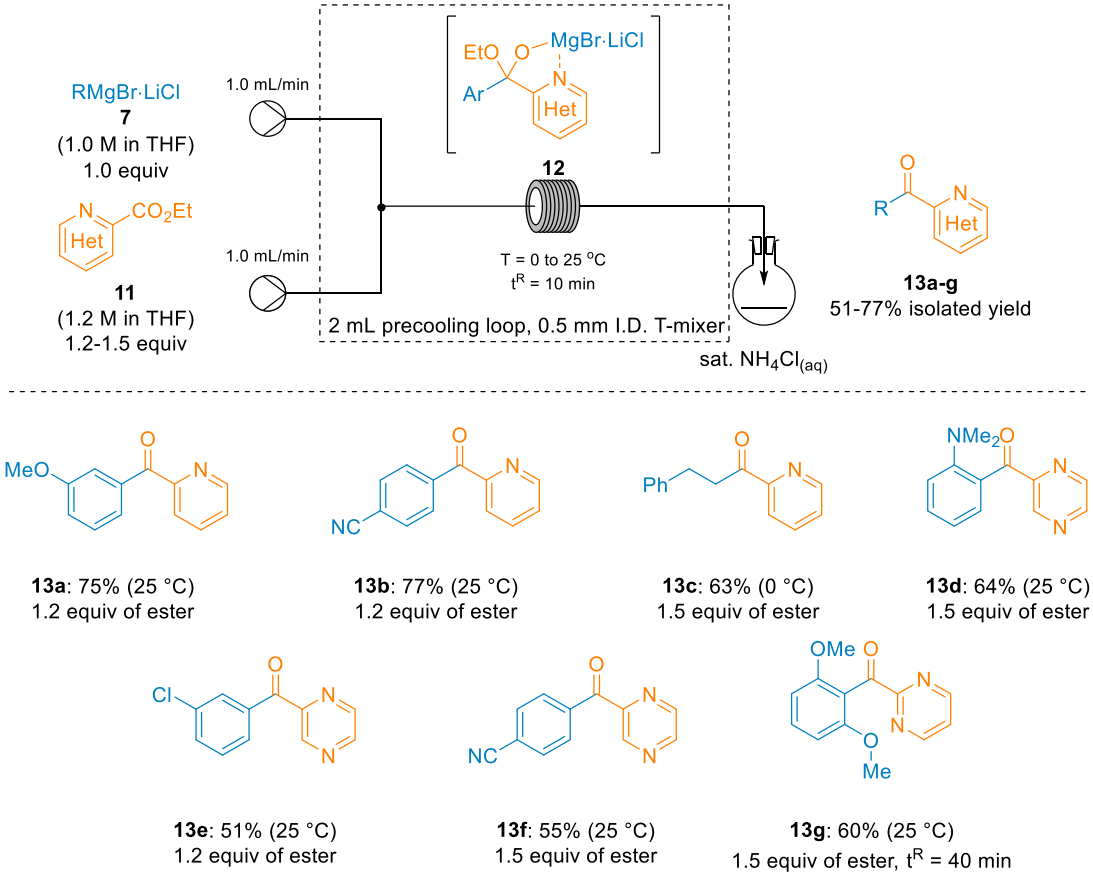


Scheme 39. Continuous flow preparation of aryl trifluoromethyl ketones **8a-i**.

Relying on the importance of coordination in this reaction we have expanded the scope of the ester electrophiles beyond ethyl trifluoroacetate. Thus, esters of electron deficient *N*-heterocycles (**11**) were explored (Scheme 40). We assumed that coordination of the nitrogen atom to the Mg would have a stabilizing effect on the tetrahedral intermediate. Indeed, both electron poor and electron rich

[104] For other procedures for preparation of trifluoromethylketones see: a) J. Wiedemann, T. Heiner, G. Mloston, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.* **1998**, *37*, 820; b) K. Funabiki, A. Hayakawa, T. Inuzuka, *Org. Biomol. Chem.* **2018**, *16*, 913.

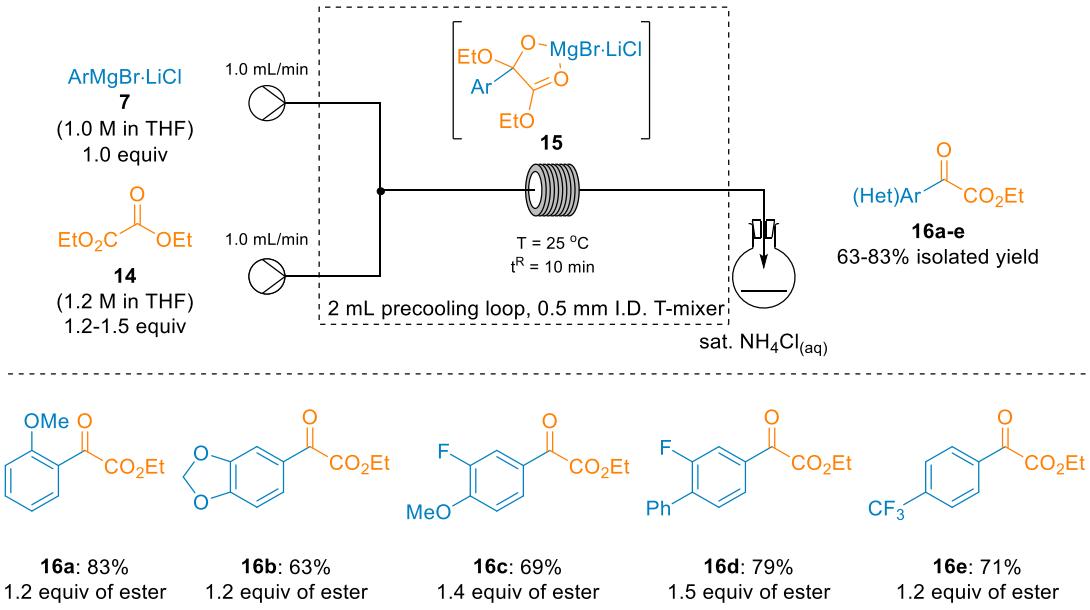
organomagnesiums **7b** and **7j** were reacted with ethyl-2-picolinate (**11a**) at 25 °C in a continuous flow to afford 2-pyridyl ketones **13a** and **13b** in 75% and 77% yield respectively. The 2-phenylethylmagnesium bromide (**7k**) gave the expected ketone **13c** in 63% isolated yield despite the destabilizing effect of alkyl substituents on the tetrahedral intermediate. More exotic methyl pyrazine-2-carboxylate was also a suitable substrate. Therefore, 2-pyrazinyl ketones **13d-f** were prepared in 51-64% yield. Finally, pyrimidinyl ketone **13g** was synthesised in 60% yield from methyl pyrimidinyl-2-carboxylate (**11xy**) and the 2,6-dimethoxyphenylmagnesium bromide (**7n**) with extended residence time (40 min).



Scheme 40. Continuous flow preparation of heteroaryl ketones **13a-g**.

Additionally, diethyl oxalate (**14**) was also investigated as an electrophile.[105] Valuable α-ketoesters[106] were obtained at room temperature within 10 min using an overall flow rate of 2 mL/min (Scheme 41). Thus, both electron-rich and electron-poor organomagnesiums reacted with diethyl oxalate to afford ketoesters **16a-e** in 63-83% isolated yield.

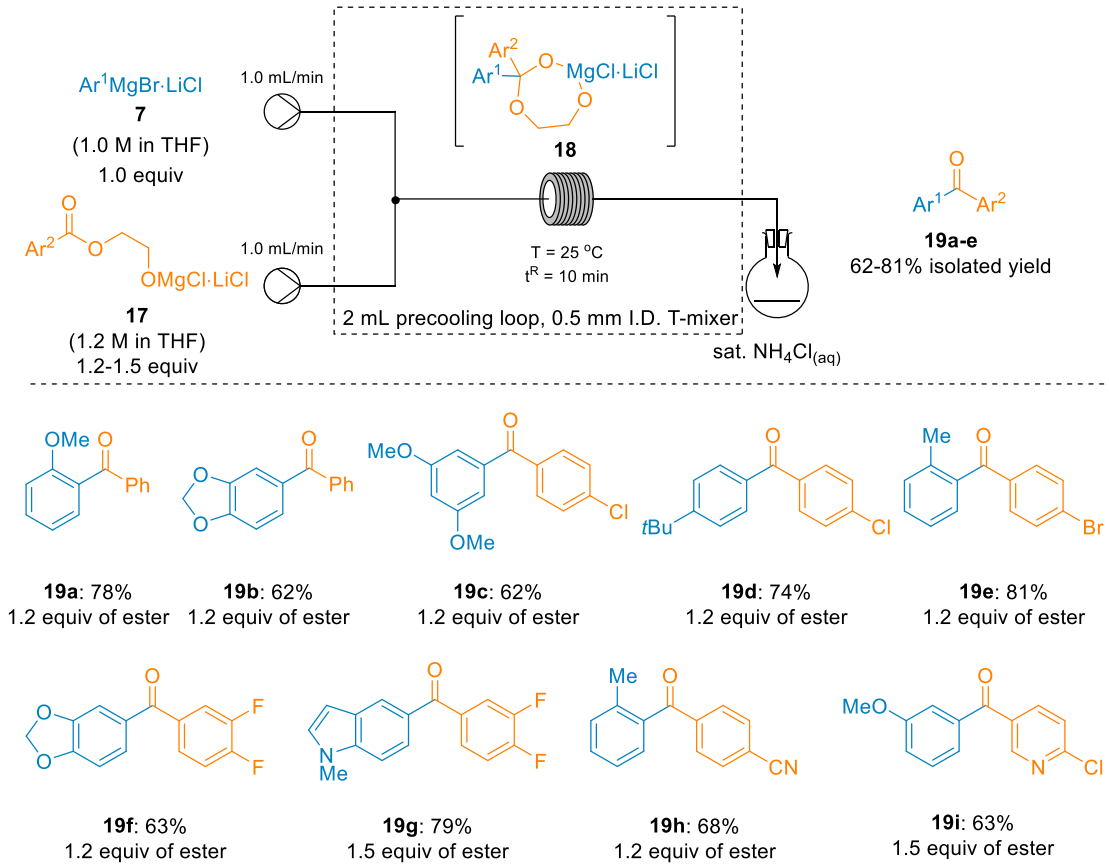
[105] a) A. Nagaki, D. Ichinari, J.-I. Yoshida, *Chem. Commun.* **2013**, *49*, 3242; b) J. Park, J. C. Moore, F. Xu, *Org. Process Res. Dev.* **2016**, *20*, 76.
[106] B. Efthekari-Sis, M. Zirak, *Chem. Rev.* **2015**, *115*, 151.



Scheme 41. Continuous flow preparation of 2-ketoesters **16a-g**.

Throughout our research and other literature reports[107] the effect of coordinating groups proved beneficial. So far, the coordination effect was bound to either the organometallic reagent or the ester electrophile making the methodology substrate dependent. We have found that magnesium alkoxides of 2-hydroxyethyl esters of type **17** are useful reagents for the formation of bisarylketones of type **19** with intermediacy of tetrahedral intermediate **18** (Scheme 42). These alkoxides were generated by mixing an ethylene glycol monoester[108] at 0 °C in THF with the *i*-PrMgCl·LiCl (1.05 equiv). The arylmagnesium reagents reacted smoothly with these novel electrophiles to afford unsymmetric bisaryl ketones of type **19**. Thus, benzoate **17a** in reaction with electron-rich organomagnesiums **7c-d** gave ketones **19a-b** in 62-78% isolated yield. In comparison, ethyl benzoate with 2-$MeOC_6H_4MgCl·LiCl$ gave only 10% of the intended product **19a** in a continuous flow setup and large amounts of double addition product were obtained instead. Alkoxybenzoates containing a halide substituent such as fluoride, chloride or bromide were competent reaction partners. Thus, halogen substituted ketones **19c-g** were obtained in good yields (63-81%). Furthermore, a nitrile substituent was also tolerated and ketone **19h** was obtained in 68% isolated yield. Finally, a derivative of nicotinic acid produced the 3-pyridyl ketone **19i** in 63% yield.

[107] F. Lima, M. Meisenbach, B. Schenkel, J. Sedelmeier, *Org. Biomol. Chem.* **2021**, *19*, 2420.
[108] a) A. Khalafi-Nezhad, M. N. Soltani Rad, A. Khoshnood, *Synthesis* **2003**, 16, 2552; b) D. Gupta, S. V. Gupta, K.-D. Lee, G. L. Amidon, *Mol. Pharm.* **2009**, *6*, 1604.



Scheme 42. Continuous flow preparation of bisaryl ketones **19a-i**.

In summary, selective acylation in continuous flow has been realised with economic and abundant ester electrophiles. This procedure is applicable for esters possessing strongly electron-withdrawing and/or coordinating substituents such as ethyl trifluoroacetate, diethyl oxalate and N-heterocyclic esters. Additionally, we have developed new cheap activated esters of type **17** for the general synthesis of bisaryl ketones. These new reagents exploit the crucial coordination effect for the selective synthesis of ketones and produce just ethylene glycol as the byproduct.

2. Continuous Flow Acylation of (Hetero)aryllithiums with Polyfunctional *N*,*N*-Dimethylamides and Tetramethylurea in Toluene

Ketones are of high interest in the fine chemical industry because they are irreplaceable intermediates in the synthesis of various heterocycles,[109] chiral alcohols[110] and amines.[111] The acylation of organometallics with carboxylic acid derivatives is the most straightforward way to prepare ketones. Although acyl chlorides were often used as acylation reagents, alternatives such as Weinreb amides,[100c] morpholino amides,[112] 2-thiopyridyl esters,[101f,113] *N*-acylpyrroles[101c,d] have been successfully applied in reactions with various organometallics with or without transition metal catalysts.

Reactions of organolithium and organomagnesium reagents with commercially available methyl or ethyl esters are possible in some cases[104b,107] but are generally limited when no chelation assistance from the substrates takes place. Therefore, we have developed a new acylation procedure with *N*,*N*-dimethylamides[114] in toluene which expands the scope of the transformation and does not involve toxic, expensive or sensitive electrophiles.

Continuous flow chemistry has given new perspectives on the handling of sensitive organometallic reagents. The precise control over residence time, reaction temperature and mixing offered routine handling of unstable species. Among others, Yoshida *et al*. have reported the synthesis of polyfunctional ketones from acid chlorides and lithium reagents by extremely fast micro-mixing.[115] Jamison *et al*. have showcased the use of CO_2 gas as CO synthon by double addition of organomagnesium and organolithiums reagents.[116] In our work presented below we have used the advantages of chemistry in continuous flow for the on-demand preparation of organolithiums reagents in toluene from commercially available chemicals such as aryl bromides and *s*-BuLi.

We have started our investigations with preliminary batch experiments. Our first observation was that aryllithiums are, in fact, a suspension in toluene[117] regardless of temperature, which prevents the use of

[109] a) F. Saito, N. Trapp, J. W. Bode, *J. Am. Chem. Soc.* **2019**, *141*, 5544; b) D. J. Foley, H. Waldman, *Chem. Soc. Rev.* **2022**, *51*, 4094.

[110] a) X. Wu, J. Xiao, *Chem. Commun.* **2007**, 2449; b) K. Goldberg, K. Schroer, S. Lütz, A. Liese, *Appl. Microbiol. Biotechnol.* **2007**, *76*, 237; c) K. Goldberg, K. Schroer, S. Lütz, A. Liese, *Appl. Microbiol. Biotechnol.* **2007**, *76*, 249; d) G. W. Huisman, J. Liang, A. Krebber, **2010**, *14*, 122.

[111] a) C. K. Savile, J. M. Janey, E. C. Mundorff, J. C. Moore, S. Tam, W. R. Jarvis, J. C. Colbeck, A. Krebber, F. J. Fleitz, J. Brands, P. N. Devine, G. W. Huisman, G. J. Hughes, *Science*, **2010**, *329*, 305; b) S. J. Novick, N. Dellas, R. Garcia, C. Ching, A. Bautista, D. Homan, O. Alvizo, D. Entwistle, F. Kleinbeck, T. Schlama, T. Ruch, *ACS Catal.* **2021**, *11*, 3762.

[112] a) R. Martín, P. Romea, C. Tey, F. Urpí, J. Vilarrasa, *Synlett* **1997**, 1414; b) A. T. Ung, S. G. Pyne, *Tetrahedron: Asymmetry* **1998**, *9*, 1395.

[113] a) H. Tokuyama, S. Yokoshima, T. Yamashita, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 3189; b) F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel, *Chem. Sci.* **2019**, *10*, 8241.

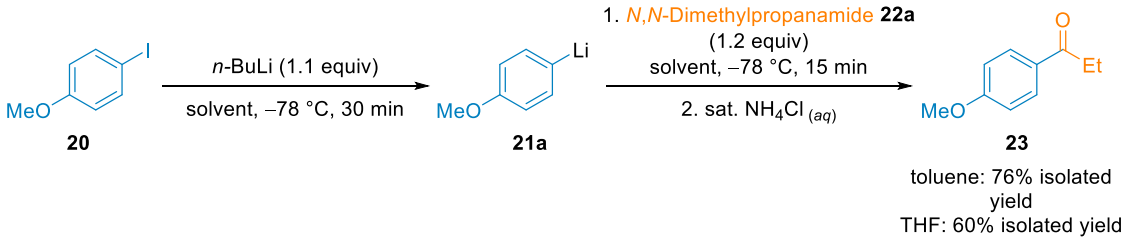
[114] a) D. C. Owsley, J. M. Nelke, J. J. Bloomfield, *J. Org. Chem.* **1973**, *38*, 901; b) G. A. Olah, G. K. S. Prakash, M. Arvanaghi, *Synthesis* **1984**, 228; c) Y. Honda, A. Ori, G. Tsuchihashi, *Bull. Chem.Soc. Jpn.* **1987**, *60*, 1027; d) M. Buswell, I. Fleming, U. Ghosh, S. Mack, M. Russell, B. P.Clark, *Org. Biomol. Chem.* **2004**, *2*, 3006; e) S. Collins, Y. Hong, G. J. Hoover, J. R. Veit, *J. Org. Chem.* **1990**, *55*, 3565; f) A. D. Benischke, L. Anthore-Dalion, G. Berionni, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 16390; g) A. D. Benischke, L. Anthore-Dalion, F. Kohl, P. Knochel, *Chem. Eur. J.* **2018**, 24, 11103; h) L. Anthore-Dalion, A. D. Benischke, B. Wei, G. Berionni, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 4046; i) S. Ghinato, G. Dilauro, F. M. Perna, V. Capriati, M. Blangetti, C. Prandi, *Chem. Commun.* **2019**, *55*, 7741; j) S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti, C. Prandi, *Chem. Eur. J.* **2021**, *27*, 2868.

[115] A. Nagaki, K. Sasatsuki, S. Ishiuchi, N. Miuchi, M. Takumi, J.-I. Yoshida, *Chem. Eur. J.* **2019**, *25*, 4946.

[116] J. Wu, X. Yang, Z. He, X. Mao, T. Alan Hatton, T. F. Jamison, *Angew. Chem.* **2014**, *53*, 8416.

[117] For preparation of organolithiums in toluene see: a) W. J. Trepka, R. J. Sonnenfeld, *Organomet. Chem.* **1969**, *16*, 317; b) M. P. R. Spee, J. Boersma, M. D. Meijer, M. Q. Slagt, G. van Koten, J. W. Geus, *J. Org. Chem.* **2001**, *66*, 1647; c) Z. Zhou, A. Wakamiya T. Kushida, S. Yamaguchi, *J. Am. Chem. Soc.* **2012**, *134*, 4529; d) J. E. Borger, A. W. Ehlers, M. Lutz, J. C.

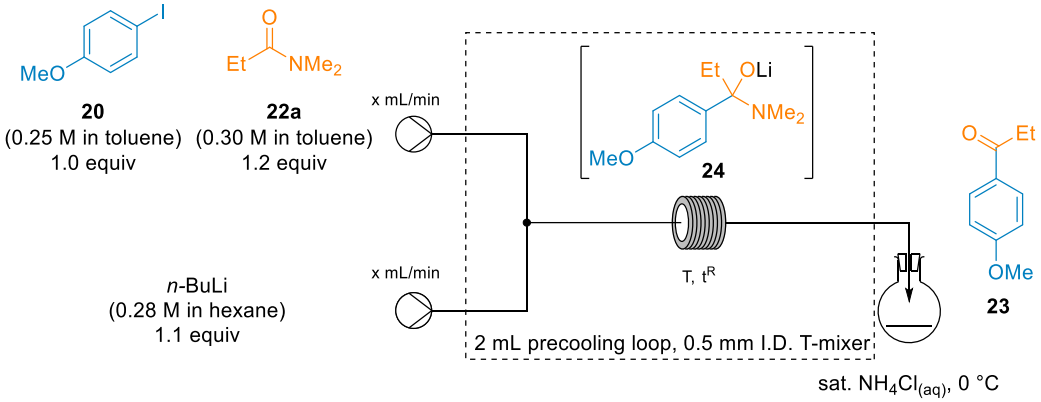
continuous flow chemistry. Nevertheless, when *N*,*N*-dimethylpropanamide was added, the suspension became a clear solution and ketone **23** was isolated in 76% yield (Scheme 43). We hypothesised that the amide was not only an electrophile but also a ligand for lithium cation solubilizing the aryllithium species before the addition took place.



Scheme 43. A preliminary experiment in batch for the I/Li exchange in toluene and subsequent acylation with *N*,*N*-dimethylpropanamide.

Treatment of a mixture of *N*,*N*-dimethylpropanamide (**22a**) and 4-iodoanisole (**20**) in toluene with *n*-BuLi in a continuous flow (Table 6) afforded the expected ketone **23** in comparable yield as in batch but at higher temperatures (–40 °C). No solubility issues were experienced.

Table 6. Optimisation of the acylation under Barbier conditions in a continuous flow setup.



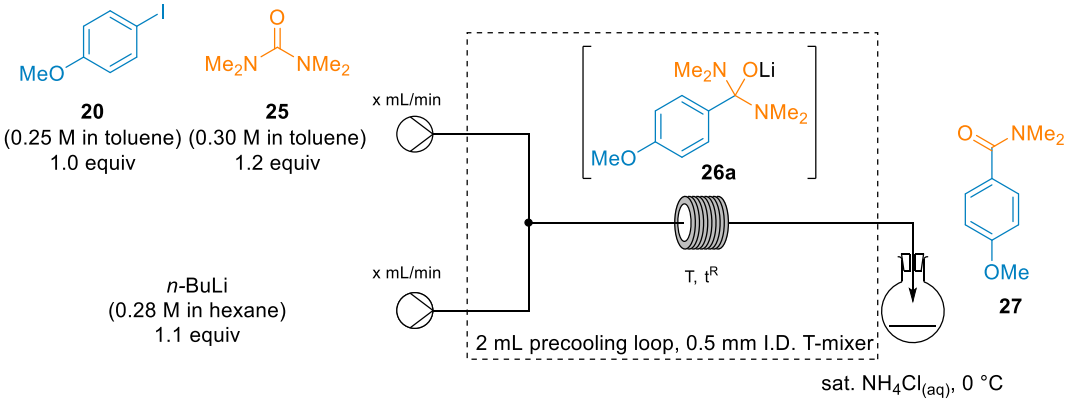
Entry	T [°C]	t^R [s]	Flowrate [mL/min]	Leftover **20** [GC-%]	Product **23** [GC-%]
1	–30	60	5	13	90
2	–30	12	5	7	100
3	–40	60	5	3	103
4	–40	12	5	<1	107 (76%)
5	–30	6	10	5	105
6	–30	30	10	3	97

Similarly, we were able to treat a mixture of tetramethylurea (**25**) and 4-iodoanisole (**20**) with *n*-BuLi in continuous flow (Table 7) to obtain a 4-methoxy-*N*,*N*-dimethylbenzamide (**27**) in 83% yield,

Slootweg, K. Lammertsma, *Angew. Chem. Int. Ed.* **2014**, *53*, 12836; e) H. Guyon, A. Boussonnière, A.-S. Castanet, *J. Org. Chem.* **2017**, *82*, 4949; f) N. Ando, H. Soutome, S. Yamaguchi, *Chem. Sci.* **2019**, *10*, 7816; g) T. T. T. Nguyen, H. Guyon, K. P. P. Nguyen, A. Boussonnière, J. Mortier, A.-S. Castanet, *Eur. J. Org. Chem.* **2020**, 3829.

therefore allowing an opportunity for two-stage synthesis of unsymmetrical ketones.[118] Experiments done in a continuous flow setup showed the benefit of higher flow rates and the simple amide **27** was isolated in 83% yield.

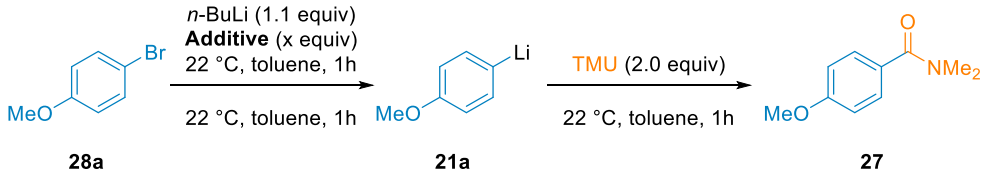
Table 7. Optimisation of carbamoylation under Barbier conditions in continuous flow setup.



Entry	T [°C]	t^R [s]	Flowrate [mL/min]	Leftover **20** [GC-%]	Product **27** [GC-%]
1	0	60	5	2	82
2	0	300	1	11	69
3	0	60	1	9	73
4	0	12	5	1	82
5	10	12	5	<1	83 (83)
6	–10	12	5	<1	80
7	–20	12	5	<1	79
8	–30	12	5	<1	75

However, in an attempt to use cheaper aryl bromides, the Barbier conditions with *n*-BuLi failed due to competitive addition to tetramethylurea. Although the lowering temperature did suppress this side reaction, the conversion of 4-bromoanisole (**28a**) was far from complete. Thus, we turned our attention to the stepwise generation of aryllithiums in toluene and a subsequent performing of electrophile quench. The main obstacle in our way was the solubility of aryllithiums in toluene. Therefore, we first screened the different donor additives and made qualitative observations of the reaction solution. Interestingly, just one equivalent of THF in toluene[119] afforded a clear solution of 4-methoxyphenyllithium and had a positive effect on the Br/Li exchange (Table 8).

Table 8. Screening of donor additives for the Br/Li exchange in toluene.

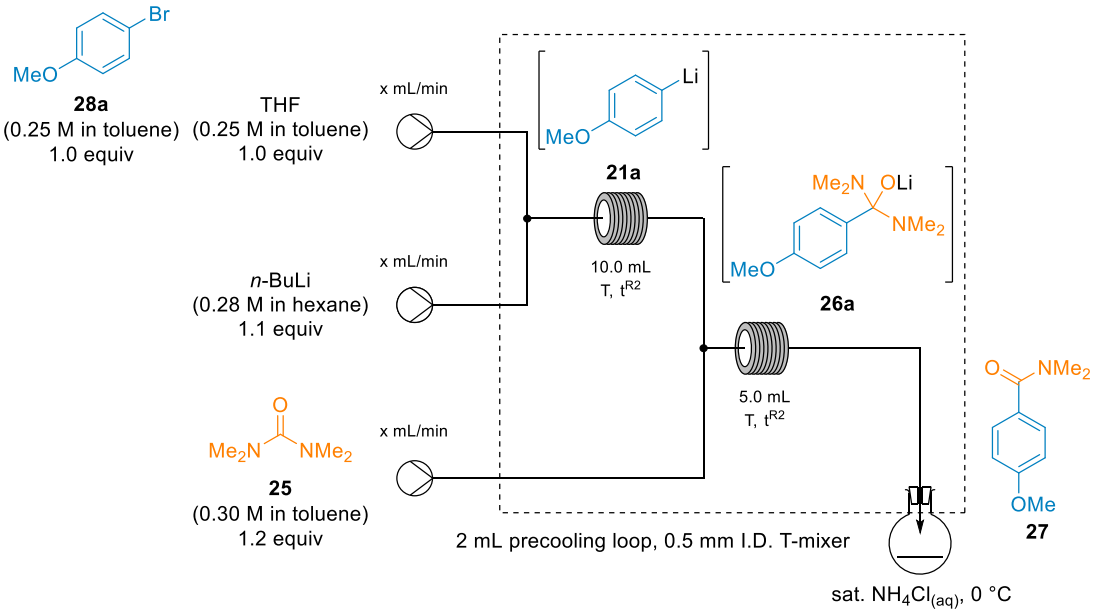


[118] N. Miyoshi, S. Kimura, S. Kubo, S. D. Ohmura, M. Ueno, *Asian J. Org. Chem.* **2020**, *9*, 1660.
[119] „Dopping“ of hydrocarbons with donor solvents was a strategy used before: a) H. R. Rogers, J. Houk, *J. Am. Chem. Soc.* **1982**, *104*, 522; b) D. W. Slocum, P. Dietzel, *Tetrahedron Lett.* **1999**, *40*, 1823; c) D. W. Slocum, A. Carroll, P. Dietzel, S. Eilerman, J. P. Culver, B. McClure, S. Brown, R. W. Holman, *Tetrahedron Lett.* **2006**, *47*, 865; d) D. W. Slocum, D. Kusmic, J. C. Raber, T. K. Reinscheld, P. E. Whitley, *Tetrahedron Lett.* **2010**, *51*, 4793.

Entry	Additive	Equiv of additive	Conversion [GC-%]	Appearance before TMU addition
1	/	/	70%	suspension
2	THF	1.0	97	solution
3	Et_2O	1.0	89	suspension
4	MTBE	1.0	92	suspension
5	Bu_2O	1.0	89	suspension
6	THF	0.2	81	suspension

The 4-methoxyphenyllithium was soluble even at −78 °C in toluene with 1 equiv THF, while in pure THF a suspension is formed bellow −50 °C. Interestingly, monosolvated Grignard reagents can also be prepared in toluene using 1.0 equiv of Et_2O.[120] With the solubility of the aryllithiums in toluene solved, we have pursued the optimisation of the Br/Li exchange in a continuous flow setup. However, *n*-BuLi did not give full conversion even at elevated temperatures (Table 9).

Table 9. Br/Li exchange of 4-bromoanisole (**28a**) with *n*-BuLi in toluene in the presence of 1.0 equiv of THF.

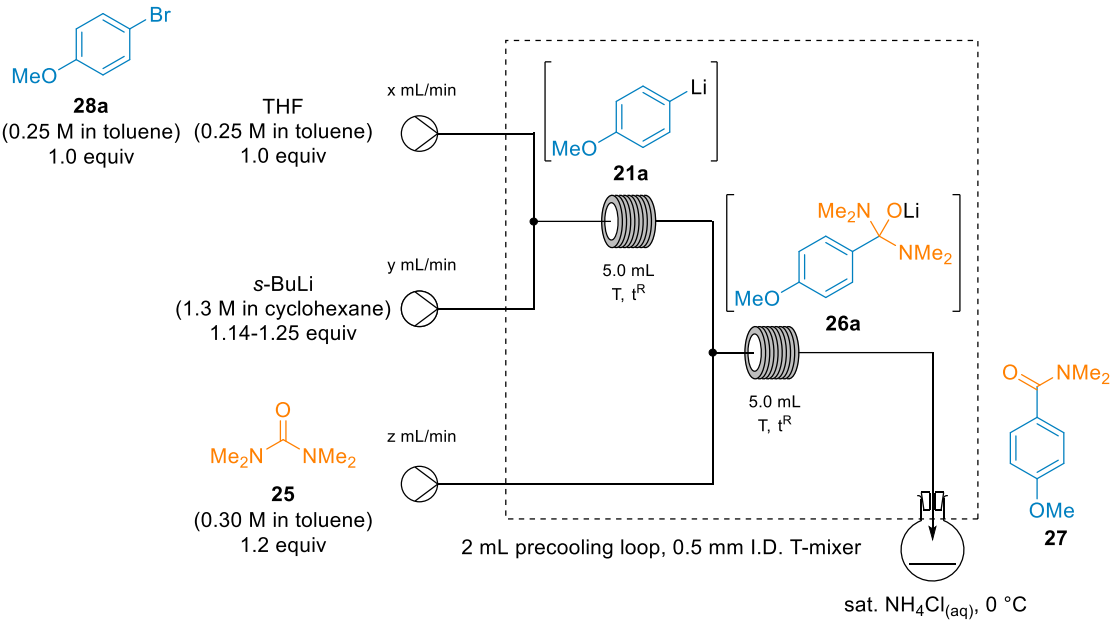


Entry	T [°C]	t^{R1} [s]	t^{R2} [s]	Flowrate [mL/min]	Conversion **28a** [GC-%]
1	−10	60	20	5+5+5	43
2	40	60	20	5+5+5	44
3	50	300	100	1+1+1	75
4	60	300	100	1+1+1	83

Finally, *s*-BuLi in cyclohexane was examined as an exchange reagent. After a short screening (Table 10) full conversion was achieved at very convenient temperatures (22 °C) and **27** was isolated in 81% yield. It is important to note that 4-bromoanisole is a challenging substrate for halogen/metal exchange. Other, less electron-rich aryl bromides can be suitable for Br/Li exchange with *n*-BuLi. We have, for the sake of wider substrate scope, used *s*-BuLi as the reagent of choice. For the first time, we have obtained the aryllithiums in toluene without Barbier conditions. This opens a possibility for a reaction with a variety of electrophiles.

[120] M. Sassian, D. Panov, A. Tuulmets, *Appl. Organometal. Chem.* **2002**, *16*, 525.

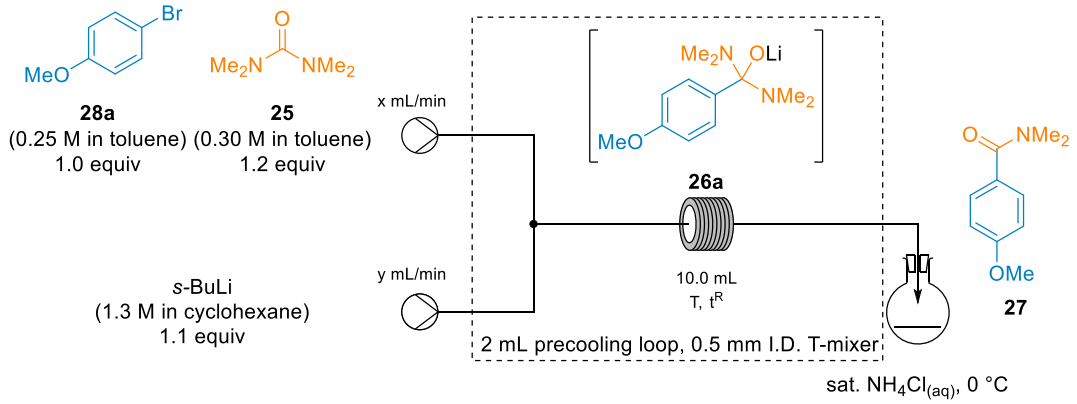
Table 10. Br/Li exchange of 4-bromoanisole (**28a**) with *s*-BuLi in toluene in the presence of 1 equiv of THF.



Entry	T [°C]	t^R [s]	Flowrate x+y+z [mL/min]	Conversion **28a** [GC-%]	Product **27** [GC-%]
1	22	50+27.3	5+1+5	92	75
2	22	49.2+100	8+1.6+8	95	77
3	22	49.2+26.8	5+1.1+5.1	97	79
4	22	48.4+26.3	5+1.2+5.2	99	82 (81)

To further simplify the setup we have also optimised a Barbier approach for the reaction with tetramethylurea (**25**) (Table 11) to obtain 4-methoxy-*N*,*N*-dimethylbenzamide (**27**) in 83% yield. The Barbier conditions required lower reaction temperature but allowed the reduction of the pumps from three to two.

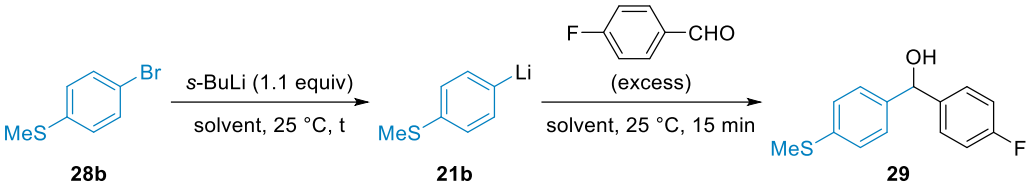
Table 11. Optimisation of carbamoylation under Barbier conditions in continuous flow setup with 4-bromoanisole (**28a**) as substrate and *s*-BuLi as an Br/Li exchange reagent.



Entry	T [°C]	Flowrate x+y [mL/min]	Conversion [GC-%]	GC yield **27** [%]
1	22	5+1	75	41
2	22	10+2	78	52
3	0	10+2	87	73
4	–10	10+2	93	83
5	–20	10+2	96	83 (83)
6	–30	10+2	99	82

Finally, optimization of the aryllithium preparation was exemplified on 4-bromothioanisole (**28b**).[121] We further confirmed the positive effect of THF (1.0 equiv) on the Br/Li exchange and that the lithium species was not stable at 25 °C as shown by quenching with 4-fluorobenzaldehyde. In toluene, the Br/Li exchange was slow and required up to 2 h reaction time. These reaction times were not compatible with the stability of the Li-species. The stability of aryllithiums in toluene was much higher than in THF (Table 12, entries 1 and 6). The use of flow apparatus was beneficial (Table 12, entry 9).

Table 12. Optimization of the aryllithium generation from 4-bromothioanisole (**28b**) in batch and flow.



28b **21b** **29**

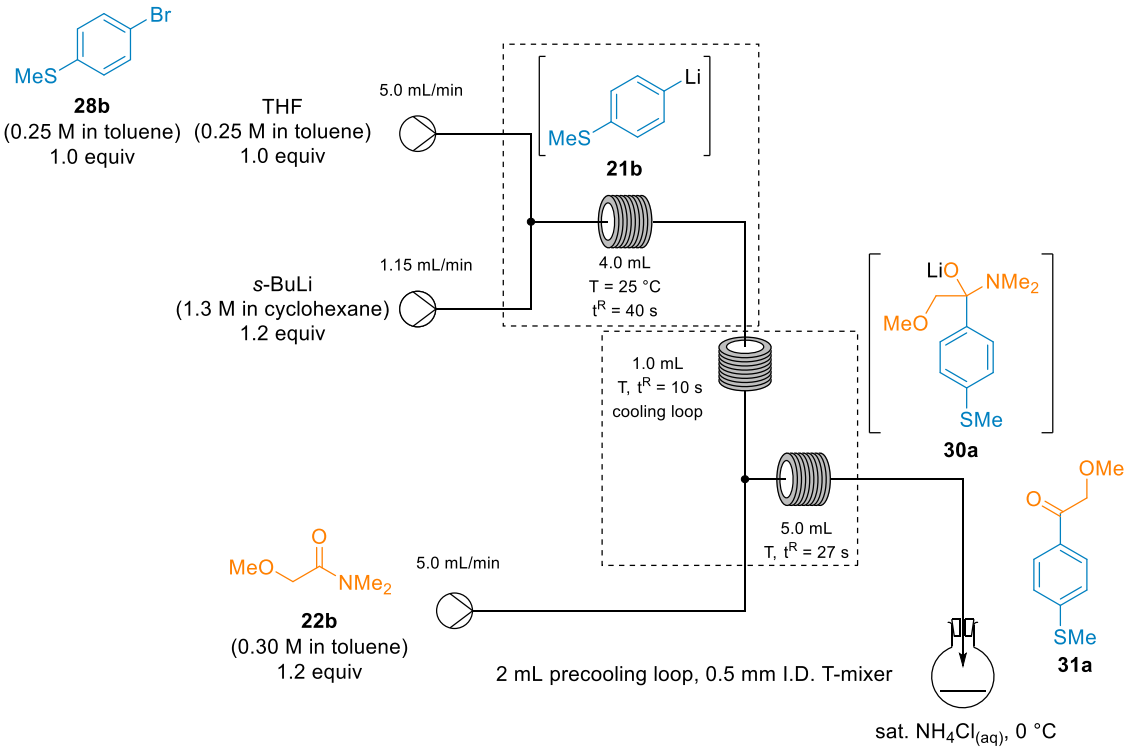
Entry	Setup	Solvent	t [min]	Conversion of **28b** [GC-%]	Formation of **29** [GC-%]
1	batch	THF	1	90	24
2	batch	THF	30	93	27
3	batch	Toluene	1	18	8
4	batch	Toluene	30	75	49
5	batch	Toluene	120	94	57
6	batch	Toluene[a]	1	96	95
7	batch	Toluene[a]	10	98	85
8	batch	Toluene[a]	30	>99	60
9	flow	Toluene[a]	1	>99	99

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

Next, we optimised the reaction of 4-methylthiophenyllithium with *N*,*N*-dimethylamide **22b** in continuous flow (Table 13). Pumping a solution of aryl bromide **28b** (0.25 M in toluene with 1.0 equiv of THF) with a flow rate of 5.0 mL/min and *s*-BuLi (1.35 M in cyclohexane) with a flow rate of 1.1 mL/min at 25 °C (residence times 40 s) gave quantitatively the aryllithium species. The solution of aryllithium was precooled to −20 °C (10 s) and then mixed *via* T-mixer with a solution of *N*,*N*-dimethylamide in toluene at −20 °C (residence time 27 s). After quenching with saturated $NH_4Cl_{(aq)}$ the expected ketone **31a** was isolated in 82% yield. A 10-fold scale-out of this reaction in continuous flow was easily achieved by prolonging the suction time from 0.5 min to 5.0 min and resulted in a comparable yield of 78%.

[121] Most of arylilithums prepared in this work were not stable enough for convenient batch procedure. For full stability study of various aryllithiums see Experimental part page 110. 4-Bromoanisole was an exception with its stability in THF (40% of the product of type **29** after 10 min at 25 °C). Thus, we have chosen 4-methylthiobromobenzene as a more suitable exemplar.

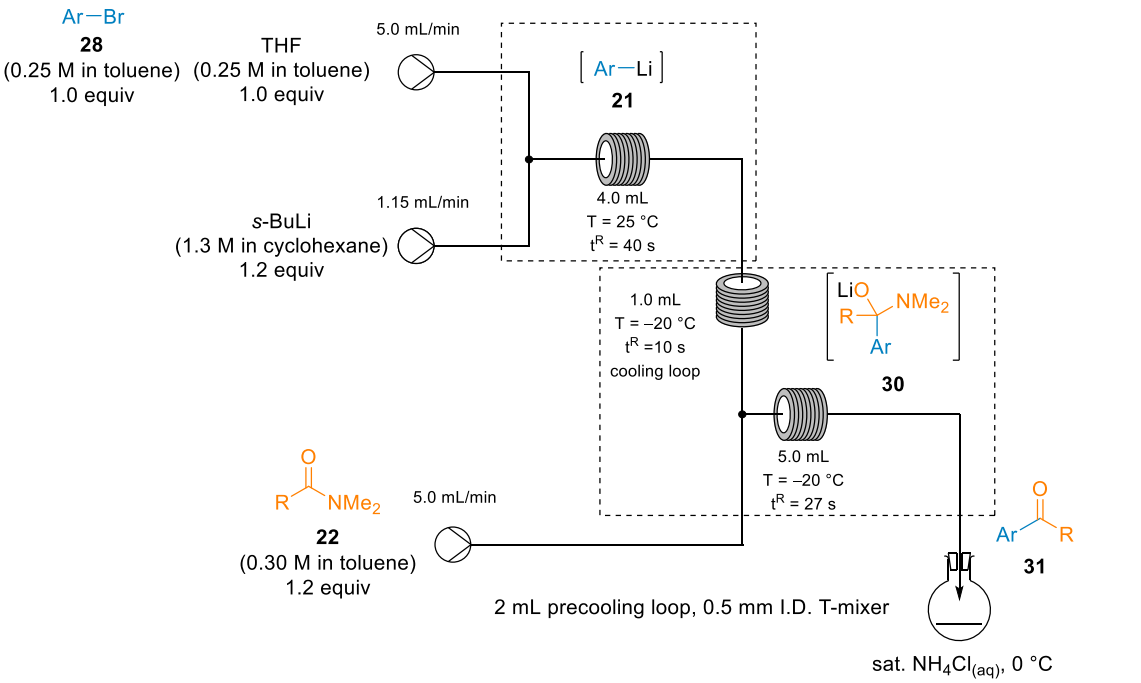
Table 13. Optimization of the acylation temperature.

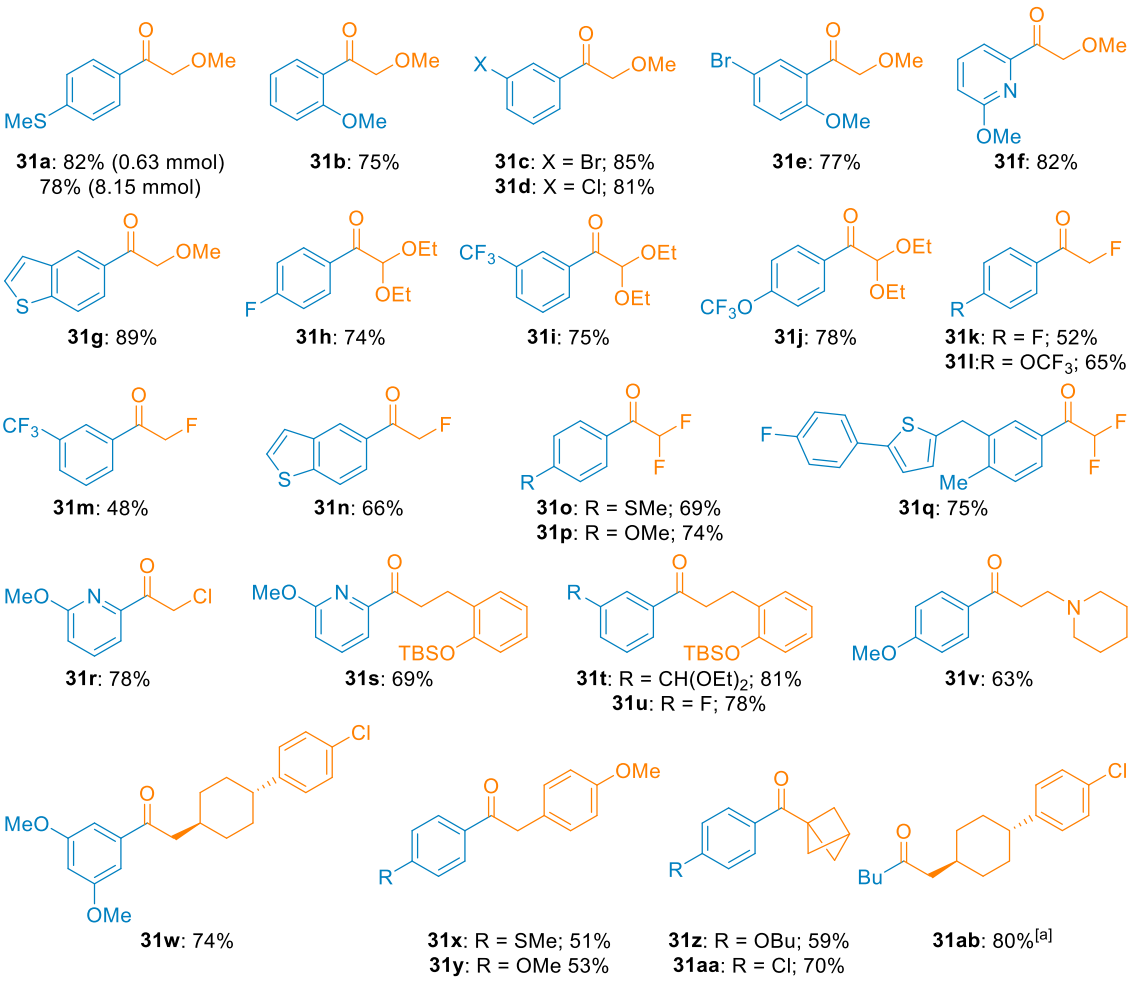


Entry	T [°C]	Conversion **28b** [GC-%]	Product formation **31a** [GC-%]
1	25	>99	50
2	0	>99	67
3	–20	>99	82
4	–40	>99	84

Finally, with optimized conditions in hand, we explored the scope of this transformation (Scheme 44). Thus, aryllithiums bearing methoxy, fluoro, chloro and bromo substituents were competent reaction partners with amide **22b** and gave expected ketones **31b-e**. Heterocyclic organolithium reagents containing pyridine and benzothiophene gave methoxymethyl ketones **31f** and **31g**. Glyoxal derivatives **31h-j** were obtained in good yields (74-78%) from amide **22c** using electron-deficient aryllithiums with fluoro, trifluoromethyl and trifluoromethoxy substituents. Remarkably, 2-fluoro-*N*,*N*-dimethylacetamide (**22d**) and 2,2-difluoro-*N*,*N*-dimethylacetamide (**22e**) with very acidic protons in alpha position also afforded the expected ketones **31k-q** in 48-75% yield. Similarly, chloroacetamide **22f** gave a sensitive chloromethyl ketone **31r** in 78% isolated yield. Compared to THF, the use of toluene as solvent significantly reduced enolization side reactions. We found that *N*,*N*-dimethylphenylacetamide **22j** gave moderate yields of benzylic ketones **31x-y** (51-53%). Enolization of 4-methoxyphenylacetamide **22j** (Table 14) by aryllithium **21b** in toluene gave 25% of proto-debromination of the starting material (compared to >70% in pure THF).[122] Sterically hindered amide such as [1.1.1]-cyclopentanecarboxamide (**22k**) reacted with 4-butoxyphenyllithium (**21p**) and 4-chlorophenyllithium (**21r**) to give bicyclopen-1-yl ketones **31z** and **31aa** in 59% and 70% yield respectively. Also, dialkyl ketone **31ab** was synthesised in 80% yield by reacting *n*-BuLi in *n*-hexane as a nucleophile *via* a 2-pump system.

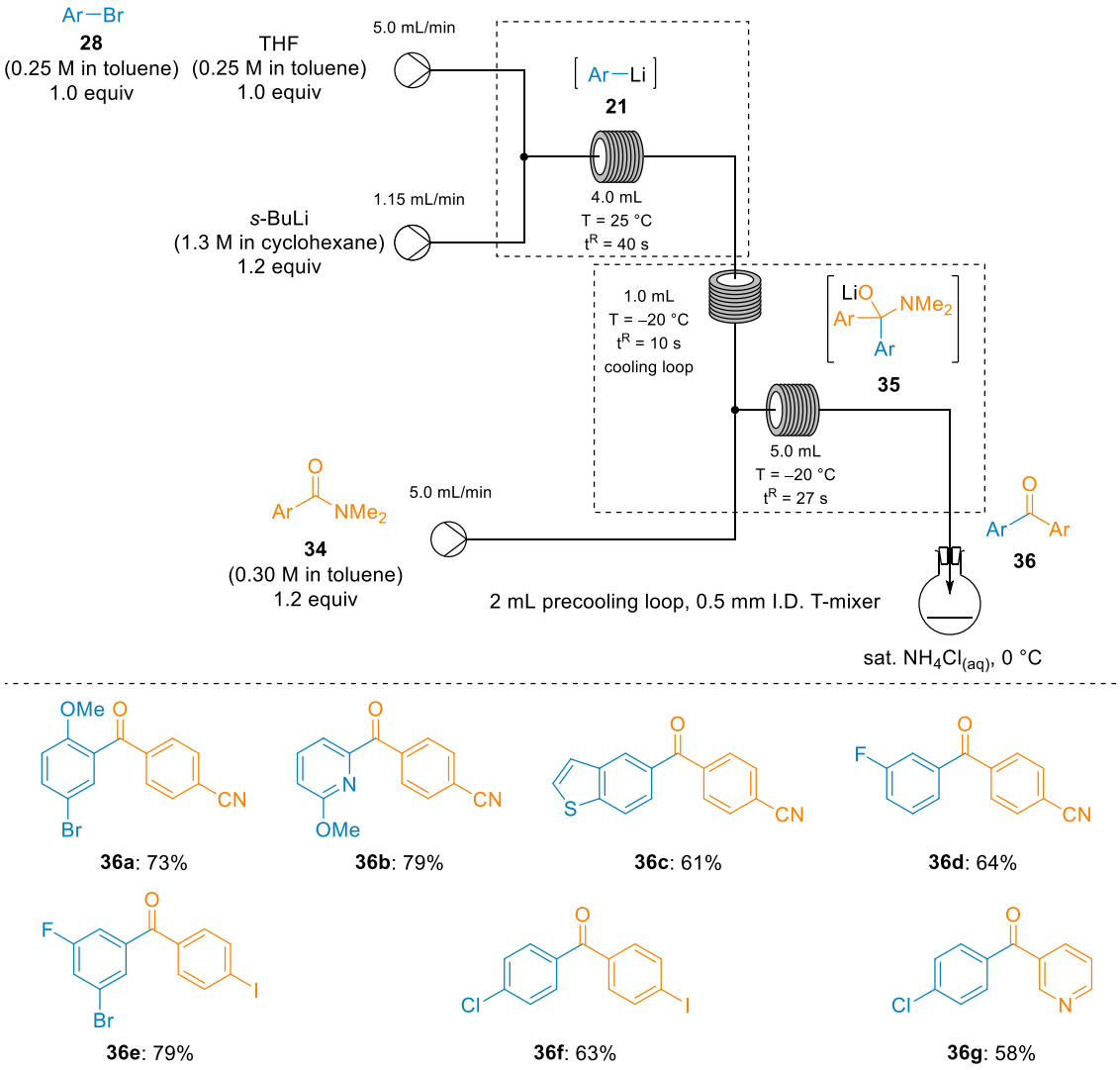
[122] See Experimental Part pages 111-112, Table 19, Entries 3 and 6.





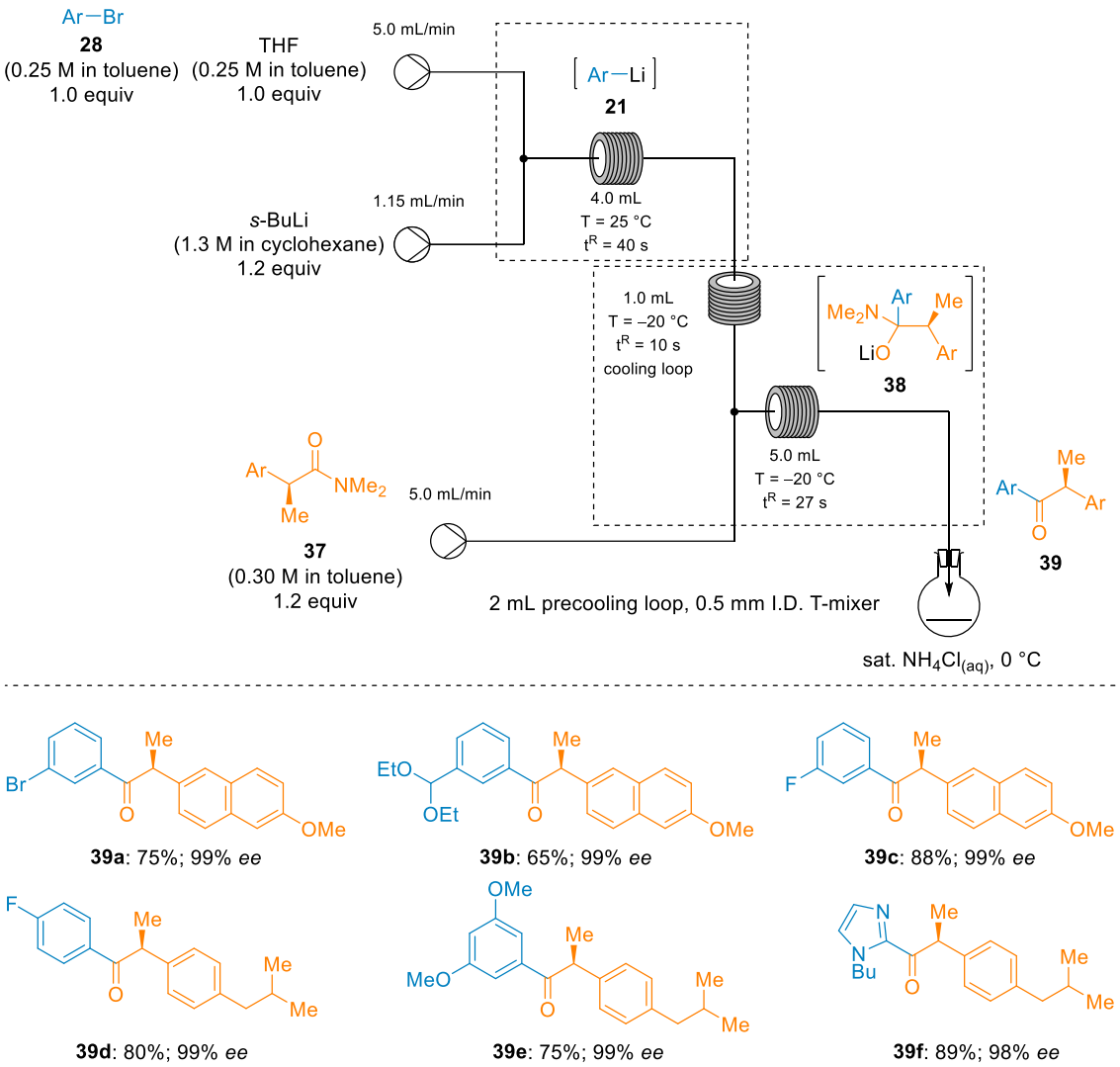
Scheme 44. Continuous flow acylation of various *N*,*N*-dimethylamides with aryllithiums in toluene. [a] *n*-BuLi reacted with amide **22i** in a two-pump continuous flow setup.

Next, we explored the synthesis of diaryl ketones along with the functional group tolerance (Scheme 45). Thus, *N*,*N*-dimethyl-4-cyanobenzamide **34a** reacted chemoselectively to afford cyanobenzophenones **36a-d** in 61-73% yield. Also, *N*,*N*-dimethyl-4-iodobenzamide (**34b**) gave **36e** and **36f** in 63-79% isolated yield. Interestingly, no I/Li exchange was observed. Lastly, *N*,*N*-diethylnicotinamide (**34c**) gave 3-pyridyl ketone **36g** in 58% yield.



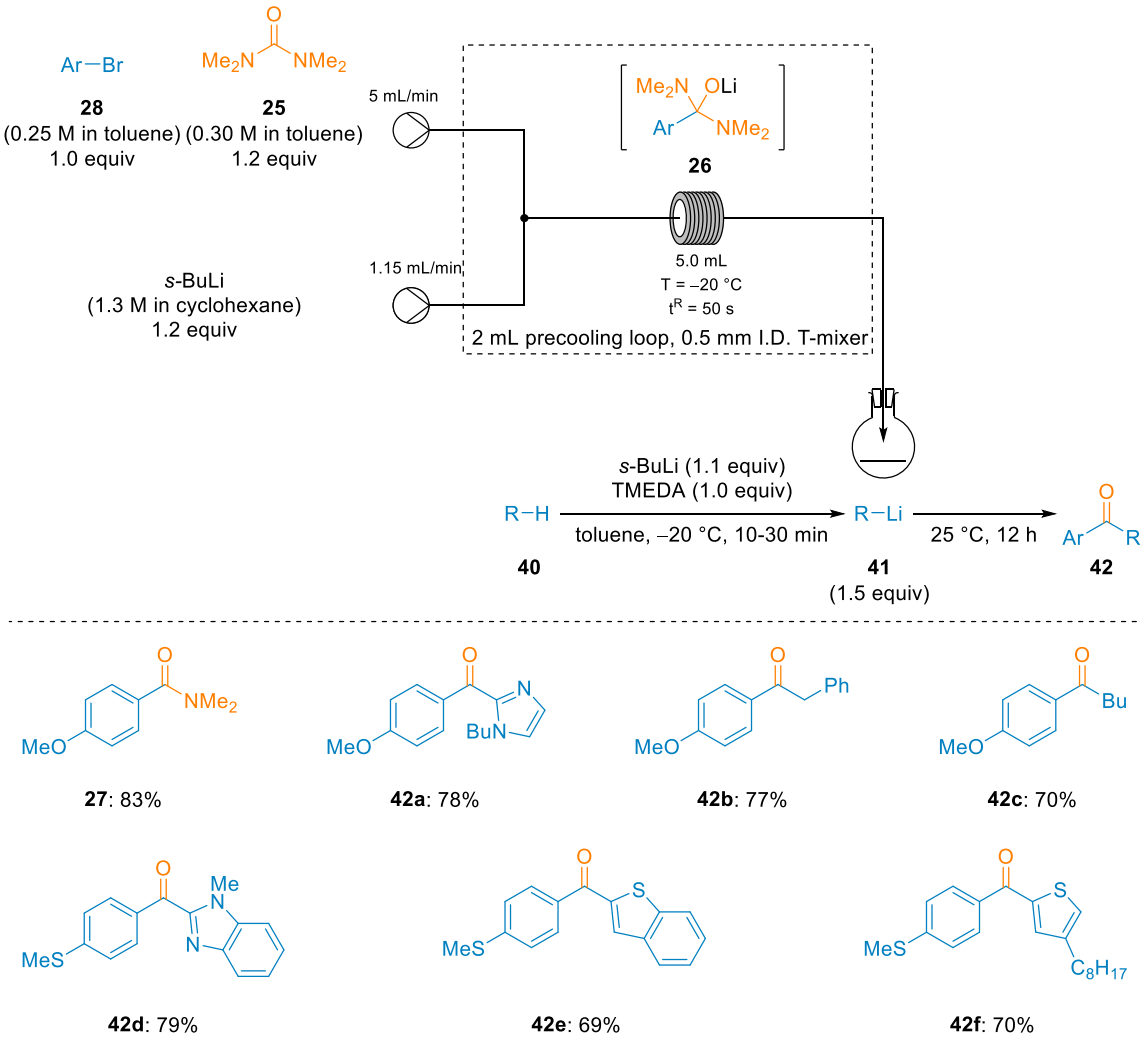
Scheme 45. Preparation of functionalized diaryl ketones by continuous flow acylation of (hetero)aryllithiums in toluene with (hetero)aryl *N*,*N*-dimethylamides.

Easily racemizable α-chiral amides derived from naproxen **37a** and ibuprofen **37b** were also used (Scheme 46). Thus, α-chiral ketones **39a-e** were obtained under standard reaction conditions with complete retention of chirality (99% *ee*). Additionally, *N*-butylimidazole with 1.0 equiv TMEDA instead of THF was successfully metalated with *s*-BuLi in our setup and gave the expected chiral ketone **39f** in 89% isolated yield and 98% *ee*.



Scheme 46. Preparation of chiral naproxen and ibuprofen ketone derivatives of type **27** in continuous flow.

At last, we extended this acylation procedure to a telescoped procedure for the preparation of unsymmetrical ketones of type **42** using tetramethylurea (TMU) as CO synthon (Scheme 47). A Barbier procedure with a 2-pump setup was used. Thus, pumping of a mixture of aryl bromide (0.25 M in toluene) and TMU (0.3 M in toluene) with 5.0 mL/min flow rate and *s*-BuLi (1.3 M in cyclohexane) with 1.15 mL/min afforded, after quench with saturated $NH_4Cl_{(aq)}$ the 4-methoxy-*N*,*N*-dimethylbenzamide (**27**) in 83% isolated yield. Alternatively, when the reaction mixture was poured into a toluene solution of various organolithiums (1.5 equiv) various unsymmetrical ketones were obtained. The solutions of organolithiums were conveniently prepared by metalation using *s*-BuLi and TMEDA (1.0 equiv) in toluene at –20 °C (30 min) in batch. Probably due to the high stability of the TMU-derived tetrahedral intermediate, the addition of the second organolithiums reagent was slow and took 12 h at 25 °C. After quenching with saturated $NH_4Cl_{(aq)}$ ketones **42a-f** were isolated in 69-79% yield. Interestingly, when the Br/Li exchange was done in the presence of TMU no additional equivalent of THF was necessary.



Scheme 47. Semi-batch telescoped procedure for the synthesis of unsymmetrical aryl ketones **42a-f** using tetramethylurea (**25**) as C1 synthetic equivalent.

3. Regioselective Difunctionalization of Pyridines *via* 3,4-Pyridynes

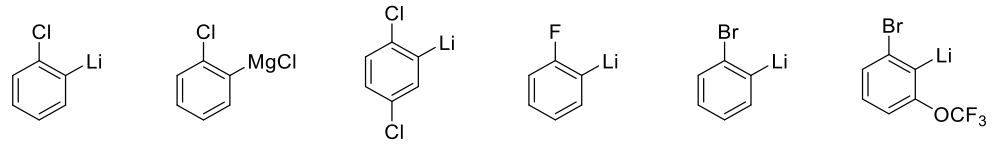
Functionalized arenes are commonly prepared using transition metal cross-coupling chemistry. Transition metal-free methods are an intriguing but underexplored alternative. One such method is nucleophilic substitution[123] *via* aryne intermediates.[124] Although postulated at the very beginning of the 20th century,[125] a valid proof of aryne intermediates appeared only in the 1950s.[126] Over time, a large number of substituted benzynes and heteroarynes have been proposed.[127] The existence of 6-membered arynes has been well established and proved by STM/AFM imaging.[128]

There are numerous ways to generate arynes but due to their extreme electrophilicity arynes can only be prepared *in situ*.[129] One of the oldest ways is the thermal decomposition of diazonium anthranilate, a very cheap, but unstable and explosive compound.[130] Over the years more convenient ways have been developed so that the aryne generation can be tuned depending on reaction conditions employed.[131] Most commonly used are Kobayashi precursors (2-(trimethylsilyl)phenyl trifluoromethane sulfonates).[132] Arynes can be generated from organometallic compounds which possess a leaving group in the *ortho* position. Most commonly employed are organolithiums and other alkali metals[133] but also organomagnesiums.[134] Although a halogen leaving group was most common, Knochel and coworkers

[123] a) M. S. Viciu, L. Gupta, D. B. Collum, *J. Am. Chem. Soc.* **2010**, *132*, 6361; b) E. E. Kwan, Y. Zeng, H. A. Besser, E. N. Jacobsen, *Nat. Chem.* **2018**, *10*, 917.
[124] J.-A. García-López, M. F. Greaney, *Chem. Soc. Rev.* **2016**, *45*, 6766.
[125] R. Störmer, B. Kahlert, *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1633.
[126] a) J. D. Roberts, H. E. Simmons Jr., L. A. Carlsmith, C. W. Vaughan, *J. Am. Chem. Soc.* **1953**, *75*, 3290; b) R. Hoffmann, A. Imamura, W. J. Hehre, *J. Am. Chem. Soc.* **1968**, *90*, 1499.
[127] a) M. G. Reinecke, *Tetrahedron* **1982**, *38*, 427; b) A. E. Goetz, T. K. Shah, N. K. Garg, *Chem. Commun.* **2015**, *51*, 34; c) A. Guin, S. Bhattacharjee, A. T. Biju, Hetarynes, Cycloalkynes and Related Intermediates. In *Modern Aryne Chemistry*, (Eds.: A. T. Biju), Wiley-VCH, **2021**, pp. 359-406.
[128] N. Pavliček, B. Schuler, S. Collazos, N. Moll, D. Pérez, E. Guitián, G. Meyer, D. Peña, L. Gross, *Nat. Chem.* **2015**, *7*, 623.
[129] N. F. F. Nathel, L. A. Morrill, H. Mayr, N. K. Garg, *J. Am. Chem. Soc.* **2016**, *138*, 10402.
[130] a) J. M. Sullivan, *J. Chem. Educ.* **1971**, *48*, 419; b) J. D. Firth, I. J. S. Fairlamb, *Org. Lett.* **2020**, *22*, 7057.
[131] a) L. Friedman, F. M. Logullo, *J. Am. Chem. Soc.* **1963**, *85*, 1549 (diazonium carboxylate); b) Fluoro Magnesium and Fluoro Lithium: R. W. Hoffmann, *Dehydrobenzene and Cycloalkanes*, Academic Press, New York, **1967**; c) C. D. Campbell, C. W. Rees, *J. Chem. Soc. C* **1969**, 742 (aminobenzotriazole); d) G. Wittig, R. W. Hoffmann, *Organic Syntheses* **1973**, *5*, 60; **1967**, *47*, 4 (1,2,3-benzothiadiazole-1,1-dioxide); e) L. Friedman, F. M. Logullo, *J. Org. Chem.* **1969**, *34*, 3089 (diazonium carboxylate); f) Jr. M. Jones, M. R. DeCamp, *J. Org. Chem.* **1971**, *36*, 1536 (phtaloyl peroxide); g) R. T. Luibrand, R. W. Hoffmann, *J. Org. Chem.* **1974**, *39*, 3887 (phtaloyl peroxide); h) Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211 (silyl triflate); i) T. Matsumoto, T. Hosoya, M. Katsuki, K. Suzuki, *Tet. Lett.* **1991**, *32*, 6735 (halo triflate); j) T. Kitamura, M. Yamane, *J. Chem. Soc., Chem. Commun.* **1995**, 983 (iodonium triflate); k) D. Chang, L. Shi, *J. Org. Chem.* **2015**, *80*, 5928 (phtaloyl peroxide); l) M. Mesgar, O. Daugulis, *Org. Lett.* **2016**, *18*, 3910 (silylaryl halides) m) M. Lanzi, Q. Dherbassy, J. Wancel-Delord, *Angew. Chem. Int. Ed.* **2021**, *60*, 14852 (Λ^3-bromanes).
[132] a) D. Rodríguez-Lojo, A. Cobas, D. Peña, D. Pérez, E. Guitián, *Org. Lett.* **2012**, *14*, 1363; b) S. Ghorai, D. Lee, *Synlett* **2020**, *31*, 750; c) J. Shi, L. Li, Y. Li, *Chem. Rev.* **2021**, *121*, 3892.
[133] a) E. R. Biehl, E. Nieh, K. C. Hsu, *J. Org. Chem.* **1969**, *34*, 3595; b) E. R. Biehl, K. C. Hsu, E. Nieh, *J. Org. Chem.* **1970**, *35*, 2454; c) E.R. Biehl, S. M. Smith, P. C. Reves, *J. Org. Chem.* **1971**, *36*, 1841; d) E. R. Biehl, S. Lapis, P. C. Reeves, *J. Org. Chem.* **1974**, *39*, 1900; e) R. Levine, E. R. Biehl, *J. Org. Chem.* **1975**, *40*, 1835; f) M. I. El-Sheikh, A. Marks, E. R. Biehl, *J. Org. Chem.* **1981**, *46*, 3256; g) H. Y. Xin, E. R. Biehl, *J. Org. Chem.* **1983**, *48*, 4397; h) Y. X. Han, M. V. Jovanovic, E. R. Biehl, *J. Org. Chem.* **1985**, *50*, 1334; i) E. R. Biehl, A. Razzuk, M. V. Jovanovic, S. P. Khanapure, *J. Org. Chem.* **1986**, *51*, 5157; j) A. Razzuk, E.R. Biehl, *J. Org. Chem.* **1987**, *52*, 2619; k) S. P. Khanapure, R. T. Reddy, E. R. Biehl, *J. Org. Chem.* **1987**, *52*, 5685; l) B. M. Bhawal, S. P. Khanapure, H. Zhang, E. R. Biehl, *J. Org. Chem.* **1991**, *56*, 2846; m) M. Dutt, B. Fravel, G. P. Ford, E. R. Biehl, *J. Org. Chem.* **1994**, *59*, 497; n) G. E. Morton, A. G. M. Barrett, *J. Org. Chem.* **2005**, *70*, 3525; o) G. E. Morton, A. G. M. Barrett, *Org. Lett.* **2006**, *8*, 2859; p) K. R. Buszek, N. Brown, D. Luo, *Org. Lett.* **2009**, *11*, 201; q) E. P. Jones, P. Jones, A. G. M. Barrett, *Org. Lett.* **2011**, *13*, 1012; r) M. Mesgar, J. Nguyen-Le, O. Daugulis, *J. Am. Chem. Soc.* **2018**, *140*, 13703.
[134] a) H. Hart, C. Y. Lai, G. Nwokogu, S. Shamouilian, A. Teuerstein, C. Zlatogorski, J. *Am. Chem. Soc.* **1980**, *102*, 6651; b) H. Hart, S. Shamouilian, Y. Takehira, *J. Org. Chem.* **1981**, *46*, 4427; c) K. Harada, H. Hart, C. J. F. Du, *J. Org. Chem.* **1985**, *50*, 5524; d) H. Hart, K. Harada, C. J. F. Du, *J. Org. Chem.* **1985**, *50*, 3104; e) H. Hart, D. Ok, *J. Org. Chem.* **1986**, *51*, 979; f) J. Luo, H. Hart, *J. Org. Chem.* **1987**, *52*, 3631; g) C. J. F. Du, H. Hart, *J. Org. Chem.* **1987**, *52*, 4311; h) H. Hart, C.-Y. Lai, G. C. Nwokogu, S. Shamouilian, *Tetrahedron* **1987**, *43*, 5203; i) H. Hart, A. Saednya, *Synth. Commun.* **1988**, *18*, 1749 j) T.

have shown that tunable arylsulfonate leaving groups can be used as well.[135] Moreover, this approach resulted in a mild method, compatible with a range of nucleophiles such as Mg-amides and Mg-thiolates. This method was also applied in the generation of pyridyne.[136] Similarly, sulfonate/Mg and phosphine oxide exchanges were applied.[137] It should be noted that some η^2-complexes of transition metals and benzyne are known.[138] These complexes exhibit benzyne-type reactivity. For instance, they insert into σ-bonds but are in general nucleophilic (umpolung of reactivity compared to arynes).

In the case of ortho halo-substituted organometallics, the temperature at which aryne generation occurs depends on the type of the metal, leaving group and arene backbone. Organolithiums generate arynes at lower temperatures than organomagnesiums.[139] Regarding the halogen leaving groups the temperature of the aryne formation in THF decreases in the following order: F>Cl>Br>I (Scheme 48).[140] Thus, whereas 2-bromophenyllithium[141] has a short lifetime above −125 °C, 2-chlorophenyllithium[142] decomposes above −100 °C within a few hours. 2-Fluorophenyllithium[143] can be prepared and preserved below −75 °C. Electron donating substituents on the aromatic backbone destabilise[144] 2-halophenyl metals while electron-withdrawing substituents stabilise them. For example, 2-bromo-6-trifluoromethoxyphenyllithium slowly eliminates LiBr at −30 °C.[145] Similar trends follow in 2-halophenylmagnesium cases.[146]



43: −100 °C **7s**: 25 °C **45**: −40 °C **46**: −78 °C **47**: −125 °C **48**: −30 °C

Scheme 48. Stability comparison of 2-haloarylmetals.

Despite a variety of ways to generate simple benzynes, the atom economy of the reactions involving arynes is often very poor having in mind that most precursors are *o*,*o*-disubstituted molecules and the products are very often monosubstituted. Thus, from an atom economy perspective it would be most desirable to start from a monosubstituted precursor and furnish a disubstituted product. This point

Ghosh, H. Hart, *J. Org. Chem.* **1988**, *53*, 3555; T. K. Vinod, H. Hart, *Tetrahedron Lett.* **1988**, *29*, 885; k) H. Hart, T. Ghosh, *Tetrahedron Lett.* **1988**, *29*, 881; l) C. J. F. Du, H. Hart, K. K. D. Ng, *J. Org. Chem.* **1986**, *51*, 3162; m) T. K. Vinod, H. Hart, *J. Org. Chem.* **1990**, *55*, 5461; n) H. Hart, *Pure Appl. Chern.* **1993**, *65*, 27; o) D. Soorukram, T. Qu, A. Berret, *Org. Lett.* **2008**, *10*, 3833.

[135] a) I. Sapountzis, W. Lin, M. Fischer, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 4364; b) W. Lin, I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 4258; c) J.-A. García-López, M. Çetin, M. F. Greaney, *Angew. Chem. Int. Ed.* **2015**, *54*, 2156; d) J.-A. García-López, M. Çetin, M. F. Greaney, *Org. Lett.* **2015**, *17*, 2649.

[136] W. Lin, L. Chen, P. Knochel, *Tetrahedron* **2007**, *63*, 2787.

[137] a) S. Yoshida, K. Uchida, T. Hosoya, *Chem. Lett.* **2014**, *43*, 116; b) Y. Nishiyama, S. Kamada, S. Yoshida, T. Hosoya, *Chem. Lett.* **2018**, *47*, 1216.

[138] a) M. A. Bennet, T. W. Hambley, N. C. Roberts, G. B. Robertson, *Organometallics* **1985**, *4*, 1992; b) S. L. Buchwald, R. B. Nielsen, *Chem. Rev.* **1988**, 1047; c) J. F. Hartwig, R. A. Andersen, R. C. Bergman, *J. Am. Chem. Soc.* **1989**, *111*, 2717; d) Y. Sumida, T. Sumida, D. Hashizume, T. Hosoya, *Org. Lett.* **2016**, *18*, 5600.

[139] a) K. C. Caster, C. G. Keck, R. D. Walls, *J. Org. Chem.* **2001**, *66*, 2932; b) M. Fossatelli, L. Brandsma, *Synthesis* **1992**, *8*, 756; c) H. L. Gingrich, Q. Huang, A. L. Morales, M. J. Jones, *Org. Chem.* **1992**, *57*, 3803.

[140] This order follows in THF. In toluene fluoride elimination can happen over chloride/bromide: a) A. Ramirez, J. Candler, C. G. Bashore, M. C. Wirtz, J. W. Coe, D. B. Colum, *J. Am. Chem. Soc.* **2004**, *126*, 14700; b) J. W. Coe, M. C. Wirtz, C. G. Bashore, J. Candler, *Org. Lett.* **2004**, *6*, 1589.

[141] a) H. Gilman, R. D. Gorisch, *J. Am. Chem. Soc.* **1956**, *78*, 2217; b) L. S. Chen, G. J. Chen, C. Tamborski, *J. Org. Chem.* **1980**, *193*, 283.

[142] M. Iwao, *J. Org. Chem.* **1990**, *55*, 3622.

[143] H. Gilman, T. S. Soddy, *J. Org. Chem.* **1957**, *22*, 1715.

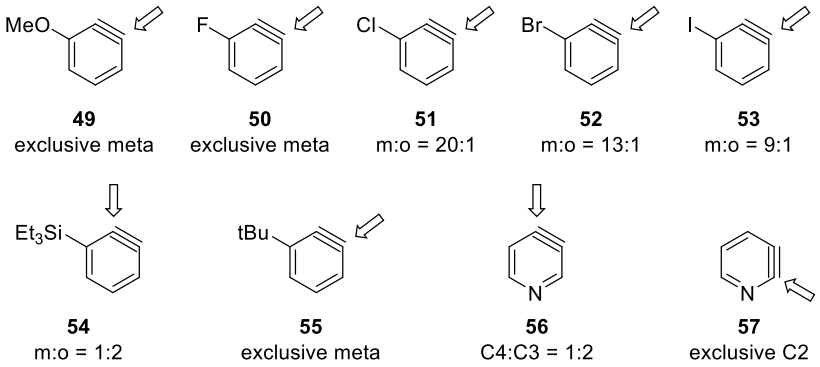
[144] a) P. A. Huddle, G. W. Perold, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2617; b) R. D. Clark, J. M. Caroon, *J. Org. Chem.* **1982**, *47*, 2804; c) L. E. Fisher, J. M. Caroon, *Synth. Commun.* **1989**, *19*, 233.

[145] M. Schlosser, E. Castagnetti, *Eur. J. Org. Chem.* **2001**, 3991.

[146] a) Half-life of 2-bromophenylmagnesium chloride-lithiumchloride at −10 °C is 24 h (see ref. 40); b) 2-chlorophenylmagnesium bromide was made at rt *via* magnesium insertion: N. Zekri, R. Fareghi-Alamdari, B. Momeni-Fard, *J. Chem. Sci.* **2020**, *132*, 1.

becomes even more evident when one considers potential heteroaryne precursors. The lack of suitable building blocks and the cost of starting materials make an exciting journey toward the new heteroarynes slow and hard.

Regioselectivity of nucleophilic attack on the aryne should be carefully considered when planning such reactions (Scheme 49). The new aryne distortion model developed and popularised by Garg and Houk has shown the best predictions and explanations.[147,148] Sterics and charge separations play only a minor role.[149] According to Bent's rule,[150] the inductive effect of the substituent will cause a change in the hybridisation of the atoms and therefore the geometry of the aryne. Such distortion causes desymmetrisation of the triple bond and a change in regioselectivity.



Scheme 49. Regioselectivity of nucleophile addition in substituted (hetero)arynes.[146]

The stronger the inductive effect of the substituent, the bigger the distortion leading to better regioselectivities. Thus, by running a geometry optimization of the aryne and analysing the structure one can predict regioselectivity. Similar to the methoxy group and fluorine, other halogens give the same major product but with inferior regioselectivities. On the other hand, silyl groups give opposite regioselectivities despite strong sterical shielding.[151] This is a consequence of the strong positive inductive effect of the silyl substituent. Simple alkyl residues such as the *t*-Bu group cause minimal distortion and sterical effects dominate to give meta adduct as a major isomer. Regioselectivity in the case of 3,4-pyridyne is poor but C4 products are slightly favoured. On the other hand, 2,3-piridyne reacts on C2 with complete regioselectivity.

Interestingly, E values show that 3-methoxybenzyne and benzyne have similar electrophilicity (Scheme 50).[129] However, a drastically bigger E value was found in the case of 3-fluorobenzyne. Thus, it would seem that the positive resonance (mesomeric) effect of the methoxy group nullifies its negative inductive effect. In contrast, fluoride with a dominant negative inductive effect drastically increases the

[147] The aryne distortion model is an application of distortion/interaction (activation/strain) model which divides the activation energy in two components: the energy needed to distort reactants to the transition state geometry and the energy of interaction between the distorted fragments: F. M. Bickelhaupt, K. N. Houk, *Angew. Chem. Int. Ed.* **2017**, *56*, 10070.

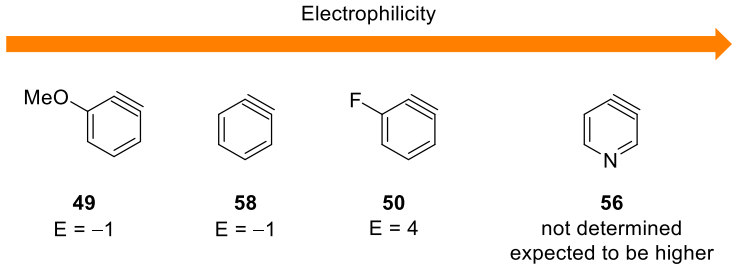
[148] a) R. V. Kolakowski, L. J. Williams, *Nat. Chem.* **2010**, *2*, 303; b) P. H.-Y Cheong, R. S. Paton, S. M. Bronner, G.-Y Im, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 1267; c) G.-Y. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, N. K. Garg *J. Am. Chem. Soc.* **2010**, *132*, 17933; d) J. M. Medina, J. L. Mackey, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 15798.

[149] For examples involving the Charge Distribution and Steric Models to rationalize regioselectivities in trapping experiments of 3-substituted arynes, see: a) S. V. Kessar, *Comprehensive Organic Synthesis*, Vol. 4 (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, pp. 483−515; b) H. Yoshida, S. Sugiura, A. Kunai, *Org. Lett.* **2002**, *4*, 2767; c) T. Hamura, Y. Ibusuki, K. Sato, T. Matsumoto, Y. Osamura, K. Suzuki, *Org. Lett.* **2003**, *5*, 3551; d) Z. Liu, R. C. Larock, *Org. Lett.* **2003**, *5*, 4673; e) Z. Liu, R. C. Larock, J. *Org. Chem.* **2006**, *71*, 3198; f) P. M. Tadross, C. D. Gilmore, P. Bugga, S. C. Virgil, B. M. Stoltz, *Org. Lett.* **2010**, *12*, 1224; For NMO model see: g) A. Takagi, T. Ikawa, Y. Kurita, K. Saito, K. Azechi, M. Egi, Y. Itoh, H. Tokiwa, Y. Kita, S. Akai, *Tetrahedron* **2013**, *69*, 4338; h) A. Takagi, T. Ikawa, K. Saito, S. Masuda, T. Ito, S. Akai, *Org. Biomol. Chem.* **2013**, *11*, 8145.

[150] H. Bent, *Chem. Rev.* **1961**, *61*, 275.

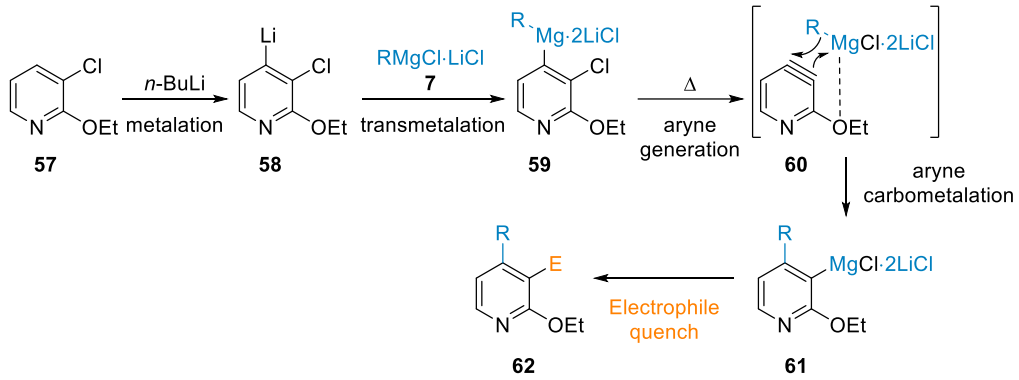
[151] S. M. Bronner, J. L. Mackey, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2012**, *134*, 13966.

electrophilicity of the benzyne. In the case of parent pyridyne[152] effect similar to fluoride is expected. However, substituents with a positive resonance effect could be used to attenuate the likely extreme electrophilicity of the pyridyne.



Scheme 50. Comparison of electrophilicity of substituted arynes.

We have chosen 3-chloro-2-ethoxypyridine (**57**) as the inexpensive pyridyne precursor.[153] It is readily available from 2,3-dicloropyridine, a commercial building block. Metalation in position C4 would set the stage for the pyridyne formation by elimination of the chloride. Moreover, transmetalation from organolithium species can give more stable organomagnesium and organozinc species. Therefore, fine-tuning of the metal centre can give additional versatility to the method. The alkoxy substituent has proven to give excellent regioselectivities on benzyne systems.[133g,j,k,l,n,o,q,134o] Additionally, using organomagnesium Hart *et al*. have shown excellent regioselectivity in the synthesis of terphenyls from polyhalogenated benzenes.[134a-n] After a successful lithiation of 3-chloro-2-ethoxypyridine (**54**) to obtain 4-lithiopyridine **58**, transmetalation with organomagnesium reagent should give the mixed diorganomagnesiums of type **59** (Scheme 51).



Scheme 51. A general overview of 3,4-difunctionalization of pyridines *via* 3,4-pyridyne.

At proper temperature, an elimination should occur leading to the *in situ* formation of 2-ethoxy-3,4-pyridyne **60** which would be immediately trapped with organomagnesium nucleophile giving the

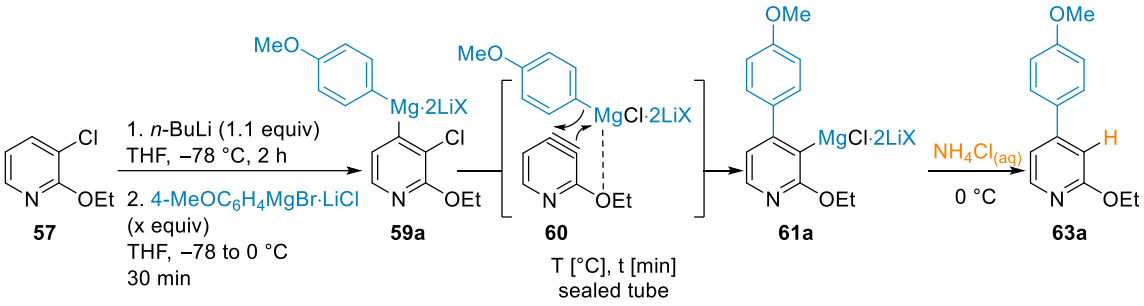
[152] a) R. Levine, W. W. Leake, *Science* **1955**, *121*, 780; b) J. A. Zoltewics, C. Nisi, *J. Org. Chem.* **1969**, *34*, 765; c) G. W. J. Fleet, I. Fleming, D. Philippides, *J. Chem. Soc. (C)*, **1971**, 3948; d) C. May, C. J. A. Moody, *J. Chem. Soc. Chem. Commun.* **1984**, 925; e) G. W. Gribble, M. G. Saulnier, M. P. Sibi, J. A. Obaza-Nutaitis, *J. Org. Chem.* **1984**, *49*, 4518; f) C. May, C. J. A. Moody, *J. Chem. Soc. Perkin. Trans. 1* **1988**, 247; g) M. Tsukazaki, V. Snieckus, *Heterocycles* **1992**, *33*, 533; h) H-H. Nam, G. E. Leroi, *J. Am. Chem. Soc.* **1988**, *110*, 4096; i) B. Jamart-Gregoire, C. Leger, P. Caubère, *Tetrahedron Lett.* **1990**, *31*, 7599; j) C.-K. Sha, J-F. Yang, *Tetrahedron* **1992**, *48*, 10645; k) G. W. Gribble, M. G. Saulnier, *Heterocycles* **1993**, *35*, 151; l) M. A. Walters, J. J. Shay, *Synth. Commun.* **1997**, *27*, 3573; m) K. Vinter-Pasquier, B. Jamart-Grégoire, P. Caubère, *Heterocycles* **1997**, *45*, 2113; n) M. T. Díaz, A. Cobas, E. Guitián, L. Castedo, *Synlett* **1998**, 157; o) M. T. Díaz, A. Cobas, E. Guitián, L. Castedo, *Eur. J. Org. Chem.* **2001**, 4543; p) F. Ivy Carroll, T. P. Robinson, L. E. Brieaddy, R. N. Atkinson, S. W. Mascarella, M. I. Damaj, B. R. Martin, H. A. Navarro, *J. Med. Chem.* **2007**, *50*, 6383; q) M. F. Enamorado, P. W. Ondachi, D. I. A. Commins, *Org. Lett.* **2010**, *12*, 4513; r) Y. Fang, R. C. Larock, *Tetrahedron*, **2012**, *68*, 2819; s) L. Jiang, X. Yu, B. Fang, J. Wu, *Org. Biomol. Chem.* **2012**, *10*, 8102; t) A. E. Goetz, N. K. Garg, *Nat. Chem.* **2013**, *5*, 54; u) A. E. Goetz, N. Garg, *J. Org. Chem.* **2014**, *79*, 846; v) J. Medina, M. K. Jackl, R. B. Susick, N. K. Garg, *Tetrahedron* **2016**, *72*, 3629.

[153] a) S. J. Connon, A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1245; b) S. J. Connon, A. F. Hegarty, *Eur. J. Org. Chem.* **2004**, *2004*, 3477.

magnesiated pyridine of type **61**. Subsequent quench with electrophiles should produce polyfunctional pyridines of type **62**.

Our preliminary findings have confirmed our expectations. By treating 3-chloro-2-ethoxypyridine **57** with *n*-BuLi in THF at −78 °C regioselective metalation at position C4 took place.[154] Transmetalation with 4-$MeOC_6H_4MgBr{\cdot}LiCl$ (**7a**, prepared by the reaction of 4-$MeOC_6H_4Br$ with Mg turnings in the presence of LiCl) gave presumably the mixed diorganomagnesium reagent **59a**. By stirring the reaction mixture for 48 h at 22 °C and quenching with saturated $NH_4Cl_{(aq)}$ only a negligible amount of the expected 2-ethoxy-4-(4-methoxyphenyl)pyridine **63a** was observed. However, the regioisomer 2-ethoxy-3-(4-methoxyphenyl)pyridine was not observed. It is of note that metalation of 3-chloro-2-ethoxypyridine with LDA or TMPLi did proceed but subsequent reactions were complicated due to the presence of amine nucleophile. Therefore metalation with *n*-BuLi, which gives just butane as a side product, was the method of choice. With a proof of concept in hand, we have performed screenings of parameters such as reaction temperature and equivalents of organomagnesium nucleophile (Table 14).

Table 14. Optimization of the reaction temperature, time and equivalents of organomagnesium reagent for pyridyne formation/carbometalation sequence.



Entry	t [min]	T [°C]	Equiv of 4-$MeOC_6H_4MgBr{\cdot}LiCl$	Yield of **63a** [GC-%]
1	60	50	2	43
2	60	60	2	53
3	60	75	2	56
4	60	95	2	55
5	5	75	2	33
6	15	75	2	55
7	30	75	2	56
8	60	75	2	57
9	90	75	2	57
10	120	75	2	58
11	60	75	1	32
12	60	75	1.5	46
13	60	75	2.0	56 (64)[a]
14	60	75	3.0	67
15	60	75	4.0	71
16	60	75	5.0	76
17	60	75	10.0	79

[a]Isolated yield of the analytically pure product shown in the brackets

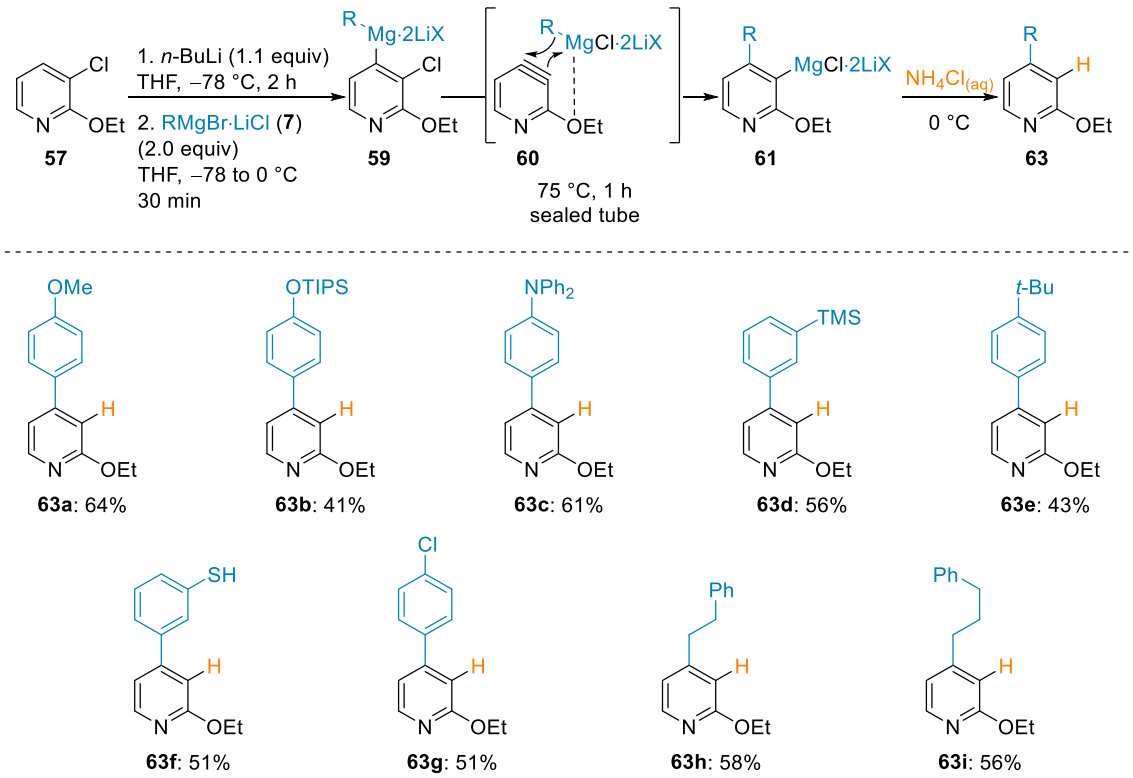
[154] The yield of this metalation was 80% as confirmed by quench with I_2 in THF. For full data see Experimental Part, page 164.

Temperature screening in a sealed tube showed that optimal conditions were reached at 75 °C. Higher temperature resulted in a slight yield decrease, probably due to the loss of selectivity of the pyridyne towards other nucleophiles present in the reaction mixture such as THF[155] and pyridine nitrogen.[156] Temperatures lower than 70 °C led to slower conversions and lower yields of **63a**.

Screening of equivalents of 4-MeOC$_6$H$_4$MgBr·LiCl (**7a**) unfortunately showed that excess (2.0 equiv) of organomagnesium reagent is necessary to obtain reasonable yields. A significant increase in yield was observed between 1.5 and 3.0 equiv, but the addition of more organomagnesium reagent did not lead to proportional improvement. Maximum yields that were reached with a total of 10 equiv of organomagnesium reagent were 79%.

During these screenings, only traces of regioisomeric 3-arylated product were observed. Previous reports on pyridyne chemistry have shown only moderate regioselectivities[136,152b,o,p,q,v]. These were mainly cycloaddition reactions which did not involve any organometallic component. We assume that coordination of the Mg-centre to the ethoxy group in position C2 of the pyridyne enhanced the innate regioselectivity of the pyridyne both kinetically (coordination in enhancing of carbometalation step) and thermodynamically (furnishing a more stabilized organometallic with coordination in ortho position).

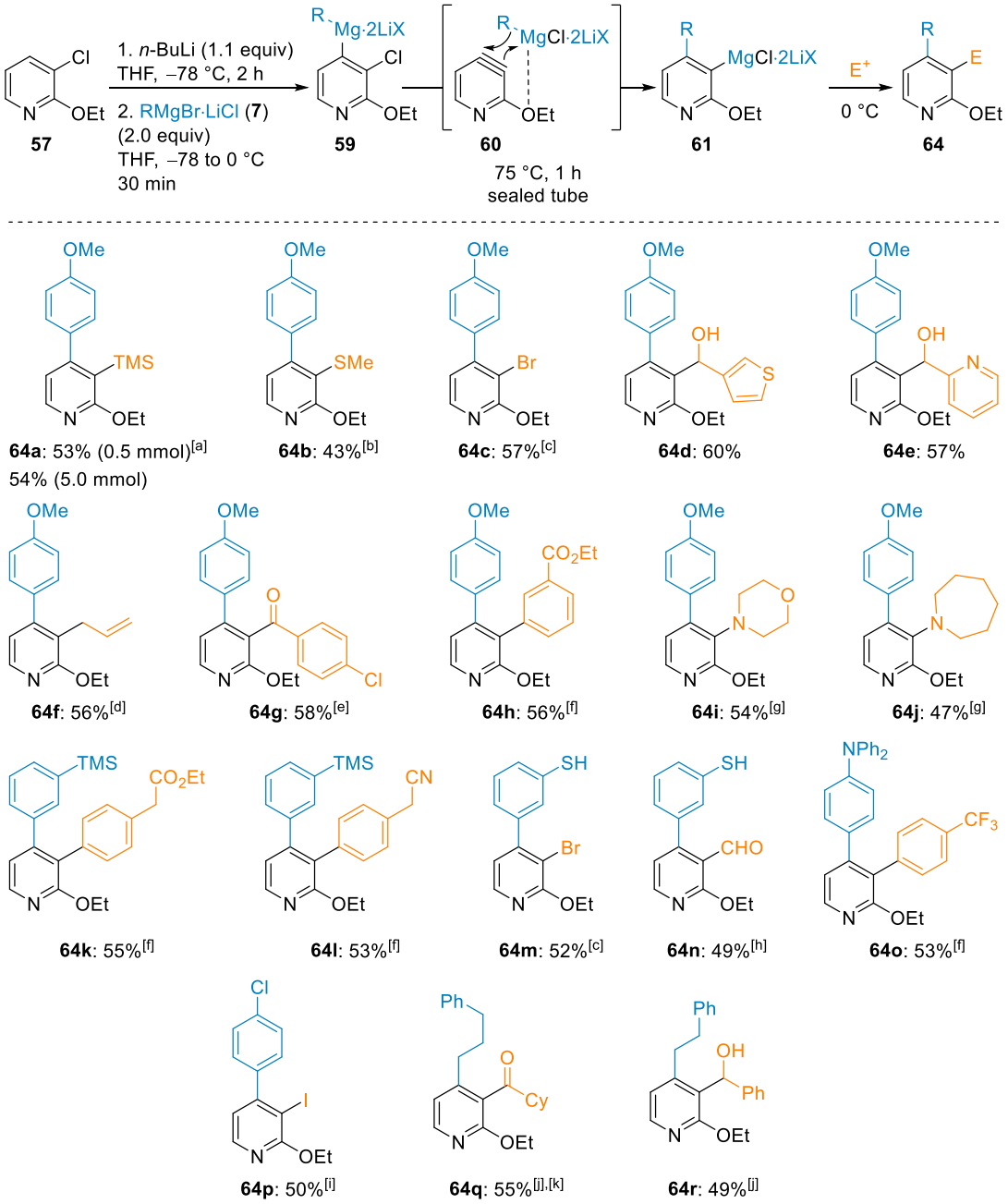
Thus, with the new highly regioselective method in hand, we have examined the scope of the reaction. The 4-arylated pyridines **63a-g** were obtained in 41-64% yield (Scheme 52). We observed that by using 3-methylthiophenylmagnesium bromide (**7l**) the resulting product **63f** is obtained as a free thiol. It is probable that a magnesiation of the methylthio group takes place during the reaction, resulting in a magnesium carbenoid which decomposes under reaction conditions (75 °C).



Scheme 52. Synthesis of 4-substituted pyridines **63** *via* regioselective addition of organomagnesium reagents to the pyridyne intermediate **60**.

[155] K. Okuma, Y. Fukuzaki, A. Nojima, K. Shioji, Y. Yokomori, *Tetrahedron Lett.* **2008**, *49*, 3063.
[156] A. Bhunia, D. Porwal, R. G. Gonnade, A. T. Biju, *Org. Lett.* **2013**, *15*, 4620.

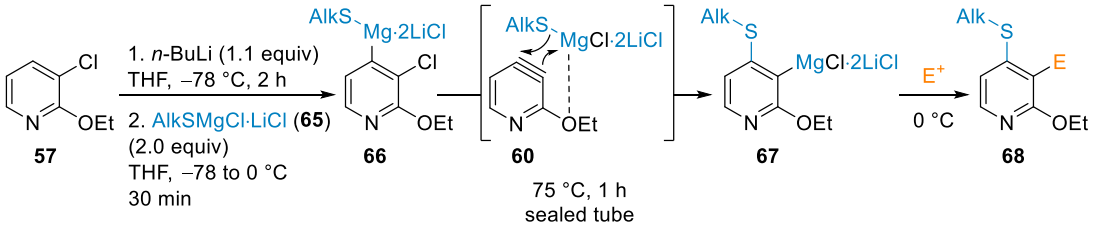
Additionally, alkylmagnesium halides such as 2-phenylethylmagnesium bromide (**7k**) and 3-phenylpropylmagnesium bromide (**7aa**) were also competent nucleophiles but required higher excess (5.0 equiv of organomagnesium) to obtain similar yields. The reason for difference in reactivity between alkyl and arylmagnesium reagents is not clear. In addition to saturated $NH_4Cl_{(aq)}$, we have trapped the intermediary 3-pyridyl magnesium halides **61** with various electrophiles (Scheme 53).

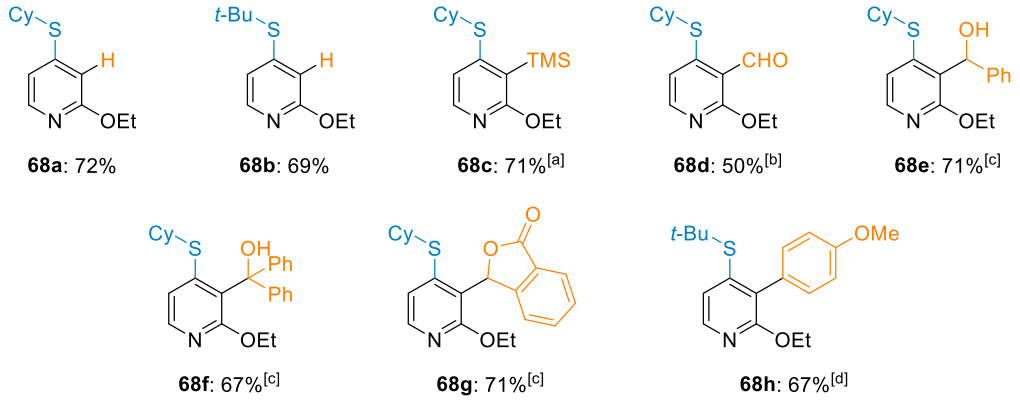


Scheme 53. 3,4-Difunctionalization of 3-chloro-2-ethoxypyridine (**57**) *via* the pyridyne intermediate **60** and trapping of pyridyl-3-magnesium **61** with different electrophiles. [a] TMSCl (2.5 equiv), 0 °C; [b] $MeSO_2SMe$ (2.5 equiv), 0 °C; [c] $(CCl_2Br)_2$ (2.5 equiv), 0 °C; [d] CuCN·2LiCl (10 mol%), 0 °C, 10 min, then allyl bromide (2.5 equiv), 25 °C, 12 h; [e] CuCN·2LiCl (2.0 equiv), 0 °C, 10 min, then acyl chloride (2.5 equiv), 25 °C, 12 h; [f] $ZnCl_2$ (2.0 equiv), 0 °C, 10 min, then a mixture of aryl halide (ArBr/ArI) (2.5 equiv), $Pd(OAc)_2$ (5 mol%) and SPhos (10 mol%), 25 °C, 12 h; [g] $ZnCl_2$ (1.0 equiv), 0 °C, 10 min, then *N*-hydroxylamino benzoates (2.0 equiv) and $Cu(OTf)_2$ (10 mol%), 0 °C to 25 °C, 12 h; [h] DMF (excess), 75 °C, 1 h; [i] I_2 (2.5 equiv), 0 °C; [j] AlkylMgBr·LiCl (5.0 equiv); [k] CuCN·2LiCl (5.0 equiv), 0 °C, 10 min, then acyl chloride (5.5 equiv), 25 °C, 12 h; [l] benzaldehyde (5.5 equiv), 0 °C, 12 h.

Thus, after the treatment of 3-chloro-2-ethoxypyridine with *n*-BuLi followed by the addition of arylmagnesium halide and heating in a sealed tube at 75 °C for 1 h, we obtained 3-pyridylmagnesium halides **61**. The reaction of **61a** with TMSCl afforded trisubstituted pyridine **64a** in 53% yield. A scale up of this reaction provided essentially the same yield (54%). Next, S-methyl methanesulfonothioate gave thioether **64b** in 43% overall yield. Similarly, the addition of CCl_2CBr_2 led to bromopyridine **64c** in 57% isolated yield. Aldehyde quenches with both electron rich and electron poor heterocyclic aldehydes gave secondary alcohols **64d-e** in 57-60% yield. Also, CuCN·2LICl catalyzed allylation with allyl bromide furnished **64f**. Additionally, ketone **64g** was obtained by Cu-mediated acylation using 4-chlorobenzoyl chloride. Negishi cross-coupling (transmetalation with $ZnCl_2$) gave **64h** in 56% isolated yield. By using a catalytic amount (10 mol%) of $Cu(OTf)_2$ electrophilic aminations with hydroxylamine benzoates were possible giving 3-aminopyridines **64i** and **64j** in 47% and 54% isolated yield respectively. After transmetalation of 4-(3-(trimethylsilyl)phenyl)-3-pyridylmagnesium bromide with $ZnCl_2$, Negishi cross-coupling with aryl bromides using $Pd(OAc)_2$/SPhos catalytic system provided 3,4-bisarylated pyridines **64k-l** in 53-55% yield. The 4-(3-thiophenyl)-3-pyridylmagnesium successfully reacted with $(CCl_2Br)_2$ and DMF (excess) to give free thiols **50m** and **50n** in moderate yields (49-52%). 4-Iodobenzotrifluoride was routinely coupled using Negishi coupling ($Pd(OAc)_2$/SPhos) giving the trisubstituted pyridine **64o** in 53% isolated yield. Quench with a solution of I_2 in THF led to 3-iodopyridine **64p** in 50 % yield. Finally, 4-alkyl-3-pyridylmagnesiums **61h-i** gave after CuCN·2LiCl mediated acylation and benzaldehyde quench aryl alkyl ketone **64q** and benzylic alcohol **64r** in 55% and 49% yield respectively.

Looking to expand the scope of these functionalizations, we explored the use of magnesium thiolates (Scheme 54). Magnesium thiolates (prepared by mixing equimolar amounts of *i*-PrMgCl·LiCl and alkyl thiols) were excellent reaction partners. Thus, the transmetalation of lithiated pyridine with RSMgX LiCl (**65**) gave **66** which, after heating at 75 °C in sealed tube for 1 h (and proton quench), produced 4-alkylthiopyridines **68a** and **68b** in good yields (69-72%). Switching from proton quench to other electrophiles led to a range of 3,4-disubstituted pyridines **68c-h** in 50-71%. Interestingly, cross-coupling with $Pd(OAc)_2$/SPhos gave the expected product **68h** (67%) on a sterically demanding substrate even in the presence of excess magnesium thiolate. Surprisingly, the magnesium arylthiolates failed to provide a product on our system despite previous successful reports on benzynes[135b,c,d] and pyridynes[136,152b,g]. We hypothesise that the difference in the leaving group choice led to this result.

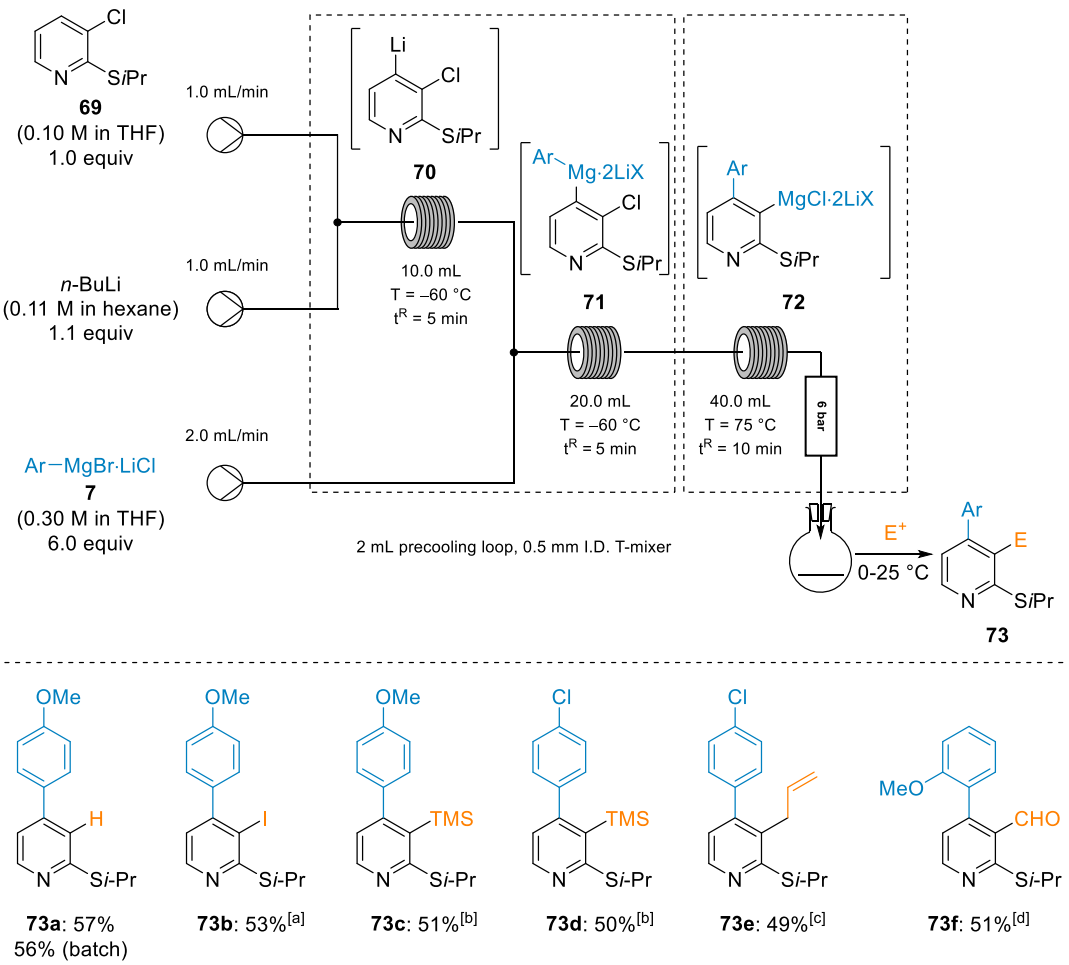




Scheme 54. Mono- and difunctionalization of 3-chloro-2-ethoxypyridine (**57**) *via* pyridyne intermediate with Mg-alkylthiolates as nucleophiles. [a] TMSCl (2.5 equiv), 0 °C; [b] DMF (excess), 75 °C, 1 h; [c] aldehyde/ketone (2.5 equiv), 0 °C; [d] $ZnCl_2$ (2.0 equiv), 0 °C, 10 min, then a mixture of 4-iodoanisole (2.5 equiv), $Pd(OAc)_2$ (10 mol%) and SPhos (20 mol%), 25 °C, 12 h.

In order to enhance the overall efficacy of the reaction, we have tried to transfer our batch protocol into a continuous flow. Using **57** we realised that the metalation took long time for continuous flow experimentation and had to be balanced with the competitive pyridyne formation.[157] After transmetalation at –60 °C (5 min residence time), the following reactor was heated to 75 °C (10 min residence time) using a back-pressure regulator which prevented boiling of THF and bubble formation. The reaction mixture was collected into an argon filled flask and quenched with various electrophiles in batch. Due to high pressures caused by the high viscosity of the organomagnesium solutions at low temperatures we had problems achieving the right stoichiometry. Furthermore, with residence times of 25 minutes, reaching a steady state took a long time and was costly due to the big amount of starting material which had to be used. Therefore, 3-chloro-2-(isopropylthio)pyridine (**69**) was selected as a suitable substrate for continuous flow experiments because of its shorter metalation times (5 min). Interestingly, we found that this substrate required higher excess of an organomagnesium reagent to reach good yields. Thus, mixing *n*-BuLi with **69** afforded the lithiated species **70** after 5 min residence time at –60 °C (Scheme 55). *Via* the third pump a solution of arylmagnesium reagent (6.0 equiv) was added for the transmetalation step to obtain **71** (–60 °C, 5 min) and the reaction mixture was heated to 75 °C for 10 min. In this way, the 3-pyridylmagnesium reagent (**72**) was made and directly pumped into a flask containing different electrophiles. Quenching with saturated ammonium chloride provided the pyridine **73a** in 57 % yield.

[157] For details on continuous flow procedure using 3-chloro-2-ethoxypyridine see Experimental Part, page 165.



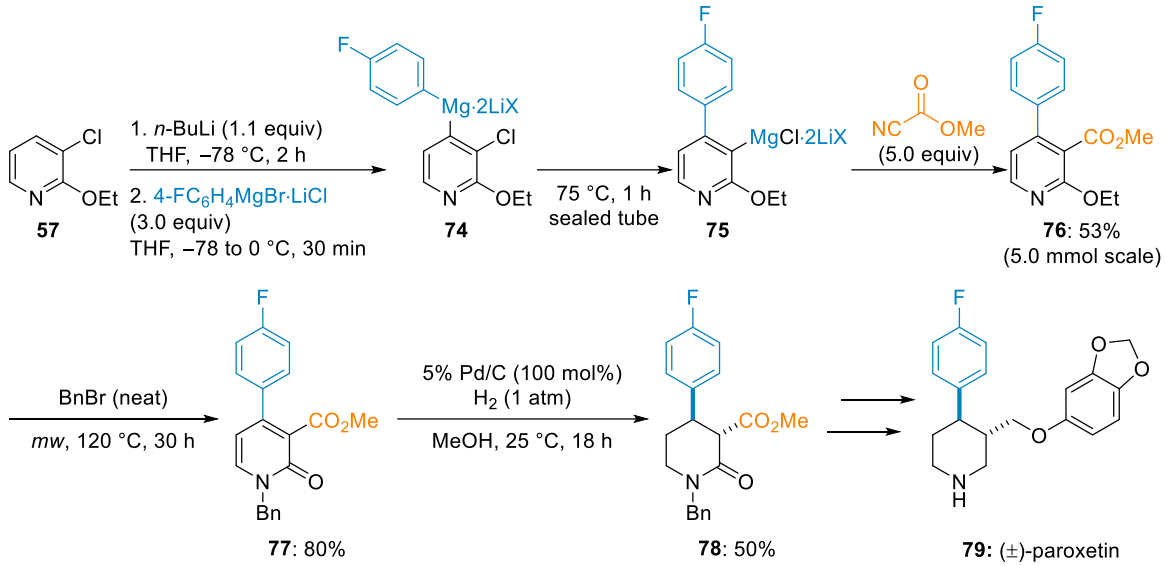
Scheme 55. Difunctionalization of 3-chloro-2-(isopropylthio)pyridine **69** *via* pyridyne intermediate in continuous flow setup. [a] I_2 (2.5 equiv), 0 °C; [b] TMSCl (2.5 equiv), 0 °C; [c] CuCN·2LiCl (10 mol%), 0 °C, 10 min, then allyl bromide (2.5 equiv), 25 °C, 12 h; [d] DMF (excess), 75 °C, 1 h.

Allylation (allyl bromide/CuCN·2LiCl), iodination (with I_2), silylation (with TMSCl) and formylation (with DMF) gave the expected polyfunctional pyridines **73b-f** in 49-53% isolated yield. The flow procedure offered good temperature control, was very reproducible and shortened overall reaction time. Many aryne reactions present in the literature are heterogeneous reactions that involve precipitation of salts or solvent systems which do not offer complete dissolution of the reagents[133r,158] are not suitable for application in continuous flow setups.

We have also applied this methodology for the preparation of a key intermediate in the synthesis of (+-)-paroxetine (Scheme 56).[159] According to the developed procedure, 3-chloro-2-ethoxypyrine (**57**) was transformed into polyfunctional pyridine **76**. Heating of **76** in neat benzyl bromide at 120 °C for 30 h afforded N-benzylated pyridone **77** in 80% isolated yield.[160] Finally, selective hydrogenation of the

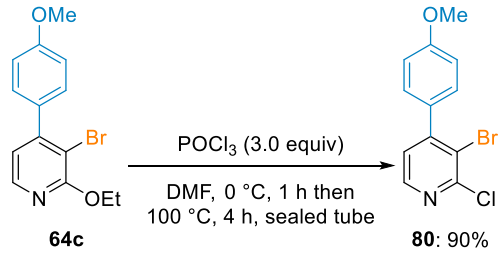
[158] a) T. Truong, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 4243; b) T. Truong, O. Daugulis, *Org. Lett.* **2011**, *13*, 4172; c) T. Truong, O. Daugulis, *Org. Lett.* **2012**, *14*, 5964; d) T. Truong, O. Daugulis, *Chem. Sci.* **2013**, *4*, 531; e) T. Truong, M. Mesgar, K. K. A. Le, O. Daugulis, *J. Am. Chem. Soc.* **2014**, *136*, 8568.
[159] a) C. De Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente, V. Zanirato, *Tetrahedron: Asymmetry* **2008**, *19*, 131; b) S. Ötvös, M. Pericàs and C. O. Kappe, *Chem. Sci.* **2019**, *10*, 11141; c) S. Jara, S. Sarkar and S. A. Morris *Tetrahedron* **2020**, *76*, 131215.
[160] W. R. Bowman, C. F. Bridge, *Synth. Commun.* **1999**, *29*, 4051.

pyridone **77** using H_2 gas and Pd/C gave, after isomerisation on silica gel, the *trans*-piperidone **78** in 50% yield.[161]



Scheme 56. Formal synthesis of (±)-paroxetine.

Lastly, we were able to replace the seemingly inert ethoxy group on the pyridine ring of the compound **64c** with chloride using Vilsmeier chemistry (Scheme 57).[162]



Scheme 57. Chlorination of pyridine **64c** using $POCl_3$ in DMF.

In conclusion, a new regioselective 3,4-difunctionalization of 3-chloropyridines **57** and **69** *via* 2-substituted pyridynes using organomagnesium nucleophiles (aryl- and alkylmagnesium halides and magnesium alkylthiolates) was developed. The reaction was adapted in a continuous flow setup. This method was applied in the formal synthesis of racemic paroxetine.

[161] a) S. Maris, N. Castagnoli, *J. Org. Chem.* **1996**, *61*, 309; b) J. Wysocki, C. Schkepphorst, F. Glorius, *Synlett*, **2015**, *26*, 1557; c) B. Zacharie, S. D. Abbott, C. B. Baigent, C. Doyle, R. Se. Yalagala, *Eur. J. Org. Chem.* **2018**, *46*, 6486; d) Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander, F. Glorius, *Nat. Chem.* **2019**, *11*, 264.
[162] a) T. R. Kasturi, H. R. Y. Jois, L. Mathew, *Synthesis* **1984**, *9*, 743; b) M. Shiao, L. Shyu, K. Tarng, *Synth. Commun*, **1990**, *20*, 2971.

4. Preparation of Functionalized Amides using Dicarbamoylzincs

CO gas is an excellent ligand for transition metals due to strong σ-binding and excellent π-back bonding. As a consequence, myriads of carbonyl complexes are known.[163] Moreover, CO played an important role in the industrial synthesis of bulk chemicals such as acetic acid (Monsanto and Cativa processes) and liquid hydrocarbons (Fisher-Tropsch process).[164] Hydroformylations of alkenes discovered by Roelen are today processes done on million-ton scales for the production of aldehydes.[165] Carbonylative versions of transition metal coupling reactions are not only forming C-C bonds but also introduce versatile functionalities such as aldehyde, ketone, ester or amide in the molecule.[166] Thus, developing carbonylative reactions is of huge importance.

Main group organometallics react with CO gas in a nucleophilic manner often resulting in a mixture of products due to the instability of intermediary acyl anions.[167] Because these intriguing entities are very unstable, many synthetic equivalents of acyl anion have been successfully developed.[168] Compared to acyl anions analogous carbamoyl metal reagents are more stable.

Having in mind that CO gas reacts with NaOH to produce sodium formate it is no wonder that a similar reaction with ammonia gives parent formamide.[169] Carbamoyl sodium was first postulated in 1965 by Bredereck.[170] He found that the reaction of *N*,*N*-dialkylformamides with alkali metals (Li, Na and K) proceeds with the evolution of hydrogen and concomitant formation of glioxamides and alkali metal amides. The first proof of these intermediates was published in 1967 when Schölkopf and Gerhart

[163] a) M. O. Albers, N. J. Coville, *Coord. Chem. Rev.* **1984**, *53*, 227; b) W. A. Herrmann, *Chemie in unserer Zeit* **1988**, *22*, 113; c) G. Frenking, I. Fernandez, N. Holzmann, S. Pan, I. Krossing, M. Zhou, *JACS Au* **2021**, *1*, 623.

[164] a) N. von Kutepow, W. Himmle, H. Hohenschutz, *Chem. Ing. Tech.* **1965**, *37*, 383; b) H. Hohenschutz, N. von Kutepow, W. Himmle, *Hydrocarbon Process.* **1966**, *45*, 141; c) F.E. Paulik, J.F. Roth, *Chem. Commun. (London)* **1968**, 1578; d) W. A. Herrmann, *Angew. Chem. Int. Ed.* **1982**, *21*, 117 (Fischer-Tropsch processd); e) R. B. Anderson, *Fischer-Tropsch Synthesis*, Academic Press Inc, **1984**; f) G. P. van der Laan, A. A. C. M. Beenackers, *Catal. Rev. – Sci. Eng.* **1999**, *41*, 255; g) H. Schulz, *Appl. Catal. A: Gen.* **1999**, *186*, 3; h) Monsanto process: G. J. Sunley, D. J. Watson, *Catal. Today* **2000**, *58*, 293; i) A. Haynes, P. M. Maitlis, G. E. Morris, G. J. Sunley, H. Adams, P. W. Badger, C. M. Bowers, D. B. Cook, P. I. P. Elliott, T. Ghaffar, H. Green, T. R. Griffin, M. Payne, J. M. Pearson, M. J. Taylor, P. W. Vickers, R. J. Watt, *J. Am. Chem. Soc.* **2004**, *126*, 2847; j) B. H. Davis, *Top. Catal.* **2005**, *32*, 143; j) A. Haynes, Acetic Acid Synthesis by Catalytic Carbonylation of Methanol. In: *Catalytic Carbonylation Reactions. Topics in Organometallic Chemistry*, vol 18 (Eds. M. Beller) Springer, Berlin, Heidelberg, **2006**; k) M. Ojeda, R. Nabar, A. U. Nilekar, A. Ishikawa, M. Mavrikakis, E. Iglesia, *J. of Catal.* **2010**, *272*, 287.

[165] a) R. F. Heck, D. S. Breslow, *J. Am. Chem. Soc.* **1961**, *83*, 4023; b) D. Evans, J. A. Osborn, G. Wilkinson, *J. Chem. Soc. A* **1968**, 3133; c) B. Cornils, W. A. Herrmann, M. Rasch, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2133; d) M. Beller, B. Cornils, C. D. Frohning, C. W. Kohlpaintner, *Journal of Molecular Catalysis A: Chemical* **1995**, *104*, 17; e) G. J. Sunnley, D. J. Watson, *Catal. Today* **2000**, *58*, 293; f) K.-D. Wiese, D. Obst, Hydroformylation, In *Catalytic Carbonylation Reactions. Topics in Organometallic Chemistry*, Vol 18 (Eds.: M. Beller), Springer, Berlin, Heidelberg, **2006**; g) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725; h) R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675.

[166] a) T. Ishiyama, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6923; b) T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, N. Miyaura, *J. Org. Chem.* **1998**, *63*, 4726; c) Q. Wang, C. Chen, *Tetrahedron Lett.* **2008**, *49*, 2916; d) X.-F. Wu, H. Neumann, M. Beller, *Angew. Chem.Int. Ed.* **2010**, *49*, 5284; e) X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986; f) X.-F. Wu, *RCS Adv.* **2016**, *6*, 83831; g) P. Devendar, R.-Y. Qu, W.-M. Kang, B. He, G.-F. Yang, *J. Agric. Food Chem.* **2018**, *66*, 8914.

[167] C. Narayana, M. Periasamy, *Synthesis* **1985**, *3*, 253.

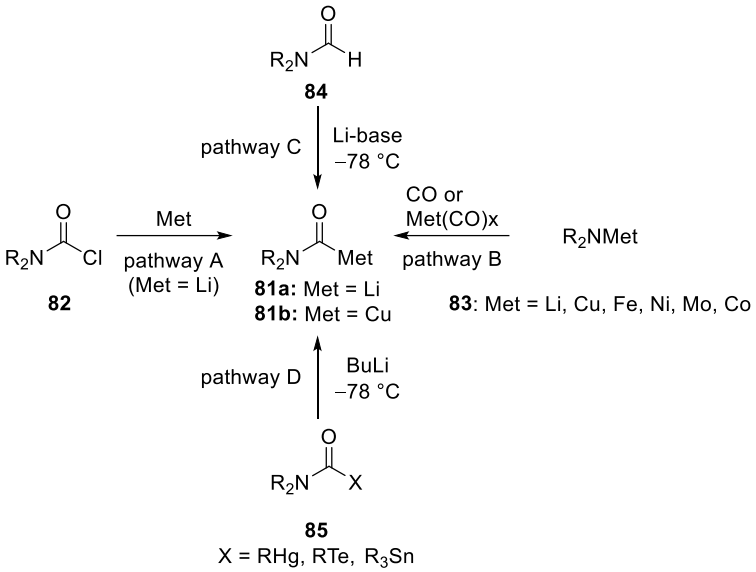
[168] a) D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239; b) T. A. Hase, *Umpoled Synthons*, John Wiley&Sons, New York, **1987;** c) R. Brehme, D. Enders, R. Fernandez, J. M. Lassaletta, *Eur. J. Org. Chem.* **2007**, *2007*, 5629.

[169] a) Q. Liu, L. Wu, S. Gülak, N. Rockstroh, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 7085; b) M. C. Boswell, J. V. Dickson, *J. Am. Chem. Soc.* **1918**, *40*, 1779; c) H. Bipp, H. Kieczka, Formamides, In *Ullmann's Encyclopedia of Industrial Chemistry*, 7. Edition (Eds.: G. Bellussi, M. Bohnet, J. Bus, K. Drauz, H. Greim, K.-P. Jäckel, U. Karst, A. Kleemann, G. Kreysa, T. Laird, W. Meier, E. Ottow, M. Röper, J. Scholtz, K. Sundmacher, R. Ulber, U. Wietelmann), Wiley-VCH, Weinheim, **2012**.

[170] H. Brederick, F. Effenberger, R. Gleiter, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 951.

treated bis(*N*,*N*-diethylcarbamoyl)mercury[171] with *n*-BuLi and trapped the resulting species with aldehydes, ketones, MeI and Bu_3SnCl.[171b,172] Next, in 1973 Schölkopf and Banhidai showed that the deprotonation of formamides at −78 °C by LDA results in a similar outcome.[173] In the same year, Enders and Seebach reported that thiocarbamoyllithiums react in the similar way but required lower reaction temperatures (−100 °C).[174] Rautenstrauch and Joyeux have reported that CO gas reacts with Li-dialkylamides at −78 °C to produce carbamoyllithium reagents in essentially quantitative yields.[175] Similarly, Saegusa *et al*. reported that diamidocuprates gave bis(carbamoyl)cuprates when exposed to carbon monoxide.[176]

In another report, Saegusa *et al*. reacted silver acetate, amine and carbon monoxide to obtain oxamides.[177] More recently, Sonoda showed that carbamoyltelluriums can be used in Te/Li exchange as carbamoyllithium precursors.[178] On the other hand, the insertion of Li metal into (thio)carbamoyl chlorides was explored by Yus and Ramon.[179]



Scheme 58. General ways for preparation of carbamoyl metal reagents.

This method employed Barbier conditions to obtain good yields. When the reaction was conducted in a stepwise manner significantly lower yields were obtained. First stereoselective reactions with (*S*)-2-(methoxymethyl)pyrrolidine-1-carbamoyllithium were done by Enders and Lotter.[180] Recently, Reeves and coworkers have used different imines to obtain excellent diastereoselectivities in the synthesis of

[171] a) R. Kh. Freidlina and E. I. Kan, *Izv. Akad. Nauk SSSR, otd. Khim. Nauk.* **1948**, 548; *Chem. Abst.* **1949**, *43*, 2111; b) U. Schöllkopf, F. Gerhart, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 664; c) for related alkoxycarbonylmercurials see: W. Schoeller, W. Schrauth, W. Essers, *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 2864 and B. K. Nefedov, N. S. Sergeeva, Ya. T. Éidus, *Uzv. Akad. Nauk SSR, Ser. Khim Nauk* **1972**, *11*, 2494; *Bull. Akad. Sci. USSR, Div. Chem. Sci.* **1972**, 2426.
[172] a) U. Schöllkopf, F. Gerhard, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 560.
[173] a) B. Banhidai, U. Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 836; b) U. Schöllkopf, H. Beckhaus, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 293.
[174] a) D. Enders, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 1014; b) D. Seebach, W. Lubosch, D. Enders, *Chem. Ber.* **1976**, *109*, 1309.
[175] a) V. Rautenstrauch, M. Joyeux, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 83; b) V. Rautenstrauch, M. Joyeux, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 85.
[176] a) T. Tsuda, M. Miwa, T. Saegusa, *J. Org. Chem.* **1979**, *44*, 3734; b) T. Mizuno, I. Nishiguchi, T. Okushi, T. Hirashima, *Tetrahedron Lett.* **1991**, *32*, 6867; c) T. Mizuno, I. Nishiguchi, T. Hirashima, *Tetrahedron Lett.* **1993**, *49*, 2403.
[177] T. Saegusa, T. Tsuda, K. Isayama, K. Nishijama, Y. Isegawa, *Tetrahedron Lett.* **1968**, *13*, 1641.
[178] a) T. Hiiro, T. Mogami, N. Kambe, S.-I. Fujiwara, N. Sonoda, *Synth. Commun.* **1990**, *20*, 703; b) N. Kambe, T. Inoue, T. Takeda, S.-I. Fujiwara, N. Sonoda, *J. Am. Chem. Soc.* **2006**, *128*, 12650.
[179] a) D. J. Ramon, M. Yus, *Tetrahedron Lett.* **1993**, *44*, 7115; b) D. J. Ramon, M. Yus, *Tetrahedron* **1996**, *52*, 13739.
[180] D. Enders, H. Lotter, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 795.

aminoamides.[181] Carbamoyl complexes of transition metals are also known.[182] These are usually made by reaction of amines or alkali amides with metal carbonyls. The synthesis of different carbamoylmetals is summarized in scheme 58.

Using continuous microflow technologies Yoshida *et al.* prepared carbamoyllithiums by insertion of Li-naphtalenide into carbamoyl chlorides and quenched them successfully by introducing an electrophile solution *via* third pump.[183] On the other hand, Knochel *et al.* used the Barbier approach with *in situ* quench of carbamoyllithium reagents.[102g] Thus, by treating a mixture of formamide and electrophile with a solution of LDA, the reaction could be conducted at room temperature. Remarkably, aliphatic ketones and aldehydes were tolerated despite having more acidic protons compared to formamides (pKa = 31).Therefore, a highly kinetic metalation seems to take place due to CIPE (Complex induced Proximity Effect). Moreover, under high flow rates very sensitive thiocarbamoyllithiums could be generated and successfully trapped at 25 °C.

Carbamoyllithium reagents were also explored by others[184] and were used to prepare more stable carbamoyl reagents. Particularly versatile are carbamoylsilanes discovered and explored by Cunico and coworkers.[185] These reagents were used in Pd-catalyzed processes for the synthesis of aryl and alkenyl amides. Despite their stability, the tedious preparation which relied on carbamoyllithium chemistry limited the scope of these reagents. Nevertheless, it was clear that more stable reagents for nucleophilic carbamoylation were beneficial.

We hypothesised that moving from carbamoyllithiums to carbamoylzincs would result in more stable reagents suitable for the catalytic reactions. Formamides were selected as precursors due to their easy preparation and bench stability. Thus, in preliminary experiments, we have treated *N*,*N*-dibutylformamide **86a** (1.0 equiv) and $ZnCl_2$ (0.5 equiv) with or without Et_3N (0.5 equiv) with various lithium amide bases such as LDA, Cy_2NLi or TMPLi. The conversion to the zinc reagent **87a** was evaluated by performing the CuCN·2LiCl catalyzed allylation with allyl bromide on the reaction aliquots. These experiments showed that TMPLi (1.1 equiv) was the best base to provide *in situ* formation of carbamoyllithium which transmetalated in the presence of $ZnCl_2$ to furnish dicarbamoylzinc reagents (Method A). After a copper-catalyzed allylation with allyl bromide amide **88a** was isolated in 94% yield (both carbamoyl moieties reacted). Various formamides were zincated with this procedure to give the expected amides **88b-f** in 70-97% isolated yield (Scheme 59).

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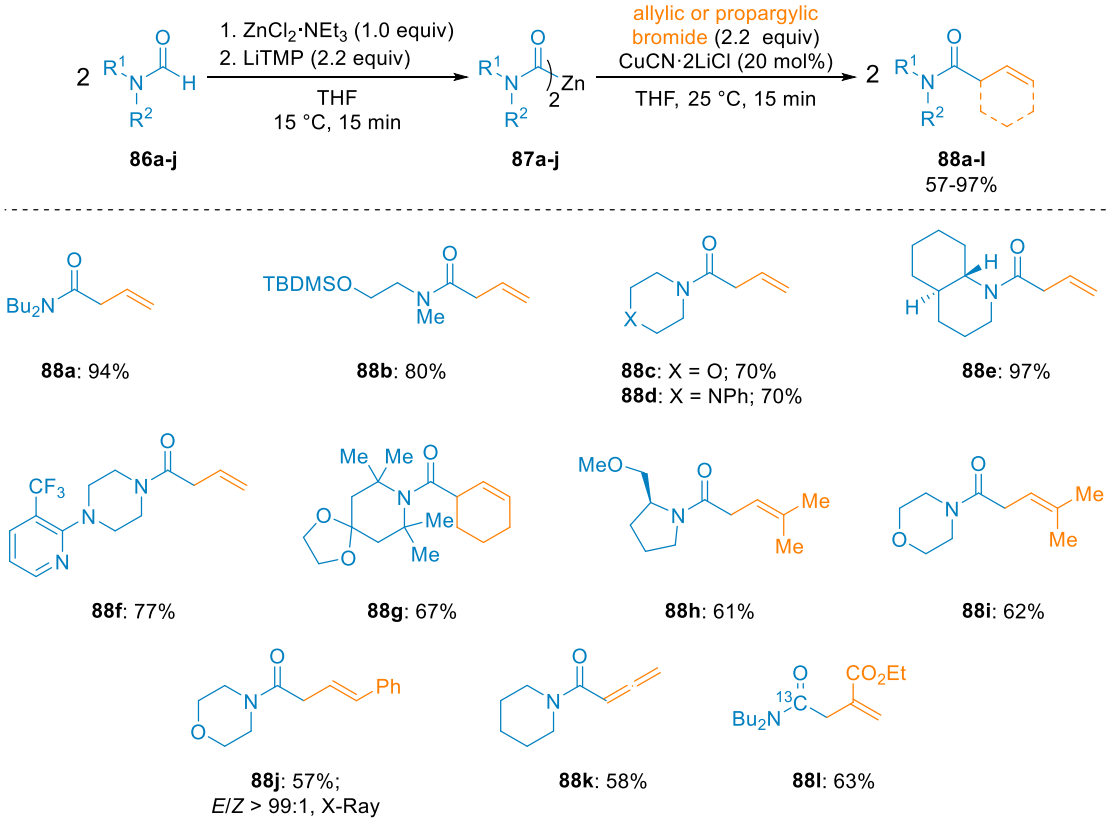
[181] a) J. T. Reeves, Z. Tan, M. A. Herbage, Z. S. Han, M. A. Marsini, Z. Li, G. Li, Y. Xu, K. R. Fandrick, N. C. Gonnella, S. Campbell, S. Ma, N. Grinberg, H. Lee, B. Z. Lu, C. H. Senanayake, *J. Am. Chem. Soc.* **2013**, *135*, 5565; b) J. T. Reeves, C. Lorenc, K. Camara, Z. Li, H. Lee, C. A. Busacca, C. H. Senanayake, *J. Org. Chem.* **2014**, *79*, 5895; c) C. W. Seifert, S. Pindi, G. Li, *J. Org. Chem.* **2015**, *80*, 447; d) M. J. Kerner, C. A. Kuttruff, M. Chevliakov, F. G. Buono, D. A. Gao, M. Krawiec, C. A. Busacca, C. H. Senanayake, P. Wipf, J. T. Reeves, *Org. Lett.* **2021**, *23*, 4396.

[182] a) E. W. Abel, F. G. A. Stone, *Quarterly Reviews, Chemical Society* **1969**, *23*, 325; b) E. J. Corey, L. S. Hegedus, *J. Am. Chem. Soc.* **1969**, *91*, 1233; c) D. Bauernschmitt, H. Behrens, J. Ellermann, *Z. Naturforsch.* **1979**, *34b*, 1362; d) S. Fukuoka, M. Ryang, S. Tsutsumi, *J. Org. Chem.* **1971**, *36*, 2721; e) R. W. Brink, R. J. Angelici, *Inorg. Chem.* **1973**, *12*, 1062; f) E. W. Abel, S. J. Skittrall, *J. Organomet. Chem.* **1980**, *185*, 391; g) G. B. Gill, G. Pettenden, S. J. Reynolds, *J. Chem. Soc., Perkin. Trans. 1* **1994**, *4*, 369; h) C. Nájera, M. Yus, *Org. Prep. Proced. Int.* **1995**, *27*, 383; i) D. Luart, N. la Gall, J.-Y. Salaün, L. Toupet, H. des Abbayes, *Inorganica Chim. Acta* **1999**, *291*, 166; j) S. Anderson, T. E. Berridge, A. F. Hill, Y. T. Ng, A. J. P. White, D. J. Williams, *Organometallics*, **2004**, *23*, 2686; k) W. Ren, M. Yamane, *J. Org. Chem.* **2010**, *75*, 8410; l) Z.-L. Xie, G. Durgaprasad, A. K. Ali, M. J. Rose, *Dalton Trans.* **2017**, *46*, 10814; m) M. A. Wright, M. A. O'Connell, J. A. Wright, *Inorganica Chim. Acta* **2021**, *520*, 120283.

[183] A. Nagaki, Y. Takahashi, J.-I. Yoshida, *Angew. Chem. Int. Ed.* **2016**, *55*, 5327.

[184] a) A. S. Fletcher, K. Smith, K. Swaminathan, *J. Chem. Soc., Perkin Trans. 1* **1977**, *16*, 1881; b) N. S. Nudelman, D. Pérez, *J. Org. Chem.* **1983**, *48*, 133; c) Y. Wakita, S.-Y. Noma, M. Maeda, M. Kojima, *J. Organomet. Chem.* **1985**, *297*, 379; d) P. Viruela-Martin, R. Viruela-Martin, F. Tomás, and N. S. Nudelman, *J. Am. Chem. Soc.* **1994**, *116*, 10110; e) X. Creary, C. Zhu, *J. Am. Chem. Soc.* **1995**, *117*, 5859; f) N. S. Nudelman, G. E. García Liñares, *J. Org. Chem.* **2000**, *65*, 1629; g) C.-Y. Lin, P.-J. Ma, Z. Sun, C.-D. Lu, Y.-J. Xu, *Chem. Commun.* **2016**, *52*, 912; h) M. Xu, Z.-W. Qu, S. Grimme, D. W. Stephan, *J. Am. Chem. Soc.* **2021**, *143*, 634.

[185] a) R. F. Cunico, *Tetrahedron Lett.* **2001**, *42*, 2931; b) R. F. Cunico, B. C. Maity, *Org. Lett.* **2002**, *4*, 4357; c) R. F. Cunico, B. C. Maity, *Org. Lett.* **2003**, *5*, 4947; d) R. F. Cunico, J. Chen, *Synth. Commun.* **2003**, *33*, 1963; e) J. Chen, R. F. Cunico, *J. Org. Chem.* **2004**, *69*, 5509; f) R. F. Cunico, A. R. Motta, *Org. Lett.* **2005**, *7*, 771; g) R. F. Cunico, R. K. Pandey, *J. Org. Chem.* **2005**, *70*, 9048; h) R. F. Cunico, A. R. Motta, *J. Organomet. Chem.* **2006**, *691*, 3109; i) Y. Yao, W. Tong, J. Chen, *Mendeleev Commun.* **2014**, *24*, 176.



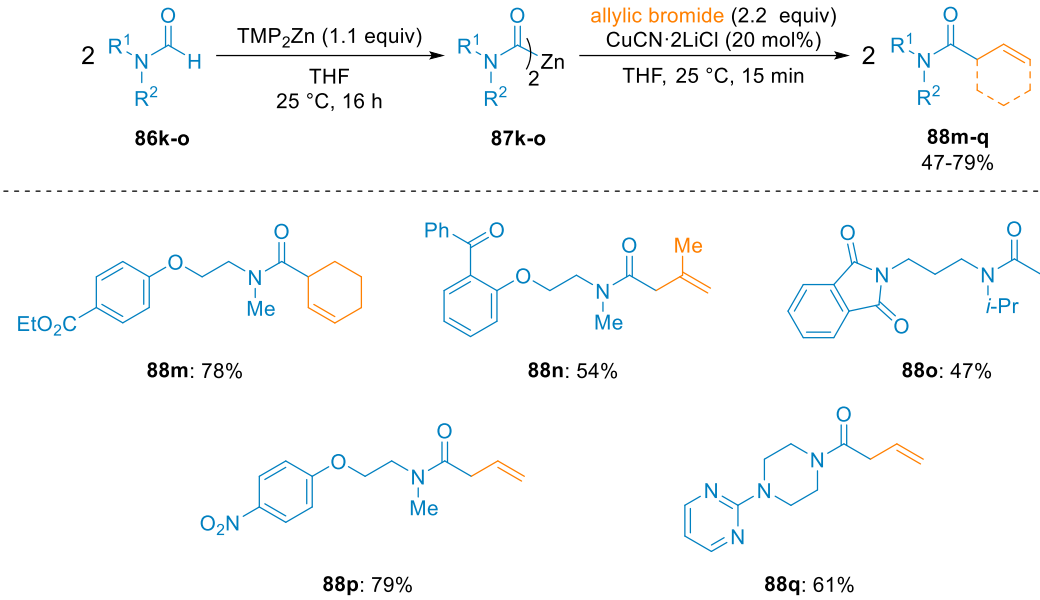
Scheme 59. Allylation of dicarbamoylzincs of type **87** with allylic and propargylic bromides.

The bulky formamide **86h** required 2.0 equiv TMPLi for the metalation and furnished **88g** in 67% yield after reaction with 3-bromocyclohex-1-ene. Carbamoylzinc reagents **87g** and **87c** reacted regioselectively with unsymmetrical allyl bromides such as prenyl bromide and cinnamyl bromide to give S_N2 products. Thus, CuCN·2LiCl catalyzed allylations of dicarbamoylzincs **87g** and **87c** with prenyl bromide gave almost exclusively the S_N2 products **88h** and **88i** in 61% and 62% yield. Cinnamyl bromide reacted less selectively (S_N2:S_N2' > 9:1) but the S_N2 product **88j** was still dominant and was isolated in 57% yield. X-ray diffraction studies confirmed the structure of the **88j**. Interestingly, the reaction of carbamoylzinc reagent **87i** with propargyl bromide gave allenic amide **88k** as the S_N2' product. Moreover, we were able to prepare ^{13}C labelled carbamoylzinc reagent **87j** and use it to obtain the polyfunctional product **88l** after reaction with ethyl 2-(bromomethyl)acrylate under copper catalysis.

Dicarbamoylzinc reagents proved to be stable for longer than 16 h at 25 °C.[186] Despite this, because their preparation goes through highly reactive carbamoyllithiums, sensitive functional groups such as ester or ketone could not be tolerated. A more direct approach had to be undertaken. Thus, after treating the *N*,*N*-dibutylformamide with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.55 equiv) the dicarbamoylzinc reagent **87a** was obtained (Method B) but in a somewhat longer reaction time (2 h). Similarly, when the formamides containing ester, ketone or imide function were submitted to the new reaction conditions, selective metalation of the formamide proton led to the polyfunctional dicarbamoylzinc reagents **87k**, **87l** and **87m**. Allylation with 3-bromocyclohex-1-ene and metallyl bromide gave the expected products **88m-o** in 47-78% isolated yield (Scheme 60). Unfortunately, when the formamide **86n** containing an aromatic nitro group in the side chain was treated with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ a decomposition occurred. By using $TMP_2Zn{\cdot}2LiCl$ (without $MgCl_2$) as a milder metalation agent, a successful zincation was achieved and allylation led to the product **88p** in 79% isolated yield. Moreover, a sensitive heterocycle such as pyrimidine was tolerated. The metalation of the pyrimidine ring was not observed. Thus, starting material **86o** routinely furnished the expected product **88q** in 61% yield. It is important to note that the

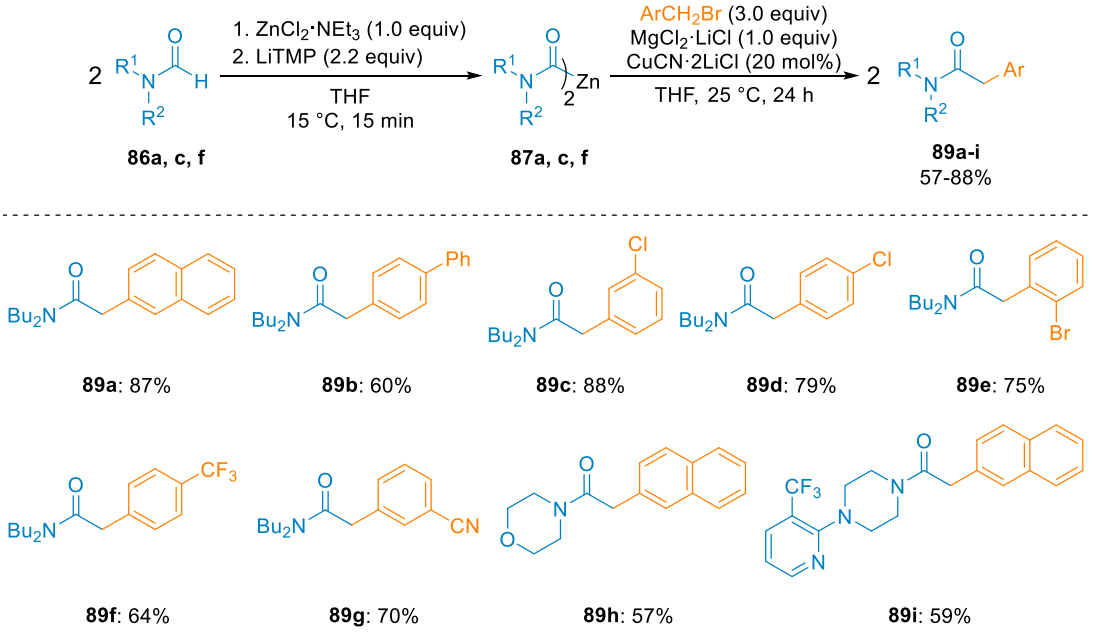
[186] The stability of di(*N*,*N*-dibutylcarbamoyl)zinc reagent **87a** was evaluated by performing CuCN·2LiCl catalyzed allylation with allyl bromide on aliquots taken up to 48 h after the reagent preparation. See Experimental part page 212 for full data.

metalation of this substrate failed using method A due to its poor solubility in THF in the presence of $ZnCl_2$.



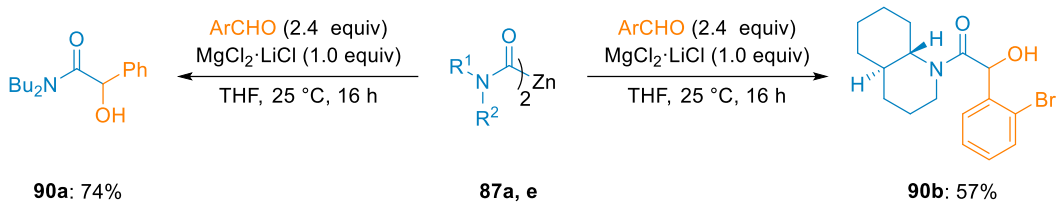
Scheme 60. Metalation of formamides **86k-o** with TMP_2Zn and allylation of the resulting dicarbamoylzinc reagents **87k-o**.

Dicarbamoylzinc reagents of type **87** also underwent benzylations with various benzyl bromides in the presence of $MgCl_2$·LiCl (0.5 equiv) and CuCN·2LiCl (10 mol%) as a catalyst affording arylacetamides **89a-i** in 57-88% yield (Scheme 61). In the absence of $MgCl_2$·LiCl significant amounts of homocoupling products were observed.



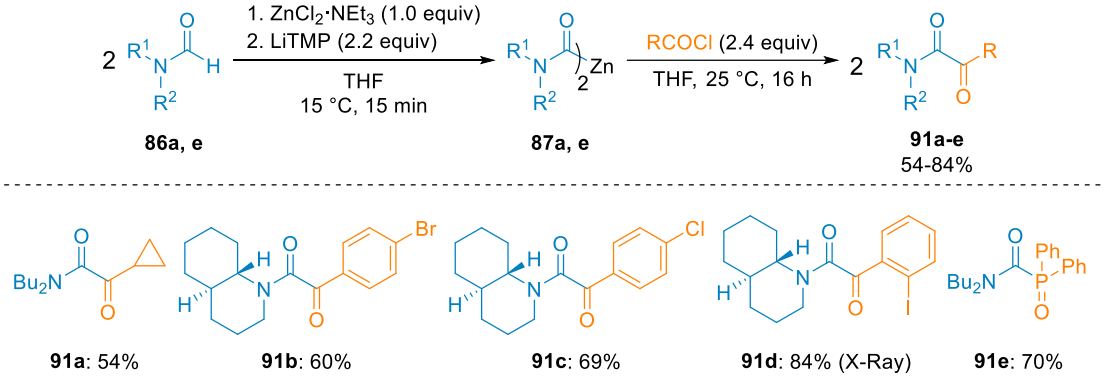
Scheme 61. Benzylation of dicarbamoylzinc reagents of type **87**.

This presence of $MgCl_2$·LiCl was also mandatory for performing addition reactions to aldehydes. Quenching of dicarbamoylzincs **87a** and **87e** with benzaldehyde and 2-bromobenzaldehyde gave α-hydroxyamides **90a** and **90b** in 57-74% yield (Scheme 62).



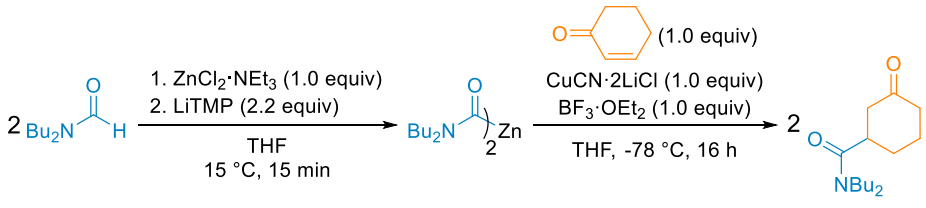
Scheme 62. $MgCl_2$ mediated addition of dicarbamoylzincs **87a** and **87e** to aldehydes.

Interestingly, the reaction of dicarbamoylzinc reagents with acyl chlorides at 25 °C proceeded without any catalyst and various ketoamides **91a-d** were obtained in 54-84% yield (Scheme 63). In the reaction of **87a** with diphenylphosphinic chloride *N*,*N*-dibutyl-1-(diphenylphosphoryl)amide **91e** was produced in 70 % isolated yield.



Scheme 63. Acylation of dicarbamoylzincs of type **87** with acyl chlorides.

A Micheal addition on 2-cyclohexen-1-one was very challenging (Scheme 64). The carbamoylzinc reagent **87a** prepared by method A was treated with 0.5 equiv of CuCN·2LiCl and the tentative dicarbamoylcuprate was reacted with 2-cyclohexen-1-one. Without any additive, the reaction did not give the expected product both at −78 °C and 25 °C. Thus, various Lewis acids such as $MgCl_2$, $MgBr_2$, $Y(OTf)_3$, $Sc(OTf)_3$, $TiCl_4$, $ZnBr_2$, $Zn(OTf)_2$ $AlCl_3$, $AlClEt_2$ and $InCl_3$ were screened. Traces of product were observed when $Y(OTf)_3$ and $Sc(OTf)_3$ were used. The addition of TMSCl did not give any improvement. After significant experimentation, it was found that $BF_3{\cdot}OEt_2$ was crucial for the success of the reaction. The ketoamide **92** was isolated in 54% yield. These, so called Yamamoto copper reagents, have been used in organic synthesis for very challenging Michael additions.[187]

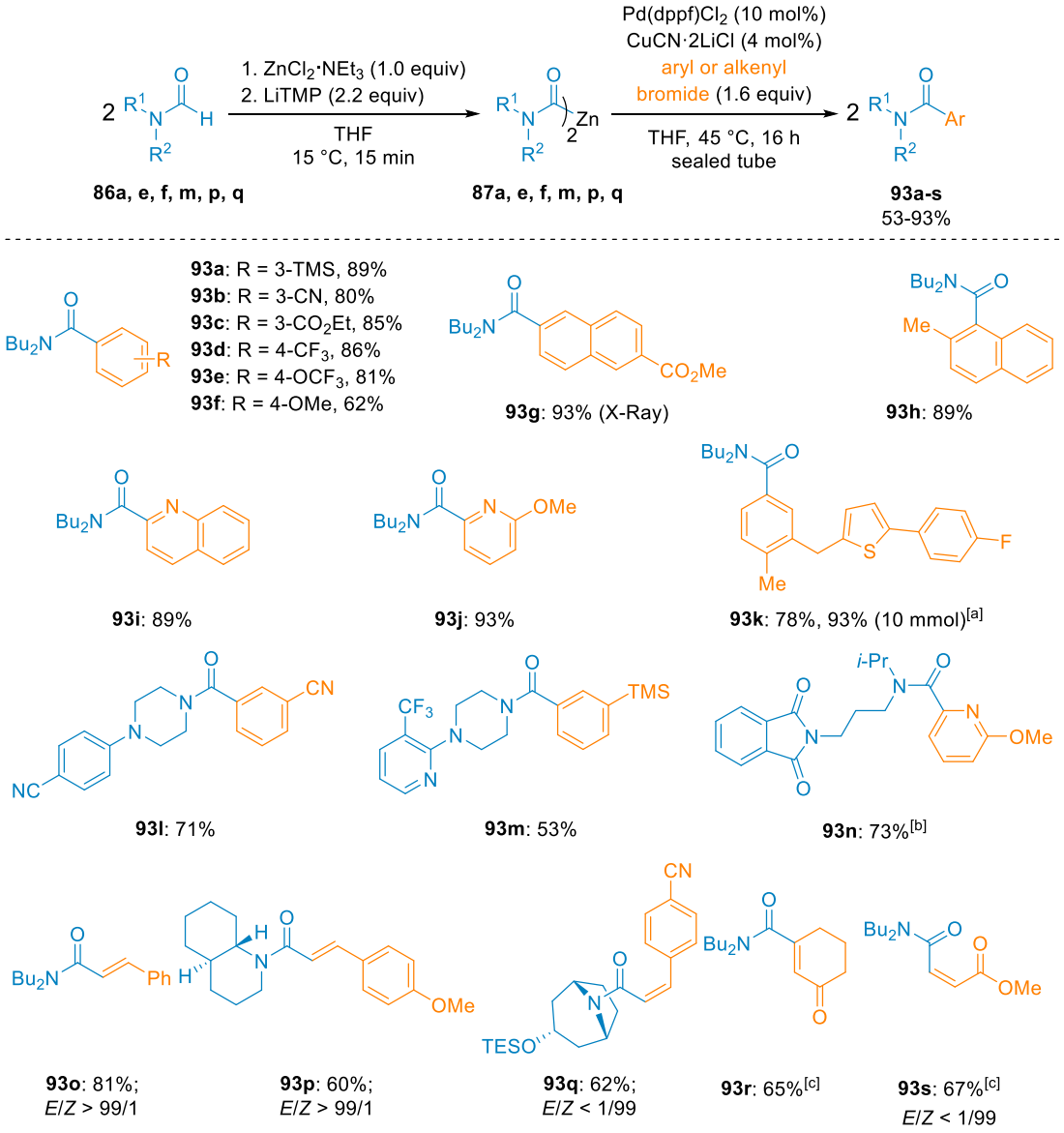


Scheme 64. Cu-catalyzed 1,4-addition of dicarbamoylzinc **87a** to 2-cyclohexen-1-one In the presence of $BF_3{\cdot}OEt_2$.

Finally, we focused on cross-coupling reactions of dicarbamoylzinc reagents with aryl bromides (Scheme 65). During the optimisation, it was noticed that elevated temperatures and long reaction times are not compatible with these organozincs which decompose mainly through decarbonylation. Thus, reactions were conducted in a sealed tube to prevent the loss of CO gas. The ligand screening showed that bidentate ligands perform best, which is typical for coupling reactions involving carbon monoxide.

[187] Y. Yamamoto, *Angew. Chem. Int. Ed.* **1986**, *25*, 947.

On the other hand, some common catalytic systems for Negishi couplings such as $Pd(OAc)_2$/SPhos[188] failed to produce a significant amount of product. Interestingly, the use of CuCN·2LiCl as cocatalyst had a tremendous impact on the reactions conducted with $Pd(dppf)Cl_2$. Similar catalytic systems for Negishi cross-coupling have been reported earlier.[189] Although ligands such as XantPhos and dppe led to good yields in combination with $Pd(dba)_2$ as the Pd-precatalyst, the dual catalytic system ($Pd(dppf)Cl_2$/CuCN·2LiCl) gave the best results. The role of Cu catalyst was not investigated, but we assume that it works as a shuttle between carbamoylzinc and palladium catalyst. Additionally, in the case of the decarbonylation of carbamoylzinc, it may enable the regeneration of the dicarbamoylzinc reagent.



Scheme 65. Cross-coupling of dicarbamoylzinc reagents with aryl and alkenyl bromides. [a] 10-fold scale up, $Pd(dppf)Cl_2$ (2 mol%), CuCN·2LiCl (0.8 mol%); [b] Metalation with $TMP_2Zn·2MgCl_2·2LiCl$; [c] 3-iodocyclohex-2-en-1-one and methyl (Z)-3-iodoacrylate were used as electrophiles with stoichiometric CuCN·2LiCl (no [Pd] catalyst).

In a typical experiment, a mixture of the Pd-precatalyst and aryl bromide in THF was added to the solution of dicarbamoylzinc reagent, followed by CuCN·2LiCl. The resulting reaction mixture was

[188] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028.
[189] a) E. G. Corley, K. Conrad, J. A. Murry, C. Savarin, J. Holko, G. Boice, *J. Org. Chem.* **2004**, *69*, 5120; b) K. Schwärzer, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 20235.

briefly stirred until complete dissolution of Pd(dppf)Cl_2, the tube was sealed and placed into an oil bath warmed to 45 °C. After 16 h, various tertiary amides were isolated *via* column chromatography. Thus, *N*,*N*-dibutylbenzamides **93a-f** were successfully obtained in 62-89%. Sensitive groups such as nitrile and ester were tolerated. Similarly, naphthalene derivative **93g** was prepared in 93% yield and the structure was confirmed by X-Ray diffraction analysis. Also, sterically hindered 1-bromo-2-methylnaphthalene gave the expected amide **93h** in 89% yield. Furthermore, heterocyclic bromides were smoothly reacted with carbamoylzinc reagent **87a** under dual catalysis to afford compounds **93i** and **93j** in 89-93% yield. Also, complex aryl bromide gave the expected amide **93k** in 78% isolated. To show the reliability of the procedure this particular example was scaled-up to 10 mmol with a reduction of catalyst loading to 2 mol% of Pd(dppf)Cl_2 and 0.8 mol% CuCN·2LiCl. To our delight with prolongation of reaction time to 72 h compound **93k** was isolated in 93%, a superior yield compared to the 1 mmol scale. Next, attention was given to the more complex dicarbamoylzinc reagents. The nitrile containing carbamoylzinc **87p** was coupled with 3-bromobenzonitrile to give polyfunctional piperazine amide **93l** in 71% yield. Similarly, the complex pyridine derivative **93m** was synthesised in 53% yield from dicarbamoylzinc reagent **87f** and (3-bromophenyl)trimethylsilane. Moreover, dicarbamoylzinc **87m** obtained by metalation with $TMP_2Zn·2MgCl_2·2LiCl$ (0.55 equiv) was also coupled using this procedure although 2.0 equiv (compared to aryl bromide) of carbamoylzinc reagent had to be used. We believe that the bulkiness of the isopropyl group as well as the detrimental effect of $MgCl_2$, result in low yield when standard procedure is used. Remarkably, our conditions were also suitable for couplings of alkenyl bromides. Thus, cross-coupling of (*E*)-(2-bromovinyl)benzene and (*E*)-1-(2-bromovinyl)-4-methoxybenzene with dicarbamoylzincs **86a** and **86e** led to (*E*)-acrylamides **93o-p** in 60-81% isolated yield. A stereoretentive coupling of (Z)-alkenyl bromide led to complex (*Z*)-acrylamide **93q** in 62% isolated yield.

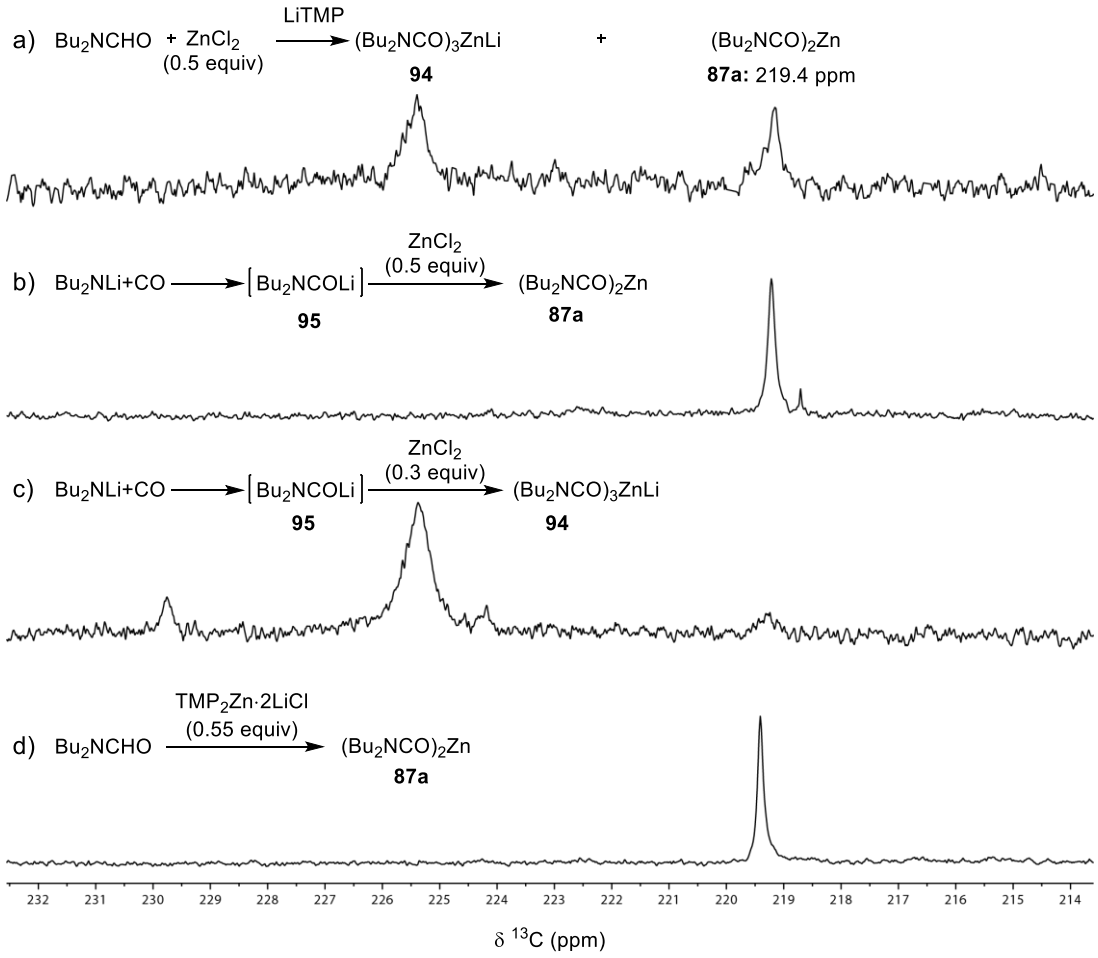


Figure 4. ^{13}C NMR spectra of dicarbamoylzinc **87a** and tricarbamoylzincate **94** generated using different methods.

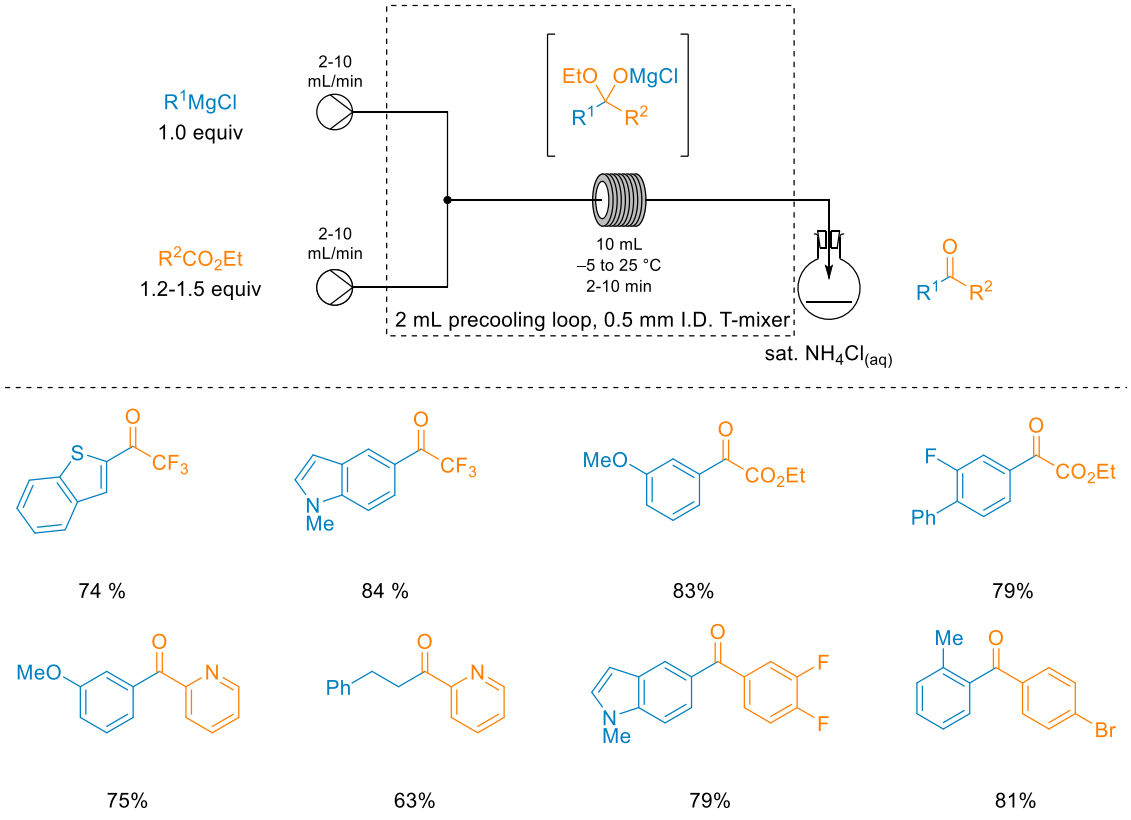
Aryl and alkenyl iodides were not good substrates for our dual catalytic system. However, addition of stoichiometric amounts of CuCN·2LiCl (0.5 equiv) to the dicarbamoylzinc reagent **87a** at −78 °C and subsequent addition of 3-iodocyclohex-2-en-1-one and methyl (Z)-3-iodoacrylate resulted in expected α,β-unsaturated amides **93r-s** in 65-67% yield.

A ^{13}C NMR-characterisation of di(*N*,*N*-dibutylcarbamoyl)zinc **87a** reagent was done. Thus, the ^{13}C NMR spectra of the reaction mixture obtained by treating the **86a**/$ZnCl_2$ mixture with TMPLi showed a new characteristic carbonyl signal (δ = 219.4 ppm), together with a broad signal around δ = 225 ppm (Figure 4a). To confirm the assignment of these resonances, we have prepared dicarbamoylzinc **87a** by an alternative method. Thus, treatment of Bu_2NLi at −78 °C with CO gas led to *N*,*N*-dibutylcarbamoyllithium (1.0 equiv) which was transmetalated under CO atmosphere with $ZnCl_2$ (0.5 equiv) to give the dicarbamoyl reagent **87a** (Figure 4b). Indeed, an identical ^{13}C NMR signal with chemical shift for the carbonyl group δ = 219.4 ppm was observed. By using 0.3 equiv of $ZnCl_2$ we obtained the zincate **94** (Figure 4c), whose shift was the same as the shift of the broad signal around δ = 225 ppm (Figure 4a). Finally, metalation with $TMP_2Zn·2LiCl$ also afforded spectroscopically pure diorganozinc reagent **87a** (Figure 4d).

5. Summary

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

A continuous flow acylation of organomagnesium reagents with commercially available ester electrophiles has been described (Scheme 66). Explored substrates featured a coordination group in both ester electrophiles and in organomagnesium nucleophiles. Thus, this procedure was applicable to commercially available ethyl trifluoroacetate, diethyl oxalate and N-heterocyclic esters. Moreover, simple bisaryl ketones were obtained from magnesiated 2-hydroxyethyl esters. In this case, the pending alkoxide group played a crucial role in the stabilization of the tetrahedral intermediate. The use of a continuous flow setup enabled the reactions at convenient reaction temperatures (–5-25 °C) due to excellent mixing and stoichiometry control.

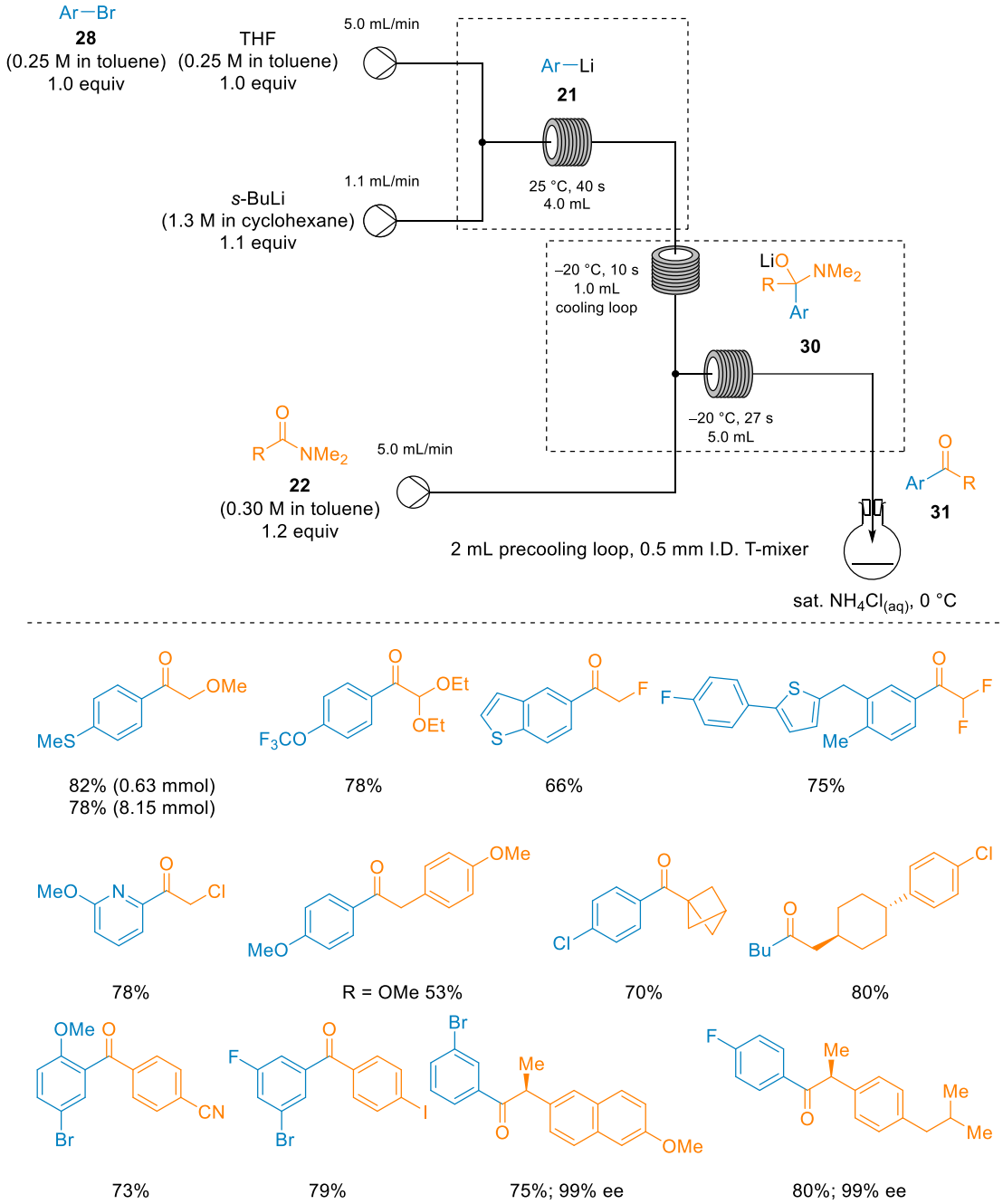


Scheme 66. Selective Acylation of Aryl- and Heteroarylmagnesium Reagents with Esters in Continuous Flow.

5.2 Continuous Flow Acylation of (Hetero)aryllithiums with Polyfunctional *N*,*N*-dimethylamides and Tetramethylurea in Toluene

Next, a convenient acylation of organolithiums with simple *N*,*N*-dimethylamides in continuous flow was reported (Scheme 67). The aryllithiums reagents in toluene were successfully prepared using Br/Li exchange with *s*-BuLi in cyclohexane as an exchange reagent. The addition of 1.0 equivalent of THF was key to overcoming the solubility issues of organolithiums in toluene. Although not stable enough

for convenient batch protocol, the organolithiums reagents in toluene (with 1.0 equiv THF) showed better stability compared to pure THF. Therefore, we were able to perform Br/Li exchange reactions at 25 °C within 40 s in continuous flow. These organolithiums reagents were reacted with functional *N*,*N*-dimethylamides at –20 °C within 27 s. A broad range of amides possessing sensitive functionalities such as nitrile and aryl iodide were compatible with this protocol.



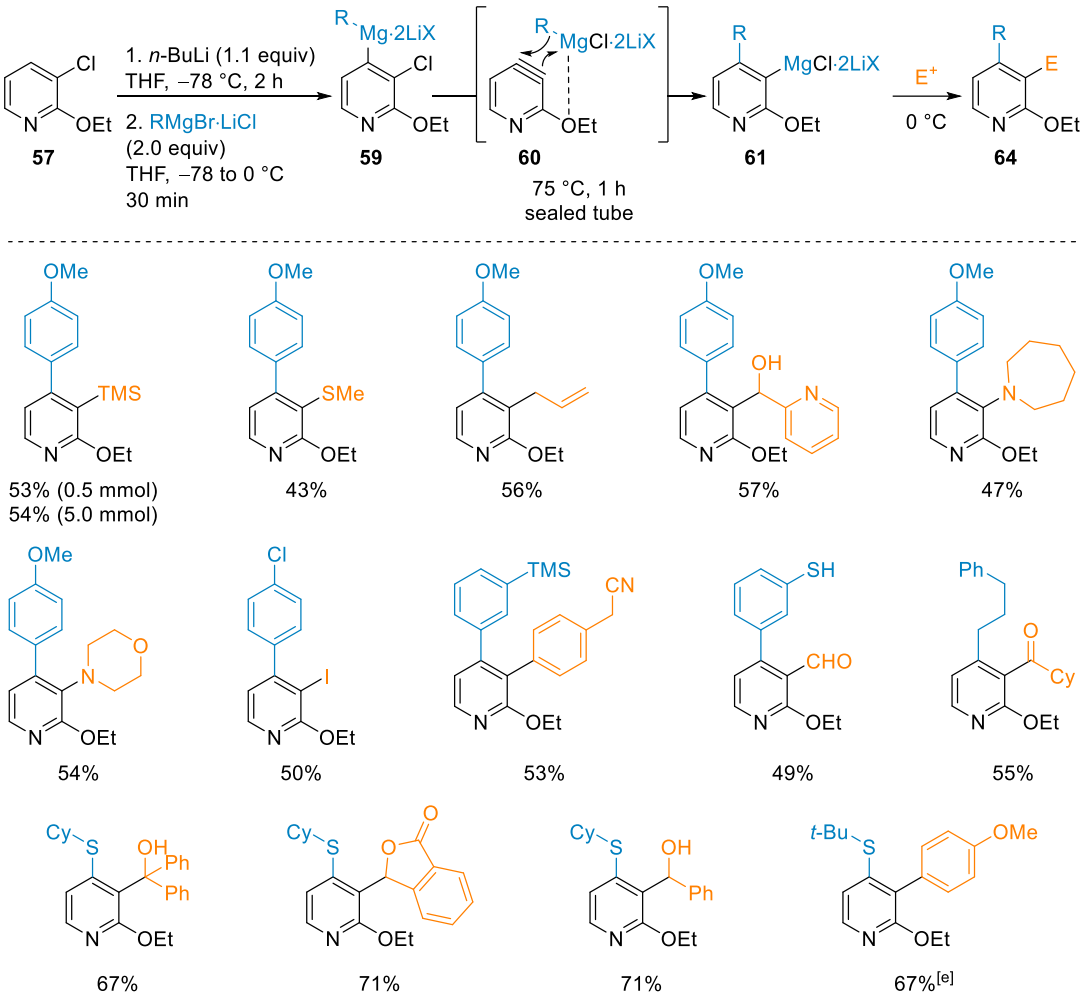
Scheme 67. Continuous Flow Acylation of (Hetero)aryllithiums with Polyfunctional *N*,*N*-dimethylamides and Tetramethylurea in Toluene.

A particularly interesting feature of this method is the high tolerance of relatively acidic alpha protons in the amide electrophile. This is showcased in the use of very challenging substrates such as 2-fluoro-*N*,*N*-dimethylacetamide and 2-(4-methoxyphenyl)-*N*,*N*-dimethylacetamide. Additionally, using this method naproxen and ibuprofen-derived α-chiral ketones were synthesised with full retention of configuration (99% *ee*). Finally, a semi-batch telescoped procedure for the preparation of

unsymmetrical ketones was developed where tetramethylurea was used as CO synthetic equivalent. Thus, a mixture of tetramethylurea and aryl bromide was treated with *s*-BuLi at −20 °C for 50 s leading to the formation of *N*,*N*-dimethylamide. This reaction mixture was poured into a solution of another organolithium species (1.5 equiv), which was prepared separately in flask. After 12 h reaction time, diaryl ketones were isolated in good yields.

5.3 Regioselective Difunctionalization of Pyridines *via* 3,4-Pyridynes

A transition metal free approach toward 3,4-difunctionalized pyridines *via* pyridyne intermediates was explored (Scheme 68). Previous literature reports used elaborated precursors, obtained through multistep reaction sequences. In addition, the reaction scope was limited to monofunctionalizations with simple amines or thiols and cycloaddition reactions complicated by regioselectivity issues. Thus, our efforts focused on the atom economy of the reaction and expanding nucleophile scope beyond simple cycloadditions. In our work, we have explored the 3-chloropyridines as precursors of 3,4-pyridyne.



Scheme 68. Regioselective Difunctionalization of Pyridines *via* 3,4-Pyridynes.

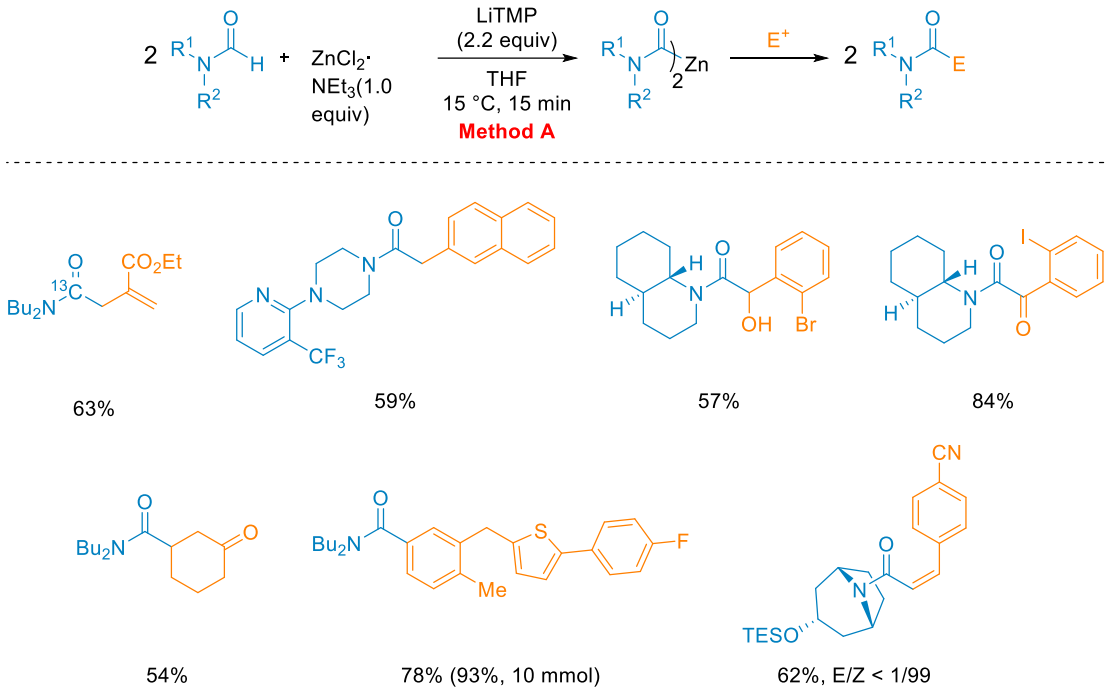
Therefore, by treating 2-ethoxy-3-chloropyridine with *n*-BuLi (−78 °C, 2 h), a regioselective metalation in position C4 was achieved. The addition of Grignard reagent (2.0 equiv) gave tentatively, after transmetalation, a mixed diorganomagnesium species. At appropriate temperature (75 °C), elimination of chloride took place with concomitant *in situ* generation of 2-ethoxy-3,4-pyridyne. After

carbomagnesiation of the pyridyne, a stable 3-magnesio pyridine was obtained. This species was routinely reacted with a variety of electrophiles such as TMSCl, DMF, $(CCl_2Br)_2$ *etc*. to give polyfunctional pyridines. Upscale of the reaction to 5 mmol was demonstrated.

In addition, an analogous reaction with magnesium alkylthiolates gave regioselectively 4-alkylthiopyridines in good yields. The reaction was transferred into a continuous flow setup. 3-Chloro-2-isopropylthiopyridine was metalated in continuous flow within 5 min at −60 °C and transmetalated with a Grignard reagent (6.0 equiv). Heating to 75 °C with a backpressure regulator, afforded the expected 3-magnesio pyridines. These were subsequently quenched with different electrophiles. As an application, formal synthesis of paroxetine was done.

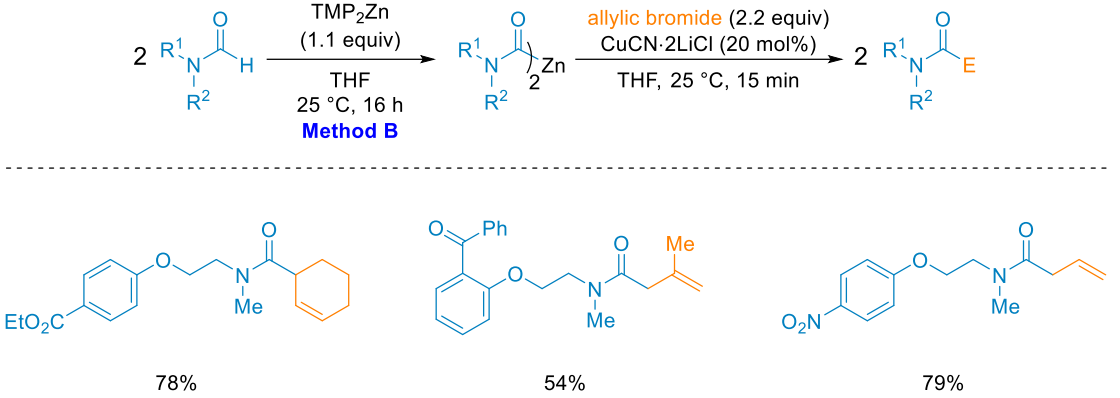
5.4 Preparation of Functionalized Amides using Dicarbamoylzincs

In the last project, we developed new room temperature stable reagents for nucleophilic carbamoylation. The dicarbamoylzinc reagents were obtained in a convenient way by *in situ* lithiation with TMPLi of various formamides in the presence of $ZnCl_2$ (Method A; Scheme 69). Under mild conditions these reagents underwent allylations, benzylations, arylations, alkenylations, acylations, hydroxyalkylations and 1,4-additions furnishing polyfunctional amides in good to excellent yields.



Scheme 69. Preparation of dicaramoylzinc reagents by treating a mixture of formamide and $ZnCl_2$ with TMPLi and reaction with different electrophiles.

Alternatively, we have also demonstrated that the reaction of polyfunctional formamides with TMP_2Zn provides dicarbamoylzincs containing sensitive functional groups such as an ester, ketone, imide or nitro group (Method B; Scheme 70). ^{13}C NMR investigations confirmed the formation of $(R_2NCO)_2Zn$ and the related aggregate $(R_2NCO)_3ZnLi$ under these reaction conditions.



Scheme 70. Preparation of dicarbamoylzinc reagents by treating a formamide with TMP_2Zn and reaction with different allylic bromides.

C. EXPERIMENTAL PART

1. General Information

Batch reactions

All reactions 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 ^{1}H-NMR (25 °C) and capillary GC. Unless otherwise indicated, all reagents were obtained from commercial sources.

Flow reactions

Flow reactions were carried out with solutions of the reactants in dry THF. Flame-dried glassware was used for the reagent solutions and kept under an argon atmosphere during the reactions. Tetradecane was used as internal standard. For all flow reactions a Vapourtec E-series Integrated Flow Chemistry System with 3rd Pump Kit, Organometallic Kit, Collection Valve Kit and Cryogenic Reaction Kit was used. Reactions were performed in coiled tube reactors. Coiled reactors (1.0, 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). Prior to performing reactions, the system was dried by flushing it with dry THF (blue tubing) or MeOH, followed by hexane (red tubing) (flow rate of all pumps: 1.00 mL·min-1; run-time: 30 min).

1.1 Solvents

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

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

THF 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

***n*-BuLi** solution in hexane was obtained from Albemarle and the concentration was determined by titration agains 1,10-phenantroline in THF with dry isopropanol at 0 °C.[190]

***s*-BuLi** solution in hexane was obtained from Albemarle and the concentration was determined by titration agains 1,10-phenantroline in THF with dry isopropanol at –40 °C.

Organomagnesium reagents were titrated according to known procedure. [191]

***i*-PrMgCl·LiCl:** Magnesium turnings (2.67 g, 110 mmol) and anhydrous LiCl (4.66 g, 110 mmol) were placed in an argon-flushed flask and THF (50 mL) was added. A solution of *i*-PrCl

[190] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[191] P. Knochel, A. Krasovskiy, *Synthesis* **2006**, *2006*, 890.

(9.13 mL, 100 mmol) in THF (50 mL) was slowly added at 25 °C. The reaction begins within a few minutes. After addition, the reaction mixture was stirred for 12 h at 25 °C. The grey solution of *i*PrMgCl·LiCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 95-98% of *i*-PrMgCl·LiCl is obtained. [41]

Magnesium thiolates: *i*-PrMgCl·LiCl (1.05 equiv) was slowly added to a solution of the representative thiol in THF (1 mmol/ mL) at 0 °C and stirred for 30 min.[192]

CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.78 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.[55c]

$ZnCl_2$ 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.

TMPH (2,2,6,6-tetramethylpiperidine) was distilled under atmospheric pressure (bp. 152 °C) to obtain a yellow liquid. Drying and distillation over CaH_2 under reduced pressure (65 mbar) afforded near-colorless liquid. It was stored protected from light under argon in a bottle sealed with septum.

TMPMgCl·LiCl: A dry and argon flushed 250 mL flask, equipped with a magnetic stirrer and a septum,was charged with freshly titrated *i*-PrMgCl·LiCl (100 mL, 1.2 M in THF, 120 mmol). TMPH (19.8 g, 126 mmol, 1.05 equiv) was dropwise added at room temperature. The reaction mixture was stirred at 25 °C until gas evolution was completed (ca. 24 h). Titration of the base with benzoic acid using 4-(phenylazo)diphenylamine as an indicator afforded ca. 1 M solution of TMPMgCl·LiCl.[48a]

TMPLi: Tetramethylpiperidine (169 mg, 1.2 mmol) was dissolved in THF (2 mL) and cooled to −40 °C. Then, *n*-BuLi 1.75 M in hexane (0.7 mL, 1.2 mmol) was dropwise added and the reaction allowed to warm to 0 °C over 1 h.[193]

$TMP_2Zn·2MgCl_2·2LiCl$: Freshly titrated TMPMgCl·LiCl (100 mmol, 1.0 equiv) was dropwise added to a solution of $ZnCl_2$ in THF (1.0 M, 50 mL, 50 mmol, 0.5 equiv). The resulting mixture was protected from light using aluminium foil and stirred at r.t. for 24 h before titrating the base with benzoic acid using 4-(phenylazo)diphenylamine as an indicator.[194]

$MgCl_2·LiCl$: A dry and argon flushed Schlenk-flask, equipped with a magnetic stirrer and a septum was charged with Mg turnings (2.55 g, 105 mmol), anhydrous LiCl (4.45 g, 105 mmol) and THF (200mL). 1,2-Dichloroethane (9.90 g, 100 mmol) was dropwise added over 1h. The reaction mixture was stirred at 25 °C until gas evolution was complete.

$BF_3·Et_2O$ was distilled and stored in fridge (5-8 °C) under argon.

1.3 Chromatography

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

[192] B. Heinz, M. Balkenhohl, P. Knochel, *Synthesis* **2019**, *51*, 4452.
[193] a) R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95*, 582; b) M. Campbell, V. Snieckus, E. W. Baxter *Encyclopedia of Reagents for Organic Synthesis*, Wiley, **2001**.
[194] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

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 $KMnO_4$ 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.

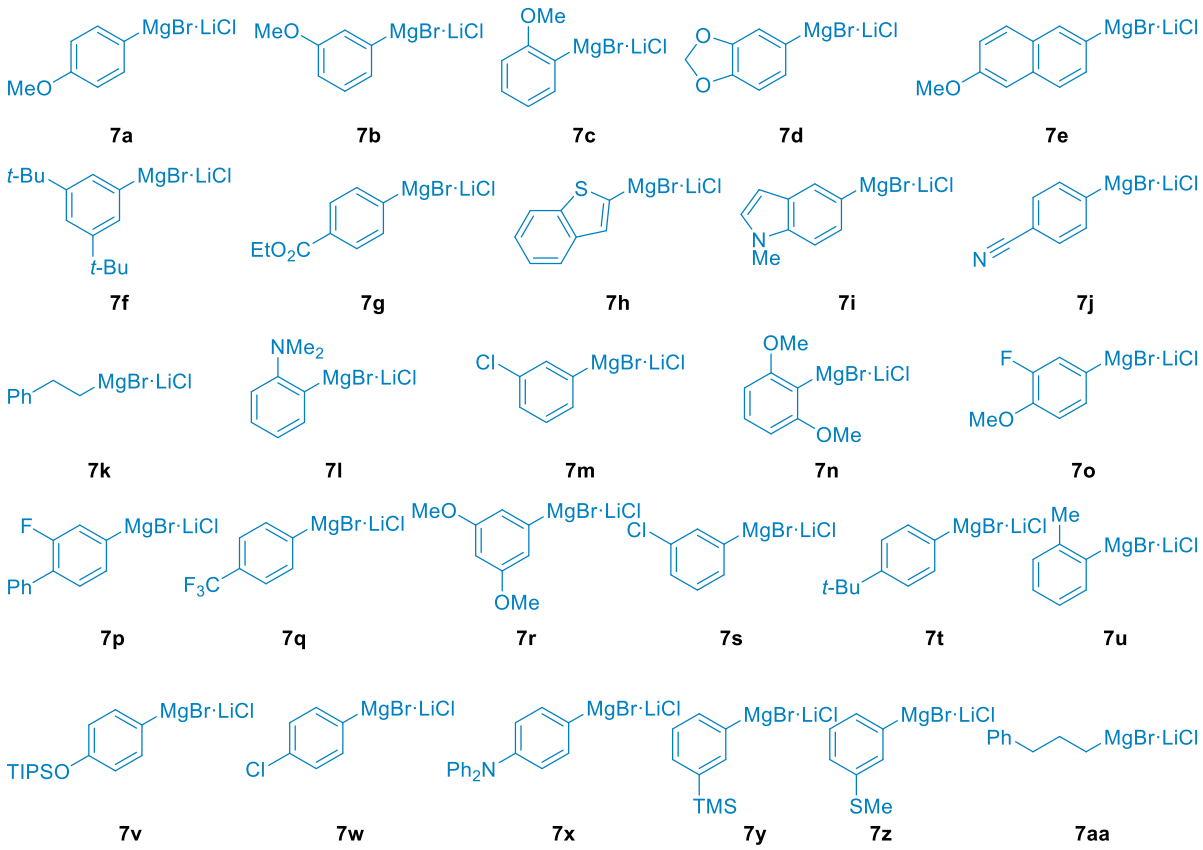
Single crystall X-ray diffraction studies: Single crystals, suitable for X-ray diffraction, were obtained by slow evaporation of appropriate solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection 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.[195] Absorption correction using the multiscan method6 was applied. The structures were solved with SHELXS-97,[196] refined with SHELXL-97[197] and finally checked using PLATON.[198] 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:

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

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

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.



Scheme 71. A list of organomagnesium reagents used in this thesis.

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.

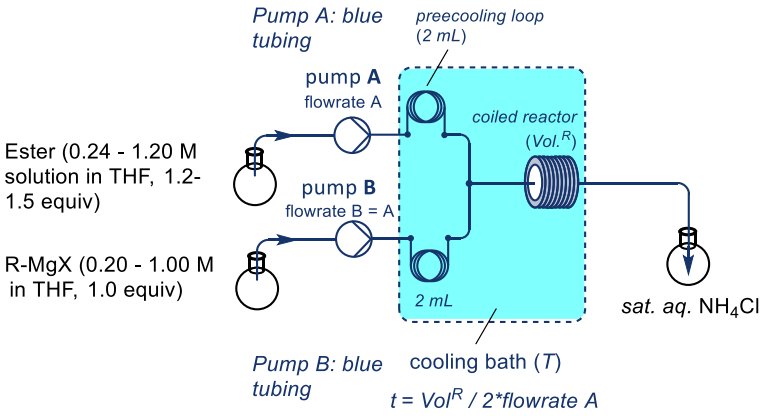
A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the substituted aryl iodide (10.0 mmol, 1.0 equiv) and dry THF (10 mL). The reaction mixture was cooled to the appropriate temperature before *i*-PrMgCl·LiCl (11.0 mmol, 1.1 equiv.) was added dropwise. The progress of the iodine-magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with *sat*. *aq.* 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 **13** and subsequent formation to Mg-alkoxides of type **14**.

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 **13**.

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 an additional 5 min prior to use.

Typical Procedure 4: Preparation of ketones starting from esters and organomagnesium reagents in flow.



Scheme 72. Flow chemistry setup for preparation of ketones.

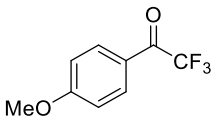
An organomagnesium reagent in THF (0.20 – 1.00 M, 1.0 equiv) and a solution of ester in THF (0.24 – 1.20 M, 1.2 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 1.0 - 5.0 mL·min^{-1} and flowrate B = flowrate A. After passing a PTFE tubing (vol^{pre} = 2.0 mL, T = –5 °C to 25 °C, residence time: 24 – 120 s) for precooling, the solutions were mixed in a T-mixer[199] (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 – 25 °C) and was subsequently injected into 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 *i*-hexane:EtOAc mixtures afforded the pure products.

Batch Comparison Experiments

An argon-flushed, flame dried flask was charged with ethyl trifluoroacetate (**6**) (0.07 mL, 1.2 equiv, 0.60 mmol) 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.

2.2 Preparation of Products

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethan-1-one (8a)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (7) (1.18 M, 1.2 equiv, 0.40 mmol) and (4-methoxyphenyl)magnesium bromide (0.98 M, 1.0 equiv, 0.33 mmol), 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give **8a** (45.0 mg, 0.22 mmol, 67%) as a colorless solid.

[199] The use of a Y-mixer (I.D. = 0.5 mm) led to the same results.

^{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).

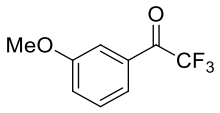
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 178.9 (q, *J* = 34.5 Hz), 165.4, 132.8, 122.8, 118.4 (q, *J* = 291.5 Hz), 114.4, 55.7.

The spectra matched those of the literature.[200]

Upscale Experiment for Compound 8a

(4-Methoxyphenyl)magnesium bromide (0.50 M, 1.0 equiv, 2.00 mmol), prepared *via* TP1 and a solution of ethyl trifluoroacetate (**6**) in THF (0.60 M, 1.2 equiv, 2.40 mmol) 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 (volpre = 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 (VolR = 20 mL; residence time: t = 2 min, T = –5 °C) and was subsequently injected into 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 purification (*i*-hexane:ethyl acetate = 9.5:0.5) afforded the pure product **8a** (270 mg, 1.32 mmol, 66%) as a colorless solid.

2,2,2-Trifluoro-1-(3-methoxyphenyl)ethan-1-one (8b)



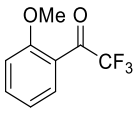
Following **TP4**, precooled solutions of ethyl trifluoroacetate (**7**) (1.12 M, 1.2 equiv, 0.40 mmol) and (3-methoxyphenyl)magnesium bromide (0.93 M, 1.0 equiv, 0.33 mmol), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 10 mL·min^{-1}, Vol^{R} = 20 mL, residence time: t = 1 min , T = -5 °C). Thereafter, the reaction mixture was quenched with *sat. aq.* NH_4Cl. After workup, the crude product was purified via column chromatography (*i*-hexane:ethyl acetate = 9.8:0.2) to give **6b** (201.0 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.[200]

2,2,2-Trifluoro-1-(2-methoxyphenyl)ethan-1-one (8c)



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

Following **TP4**, precooled solutions of ethyl trifluoroacetate (**7**) (1.20 M, 1.2 equiv, 0.40 mmol) and (2-methoxyphenyl)magnesium bromide (1.00 M, 1.0 equiv, 0.33 mmol), 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give **8c** (51.0 mg, 0.25 mmol, 75%) as a colorless 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.

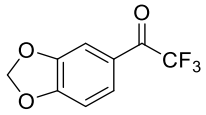
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2949, 2845, 2355, 1709, 1600, 1489, 1278, 1145, 1114, 1020, 930, 753, 657.

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.

The spectra matched those of the literature.[200]

1-(Benzo[d][1,3]dioxol-5-yl)-2,2,2-trifluoroethan-1-one (8d)



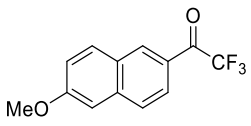
Following TP4, precooled solutions of ethyl trifluoroacetate (**6**) (0.60 M, 1.2 equiv, 0.45 mmol) and benzo[d][1,3]dioxol-5-ylmagnesium bromide (0.50 M, 1.0 equiv, 0.37 mmol), prepared *via* TP1, were mixed in continuous flow (flowrate A = 5 mL·min^{-1}, Vol^{R} = 20 mL, residence time: t = 2 min , T = –5 °C). Thereafter, the reaction mixture was quenched with *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.7:0.3) to give **8d** (50.0 mg, 0.23 mmol, 62%) as a colorless 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. [201]

2,2,2-Trifluoro-1-(6-methoxynaphthalen-2-yl)ethan-1-one (8e)



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

Following **TP4**, precooled solutions of ethyl trifluoroacetate (**6**) (1.20 M, 1.2 equiv, 0.48 mmol) and (6-methoxynaphthalen-2-yl)magnesium (1.00 M, 1.0 equiv, 0.40 mmol), 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give **8e** (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.

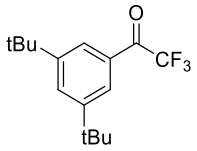
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 3015, 2940, 1697, 1618, 1481, 1400 1266, 1194, 1140, 1028, 900, 749.

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 (8f)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**6**) (0.89 M, 1.2 equiv, 1.78 mmol) and (3,5-di-tert-butylphenyl)magnesium bromide (0.74 M, 1.0 equiv, 1.48 mmol), 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 (pentane + 1% triethylamine) to give **8f** (272 mg, 0.95 mmol, 64%) as a colorless 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.

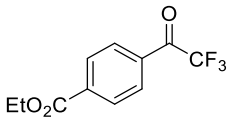
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –71.0.

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.

Ethyl 4-(2,2,2-trifluoroacetyl)benzoate (8g)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**6**) (0.6 M, 1.2 equiv, 1.50 mmol) and (4-(ethoxycarbonyl)phenyl)magnesium chloride (0.50 M, 1.0 equiv, 1.25 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified via column chromatography (pentane:diethyl ether = 7.0:3:0) to give **8g** (218 mg, 0.89 mmol, 71%) as a colorless 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.

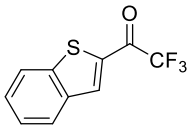
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –71.7.

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.

1-(Benzo[b]thiophen-2-yl)-2,2,2-trifluoroethan-1-one (8h)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**6**) (0.6 M, 1.2 equiv, 0.60 mmol) and benzo[b]thiophen-2-ylmagnesium bromide (0.50 M, 1.0 equiv, 0.50 mmol), 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 (*i*-hexane:ethyl acetate = 9.9:0.1) to give **8h** (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.

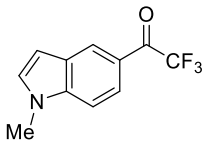
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1682, 1595, 1508, 1345, 1250, 1225, 1189, 1139, 882, 842, 760, 744, 718.

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 (8i)



Following **TP4**, precooled solutions of ethyl trifluoroacetate (**6**) (0.27 M, 1.2 equiv, 0.27 mmol) and (1-methyl-1H-indol-5-yl)magnesium bromide (0.22 M, 1.0 equiv, 0.22 mmol), 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 (*i*-hexane:ethyl acetate = 9.0:1.0) to give **8i** (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.

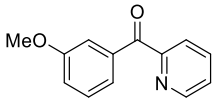
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2360, 1696, 1606, 1218, 1192, 1138, 1099, 962, 752, 718.

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.

(3-Methoxyphenyl)(pyridin-2-yl)methanone (13a)



Following **TP4**, solutions of ethyl 2-picolinate **11a** (0.6 M, 1.2 equiv, 0.60 mmol) and (3-methoxyphenyl)magnesium bromide (0.50 M, 1.0 equiv, 0.50 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.9:0.1) to give **13a** (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).

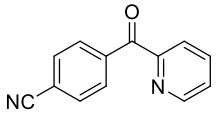
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.7, 159.4, 155.1, 148.6, 137.5, 137.1, 129.2, 126.2, 124.6, 123.9, 119.5, 115.1, 55.5.

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 (13b)



Following **TP4**, solutions of ethyl 2-picolinate **11a** (0.23 M, 1.2 equiv, 0.23 mmol) and (4-cyanophenyl)magnesium chloride (0.19 M, 1.0 equiv, 0.19 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **13b** (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.

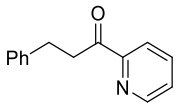
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 1730, 1669, 1584, 1437, 1407, 1309, 1285, 1244, 1157, 996, 938, 856, 804, 749, 705, 680.

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 (13c)



Following **TP4**, solutions of ethyl 2-picolinate **11a** (0.27 M, 1.5 equiv, 0.27 mmol) and phenethylmagnesium bromide (0.18 M, 1.0 equiv, 0.18 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 8.0:2.0) to give **13c** (24 mg, 0.12 mmol, 63%) as a colorless 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).

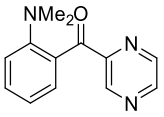
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 201.0, 153.3, 149.0, 141.4, 136.9, 128.5, 128.4, 127.1, 126.0, 121.8, 39.4, 29.9.

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 (13d)



Following **TP4**, solutions of methyl pyrazine-2-carboxylate **11b** (0.32 M, 1.5 equiv, 0.32 mmol) and (2-(dimethylamino)phenyl)magnesium bromide (0.21 M, 1.0 equiv, 0.21 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 7.0:3.0) to give **13d** (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).

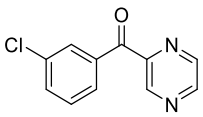
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.6, 153.0, 150.7, 146.4, 145.2, 143.6, 133.0, 131.2, 128.7, 120.3, 117.5, 43.9.

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 (13e)



Following **TP4**, solutions of methyl pyrazine-2-carboxylate **11b** (0.9 M, 1.2 equiv, 1.08 mmol) and (3-chlorophenyl)magnesium bromide (0.75 M, 1.0 equiv, 0.75 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product

was purified *via* column chromatography (*i*-hexane:ethyl acetate = 8.0:2.0) to give **13e** (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).

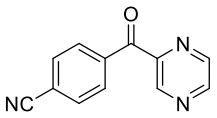
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.8, 149.2, 147.2, 146.2, 142.9, 137.0, 134.5, 133.4, 130.8, 129.7, 129.0.

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 (13f)



Following **TP4**, solutions of pyrazine-2-carboxylate **11b** (0.27 M, 1.5 equiv, 0.27 mmol) and (4-cyanophenyl)magnesium chloride (0.19 M, 1.0 equiv, 0.19 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **13f** (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.

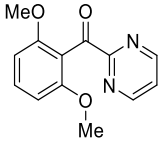
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2064, 2360, 2234, 1673, 1406, 1302, 1153, 1019, 934, 770.

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 (13g)



Following **TP4**, solutions of methyl pyrimidine-2-carboxylate **11c** (0.27 M, 1.5 equiv, 0.27 mmol) and (2,6-dimethoxyphenyl)magnesium bromide (0.18 M, 1.0 equiv, 0.18 mmol), 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 (*i*-hexane:ethyl acetate = 8.0:2.0) to give **13g** (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.

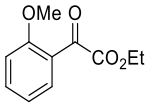
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2845, 1705, 1590, 1473, 1434, 1407, 1306, 1286, 1250, 1104, 943, 784, 759, 740, 702.

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 (16a)



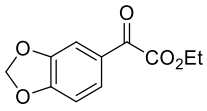
Following **TP4**, solutions of diethyl oxalate (**14**) (0.53 M, 1.2 equiv, 1.32 mmol) and (2-methoxyphenyl)magnesium bromide (0.44 M, 1.0 equiv, 1.10 mmol), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, Vol^R = 20 mL, residence time: t = 10 min , T = 25 °C). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified via column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **12a** (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), 7.52 (dddt, *J* = 8.0, 7.3, 1.6, 0.8 Hz, 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.[202]

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-oxoacetate (16b)



Following **TP4**, solutions of diethyl oxalate (**14**) (0.60 M, 1.2 equiv, 0.60 mmol) and benzo[d][1,3]dioxol-5-ylmagnesium bromide (0.50 M, 1.0 equiv, 0.50 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude

[202] Y. Kumar, Y. Jaiswal, A. Kumar, *J. Org. Chem.* **2016**, *81*,12247.

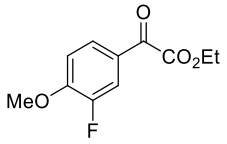
product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 8.5:1.5) to give **16b** (70.0 mg, 0.31 mmol, 63%) as an orange oil.

^{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.[202]

Ethyl 2-(3-fluoro-4-methoxyphenyl)-2-oxoacetate (16c)



Following **TP4**, solutions of diethyl oxalate (**14**) (0.32 M, 1.4 equiv, 0.32 mmol) and (3-fluoro-4-methoxyphenyl)magnesium bromide (0.23 M, 1.0 equiv, 0.23 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **16c** (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).

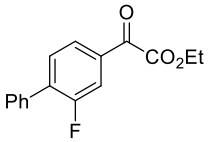
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 183.9, 163.4, 153.4 (d, *J* = 32.0 Hz), 150.8, 128.3, 125.7, 117.2 (d, *J* = 19.5 Hz), 112.6, 62.4, 56.4, 14.1.

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 (16d)



Following **TP4**, solutions of diethyl oxalate (**14**) (0.30 M, 1.5 equiv, 0.30 mmol) and (2-fluoro-[1,1'-biphenyl]-4-yl)magnesium bromide (0.20 M, 1.0 equiv, 0.20 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified via column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **16d** (45.0 mg, 0.17 mmol, 79%) as a colorless 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).

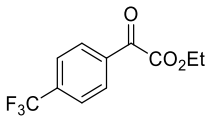
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 184.6, 163.1, 160.9, 158.4, 135.8 (d, *J* = 13.7 Hz), 134.3 (d, *J* = 1.5 Hz), 133.1 (d, *J* = 7.0 Hz), 131.3 (d, *J* = 3.5 Hz), 129.1 (d, *J* = 3.2 Hz), 128.7, 126.3 (d, *J* = 3.5 Hz), 117.5 (d, *J* = 24.9 Hz), 62.6, 14.1.

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 (16e)



Following **TP4**, solutions of diethyl oxalate (**14**) (0.30 M, 1.2 equiv, 0.30 mmol) and (4-(trifluoromethyl)phenyl)magnesium bromide (0.24 M, 1.0 equiv, 0.24 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified via column chromatography (*i*-hexane:ethyl acetate = 8.0:2.0) to give **16e** (41.0 mg, 0.17 mmol, 71%) as a colorless 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.

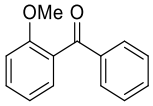
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –63.4.

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 (19a)



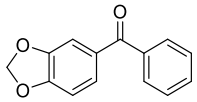
Following **TP4**, solutions of alkoxide **17a** (0.60 M, 1.2 equiv, 0.60 mmol), prepared *via* **TP3**, and (2-methoxyphenyl)magnesium bromide (0.48 M, 1.0 equiv, 0.48 mmol), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, Vol^R = 20 mL, residence time: t = 10 min , T = 25 °C). Thereafter, the reaction mixture was quenched with *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **19a** (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.[203]

Benzo[d][1,3]dioxol-5-yl(phenyl)methanone (19b)



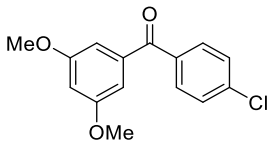
Following **TP4**, solutions of alkoxide **17a** (0.27 M, 1.2 equiv, 0.27 mmol), prepared *via* **TP3**, and benzo[d][1,3]dioxol-5-ylmagnesium bromide (0.23 M, 1.0 equiv, 0.23 mmol), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, Vol^{R} = 20 mL, residence time: t = 10 min , T = 25 °C). Thereafter, the reaction mixture was quenched with *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **19b** (32.0 mg, 0.14 mmol, 62%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.76 – 7.73 (m, 2H), 7.56 (ddt, *J* = 8.7, 7.0, 1.3 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.39 – 7.35 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.2, 151.5, 148.0, 138.1, 132.0, 131.9, 129.7, 128.2, 126.9, 109.9, 107.7, 101.9.

The spectra matched those of the literature.[204]

(4-Chlorophenyl)(3,5-dimethoxyphenyl)methanone (19c)



Following **TP4**, solutions of alkoxide **17b** (0.84 M, 1.2 equiv, 0.84 mmol), prepared *via* **TP3**, and (3,5-dimethoxyphenyl)magnesium bromide (0.70 M, 1.0 equiv, 0.70 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.5:0.5) to give **19c** (120 mg, 0.43 mmol, 62%) as a colorless 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.

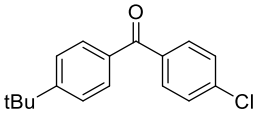
[203] H. Neumann, A. Brennführer, M- Beller, *Chem. Eur. J.*, **2008**, *14*, 3645.
[204] A. M. Echavarren, J. K. Stille, *J. Am. Chem. Soc.* **1988**, *110*, 1557.

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 (19d)



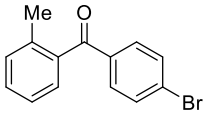
Following **TP4**, solutions of alkoxide **17b** (0.60 M, 1.2 equiv, 0.60 mmol), prepared *via* **TP3**, and (4-(tert-butyl)phenyl)magnesium bromide (0.45 M, 1.0 equiv, 0.45 mmol), prepared *via* **TP1**, were mixed in continuous flow (flowrate A = 1 mL·min^{-1}, Vol^R = 20 mL, residence time: t = 10 min , T = 25 °C). Thereafter, the reaction mixture was quenched with *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **19d** (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.[205]

(4-Bromophenyl)(o-tolyl)methanone (19e)



Following **TP4**, solutions of alkoxide **17c** (0.33 M, 1.2 equiv, 0.33 mmol), prepared *via* **TP3**, and o-tolylmagnesium bromide (0.27 M, 1.0 equiv, 0.27 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.9:0.1) to give **19e** (60.0 mg, 0.22 mmol, 81%) as a colorless 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.

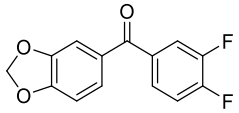
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 2926, 2362, 1665, 1584, 1480, 1454, 1395, 1265, 1068, 1011, 924, 845, 743.

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

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).

Benzo[d][1,3]dioxol-5-yl(3,4-difluorophenyl)methanone (19f)



Following **TP4**, solutions of alkoxide **17d** (0.27 M, 1.2 equiv, 0.27 mmol), prepared *via* **TP3**, and benzo[d][1,3]dioxol-5-ylmagnesium bromide (0.23 M, 1.0 equiv, 0.23 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **16e** (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.

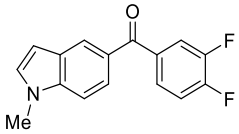
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1656, 1603, 1515, 1442, 1305, 1291, 1249, 1110, 1040, 904, 724.

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.

(3,4-Difluorophenyl)(1-methyl-1H-indol-5-yl)methanone (19g)



Following **TP4**, solutions of alkoxide **17d** (0.33 M, 1.5 equiv, 0.33 mmol), prepared *via* **TP3**, and (1-methyl-1H-indol-5-yl)magnesium bromide (0.22 M, 1.0 equiv, 0.22 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **19g** (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,

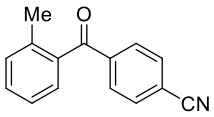
1108, 1089,773, 742, 732.

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-(2-Methylbenzoyl)benzonitrile (19h)



Following **TP4**, solutions of alkoxide **17e** (0.33 M, 1.2 equiv, 0.33 mmol), prepared *via* **TP3**, and *o*-tolylmagnesium bromide (0.27 M, 1.0 equiv, 0.27 mmol), 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 *sat*. *aq*. NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.5:0.5) to give **19h** (40.0 mg, 0.18 mmol, 68%) as a colorless 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).

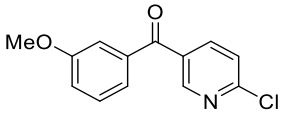
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.9, 141.2, 137.5, 137.0, 132.3, 131.5, 131.2, 130.4, 129.0, 125.5, 118.0, 116.2, 20.2.

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 (19i)



Following **TP4**, solutions of alkoxide **17f** (0.35 M, 1.5 equiv, 0.35 mmol), prepared *via* **TP3**, and (3-methoxyphenyl)magnesium (0.23 M, 1.0 equiv, 0.23 mmol), 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 (*i*-hexane:ethyl acetate = 9.0:1.0) to give **19i** (37.0 mg, 0.15 mmol, 63%) as a colorless 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. Continuous Flow Acylation of (Hetero)aryllithiums with Polyfunctional *N*,*N*-Dimethylamides and Tetramethylurea in Toluene

3.1 List of Bromides of Type **28** and of the Aryllithiums of Type **21** and **41**

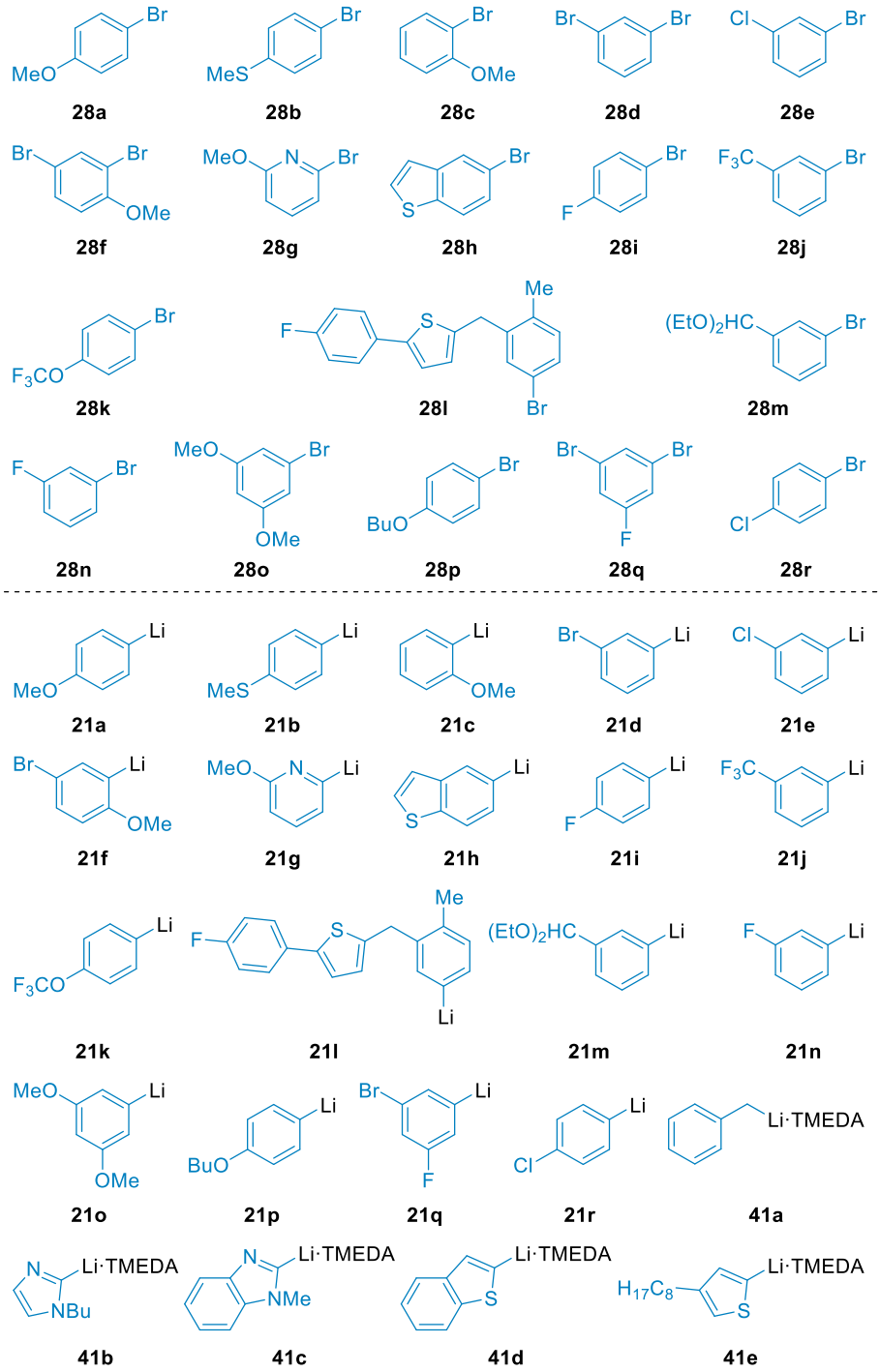


Figure 5. List of bromides of type **28** and the corresponding aryllithiums of type **21** and **41**.

3.2 List of Amides of Type **22**, **34** and **37**

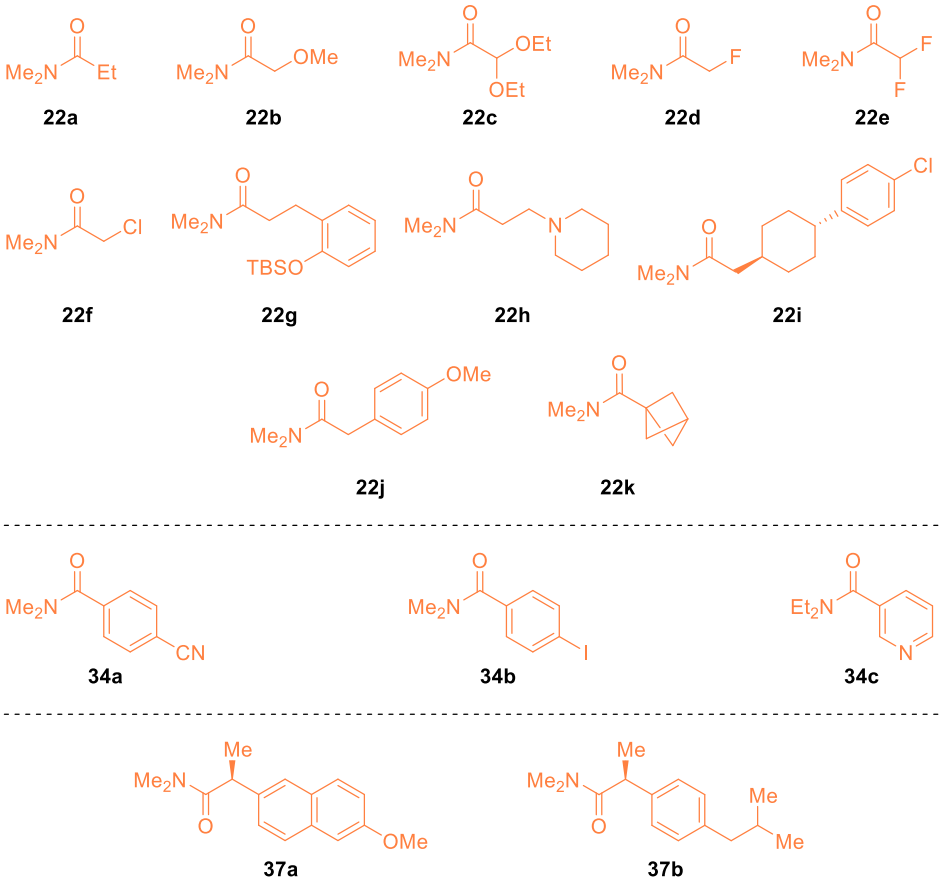
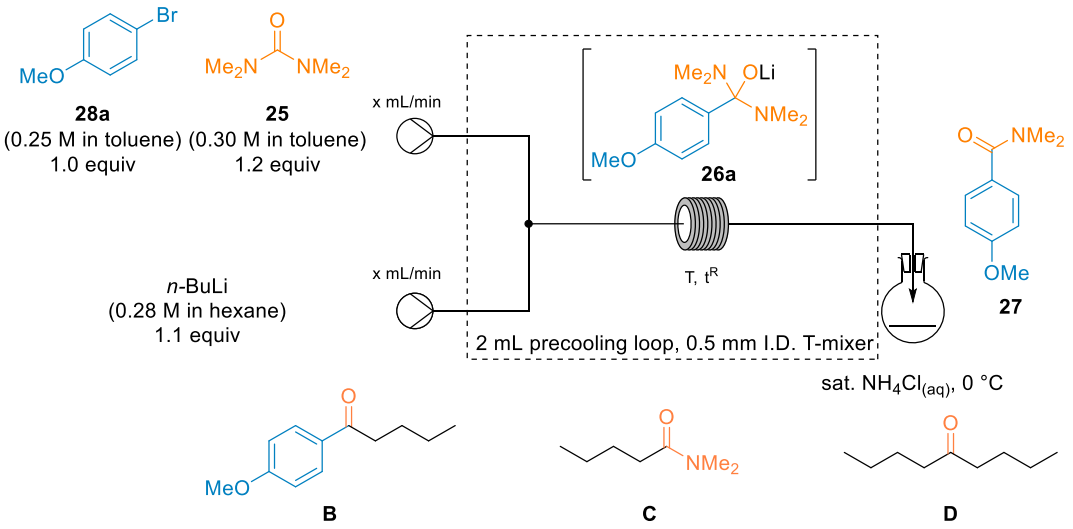


Figure 6. List of amides **22**, **34** and **37**.

3.3 Optimizations and Screenings

A) Development of Barbier-type reactions of aryl bromides with tetramethylurea (TMU) using *s*-BuLi in a continuous flow

Table 16. Screening for Barbier-type acylations in continuous flow starting from aryl bromide **28a** in toluene, tetramethylurea **25** and *n*-BuLi.

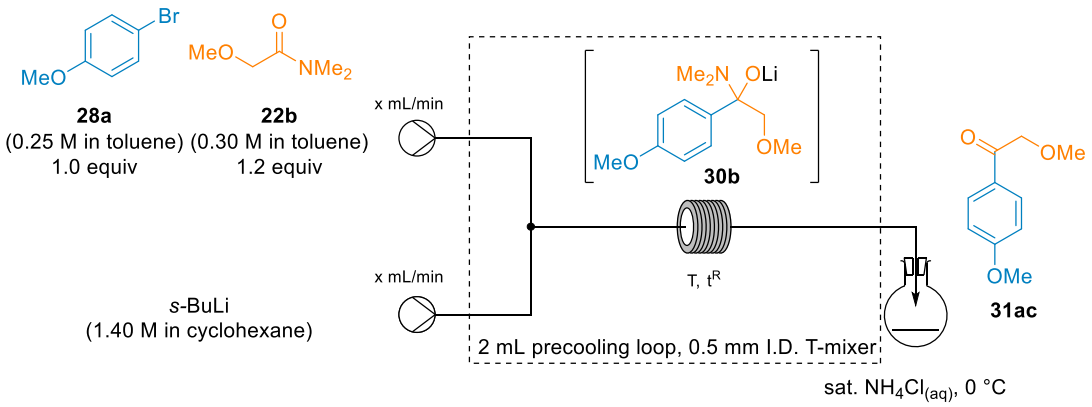


Entry	T [°C]	t [s]	Flowrate A+B [X mL/min]	Leftover **28a** [GC-%]	Product **27** [GC-%]	BuLi-Addition **B** [GC-%]
1	22	12	5+5	66	17	11
2	0	12	5+5	61	22	14
3	–20	12	5+5	52	43	8
4	–40	12	5+5	36	54	7
5	–54	12	5+5	32	42	6
6	–20	60	5+5	54	43	7

- Aryl bromides proved to be more challenging than aryl iodides. Side-products of the addition of *n*-BuLi to the urea such as **C** and **D** have been observed due to a slow exchange.
- Lower temperatures helped to control all side reactions, but a longer reaction time did not lead to a complete reaction conversion of **28a**.

B) Development of stepwise reactions of aryl bromides with *N,N*-dimethylamides using *s*-BuLi in a continuous flow

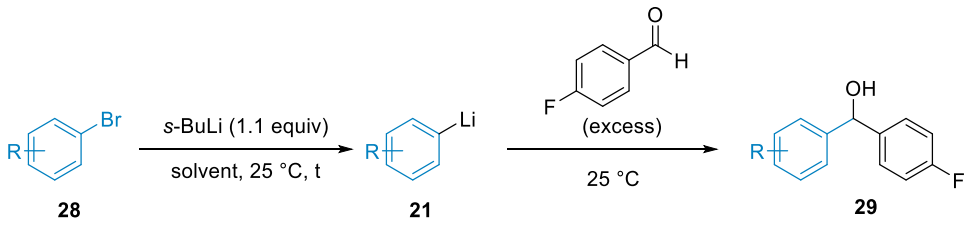
Table 17. Screening for Barbier-type acylations in continuous flow starting from aryl bromide 2**8a** in toluene, *N,N*-dimethylamide **22a** and *s*-BuLi.

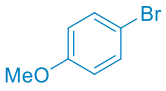


Entry	T [°C]	t [s]	Flow rate x [mL/min]	Leftover **28a** [GC-%]	Product **31ac** [GC-%]
1	0	50	5+5	40	23
2	–20	50	5+5	36	34
3	–40	50	5+5	clogging	

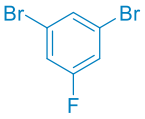
- Barbier-type conditions with electron rich aryl bromides failed to deliver a product in good yield even when *s*-BuLi was used as an exchange reagent.
- Conclusion: Amides are less good promotors of the Br/Li-exchange compared to TMU, leading to incomplete conversion and side reactions. Use of such Barbier conditions might be possible in the case of electron deficient aryl bromides.

C) Batch screening for Br/Li-exchange in toluene and THF





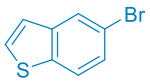
21a



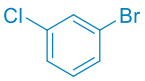
21q

entry	set-up	solvent	time [min]	conversion of **21a** [GC-%]	Product **29** [GC-%]
1	batch	THF	10	91	40
1	batch	THF	60	95	9
1	batch	toluene*	10	99	81
1	batch	toluene*	60	99	61
1	flow	toluene*	1	99	99

entry	set-up	solvent	time [min]	conversion of **21q** [GC-%]	Product **29** [GC-%]
1	batch	THF	10	93	-
1	batch	THF	60	94	-
1	batch	toluene*	10	99	5
1	batch	toluene*	60	99	-
1	flow	toluene*	1	99	98



21h



21e

entry	set-up	solvent	time [min]	conversion of **21h** [GC-%]	Product **29** [GC-%]
1	batch	THF	10	95	10
1	batch	THF	60	94	8
1	batch	toluene*	10	99	25
1	batch	toluene*	60	99	23
1	flow	toluene*	1	99	98

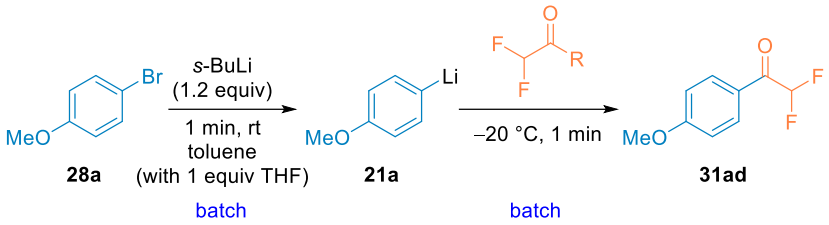
entry	set-up	solvent	time [min]	conversion of **21e** [GC-%]	Product **29** [GC-%]
1	batch	THF	10	91	-
1	batch	THF	60	93	-
1	batch	toluene*	10	99	85
1	batch	toluene*	60	99	76
1	flow	toluene*	1	99	99

* with 1.0 equiv of THF

Scheme 73. Br/Li-exchange screening for various aryl bromides of type **28** with *s*-BuLi at 25 °C in THF or toluene with 1.0 equiv of THF.

D) Comparison experiments for different amides and esters for the acylation of the aryllithium 21a

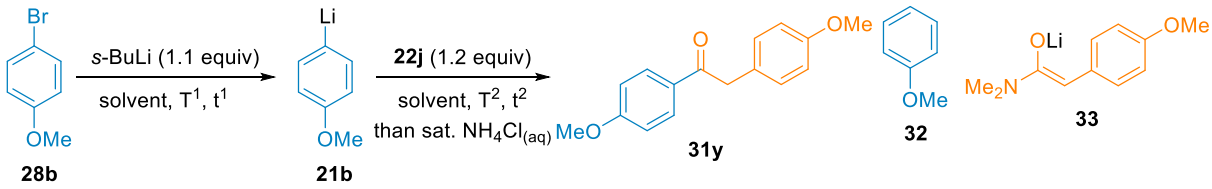
Table 18. Comparison experiments for different amides and esters for the acylation of the aryllithium **21a**.



entry	R	conversion of **28a** [GC-%]	product formation **31ad** [GC-%]	double addition [GC-%]
1	NMe_2	>99	79	-
2	NEt_2	>99	78	-
3	Morpholine	>99	81	-
4	OEt	97	43	14

E) Comparison of THF and toluene on the enolization side reactions in addition of ArLi to *N,N*-dimethylamides.

Table 19. Comparison of THF and toluene on the enolization side reactions in addition of ArLi to *N,N*-dimethylamides.



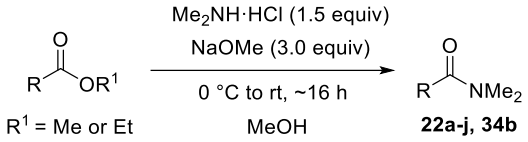
Entry	Setup	Solvent	t_1 [min]	T_1 [°C]	t_2 [min]	T_2 [°C]	Conversion of **28a** [GC-%]	Hydrolysis **32**	**31y** [GC-%]	Ratio **31y/32**
1	batch	THF	1	25	5	–20	80	40	33	0.8/1
2	batch	THF	5	–20	5	–20	88	38	35	0.9/1[a]
3	batch	THF	30	–78	30	–78	>99	28	45	1.6/1
4	batch	toluene[b]	1	25	5	–20	97	18	59	3.3/1
5	flow	toluene[b]	0.67	25	0.5	0	>99	18	53	3.0/1

6	flow	toluene[b]	0.67	25	0.5	–20	>99	17	60	3.4/1
7	flow	toluene[b]	0.67	25	0.5	–40	>99	20	59	3.0/1

[a] Reaction was quenched with benzaldehyde instead of saturated $NH_4Cl_{(aq)}$ to prove that **32** is formed during the reaction and during the quench; [b] THF (1.0 equiv) was added.

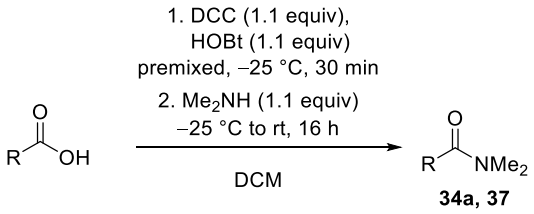
3.4 Typical Procedures

Typical Procedure 1A: Preparation of *N,N*-dimethylamides of type **22, 34** or **37** starting from the corresponding methyl or ethyl carboxylates.



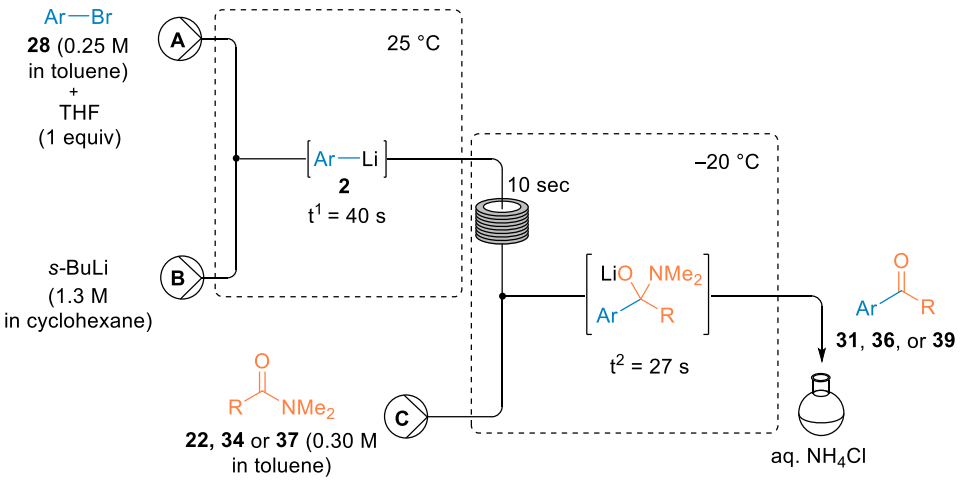
To a 1 M solution of ethyl or methyl ester in MeOH was added $Me_2NH{\cdot}HCl$ (1.5 equiv). Then, 30% NaOMe in MeOH (3.0 equiv) was added at 0 °C while stirring. After full conversion to the corresponding *N,N*-dimethylamide (checked *via* GC or TCL analysis), the reaction mixture was quenched with *sat. aq.* NH_4Cl. Methanol was removed under vacuum (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 1B: Preparation of *N,N*-dimethylamides of type **34** and **37** starting from the corresponding carboxylic acids.



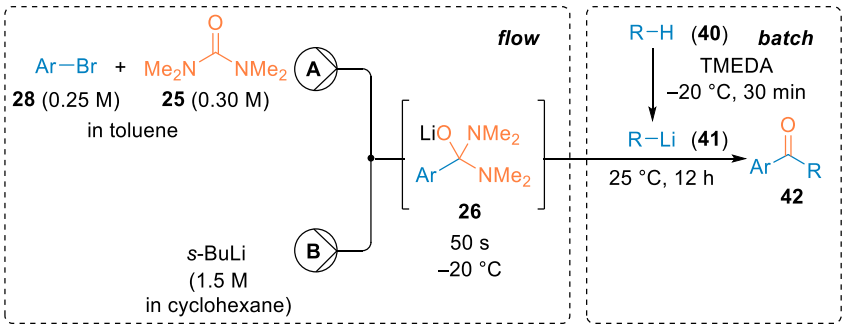
To DCC (dicyclohexylcarbodiimide, 1.1 equiv), dissolved in 60 mL of dry DCM, was added HOBt (hydroxybenzotriazole, 1.1 equiv) in one portion at 25 °C. After 20-30 min, a clear solution was obtained and cooled to –25 °C. In a separate flask, carboxylic acid (0.5 M, 1.1 equiv) was dissolved or suspended 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 a sinter to remove *N,N'*-dicyclohexylurea and the DCM layer was washed with 10% $Na_2CO_{3(aq)}$ (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*-dimethylamide.

Typical Procedure 2: A continuous flow acylation of various amides **22**, **34** or **37** with continuous flow generated aryllithiums **21** leading to polyfunctional ketones of type **31**, **36** and **39**.



A solution of **28** (0.25 M, 1.0 equiv) and THF (1.0 equiv) in toluene and a solution of *s*-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 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_{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 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 of type **31**, **36** and **39**.

Typical Procedure 3: One-pot preparation of unsymmetrical ketones of type **42** by two successive acylations of TMU (**25**) with various lithium organometallics.



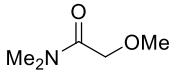
A solution of **28** (0.25 M, 1.0 equiv) and 1,1,3,3-tetramethylurea (**25**, 1.2 equiv) in toluene and a solution of *s*-BuLi in cyclohexane (1.5 M, 1.2 equiv) were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 5.0 mL·min^{-1} and flowrate B =1 mL·min^{-1}. 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_{R1} = 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 *s*-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 *i*-hexane (or pentane):EtOAc mixtures afforded the pure product of type **42**.

3.5 Preparation of Starting Materials

Preparation of *N,N*-dimethylamides of type 22, 34 and 37

2-Methoxy-*N,N*-dimethylacetamide (22b)



Following **TP1A**, 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 (**22b**) (19.4 g, 166 mmol, 83% yield) as a colorless 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).

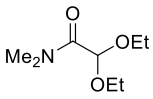
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.1, 71.5, 59.1, 36.2, 35.5.

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 (22c)



Following **TP1A**, 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 (**22c**) (19.1 mg, 108 mmol, 54% yield) as a colorless 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).

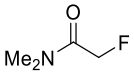
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.5, 101.1, 63.2 (2C), 36.4, 35.8, 15.1 (2C).

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 (22d)



Following **TP1A**, 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 (**22d**) (8.20 g, 78.0 mmol, 78% yield) as a colorless 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.

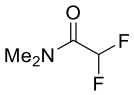
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –225.3.

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 (22e)



Following **TP1A**, 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 product was extracted with Et_2O. After drying with $MgSO_4$ over night solvents were evaporated (atmospheric pressure, 40 °C, then 200 mbar, 40 °C, 15 min) to give 2,2-difluoro-*N,N*-dimethylacetamide (**22e**) (21.3 g, 173 mmol, 87% yield) as a colorless 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).

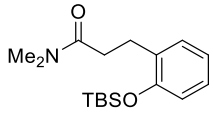
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –121.8.

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 (22g)



Following **TP1A**, 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 rt. 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 (**22g**) (10.3 g, 33.5 mmol, 67% overall yield) as a colorless 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).

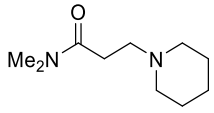
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.4, 153.5, 131.8, 130.3, 127.0, 121.0, 118.2, 36.9, 35.2, 33.2, 26.6, 25.6 (3C), 18.1, -4.3 (2C).

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 (22h)**



Following **TP1A**, 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 (**22h**) (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).

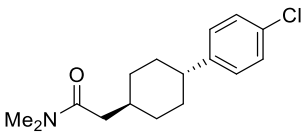
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.0, 54.8, 54.6 (2C), 37.2, 35.3, 31.2, 26.0 (2C), 24.3.

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 (22i)



Following **TP1A**, 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 (**22i**) (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).

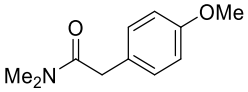
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2846, 1637, 1490, 1446, 1408, 1394, 1150, 1127, 1089, 1012, 820.

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.

2-(4-Methoxyphenyl)-*N*,*N*-dimethylacetamide (22j)



Following **TP1A**, 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 (**22j**) (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).

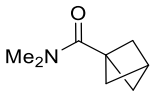
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.4, 158.4, 129.8 (2C), 127.1, 114.1 (2C), 55.3, 40.1, 37.7, 35.6.

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.

***N*,*N*-Dimethylbicyclo[1.1.1]pentane-1-carboxamide (22k)**



Bicyclo[1.1.1]pentane-1-carboxylic acid[206] (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 rt 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 (**22k**) (2.50 g, 18.0 mmol, 90% yield) as a colorless 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).

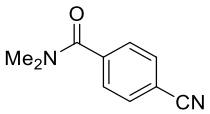
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.4, 52.6 (3C), 45.2, 37.3, 35.9, 28.6.

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 (34a)



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 rt, 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 (**34a**) (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.

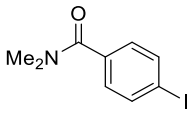
MS (EI, 70 eV): *m/z* (%) = 173 (67), 130 (100), 102 (54), 44 (18), 43 (21).

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 (34b)

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



Following **TP1A**, 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 (**34b**) (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.

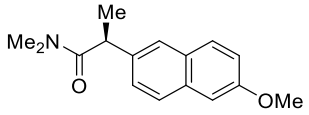
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 1622, 1584, 1475, 1393, 1264, 1080, 1006, 831, 751.

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 $[M\text{-}H]^+$.

m.p: 105.4-106.3 °C.

(*S*)-2-(6-Methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (37a)



Following **TP1B**, 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 (**37a**) (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).

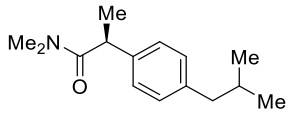
HRMS (EI): *m/z* calc. for $[C_{16}H_{19}O_2N]$: 257.1408; found 257.1416.

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 (37b)



Following **TP1B**, (*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 (**37b**) (5.13 g, 22.0 mmol, 91% yield) as a colorless 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).

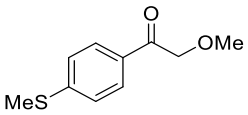
HRMS (EI): *m/z* calc. for [$C_{15}H_{23}ON$]: 233.1780; found 233.1771.

Optical rotation: $[\alpha]_D^{20}$ = 87 (c 1.09, $CHCl_3$)

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

3.6 Preparation of Products

2-Methoxy-1-(4-(methylthio)phenyl)ethan-1-one (31a)



Following **TP2**, solutions of 4-bromothioanisole (**28b**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N,N*-dimethylacetamide (**22b**) (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 **28b**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **31a** (101 mg, mmol, 82%) as a colorless 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).

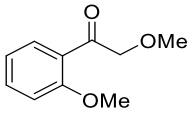
HRMS (EI): *m/z* calc. for [$C_{10}H_{12}O_2S$]:196.0558; found 196.0553.

m.p: 61.1-61.9 °C.

Scale Up of 2-Methoxy-1-(4-(methylthio)phenyl)ethan-1-one (31a)

Following **TP2**, solutions of 4-bromothioanisole (**28b**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**22b**) (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 **28b**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **31a** (1.25 g, 6.37 mmol, 78%) as a colorless solid.

2-Methoxy-1-(2-methoxyphenyl)ethan-1-one (31b)



Following **TP2**, solutions of 2-bromoanisole (**28c**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**22b**) (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 **28c**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **31b** (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.

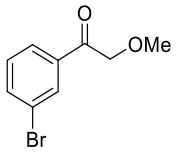
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2942, 1681, 1597, 1484, 1466, 1437, 1286, 1243, 1193, 1182, 1163, 1129, 1108, 1022, 757.

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 (31c)



Following **TP2**, solutions of 1,3-dibromobenzene (**28d**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**22b**) (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 **28d**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **31c** (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).

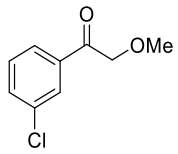
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.1, 136.6, 131.1, 130.4, 126.6, 123.2, 75.4, 59.6, 29.8.

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.

2-Methoxy-1-(2-methoxyphenyl)ethan-1-one (31d)



Following **TP2**, solutions of 1-bromo-3-chlorobenzene (**28e**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**22b**) (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 **28e**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **31d** (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.

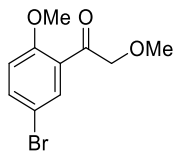
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2824, 1703, 1571, 1424, 1418, 1223, 1196, 1131, 789, 724, 681.

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.

1-(5-Bromo-2-methoxyphenyl)-2-methoxyethan-1-one (31e)



Following **TP2**, solutions of 2,4-dibromo-1-methoxybenzene (**28f**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**22b**) (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 **31e** (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.

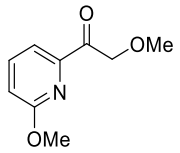
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 2822, 1684, 1588, 1479, 1463, 1439, 1395, 1269, 1247, 1177, 1138, 1116, 1016, 988, 928, 810, 661.

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 (31f)



Following **TP2**, solutions of 2-bromo-6-methoxypyridine (**28g**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**22b**) (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 **8f**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **31f** (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).

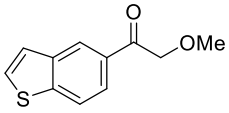
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.9, 163.4, 149.5, 139.4, 116.1, 115.1, 75.3, 59.6, 53.6.

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 (31g)



Following **TP2**, solutions of 5-bromobenzo[*b*]thiophene (**28h**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-methoxy-*N*,*N*-dimethylacetamide (**22b**) (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 **28h**. After

workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **31g** (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.

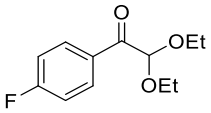
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3087, 2926, 2820, 1688, 1594, 1319, 1240, 1201, 1171, 1154, 1122, 1087, 1050, 817, 779, 755, 697.

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 (31h)



Following **TP2**, solutions of 1-bromo-4-fluorobenzene (**28i**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2,2-diethoxy-*N*,*N*-dimethylacetamide (**22c**) (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 **28i**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **31h** (104 mg, 0.46 mmol, 74%) as a colorless 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).

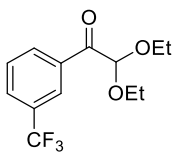
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –104.3.

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 (31i)



Following **TP2**, solutions of 1-bromo-3-(trifluoromethyl)benzene (**28j**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2,2-diethoxy-*N*,*N*-dimethylacetamide (**22c**) (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 **28j**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **31i** (130 mg, 0.47 mmol, 75%) as a colorless 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).

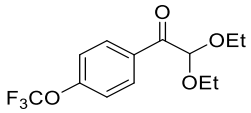
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –62.9.

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 (31j)



Following **TP2**, solutions of 1-bromo-4-(trifluoromethoxy)benzene (**28k**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2,2-diethoxy-*N*,*N*-dimethylacetamide (**22c**) (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 **22k**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **31j** (143 mg, 0.49 mmol, 78%) as a colorless 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).

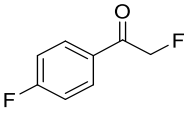
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –57.5.

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].

2-Fluoro-1-(4-fluorophenyl)ethan-1-one (31k)



Following **TP2**, solutions of 1-bromo-4-fluorobenzene (**28i**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-fluoro-*N*,*N*-dimethylacetamide (**22d**) (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 **28i**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.6:0.4) to give **31k** (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 (m), –229.39 (t, *J* = 46.9 Hz).

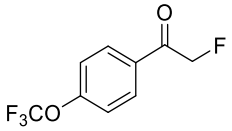
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 1698, 1683, 1593, 1507, 1407, 1231, 1163, 1158, 1102, 1081, 975, 832.

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-(4-(trifluoromethoxy)phenyl)ethan-1-one (31l)



Following **TP2**, solutions of 1-bromo-4-(trifluoromethoxy)benzene (**28k**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-fluoro-*N*,*N*-dimethylacetamide (**22d**) (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 **28k**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.6:0.4) to give **31l** (90.0 mg, 0.41 mmol, 65%) as a colorless 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).

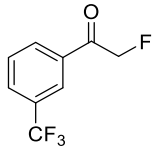
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –57.6, –229.4 (t, *J* = 46.9 Hz).

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-Fluoro-1-(3-(trifluoromethyl)phenyl)ethan-1-one (31m)



Following **TP2**, solutions of 1-bromo-3-(trifluoromethyl)benzene (**28j**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-fluoro-*N*,*N*-dimethylacetamide (**22d**) (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 **28j**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.6:0.4) to give **31m** (62.0 mg, 0.30 mmol, 48%) as a colorless 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).

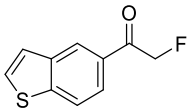
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –63.0, –229.6.

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].

1-(Benzo[*b*]thiophen-5-yl)-2-fluoroethan-1-one (31n)



Following **TP2**, solutions of 5-bromobenzo[*b*]thiophene (**28h**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-fluoro-*N*,*N*-dimethylacetamide (**22d**) (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 **28h**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **31n** (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).

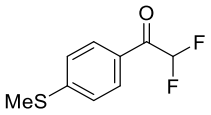
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3084, 2941, 1694, 1594, 1547, 1439, 1383, 1321, 1244, 1232, 1178, 1096, 1080, 1047, 1004, 994, 977, 897, 811, 776, 752, 717, 694, 683.

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.

2,2-Difluoro-1-(4-(methylthio)phenyl)ethan-1-one (31o)



Following **TP2**, solutions of 4-bromothioanisole (**28b**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2,2-difluoro-*N*,*N*-dimethylacetamide (**22e**) (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 **28b**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **31o** (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.

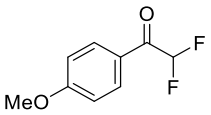
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1692, 1587, 1575, 1553, 1256, 1142, 1093, 1071, 1049, 978, 969, 964, 956, 870, 815, 747, 672.

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-(4-methoxyphenyl)ethan-1-one (31p)



Following **TP2**, solutions of 4-bromoanisole (**28a**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2,2-difluoro-*N*,*N*-dimethylacetamide (**22e**) (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 **22a**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **31p** (86.0 mg, 0.46 mmol, 74%) as a colorless 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.

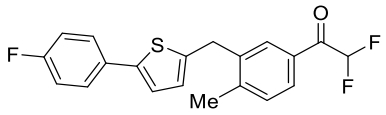
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –121.4 (d, *J* = 53.6 Hz).

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-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)ethan-1-one (31q)



Following **TP2**, solutions of 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (**28l**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2,2-difluoro-*N*,*N*-dimethylacetamide (**22e**) (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 **28l**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9:1) to give **31q** (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 – –114.9 (m), –121.8 (d, *J* = 53.7 Hz).

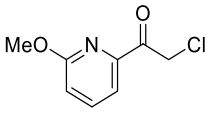
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1705, 1704, 1699, 1694, 1605, 1508, 1231, 1159, 1098, 1057, 833, 809, 802.

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 (31r)



Following **TP2**, solutions of 2-bromo-6-methoxypyridine (**28g**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-chloro-*N*,*N*-dimethylacetamide (**22f**) (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 **28g**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **31r** (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.

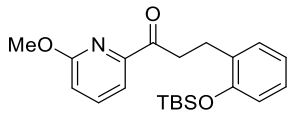
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 1709, 1601, 1589, 1470, 1430, 1380, 1346, 1285, 1209, 1187, 1155, 1041, 1010, 986, 808, 781, 735, 729.

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 (31s)



Following **TP2**, solutions of 2-bromo-6-methoxypyridine (**28g**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 3-(2-((*tert*-butyldimethy-lsilyl)oxy)phenyl)-*N*,*N*-dimethylpropanamide (**22g**) (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 **28g**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **31s** (161 mg, 0.43 mmol, 69%) as a colorless 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).

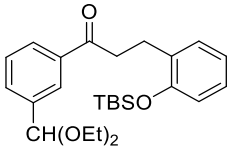
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 201.3, 163.4, 153.9, 151.1, 139.2, 132.3, 130.6, 127.2, 121.2, 118.5, 115.3, 115.0, 53.6, 38.2, 25.9, 25.3 (3C), 18.3, -4.0 (2C).

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 (31t)



Following **TP2**, solutions of 1-bromo-3-(diethoxymethyl)benzene (**28m**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 3-(2-((*tert*-butyldimethyl-silyl)oxy)phenyl)-*N*,*N*-dimethylpropanamide (**22g**) (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 **28m**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **31t** (225 mg, 0.51 mmol, 81%) as a colorless 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).

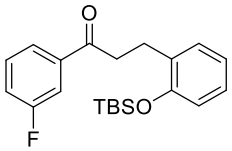
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.6, 153.9, 139.9, 137.2, 131.9, 131.3, 130.6, 128.6, 128.0, 127.3, 126.5, 121.3, 118.6, 101.2, 61.3 (2C), 39.0, 25.9 (3C), 25.6, 18.3, 15.3 (2C), -4.0 (2C).

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 (31u)



Following **TP2**, solutions of 1-bromo-3-fluorobenzene (**28n**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 3-(2-((*tert*-butyldimethy-lsilyl)oxy)phenyl)-*N*,*N*-dimethylpropanamide (**22g**) (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 **28n**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **31u** (176 mg, 0.49 mmol, 78%) as a colorless 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).

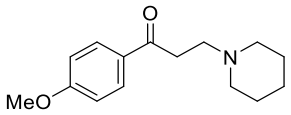
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –112.0.

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 (31v)



Following **TP2**, solutions of 4-bromoanisole (**28a**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and *N*,*N*-dimethyl-3-(piperidin-1-yl)propanamide (**22h**) (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 **28a**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 4:6) to give **31v** (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.

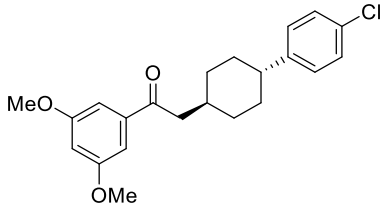
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 2841, 1672, 1598, 1575, 1509, 1304, 1256, 1241, 1208, 1167, 1154, 1109, 1028, 977, 836.

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 (31w)



Following **TP2**, solutions of 1-bromo-3,5-dimethoxybenzene (**28o**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-((1*r*,4*r*)-4-(4-chlorophenyl)-cyclohexyl)-*N*,*N*-dimethylacetamide (**22i**) (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 **28o**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.7:0.3) to give **31w** (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).

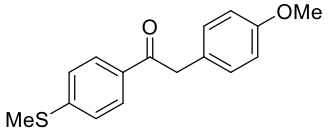
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920, 2843, 1686, 1682, 1601, 1591, 1492, 1454, 1447, 1424, 1356, 1314, 1296, 1204, 1153, 1089, 1065, 1028, 1013, 909, 846, 829, 730, 719, 715, 679.

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 (31x)



Following **TP2**, solutions of 4-bromothioanisole (**28b**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-(4-methoxyphenyl)-*N*,*N*-dimethylacetamide (**31y**) (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 **28b**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **31x** (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.

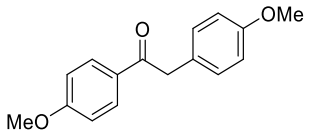
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2833, 2364, 1681, 1586, 1518, 1250, 1034, 824, 813, 795, 668.

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 (31y)



Following **TP2**, solutions of 4-bromoanisole (**28a**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 2-(4-methoxyphenyl)-*N*,*N*-dimethylacetamide (**22j**) (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 **28a**. After workup,

the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.2:0.8) to give **31y** (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.

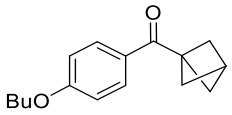
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2904, 2836, 1679, 1601, 1578, 1514, 1257, 1249, 1228, 1202, 1174, 1031, 994, 828, 807.

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 (31z)



Following **TP2**, solutions of 1-bromo-4-butoxybenzene (**28p**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and *N*,*N*-dimethylbicyclo[1.1.1]pentane-1-carboxamide (**22k**) (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 **28p**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **31z** (91.0 mg, 0.37 mmol, 59%) as a colorless 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).

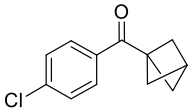
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.9, 163.0, 131.4, 129.4, 114.2, 68.0, 53.5 (3C), 49.5, 31.3, 28.5, 19.3, 13.9.

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 (31aa)



Following **TP2**, solutions of 1-bromo-3-chlorobenzene (**28r**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and *N*,*N*-dimethylbicyclo[1.1.1]pentane-1-carboxamide (**22k**) (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 **28r**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **31aa** (90.0 mg, 0.44 mmol, 70%) as a colorless 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).

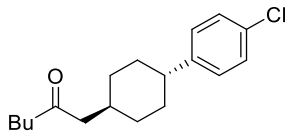
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.2, 139.4, 134.9, 130.5, 128.9, 53.5 (3C), 49.4, 28.7.

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 (31ab)



A solution of 2-((1*r*,4*r*)-4-(4-chlorophenyl)-cyclohexyl)-*N*,*N*-dimethylacetamide (**22i,** 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 $mL \cdot min^{-1}$ and flowrate B = 5.0 $mL \cdot min^{-1}$. The solutions passed a PTFE reactor tube (i.d = 0.8 mm, Vol_{R1} = 2 mL; residence time: t = 24 s, 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 s, 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 **31ab** (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.

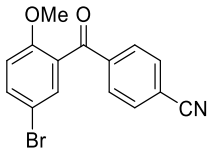
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2871, 2849, 1698, 1491, 1406, 1380, 1355, 1128, 1089, 1046, 1012, 960, 823.

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 (36a)



Following **TP2**, solutions of 2,4-dibromo-1-methoxybenzene (**28f**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 4-cyano-*N*,*N*-dimethylbenzamide (**34a**) (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 **28f**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **36a** (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.

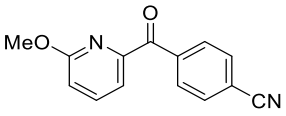
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2935, 2840, 2229, 1672, 1590, 1480, 1460, 1408, 1391, 1293, 1289, 1259, 1235, 1182, 1121, 1020, 949, 937, 859, 818, 770, 675.

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 (36b)



Following **TP2**, solutions of 2-bromo-6-methoxypyridine (**28g**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 4-cyano-*N*,*N*-dimethylbenzamide (**34a**) (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 **28g**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **36b** (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.

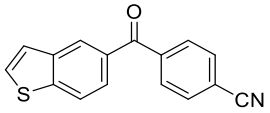
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2991, 2949, 2230, 1662, 1590, 1464, 1336, 1290, 1267, 1151, 1031, 989, 974, 868, 851, 814, 762.

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 (36c)



Following **TP2**, solutions of 5-bromobenzo[*b*]thiophene (**28h**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 4-cyano-*N*,*N*-dimethylbenzamide (**34a**) (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 **28h**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.5:0.5) to give **36c** (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.

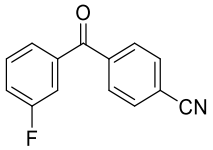
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 2229, 1651, 1592, 1402, 1325, 1289, 1274, 1251, 1198, 1088, 1048, 979, 956, 853, 817, 758, 728, 712, 691.

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 (36d)



Following **TP2**, solutions of 1-bromo-3-fluorobenzene (**28n**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 4-cyano-*N*,*N*-dimethylbenzamide (**34a**) (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 **28n**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.3:0.7) to give **36d** (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.

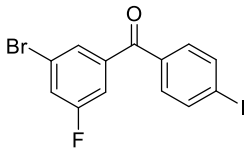
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3069, 2232, 1664, 1585, 1482, 1440, 1404, 1311, 1294, 1277, 1272, 1208, 857, 839, 758, 710.

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 (36e)



Following **TP2**, solutions of 1,3-dibromo-5-fluorobenzene (**28q**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 4-iodo-*N*,*N*-dimethylbenzamide (**34b**) (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 **28q**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **36e** (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.

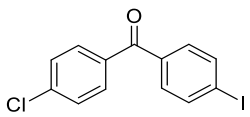
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 1661, 1575, 1557, 1427, 1390, 1304, 1278, 1214, 1179, 1001, 989, 864, 835, 766, 750, 658.

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 (36f)



Following **TP2**, solutions of 1-bromo-4-chlorobenzene (**28r**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and 4-iodo-*N*,*N*-dimethylbenzamide (**34b**) (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 **28r**. After workup,

the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **36f** (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.

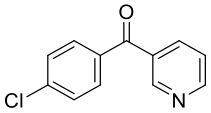
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1643, 1580, 1391, 1306, 1302, 1287, 1282, 1093, 1058, 1015, 1008, 926, 905, 853, 825, 748, 730, 665.

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 (36g)



Following **TP2**, solutions of 1-bromo-4-chlorobenzene (**28r**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and *N*,*N*-diethylnicotinamide (**34c**) (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 **28r**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 7:3) to give **36g** (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.

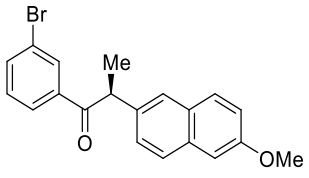
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3050, 1644, 1581, 1570, 1484, 1418, 1401, 1337, 1299, 1282, 1149, 1093, 1024, 1011, 935, 923, 850, 845, 819, 745, 711, 678.

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 (39a)



Following **TP2**, solutions of 1,3-bromobenzene (**28d**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (**37a**) (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 **28d**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **39a** (173 mg, 0.47 mmol, 75%, 99% *ee*) as a colorless 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.

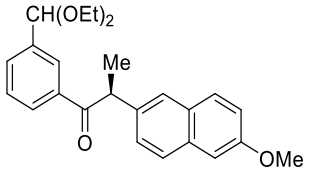
MS (EI, 70 eV): *m/z* (%) = 185 (100), 170 (24), 153 (10), 141 (12).

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 (39b)



Following **TP2**, solutions of 1-bromo-3-(diethoxymethyl)benzene (**28m**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (**37a**) (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 **28m**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **39b** (159 mg, 0.41 mmol, 65%, 99% *ee*) as a colorless 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.

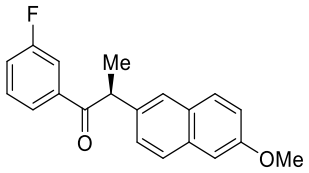
MS (EI, 70 eV): *m/z* (%) = 207 (11), 185 (100), 183 (17), 170 (24), 153 (13).

HRMS (EI): *m/z* calc. for [$C_{25}H_{28}O_4$]: 392.1988, found 392.1984.

Optical rotation: $[\propto]_D^{20}$ = 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 (39c)



Following **TP2**, solutions of 1-bromo-3-fluorobenzene (**28n**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (**37a**) (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 **28n**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **14an** (170 mg, 0.55 mmol, 88%, 99% *ee*) as a colorless 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.

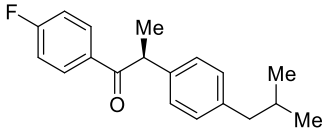
MS (EI, 70 eV): *m/z* (%) = 185 (100), 170 (42), 154 (14), 153 (21), 141 (16).

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 (39d)



Following **TP2**, solutions of 1-bromo-4-fluorobenzene (**28i**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(4-*iso*butylphenyl)-*N*,*N*-dimethylpropanamide (**37b**) (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 **28i**.

After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.8:0.2) to give **39d** (150 mg, 0.50 mmol, 80%, 99% *ee*) as a colorless 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.

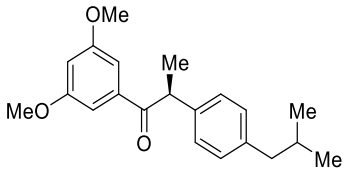
MS (EI, 70 eV): *m/z* (%) = 162 (13), 161 (100), 123 (57), 119 (20), 117 (14), 105 (13), 91 (11).

HRMS (EI): *m/z* calc. for [$C_{19}H_{21}OF$]: 284.1576; found 284.1571.

Optical rotation: $[\alpha]_D^{20}$ = 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 (39e)



Following **TP2**, solutions of 1-bromo-3,5-dimethoxybenzene (**28o**) (0.25 M, 1.0 equiv) with THF (1.0 equiv) in toluene, *s*-BuLi (1.4 M, 1.2 equiv) and (*S*)-2-(4-*iso*butylphenyl)-*N*,*N*-dimethylpropanamide (**37b**) (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 **28o**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **39e** (160 mg, 0.47 mmol, 75%, 99% *ee*) as a colorless 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.

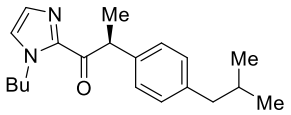
MS (EI, 70 eV): *m/z* (%) = 165 (100), 137 (24), 122 (10).

HRMS (EI): *m/z* calc. for [$C_{21}H_{26}O_3$]: 326.1877; found 326.1882.

Optical rotation: $[\alpha]_D^{20}$ = 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 (39f)



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 *s*-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 s, T = –20 °C) for precooling the reaction mixture. A (*S*)-2-(4-*iso*butylphenyl)-*N*,*N*-dimethylpropanamide (**37b**) 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 **39f** (174 mg, 0.56 mmol, 89%, 98% *ee*) as a colorless 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.

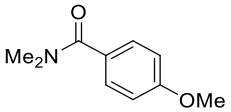
MS (EI, 70 eV): *m/z* (%) = 311 (100), 295 (52), 283 (24), 255 (31), 161 (42), 151 (50), 123 (35), 117 (52), 91 (27).

HRMS (EI): *m/z* calc. for [$C_{20}H_{28}ON_2$]: 312.2197; found 312.2202.

Optical rotation: $[\alpha]_D^{20}$ = 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 (27)



Following **TP3**, solutions of 4-bromoanisole (**28a**) (0.25 M, 1.0 equiv) plus tetramethylurea **25** (0.3 M, 1.2 equiv) in toluene and *s*-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 **28a**. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate= 9.9:0.1) to give **27** (93.0 mg, 0.52 mmol, 83%) as a colorless 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).

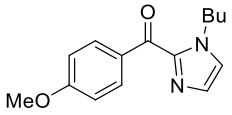
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.7, 160.8, 129.3 (2C), 128.4, 113.7 (2C), 55.5.

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 (42a)



Following **TP3**, solutions of 4-bromoanisole (**28a**) (0.25 M, 1.0 equiv) plus tetramethylurea **25** (0.3 M, 1.2 equiv) in toluene and *s*-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-butyl-1H-imidazole (1.00 mmol, 1.6 equiv) plus TMEDA (1.00 mmol, 1.6 equiv) in toluene and *s*-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 **42a** (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).

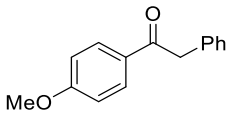
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 183.0, 163.5, 143.1, 133.4 (2C), 130.5, 129.1, 125.3, 113.6 (2C), 55.6, 48.7, 33.5, 20.0, 13.8.

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-(4-Methoxyphenyl)-2-phenylethan-1-one (42b)



Following **TP3**, solutions of 4-bromoanisole (**28a**) (0.25 M, 1.0 equiv) plus tetramethylurea **25** (0.3 M, 1.2 equiv) in toluene and *s*-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 toluene plus TMEDA (1.00 mmol, 1.6 equiv) and *s*-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 **42b** (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.

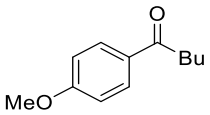
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2932, 2838, 1676, 1670, 1667, 1598, 1574, 1509, 1257, 1223, 1167, 1029, 990, 828, 727, 705, 696.

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 (42c)



Following **TP3**, solutions of 4-bromoanisole (**28a**) (0.25 M, 1.0 equiv) plus tetramethylurea **4** (0.3 M, 1.2 equiv) in toluene and *s*-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 **42c** (84.0 mg, 0.44 mmol, 70%) as a colorless 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).

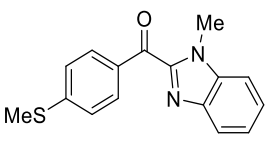
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.3, 163.3, 130.3 (2C), 113.7 (2C), 55.5, 38.0, 26.8, 22.6, 14.0.

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.

(1-Methyl-1H-benzo[*d*]imidazol-2-yl)(4-(methylthio)phenyl)methanone (42d)



Following **TP3**, solutions of 4-bromothioanisole (**28b**) (0.25 M, 1.0 equiv) plus tetramethylurea **25** (0.3 M, 1.2 equiv) in toluene and *s*-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) and TMEDA (1.00 mmol, 1.6 equiv) in toluene and *s*-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 **42d** (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).

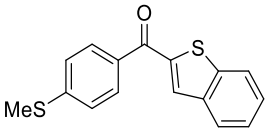
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 185.3, 147.0, 147.0, 142.0, 136.7, 133.2, 131.8 (2C), 125.7, 125.0 (2C), 123.7, 122.1, 110.5, 32.4, 14.9.

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 $[M-H]^+$.

Benzo[*b*]thiophen-2-yl(4-(methylthio)phenyl)methanone (42e)



Following **TP3**, solutions of 4-bromothioanisole (**28b**) (0.25 M, 1.0 equiv) plus tetramethylurea **25** (0.3 M, 1.2 equiv) in toluene and *s*-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) and TMEDA (1.00 mmol, 1.6 equiv) in toluene and *s*-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 **42e** (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.

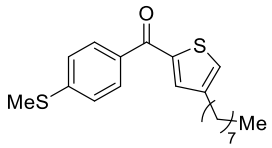
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 2917, 1621, 1589, 1513, 1296, 754, 742, 727, 723.

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 (5f)



Following **TP3**, solutions of 4-bromothioanisole (**28b**) (0.25 M, 1.0 equiv) plus tetramethylurea **25** (0.3 M, 1.2 equiv) in toluene and *s*-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) and TMEDA (1.00 mmol, 1.6 equiv) in toluene and *s*-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 **5f** (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.

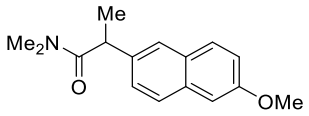
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2853, 1629, 1589, 1418, 1290, 1185, 1087, 855.

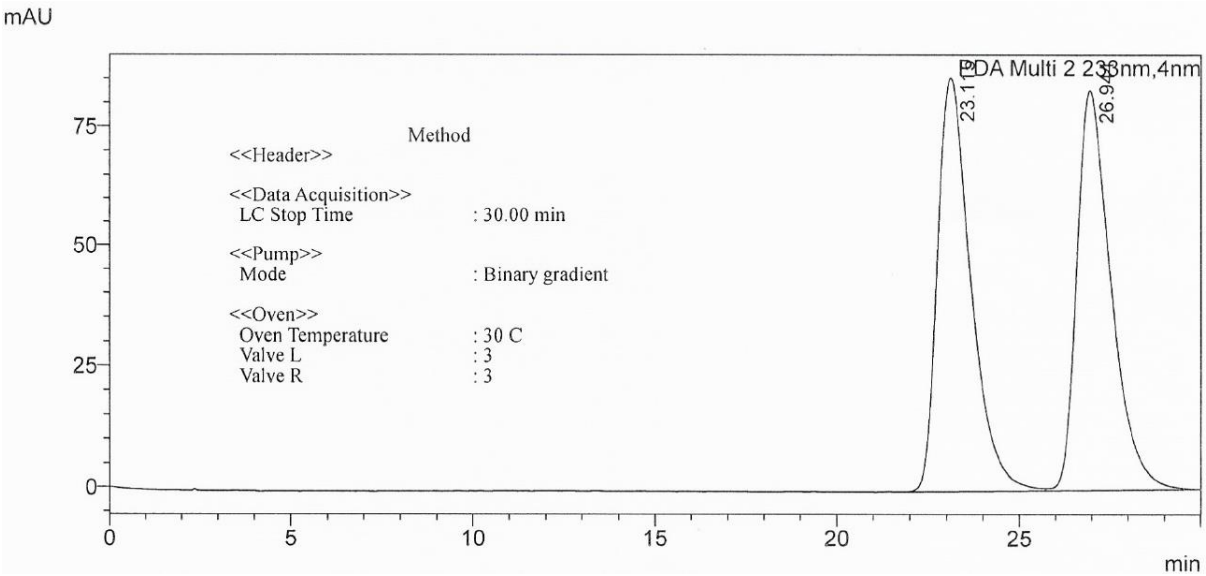
MS (EI, 70 eV): *m/z* (%) = 346 (16), 248 (41), 247 (14), 151 (100).

HRMS (EI): *m/z* calc. for [$C_{20}H_{26}OS_2$]: 346.1425; found 346.1420.

3.7 Chiral HPLC Analysis

(*R/S*)-2-(6-Methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (*rac*-37a)





PDA Ch2 233nm

Peak#	Ret. Time	Area	Height	Area%
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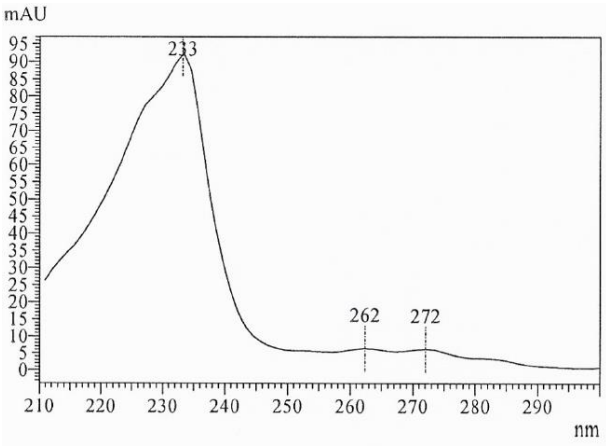
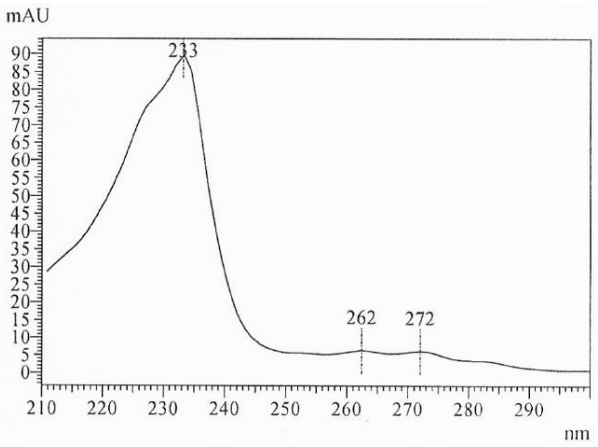
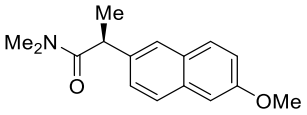
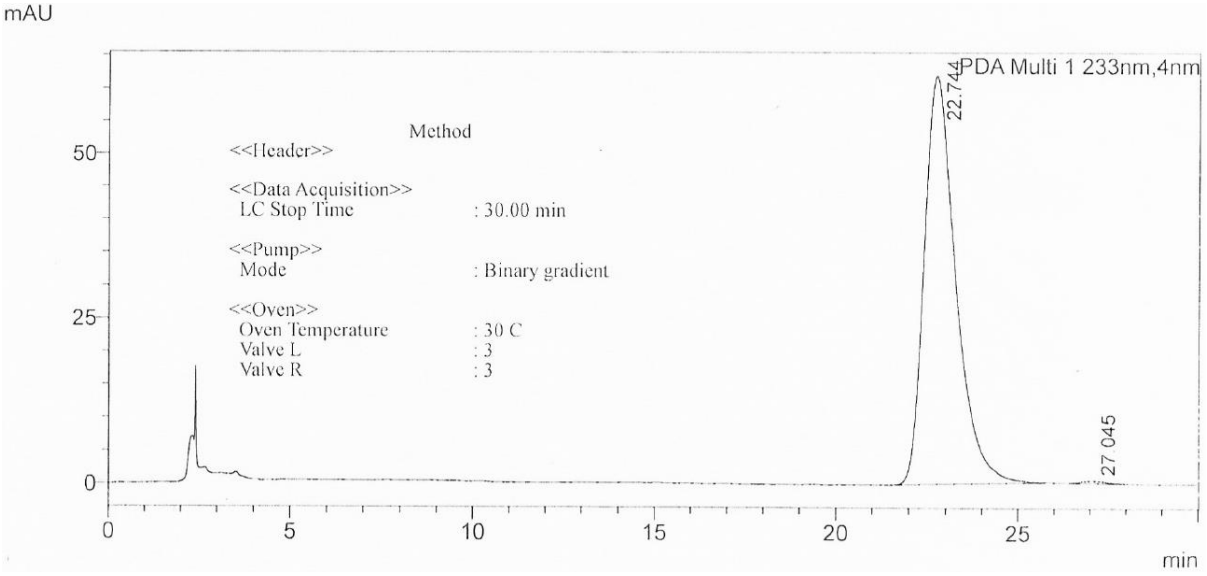
2	26.944	5448902	83150	50.010
Total		10895629	169048	100.000





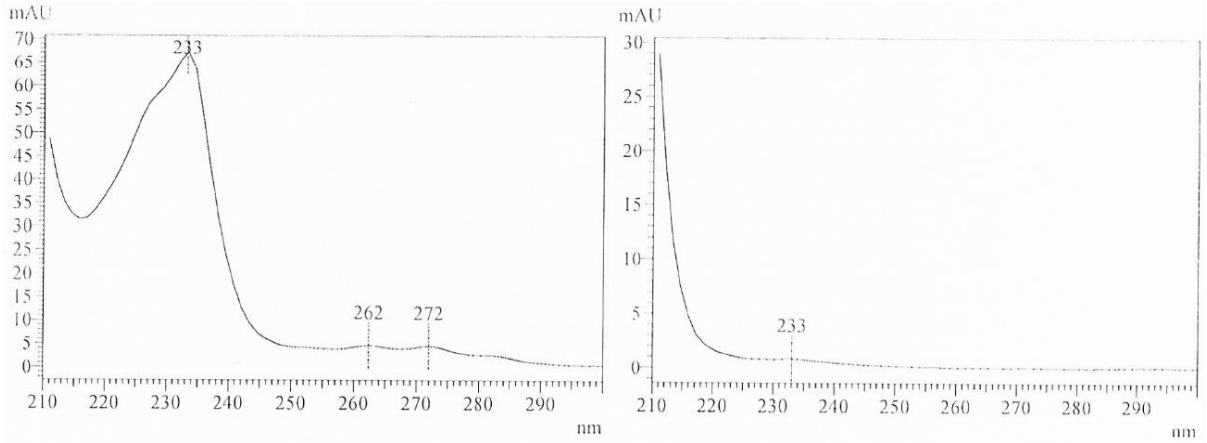
(*S*)-2-(6-Methoxynaphthalen-2-yl)-*N*,*N*-dimethylpropanamide (37a)



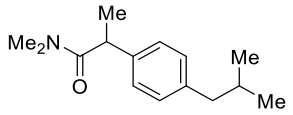


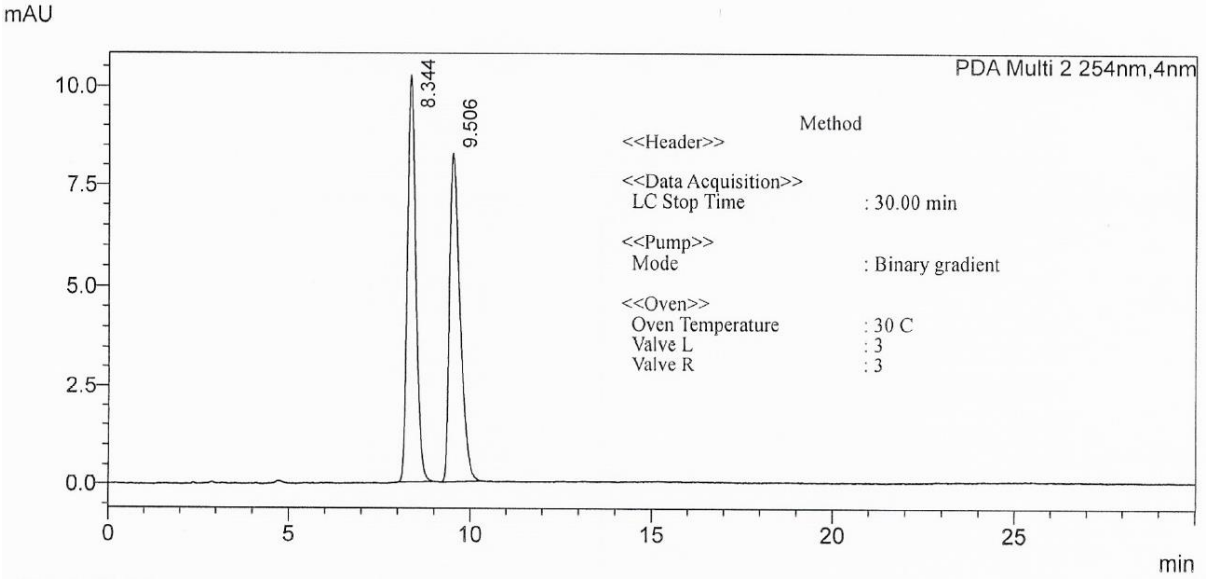
PDA Ch1 233nm

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



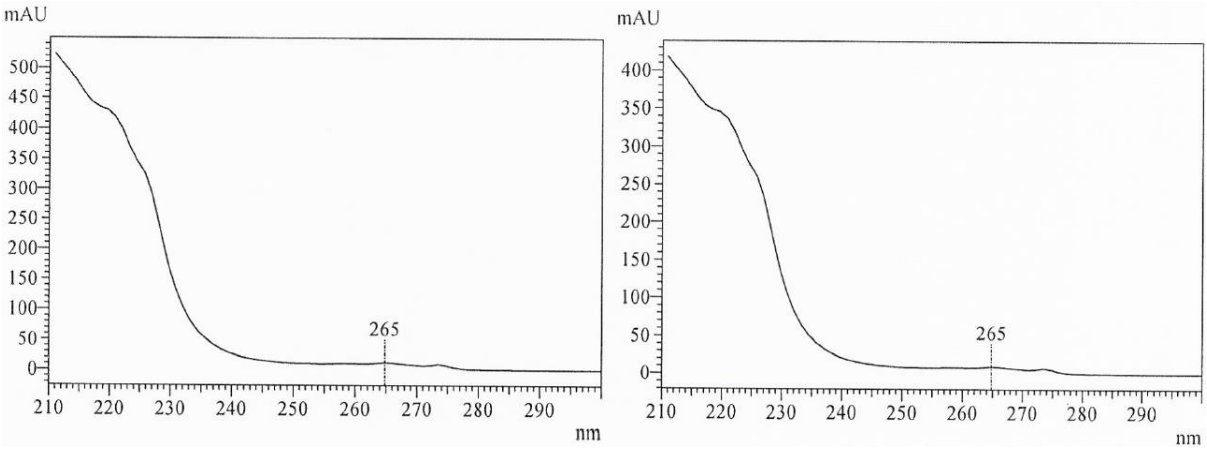
(*R/S*)-2-(4-*Iso*butylphenyl)-*N*,*N*-dimethylpropanamide (*rac*-37b)



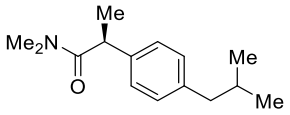


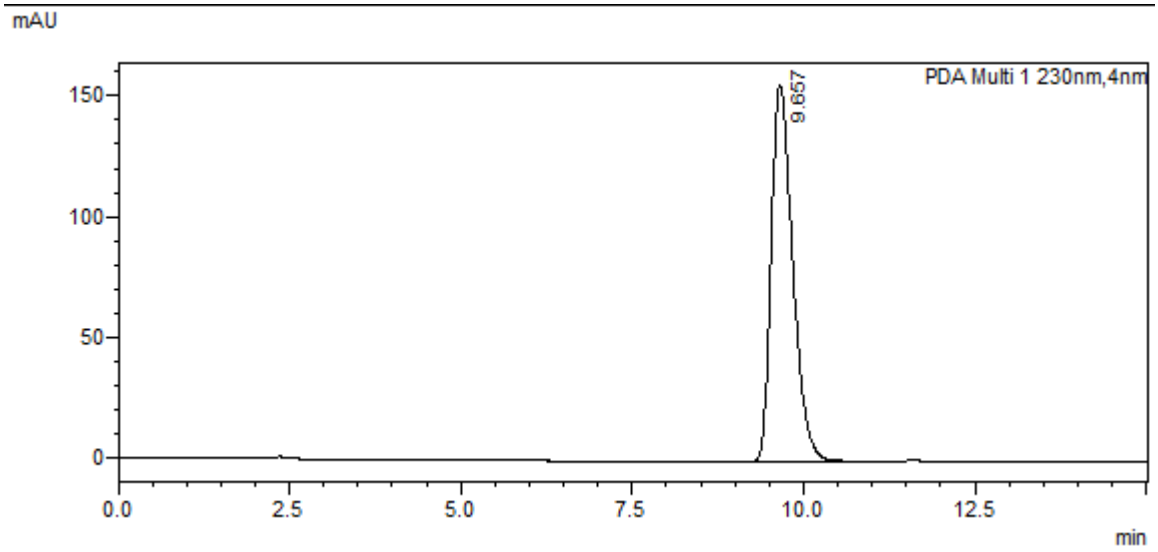
PDA Ch2 254nm

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 (37b)

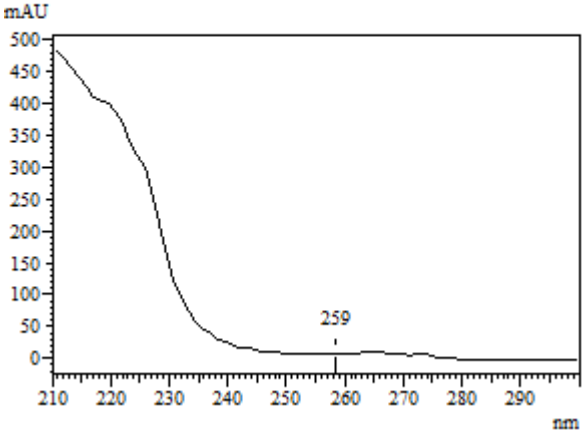




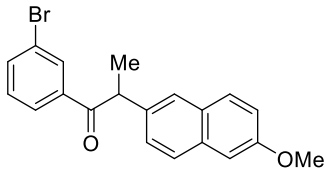
PDA Ch1 230nm

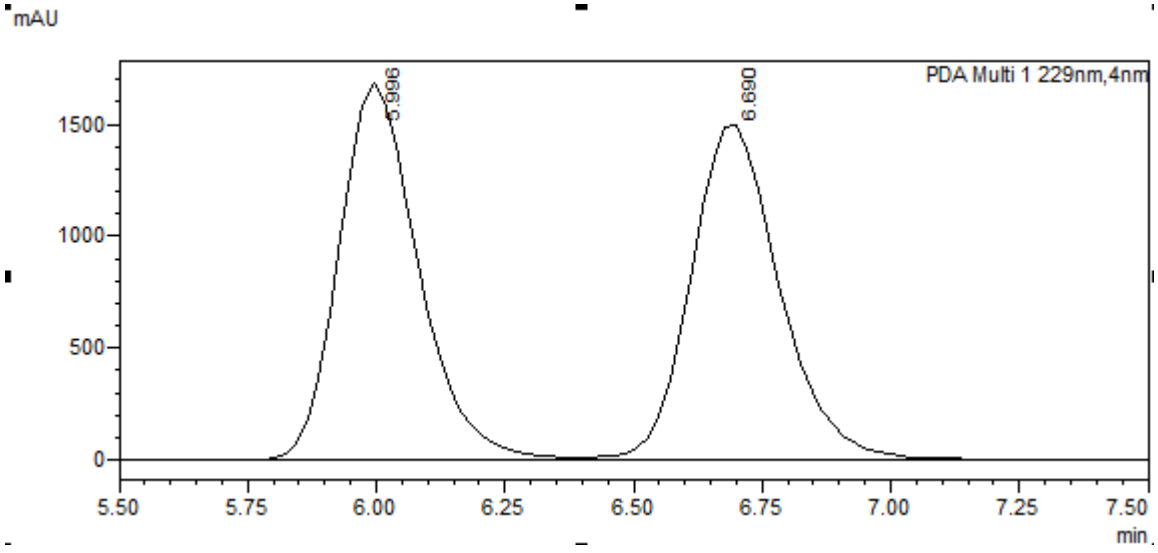
Peak#	Ret. Time	Area	Height	Area%
1	9.657	3409172	156051	100.000
Total		3409172	156051	100.000

UV Spectrum
Peak# : 1 Retention Time : 9.657 min
Lambda max : 259/488/433/390/604



(*R/S*)-1-(3-Bromophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (*rac*-39a)





PDA Ch1 229nm

Peak#	Ret. Time	Area	Height	Area%
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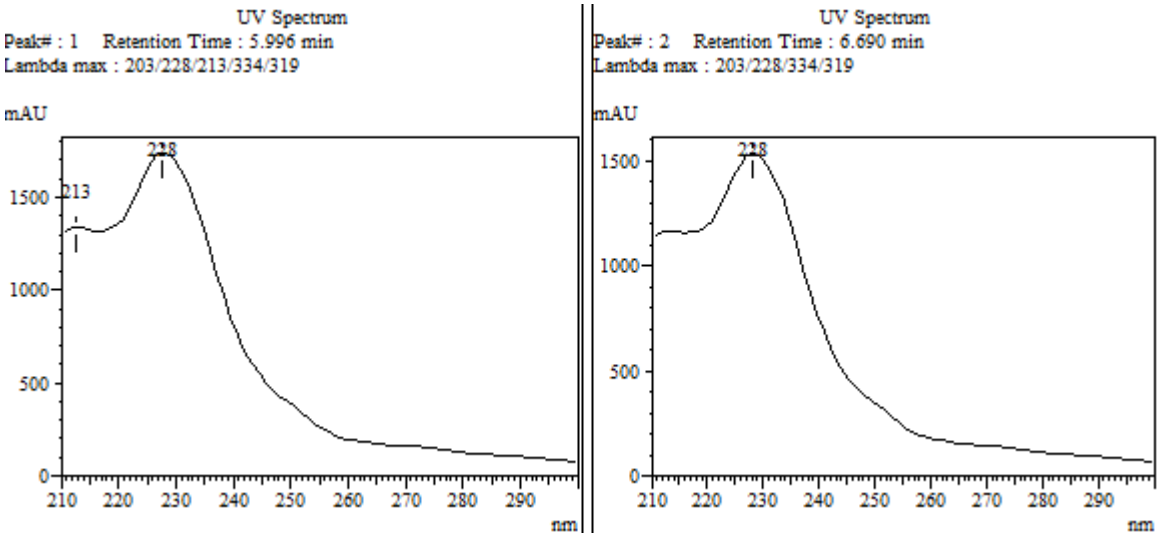
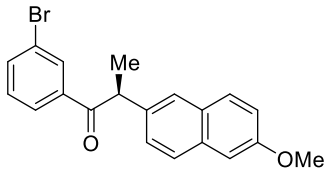
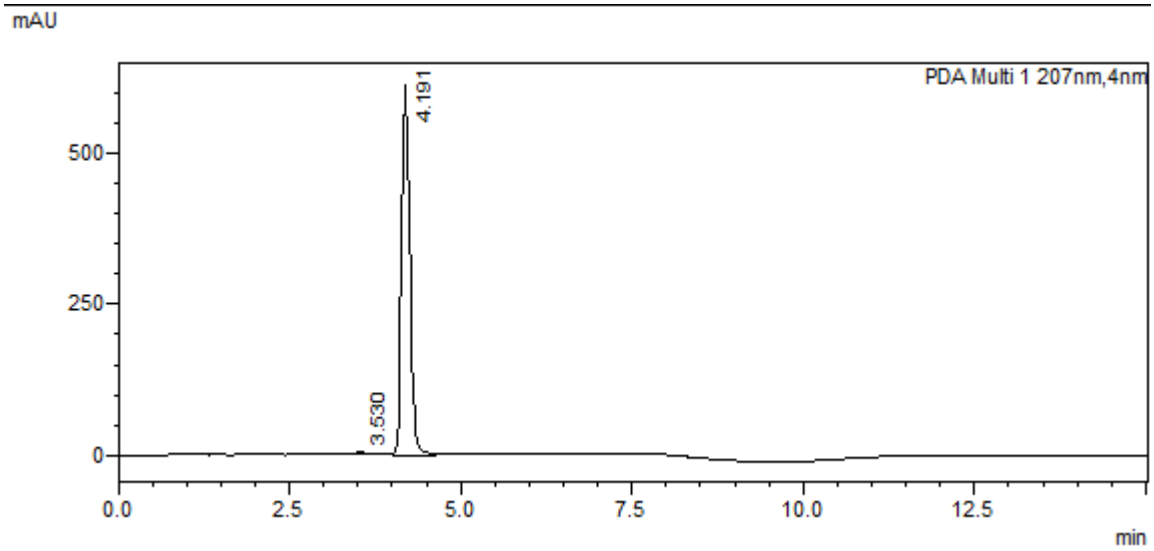
2	6.690	18082376	1495748	49.984
Total		36176356	3180965	100.000



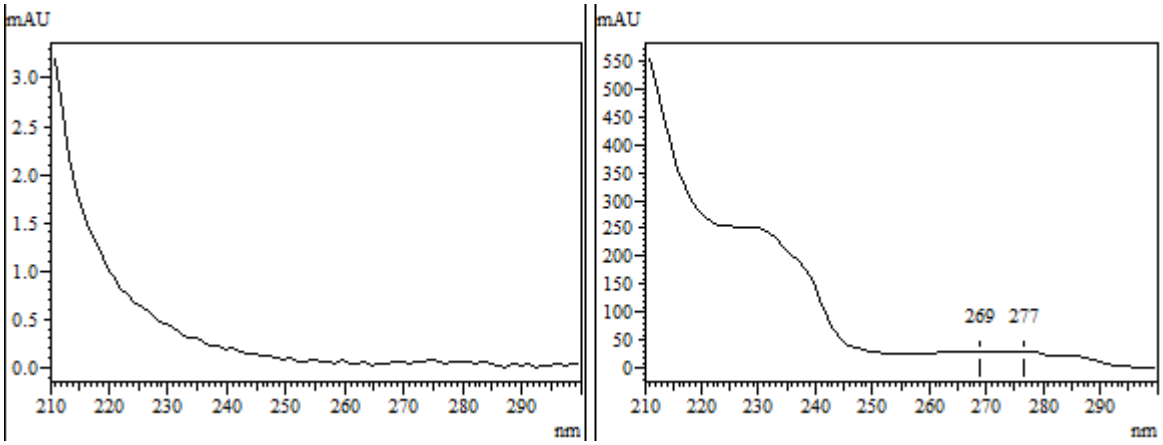
(*S*)-1-(3-Bromophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (39a)



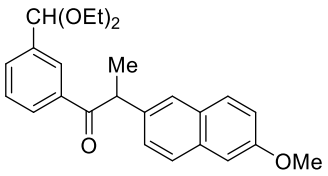


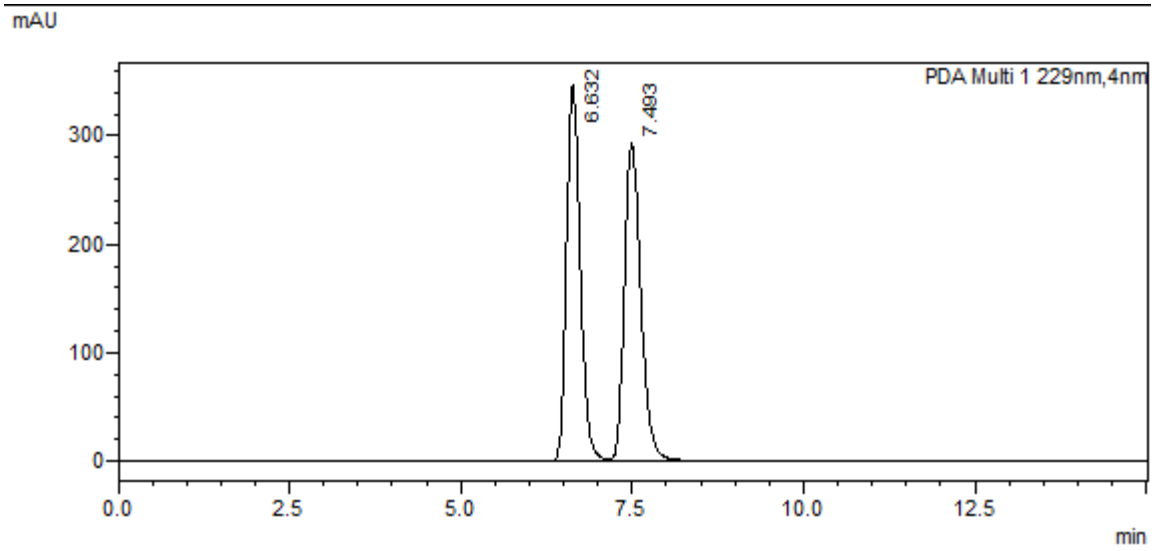
PDA Ch1 207nm

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



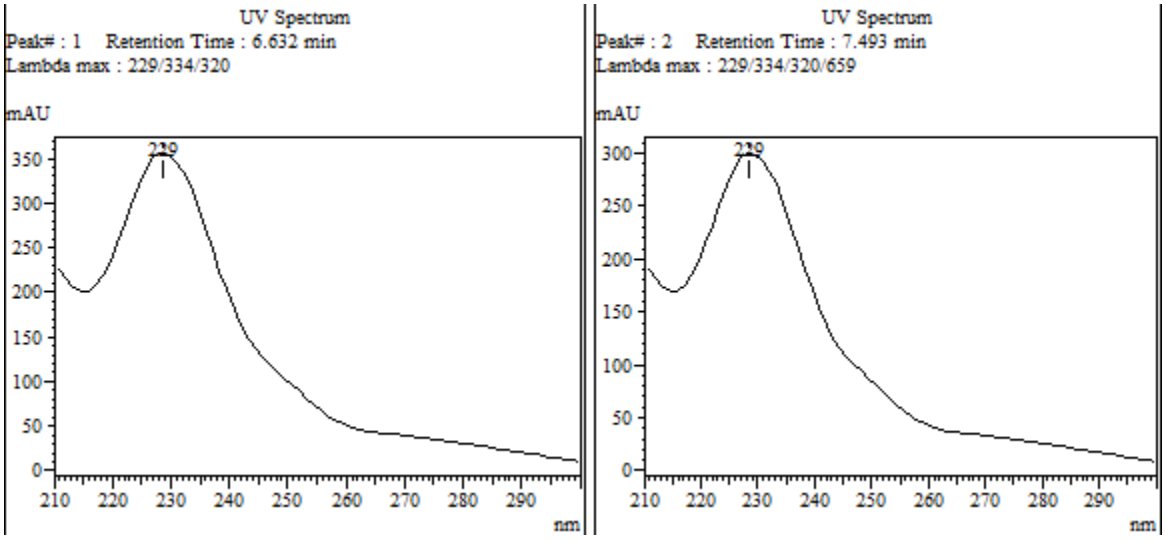
(*R/S*)-1-(3-(Diethoxymethyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (*rac*-39b)



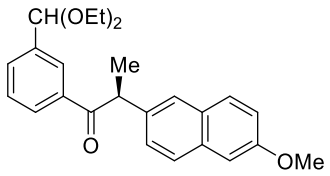


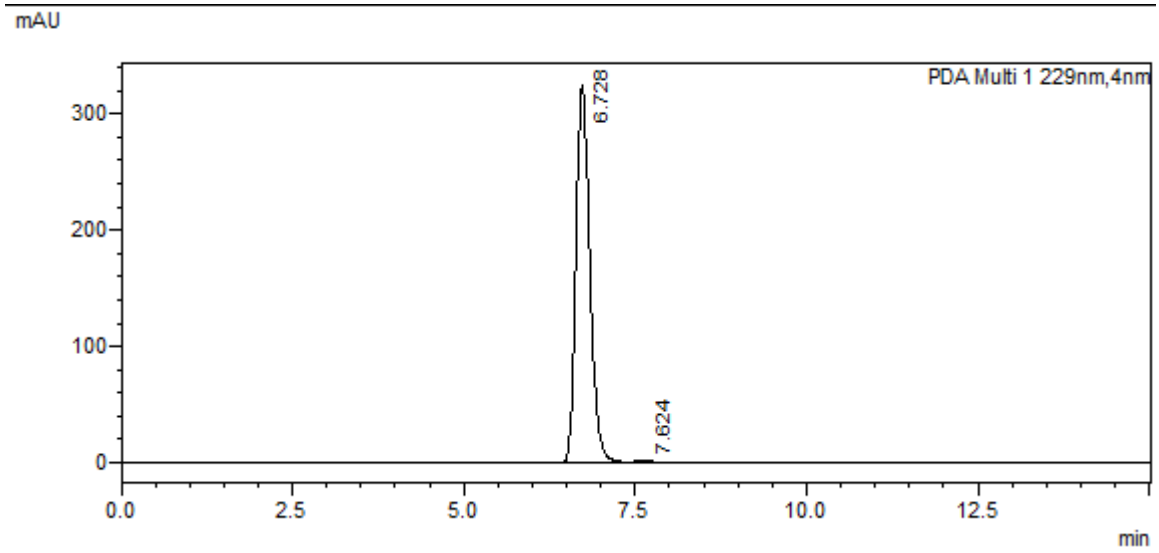
PDA Ch1 229nm

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



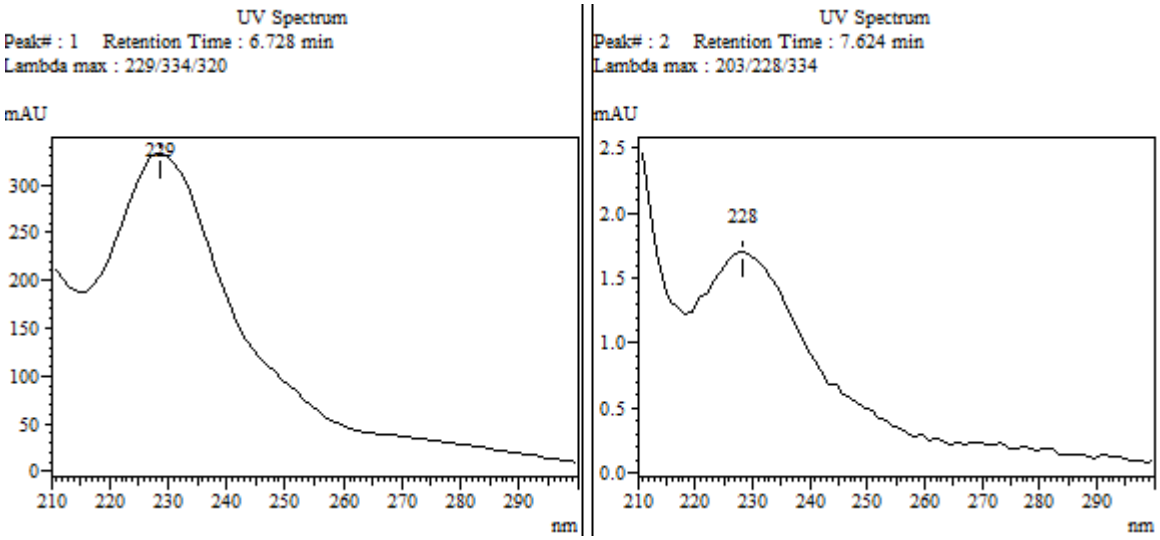
(*S*)-1-(3-(Diethoxymethyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (39b)



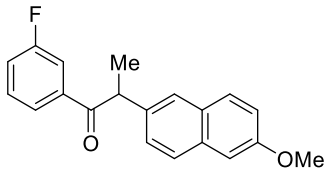


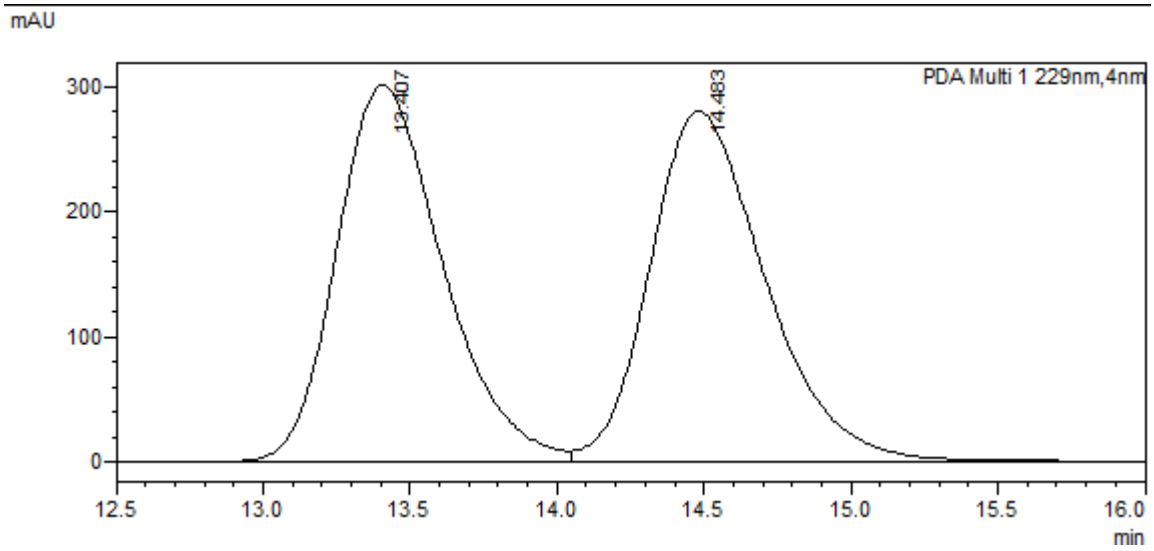
PDA Ch1 229nm

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



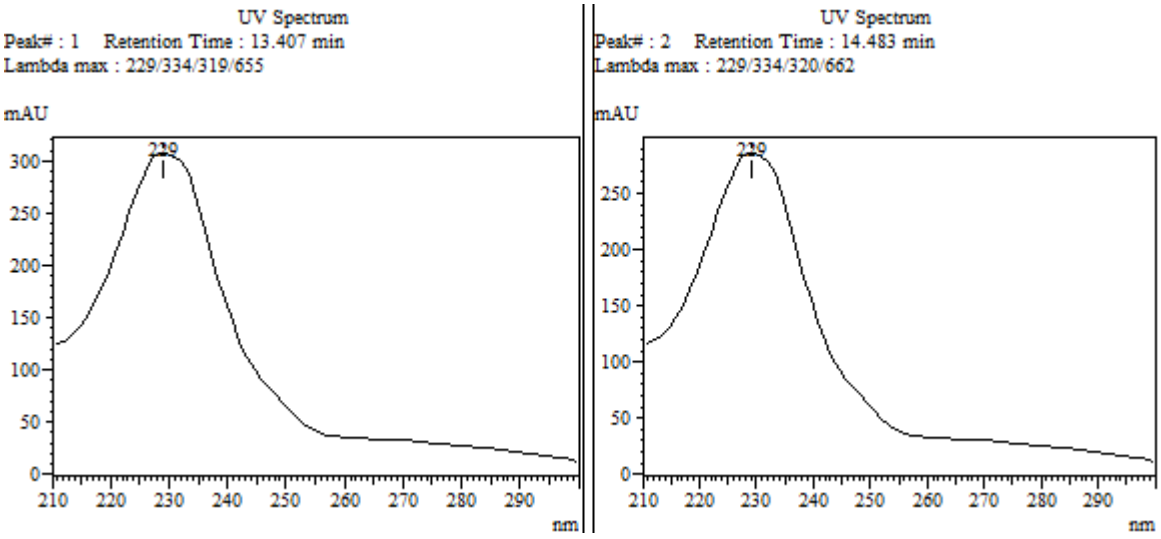
(*R*/*S*)-1-(3-Fluorophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (*rac*-39c)



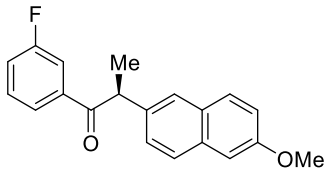


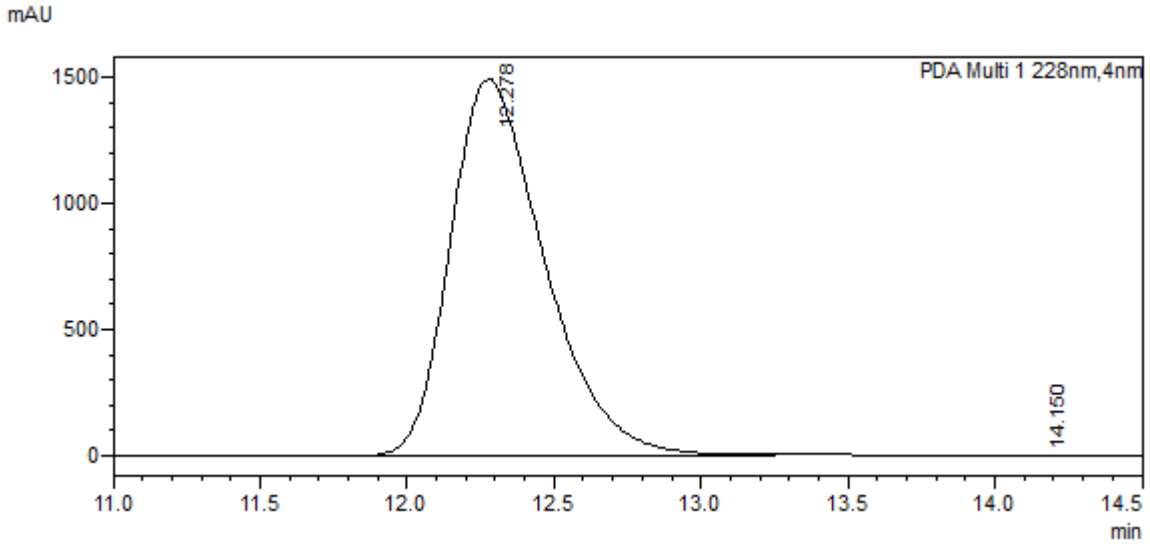
PDA Ch1 229nm

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



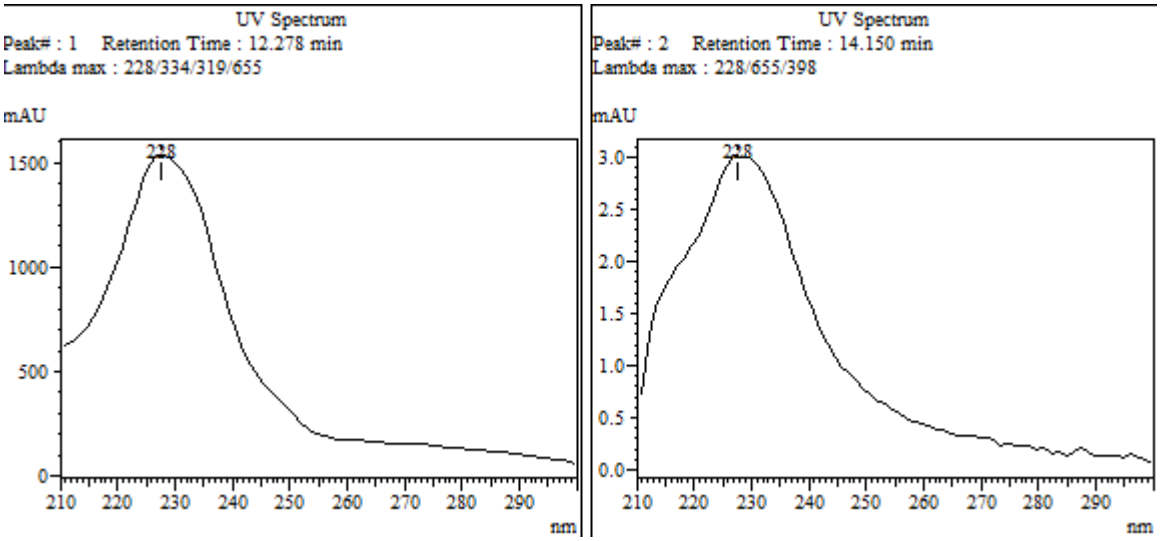
(*S*)-1-(3-Fluorophenyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (39c)



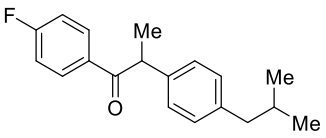


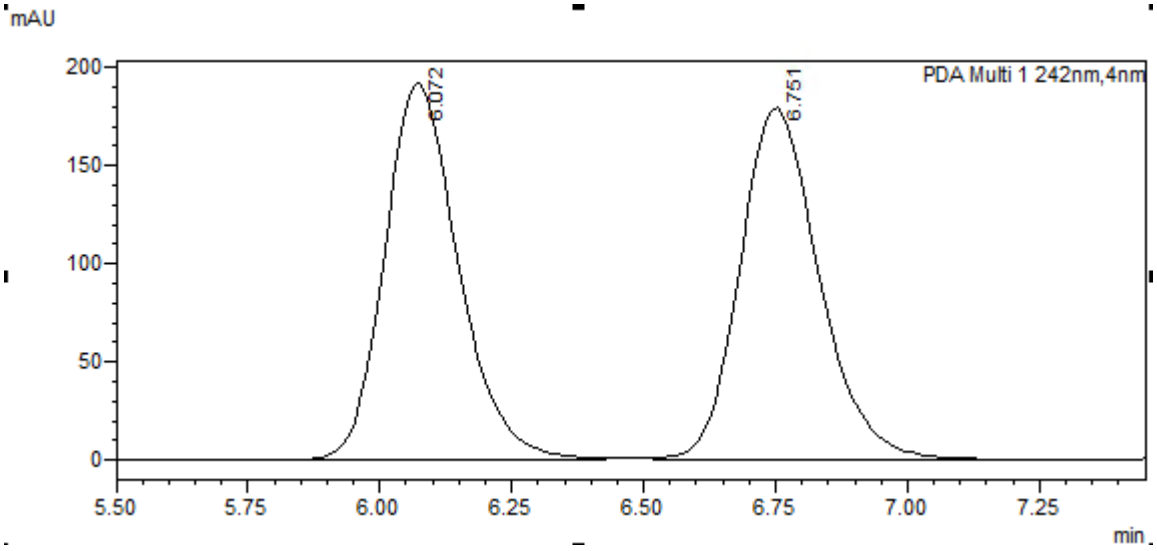
PDA Ch1 228nm

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



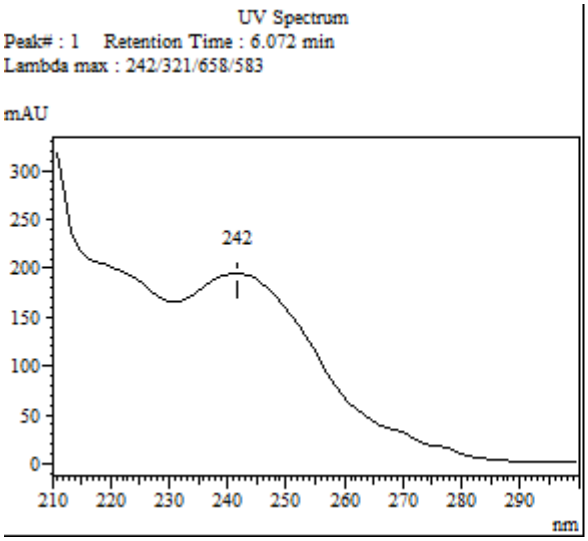
(*R/S*)-1-(4-Fluorophenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one (*rac*-39d)

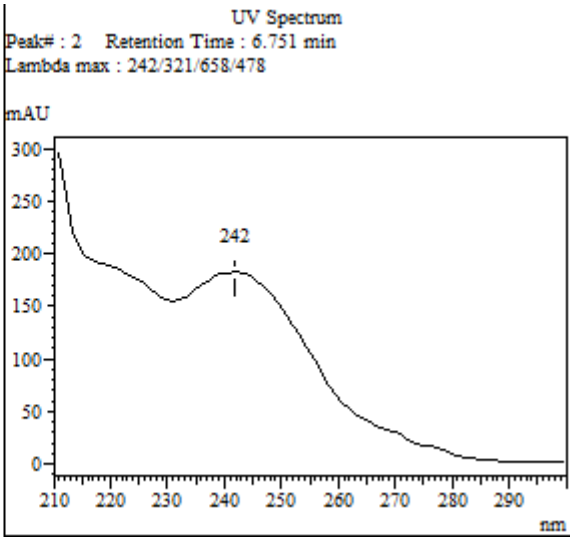




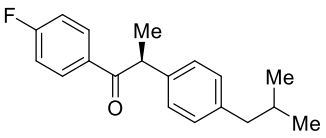
PDA Ch1 242nm

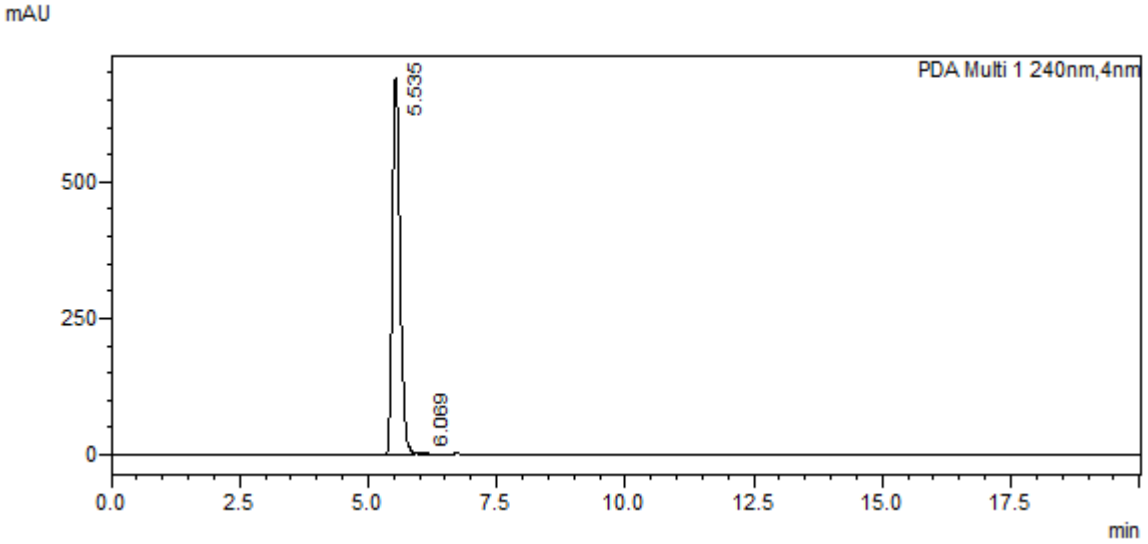
Peak#	Ret. Time	Area	Height	Area%
1	6.072	1880990	192205	49.908
2	6.751	1887911	179719	50.092
Total		3768901	371925	100.000





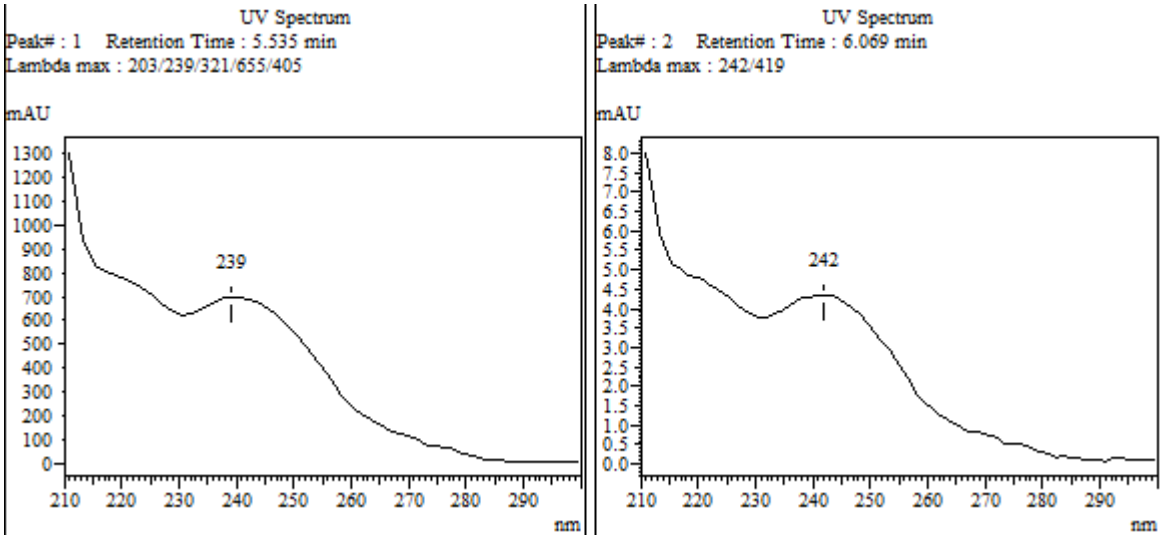
(*S*)-1-(4-Fluorophenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one (39d)



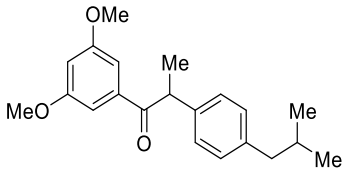


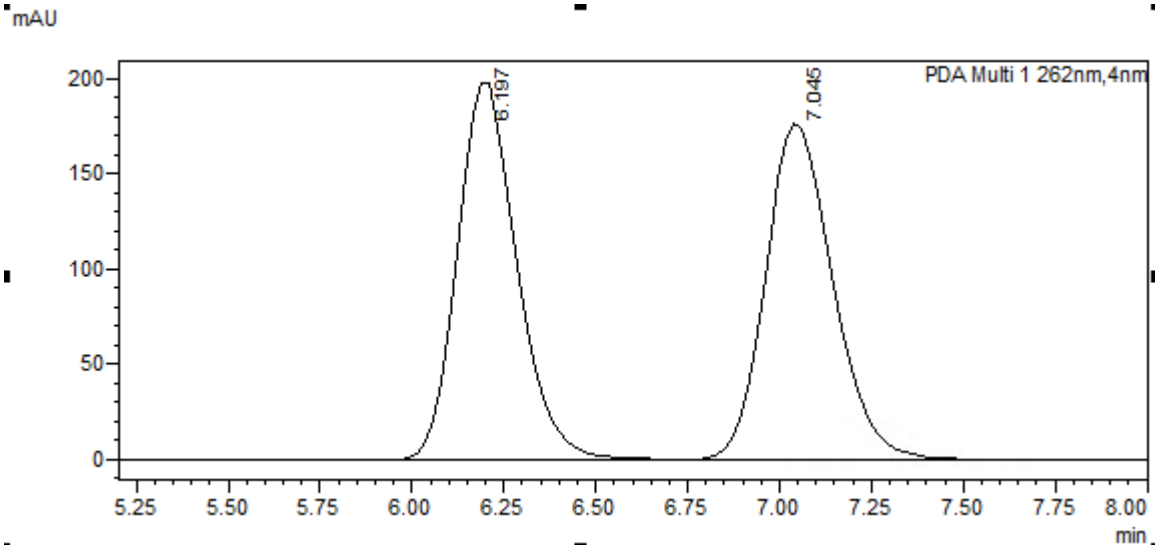
PDA Ch1 240nm

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



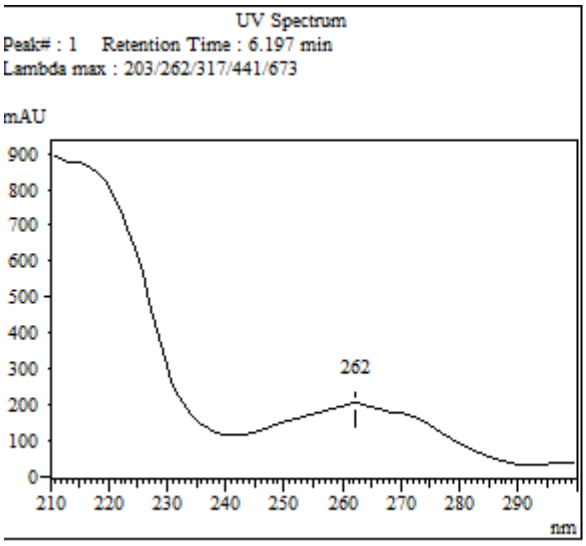
(*R*/*S*)-1-(3,5-Dimethoxyphenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one (*rac*-39e)

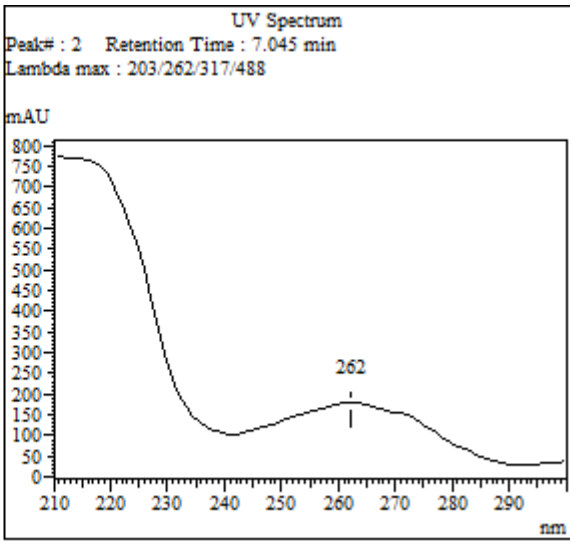




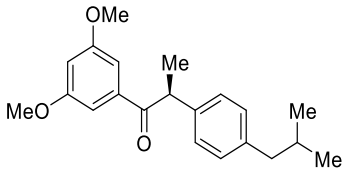
PDA Ch1 262nm

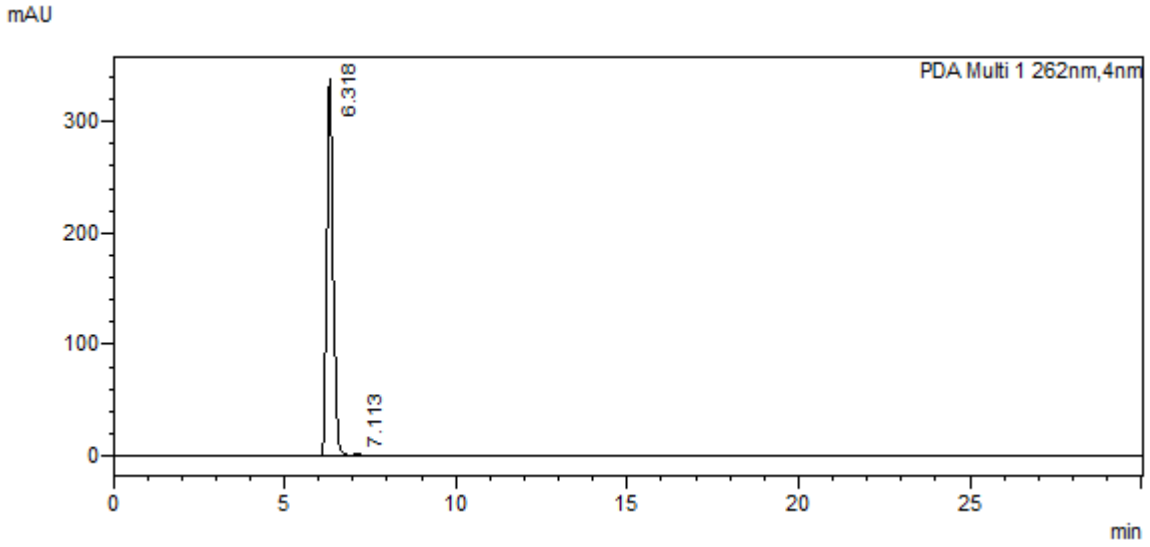
Peak#	Ret. Time	Area	Height	Area%
1	6.197	2242498	198179	49.966
2	7.045	2245589	176629	50.034
Total		4488087	374807	100.000





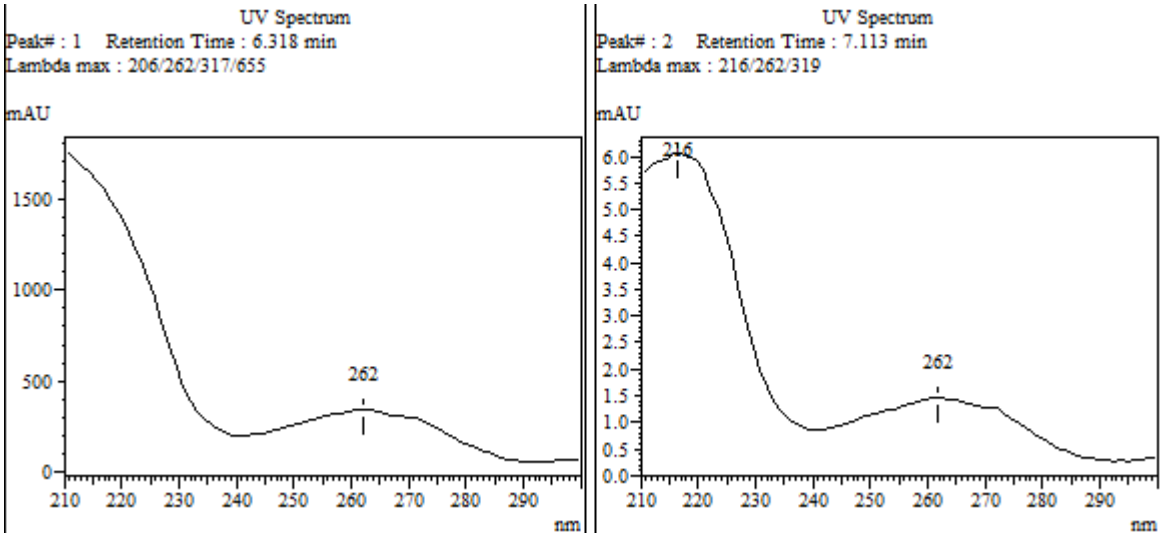
(*S*)-1-(3,5-Dimethoxyphenyl)-2-(4-(2-methoxypropyl)phenyl)propan-1-one (39e)



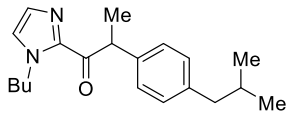


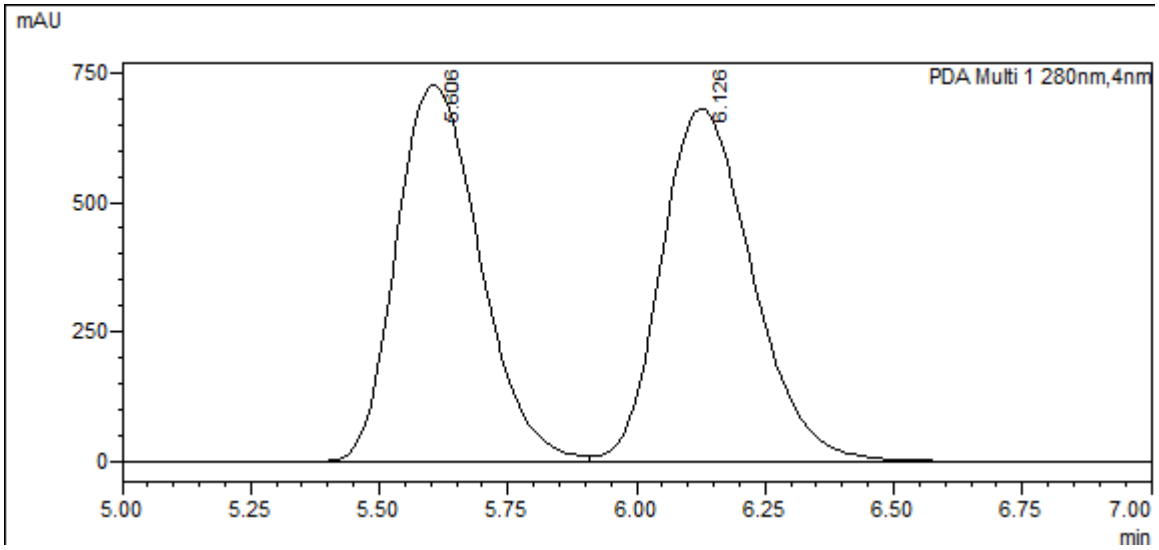
PDA Ch1 262nm

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



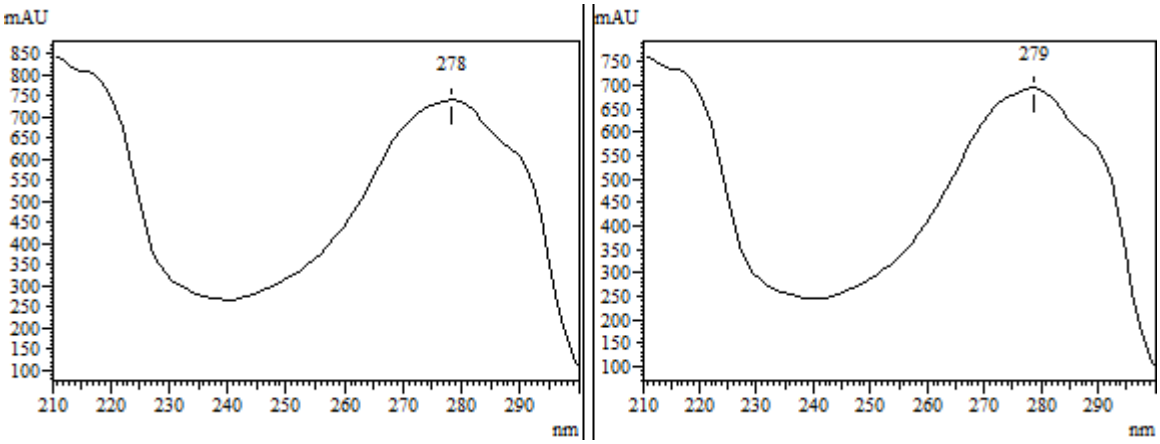
(*R/S*)-1-(1-butyl-1H-imidazol-2-yl)-2-(4-isobutylphenyl)propan-1-one (*rac*-39f)



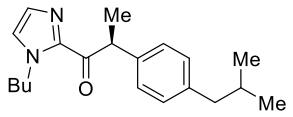


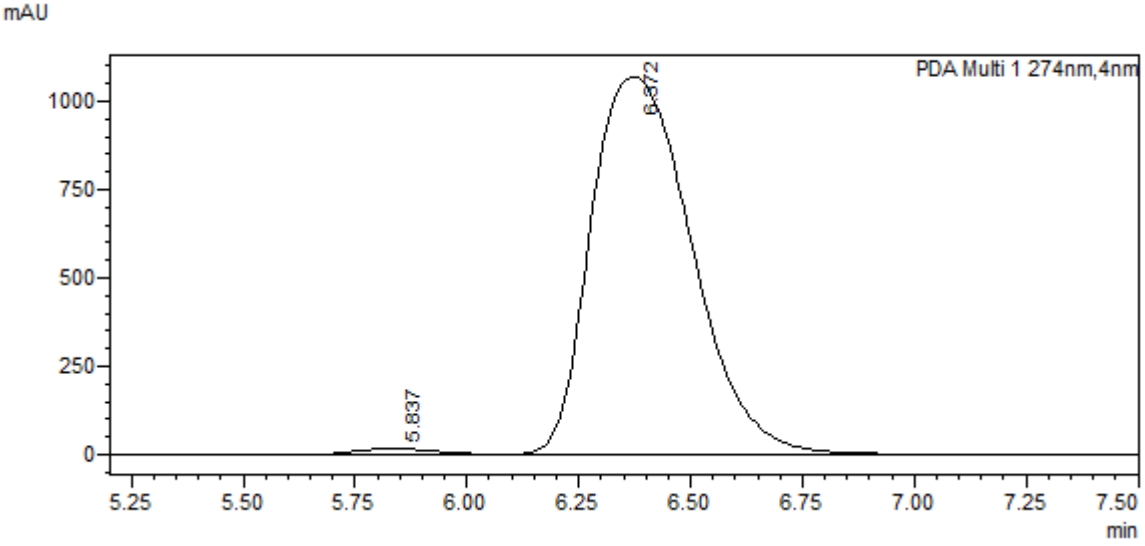
PDA Ch1 280nm

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



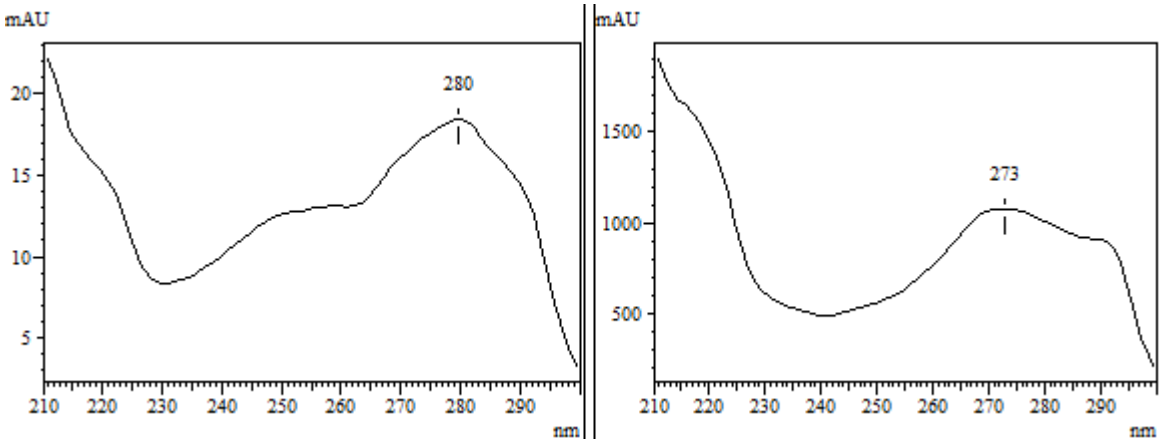
(*S*)-1-(1-butyl-1H-imidazol-2-yl)-2-(4-isobutylphenyl)propan-1-one (39f)





PDA Ch1 274nm

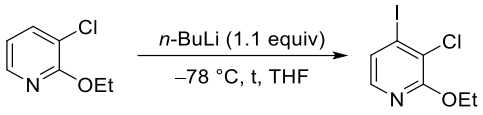
Peak#	Ret. Time	Area	Height	Area%
1	5.837	210373	16982	1.237
2	6.372	16802645	1068054	98.763
Total		17013018	1085036	100.000



4. Regioselective Difunctionalization of Pyridines *via* 3,4-Pyridynes

4.1 Optimization of the Metalation of 2-ethoxy-3-chloropyridine

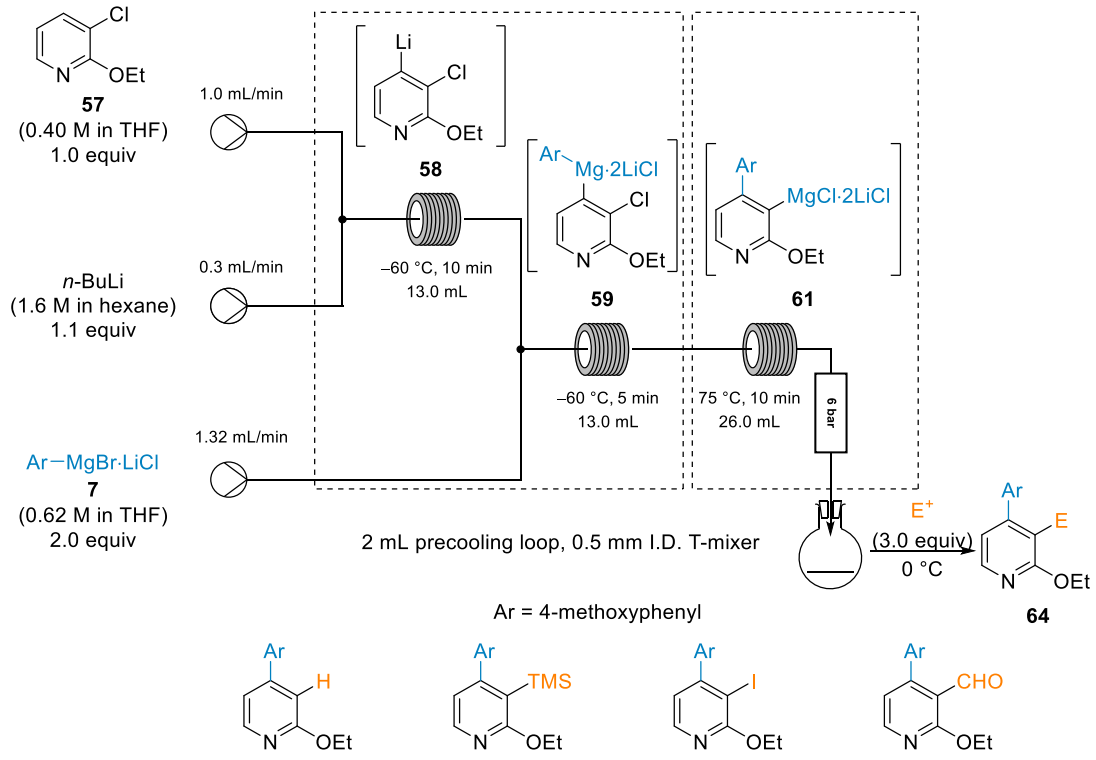
Table 20. Metalation of 2-ethoxy-3-chloropyridine with *n*-BuLi.



57 **58**

Entry	t [min]	Conversion **57** [GC-%]	Yield **57a** [GC-%]
1	15	53	53
2	30	64	60
3	60	78	70
4	120	93	81
5	300	94	81

4.2 3,4-Difunctionalization of 3-chloro-2-ethoxypyridine *via* Pyridyne Intermediate in Continuous Flow



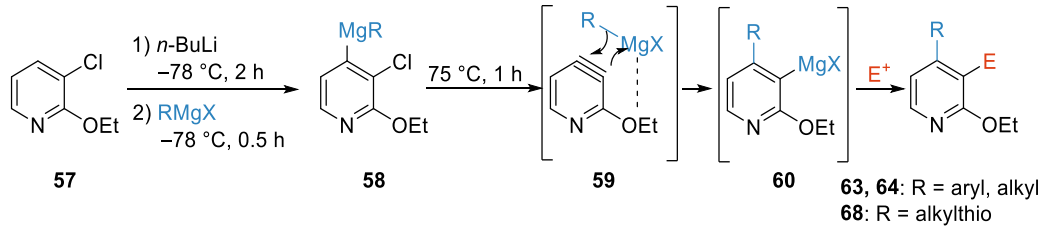
Scheme 74. 3,4-Difunctionalization of 3-chloro-2-ethoxypyridine (57) *via* pyridyne intermediate **60** and trapping of pyridyl-3-magnesium **61** with different electrophiles in semi-batch set-up.

4.3 Typical Procedures

Typical Procedure 1: Preparation of organomagnesium reagents of type **7** *via* Mg-insertion.

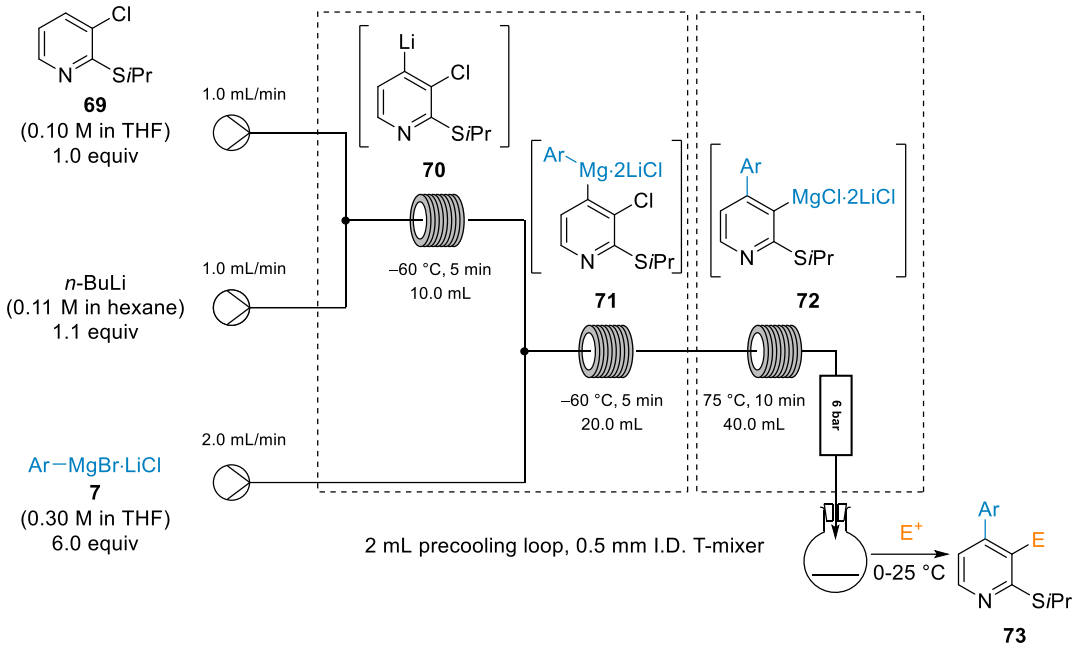
LiCl (509 mg, 12.0 mmol, 1.2 equiv) was flame dried and cooled to room temperature *in vacuo*. Then, magnesium turnings (288 mg, 12.0 mmol, 1.2 equiv) and THF (10 mL) were added and the reaction mixture was cooled to 0 °C. The organic bromide (10.0 mmol, 1.0 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 1-3 h. Upon complete conversion, the concentration of the organomagnesium reagent **7** was determined by titration against iodine in THF.

Typical Procedure 2: Preparation of 2,3,4-trifunctionalized pyridines of type **7** and **10** *via* 3,4-pyridyne intermediates.



n-Butyllithium (1.1 equiv, 2.6 M) was slowly added to a stirred solution of 3-chloro-2-ethoxypyridine (**57**) (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 removal of the solvent *in vacuo*, flash column chromatography purification with *i*-hexane (or pentane):EtOAc mixtures afforded the pure products of type **63**, **64** and **68**.

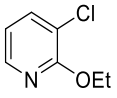
Typical Procedure 3: Preparation of 2,3,4-trifunctionalized pyridines of type **73** *via* 3,4-pyridyne intermediates in continuous flow.



A solution of **11** 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_{pre} = 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_{pre} = 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 into 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 *i*-hexane (or pentane):EtOAc mixtures afforded the pure product.

4.4 Preparation of Products

3-Chloro-2-ethoxypyridine (57)



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 (*i*-hexane:ethyl acetate = 9.7:0.3) afforded the 3-chloro-2-ethoxypyridine (1) (13.4 g, 85.0 mmol, 85% yield) as an colorless 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).

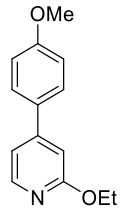
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.2, 144.7, 138.3, 118.3, 117.2, 62.8, 14.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 1583 (s), 1472 (m), 1448 (s), 1431 (vs), 1383 (s), 1362 (w), 1352 (m), 1317 (s), 1302 (m), 1281 (w), 1254 (s), 1246 (s), 1129 (m), 1105 (w), 1092 (w), 1072 (s), 1045 (s), 1027 (s), 929 (m), 910 (w), 784 (s), 753 (s), 713 (m), 696 (w).

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 (63a)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give 2-ethoxy-4-(4-methoxyphenyl)pyridine (**63a**) (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.

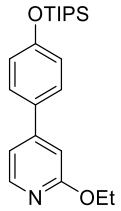
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2977 (w), 1605 (vs), 1582 (m), 1544 (s), 1518 (s), 1473 (m), 1441 (m), 1425 (m), 1405 (w), 1379 (s), 1350 (w), 1327 (s), 1288 (m), 1246 (vs), 1205 (s), 1180 (s), 1056 (m), 1027 (s), 838 (w), 818 (s).

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-(4-((tri*iso*propylsilyl)oxy)phenyl)pyridine (63b)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-((tri*iso*propylsilyl)oxy)phenyl)magnesium bromide (1.04 mL, 1.00 mmol), prepared *via* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.8:0.2) to give 2-ethoxy-4(4((tri*iso*propylsilyl)oxy)phenyl)pyridine (**63b**) (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).

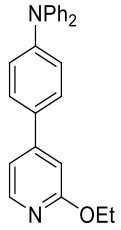
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.5, 157.4, 151.2, 146.8, 130.8, 130.7, 128.2, 120.5, 114.9, 107.9, 62.2, 18.0, 14.9, 12.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2943 (m), 2865 (m), 1604 (s), 1543 (m), 1515 (vs), 1471 (s), 1423 (m), 1379 (m), 1326 (m), 1272 (s), 1265 (s), 1249 (s), 1204 (vs), 1174 (m), 1056 (m), 1035 (m), 910 (s), 882 (s), 841 (m), 817 (s), 761 (m), 684 (s).

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.

4-(2-Ethoxypyridin-4-yl)-*N*,*N*-diphenylaniline (63c)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give 4-(2-ethoxypyridin-4-yl)-*N*,*N*-diphenylaniline (**63c**) (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.

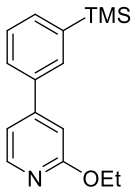
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 1603 (s), 1589 (vs), 1542 (m), 1515 (s), 1486 (s), 1471

(s), 1451 (w), 1425 (m), 1406 (m), 1380 (m), 1350 (m), 1325 (s), 1274 (s), 1251 (s), 1206 (vs), 1180 (m), 1056 (m), 1035 (m), 942 (w), 840 (w), 815 (s), 754 (s), 732 (m), 696 (vs).

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.

2-Ethoxy-4-(3-(trimethylsilyl)phenyl)pyridine (63d)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 2-ethoxy-4-(3-(trimethylsilyl)phenyl)pyridine (**63d**) (76.0 mg, 0.28 mmol, 56% yield) as a colorless 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).

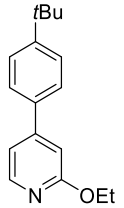
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.6, 151.9, 147.2, 141.7, 137.7, 134.1, 131.9, 128.5, 127.6, 115.5, 108.9, 62.1, 14.9, -1.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953 (w), 1615 (m), 1603 (s), 1589 (w), 1546 (m), 1470 (m), 1422 (m), 1376 (m), 1348 (m), 1326 (s), 1248 (s), 1206 (s), 1119 (m), 1060 (w), 1039 (s), 990 (w), 951 (w), 862 (s), 836 (vs), 791 (s), 779 (w), 752 (s), 704 (w), 694 (w).

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].

4-(4-(*Tert*-butyl)phenyl)-2-ethoxypyridine (63e)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 79.0 mg, 0.50 mmol), *n*-butyllithium (0.21 mL, 0.55 mmol) and (4-(*tert*-butyl)phenyl)magnesium bromide (1.11 mL, 1.00 mmol), prepared *via* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.8:0.2) to give 4-(4-(*tert*-butyl)phenyl)-2-ethoxypyridine (**63e**) (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).

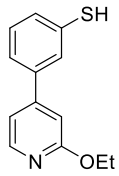
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.7, 152.4, 151.2, 147.2, 135.4, 126.8, 126.1, 115.2, 108.4, 62.0, 34.8, 31.4, 14.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964 (m), 1605 (vs), 1543 (s), 1476 (m), 1421 (s), 1379 (s), 1328 (s), 1208 (s), 1056 (s), 1036 (m), 817 (s).

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].

3-(2-Ethoxypyridin-4-yl)benzenethiol (63f)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 *sat. aq.* NH_4Cl. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.7:0.3) to give 3-(2-ethoxypyridin-4-yl)benzenethiol (**63f**) (60.0 mg, 0.26 mmol, 51% yield) as a colorless 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).

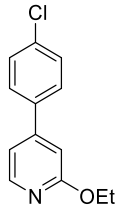
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.9, 145.9, 135.3, 129.9, 129.7, 129.4, 114.6, 107.2, 62.2, 14.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 1586 (vs), 1580 (vs), 1559 (w), 1542 (s), 1475 (m), 1457 (m), 1440 (m), 1412 (m), 1378 (m), 1347 (m), 1312 (m), 1280 (m), 1221 (w), 1091 (w), 1082 (w), 1043 (s), 1024 (w), 986 (w), 949 (w), 806 (w), 749 (m), 690 (m).

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-(4-Chlorophenyl)-2-ethoxypyridine (63g)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 4-(4-chlorophenyl)-2-ethoxypyridine (**63g**) (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.

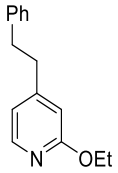
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (vw), 1608 (w), 1575 (vw), 1545 (w), 1502 (w), 1472 (w), 1423 (w), 1380 (w), 1350 (vw), 1327 (w), 1250 (vw), 1207 (w), 1093 (w), 1057 (w), 1034 (w), 1014 (w), 992 (vw), 904 (s), 874 (w), 838 (w), 814 (m), 725 (vs), 674 (vw).

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.

2-Ethoxy-4-phenethylpyridine (63h)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.8:0.2) to give 2-ethoxy-4-phenethylpyridine (**63h**) (64.0 mg, 0.28 mmol, 56% yield) as a colorless 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).

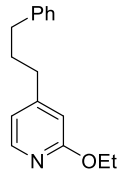
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.1, 153.1, 146.4, 140.8, 128.3, 128.2, 126.0, 117.1, 110.2, 61.3, 36.8, 36.2, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2975 (m), 2927 (m), 1609 (vs), 1558 (s), 1496 (m), 1480 (m), 1453 (m), 1440 (w), 1422 (s), 1381 (s), 1319 (s), 1291 (m), 1159 (m), 1050 (s), 814 (w), 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-(3-phenylpropyl)pyridine (63i)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.8:0.2) to give 2-ethoxy-4-(3-phenylpropyl)pyridine (**63i**) (70.0 mg, 0.29 mmol, 58% yield) as a colorless 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).

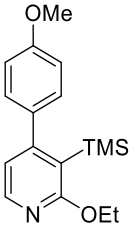
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.2, 154.5, 146.4, 141.8, 128.5, 128.5, 126.1, 117.5, 110.6, 61.9, 35.4, 34.7, 31.7, 14.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2934 (m), 1610 (vs), 1558 (s), 1496 (w), 1478 (m), 1453 (m), 1420 (s), 1381 (s), 1351 (w), 1318 (s), 1288 (m), 1158 (m), 1050 (s), 749 (w), 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-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (64a)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 2-ethoxy-4-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (**64a**) (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.

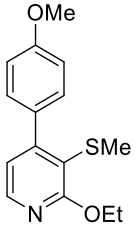
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2953 (w), 1611 (m), 1574 (m), 1528 (m), 1515 (s), 1462 (w), 1448 (m), 1441 (m), 1373 (m), 1331 (s), 1319 (m), 1290 (m), 1269 (m), 1245 (vs), 1174 (m), 1112 (m), 1030 (m), 843 (s), 825 (s), 761 (w), 755 (w).

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.: 43.1-45.2 °C.

2-Ethoxy-4-(4-methoxyphenyl)-3-(methylthio)pyridine (64b)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.6:0.4) to give 2-ethoxy-4-(4-methoxyphenyl)-3-(methylthio)pyridine (**64b**) (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).

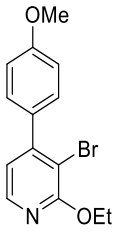
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.8, 160.0, 154.9, 145.1, 132.1, 130.9, 119.1, 118.2, 113.9, 63.1, 55.7, 18.4, 15.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2926 (w), 1609 (m), 1577 (m), 1515 (s), 1453 (m), 1441 (m), 1416 (m), 1402 (w), 1376 (m), 1350 (m), 1337 (s), 1324 (m), 1292 (m), 1273 (m), 1248 (vs), 1177 (m), 1137 (w), 1114 (s), 1028 (s), 1010 (w), 947 (w), 839 (w), 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 [C15H18O2NS]: 275.0980; found 275.0974.

3-Bromo-2-ethoxy-4-(4-methoxyphenyl)pyridine (64c)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 3-bromo-2-ethoxy-4-(4-methoxyphenyl)pyridine (**64c**) (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.

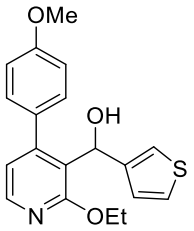
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928 (m), 2853 (m), 1561 (vs), 1519 (m), 1448 (m), 1358 (m), 1262 (m), 1150 (m), 1087 (m), 809 (m), 792 (s).

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.

(2-Ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)(thiophen-3-yl)methanol (64d)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 8.0:2.0) to give (2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)(thiophen-3-yl)methanol (**64d**) (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).

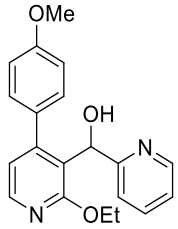
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.8, 159.8, 150.6, 145.9, 145.2, 130.6, 130.0, 126.7, 125.5, 122.6, 120.8, 119.2, 114.1, 68.5, 62.4, 55.5, 14.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3547 (w), 2976 (w), 2835 (w), 1609 (s), 1592 (m), 1578 (w), 1550 (m), 1514 (s), 1463 (m), 1441 (w), 1420 (m), 1405 (m), 1379 (m), 1349 (w), 1324 (m), 1293 (m), 1246 (vs), 1227 (m), 1208 (m), 1178 (s), 1148 (w), 1125 (s), 1110 (w), 1089 (w), 1026 (vs), 953 (w), 841 (m), 826 (m), 788 (m), 738 (w), 729 (w).

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 (64e)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 7.0:3.0) to give (2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)(pyridin-2-yl)methanol (**64e**) (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.

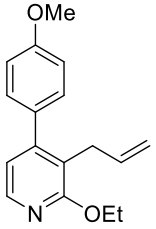
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2364 (s), 2355 (s), 2342 (s), 1609 (s), 1591 (s), 1558 (s), 1539 (m), 1516 (vs), 1506 (s), 1472 (s), 1464 (s), 1456 (s), 1436 (s), 1424 (s), 1419 (s), 1249 (vs), 1030 (s), 668 (s).

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 (64f)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.6:0.4) to give 3-allyl-2-ethoxy-4-(4-methoxyphenyl)pyridine (**64f**) (75.0 mg, 0.28 mmol, 56% yield) as a colorless 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).

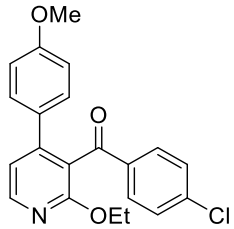
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.5, 159.4, 151.3, 143.8, 136.8, 131.9, 130.0, 120.1, 118.6, 115.2, 113.7, 61.9, 55.4, 31.4, 14.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960 (w), 2927 (w), 2836 (w), 1609 (m), 1588 (s), 1530 (m), 1514 (vs), 1459 (s), 1440 (m), 1417 (w), 1368 (m), 1305 (w), 1290 (m), 1248 (vs), 1180 (s), 1129 (m), 1114 (m), 1097 (m), 1050 (m), 1028 (m), 986 (m), 915 (m), 841 (w), 817 (vs), 770 (m), 696 (w).

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 (64g)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give (4-chlorophenyl)(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)methanone (**64g**) (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).

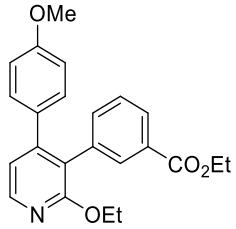
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm 194.8, 160.9, 160.1, 150.3, 147.6, 139.8, 135.9, 130.7, 129.9, 129.8, 128.9, 121.1, 117.9, 114.2, 62.5, 55.3, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1674 (s), 1609 (m), 1585 (vs), 1547 (m), 1517 (s), 1463 (m), 1420 (m), 1378 (m), 1327 (m), 1298 (m), 1272 (s), 1252 (vs), 1180 (m), 1128 (s), 1091 (m), 1027 (m), 925 (m), 823 (m), 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 (64h)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give ethyl 3-(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)benzoate (**64h**) (106 mg, 0.28 mmol, 56% yield) as a 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).

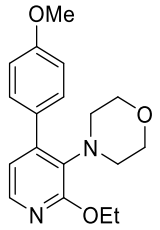
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.4, 161.2, 158.8, 150.1, 145.5, 135.7, 135.4, 132.3, 130.9, 130.4, 129.7, 127.7, 127.5, 121.5, 118.3, 113.3, 61.8, 60.6, 55.0, 14.4, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 1718 (s), 1700 (w), 1609 (m), 1587 (m), 1546 (w), 1515 (s), 1464 (w), 1457 (w), 1441 (w), 1418 (m), 1404 (w), 1378 (m), 1367 (w), 1347 (w), 1323 (w), 1296 (m), 1248 (vs), 1216 (m), 1178 (w), 1132 (m), 1110 (m), 1082 (w), 1031 (m), 823 (m), 754 (w).

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 (64i)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.3:0.7) to give 4-(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)morpholine (**64i**) (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.

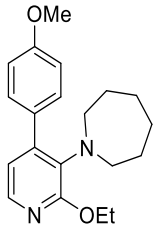
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953 (w), 2849 (w), 1608 (m), 1585 (m), 1513 (s), 1464 (m), 1450 (m), 1440 (m), 1424 (s), 1408 (m), 1380 (s), 1350 (m), 1325 (m), 1290 (m), 1261 (m), 1244 (vs), 1205 (m), 1175 (m), 1127 (s), 1110 (vs), 1028 (s), 952 (w), 925 (m), 844 (m), 820 (s).

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 (64j)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.3:0.7) to give 1-(2-ethoxy-4-(4-methoxyphenyl)pyridin-3-yl)azepane (**64j**) (77.0 mg, 0.24 mmol, 47% yield) as an orange solid. *N*-azepan-1-yl benzoate (274 mg, 1.25 mmol).

^{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.

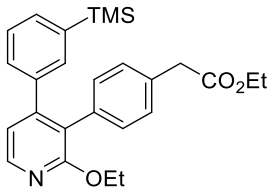
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926 (m), 1609 (m), 1514 (vs), 1464 (m), 1440 (m), 1423 (s), 1379 (m), 1326 (m), 1292 (m), 1246 (vs), 1175 (m), 1128 (s), 1031 (s), 819 (m).

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 (64k)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give ethyl 2-(4-(2-ethoxy-4-(3-(trimethylsilyl)phenyl)pyridin-3-yl)phenyl)acetate (**64k**) (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).

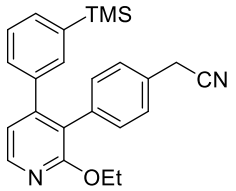
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.6, 161.6, 150.9, 145.5, 140.0, 138.4, 135.0, 134.3, 132.6, 132.3, 131.4, 129.6, 128.6, 127.6, 122.7, 118.6, 62.2, 60.9, 41.3, 14.7, 14.3, -1.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979 (w), 2955 (w), 1736 (s), 1584 (m), 1573 (w), 1547 (m), 1467 (w), 1462 (w), 1419 (m), 1408 (m), 1377 (m), 1346 (m), 1322 (m), 1271 (m), 1262 (m), 1248 (s), 1151 (m), 1138 (s), 1116 (m), 1036 (s), 1002 (m), 863 (m), 838 (vs), 795 (m), 754 (m), 707 (m), 695 (w).

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 (64l)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 2-(4-(2-ethoxy-4-(3-(trimethylsilyl)phenyl)pyridin-3-yl)phenyl)acetonitrile (**64l**) (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.

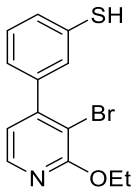
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955 (w), 1584 (m), 1547 (m), 1413 (s), 1378 (s), 1347 (m), 1322 (m), 1276 (m), 1263 (m), 1249 (m), 1138 (m), 1117 (m), 1040 (m), 863 (m), 838 (vs), 794 (m), 754 (m), 708 (m).

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.

3-(3-Bromo-2-ethoxypyridin-4-yl)benzenethiol (64m)



Following **TP2**, 3-chloro-2-ethoxypyridine (**1**, 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 1,2-dibromotetrachloroethane (407 mg, 1.25 mmol). After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.8:0.2) to give 3-(3-bromo-2-ethoxypyridin-4-yl)benzenethiol (**7ca**) (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).

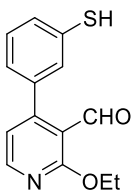
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.4, 150.9, 146.8, 137.3, 133.4, 132.6, 132.4, 131.2, 123.4, 115.1, 108.1, 62.0, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 1584 (vs), 1574 (s), 1562 (s), 1542 (s), 1459 (s), 1411 (m), 1378 (s), 1347 (m), 1312 (s), 1280 (m), 1222 (m), 1084 (m), 1070 (w), 1042 (vs), 986 (w), 949 (m), 851 (w), 806 (m), 780 (m), 757 (m), 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 (64n)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give 2-ethoxy-4-(3-mercaptophenyl)nicotinaldehyde (**64n**) (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).

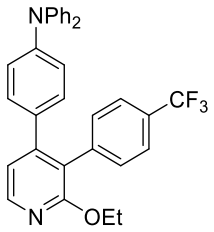
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.2, 164.4, 150.6, 146.9, 140.3, 137.8, 135.7, 132.2, 130.6, 130.3, 115.2, 108.3, 62.1, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979 (w), 1699 (s), 1583 (vs), 1543 (s), 1469 (m), 1460 (m), 1412 (m), 1378 (s), 1348 (m), 1312 (m), 1280 (m), 1222 (m), 1197 (s), 1086 (m), 1042 (s), 986 (w), 950 (w), 865 (w), 795 (m), 731 (w), 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-(2-Ethoxy-3-(4-(trifluoromethyl)phenyl)pyridin-4-yl)-*N*,*N*-diphenylaniline (64o)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 4-(2-ethoxy-3-(4-(trifluoromethyl)phenyl)pyridin-4-yl)-*N*,*N*-diphenylaniline (**64o**) (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).

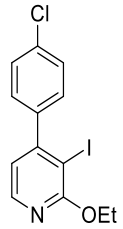
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.3, 150.8, 147.5, 147.4, 146.2, 139.8, 132.2, 131.7, 130.3, 129.4, 124.8, 124.5, 124.2, 123.4, 122.4, 121.5, 118.3, 62.3, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976 (vw), 2929 (vw), 1588 (m), 1511 (m), 1494 (m), 1487 (m), 1324 (vs), 1292 (w), 1273 (m), 1164 (m), 1126 (m), 1105 (m), 1068 (m), 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.

4-(4-Chlorophenyl)-2-ethoxy-3-iodopyridine (64p)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 4-(4-chlorophenyl)-2-ethoxy-3-iodopyridine (**64p**) (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.

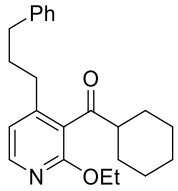
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 1598 (m), 1579 (m), 1522 (m), 1492 (m), 1467 (w), 1450 (m), 1413 (s), 1397 (w), 1377 (s), 1338 (vs), 1321 (m), 1277 (w), 1264 (w), 1131 (w), 1102 (m), 1088 (vs), 1034 (m), 1016 (s), 1005 (s), 948 (w), 817 (s).

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 (64q)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give cyclohexyl(2-ethoxy-4-(3-phenylpropyl)pyridine-3-yl) methanone (**64q**) (97.0 mg, 0.28 mmol, 55% yield) as a colorless 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).

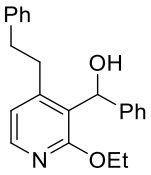
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 209.4, 160.5, 151.3, 146.8, 141.8, 128.5, 126.0, 124.4, 117.8, 62.2, 51.4, 35.8, 32.4, 32.3, 28.4, 26.0, 26.0, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938 (m), 1610 (vs), 1558 (s), 1496 (w), 1478 (w), 1453 (m), 1420 (s), 1381 (s), 1319 (s), 1288 (m), 1159 (m), 1051 (s), 748 (w), 733 (m), 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 (64r)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.4:0.6) to give (2-ethoxy-4-phenethylpyridin-3-yl)(phenyl)methanol (**64r**) (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).

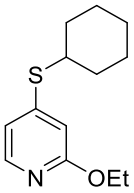
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5, 145.3, 143.6, 140.8, 128.7, 128.5, 128.3, 127.1, 126.4, 125.8, 123.5, 119.0, 69.7, 62.5, 36.8, 34.7, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3026 (w), 2978 (w), 1595 (m), 1564 (m), 1416 (m), 1381 (m), 1333 (m), 1316 (m), 1058 (m), 1035 (m), 1024 (m), 904 (m), 727 (s), 698 (vs).

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 (68a)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.9:0.1) to give 4-(cyclohexylthio)-2-ethoxypyridine (**10a**) (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).

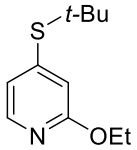
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.4, 148.7, 119.4, 118.0, 43.6, 33.0, 26.0, 25.7, 24.7, 14.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928 (m), 2852 (m), 1583 (vs), 1538 (s), 1460 (m), 1449 (m), 1409 (m), 1376 (s), 1346 (m), 1310 (s), 1280 (s), 1263 (m), 1220 (m), 1087 (s), 1042 (vs), 997 (m), 986 (m), 949 (m), 931 (m), 842 (m), 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 (68b)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.9:0.1) to give 4-(*tert*-butylthio)-2-ethoxypyridine (**68b**) (73.0 mg, 0.35 mmol, 69% yield) as a colorless 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).

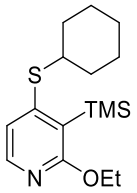
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.9, 146.2, 122.7, 116.8, 62.2, 47.1, 31.4, 14.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974 (m), 2963 (m), 1583 (vs), 1540 (vs), 1471 (m), 1461 (m), 1407 (m), 1377 (s), 1364 (m), 1345 (s), 1311 (m), 1273 (m), 1218 (m), 1164 (m), 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 (68c)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.8:0.2) to give 4-(cyclohexylthio)-2-ethoxy-3-(trimethylsilyl)pyridine (**68c**) (110 mg, 0.36 mmol, 71% yield) as a colorless 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).

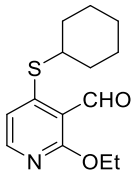
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.5, 157.4, 146.5, 119.3, 115.5, 61.9, 45.2, 33.2, 26.2, 25.9, 14.7, 2.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930 (m), 2900 (w), 2854 (w), 1558 (s), 1524 (s), 1448 (m), 1427 (m), 1372 (m), 1328 (s), 1290 (m), 1262 (m), 1245 (s), 1048 (s), 1035 (s), 997 (w), 953 (w), 842 (vs), 800 (m), 782 (m), 762 (w), 750 (m), 736 (m), 693 (w), 686 (w).

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 (68d)



Following **TP2**, 3-chloro-2-ethoxypyridine (**1**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 4-(cyclohexylthio)-2-ethoxynicotinaldehyde (**68d**) (66.0 mg, 0.25 mmol, 50% yield) as a colorless 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).

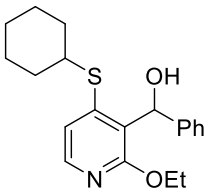
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 189.4, 165.7, 157.7, 148.2, 115.0, 113.4, 64.1, 43.0, 32.6, 26.2, 25.7, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930 (m), 1670 (s), 1571 (s), 1530 (vs), 1447 (s), 1376 (m), 1339 (m), 1297 (w), 1274 (m), 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 (68e)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give (4-(cyclohexylthio)-2-ethoxypyridin-3-yl)(phenyl)methanol (**68e**) (121 mg, 0.36 mmol, 71% yield) as a colorless 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).

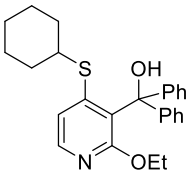
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.2, 147.8, 144.9, 143.3, 128.1, 126.9, 125.6, 124.1, 116.7, 70.5, 62.3, 45.5, 33.1, 26.0, 25.7, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929 (m), 2852 (w), 1575 (s), 1541 (s), 1448 (s), 1406 (m), 1378 (s), 1346 (m), 1331 (w), 1306 (m), 1261 (m), 1221 (s), 1203 (m), 1181 (w), 1168 (w), 1034 (vs), 1023 (s), 997 (m), 958 (m), 941 (w), 909 (m), 863 (m), 815 (w), 802 (m), 732 (s), 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 (68f)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.6:0.4) to give (4-(cyclohexylthio)-2-ethoxypyridin-3-yl)diphenylmethanol (**68f**) (141 mg, 0.34 mmol, 67% yield) as a colorless 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).

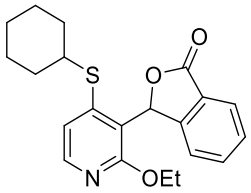
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5, 149.0, 146.3, 144.1, 129.2, 128.1, 127.8, 127.4, 118.4, 81.9, 62.4, 46.3, 32.6, 25.9, 25.7, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928 (m), 2852 (w), 1568 (m), 1531 (s), 1492 (w), 1445 (s), 1405 (m), 1377 (m), 1335 (s), 1294 (m), 1271 (w), 1262 (w), 1248 (m), 1034 (s), 1012 (m), 956 (m), 922 (w), 905 (m), 886 (m), 759 (s), 732 (m), 698 (vs), 655 (w).

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 (68g)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.4:0.6) to give 3-(4-cyclohexylthio)-2-ethoxypyridin-3-yl) isobenzofuran-1(3*H*)-one (**68g**) (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).

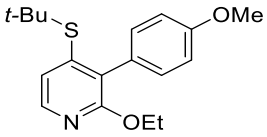
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.4, 162.3, 149.7, 149.5, 146.9, 133.7, 128.8, 127.7, 125.1, 121.7, 117.3, 62.1, 46.6, 33.2, 33.2, 26.0, 25.9, 25.7, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929 (m), 2853 (w), 1762 (vs), 1573 (m), 1545 (m), 1465 (m), 1450 (m), 1417 (m), 1381 (m), 1328 (m), 1308 (m), 1284 (m), 1263 (w), 1207 (w), 1091 (w), 1057 (m), 1039 (s), 1013 (m), 997 (m), 964 (m), 816 (w), 744 (m), 723 (w), 687 (w).

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 (68h)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 4-(*tert*-butylthio)-2-ethoxy-3-(4-methoxyphenyl)pyridine (**10ba**) (106 mg, 0.34 mmol, 67% yield) as a colorless 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).

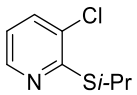
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.6, 158.8, 143.9, 132.2, 127.8, 127.6, 121.9, 113.1, 62.4, 55.3, 47.8, 31.4, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974 (m), 2961 (m), 1611 (m), 1565 (m), 1541 (s), 1511 (m), 1465 (m), 1456 (m), 1441 (m), 1415 (m), 1407 (m), 1377 (s), 1364 (m), 1345 (m), 1291 (m), 1269 (m), 1245 (vs), 1226 (m), 1175 (s), 1161 (m), 1041 (s), 996 (m), 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 (69)



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 (*i*-hexane:ethyl acetate = 9.8:0.2) afforded the pure product (**69**) (5.24 g, 27.9 mmol, 93% yield) as a colorless 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).

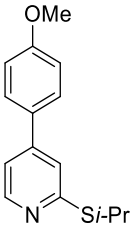
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.0, 147.1, 135.9, 129.2, 119.5, 35.2, 23.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964 (w), 2926 (w), 1566 (m), 1461 (w), 1454 (w), 1432 (w), 1386 (vs), 1365 (w), 1242 (w), 1145 (m), 1126 (m), 1055 (m), 1037 (m), 1028 (m), 785 (m), 762 (m), 729 (m), 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 (73a)



Flow procedure: A solution of 3-chloro-2-(isopropylthio)pyridine (**69**) 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 **TP3**, 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 (**73a**) (444 mg, 1.71 mmol, 57% yield) as a yellow solid.

Batch procedure: Following **TP2**, 3-chloro-2-(isopropylthio)pyridine (**69**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give 2-(isopropylthio)-4-(4-methoxyphenyl)pyridine (**73a**) (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.

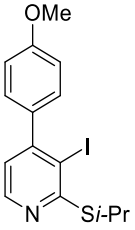
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962 (w), 2928 (w), 1610 (m), 1590 (vs), 1531 (m), 1516 (vs), 1460 (s), 1441 (m), 1367 (m), 1291 (m), 1251 (vs), 1181 (m), 1130 (m), 1114 (w), 1054 (m), 1029 (w), 820 (s).

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 (73b)



A solution of 3-chloro-2-(isopropylthio)pyridine (**69**) 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 **TP3**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 3-iodo-2-(isopropylthio)-4-(4-methoxyphenyl)pyridine (**73b**) (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.

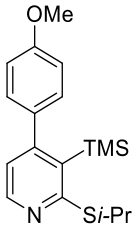
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961 (w), 2925 (w), 1609 (m), 1562 (m), 1514 (vs), 1462 (m), 1428 (s), 1412 (w), 1325 (m), 1304 (m), 1287 (m), 1247 (vs), 1194 (m), 1176 (m), 1156 (m), 1109 (w), 1063 (m), 1054 (m), 1031 (m), 1000 (m), 824 (s), 767 (w).

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 (73c)



A solution of 3-chloro-2-(isopropylthio)pyridine (**69**) 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 **TP3**, 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 (*i*-hexane:ethyl acetate = 9.7:0.3) to give 2-(isopropylthio)-4-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (**73c**) (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.

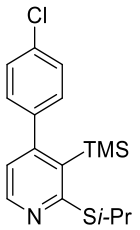
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961 (w), 1608 (m), 1556 (m), 1512 (s), 1462 (w), 1442 (w), 1422 (m), 1409 (m), 1319 (m), 1304 (w), 1283 (m), 1244 (vs), 1172 (s), 1154 (m), 1107 (w), 1058 (m), 1032 (m), 841 (s), 824 (vs), 783 (m), 772 (m), 758 (m), 752 (m), 734 (m), 693 (w), 684 (w).

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 (73d)



A solution of 3-chloro-2-(isopropylthio)pyridine (**69**) 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 **TP3**, 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 (*i*-hexane:ethyl acetate = 9.8:0.2) to give 4-(4-chlorophenyl)-2-(isopropylthio)-3-(trimethylsilyl)pyridine (**73d**) (84.0 mg, 0.25 mmol, 50% yield) as a colorless 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).

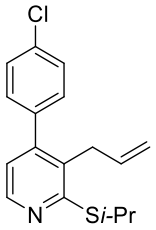
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.2, 156.6, 148.1, 141.6, 134.2, 132.0, 130.2, 128.4, 121.1, 36.9, 23.3, 2.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962 (m), 1597 (m), 1572 (s), 1533 (s), 1492 (s), 1449 (s), 1433 (m), 1362 (vs), 1184 (m), 1164 (m), 1155 (m), 1092 (vs), 1056 (m), 1015 (s), 927 (m), 916 (m), 834 (s), 820 (vs), 792 (vs).

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 (73e)



A solution of 3-chloro-2-(isopropylthio)pyridine (**69**) 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 **TP3**, 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 (*i*-hexane:ethyl acetate = 9.8:0.2) to give 3-allyl-4-(4-chlorophenyl)-2-(isopropylthio)pyridine (**73e**) (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).

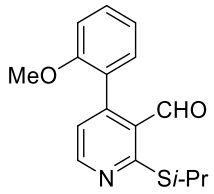
^{13}C-NMR (101 MHz, $CDCl_3$): 159.9, 149.2, 146.5, 137.7, 135.0, 134.4, 130.4, 130.0, 128.6, 120.7, 116.6, 35.7, 33.8, 23.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963 (vw), 1555 (vw), 1520 (w), 1486 (vw), 1422 (w), 1318 (vw), 1250 (w), 1174 (w), 1091 (w), 1052 (vw), 1015 (w), 904 (s), 846 (m), 823 (w), 802 (vw), 726 (vs).

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 (73f)



A solution of 3-chloro-2-(isopropylthio)pyridine (**69**) 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 **TP3**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give 2-(isopropylthio)-4-(2-methoxyphenyl) nicotinaldehyde (**73f**) (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).

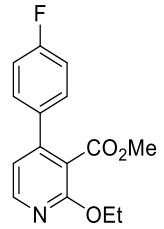
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.7, 161.8, 156.3, 152.1, 151.9, 131.1, 130.8, 125.8, 125.1, 121.2, 121.1, 110.9, 55.6, 34.2, 23.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963 (w), 1686 (vs), 1599 (m), 1581 (w), 1558 (s), 1538 (s), 1492 (m), 1462 (m), 1436 (m), 1396 (w), 1359 (m), 1301 (w), 1274 (m), 1242 (s), 1197 (m), 1185 (m), 1124 (m), 1061 (w), 1023 (m), 864 (m), 814 (m), 755 (m), 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 (76)



Following **TP2**, 3-chloro-2-ethoxypyridine (**57**, 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* **TP1**, 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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give methyl 2-ethoxy-4-(4-fluorophenyl)nicotinate (**76**) (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).

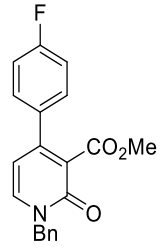
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.45, 163.23 (d, J = 248.8 Hz), 160.70, 148.99, 147.84, 134.04 (d, J = 3.4 Hz), 129.83 (d, J = 8.4 Hz), 117.32, 116.75, 115.90 (d, J = 21.7 Hz), 62.83, 52.53, 14.68.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981 (w), 2951 (w), 1734 (vs), 1607 (m), 1589 (m), 1555 (s), 1514 (s), 1468 (m), 1434 (m), 1421 (s), 1380 (m), 1349 (w), 1328 (s), 1290 (m), 1273 (s), 1227 (s), 1161 (m), 1140 (m), 1117 (s), 1099 (w), 1069 (s), 1032 (m), 824 (m), 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 (77)



Methyl 2-ethoxy-4-(4-fluorophenyl)nicotinate (**76**, 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 (*i*-hexane:ethyl acetate = 6.0:4.0) to give methyl 1-benzyl-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (7**7**) (351 mg, 1.04 mmol, 80% yield) as a colorless 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).

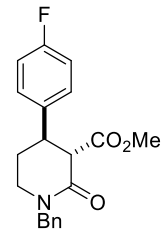
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.9, 163.3 (d, J = 249.7 Hz), 159.6, 149.7, 137.5, 135.6, 133.3 (d, J = 3.4 Hz), 129.4 (d, J = 8.4 Hz), 129.1, 128.7, 128.4, 124.1, 115.9 (d, J = 21.7 Hz), 107.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2359 (w), 1733 (s), 1647 (vs), 1602 (m), 1599 (m), 1592 (m), 1538 (m), 1533 (m), 1521 (w), 1512 (m), 1456 (w), 1371 (w), 1256 (m), 1239 (w), 1228 (m), 1163 (w), 1127 (m), 1090 (w), 703 (w).

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 (78)



(±)-trans

Methyl 1-benzyl-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**77**, 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 the 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 (**78**) (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).

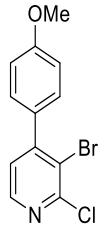
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3207 (w), 2952 (w), 1738 (s), 1666 (vs), 1605 (w), 1511 (s), 1491 (m), 1464 (w), 1457 (w), 1435 (w), 1424 (w), 1342 (m), 1304 (w), 1267 (m), 1223 (m), 1210 (m), 1195 (w), 1161 (m), 1121 (w), 1032 (w), 834 (m), 782 (w), 731 (w).

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.

3-Bromo-2-chloro-4-(4-methoxyphenyl)pyridine (80)



The pyridine **64c** (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 (*i*-hexane:ethyl acetate = 9.5:0.5) to give 3-bromo-2-chloro-4-(4-methoxyphenyl)pyridine (**80**) (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 (s), 2358 (s), 2339 (m), 1608 (m), 1570 (m), 1515 (s), 1506 (m), 1434 (s), 1346 (s), 1297 (m), 1248 (vs), 1180 (s), 1063 (s), 1030 (m), 827 (s), 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.

4.5 Single crystal X-ray Diffraction Studies

Single crystals of compound **64a**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[207] Absorption correction using the multiscan method[202] was applied. The structures were solved with SHELXS-97,[208] refined with SHELXL-97[209] and finally checked using PLATON.[210] Details for data collection and structure refinement are summarized in Table 21.

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.

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

Table 21. Details for X-ray data collection and structure refinement for compound **64a**.

	64a
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	colorless 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

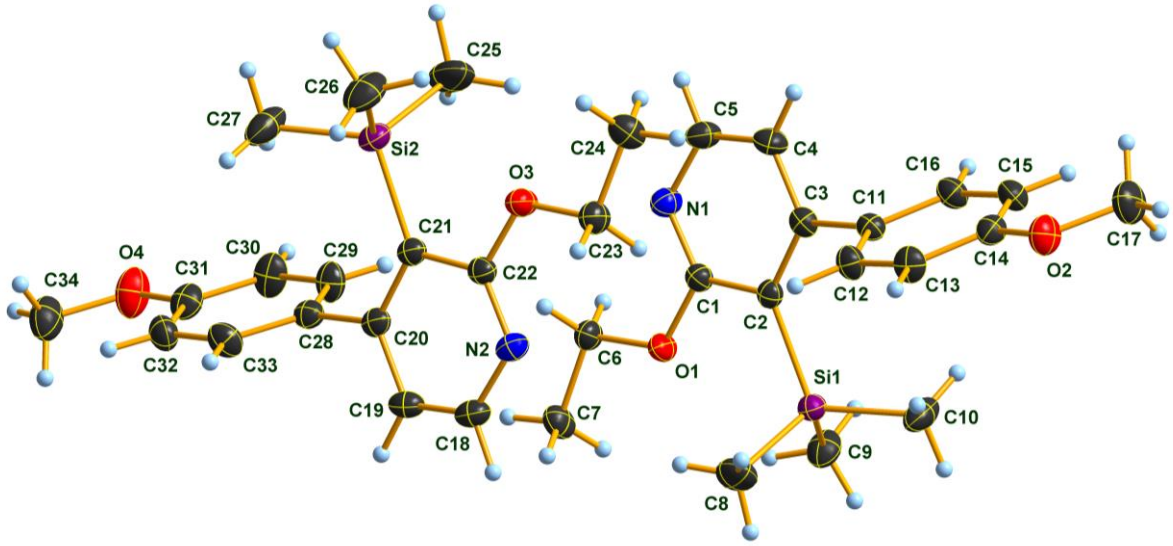


Figure 7. Molecular structure of compound **64a** in the crystal. DIAMOND[211] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 22. Selected bond lengths (Å) of compound **64a**.

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)
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)

[211] DIAMOND, Crystal Impact GbR., Version 3.2i.

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 23. Selected bond angles (°) of compound **64a**.

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 24. Selected torsion angles (°) of compound **64a**.

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 **73a**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[202] Absorption correction using the multiscan method[202] was applied. The structures were solved with SHELXS-97,[203] refined with SHELXL-97[204] and finally checked using PLATON.[205] Details for data collection and structure refinement are summarized in Table 25.

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 25. Details for X-ray data collection and structure refinement for compound **73a**.

	73a
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	colorless 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

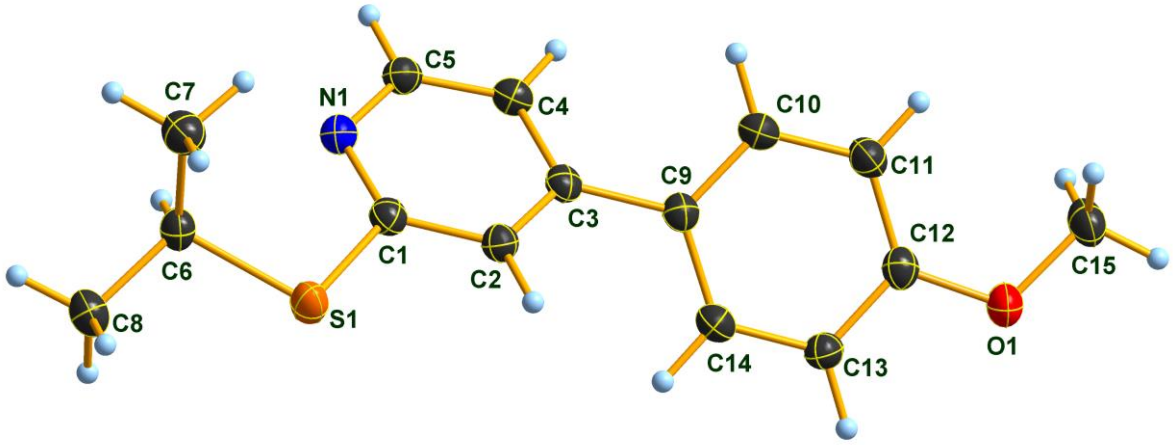


Figure 8. Molecular structure of compound **73a** in the crystal. DIAMOND[206] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 26. Selected bond lengths (Å) of compound **73a**.

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 27. Selected bond angles (°) of compound **73a**.

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 28. Selected torsion angles (°) of compound **73a**.

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 **73b**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[202] Absorption correction using the multiscan method[202] was applied. The structures were solved with SHELXS-97,[203] refined with SHELXL-97[204] and finally checked using PLATON.[205] Details for data collection and structure refinement are summarized in Table 29.

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 29. Details for X-ray data collection and structure refinement for compound **73b**.

	73b
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	colorless 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

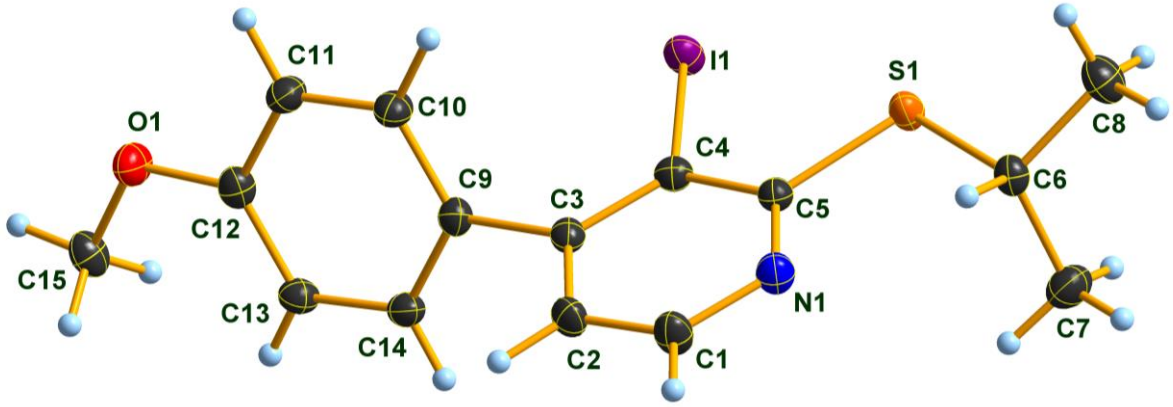


Figure 9. Molecular structure of compound **73b** in the crystal. DIAMOND[206] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 30. Selected bond lengths (Å) of compound **73b**.

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 31. Selected bond angles (°) of compound **73b**.

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 32. Selected torsion angles (°) of compound **73b**.

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. Preparation of Functionalized Amides Using Dicarbamoylzincs

5.1 List of Formamides

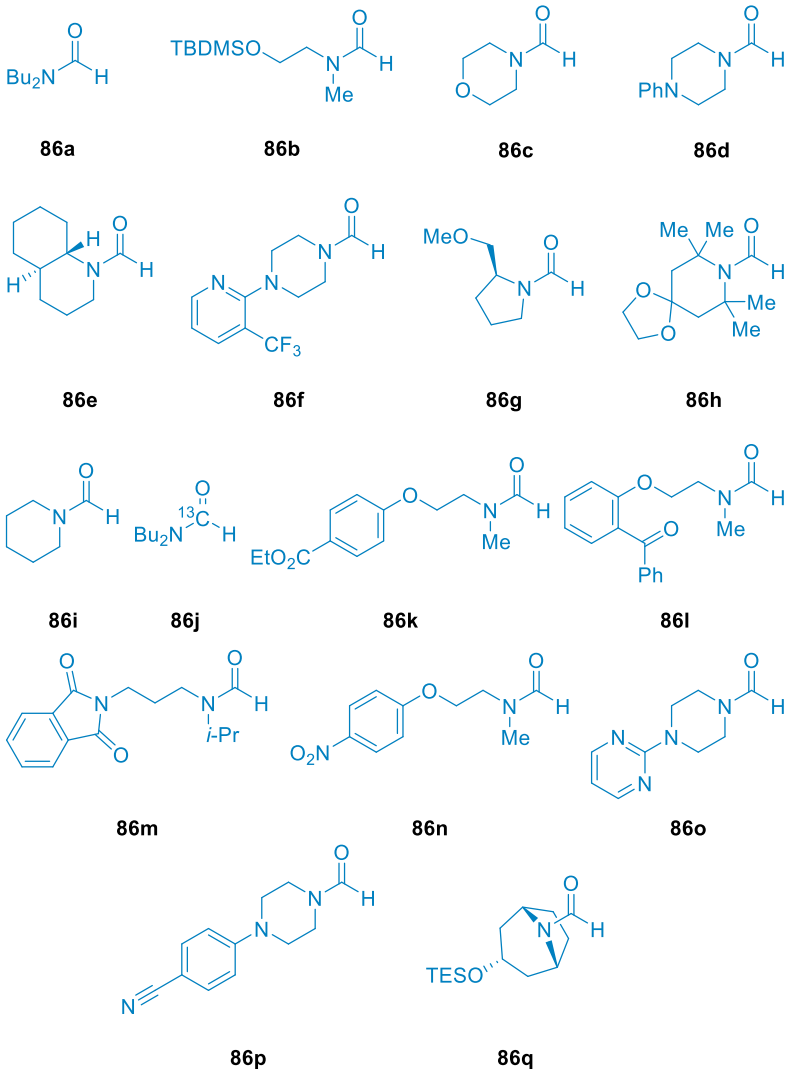


Figure 10. List of formamides.

5.2 List of Dicarbamoylzinc Reagents

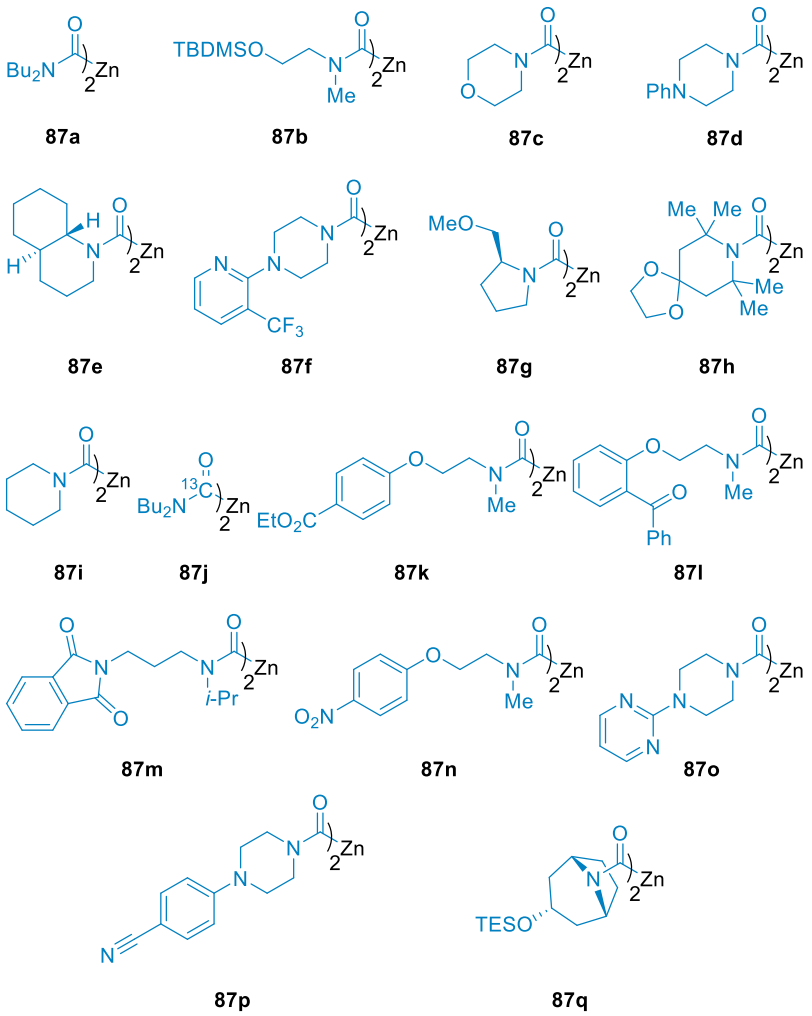
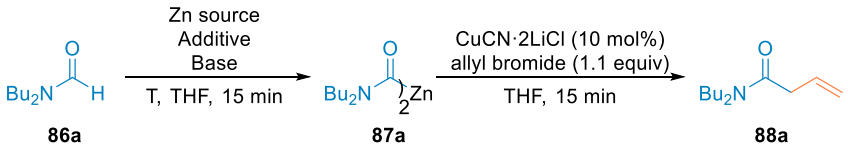


Figure 11. List of dicarbamoylzinc reagents.

5.3 Optimizations and Screenings

5.3.1 Optimization of metalation conditions

Table 33. Optimization of metalation conditions.



86a 87a 88a

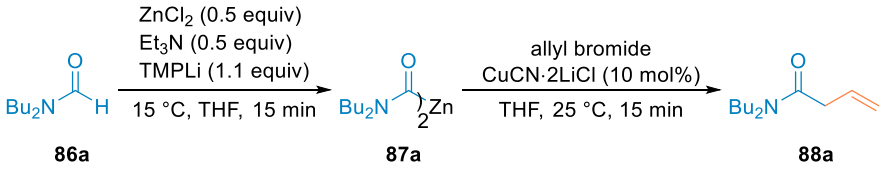
Entry	T [°C]	Base	Zinc source	Additive	Conversion [%]	GC yield [%]
1	15	LDA (1.1 equiv)	$ZnCl_2$ (0.5 equiv)	/	85	70
2	15	Cy_2NLi (1.1 equiv)	$ZnCl_2$ (0.5 equiv)	/	86	71
3	15	TMPLi (1.1 equiv)	$ZnCl_2$ (1.0 equiv)	/	72	53
4	15	TMPLi (1.1 equiv)	$ZnCl_2$ (0.5 equiv)	/	99	97
5	15	TMPLi (1.1 equiv)	$ZnCl_2$ (0.33 equiv)	/	>99	97
6	15	TMPLi (1.1 equiv)	$ZnCl_2$ (0.5 equiv)	Et_3N (0.5 equiv)	>99	98 (94)
6	25	TMPLi (1.1 equiv)	$ZnCl_2$ (0.5 equiv)	Et_3N (0.5 equiv)	>99	90
7	0	TMPLi (1.1 equiv)	$ZnCl_2$ (0.5 equiv)	Et_3N (0.5 equiv)	>99	98
8	15	TMPLi (1.1 equiv)	TMPZnCl·LiCl (0.5 equiv)	/	>99	40
9	15	TMPLi (1.1 equiv)	TMP_2Zn·2LiCl (0.5 equiv)	/	78	<5
10	15	TMPLi (1.5 equiv)	$ZnCl_2$ (0.5 equiv)	/	>99	75

11	15	$TMP_2Zn·2LiCl$ (0.5 equiv)	/	/	39	<5

In all reaction where excess base was used (entries 8, 9, 10), double allylation side product was observed.

*5.3.2 Stability study of dicarbamoylzinc **86a***

Table 34. Stability study of dicarbamoylzinc **86a.**



86a **87a** **88a**

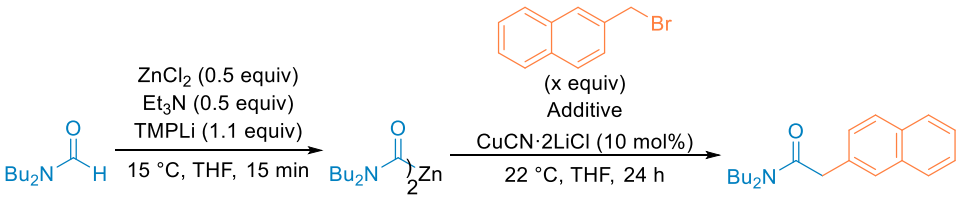
Entry	Time [h]	86a/Standard ratio	GC yield [%]*
1	0	4.41	100
2	12	4.41	100
3	24	4.36	98.9
4	48	4.30	97.5

*Entry at t = 0 h was calibrated to 100%.

From our experience in the reactions with various electrophiles and based on the results of these stability studies we suggest using the reagent within 16 h.

5.3.3 Optimization of the benzylation quench

Table 35. Optimization of benzylation quench.



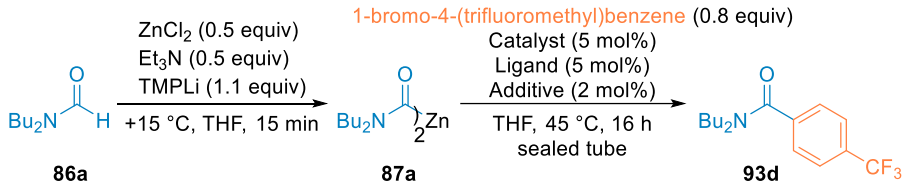
86a **87a** **89a**

Entry	Additive	Equiv x	Conversion [%]	Yield [%]
1	/	1.5	73	60
2	$MgCl_2·LiCl$	1.2	>99	62
3	$MgCl_2·LiCl$	1.5	>99	87 (87)
4	$MgCl_2·LiCl$	2.0	>99	86
5	$MgCl_2·LiCl$*	1.5	>99	87

*Without Et_3N

5.3.4 Optimization of the cross-coupling reaction

Table 36. Optimization of cross-coupling reaction.



Entry	Precatalyst	Ligand	Additive	Conversion of ArBr [%]	GC yield [%]
1	$PdCl_2(dppf)$	/	CuCN·2LiCl	>99	88 (86)
2*	$PdCl_2(dppf)$	/	CuCN·2LiCl	>99	29
3	$PdCl_2(dppf)$	/	/	15	14
4	/	dppf	/	<5	0
5	/	dppf	CuCN·2LiCl	<5	0
6	/	/	CuCN·2LiCl	<5	0
7	$Pd(dba)_2$	dppf	CuCN·2LiCl	ND	82
8	$Pd(dba)_2$	dppf	/	ND	55
9	$Pd(OAc)_2$	dppf	CuCN·2LiCl	ND	78
10	$Pd(OAc)_2$	dppf	/	ND	54
11	$PdCl_2(PPh_3)$	/	/	ND	15
12	$PdCl_2(PPh_3)$	/	CuCN·2LiCl	ND	6
13	Pd1	/	/	ND	6
14	Pd1	/	CuCN·2LiCl	ND	0
15	$XantPhosPdCl_2$	/	/	>99	84
16	$XantPhosPdCl_2$	/	CuCN·2LiCl	20	17
17	$Pd(OAc)_2$	SPhos	/	<5	0
18	$Pd(OAc)_2$	SPhos	CuCN·2LiCl	<5	0
19	Pd2	/	/	>99	78
20	Pd2	/	CuCN·2LiCl	<5	0
21	$Pd(dba)_2$	dppbe	/	<5	1

22	$Pd(dba)_2$	dppbe	CuCN·2LiCl	<5	9

*Metalation performed with $TMP_2Zn·2MgCl_2·2LiCl$ ($MgCl_2$ has a negative impact on cross-coupling). Tetradecane was used as an internal standard

Pd1: Bis(di-tert-butyl(4-dimethylaminophenyl)phoshine)dichloropalladium(II)

Pd2: [1,2-Bis(diphenylphosphino)ethane]dichloropalladium(II)

dppf: 1,1′-Ferrocenediyl-bis(diphenylphosphine); dppbe: 1,2-Bis(diphenylphosphino)benzene

5.4 Typical Procedures

Typical Procedure 1A (TP1A): Cu-catalyzed allylation/propargylation of carbamoylzinc reagents **87a-j** with allylic or propargylic bromides (Method A)

Heat and vacuum dried flask flushed with argon was placed into a water bath at 15 °C. Formamide (1.00 mmol, 1.0 equiv), $ZnCl_2$ solution 1 M in THF (500 µL, 0.50 mmol, 0.5 equiv), Et_3N (51 mg, 0.50 mmol, 0.5 equiv) and THF (2 mL) were added. A freshly prepared TMPLi as ca. 0.5 M solution in THF (1.1 mmol, 1.1 equiv) was dropwise added over 1-2 min. The reaction mixture was stirred for an additional 15 min. A solution of dicarbamoylzinc reagent $(R^1R^2NCO)_2Zn$ was obtained. The allylic or propargylic bromide (1.1 mmol, 1.1 equiv) was added neat at 22 °C quickly followed by CuCN·2LiCl 1 M solution in THF (100 µL, 0.01 mmol, 10 mol%). The reaction mixture was stirred for 15 min and then quenched with saturated $NH_4Cl_{(aq)}$ (2 mL). The product was extracted with ethyl acetate or dichloromethane (3 x 100 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent *in vacuo*, flash column chromatography purification afforded analytically pure products of type **88**.

Typical Procedure 1B (TP1B): Cu-catalyzed allylation of carbamoylzinc reagents **87k-o** with allylic or propargylic bromides (Method B)

Heat and vacuum dried flask flushed with argon was placed into a water bath at 22 °C. Neat formamide (1.00 mmol, 1.0 equiv) was placed in the flask (oily substrates were transferred as a THF solution and THF was removed under high vacuum) and a solution of TMP_2Zn (0.55 mmol, 0.55 equiv) in THF was dropwise added. After stirring for the indicated time (2-24 h) a solution of dicarbamoylzinc reagent $(R^1R^2NCO)_2Zn$ was obtained. After dilution with THF (10 mL) allylic bromide (1.1 mmol, 1.1 equiv) was added neat at 22 °C quickly followed by CuCN·2LiCl 1 M solution in THF (100 µL, 0.01 mmol, 10 mol%). The reaction mixture was stirred for the indicated time (15 min to 12 h) and then quenched with saturated $NH_4Cl_{(aq)}$ (2 mL). The product was extracted with ethyl acetate or DCM (3 x 100 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent *in vacuo*, flash column chromatography purification afforded analytically pure products of type **88**.

NOTE: Examples **88l**, **88m**, **88n** and 8**8p** were made using $TMP_2Zn·2MgCl_2·2LiCl$ and example 8**8o** was prepared using $TMP_2Zn·2LiCl$ (without $MgCl_2$).

Typical Procedure 2 (TP2): Benzylation of carbamoylzinc reagents **87a**, **87d** and **87g** with benzylic bromides

Heat and vacuum dried flask flushed with argon was placed into a water bath at 15 °C. Formamide (1.00 mmol, 1.0 equiv), $ZnCl_2$ solution 1 M in THF (500 µL, 0.50 mmol, 0.5 equiv), Et_3N (51 mg, 0.50 mmol, 0.5 equiv) and THF (2 mL) were added. Freshly prepared TMPLi as ca. 0.5 M solution in

THF (1.1 mmol, 1.1 equiv) was dropwise added over 1-2 min. The reaction mixture was stirred for an additional 15 min. A solution of dicarbamoylzinc reagent $(R^1R^2NCO)_2Zn$ was obtained. A solution of $MgCl_2$·LiCl ca. 0.5 M in THF (2.0 mL) was dropwise added at 22 °C. After 5 min of stirring CuCN·2LiCl 1 M solution in THF (100 µL, 0.01 mmol, 10 mol%) at room temperature. The benzylic bromide was added to the reaction mixture at room temperature neat if it is a liquid or as a 1 M solution in THF if it is solid. The reaction mixture was stirred for 24 h and then quenched with saturated $NH_4Cl_{(aq)}$ (2 mL). The product was extracted with ethyl acetate or DCM (3 x 100 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent *in vacuo*, flash column chromatography purification afforded analytically pure products of type **89**.

Typical Procedure 3 (TP3): Reaction of carbamoylzinc reagents **87a** and **87f** with aldehydes

Heat and vacuum dried flask flushed with argon was placed into a water bath at 15 °C. Formamide (1.00 mmol, 1.0 equiv), $ZnCl_2$ solution 1 M in THF (500 µL, 0.50 mmol, 0.5 equiv), Et_3N (51 mg, 0.50 mmol, 0.5 equiv) and THF (2.0 mL) were added. Freshly prepared TMPLi as ca. 0.5 M solution in THF (1.1 mmol, 1.1 equiv) was dropwise added over 1-2 min. The reaction mixture was stirred for an additional 15 min. A solution of dicarbamoylzinc reagent $(R^1R^2NCO)_2Zn$ was obtained. A solution of $MgCl_2$·LiCl ca. 0.5 M in THF (2.0 mL, 1.0 mmol, 1.0 equiv) was dropwise added at 22 °C. After 5 min of stirring, neat aldehyde (1.2 mmol, 1.2 equiv) was added at room temperature. The reaction mixture was stirred for 24 h and then quenched with saturated $NH_4Cl_{(aq)}$ (2 mL). The product was extracted with ethyl acetate or DCM (3 x 100 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent *in vacuo*, flash column chromatography purification afforded analytically pure products of type **90**.

Typical Procedure 4 (TP4): Acylation of carbamoylzinc reagents **87a** and **87f** with acyl chlorides

Heat and vacuum dried flask flushed with argon was placed into a water bath at 15 °C. Formamide (1.00 mmol, 1.0 equiv), $ZnCl_2$ solution 1 M in THF (500 µL, 0.50 mmol, 0.5 equiv), Et_3N (51 mg, 0.50 mmol, 0.5 equiv) and THF (2.0 mL) were added. Freshly prepared TMPLi as ca. 0.5 M solution in THF (1.1 mmol, 1.1 equiv) was dropwise added over 1-2 min. The reaction mixture was stirred for an additional 15 min. A solution of dicarbamoylzinc reagent $(R^1R^2NCO)_2Zn$ was obtained. Freshly distilled acyl chloride was added at 22 °C. The reaction mixture was stirred for 16 h and then quenched with saturated $NH_4Cl_{(aq)}$ (2 mL). The product was extracted with ethyl acetate or DCM (3 x 100 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent *in vacuo*, flash column chromatography purification afforded analytically pure products of type **91**.

Typical Procedure 5 (TP5): 1,4-Addition of carbamoylzinc reagents **87a**

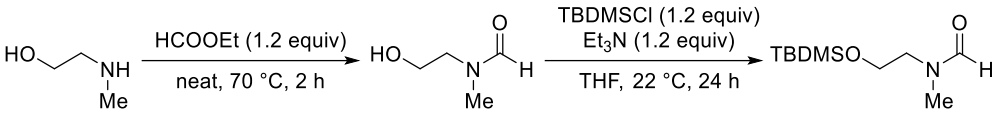
Heat and vacuum dried flask flushed with argon was placed into a water bath at 15 °C. Formamide (2.00 mmol, 2.0 equiv), $ZnCl_2$ solution 1 M in THF (1.00 mL, 1.00 mmol, 1.0 equiv), Et_3N (101 mg, 1.00 mmol, 1.0 equiv) and THF (4.0 mL) were added. Freshly prepared TMPLi as ca. 0.5 M solution in THF (2.2 mmol, 2.2 equiv) was dropwise added over 1-2 min. The reaction mixture was stirred for an additional 15 min and then cooled to −78 °C. A solution of dicarbamoylzinc reagent $(R^1R^2NCO)_2Zn$ was obtained. CuCN·2LiCl 1 M solution in THF (1.00 mL, 1.00 mmol, 1.0 equiv) was dropwise added. Stirring was continued for 30 min after which a BF_3·Et_2O (123 µL, 1.0 mmol, 1.0 equiv) was added. It was immediately followed by a neat cyclohex-2-en-1-one (96.0 mg, 1.00 mmol, 1.0 equiv). The reaction temperature was maintained at −78 °C using a cryostat for 24 h. It was then quenched with 10 mL of saturated $NH_4Cl_{(aq)}$. The product was extracted with ethyl acetate (3 x 100 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent *in vacuo*, flash column chromatography purification afforded analytically pure product **92a**.

Typical Procedure 6 (TP6): Cross-coupling of carbamoyl zinc reagents **87a**, **87e**, **87f**, **87m**, **87p** and **87q** with aryl or alkenyl bromides

To a flame dried 20 mL pressure tube formamide (1.00 mmol, 1.0 equiv) in THF, $ZnCl_2$ as 1 M solution in THF (500 µL, 0.50 mmol, 0.5 equiv) and Et_3N (51.0 mg, 0.50 mmol, 0.5 equiv) and THF (2 mL) were added. At 15 °C, a 0.5 M solution of TMPLi (1.1 equiv) in THF was dropwise added over 2 min. The mixture was left to stir for 15 min to obtain the clear solution of dicarbamoylzinc $(R^1R^2NCO)_2Zn$. In a separate flask $Pd(dppf)Cl_2$ (36.6 mg, 0.05 mmol, 5 mol%), aryl bromide (0.80 mmol, 0.8 equiv) and THF (2 mL) were added to form a fine suspension. The suspension was quantitatively transferred into a solution of the dicarbamoylzinc reagent followed by a 1 M solution of CuCN·2LiCl (20 µL, 20.0 µmol, 2 mol%). The pressure tube was sealed with a single-use Teflon stopper and the reaction mixture was stirred at 45 °C for 16 h. After cooling the reaction mixture to 22 °C, the sealed tube was carefully opened and saturated $NH_4Cl_{(aq)}$ (2 mL) was added. The product was extracted with ethyl acetate or DCM (3 x 100 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent *in vacuo*, flash column chromatography purification afforded analytically pure products of type **93**.

5.5 Preparation of Starting Materials

_N_-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-_N_-methylformamide (86b)



N-Methylaminoethanol (51.08 g, 0.68 mol, 1.0 equiv) was cooled to 0 °C (ice/water bath) and HCOOEt (74.08, 1.00 mol, 1.47 equiv) was added portionwise. The reaction mixture was heated to reflux for 1 h, concentrated *in vacuo* and then distilled by slow fractional distillation (6 mbar, 160-165 °C) to give N-(2-hydroxyethyl)-N-methylformamide (64.4 g, 0.624 mol, 92% yield) as clear, colorless liquid. A small amount of bisformylation impurities can be present.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92/7.88 (2 x s, 1H), 4.40/3.96 (t, *J* = 5.7 Hz, 1H), 3.68 – 3.54 (m, 2H), 3.39 – 3.33/3.29 – 3.21 (2 x m, 2H), 2.93/2.81 – 2.73 (s + m, 3H) (mixture of rotamers).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.6, 163.6, 59.5, 58.4, 52.1, 47.1, 35.8, 29.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3368, 2961, 2923, 1646, 1441, 1394, 1258, 1204, 1081, 1049, 866, 795.

MS (EI, 70 eV): *m/z* (%) = 72 (14), 45 (14), 44 (51), 43 (100), 42 (15).

HRMS (EI): *m/z* calc. for $[C_4H_9NO_2]$: 103.0633; found 103.0636.

N-(2-Hydroxyethyl)-*N*-methylformamide (2.50 g, 24.2 mmol, 1.0 equiv) was dissolved in THF (30 mL) and TBDMSCl (4.39 g, 29.1 mmol, 1.2 equiv) and Et_3N (2.94 g, 29.0 mmol, 1.2 equiv) were added. After 24 h, the white suspension was quenched with 50 mL distilled H_2O and transferred into a separatory funnel. The mixture was extracted with DCM (3 x 200 mL), combined organic layers dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography with pentane:ethyl acetate = 1:1 afforded *N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)-*N*-methylformamide (**86b)** (4.78 g, 22 mmol, 91% yield) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 (s, 1H), 3.66 (t, *J* = 5.1 Hz, 2H), 3.30 (t, *J* = 5.1 Hz, 2H), 2.86 (s, 3H), 0.85 – 0.82 (m, 9H), 0.02 – 0.00 (m, 6H) (major rotamer).

8.02 (s, 1H), 3.74 (t, *J* = 5.4 Hz, 2H), 3.41 (t, *J* = 5.4 Hz, 2H), 3.02 (s, 3H), 0.88 – 0.85 (m, 9H), 0.04 – 0.02 (m, 6H) (minor rotamer).

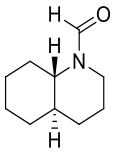
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.42, 162.7, 61.4, 60.2, 52.1, 47.2, 36.6, 30.2, 25.9, 25.9, 18.3, 18.2, -5.4, -5.4, -5.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2852, 1649, 1462, 1443, 1414, 1366, 1352, 1318, 1302, 1269, 1253, 1245, 1207, 1186, 1154, 1136, 1098, 1060, 992, 958, 904, 891, 840, 821, 774, 717.

MS (EI, 70 eV): *m/z* (%) = 160 (100), 116 (33), 86 (21), 75 (45).

HRMS (EI): *m/z* calc. for [$C_{12}H_{23}NO$]: 217.1498; found: 202.1256 (M-CH_3).

***trans*-Octahydroquinoline-1(2H)-carbaldehyde (86e)**



The flask was heat dried under a vacuum and filled with Ar. Acetic acid anhydride (7.37 mL, 78.0 mmol, 2.6 eq.) and formic acid (3.62 mL, 96.0 mmol, 3.2 equiv) were mixed in THF (100 mL) and heated at 40 °C for 1 h. The reaction mixture was cooled to −10 °C with an ice/$NaCl_{(aq)}$ bath. (*trans*)-Decahydroisoquinoline (4.1 g, 30.0 mmol, 1.0 equiv) was dissolved in THF (50 mL), dropwise added to the reaction mixture and stirred for 2 h in the ice/$NaCl_{(aq)}$ bath. The solution was neutralized with saturated $Na_2CO_{3(aq)}$ solution. Complete consumption of starting material and product formation was verified by GC/MS analysis. The product was extracted with DCM (4 x 300 mL), combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. After a flash column chromatography with ethyl acetate:pentane = 4:6, *trans*-octahydroisoquinoline-2(1H)-carbaldehyde (**86e**) (4.82 g, 28.8 mmol, 96% yield) was obtained as a yellowish solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (s, 1H), 4.63 – 4.55 (m, 1H), 2.83 – 2.72 (m, 1H), 2.39 (td, *J* = 12.9, 3.0 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.94 – 1.87 (m, 1H), 1.78 – 1.71 (m, 1H), 1.70 – 1.61 (m, 3H), 1.61 – 1.52 (m, 1H), 1.51 – 1.36 (m, 1H), 1.35 – 1.10 (m, 4H), 1.09 – 0.96 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.7, 62.7, 43.4, 42.0, 32.8, 32.7, 29.2, 25.8, 25.5, 25.4.

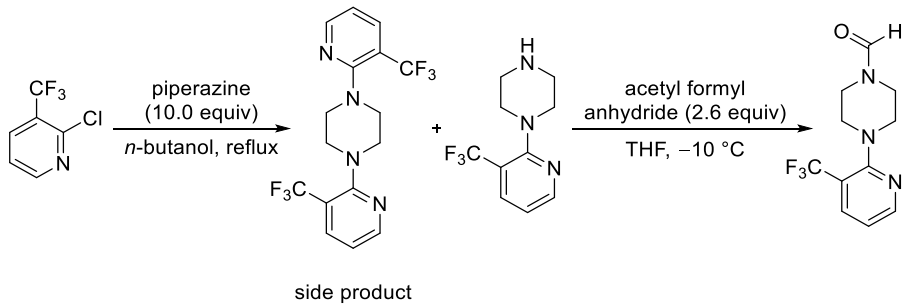
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2852, 1649, 1462, 1443, 1414, 1366, 1352, 1318, 1302, 1269, 1253, 1245, 1207, 1186, 1154, 1136, 1098, 1060, 992, 958, 904, 891, 840, 821, 774, 717.

MS (EI, 70 eV): *m/z* (%) = 167 (29), 124 (100), 96 (61), 79 (12).

HRMS (EI): *m/z* calc. for [$C_{12}H_{23}NO$]: 167.1310; found: 167.1303 (M+H).

M.p. (°C): 41.5-43.6.

4-(3-(Trifluoromethyl)pyridin-2-yl)piperazine-1-carbaldehyde (86f)



To a solution of 2-chloro-3-(trifluoromethyl)pyridine (4.5 g, 25 mmol, 1.0 equiv) in *n*-butanol was added piperazine (21.5 g, 250 mmol, 10.0 equiv) in one portion and the resulting suspension was heated under reflux (oil bath temperature 130 °C) for 17 h. Heating was stopped, the warm reaction mixture was transferred into an aqueous 2M $NaOH_{(aq)}$ solution (400 mL) and the product was extracted with ethyl acetate (4x700 mL). Organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to obtain crude 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine. The product was purified *via* column chromatography using first pentane:ethyl acetate:Et_3N = 6:3:1 to elute bisarylation side product and then increasing polarity to ethyl acetate:Et_3N=9:1. The fractions containing the product were combined and concentrated *in vacuo* to yield 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine (5.3 g, 22.9 mmol, 92% yield) as reddish oil.

The flask was heat dried under a vacuum and filled with Ar. Acetic acid anhydride (5.4 mL, 57.2 mmol, 2.6 eq.) and formic acid (2.66 mL, 70.2 mmol, 3.2 equiv) were mixed in THF (100 mL) and heated at 40 °C for 1 h. The reaction mixture was cooled to −10°C with an ice/$NaCl_{(aq)}$ bath. 1-(3-(Trifluoromethyl)pyridin-2-yl)piperazine (5.09 g, 22.0 mmol, 1.0 equiv) was dissolved in THF (50 mL), dropwise added to the reaction mixture and stirred for 2 h in the ice/$NaCl_{(aq)}$ bath. The solution was neutralized with sat. Na_2CO_3. Complete consumption of starting material and product formation was verified by GC/MS analysis. The product was extracted with DCM (4 x 300 mL), combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. After a flash column chromatography with ethyl acetate:pentane 1:1, 4-(3-(Trifluoromethyl)pyridin-2-yl)piperazine-1-carbaldehyde (**86f**) (5.08 g, 19.6 mmol, 89% yield) was obtained as a reddish solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 – 8.41 (m, 1H), 8.08 (s, 1H), 7.89 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.11 – 7.02 (m, 1H), 3.71 – 3.65 (m, 2H), 3.54 – 3.46 (m, 2H), 3.28 – 3.23 (m, 2H), 3.22 – 3.17 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.0, 151.4 (q, *J* = 1.2 Hz), 137.3 (q, *J* = 5.0 Hz), 123.9 (q, *J* = 272.6 Hz), 118.3, 118.1 (q, *J* = 30.9 Hz), 51.5 (q, *J* = 1.2 Hz), 50.7 (q, *J* = 1.3 Hz), 45.8, 40.2.

^{19}F-NMR (377 MHz, $CDCl_3$): −60.4.

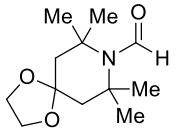
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1664, 1589, 1571, 1438, 1401, 1368, 1307, 1280, 1251, 1225, 1192, 1137, 1116, 1079, 1062, 1024, 1010, 932, 812, 796, 782, 671.

MS (EI, 70 eV): *m/z* (%) = 201 (20), 189 (21), 188 (41), 187 (100), 175 (70), 173 (14), 167 (18), 155 (34), 147 (34), 146 (22), 128 (54), 127 (12).

HRMS (EI): *m/z* calc. for [$C_{12}H_{23}NO$]: 259.0932; found: 260.1005 (M+H).

M.p. (°C): 76.6-77.8.

7,7,9,9-Tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carbaldehyde (86h)



The compound was synthesized according to the modified literature procedure. [212]

4,4-Ethylenedioxy-2,2,6,6-tetramethylpiperidine (2.12 g, 10.6 mmol, 1.0 equiv), benzyltriethylammonium chloride (1.55 g, 6.80 mmol, 0.6 eq.) as phase-transfer-catalyst, 50 wt.-% aqueous NaOH (37 mL), $CHCl_3$ (11.1 mL, 136 mmol, 8.5 equiv) and CH_2Cl_2 (49 mL) were mixed and refluxed for 24 h at 50 °C. On cooling, the mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were dried, filtered and evaporated for the purification of the crude product by column chromatography (SiO_2, 1 L *i*-hexane:ethyl acetate = 4:1, then *i*-hexane:ethyl acetate = 7:3). The fractions containing the product were combined and concentrated *in vacuo* to yield *N*-formyl-4,4-ethylenedioxy-2,2,6,6-tetramethylpiperidine (**86h**) (2.14 g, 9.44 mmol, 89% yield) as a light brown oil which solidified over time.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 (s, 1H), 3.88 (s, 4H), 1.96 (s, 2H), 1.93 (s, 2H), 1.52 (s, 6H), 1.43 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.7, 105.7, 63.9, 56.1, 55.5, 48.0, 47.9, 32.4, 28.2.

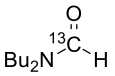
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974, 2928, 2882, 1646, 1453, 1434, 1422, 1398, 1376, 1363, 1332, 1319, 1282, 1242, 1220, 1188, 1178, 1135, 1100, 1068, 1021, 994, 978, 952, 934, 910, 861, 846, 801, 710.

MS (EI, 70 eV): *m/z* (%) = 212 (16), 127 (100), 98 (24), 83 (15).

HRMS (EI): *m/z* calc. for [$C_{12}H_{23}NO$]: 227.1521; found 227. 1513.

M.p. (°C): 50.6-51.9.

N,*N*-Dibutyl[^{13}C]formamide (86j)



To DCC (5.11 g, 24.8 mmol, 1.2 equiv) dissolved in dry DCM (20 mL), was added HOBt (3.35 g, 24.8 mmol, 1.2 equiv) in one portion at 25 °C. After 20-30 min, a clear solution was obtained and cooled to –25 °C. In a separate flask, H^{13}COOH (95 wt% in H_2O, 99% ^{13}C atom) was dissolved in dissolved DCM (20 mL) and cooled to –25 °C (suspension formed). The solution of DCC/HOBt was dropwise added over 15 min into the solution of H^{13}COOH. After stirring for 30 min at –25 °C, neat Bu_2NH (3.33 g, 25.8 mmol, 1.25 equiv) was dropwise added. The suspension was allowed to slowly warm to 22 °C and stirred for 24 h. The reaction mixture was filtered over a sinter to remove *N*,*N'*-dicyclohexylurea. The DCM layer was washed with 10% Na_2CO_3(aq) (3 x 30 mL) and then with 1 M HCl (3 x 10 mL). After drying over $MgSO_4$, filtrating and concentrating the organic layers distillation under reduced pressure (69 °C, 0.15 mbar) gave pure $Bu_2N^{13}CHO$ (**86j**) (2.06 g, 13.1 mmol, 64% yield) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01 (d, *J* = 190.5 Hz, 1H), 3.30 – 3.22 (m, 2H), 3.21 – 3.12 (m, 2H), 1.54 – 1.43 (m, 4H), 1.35 – 1.21 (m, 4H), 0.91 (td, *J* = 7.3, 2.8 Hz, 6H).

[212] Z. Blum, K. Nyberg, *Acta Chem. Scand. Ser. B* **1981**, *35*, 743.

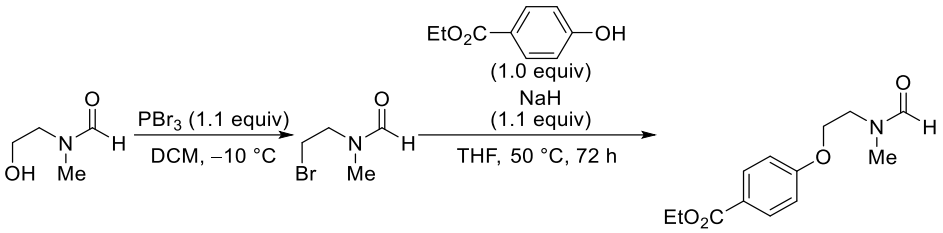
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.8, 47.2 (d, *J* = 4.6 Hz), 41.9, 30.8, 29.5, 20.3, 19.7, 13.9, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2932, 2873, 1626, 1460, 1422, 1398, 1378, 1212, 1198, 1113, 950, 733.

MS (EI, 70 eV): *m/z* (%) = 158 (12), 114 (100), 72 (50).

HRMS (EI): *m/z* calc. for [^{13}C-$C_9H_{19}NO$]: 158.1501; found 159.1572 (M+H).

Ethyl 4-(2-(*N*-methylformamido)ethoxy)benzoate (86k)



N-(2-Hydroxyethyl)-*N*-methylformamide (10.31 g, 100 mmol, 1.0 equiv) in DCM (100mL) was cooled to –10 °C and PBr_3 (28.4 g, 105 mmol, 1.05 equiv) was added via dropping funnel over 1 h. The solution was stirred for 12 h and was then neutralized with distilled water (200 mL). After stirring for ca. 45 min the reaction mixture was extracted with DCM (3 x 200 mL). Combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. After a fractional distillation (63 °C, 0.12 mbar), *N*-(2-bromoethyl)-*N*-methylformamide (6.43 g, 39.0 mmol, 39% yield) was obtained as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02 (s, 1H), 3.65/3.58 (t, J = 6.6 Hz/6.1 Hz, 2H), 3.46 – 3.40 (m, 2H), 2.99/2.82 (2 x s, 3H) (mixture of rotamers).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.9, 162.9, 50.9, 46.3, 35.5, 29.4, 29.3, 28.1 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3356, 2957, 2775, 1717, 1584, 1461, 1422, 1390, 1353, 1153, 1074, 1026, 994, 900, 847, 794, 661.

MS (EI, 70 eV): *m/z* (%) = 82 (14), 80 (14), 72 (20), 70 (11), 61 (16), 45 (15), 44 (99), 43 (100), 41 (11).

HRMS (EI): *m/z* calc. for [C_4H_8BrNO]: 164.9789; found 164.9789.

Ethyl 4-hydroxybenzoate (4.15 g, 25 mmol, 1.0 equiv) was dissolved in THF (50 mL) and 60% NaH (1.20 g, 30 mmol, 1.2 equiv) was added portion-wise over 30 min at 22 °C. Thereafter *N*-(2-bromoethyl)-*N*-methylformamide was dropwise added and the solution was heated to 50 °C (oil bath temp.) over 72 h. Extracted with DCM (3 x 200 mL) and combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Column chromatography on SiO_2 with ethyl acetate afforded ethyl 4-(2-(N-methylformamido)ethoxy)benzoate (**86k**) (3.68 g, 14.6 mmol, 59% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11/8.05 (2 x s, 1H), 7.99 – 7.92 (m, 2H), 6.91 – 6.80 (m, 2H), 4.36 – 4.25 (m, 2H), 4.15 (t, *J* = 5.2 Hz, 1H), 4.08 (t, *J* = 5.1 Hz, 1H), 3.70 (t, *J* = 5.2 Hz, 1H), 3.62 (t, *J* = 5.1 Hz, 1H), 3.08/2.92 (2 x s, 2H), 1.37 – 1.31 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.2, 166.2, 163.2, 162.9, 162.0, 161.7, 131.6, 131.6, 123.7, 123.4, 114.0, 114.0, 77.2, 66.3, 65.0, 60.8, 60.7, 48.8, 44.1, 36.4, 30.2, 14.4.

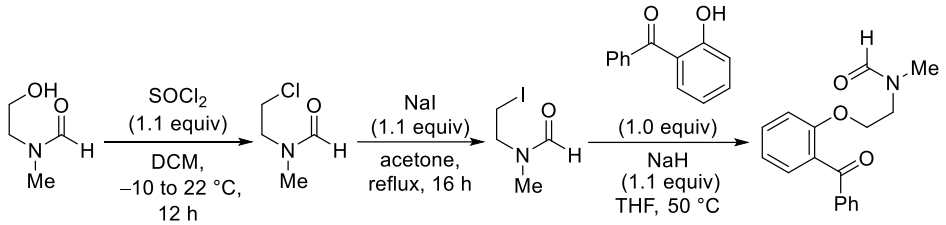
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1696, 1677, 1665, 1606, 1582, 1510, 1470, 1425, 1391, 1363, 1271, 1252, 1213, 1175, 1126, 1102, 1087, 1078, 1043, 1016, 980, 904, 878, 844, 770, 694, 657.

MS (EI, 70 eV): *m/z* (%) = 86 (100), 72 (13), 58 (19), 44 (19).

HRMS (EI): *m/z* calc. for [$C_{13}H_{17}NO_4$]: 251.1158; found 250.1075 (M-H).

M.p. (°C): 94.7-97.3.

***N*-(2-(2-Benzoylphenoxy)ethyl)-*N*-methylformamide (86l)**



N-(2-Hydroxyethyl)-*N*-methylformamide (10.31 g, 0.10 mol, 1.0 equiv) in DCM (100 mL) was cooled to −10 °C and $SOCl_2$ (38.07 g, 0.32 mol, 1.02 equiv) was added via dropping funnel over 2 h. The solution was stirred for 12 h and was then concentrated *in vacuo*. Fractional distillation under reduced pressure with vigreaux column (0.1 mbar, 85-90 °C) afforded *N*-(2-chloroethyl)-*N*-methylformamide (36.0 g, 0.296 mol, 95% yield) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02/8.01 (2 x s, 1H), 3.64 – 3.55 (m, 3H), 3.54 – 3.49 (m, 1H), 3.00/2.83 (2 x s, 3H) (mixture of rotamers).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.1, 163.0, 51.0, 46.4, 41.2, 40.8, 35.8, 29.5 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1659, 1485, 1439, 1396, 1362, 1298, 1261, 1235, 1163, 1072, 1035, 675.

MS (EI, 70 eV): *m/z* (%) = 121.0288 (19), 72 (83), 44 (100), 42 (38), 41 (14).

HRMS (EI): *m/z* calc. for [C_4H_8ClNO]: 121.0294; found 121.0288.

N-(2-Chloroethyl)-*N*-methylformamide (29.2 g, 0.24 mol, 1.0 equiv) in anhydrous acetone (25 mL) was dropwise added to NaI (37.5 g, 250 mmol, 1.04 equiv) in anhydrous acetone (250 mL) over 45 min at 22 °C. The solution was heated to 70 °C (oil bath temp) for 16 h. A small amount of *N*-(2-chloroethyl)-*N*-methylformamide (<5%) was left in the reaction mixture. The fractional distillation under reduced pressure (0.2 mbar, 118-122 °C) afforded *N*-(2-iodooethyl)-*N*-methylformamide (44.73 g, 210 mmol, 87% yield) as slightly yellowish oil. The iodide was stored in the freezer under argon.

(2-Hydroxyphenyl)(phenyl)methanone (5.94 g, 30 mmol, 1.0 equiv) was dissolved in THF (50 mL) and 60% NaH (1.32 g, 33 mmol, 1.1 equiv) was added portion-wise over 30 min at 22 °C. Thereafter *N*-(2-iodoethyl)-*N*-methylformamide was dropwise added and the solution was heated to 50 °C (oil bath temp.) over 24 h. Extracted with DCM (3 x 200 mL) and combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Column chromatography on SiO_2 with ethyl acetate afforded *N*-(2-(2-benzoylphenoxy)ethyl)-*N*-methylformamide (**86l**) (3.41 g, 12.0 mmol, 40% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.80 – 7.71 (m, 2H), 7.57 – 7.49 (m, 2H), 7.46 – 7.31 (m, 4H), 7.09 – 6.99 (m, 1H), 6.93 – 6.87 (m, 1H), 4.04 (t, *J* = 5.0 Hz, 1H), 3.95 (t, *J* = 5.0 Hz, 1H), 3.36 (t, *J* = 5.0 Hz, 1H), 3.22 (t, *J* = 5.0 Hz, 1H), 2.60/2.52 (2 x s, 3H) (mixture of rotamers).

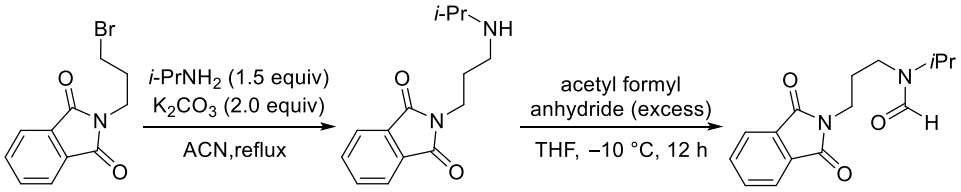
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.4, 196.1, 162.8, 162.6, 156.0, 155.9, 138.0, 137.8, 133.1, 133.1, 132.1, 132.1, 130.0, 129.7, 129.6, 129.5, 129.1, 128.8, 128.3, 121.5, 121.1, 112.4, 112.0, 66.8, 66.2, 48.7, 44.2, 36.1, 30.0 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1658, 1597, 1580, 1486, 1449, 1388, 1316, 1295, 1238, 1152, 1110, 1090, 1074, 927, 905, 750, 701.

MS (EI, 70 eV): *m/z* (%) = 197 (11), 152 (10), 91 (27), 86 (100), 77 (13), 58 (17).

HRMS (EI): *m/z* calc. for [$C_{17}H_{17}NO_3$]: 283.1208; found 282.1208.

***N*-(3-(1,3-Dioxoisoindolin-2-yl)propyl)-*N*-isopropylformamide (86m)**



2-(3-Bromopropyl)isoindoline-1,3-dione (8.04 g, 30 mmol, 1.0 equiv), isopropylamine (2.66 g, 45.0 mmol, 1.5 equiv) and K_2CO_3 (10.37 g, 75.0 mmol, 2.5 equiv) were mixed in acetonitrile (100 mL) and refluxed for 16 h. Complete consumption of starting material and formation of 2-(3-(isopropylamino)propyl)isoindoline-1,3-dione was verified by GC/MS analysis. In a separate flask acetyl formyl anhydride (AFA) in dry THF was generated by heating a mixture of formic acid (12.1 mL, 320 mmol) and acetanhydride (24.6 mL, 260 mmol) in THF (150 mL) over 2 h at 40 °C. The reaction mixture was cooled to −10 °C with an ice/$NaCl_{(aq)}$ bath. A crude reaction mixture containing 2-(3-(isopropylamino)propyl)isoindoline-1,3-dione in acetonitrile was added in small portions over 20 min to the cooled solution of acetyl formyl anhydride (AFA) in dry THF. After 12 h the reaction mixture was concentrated *in vacuo* (no aqueous work up). After a flash column chromatography on SiO_2 with pentane:ethyl acetate =1:1, *N*-(3-(1,3-dioxoisoindolin-2-yl)propyl)-*N*-isopropylformamide (**86m**) (7.01 g, 25.6 mmol, 85% yield) was obtained as a colorless oil which solidified over time.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.08/7.98 (2 x s, 1H), 7.78 – 7.72 (m, 2H), 7.68 – 7.61 (m, 2H), 3.70 – 3.59 (m, 3H), 3.26 – 3.15 (m, 2H), 1.92 – 1.82 (m, 2H), 1.24 – 1.10 (m, 6H) (mixture of rotamers).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.1, 168.1, 162.8, 162.2, 134.1, 133.9, 131.9, 131.7, 123.2, 123.1, 49.9, 44.6, 42.4, 38.2, 35.8, 35.3, 30.3, 28.2, 22.1, 20.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1767, 1711, 1641, 1433, 1398, 1364, 1311, 1195, 1128, 1084, 1036, 1028, 1019, 890, 778, 713.

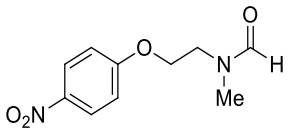
MS (EI, 70 eV): *m/z* (%) = 245 (27), 231 (20), 188 (41), 160 (100), 133 (14), 130 (25), 114 (24), 98 (12), 77 (12), 72 (18).

HRMS (EI): *m/z* calc. for [$C_{15}H_{18}N_2O_3$]: 274.1312; found 275.1383 (M+H).

M.p. (°C): 102.2 (ethyl acetate).

X-Ray: Crystals suitable for X-Ray diffraction were obtained from ethyl acetate at −18 °C. See pages 264-268.

_N_-Methyl-_N_-(2-(4-nitrophenoxy)ethyl)formamide (86n)



To a 2-(methylamino)ethanol (3.76 g, 50 mmol, 1.0 equiv) in THF (100 mL) at 0 °C was added 60% NaH (2.20 g, 55 mmol, 1.1 equiv) portionwise over 30 min. After stirring the obtained suspension for an additional 30 min at 22 °C, 1-fluoro-4-nitrobenzene (7.06 g, 50.0 mmol, 1.0 equiv) was added in one portion to the reaction mixture. In 1 h the reaction mixture was quenched with 2 M $NaOH_{(aq)}$ (200 mL). A deep red water layer was immediately extracted with DCM (3 x 200 mL), combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. After a flash column chromatography on SiO_2 with ethyl acetate followed by ethyl acetate:triethylamine:methanol = 9:0.5:0.5, *N*-methyl-2-(4-nitrophenoxy)ethanamine (6.01 g, 31.1 mmol, 62% yield) was obtained as a yellow/orange liquid.

The flask was heat dried under a vacuum and filled with Ar. Acetic acid anhydride (7.37 mL, 78.0 mmol, 2.6 eq.) and formic acid (3.62 mL, 96.0 mmol, 3.2 equiv) were mixed in THF (100 mL) and heated at 40 °C for 1 h. The reaction mixture was cooled to −10 °C with an ice/$NaCl_{(aq)}$ bath. *N*-methyl-2-(4-nitrophenoxy)ethanamine (5.89 g, 30.0 mmol, 1.0 equiv) was dissolved in THF (50 mL), dropwise added to the reaction mixture and stirred for 2 h in the ice/$NaCl_{(aq)}$ bath. The solution was neutralized with sat. Na_2CO_3. Complete consumption of starting material and the product formation was verified by GC/MS analysis. The product was extracted with DCM (4 x 300 mL), combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. After a flash column chromatography with ethyl acetate, *N*-methyl-*N*-(2-(4-nitrophenoxy)ethyl)formamide (**86n**) (5.90 g, 26.3 mmol, 88% yield) was obtained as an orange liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.08 – 8.03/7.99 (m + s, 3H), 6.94 – 6.81 (m, 2H), 4.14 (t, *J* = 5.4 Hz, 1H), 4.10 (t, *J* = 5.1 Hz, 1H), 3.66 (t, *J* = 5.4 Hz, 1H), 3.62 (t, *J* = 5.1 Hz, 1H), 3.03/2.87 (2 x s, 3H) (mixture of rotamers).

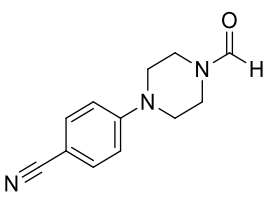
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.2, 163.0, 163.0, 162.8, 162.8, 141.6, 141.4, 125.7, 125.7, 125.7, 114.4, 114.3, 66.4, 65.4, 48.5, 43.7, 36.1, 29.9 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1664, 1608, 1591, 1507, 1497, 1389, 1336, 1299, 1253, 1173, 1110, 1090, 1040, 906, 844, 751, 690.

MS (EI, 70 eV): *m/z* (%) = 165 (10), 86 (100), 72 (39), 58 (16), 44 (43).

HRMS (EI): *m/z* calc. for [$C_{10}H_{12}N_2O_4$]: 224.0797; found 224.0790.

4-(4-Formylpiperazin-1-yl)benzonitrile (86p)



To a toluene solution of 4-fluorobenzonitrile (6.05 g, 50 mmol, 1.0 equiv) was added piperazine (43.07 g, 500 mmol, 10.0 equiv) in one portion and the resulting suspension was heated under reflux (oil bath temperature 130 °C). During heating, piperazine dissolved. After 12 h, heating was stopped, the warm reaction mixture was transferred into aqueous 2M NaOH (400 mL) and the product was extracted with Et_2O (4x700 mL). Organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to obtain 4-(piperazin-1-yl)benzonitrile. This crude product was used in the following step without further purification.

The flask was heat dried under Ar-atmosphere. Acetic acid anhydride (12.0 mL, 127 mmol, 2.5 equiv) and formic acid (6.00 mL, 159 mmol, 3.2 equiv) were mixed in THF (100 mL) and heated at 40 °C for 1 h. The reaction mixture was cooled to −10 °C (ice/$NaCl_{(aq)}$). Crude 4-(piperazin-1-yl)benzonitrile was dissolved in THF (50 mL), dropwise added to the reaction mixture and stirred for 2 h at −10 °C. The white suspension was neutralized with sat. Na_2CO_3 (400 mL). Complete consumption of the starting material and the product formation was verified by GC/MS analysis. The product was extracted with Et_2O (4x700 mL), combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. After a flash column chromatography with ethyl acetate:pentane = 1:1 (1 L), followed by pure ethyl acetate (3 L), 4-(4-formylpiperazin-1-yl)benzonitrile (**86p**) (8.14 g, 37.9 mmol, 76% yield over 2 steps) was obtained as a white crystalline solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (s, 1 H), 7.42 (d, *J* = 9.0 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 3.61 (dd, *J* = 6.6, 5.1 Hz, 2 H), 3.47 (dd, *J* = 6.9, 4.9 Hz, 2 H), 3.30 (dd, *J* = 5.4, 3.4 Hz, 2 H), 3.25 (dd, *J* = 5.5, 3.5 Hz, 2 H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.6, 152.9, 133.4, 119.6, 114.9, 101.1, 48.1, 46.9, 44.7, 39.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2846, 2210, 1666, 1600, 1514, 1436.

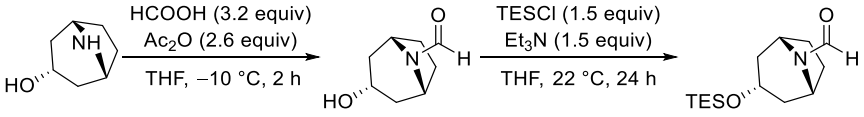
MS (EI, 70 eV): *m/z* (%) = 215 (39), 186 (24), 157 (81), 145 (41), 144 (100), 130 (10), 129 (93), 116 (13).

HRMS (EI): *m/z* calc. for [$C_{12}H_{13}N_3O$]: 215.1059; 215.1052.

M.p. (°C): 144.2-146.3.

X-Ray: Crystals suitable for X-Ray diffraction were obtained from $CDCl_3$ by slow evaporation of the solvent at rt. See pages 269-272.

(1*R*,3*r*,5*S*)-3-((Triethylsilyl)oxy)-8-azabicyclo[3.2.1]octane-8-carbaldehyde (86q)



The flask was heat dried under Ar-atmosphere. Acetic acid anhydride (4.92 mL, 52.0 mmol, 2.6 equiv) and formic acid (2.41 mL, 64 mmol, 3.2 equiv) were mixed in THF (50 mL) and heated at 40 °C for 1 h. The reaction mixture was cooled to −10 °C (ice/$NaCl_{(aq)}$). Nortropine (2.54 g, 20 mmol, 1.0 equiv) was added as a suspension in THF (50 mL) and stirred for 2 h at −10 °C. The white suspension was neutralized with aqueous 2M NaOH (150 mL). Complete consumption of starting material and product formation was verified by GC/MS analysis. The product was extracted with CH_2Cl_2 (3 x 300 mL), combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. After a flash column chromatography on SiO_2 with CH_2Cl_2:EtOH=95:5, followed by CH_2Cl_2:MeOH=90:10

(1*R*,3*r*,5*S*)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carbaldehyde (2.64 g, 19.4 mmol, 97% yield) was obtained as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (s, 1H), 4.56 – 4.50 (m, 1H), 4.17 – 4.11 (m, 1H), 4.03 – 3.97 (m, 1H), 2.47 (d, *J* = 10.0 Hz, 1H), 2.30 – 2.21 (m, 2H), 2.09 – 2.03 (m, 1H), 1.99 – 1.93 (m, 2H), 1.93 – 1.83 (m, 3H), 1.83 – 1.78 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.4, 64.9, 54.1, 49.2, 41.4, 38.9, 28.3, 27.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3341, 1634, 1448, 1399, 1360, 1310, 1085, 1047, 958, 902, 818, 778, 740, 691, 662.

MS (EI, 70 eV): *m/z* (%) = 155 (46), 127 (14), 126 (38), 126 (12), 112 (42), 110 (20), 108 (12), 99 (21), 98 (21), 97 (10), 96 (13), 95 (12), 84 (13), 83 (23), 82 (69), 80 (16), 69 (31), 68 (100), 67 (18), 56 (12), 55 (12), 54 (10), 54 (16), 43 (12), 41 (25).

HRMS (EI): *m/z* calc. for [$C_8H_{13}NO_2$]: 155.0946; found 155.0940.

M.p. (°C): 136.3-138.0.

(1*R*,3*r*,5*S*)-3-Hydroxy-8-azabicyclo[3.2.1]octane-8-carbaldehyde (2.33 g, 15.0 mmol, 1.0 equiv), TESCl (3.39 g, 22.5 mmol, 1.5 equiv) and Et_3N (2.28 g, 22.5 mmol, 1.5 equiv) were mixed in THF (30 mL) at 22 °C and stirred for 24 h. The reaction mixture was quenched with distilled water (100 mL) and the product was extracted with CH_2Cl_2 (3 x 300 mL). Combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. After a flash column chromatography on SiO_2 with pentane:ethyl acetate = 1:1, (1R,3r,5S)-3-((triethylsilyl)oxy)-8-azabicyclo[3.2.1]octane-8-carbaldehyde (**86q**) (3.68 g, 13.6 mmol, 91% yield) was obtained as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.08 (s, 1H), 4.58 – 4.50 (m, 1H), 4.10 – 4.04 (m, 1H), 4.01 – 3.96 (m, 1H), 2.36 – 2.29 (m, 2H), 2.07 – 1.99 (m, 1H), 1.96 – 1.90 (m, 1H), 1.88 – 1.81 (m, 3H), 1.80 – 1.73 (m, 1H), 0.98 – 0.92 (m, 9H), 0.61 – 0.53 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.3, 65.5, 54.4, 49.4, 42.2, 39.5, 28.3, 27.6, 7.0, 4.8.

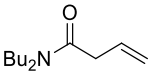
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2912, 2875, 1665, 1458, 1429, 1371, 1318, 1308, 1298, 1238, 1224, 1167, 1081, 1051, 1003, 972, 923, 859, 836, 788, 723, 685.

MS (EI, 70 eV): *m/z* (%) = 269 (37), 241 (15), 240 (100), 212 (14), 198 (14), 171 (50), 143 (11), 138 (12), 110 (12), 103 (49), 93 (18), 87 (13), 82 (13), 75 (55), 70 (77), 68 (19), 67 (12), 59 (15), 46 (15), 40 (10).

HRMS (EI): *m/z* calc. for [$C_{12}H_{23}NO$]: 269.1811; found 270.1820 (M+H).

5.6 Preparation of Products

***N*,*N*-Dibutylbut-3-enamide (88a)**



Following **TP1A**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by allyl bromide (145 mg, 1.20 mmol, 1.2 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100

mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:Et_2O = 7:3) to give **88a** (185 mg, 0.940 mmol, 94% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.98 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.19 – 5.08 (m, 2H), 3.33 – 3.27 (m, 2H), 3.24 – 3.18 (m, 2H), 3.11 (dt, *J* = 6.6, 1.5 Hz, 2H), 1.59 – 1.45 (m, 4H), 1.38 – 1.22 (m, 5H), 0.99 – 0.89 (m, 5H).

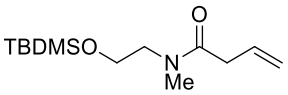
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.5, 132.4, 117.4, 48.0, 45.8, 38.8, 31.4, 30.0, 20.4, 20.3, 14.0, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2932, 2874, 1545, 1456, 1426, 1376, 1144, 1112, 1101, 994, 911.

MS (EI, 70 eV): *m/z* (%) = 198 (11), 182 (36), 168 (22), 156 (65), 154 (100), 140 (22), 126 (13), 113 (34), 112 (48), 100 (21), 86 (70), 57 (27), 44 (19).

HRMS (EI): *m/z* calc. for [$C_{12}H_{23}NO$]: 197.1780; found 198.1850 (M+H).

_N_-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-_N_-methylbut-3-enamide (88b)



Following **TP1A**, *N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)-N-methylformamide (**86b**) (217 mg, 1.0 equiv, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.5 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by allyl bromide (145 mg, 1.20 mmol, 1.2 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 85:15) to give **88b** (206 mg, 0.800 mmol, 80% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.04 – 5.87 (m, 1H), 5.19 – 5.04 (m, 2H), 3.78 – 3.68 (m, 2H), 3.46 (t, *J* = 5.4 Hz, 1H), 3.41 (t, *J* = 5.5 Hz, 1H), 3.21 (dt, *J* = 6.7, 1.6 Hz, 1H), 3.13 – 3.10 (m, 1H), 3.08/2.93 (2 x s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

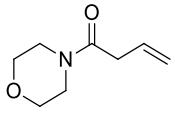
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.6, 171.0, 132.2, 131.6, 117.8, 117.5, 61.8, 60.7, 52.1, 50.9, 39.1, 38.7, 37.9, 33.9, 26.0, 25.9, 18.3, 18.3, -5.3, -5.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2929, 2886, 2857, 1647, 1472, 1464, 1399, 1361, 1253, 1100, 1005, 921, 828, 811, 775, 733, 662.

MS (EI, 70 eV): *m/z* (%) = 200 (100), 132 (15).

HRMS (EI): *m/z* calc. for [$C_{13}H_{27}NO_2Si$]: 242.1576 (M-CH_3); found 242.1569 (M-CH_3).

1-Morpholinobut-3-en-1-one (88c)



Following **TP1A**, morpholine-4-carbaldehyde (**86c**) (115 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by allyl bromide (145 mg, 1.20 mmol, 1.2 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:Et_2O = 3:7) to give **88c** (109 mg, 0.700 mmol, 70% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.03 – 5.86 (m, 1H), 5.23 – 5.07 (m, 2H), 3.70 – 3.59 (m, 6H), 3.50 – 3.41 (m, 2H), 3.14 (dt, *J* = 6.6, 1.6 Hz, 2H).

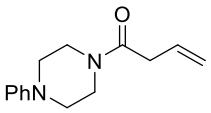
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.6, 131.3, 118.1, 67.0, 66.7, 46.3, 42.1, 38.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2858, 1645, 1436, 1300, 1272, 1255, 1228, 1197, 1114, 1069, 1038, 995, 968, 920, 850.

MS (EI, 70 eV): *m/z* (%) = 155 (16), 114 (100), 70 (29).

HRMS (EI): *m/z* calc. for [$C_8H_{13}NO_2$]: 155.0946; found 155.0940.

1-(4-Phenylpiperazin-1-yl)but-3-en-1-one (88d)



Following **TP1A**, 4-phenylpiperazine-1-carbaldehyde (**86d**) (190 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by allyl bromide (145 mg, 1.20 mmol, 1.2 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 7:3) to give **88d** (161 mg, 0.700 mmol, 70% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.78 – 7.58 (m, 2H), 7.38 – 7.19 (m, 3H), 6.34 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.67 – 5.45 (m, 2H), 4.20 – 4.11 (m, 2H), 4.03 – 3.95 (m, 2H), 3.59 – 3.54 (m, 2H), 3.56 – 3.49 (m, 4H).

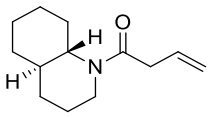
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.4, 151.0, 131.4, 129.3, 120.6, 118.0, 116.7, 49.8, 49.4, 45.8, 41.6, 38.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2917, 2855, 2820, 1643, 1598, 1579, 1495, 1436, 1386, 1334, 1276, 1258, 1227, 1208, 1154, 1119, 1096, 1028, 992, 964, 916, 898, 799, 757, 692.

MS (EI, 70 eV): *m/z* (%) = 231 (12), 230 (68), 215 (15), 202 (15), 161 (29), 160 (21), 158 (12), 133 (14), 132 (100), 124 (12), 120 (69), 119 (70), 106 (28), 105 (43), 104 (54), 91 (28), 69 (11), 56 (68), 41 (16), 40 (52).

HRMS (EI): *m/z* calc. for [$C_{14}H_{18}N_2O$]: 230.1419; found 230.1420.

1-(*trans*-Octahydroquinolin-1(2H)-yl)but-3-en-1-one (88e)



Following **TP1A**, *trans*-octahydroisoquinoline-2(1H)-carbaldehyde (**86e**) (167 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by allyl bromide (145 mg, 1.20 mmol, 1.2 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 85:15) to give **88e** (201 mg, 0.700 mmol, 97% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.03 – 5.91 (m, 1H), 5.15 – 5.07 (m, 2H), 3.82 – 3.50 (m, 1H), 3.39 – 3.27 (m, 1H), 3.23 – 3.05 (m, 3H), 2.14 – 2.05 (m, 1H), 1.84 – 1.73 (m, 2H), 1.72 – 1.61 (m, 3H), 1.60 – 1.50 (m, 2H), 1.47 – 1.37 (m, 1H), 1.33 – 1.21 (m, 2H), 1.17 – 1.00 (m, 2H).

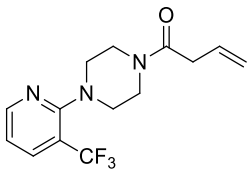
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.3 , 132.3 , 117.4 , 61.5 , 39.6 , 38.4 , 33.1 , 31.0 , 26.4 , 26.0 , 25.5 , 23.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2886, 2855, 1628, 1422, 1362, 1287, 1267, 1223, 1172, 1137, 1008, 994, 911.

MS (EI, 70 eV): *m/z* (%) = 192 (20), 167 (10), 166 (92), 164 (27), 138 (17), 136 (11), 96 (100), 86 (14), 81 (22), 79 (16), 67 (11).

HRMS (EI): *m/z* calc. for [$C_{13}H_{21}NO$]: 207.1623; found 207.1617.

1-(4-(3-(Trifluoromethyl)pyridin-2-yl)piperazin-1-yl)but-3-en-1-one (88f)



Following **TP1A**, 4-(3-(trifluoromethyl)pyridin-2-yl)piperazine-1-carbaldehyde (**86f**) (259 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by allyl bromide (145 mg, 1.20 mmol, 1.2 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 7:3) to give **88f** (230 mg, 0.770 mmol, 77% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.43 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.09 – 6.98 (m, 1H), 5.95 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1H), 5.24 – 5.09 (m, 2H), 3.84 – 3.70 (m, 2H), 3.64 – 3.54 (m, 2H), 3.29 – 3.13 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.7 , 159.7 , 151.3 , 137.3 , 131.4 , 123.9 (q, *J* = 272.5 Hz), 118.0, 118.0, 117.9 (q, *J* = 31.6 Hz), 50.9 , 50.8 , 45.9 , 41.8 , 38.9 .

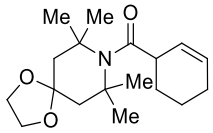
^{19}F-NMR (377 MHz, CDCl3): –60.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1646, 1591, 1568, 1436, 1369, 1308, 1248, 1223, 1144, 1102, 1082, 1024, 993, 974, 917, 793, 777.

MS (EI, 70 eV): *m/z* (%) = 213 (11), 201 (25), 189 (27), 188 (22), 187 (100), 175 (35), 173 (17), 169 (11), 167 (13), 155 (22), 149 (11), 147 (11), 146 (15), 128 (33).

HRMS (EI): *m/z* calc. for [$C_{14}H_{16}F_3N_3O$]: 299.1245; found 299.1244.

Cyclohex-2-en-1-yl(7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)methanone (88g)



Following modified **TP1A**, 7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carbaldehyde (**86h**) (227 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (2.20 mmol, 2.2 equiv) was dropwise added at 15 °C followed by 3-bromocyclohex-1-ene (320 mg, 2.00 mmol, 2.0 equiv) and CuCN·2LiCl as 1 M solution in THF (200 µL, 0.200 mmol, 0.20 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **88g** (206 mg, 0.670 mmol, 67% yield) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.86 – 5.80 (m, 1H), 5.55 – 5.49 (m, 1H), 3.92 – 3.83 (m, 4H), 3.48 – 3.41 (m, 1H), 2.14 – 2.03 (m, 3H), 2.00 – 1.93 (m, 3H), 1.89 – 1.80 (m, 2H), 1.79 – 1.71 (m, 1H), 1.56 – 1.41 (m, 13H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 181.0, 129.5, 126.0, 105.8, 63.7, 55.7, 49.2, 45.5, 30.6, 29.9, 27.2, 24.7, 21.5.

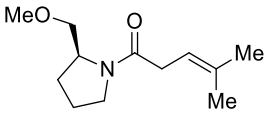
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2967, 2934, 2361, 1635, 1458, 1384, 1368, 1338, 1306, 1269, 1269, 1217, 1168, 1139, 1102, 979, 956, 922, 900, 844, 816, 777, 740, 718.

MS (EI, 70 eV): *m/z* (%) = 184 (27), 170 (100), 114 (17), 98 (24), 87 (45), 84 (23).

HRMS (EI): *m/z* calc. for [$C_{18}H_{29}NO_3$]: 292.1913 (M-CH_3); found 292.1909 (M-CH_3).

M.p. (°C): 68.7-71.8.

(*S*)-1-(2-(Methoxymethyl)pyrrolidin-1-yl)-4-methylpent-3-en-1-one (88h)



Following **TP1A**, (S)-2-(methoxymethyl)pyrrolidine-1-carbaldehyde (**86g**) (143 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by prenyl bromide (164 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 1:1) to give **88h** (129 mg, 0.610 mmol, 61% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.35 – 5.28 (m, 1H), 4.25 – 4.18/4.05 – 3.98 (2 x m, 1H), 3.56 – 3.49 (m, 1H), 3.49 – 3.41 (m, 1H), 3.40 – 3.29 (m, 5H), 3.13 – 3.08/3.01 – 2.96 (2 x m, 1H), 2.04 – 1.91 (m, 2H), 1.91 – 1.80 (m, 2H), 1.74 – 1.69 (m, 3H), 1.66 – 1.59 (m, 3H) (mixture of rotamers).

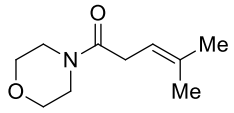
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.4, 171.0, 134.6, 134.3, 117.7, 117.0, 74.3, 72.4, 59.3, 59.1, 57.1, 56.5, 47.4, 45.8, 35.1, 34.3, 28.9, 27.5, 25.8, 24.3, 22.0, 18.2 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2973, 2926, 2877, 1638, 1410, 1376, 1343, 1273, 1196, 1170, 1110, 1074, 970, 942, 900, 852, 792, 711.

MS (EI, 70 eV): *m/z* (%) = 179 (16), 167 (10), 166 (100), 142 (11), 114 (18), 82 (18), 70 (93),

HRMS (EI): *m/z* calc. for [$C_{12}H_{21}NO_2$]: 211.1572; found 211.1565.

4-Methyl-1-morpholinopent-3-en-1-one (88i)



Following **TP1A**, morpholine-4-carbaldehyde (**86c**) (115 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by prenyl bromide (164 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 3:7) to give **88i** (113 mg, 0.620 mmol, 62% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.28 – 5.15 (m, 1H), 3.65 – 3.58 (m, 4H), 3.57 – 3.52 (m, 2H), 3.43 – 3.37 (m, 2H), 3.05 – 2.98 (m, 2H), 1.73 – 1.66 (m, 2H), 1.63 – 1.57 (m, 3H).

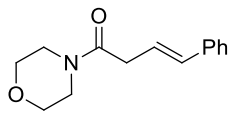
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.7, 135.0, 116.6, 66.9, 66.7, 46.2, 42.0, 33.5, 25.7, 18.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm-1 = 2970, 2921, 2857, 1621, 1435, 1377, 1361, 1300, 1270, 1232, 1155, 1115, 1069, 1045, 1023, 968, 848.

MS (EI, 70 eV): *m/z* (%) = 183 (12), 182 (28), 114 (22), 96 (28), 95 (13), 86 (36), 70 (26), 69 (17), 67 (10), 57 (14), 56 (28), 45 (13), 43 (100), 42 (12), 41 (16).

HRMS (EI): *m/z* calc. for [$C_{10}H_{17}NO_2$]: 183.1259; found 183.1253.

(*E*)-1-Morpholino-4-phenylbut-3-en-1-one (88j)



Following **TP1A**, morpholine-4-carbaldehyde (**86c**) (115 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by prenyl bromide (164 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$

solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 6:4) to give **88j** (132 mg, 0.570 mmol, 57% yield) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.39 – 7.34 (m, 2H), 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 6.51 – 6.45 (m, 1H), 6.36 – 6.29 (m, 1H), 3.71 – 3.63 (m, 6H), 3.53 – 3.48 (m, 2H), 3.30 (dd, *J* = 6.7, 1.6 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.7, 136.9, 133.1, 128.7, 127.7, 126.3, 122.8, 66.8, 46.4, 42.2, 37.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2919, 2865, 1638, 1598, 1459, 1434, 1404, 1390, 1361, 1303, 1272, 1228, 1196, 1113, 1069, 1032, 954, 937, 908, 858, 838, 778, 743, 698.

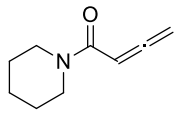
MS (EI, 70 eV): *m/z* (%) = 231 (22), 117 (25), 116 (10), 115 (33), 114 (100), 105 (15), 91 (13), 86 (13), 70 (67), 42 (21), 41 (15).

HRMS (EI): *m/z* calc. for [$C_{14}H_{17}NO_2$]: 231.1259; found 231.1253.

M.p. (°C): 94.9-95.2.

X-Ray: Crystals suitable for X-Ray diffraction were obtained by recrystalisation from Et_2O (complete dissolution on reflux). See pages 273-276.

1-(Piperidin-1-yl)buta-2,3-dien-1-one (88k)



Following **TP1A**, piperidine-1-carbaldehyde (**86i**) (113 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by propargyl bromide 80% in toluene (164 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 7:3) to give **88k** (88 mg, 0.580 mmol, 58% yield) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.90 (t, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 6.6 Hz, 2H), 3.52 (dt, *J* = 33.3, 5.4 Hz, 4H), 1.66 – 1.49 (m, 6H).

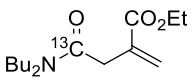
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 213.2, 163.5, 87.3, 78.6, 47.8, 43.4, 26.6, 25.6, 24.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2935, 2855, 1946, 1615, 1440, 1413, 1367, 1351, 1250, 1216, 1138, 1124, 1012, 952, 849, 805, 756.

MS (EI, 70 eV): *m/z* (%) = 150 (100), 123 (20), 122 (24), 112 (20), 108 (15), 108 (13), 94 (14), 84 (21), 82 (45), 69 (25), 67 (43).

HRMS (EI): *m/z* calc. for [$C_9H_{13}NO$]: 151.0997; found 151.0945.

Ethyl 4-(dibutylamino)-2-methylene-4-oxobutanoate-4-[^{13}C] (88l)



Following **TP1A**, *N*,*N*-dibutyl[^{13}C]formamide (**86a**) (158 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by ethyl 2-(bromomethyl)acrylate (211 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **88l** (170 mg, 0.630 mmol, 63% yield) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.27 (s, 1H), 5.62 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.34 – 3.26 (m, 4H), 3.25 – 3.19 (m, 2H), 1.61 – 1.53 (m, 2H), 1.53 – 1.45 (m, 2H), 1.36 – 1.25 (m, 7H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H) (mixture of rotamers).

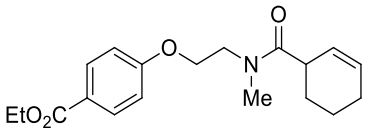
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.6, 166.7, 166.7, 135.5, 135.5, 127.2, 127.1, 77.2, 60.97, 48.1, 48.1, 46.0, 36.9, 36.5, 31.3, 29.9, 20.3, 20.2, 14.2, 14.0, 13.9 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2932, 2874, 1717, 1602, 1444, 1420, 1370, 1334, 1317, 1300, 1254, 1198, 1174, 1134, 1114, 1028, 939, 861, 821, 734.

MS (EI, 70 eV): *m/z* (%) = 225 (12), 197 (29), 157 (11), 122 (17), 142 (30), 114 (100), 86 (16), 85 (53).

HRMS (EI): *m/z* calc. for [$C_9H_{13}NO$]: 270.2024; found 271.2098 (M+H).

Ethyl 4-(2-(*N*-methylcyclohex-2-enecarboxamido)ethoxy)benzoate (88m)



Following **TP1B**, ethyl 4-(2-(*N*-methylformamido)ethoxy)benzoate (**86k**) (251 mg, 1.00 mmol, 1.0 equiv) and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ 0.33 M in THF (1.82 mL, 0.600 mmol, 0.6 equiv) were stirred at 22 °C for 24 h. 3-Bromocyclohex-1-ene (193 mg, 1.20 mmol, 1.2 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv) were added at 22 °C. After 16 h, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 6:4) to give **88m** (257 mg, 0.780 mmol, 78% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 – 7.88 (m, 2H), 6.87 – 6.78 (m, 2H), 5.85 – 5.75 (m, 1H), 5.57 – 5.46 (m, 1H), 4.32 – 4.21 (m, 2H), 4.16 – 4.05 (m, 2H), 3.80 – 3.64 (m, 2H), 3.53 – 3.45/3.34 – 3.25 (2 x m, 1H), 3.14/2.94 (2 x s, 3H), 2.09 – 1.87 (m, 2H), 1.87 – 1.64 (m, 3H), 1.57 – 1.43 (m, 1H), 1.34 – 1.25 (m, 3H) (mixture of rotamers).

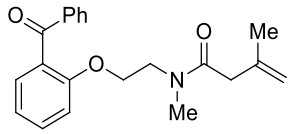
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 174.8, 166.1, 162.2, 131.4, 129.6, 124.6, 123.0, 113.9, 66.5, 60.5, 48.0, 38.8, 37.4, 25.3, 24.5, 20.9, 14.3 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2935, 1798, 1639, 1605, 1581, 1510, 1463, 1420, 1401, 1366, 1314, 1274, 1248, 1167, 1167, 1144, 1101, 1046, 1018, 922, 900, 848, 770, 730, 696, 666.

MS (EI, 70 eV): *m/z* (%) =167.1 (11), 166.1 (100), 138 (10), 81 (11).

HRMS (EI): *m/z* calc. for [$C_{19}H_{25}NO_4$]: 331.1784; found 331.1778.

***N*-(2-(2-Benzoylphenoxy)ethyl)-*N*,3-dimethylbut-3-enamide (88n)**



Following **TP1B**, *N*-(2-(2-benzoylphenoxy)ethyl)-*N*-methylformamide (**86l**) (283 mg, 1.00 mmol, 1.0 equiv) and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ 0.33 M in THF (1.67 mL, 0.55 mmol, 0.55 equiv) were stirred at 22 °C for 24 h. 3-Bromo-2-methylprop-1-ene (148 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv) were added at 22 °C. After 30 min, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 6:4) to give **88n** (181 mg, 0.540 mmol, 54% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.80 – 7.74 (m, 2H), 7.56 – 7.51 (m, 1H), 7.46 – 7.37 (m, 3H), 7.36 – 7.32 (m, 1H), 7.09 – 7.00 (m, 1H), 6.96 – 6.91 (m, 1H), 4.81 (dd, *J* = 1.9, 1.0 Hz, 1H), 4.66 – 4.55 (m, 1H), 4.06 (2, *J* = 4.9 Hz, 2H), 3.41 (t, *J* = 4.9 Hz, 2H), 2.90 (s, 1H), 2.70/2.57 (2 x s, 1H), 2.57 (s, 2H), 1.69/1.66 (2 x s, 1H) (mixture of rotamers).

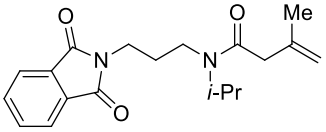
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.5, 170.9, 156.3, 139.2, 137.9, 133.0, 132.1, 129.8, 129.6, 128.8, 128.3, 120.9, 113.3, 112.0, 67.4, 48.0, 43.2, 37.7, 22.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1638, 1598, 1580, 1486, 1449, 1399, 1316, 1295, 1262, 1238, 1152, 1111, 1050, 1025, 925, 895, 804, 753, 728, 701.

MS (EI, 70 eV): *m/z* (%) = 197 (17), 152 (11), 140 (100), 124 (18), 121 (11), 105 (10), 91 (12), 83 (52), 77 (11).

HRMS (EI): *m/z* calc. for [$C_{21}H_{23}NO_3$]: 337.1678; found 337.1668.

***N*-(3-(1,3-Dioxoisoindolin-2-yl)propyl)-*N*-isopropyl-3-methylbut-3-enamide (88o)**



Following **TP1B**, *N*-(3-(1,3-dioxoisoindolin-2-yl)propyl)-*N*-isopropylformamide (**86m**) (274 mg, 1.00 mmol, 1.0 equiv), and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ 0.33 M in THF (1.67 mL, 0.55 mmol, 0.55 equiv) were stirred at 22 °C for 24 h. 3-Bromo-2-methylprop-1-ene (148 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv) were added at 22 °C. After 30 min, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 1:1) to give **88q** (155 mg, 0.470 mmol, 47% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 – 7.74 (m, 2H), 7.65 – 7.62 (m, 2H), 4.84 – 4.80 (m, 1H), 4.71 – 4.67 (m, 1H), 3.95 (hept, *J* = 6.7 Hz, 1H), 3.65 (q, *J* = 6.8 Hz, 2H), 3.24 – 3.17 (m, 2H), 3.02 (s, 2H), 1.99 – 1.84 (m, 2H), 1.74 – 1.68 (m, 3H), 1.09 (d, *J* = 1.1 Hz, 6H) (major rotamer).

7.82 – 7.75 (m, 2H), 7.72 – 7.64 (m, 2H), 4.78 – 4.71 (m, 1H), 4.63 – 4.58 (m, 1H), 4.52 (hept, *J* = 6.8 Hz, 1H), 3.65 (q, *J* = 6.8 Hz, 2H), 3.17 – 3.10 (m, 2H), 2.94 (s, 2H), 1.97 – 1.85 (m, 2H), 1.67 – 1.60 (m, 3H), 1.07 (d, *J* = 1.2 Hz, 6H) (minor rotamer).

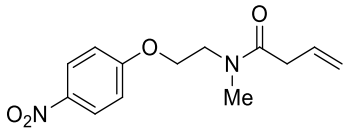
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.1, 170.0, 168.3, 168.2, 140.0, 139.9, 134.2, 133.9, 132.0, 131.8, 123.3, 123.1, 112.9, 112.9, 77.2, 48.7, 45.9, 43.8, 43.8, 41.4, 38.5, 36.2, 35.6, 30.3, 28.8, 22.6, 22.6, 21.2, 20.4 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1708, 1626, 1468, 1437, 1421, 1396, 1362, 1335, 1211, 1187, 1130, 1022, 908, 890, 717.

MS (EI, 70 eV): *m/z* (%) = 245 (14), 231 (22), 189 (11), 188 (99), 161 (10), 160 (100), 155 (13), 140 (24), 133 (10), 130 (20), 83 (25).

HRMS (EI): *m/z* calc. for [$C_{19}H_{24}N_2O_3$]: 328.1781; found 327.1697 (M-H).

N-Methyl-*N*-(2-(4-nitrophenoxy)ethyl)but-3-enamide (88p)



Following modified **TP1B**, *N*-methyl-*N*-(2-(4-nitrophenoxy)ethyl)formamide (**86n**) and $TMP_2Zn{\cdot}2LiCl$ (without $MgCl_2$; prepared by transmetalation of TMPLi with 0.5 equiv of $ZnCl_2$) in THF (1.82 mL, 0.6 mmol, 0.6 equiv) were stirred at 22 °C for 16 h. Allyl bromide (133 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv) were added at 22 °C. After 15 min, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 1:1 to 3:7) to give **88p** (210 mg, 0.790 mmol, 79% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 – 8.08 (m, 2H), 6.95 – 6.86 (m, 2H), 6.02 – 5.84 (m, 1H), 5.17 – 5.03 (m, 2H), 4.23 – 4.13 (m, 2H), 3.77 – 3.71 (m, 2H), 3.26 – 2.96 (m, 5H).

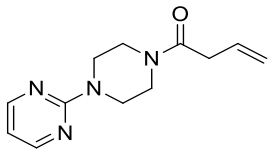
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.4, 171.3, 163.6, 163.1, 141.9, 141.6, 131.8, 131.1, 125.9, 125.9, 117.9, 117.7, 114.4, 114.4, 67.0, 66.1, 48.8, 47.7, 38.8, 38.5, 37.6, 33.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1643, 1608, 1591, 1509, 1497, 1400, 1331, 1298, 1256, 1173, 1138, 1109, 1075, 1044, 1025, 994, 915, 845, 752, 731, 690, 656.

MS (EI, 70 eV): *m/z* (%) = 126 (100).

HRMS (EI): *m/z* calc. for [$C_{13}H_{16}N_2O_4$]: 264.1110; found 265.1181 (M+H).

1-(4-(Pyrimidin-2-yl)piperazin-1-yl)but-3-en-1-one (88q)



Following **TP1B**, 4-(pyrimidin-2-yl)piperazine-1-carbaldehyde (**86o**) (192 mg, 1.00 mmol, 1.0 equiv) and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ 0.33 M in THF (1.82 mL, 0.6 mmol, 0.6 equiv) were stirred at 22 °C for 2 h. Allyl bromide (133 mg, 1.10 mmol, 1.1 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv) were added at 22 °C. After 15 min, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 1:1 to 8:2) to give **88q** (142 mg, 0.610 mmol, 61% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 (d, *J* = 4.8 Hz, 2H), 6.47 (t, *J* = 4.7 Hz, 1H), 5.91 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1H), 5.26 – 5.00 (m, 2H), 3.83 – 3.71 (m, 4H), 3.67 – 3.60 (m, 2H), 3.50 – 3.44 (m, 2H), 3.17 – 3.11 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.5, 161.5, 157.7, 131.3, 117.9, 110.4, 77.2, 45.5, 43.7, 43.5, 41.4, 38.8.

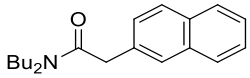
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1643, 1582, 1547, 1490, 1432, 1391, 1354, 1306, 1262, 1249, 1224, 1184, 1031, 979, 916, 796.

MS (EI, 70 eV): *m/z* (%) = 232 (36), 191 (18), 163 (22), 162 (12), 136 (14), 135 (11), 14 (68), 122 (63), 121 (43), 120 (38), 109 (10), 108 (100), 96 (11), 80 (27), 79 (16), 56 (16), 41 (16), 39 (36).

HRMS (EI): *m/z* calc. for [$C_{12}H_{16}N_4O$]: 232.1324; found 232.1317.

M.p. (°C): 85.6-87.0.

***N*,*N*-Dibutyl-2-(naphthalen-2-yl)acetamide (89a)**



Following **TP2**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL), 2-(bromomethyl)naphthalene (332 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **89a** (258 mg, 0.870 mmol, 87% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 – 7.76 (m, 3H), 7.69 (s, 1H), 7.49 – 7.38 (m, 3H), 3.86 (s, 2H), 3.38 – 3.32 (m, 2H), 3.26 – 3.19 (m, 2H), 1.58 – 1.42 (m, 4H), 1.37 – 1.22 (m, 4H), 0.90 (dt, *J* = 12.6, 7.3 Hz, 6H).

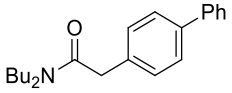
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.5, 133.7, 133.3, 132.5, 128.4, 127.7, 127.7, 126.2, 125.7, 48.2, 45.9, 41.4, 31.3, 29.9, 20.4, 20.2, 14.0, 13.9 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2930, 2872, 1636, 1456, 1423, 1374, 1316, 1296, 1268, 1210, 1132, 856, 801, 764, 764, 740.

MS (EI, 70 eV): *m/z* (%) = 297 (28), 182 (11), 156 (68), 142 (13), 142 (12), 141 (100), 139 (23), 115 (58), 100 (26), 57 (58).

HRMS (EI): *m/z* calc. for [$C_{20}H_{27}NO$]: 297.2093; found 297.2083.

2-([1,1'-Biphenyl]-4-yl)-*N*,*N*-dibutylacetamide (89b)



Following **TP2**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL) 4-(bromomethyl)-1,1'-biphenyl (371 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was

purified *via* column chromatography (*i*-hexane:ethyl acetate = 93:7) to give **89b** (194 mg, 0.600 mmol, 60% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.62 – 7.51 (m, 4H), 7.46 – 7.40 (m, 1H), 7.36 – 7.30 (m, 3H), 3.74 (s, 2H), 3.39 – 3.32 (m, 2H), 3.27 – 3.18 (m, 2H), 1.60 – 1.45 (m, 4H), 1.31 (hd, *J* = 7.3, 4.1 Hz, 4H), 0.93 (t, *J* = 7.3 Hz, 6H).

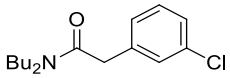
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.4, 141.0, 139.7, 134.8, 129.3 (2C), 128.8 (2C), 127.4 (2C), 127.2, 127.1 (2C), 48.2, 45.9, 40.6, 31.3, 29.9, 20.4, 20.2, 14.0, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2930, 2872, 1635, 1487, 1455, 1424, 1375, 1291, 1257, 1195, 1132, 1112, 1076, 1008, 931, 860, 821, 756, 731, 715, 696.

MS (EI, 70 eV): *m/z* (%) = 323 (35), 208 (16), 194 (13), 168 (10), 168 (14), 167 (100), 166 (11), 166 (11), 165 (91), 156 (94), 152 (37), 100 (35), 57 (68).

HRMS (EI): *m/z* calc. for [$C_{22}H_{29}NO$]: 323.2249; found 323.2243.

N,*N*-Dibutyl-2-(3-chlorophenyl)acetamide (89c)



Following **TP2**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL), 1-(bromomethyl)-3-chlorobenzene (308 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9:1) to give **89c** (247 mg, 0.880 mmol, 88% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.23 (m, 1H), 7.23 – 7.18 (m, 2H), 7.14 – 7.11 (m, 1H), 3.64 (s, 2H), 3.33 – 3.28 (m, 2H), 3.22 – 3.17 (m, 2H), 1.55 – 1.43 (m, 4H), 1.32 – 1.25 (m, 4H), 0.94 – 0.87 (m, 6H).

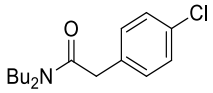
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.8, 137.6, 134.4, 129.8, 129.1, 127.1, 126.9, 48.2, 45.9, 40.4, 31.3, 29.8, 20.3, 20.2, 13.9, 13.9 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2931, 2873, 1636, 1597, 1574, 1457, 1432, 1375, 1320, 1291, 1254, 1196, 1136, 1097, 1079, 1000, 939, 868, 771, 684.

MS (EI, 70 eV): *m/z* (%) = 156 (100), 128 (11), 127 (18), 125 (54), 100 (17), 89 (18), 86 (22), 57 (26), 44 (10).

HRMS (EI): *m/z* calc. for [$C_{16}H_{24}ClNO$]: 281.1546; found 281.1540.

N,*N*-Dibutyl-2-(4-chlorophenyl)acetamide (89d)



Following **TP2**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL), 1-(bromomethyl)-4-chlorobenzene (308 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 93:7) to give **89d** (223 mg, 0.790 mmol, 79% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.25 (m, 2H), 7.23 – 7.14 (m, 2H), 3.64 (s, 2H), 3.34 – 3.28 (m, 2H), 3.23 – 3.17 (m, 2H), 1.53 – 1.45 (m, 4H), 1.34 – 1.23 (m, 4H), 0.96 – 0.87 (m, 7H).

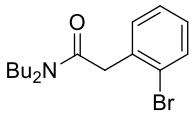
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.1, 134.2, 132.6, 130.3, 128.8, 48.2, 45.9, 40.2, 31.3, 29.9, 20.4, 20.2, 14.0, 13.9 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2931, 2873, 1635, 1492, 1456, 1425, 1375, 1319, 1296, 1255, 1198, 1131, 1113, 1090, 1016, 930, 858, 806, 735.

MS (EI, 70 eV): *m/z* (%) = 281 (18), 156 (100), 127 (28), 125 (85), 100 (29), 89 (21), 86 (24), 57 (42), 44 (12).

HRMS (EI): *m/z* calc. for [$C_{16}H_{24}ClNO$]: 281.1546; found 281.1539.

2-(2-Bromophenyl)-*N*,*N*-dibutylacetamide (89e)



Following **TP2**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL), 1-(bromomethyl)-4-(trifluoromethyl)benzene (374 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **89e** (245 mg, 0.750 mmol, 75% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.54 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.32 – 7.22 (m, 2H), 7.10 (td, *J* = 7.6, 1.9 Hz, 1H), 3.79 (s, 2H), 3.37 – 3.30 (m, 2H), 3.26 – 3.18 (m, 2H), 1.60 – 1.48 (m, 4H), 1.38 – 1.24 (m, 4H), 0.92 (q, *J* = 7.1 Hz, 6H).

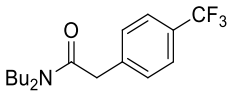
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.6, 135.8, 132.7, 131.0, 128.5, 127.6, 124.8, 48.3, 46.1, 41.0, 31.3, 29.8, 20.4, 20.2, 14.0, 14.0 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2930, 2872, 1640, 1466, 1456, 1440, 1425, 1375, 1322, 1290, 1259, 1216, 1199, 1138, 1113, 1048, 1026, 929, 745, 663.

MS (EI, 70 eV): *m/z* (%) = 247 (17), 246 (100), 190 (17), 171 (17), 169 (17), 134 (11).

HRMS (EI): *m/z* calc. for [$C_{16}H_{24}BrNO$]: 325.1036; found 326.1110 (M+H).

***N*,*N*-Dibutyl-2-(4-(trifluoromethyl)phenyl)acetamide (89f)**



Following **TP2**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL), 1-(bromomethyl)-4-(trifluoromethyl)benzene (359 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 96:4) to give **89f** (229 mg, 0.640 mmol, 64% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 3.73 (s, 2H), 3.36 – 3.28 (m, 2H), 3.26 – 3.18 (m, 2H), 1.55 – 1.46 (m, 4H), 1.36 – 1.23 (m, 4H), 0.95 – 0.86 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.6, 139.8, 129.6, 129.4, 129.3, 129.0, 128.7, 128.4, 125.7, 125.6, 125.6, 125.5, 125.5, 123.0, 120.3, 48.3, 46.0, 40.5, 31.3, 29.9, 20.4, 20.2, 14.0, 13.9 (mixture of rotamers).

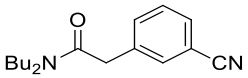
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –62.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 2960, 2875, 1638, 1457, 1428, 1377, 1323, 1162, 1120, 1066, 1020, 824.

MS (EI, 70 eV): *m/z* (%) = 159 (82), 157 (10), 156 (100), 109 (27), 100 (18), 86 (22), 57 (23), 44 (13).

HRMS (EI): *m/z* calc. for [$C_{17}H_{24}F_3NO$]: 315.1810; found 315.1803.

***N*,*N*-Dibutyl-2-(3-cyanophenyl)acetamide (89g)**



Following **TP2**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL), 1-(bromomethyl)-3-cyanobenzene (294 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **89g** (190 mg, 0.700 mmol, 70% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.55 – 7.46 (m, 3H), 7.43 – 7.38 (m, 1H), 3.69 (s, 2H), 3.35 – 3.27 (m, 2H), 3.26 – 3.18 (m, 2H), 1.58 – 1.43 (m, 4H), 1.38 – 1.20 (m, 4H), 0.99 – 0.82 (m, 6H).

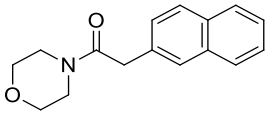
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.2, 137.2, 133.9, 132.7, 130.6, 129.3, 118.8, 112.6, 48.2, 46.1, 39.8, 31.4, 29.8, 20.3, 20.2, 13.9 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 2958, 2229, 1635, 1582, 1481, 1456, 1425, 1375, 1322, 1293, 1256, 1213, 1137, 1114, 1100, 930, 894, 781, 731, 688.

MS (EI, 70 eV): *m/z* (%) = 156 (87), 117 (13), 116 (100), 114 (10), 100 (26), 89 (27), 86 (69), 57 (18), 44 (28).

HRMS (EI): *m/z* calc. for [$C_{17}H_{24}N_2O$]: 272.1889; found 272.1882.

1-Morpholino-2-(naphthalen-2-yl)ethanone (89h)



Following **TP2**, morpholine-4-carbaldehyde (**86c**) (115 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL), 1-(bromomethyl)-4-(trifluoromethyl)benzene (374 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9:1) to give **89l** (145 mg, 0.570 mmol, 57% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.85 – 7.81 (m, 2H), 7.80 – 7.77 (m, 1H), 7.69 – 7.67 (m, 1H), 7.51 – 7.44 (m, 2H), 7.39 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.89 (s, 2H), 3.71 – 3.62 (m, 4H), 3.46 (s, 4H).

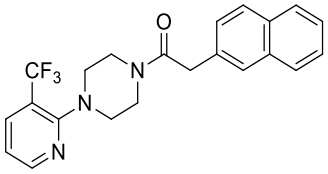
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.7, 133.6, 132.5, 132.4, 128.7, 127.8, 127.6, 127.1, 126.8, 126.4, 125.9, 66.9, 66.6, 46.6, 42.3, 41.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1631, 1600, 1508, 1429, 1361, 1300, 1272, 1257, 1227, 1112, 1068, 1036, 966, 908, 859, 818, 795, 765, 725, 673.

MS (EI, 70 eV): *m/z* (%) = 256 (13), 255 (77), 212 (15), 168 (24), 141 (89), 140 (11), 139 (27), 115 (49), 114 (100), 70 (52).

HRMS (EI): *m/z* calc. for [$C_{16}H_{17}NO_2$]: 255.1259; found 255.1252.

2-(Naphthalen-2-yl)-1-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethanone (89i)



Following **TP2**, 4-(3-(trifluoromethyl)pyridin-2-yl)piperazine-1-carbaldehyde (**86f**) (115 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL), 2-(bromomethyl)naphthalene (332 mg, 1.50 mmol, 1.5 equiv) and CuCN·2LiCl as 1 M solution in THF (100 µL, 0.100 mmol, 0.10 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9.0:1.0) to give **89i** (235 mg, 0.590 mmol, 59% yield) as a yellow amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 – 8.34 (m, 1H), 7.89 – 7.77 (m, 4H), 7.74 – 7.69 (m, 1H), 7.52 – 7.39 (m, 3H), 7.03 – 6.97 (m, 1H), 3.94 (s, 2H), 3.87 – 3.78 (m, 2H), 3.67 – 3.58 (m, 2H), 3.28 – 3.21 (m, 2H), 3.15 – 3.06 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.7, 159.6, 151.2, 137.3 (q, *J* = 5.0 Hz), 133.7, 132.5 (d, *J* = 12.3 Hz), 128.6 , 127.7 (d, *J* = 6.0 Hz), 127.1, 126.9, 126.3, 125.8, 123.9 (q, *J* = 272.6 Hz), 117.9, 117.6 (q, *J* = 31.5 Hz), 50.8 (d, *J* = 6.3 Hz), 46.2, 41.9, 41.4.

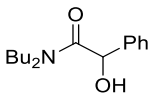
19F-NMR (377 MHz, $CDCl_3$): δ / ppm = –60.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1640, 1591, 1568, 1438, 1378, 1308, 1282, 1232, 1146, 1105, 1082, 1025, 966, 906, 858, 794, 764, 725, 679.

MS (EI, 70 eV): *m/z* (%) = 399 (17), 258 (29), 230 (11), 216 (10), 214(18), 212 (20), 211 (29), 201 (37), 189 (47), 188 (61), 187 (41), 175 (65), 169 (15), 168 (52), 163 (11), 147 (16), 146 (12), 142 (21), 141 (100), 139 (12), 128 (19), 115 (30), 70 (14), 69 (12), 56 (43), 43 (21).

HRMS (EI): *m/z* calc. for [$C_{22}H_{20}F_3N_3O$]: 399.1558; found 399.1550.

***N*,*N*-Dibutyl-2-hydroxy-2-phenylacetamide (90a)**



Following **TP3**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2$·2LiCl ca. 0.5 M in THF (2.0 mL) and neat benzaldehyde (127 mg, 1.20 mmol, 1.2 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9:1) to give **90a** (195 mg, 0.740 mmol, 74% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.39 – 7.27 (m, 6H), 5.14 (s, 1H), 4.69 (s, 1H), 3.50 (ddd, *J* = 13.4, 9.3, 6.0 Hz, 1H), 3.21 (ddd, *J* = 13.4, 9.3, 6.0 Hz, 1H), 3.08 (ddd, *J* = 14.5, 10.4, 5.7 Hz, 1H), 2.90 (ddd, *J* = 14.5, 10.6, 4.9 Hz, 1H), 1.60 – 1.44 (m, 2H), 1.43 – 1.22 (m, 3H), 1.18 – 1.04 (m, 2H), 1.03 – 0.88 (m, 4H), 0.80 (t, *J* = 7.3 Hz, 3H).

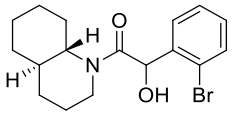
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.9, 140.0, 129.1 (2C), 128.6, 127.6 (2C), 71.8, 46.7, 46.2, 30.2, 29.5, 20.3, 20.1, 13.9, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3385, 2958, 2932, 2873, 1636, 1466, 1456, 1397, 1374, 1294, 1255, 1232, 1189, 1080, 851, 766, 734, 714, 699, 668.

MS (EI, 70 eV): *m/z* (%) = 156 (92), 114 (100), 107 (12), 100 (42), 79 (24), 77 (15), 57 (55).

HRMS (EI): *m/z* calc. for [$C_{16}H_{25}NO_2$]: 263.1885; found 264.1958 (M+H).

2-(2-Bromophenyl)-2-hydroxy-1-(*trans*-octahydroquinolin-1(2H)-yl)ethanone (90b)



Following **TP3**, *trans*-octahydroquinoline-2(1H)-carbaldehyde (**86e**) (167 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $MgCl_2 \cdot 2LiCl$ ca. 0.5 M in THF (2.0 mL) and neat 2-bromobenzaldehyde (222 mg, 1.20 mmol, 1.2 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (*i*-hexane:ethyl acetate = 9:1) to give **90b** (200 mg, 0.570 mmol, 57% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.62 – 7.56 (m, 1H), 7.31 – 7.26 (m, 1H), 7.23 – 7.13 (m, 2H), 5.54 (s, 1H), 4.85 (s, 1H), 3.61 – 3.27 (m, 1H), 3.23 – 2.96 (m, 1H), 2.94 – 2.77/2.42 – 2.03 (m, 1H), 1.85 – 1.74 (m, 2H), 1.73 – 1.60 (m, 2H), 1.59 – 1.35 (m, 4H), 1.34 – 0.93 (m, 5H).

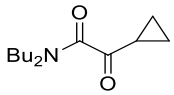
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.3, 139.4, 139.3, 133.3, 133.3, 130.1, 130.1, 128.9, 128.5, 128.4, 124.5, 124.2, 70.7, 70.6, 62.87, 62.0, 38.9, 38.5, 38.1, 37.9, 32.9, 32.9, 30.1, 29.8, 26.3, 26.2, 25.9, 25.8, 25.5, 25.4, 22.7, 21.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3376, 2925, 2886, 2857, 1634, 1592, 1568, 1460, 1440, 1391, 1359, 1220, 1287, 1273, 1248, 1214, 1188, 1172, 1138, 1120, 1072, 1046, 1020, 993, 972, 936, 917, 871, 857, 842, 832, 797, 759, 729.

MS (EI, 70 eV): *m/z* (%) = 183 (10), 167 (11), 166 (100), 138 (13), 86 (14), 81 (16).

HRMS (EI): *m/z* calc. for [$C_{17}H_{22}BrNO_2$]: 351.0834; found 350.0748 (M-H).

***N*,*N*-Dibutyl-2-cyclopropyl-2-oxoacetamide (91a)**



Following **TP4**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by neat cyclopropanecarbonyl chloride (125 mg, 1.20 mmol, 1.2 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 98:2) to give **91a** (122 mg, 0.540 mmol, 54% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.38 – 3.32 (m, 2H), 3.24 – 3.15 (m, 2H), 2.31 – 2.24 (m, 1H), 1.61 – 1.48 (m, 4H), 1.37 – 1.29 (m, 2H), 1.28 – 1.21 (m, 2H), 1.21 – 1.17 (m, 2H), 1.10 – 1.05 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H).

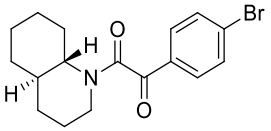
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 201.3, 167.6, 47.5, 44.6, 31.2, 29.5, 20.3, 20.0, 19.8, 13.9, 13.8, 12.8 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2933, 2874, 1693, 1633, 1458, 1436, 1374, 1191, 1100, 1068, 953, 880, 677.

MS (EI, 70 eV): *m/z* (%) = 156 (91), 128 (28), 57 (100), 41 (17).

HRMS (EI): *m/z* calc. for [$C_{13}H_{23}NO_2$]: 225.1729; found 226.1801 (M+H).

1-(4-Bromophenyl)-2-(*trans*-octahydroquinolin-1(2H)-yl)ethane-1,2-dione (91b)



Following **TP4**, *trans*-octahydroquinoline-2(1H)-carbaldehyde (**86e**) (167 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by neat 4-bromobenzoyl chloride (263 mg, 1.20 mmol, 1.2 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 98:2) to give **91b** (210 mg, 0.600 mmol, 60% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.82 – 7.72 (m, 2H), 7.65 – 7.57 (m, 2H), 4.03 – 3.24 (m, 2H), 3.17 – 2.95 (m, 1H), 2.50 – 2.31 (m, 1H), 1.89 – 1.77 (m, 1H), 1.76 – 1.51 (m, 7H), 1.50 – 1.25 (m, 2H), 1.25 – 0.92 (m, 2H).

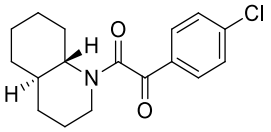
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.4, 189.5, 166.3, 166.2, 132.2, 131.1, 130.0, 63.3, 62.0, 41.9, 40.7, 40.4, 38.2, 33.0, 32.4, 30.2, 29.6, 26.9, 26.0, 25.9, 25.5, 25.5, 24.0, 23.6 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2856, 1681, 1633, 1585, 1485, 1447, 1398, 1361, 1284, 1257, 1214, 1187, 1168, 1069, 1009, 988, 948, 888, 849, 832, 798, 761, 726, 688, 661.

MS (EI, 70 eV): *m/z* (%) = 351 (14), 349 (14), 309 (15), 308 (95), 307 (16), 306 (100), 281 (11), 280 (25), 278 (26), 225 (10), 207 (26), 198 (21), 196 (21), 185 (11), 183 (11), 138 (28), 137 (92), 136 (22), 122 (20), 94 (12), 89 (21).

HRMS (EI): *m/z* calc. for [$C_{17}H_{20}BrNO_2$]: 349.0677; found 349.0670.

1-(4-Chlorophenyl)-2-(*trans*-octahydroquinolin-1(2H)-yl)ethane-1,2-dione (91c)



Following **TP4**, *trans*-octahydroquinoline-2(1H)-carbaldehyde (**86e**) (167 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by neat 4-chlorobenzoyl chloride (210 mg, 1.20 mmol, 1.2 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 97:3) to give **91c** (211 mg, 0.690 mmol, 69% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 – 7.79 (m, 2H), 7.47 – 7.37 (m, 2H), 4.05 – 3.22 (m, 2H), 3.15 – 2.96 (m, 1H), 2.53 – 2.29 (m, 1H), 1.94 – 1.77 (m, 1H), 1.76 – 1.50 (m, 7H), 1.47 – 1.23 (m, 2H), 1.23 – 0.90 (m, 2H).

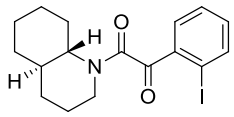
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.1, 189.3, 166.3, 166.3, 141.1, 140.7, 131.7, 131.0, 129.4, 63.3, 62.0, 41.9, 40.6, 40.4, 38.2, 33.0, 32.4, 30.2, 29.6, 26.9, 25.9, 25.8, 25.5, 25.4, 23.9, 23.5 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2856, 1682, 1634, 1586, 1571, 1489, 1446, 1400, 1364, 1287, 1257, 1214, 1187, 1167, 1138, 1087, 1012, 948, 888, 850, 832, 798, 764, 753, 690, 667.

MS (EI, 70 eV): *m/z* (%) = 167 (10), 166 (100), 164 (30), 139 (28), 136 (21), 81 (11).

HRMS (EI): *m/z* calc. for [$C_{17}H_{20}ClNO_2$]: 305.1183; found 305.1175.

1-(2-Iodophenyl)-2-(*trans*-octahydroquinolin-1(2H)-yl)ethane-1,2-dione (91d)



Following **TP4**, *trans*-octahydroquinoline-2(1H)-carbaldehyde (**86e**) (167 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by neat 2-iodobenzoyl chloride (319 mg, 1.20 mmol, 1.2 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 98:2) to give **91d** (333 mg, 0.840 mmol, 84% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.43 (td, *J* = 7.6, 1.1 Hz, 1H), 7.18 (td, 1H), 3.43 – 3.38 (m, 1H), 3.38 – 3.34 (m, 1H), 3.33 – 3.27 (m, 1H), , 2.44 – 2.38 (m, 1H), 1.90 – 1.76 (m, 2H), 1.76 – 1.57 (m, 6H), 1.56 – 1.45 (m, 1H), 1.45 – 1.34 (m, 1H), 1.34 – 1.24 (m, 1H), 1.24 – 0.90 (m, 3H) (major rotamer).

8.05 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.43 (td, *J* = 7.6, 1.1 Hz, 1H), 7.18 (td, 1H), 3.93 – 3.84 (m, 1H), 3.59 – 3.48 (m, 1H), 3.12 – 3.05 (m, 1H), 1.90 – 1.76 (m, 2H), 1.76 – 1.57 (m, 6H), 1.56 – 1.45 (m, 1H), 1.45 – 1.34 (m, 1H), 1.34 – 1.24 (m, 1H), 1.24 – 0.90 (m, 3H) (minor rotamer).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.3, 189.9, 165.5, 165.3, 142.8, 142.0, 136.7, 135.3, 133.6, 133.1, 128.3, 128.2, 94.0, 93.2, 63.3, 62.2, 41.7, 40.3, 40.1, 38.2, 33.0, 32.7, 29.7, 29.3, 26.8, 26.0, 25.6, 25.5, 23.6, 23.2 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 2855, 1685, 1629, 1578, 1560, 1445, 1428, 1364, 1278, 1266, 1253, 1210, 1185, 1170, 1126, 1053, 1016, 1008, 986, 948, 919, 907, 896, 886, 798, 732, 690.

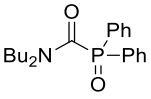
MS (EI, 70 eV): *m/z* (%) = 231 (14), 167 (11), 166 (100), 81 (22), 76 (12), 67 (12), 55 (11), 41 (14).

HRMS (EI): *m/z* calc. for [$C_{17}H_{20}INO_2$]: 397.0533; found 397.0528.

M.p. (°C): 102.4-104.7.

X-Ray: Crystals suitable for X-Ray diffraction were obtained by recrystallization from Et_2O (complete dissolution on reflux). See pages 277-281.

***N*,*N*-Dibutyl-1-(diphenylphosphoryl)formamide (91e)**



Following **TP4**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 0.50 equiv) and Et_3N (56.0 mg, 0.500 mmol, 0.50 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by neat diphenylphosphinic chloride (284 mg, 1.20 mmol, 1.2 equiv). Thereafter, the reaction mixture was quenched with NH_4Cl. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 85:15) to give **91e** (250 mg, 0.700 mmol, 70% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 – 7.83 (m, 4H), 7.57 – 7.50 (m, 2H), 7.50 – 7.41 (m, 4H), 4.00 – 3.91 (m, 2H), 3.41 – 3.32 (m, 2H), 1.60 – 1.52 (m, 2H), 1.51 – 1.42 (m, 2H), 1.37 – 1.18 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.85 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.4, 168.2, 132.2, 132.1, 132.0, 131.9, 130.8, 128.6, 128.5, 46.8, 46.2 (d, *J* = 3.1 Hz), 31.7, 29.4, 20.4, 19.9, 13.9, 13.9 (mixture of rotamers).

^{31}P-NMR (162 MHz, $CDCl_3$): δ / ppm = 20.2.

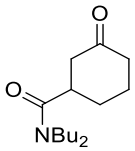
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2932, 1605, 1465, 1457, 1437, 1375, 1224, 1190, 1110, 1094, 1070, 760, 727, 714, 697.

MS (EI, 70 eV): *m/z* (%) = 202 (35), 201 (100), 183 (11), 156 (26), 128 (56), 77 (32), 57 (78), 47 (10), 41 (11), 39 (34).

HRMS (EI): *m/z* calc. for [$C_{21}H_{28}NO_2P$]: calc. 357.1858; found 357.1855.

M.p. (°C): 95.9-98.3 °C.

***N*,*N*-Dibutyl-3-oxocyclohexanecarboxamide (92)**



Following **TP5**, *N*,*N*-dibutylformamide (**86a**) (314 mg, 2.00 mmol, 2.0 equiv), $ZnCl_2$ (1.00 mL, 1.00 mmol, 1.0 equiv) and Et_3N (101 mg, 1.00 mmol, 1.0 equiv) were mixed in THF (4.0 mL) and a freshly prepared solution of TMPLi (2.20 mmol, 2.2 equiv) was dropwise added at 15 °C. After cooling to −78 °C CuCN·2LiCl (1.00 mL, 1.00 mmol, 1.0 equiv) and $BF_3{\cdot}Et_2O$ (123 µL, 1.0 mmol, 1.0 equiv) and cyclox-2-en-1-one (96.0 mg, 1.00 mmol, 1.0 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1 to 8:2) to give **92** (137 mg, 0.540 mmol, 54% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 3.40 (dt, *J* = 13.3, 7.6 Hz, 1H), 3.29 – 3.11 (m, 3H), 2.99 – 2.88 (m, 1H), 2.75 – 2.66 (m, 1H), 2.44 – 2.21 (m, 3H), 2.18 – 2.03 (m, 1H), 1.97 – 1.83 (m, 2H), 1.79 – 1.60 (m, 2H), 1.56 – 1.41 (m, 4H), 1.36 – 1.18 (m, 4H), 0.92 (dt, *J* = 10.7, 7.3 Hz, 6H).

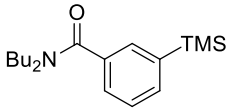
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 210.9, 173.0, 47.7, 46.1, 44.3, 41.1, 40.7, 31.9, 30.0, 28.4, 25.0, 20.3, 20.2, 14.0, 13.9 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2932, 2872, 1712, 1633, 1456, 1428, 1376, 1315, 1287, 1260, 1220, 1200, 1141, 1097, 732.

MS (EI, 70 eV): *m/z* (%) = 211 (12), 210 (100), 184 (38), 168 (20), 156 (30), 154 (22), 138 (12), 130 (11), 128 (12), 128 (10), 125 (20), 114 (16), 97 (15), 86 (98), 69 (22), 57 (14), 44 (31).

HRMS (EI): *m/z* calc. for [$C_{15}H_{27}NO_2$]: 253.2042; found 254.2114 (M+H).

***N*,*N*-Dibutyl-3-(trimethylsilyl)benzamide (93a)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl_2 (36.6 mg, 0.050 µmol, 0.05 equiv), 3-bromophenyl)trimethylsilane (183 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **93a** (217 mg, 0.712 mmol, 89% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.51 (dt, *J* = 7.1, 1.4 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.37 – 7.32 (m, 1H), 7.31 (dt, *J* = 7.6, 1.6 Hz, 1H), 3.60 – 3.38 (m, 2H), 3.23 – 3.01 (m, 2H), 1.73 – 1.59 (m, 2H), 1.55 – 1.32 (m, 4H), 1.20 – 1.07 (m, 2H), 1.02 – 0.90 (m, 3H), 0.85 – 0.70 (m, 3H), 0.26 (s, 9H).

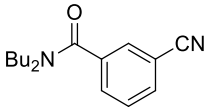
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.1, 140.9, 136.7, 134.0, 131.1, 127.7, 126.9, 48.9, 44.7, 31.1, 29.8, 20.5, 19.9, 14.1, 13.8, -1.1 (3C) (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2931, 2872, 1630, 1463, 1422, 1388, 1377, 1296, 1247, 1122, 1101, 835, 806, 746, 705, 691.

MS (EI, 70 eV): *m/z* (%) = 262 (12), 178 (10), 177 (100), 149 (22), 121 (10).

HRMS (EI): *m/z* calc. for [$C_{18}H_{31}NOSi^{\cdot+}$]: 304.2091; found 304.2084 (M-H).

***N*,*N*-Dibutyl-3-cyanobenzamide (93b)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl_2 (36.6 mg, 0.050 µmol, 0.05 equiv), 3-bromobenzonitrile (146 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 8:2) to give **93b** (165 mg, 0.640 mmol, 80% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.69 – 7.64 (m, 1H), 7.64 – 7.62 (m, 1H), 7.59 – 7.55 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 3.53 – 3.43 (m, 2H), 3.18 – 3.09 (m, 2H), 1.68 – 1.57 (m, 2H), 1.51 – 1.43 (m, 2H), 1.41 – 1.32 (m, 2H), 1.17 – 1.09 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.77 (t, *J* = 7.3 Hz, 3H).

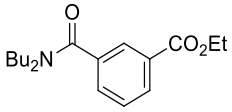
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.2, 138.7, 132.7, 130.9, 130.2, 129.5, 118.2, 112.8, 48.9, 44.8, 30.8, 29.6, 20.3, 19.8, 14.0, 13.6 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2931, 2871, 2230, 1670, 1629, 1464, 1429, 1413, 1376, 1297, 1199, 1094, 807, 747, 693, 656.

MS (EI, 70 eV): *m/z* (%) = 215 (18), 173 (16), 130 (100).

HRMS (EI): *m/z* calc. for [$C_{16}H_{22}N_2O^{+}$]: 257.1648; found 257.1645.

Ethyl 3-(dibutylcarbamoyl)benzoate (93c)



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl_2 (36.6 mg, 0.050 µmol, 0.05 equiv), ethyl 3-bromobenzoate (183 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **93c** (207 mg, 0.680 mmol, 85% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 (dt, *J* = 7.7, 1.5 Hz, 1H), 8.02 (td, *J* = 1.7, 0.6 Hz, 1H), 7.54 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.46 (td, *J* = 7.7, 0.7 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.57 – 3.44 (m, 2H), 3.22 – 3.11 (m, 2H), 1.72 – 1.56 (m, 2H), 1.55 – 1.44 (m, 2H), 1.44 – 1.33 (m, 4H), 1.19 – 1.06 (m, 2H), 0.97 (t, *J* = 6.8 Hz, 3H), 0.77 (t, *J* = 6.7 Hz, 3H).

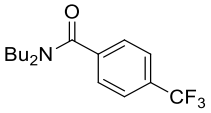
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.7, 166.1, 137.7, 131.0, 130.7, 130.2, 128.7, 127.7, 61.3, 49.0, 44.8, 30.9, 29.8, 20.4, 19.8, 14.4, 14.1, 13.7 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2931, 2872, 1718, 1630, 1464, 1418, 1367, 1251, 1227, 1178, 1121, 1097, 1080, 1022, 926, 823, 771, 731, 697, 680.

MS (EI, 70 eV): *m/z* (%) = 262 (18), 178 (11), 177 (100), 149 (37).

HRMS (EI): *m/z* calc. for [$C_{18}H_{27}NO_3$]: 305.1907; found 304.1903.

***N*,*N*-Dibutyl-4-(trifluoromethyl)benzamide (93d)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl_2 (36.6 mg, 0.050 µmol, 0.05 equiv), 1-bromo-4-(trifluoromethyl)benzene (180 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **93d** (207 mg, 0.690 mmol, 86% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.65 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 3.58 – 3.38 (m, 2H), 3.22 – 3.05 (m, 2H), 1.72 – 1.56 (m, 2H), 1.55 – 1.29 (m, 4H), 1.19 – 1.06 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.2, 141.0, 131.15 (q, *J* = 32.55 Hz), 127.0 (2C), 125.6 (q, J = 3.7 Hz) (2C), 123.95 (q, *J* = 272.15 Hz), 48.8, 44.7, 30.9, 29.7, 20.4, 19.9, 14.0, 13.7.

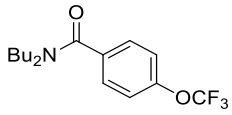
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –62.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2933, 1632, 1467, 1427, 1405, 1322, 1164, 1124, 1164, 1124, 1104, 1063, 1018, 849, 768, 737.

MS (EI, 70 eV): *m/z* (%) = 258 (15), 173 (100), 145 (18).

HRMS (EI): *m/z* calc. for [$C_{16}H_{22}F_3NO^{+}$]: 300.1570; found 300.1566.

***N*,*N*-Dibutyl-4-(trifluoromethoxy)benzamide (93e)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $Pd(dppf)Cl_2$ (36.6 mg, 0.050 µmol, 0.05 equiv), 1-bromo-4-(trifluoromethoxy)benzene (193 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **93e** (205 mg, 0.648 mmol, 81% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.34 (m, 1H), 7.25 – 7.20 (m, 1H), 3.62 – 3.32 (m, 1H), 3.31 – 3.03 (m, 1H), 1.63 (s, 2H), 1.55 – 1.28 (m, 4H), 1.22 – 1.06 (m, 2H), 1.03 – 0.87 (m, 2H), 0.87 – 0.67 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.4, 149.7 (q, *J* = 1.9 Hz), 136.1, 128.4 (2C), 120.9 (2C), 120.5 (*J* = 258.4 Hz), 48.9, 44.7, 30.9, 29.7, 20.4, 19.8, 14.0, 13.7 (mixture of rotamers).

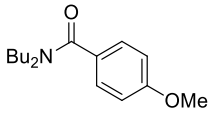
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –57.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2932, 1631, 1467, 1425, 1251, 1218, 1159, 1099, 1020, 867, 764.

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

HRMS (EI): *m/z* calc. for [$C_{16}H_{22}F_3NO_2$]: 316.1519; found 316.1514.

***N*,*N*-Dibutyl-4-methoxybenzamide (93f)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $Pd(dppf)Cl_2$ (36.6 mg, 0.050 µmol, 0.05 equiv), 1-bromo-4-methoxybenzene (150 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **93f** (130 mg, 0.496 mmol, 62% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.31 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.55 – 3.09 (m, 4H), 1.74 – 1.04 (m, 8H), 1.02 – 0.62 (m, 6H).

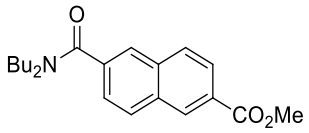
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.6, 160.3, 129.7, 128.4 (2C), 113.7 (2C), 55.4, 49.1, 44.7, 30.9, 29.8, 20.3, 20.0, 13.9 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2931, 2872, 1625, 1608, 1576, 1512, 1462, 1422, 1377, 1297, 1247, 1172, 1101, 1030, 956, 922, 838, 798, 764, 730.

MS (EI, 70 eV): *m/z* (%) = 262 (15), 135 (100).

HRMS (EI): *m/z* calc. for [$C_{16}H_{25}NO_2$]: 263.1802; found 263.1801.

Methyl 6-(dibutylcarbamoyl)-2-naphthoate (93g)



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $Pd(dppf)Cl_2$ (36.6 mg, 0.050 µmol, 0.05 equiv), methyl 6-bromo-2-naphthoate (212 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **93g** (254 mg, 0.744 mmol, 93% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$):f 8.63 – 8.56 (m, 1H), 8.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.85 – 7.83 (m, 1H), 7.49 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.95 (s, 3H), 3.61 – 3.46 (m, 2H), 3.25 – 3.11 (m, 2H), 1.80 – 1.59 (m, 2H), 1.54 – 1.34 (m, 4H), 1.17 – 1.02 (m, 2H), 1.01 – 0.92 (m, 3H), 0.78 – 0.64 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.0, 167.0, 137.1, 134.9, 132.4, 130.8, 129.7, 128.5, 128.2, 126.0, 125.7, 125.0, 52.3, 48.9, 44.6, 30.9, 29.7, 20.4, 19.7, 14.0, 13.6 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2871, 1712, 1612, 1489, 1465, 1437, 1380, 1338, 1320, 1298, 1276, 1242, 1226, 1188, 1172, 1140, 1104, 1094, 994, 947, 936, 926, 876, 833, 815, 780, 764, 733, 718.

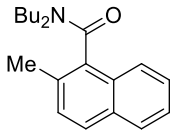
MS (EI, 70 eV): *m/z* (%) = 341 (11), 340 (15), 298 (14), 214 (14), 213 (20), 213 (100), 154 (11), 126 (10).

HRMS (EI): *m/z* calc. for [$C_{21}H_{27}NO_3$]: 340.1907; found 340.1904.

M.p. (°C): 83.7-85.1.

X-Ray: Crystals suitable for X-Ray diffraction were obtained from $CDCl_3$ by slow evaporation of the solvent at rt. See pages 282-286.

***N*,*N*-Dibutyl-2-methyl-1-naphthamide (93h)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $Pd(dppf)Cl_2$ (36.6 mg, 0.050 µmol, 0.05 equiv), 1-bromo-2-methylnaphthalene (177 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **93h** (206 mg, 0.694 mmol, 87% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.79 (d, *J* = 7.3 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.44 – 7.40 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 3.73 – 3.67 (m, 1H), 3.63 – 3.57 (m, 1H), 3.00 – 2.95 (m, 2H), 2.43 (s, 3H), 1.83 – 1.75 (m, 2H), 1.48 (h, *J* = 7.4 Hz, 2H), 1.41 – 1.27 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.95 (h, *J* = 7.4 Hz, 2H), 0.58 (t, *J* = 7.4 Hz, 3H).

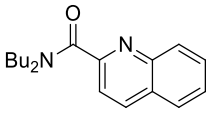
^{13}C-NMR (101 MHz, $CDCl_3$): 170.3, 133.5, 131.9, 131.4, 130.0, 128.5, 128.3, 128.1, 126.8, 125.5, 124.8, 48.3, 44.5, 30.7, 29.8, 20.7, 19.9, 19.7, 14.1, 13.5 (mixture of rotamers).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2930, 2872, 1626, 1510, 1466, 1424, 1377, 1294, 1254, 1218, 1129, 864, 810, 786, 742, 675.

MS (EI, 70 eV): *m/z* (%) = 282 (19), 170 (13), 168 (11), 141 (44), 115 (20).

HRMS (EI): *m/z* calc. for [$C_{20}H_{27}NO$]: 297.2093; found 297.2089.

***N*,*N*-Dibutylquinoline-2-carboxamide (93i)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $Pd(dppf)Cl_2$ (36.6 mg, 0.050 µmol, 0.05 equiv), 2-bromoquinoline (166 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **93i** (202 mg, 0.712 mmol, 89% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (d, *J* = 8.4 Hz, 1H), 8.12 – 8.03 (m, 1H), 7.82 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.60 – 7.54 (m, 1H), 3.60 – 3.52 (m,

2H), 3.47 – 3.34 (m, 2H), 1.76 – 1.59 (m, 4H), 1.44 (h, *J* = 7.4 Hz, 2H), 1.14 (h, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 3H).

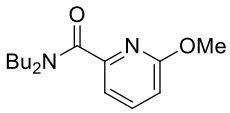
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.9, 154.9, 146.7, 136.9, 129.9, 129.8, 128.0, 127.7, 127.4, 120.7, 48.9, 46.0, 31.2, 29.9, 20.5, 20.0, 14.1, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2929, 2871, 1625, 1597, 1561, 1479, 1466, 1420, 1374, 1294, 1126, 1098, 944, 838, 775, 765, 734.

MS (EI, 70 eV): *m/z* (%) = 129 (21), 128 (100), 128 (45).

HRMS (EI): *m/z* calc. for [$C_{18}H_{24}N_2O$]: 284.1889; found 285.1962 (M+H).

***N*,*N*-Dibutyl-6-methoxypicolinamide (93j)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl_2 (36.6 mg, 0.050 µmol, 0.05 equiv), 2-bromo-6-methoxypyridine (150 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **93j** (196 mg, 0.744 mmol, 93% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.11 (dd, *J* = 7.3, 0.8 Hz, 1H), 6.74 (dd, *J* = 8.4, 0.8 Hz, 1H), 3.90 (s, 3H), 3.52 – 3.42 (m, 2H), 3.32 – 3.23 (m, 2H), 1.71 – 1.53 (m, 4H), 1.46 – 1.33 (m, 2H), 1.22 – 1.11 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H).

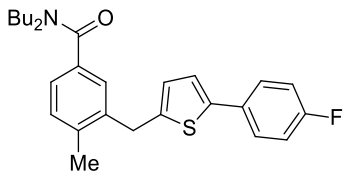
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.7, 162.8, 152.8, 139.3, 116.1, 111.6, 53.6, 48.7, 45.6, 31.2, 29.7, 20.4, 20.1, 14.1, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2930, 2871, 1630, 1593, 1574, 1461, 1415, 1407, 1376, 1320, 1288, 1262, 1235, 1195, 1148, 1124, 1075, 1031, 987, 814, 763, 733, 712.

MS (EI, 70 eV): *m/z* (%) = 128 (100), 108 (22).

HRMS (EI): *m/z* calc. for [$C_{15}H_{24}N_2O_2$]: 264.1838; found 265.1909 (M+H).

***N*,*N*-Dibutyl-3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylbenzamide (93k)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl_2 (36.6 mg, 0.050 µmol, 0.05 equiv), 2-(5-bromo-2-methylbenzyl)-5-(4-

fluorophenyl)thiophene (289 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **93k** (273 mg, 0.624 mmol, 78% yield) as a colorless oil (turns dark over time if not stored under Ar).

Scale up procedure (**modified TP6**):

A heat and vacuum dried 100 mL pressure tube was filled with argon and placed into an ice/water bath at 0 °C. *N*,*N*-Dibutylformamide (**86a**) (1.97 g, 12.5 mmol, 1.0 equiv), $ZnCl_2$ solution 1 M in THF (6.25 mL, 6.25 mmol, 0.5 equiv), Et_3N (632 mg, 6.25 mmol, 0.5 equiv) and THF (25 mL) were added. Freshly prepared TMPLi as ca. 0.5 M solution in THF (15.0 mmol, 1.2 equiv) was dropwise added over ca. 30 min. The reaction mixture was stirred for an additional 1 h at 0 °C. A solution of dicarbamoylzinc reagent $(Bu_2NCO)_2Zn$ was obtained. In a separate flask $Pd(dppf)Cl_2$ (91.5 mg, 0.125 mmol, 1 mol%), 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (3.61 g, 10.0 mmol, 0.8 equiv) and THF (10 mL) were added to form a fine suspension. The suspension was quantitatively transferred (the flask and the syringe were washed with THF 3 x 2 mL) into a solution of the dicarbamoylzinc reagent followed by a 1 M solution of CuCN·2LiCl (50 µL, 50.0 µmol, 0.4 mol%). The pressure tube was sealed using a screw cap (with a rubber O-ring) and the reaction mixture was vigorously stirred at 45 °C for 72 h. After cooling the reaction mixture to 22 °C, the sealed tube was carefully opened and saturated $NH_4Cl_{(aq)}$ (10 mL) was dropwise added. Bubbling was observed (CO gas release from a slight excess of dicarbamoylzinc reagent). The reaction mixture was transferred into a separating funnel containing diluted $NH_4Cl_{(aq)}$ (100 mL) and was extracted with ethyl acetate (3 x 200 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*, Flash column chromatography purification with pentane:ethyl acetate =9:1 to 8:2 afforded analytically pure product *N*,*N*-dibutyl-3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylbenzamide 9**3k** (4.08 g, 9.33 mmol, 93% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.49 – 7.42 (m, 2H), 7.22 (s, 1H), 7.18 (s, 2H), 7.06 – 6.97 (m, 3H), 6.71 – 6.65 (m, 1H), 4.12 (s, 2H), 3.57 – 3.36 (m, 2H), 3.32 – 3.06 (m, 2H), 2.33 (s, 3H), 1.78 – 1.55 (m, 2H), 1.54 – 1.28 (m, 4H), 1.24 – 1.06 (m, 2H), 1.03 – 0.89 (m, 3H), 0.86 – 0.68 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.6, 162.13 (d, *J* = 246.8 Hz), 143.0, 141.7, 138.3, 137.5, 135.4, 130.86 (d, *J* = 3.4 Hz), 127.7 (d, *J* = 4.1 Hz), 127.40 – 126.95 (m), 126.1 (d, *J* = 6.2 Hz), 125.2, 122.7, 115.7 (d, *J* = 21.7 Hz), 49.0, 44.7, 34.0, 31.0, 29.7, 20.4, 20.0, 19.4, 19.4, 13.9, 13.8.

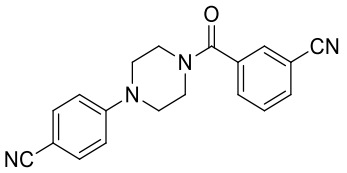
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –115.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2928, 2870, 1626, 1508, 1464, 1423, 1377, 1299, 1230, 1158, 1096, 831, 799, 756.

MS (EI, 70 eV): *m/z* (%) = 394 (14), 310 (20), 309 (100), 191 (19), 131 (21).

HRMS (EI): *m/z* calc. for $[C_{27}H_{32}FNOS^{+}]$: 436.2105; found 436.2100.

3-(4-(4-Cyanophenyl)piperazine-1-carbonyl)benzonitrile (93l)



Following **TP6**, 4-(4-formylpiperazin-1-yl)benzonitrile (**86p**) (215 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl_2 (36.6 mg, 0.050 µmol, 0.05 equiv), 3-bromobenzonitrile (146 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 1:1 to 4:6) to give **93l** (179 mg, 0.568 mmol, 71% yield) as a non-crystalline solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.75 – 7.69 (m, 2H), 7.66 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.50 – 7.45 (m, 2H), 6.85 (d, *J* = 9.0 Hz, 1H), 3.99 – 3.83 (m, 2H), 3.61 – 3.50 (m, 2H), 3.47 – 3.37 (m, 2H), 3.36 – 3.25 (m, 2H).

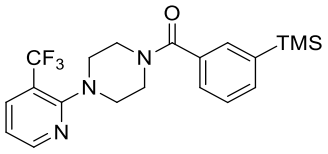
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.0, 152.9, 136.4, 133.6 (2C), 133.6, 131.5, 130.8, 129.7, 119.8, 117.9, 114.8 (2C), 113.0, 101.3, 47.7, 47.0 (2C), 41.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2214, 1632, 1602, 1680, 1515, 1486, 1460, 1438, 1415, 1391, 1287, 1244, 1221, 1198, 1179, 1139, 1016, 940, 902, 819, 797, 726, 685.

MS (EI, 70 eV): *m/z* (%) = 184 (17), 158 (10), 157 (100), 145 (19), 144 (23), 130 (19), 130 (24), 129 (60).

HRMS (EI): *m/z* calc. for [$C_{19}H_{16}N_4O$]: 316.1324; found 316.1318.

(4-(3-(Trifluoromethyl)pyridin-2-yl)piperazin-1-yl)(3-(trimethylsilyl)phenyl)methanone (93m)



Following **TP6**, 4-(3-(trifluoromethyl)pyridin-2-yl)piperazine-1-carbaldehyde (**86f**) (157 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl_2 (36.6 mg, 0.050 µmol, 0.05 equiv), (3-bromophenyl)trimethylsilane (183 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 8:2) to give **93m** (173 mg, 0.424 mmol, 53% yield) as a yellow amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 – 8.43 (m, 1H), 7.91 – 7.87 (m, 1H), 7.58 – 7.54 (m, 2H), 7.40 – 7.35 (m, 2H), 7.08 – 7.03 (m, 1H), 4.02 – 3.79 (m, 2H), 3.69 – 3.48 (m, 2H), 3.41 – 3.13 (m, 4H), 0.27 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.9 , 159.6 , 151.2 , 141.3 , 137.1 (q, *J* = 5.0 Hz), 135.0 , 134.6 , 131.7 , 127.6 , 127.2 , 123.8 (q, *J* = 272.6 Hz), 117.9 , 117.8 (q, *J* = 31.5 Hz) 51.0 (2C) , 47.8 , 42.2 , -1.2 (3C).

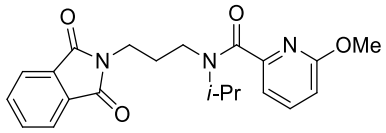
^{19}F-NMR (377 MHz, $CDCl_3$): δ / ppm = –60.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1634, 1590, 1568, 1430, 1390, 1377, 1369, 1309, 1285, 1248, 1234, 1165, 1145, 1115, 1105, 1081, 1018, 942, 896, 837, 807, 796, 779, 748, 732, 694.

MS (EI, 70 eV): *m/z* (%) =214 (13), 213 (25), 201 (38), 189 (27), 188 (22), 187 (64), 181 (12), 178 (10), 177 (100), 175 (22), 173 (16), 155 (11), 149 (19), 128 (15), 121 (17), 119 (12).

HRMS (EI): *m/z* calc. for [$C_{20}H_{24}F_3N_3OSi$]: 407.1641; found 408.1721 (M+H).

***N*-(3-(1,3-dioxoisoindolin-2-yl)propyl)-*N*-isopropyl-6-methoxypicolinamide (93n)**



Following modified **TP6**, *N*-(3-(1,3-dioxoisoindolin-2-yl)propyl)-*N*-isopropylformamide (**86m**) (548 mg, 2.00 mmol, 1.0 equiv), and TMPZn·2MgCl$_2$·2LiCl solution 0.33M in THF (3.64 mL, 1.20 mmol, 1.2 equiv) were stirred under Ar atmosphere for 24 h and the mixture was diluted with THF (5 mL). Pd(dppf)Cl$_2$ (36.6 mg, 0.025 µmol, 0.025 equiv), 2-bromo-6-methoxypyridine (180 mg, 1.00 mmol, 0.5 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv) were added. After 24 h, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After extraction with DCM, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 1:1) to give **93n** (249 mg, 0.731 mmol, 73% yield) as a colorless thick oil.

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.81 – 7.75 (m, 2H), 7.66 – 7.62 (m, 2H), 7.58 – 7.53 (m, 1H), 7.05 – 7.00 (m, 1H), 6.71 – 6.64 (m, 1H), 4.09 – 4.02 (m, 1H), 3.86 – 3.80 (m, 3H), 3.74 – 3.71 (m, 2H), 3.41 – 3.35 (m, 2H), 2.12 – 2.03 (m, 2H), 1.16 – 1.08 (m, 6H). (major rotamer).

7.75 – 7.70 (m, 2H), 7.70 – 7.66 (m, 2H), 7.36 – 7.30 (m, 1H), 6.91 – 6.84 (m, 1H), 6.19 (d, *J* = 8.1 Hz, 1H), 4.71 – 4.61 (m, 1H), 3.74 – 3.73 (m, 3H), 3.47 – 3.41 (m, 2H), 3.31 – 3.22 (m, 2H), 1.89 – 1.80 (m, 2H), 1.30 – 1.20 (m, 6H). (minor rotamer)

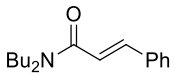
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 168.8, 168.6, 168.3 (2C), 168.0 (2C), 162.7, 162.6, 152.8, 152.5, 139.2, 138.9, 134.0 (2C), 133.9 (2C), 132.0 (2C), 131.7 (2C), 123.2 (2C), 123.1 (2C), 115.6, 114.9, 111.6, 111.0, 77.2, 53.5, 53.5, 49.8, 5.16, 41.9, 38.5, 36.1, 35.3, 30.6, 28.6, 21.3 (2C), 20.5 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1770, 1707, 1626, 1595, 1574, 1464, 1437, 1413, 1395, 1358, 1327, 1295, 1262, 1208, 1187, 1126, 1074, 1023, 987, 913, 888, 815, 764, 717.

MS (EI, 70 eV): *m/z* (%) = 246 (15), 245 (100), 188 (29), 160 (39), 136 (13), 136 (15), 109 (20), 108 (59), 98 (41), 93 (13).

HRMS (EI): *m/z* calc. for [$C_{21}H_{23}N_3O_4$]: 381.1683; found 381.1678.

***N*,*N*-Dibutylcinnamamide (93o)**



Following **TP6**, *N*,*N*-dibutylformamide (**86a**) (157 mg, 1.00 mmol, 1.0 equiv), ZnCl$_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et$_3$N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by Pd(dppf)Cl$_2$ (36.6 mg, 0.050 µmol, 0.05 equiv), (*E*)-(2-bromovinyl)benzene (146 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via*

column chromatography (pentane:ethyl acetate = 9:1 to 8:2) to give **93o** (168 mg, 0.648 mmol, 81% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 15.5 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.38 – 7.29 (m, 3H), 6.82 (d, *J* = 15.3 Hz, 1H), 3.45 – 3.39 (m, 2H), 3.39 – 3.35 (m, 2H), 1.64 – 1.59 (m, 2H), 1.58 – 1.52 (m, 2H), 1.41 – 1.29 (m, 4H), 1.00 – 0.89 (m, 6H).

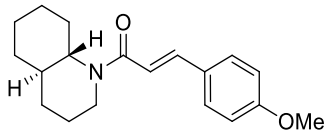
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.0, 142.2, 135.6, 129.4, 128.8 (2C), 127.8 (2C), 117.9, 77.2, 48.0, 46.7, 32.0, 30.1, 20.4, 20.2, 14.0, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2930, 2872, 1648, 1603, 1578, 1496, 1453, 1439, 1422, 1372, 1325, 1301, 1251, 1208, 1139, 1113, 1101, 976, 854, 762, 733, 706, 684, 668.

MS (EI, 70 eV): *m/z* (%) = 131 (100), 103 (38).

HRMS (EI): *m/z* calc. for [$C_{19}H_{25}NO_2$]: 259.1936; found 260.2008 (M+H).

(*E*)-3-(4-Methoxyphenyl)-1-(trans-octahydroquinolin-1(2H)-yl)prop-2-en-1-one (93p)



Following **TP6**, *trans*-octahydroisoquinoline-2(1H)-carbaldehyde (**86a**) (167 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $Pd(dppf)Cl_2$ (36.6 mg, 0.050 µmol, 0.05 equiv), (E)-1-(2-bromovinyl)-4-methoxybenzene (170 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1 to 8:2) to give **93p** (144 mg, 0.480 mmol, 60% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 (d, *J* = 15.3 Hz, 1H), 7.47 – 7.41 (m, 2H), 6.89 – 6.84 (m, 2H), 6.67 (d, *J* = 15.3 Hz, 1H), 4.13 – 4.01 (m, 1H), 3.79 (s, 3H), 3.44 – 3.35 (m, 1H), 3.20 – 3.09 (m, 1H), 2.14 – 2.06 (m, 1H), 1.88 – 1.76 (m, 2H), 1.75 – 1.66 (m, 3H), 1.65 – 1.54 (m, 2H), 1.52 – 1.39 (m, 2H), 1.38 – 1.22 (m, 2H), 1.21 – 1.02 (m, 2H).

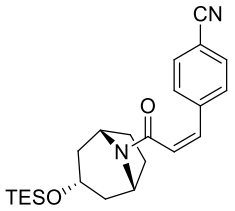
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.4, 160.7, 141.4, 129.2 (2C), 128.4, 116.2, 114.2 (2C), 61.8, 55.4, 38.6, 37.8, 33.1, 32.0, 26.3, 26.1, 25.55, 23.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 2855, 1642, 1593, 1575, 1510, 1459, 1424, 1413, 1360, 1304, 1286, 1250, 1233, 1219, 1171, 1134, 1112, 1030, 1009, 979, 824, 778, 729.

MS (EI, 70 eV): *m/z* (%) = 167 (10), 166 (100), 161 (28), 138 (93), 133 (10), 86 (14), 81 (17).

HRMS (EI): *m/z* calc. for [$C_{19}H_{25}NO_2$]: 299.1885; found 299.1879.

4-((*Z*)-3-Oxo-3-((1R,3r,5S)-3-((triethylsilyl)oxy)-8-azabicyclo[3.2.1]octan-8-yl)prop-1-en-1-yl)benzonitrile (93q)



Following **TP6**, (1R,3r,5S)-3-((triethylsilyl)oxy)-8-azabicyclo[3.2.1]octane-8-carbaldehyde (**86a**) (269 mg, 1.00 mmol, 1.0 equiv), $ZnCl_2$ (500 µL, 0.500 mmol, 1.0 equiv) and Et_3N (56.0 mg, 0.500 mmol, 1.0 equiv) were mixed in THF (2.0 mL) and a freshly prepared solution of TMPLi (1.10 mmol, 1.1 equiv) was dropwise added at 15 °C followed by $Pd(dppf)Cl_2$ (36.6 mg, 0.050 µmol, 0.05 equiv), (*Z*)-4-(2-bromovinyl)benzonitrile (166 mg, 0.80 mmol, 0.8 equiv) and CuCN·2LiCl 1M in THF (20.0 µL, 0.020 mmol, 0.02 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 65:35) to give **93q** (196 mg, 0.496 mmol, 62% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.63 – 7.47 (m, 4H), 6.61 (d, *J* = 12.5 Hz, 1H), 6.18 (d, *J* = 12.5 Hz, 1H), 4.73 – 4.59 (m, 1H), 4.00 – 3.94 (m, 1H), 3.92 – 3.87 (m, 1H), 2.28 – 2.19 (m, 1H), 2.17 – 2.09 (m, 1H), 2.03 – 1.95 (m, 1H), 1.77 – 1.61 (m, 2H), 1.61 – 1.48 (m, 2H), 1.45 – 1.33 (m, 1H), 0.93 – 0.84 (m, 9H), 0.55 – 0.46 (m, 6H).

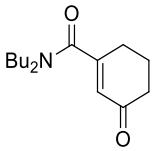
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.6, 140.1, 132.1 (2C), 132.0, 129.2 (2C), 126.8, 118.6, 111.8, 65.0, 55.4, 50.7, 41.1, 39.3, 28.4, 27.1, 6.9, 4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2912, 2875, 2227, 1612, 1505, 1453, 1410, 1370, 1322, 1313, 1238, 1223, 1169, 1085, 1051, 1004, 963, 923, 875, 845, 782, 724.

MS (EI, 70 eV): *m/z* (%) = 368 (17), 167 (74), 298 (41), 212 (15), 182 (18), 181 (10), 157 (10), 157 (10), 156 (98), 129 (16), 128 (100), 110 (51), 108 (10), 103 (17), 101 (10), 91 (18), 87 (18), 82 (12), 80 (10), 75 (38), 68 (14), 59 (10).

HRMS (EI): *m/z* calc. for [$C_{23}H_{32}N_2O_2Si$]: 396.2233; found 397.2313 (M+H).

***N*,*N*-Dibutyl-3-oxocyclohex-1-enecarboxamide (93r)**



Following modified **TP5**, *N*,*N*-dibutylformamide (**86a**) (314 mg, 2.00 mmol, 2.0 equiv), $ZnCl_2$ (1.00 mL, 1.00 mmol, 1.0 equiv) and Et_3N (101 mg, 1.00 mmol, 1.0 equiv) were mixed in THF (4.0 mL) and a freshly prepared solution of TMPLi (2.20 mmol, 2.2 equiv) was dropwise added at 15 °C. After cooling to −78 °C, CuCN·2LiCl (1.00 mL, 1.00 mmol, 1.0 equiv) and 3-iodocyclohex-2-enone (222 mg, 1.00 mmol, 1.0 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1 to 8:2) to give **93r** (163 mg, 0.650 mmol, 65% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.92 (t, *J* = 1.7 Hz, 1H), 3.37 (dd, *J* = 8.8, 6.4 Hz, 2H), 3.24 – 3.12 (m, 2H), 2.53 (td, *J* = 6.0, 1.8 Hz, 2H), 2.48 – 2.40 (m, 2H), 2.16 – 2.07 (m, 2H), 1.61 – 1.44 (m, 4H), 1.38 – 1.29 (m, 2H), 1.28 – 1.19 (m, 2H), 0.91 (dt, *J* = 14.2, 7.3 Hz, 6H).

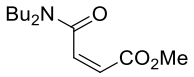
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.0, 169.6, 156.7, 126.0, 48.3, 44.0, 37.5, 31.0, 29.6, 27.4, 22.7, 20.3, 20.1, 14.0, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2931, 2872, 1675, 1630, 1616, 1456, 1427, 1377, 1345, 1321, 1290, 1248, 1224, 1188, 1079, 965, 890, 732.

MS (EI, 70 eV): *m/z* (%) = 208 (17), 194 (15), 182 (10), 180 (70), 166 (14), 166 (22), 156 (20), 153 (10), 152 (17), 138 (18), 123 (68), 111 (12), 95 (100), 67 (23), 67 (11), 55 (11).

HRMS (EI): *m/z* calc. for [$C_{15}H_{25}NO_2$]: 251.1885; found 251.1883.

(*Z*)-Methyl 4-(dibutylamino)-4-oxobut-2-enoate (93s)



Following modified **TP5**, *N*,*N*-dibutylformamide (**86a**) (314 mg, 2.00 mmol, 2.0 equiv), $ZnCl_2$ (1.00 mL, 1.00 mmol, 1.0 equiv) and Et_3N (101 mg, 1.00 mmol, 1.0 equiv) were mixed in THF (4.0 mL) and a freshly prepared solution of TMPLi (2.20 mmol, 2.2 equiv) was dropwise added at 15 °C. After cooling to □78 °C, CuCN·2LiCl (1.00 mL, 1.00 mmol, 1.0 equiv) and (*Z*)-ethyl 3-iodoacrylate (226 mg, 1.00 mmol, 1.0 equiv). Thereafter, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. After workup, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1 to 8:2) to give **93s** (171 mg, 0.670 mmol, 67% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.53 (d, *J* = 12.0 Hz, 1H), 5.95 (dd, *J* = 12.0, 0.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.45 – 3.32 (m, 2H), 3.27 – 3.13 (m, 2H), 1.65 – 1.55 (m, 2H), 1.53 – 1.44 (m, 2H), 1.41 – 1.31 (m, 2H), 1.31 – 1.20 (m, 5H), 0.92 (dt, *J* = 15.8, 7.3 Hz, 6H).

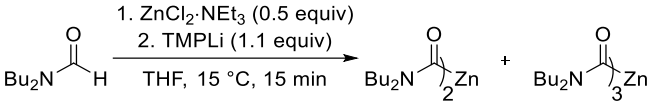
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.6, 164.9, 138.2, 123.0, 60.9, 48.2, 44.6, 30.8, 29.5, 20.4, 20.1, 14.0, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2932, 2873, 1724, 1628, 1457, 1430, 1379, 1296, 1209, 1176, 1143, 1031, 951, 819, 756.

MS (EI, 70 eV): *m/z* (%) = 226 (23), 210 (11), 128 (40), 127 (17), 99 (100).

HRMS (EI): *m/z* calc. for [$C_{14}H_{25}NO_3$]: 255.1834; found 256.1908 (M+H)

5.7 NMR characterization of Carbamoylzinc Reagents



Scheme 75. Metalation in d8-THF with TMPLi (0.5 equiv $ZnCl_2$ compared to *N*,*N*-dibutylformamide **86a**.

Sample preparation:

In a clean, flame-dried, argon-filled flask was added *n*-BuLi 1.72 M in *n*-hexane (320 µL, 0.55 mmol). The high vacuum was slowly released (water bath at 25 °C). After ca. 2 h crystals of *n*-BuLi were observed on the walls of the flask. Flask was placed into a −78 °C acetone bath (stirring stopped due to freezing of *n*-BuLi slime on the bottom of the flask). d_8-THF ampule was opened and solvent quickly taken into argon flushed syringe. d_8-THF was dropwise added to *n*-BuLi. To ensure stirring the flask was shaken gently outside of the acetone bath till the stirring bar was released from the bottom. When stirring was ensured, TMPH (72 mg, 0.5 mmol) was added in one portion and the mixture was stirred for 4 h to obtain white suspension of TMPLi. Then the flask was transferred into an ice/water bath and stirred for 15 min (yellowish solution obtained).

In another a clean, flame-dried, argon-filled flask was added $ZnCl_2$ 1M in THF (0.2 mL, 0.2 mmol) and the solvent was removed under a high vacuum (over 1 h). To the $ZnCl_2$ powder was added d_8-THF (0.75 mL). To the solution was added Bu_2NCHO (64 mg, 0.4 mmol, 1.0 equiv) and the reaction mixture was tempered to 15 °C. The solution of TMPLi in d_8-THF was dropwise added to the solution of $Bu_2NCHO/ZnCl_2$ in d8-THF at 15 °C and the reaction mixture was stirred for an additional 15 min. Into the flame dried and argon flushed NMR tube 1 mL of the solution was transferred.

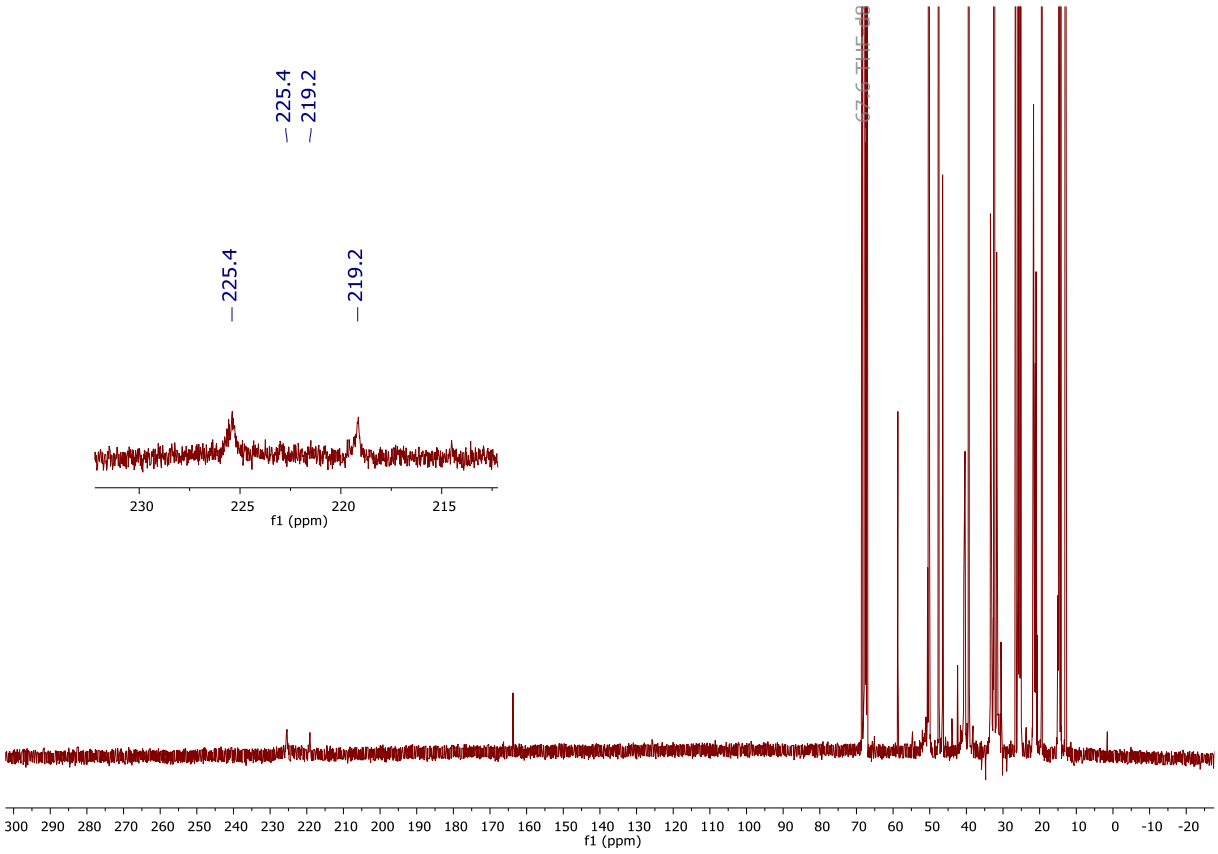
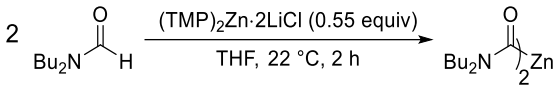


Figure 12. ^{13}C NMR of the sample prepared in d_8-THF by addition of TMPLi into the mixture of $ZnCl_2$ (0.5 equiv) and *N*,*N*-dibutylformamide **86** showing two signals for dicarbamoylzinc species **87a** and tricarbamoylzincate **94**.



Scheme 76. Metalation in THF with capillary d_6-benzene with $TMP_2Zn·2LiCl$ (0.55 equiv compared to *N*,*N*-dibutylformamide **86a**.

Sample preparation:

Heat and vacuum dried flask flushed with argon was placed into an acetone/dry ice bath at -78 °C. Tetramethylpiperidine (184 mg, 1.3 mmol) was dissolved in THF (2 mL) and cooled to −78 °C. Then, *n*-BuLi 1.63 M in hexane (0.8 mL, 1.3 mmol) was dropwise added and the reaction was allowed to warm to 0 °C over 1-2 h. Then $ZnCl_2$ (1M in THF) (600 µL, 0.6 mmol, 0.6 equiv) was added and the mixture was stirred for 30 minutes to produce $TMP_2Zn·2LiCl$. Neat *N*,*N*-dibutylformamide (1.00 mmol, 1.0 equiv) was added and the mixture was stirred for an additional 2 h. Into the flame dried and argon flushed NMR tube equipped with capillary C_6D_6 1 mL of the solution was transferred.

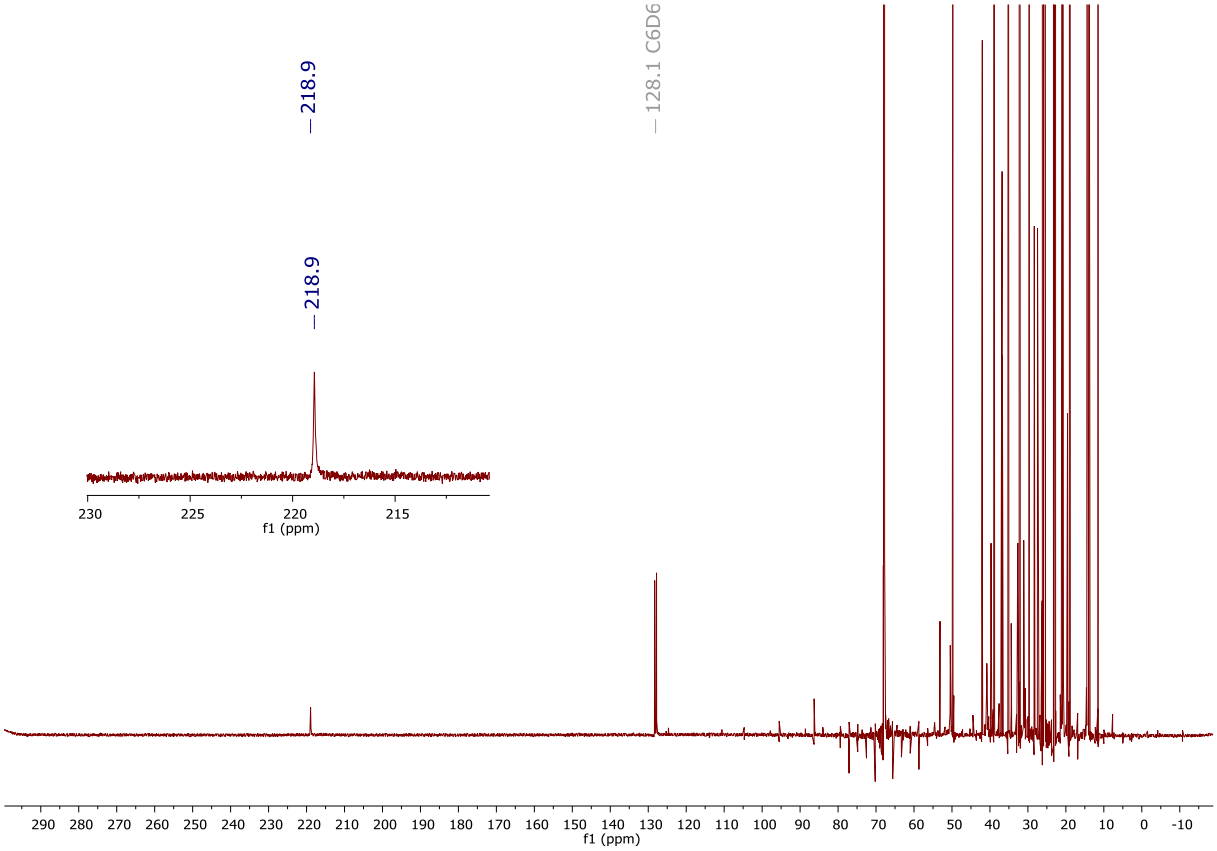
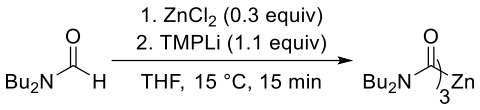


Figure 13. ^{13}C NMR of the sample prepared in THF (capillary C_6D_6) by treating the *N*,*N*-dibutylformamide **86** with $TMP_2Zn·2LiCl$ showing solely the presence of dicarbamoylzinc **87a**.



Scheme 77. Metalation in THF with capillary d6-benzene with TMPLi (0.3 equiv $ZnCl_2$ compared to *N*,*N*-dibutylformamide **86a**.

Sample preparation:

Heat and vacuum dried flask flushed with argon was placed into an ice/water bath at 0 °C. Formamide (1.00 mmol, 1.0 equiv), $ZnCl_2$ solution 1 M in THF (330 µL, 0.330 mmol, 0.33 equiv), Et_3N (51.0 mg, 0.500 mmol, 0.5 equiv) and THF (2 mL) were added. Freshly prepared TMPLi as ca. 0.5 M solution in THF (1.2 mmol, 1.2 equiv) was dropwise added over 1-2 minutes. The reaction mixture was stirred for additional 15 minutes. Into the flame dried and argon flushed NMR tube equipped with capillary C_6D_6 1 mL of the solution was transferred.

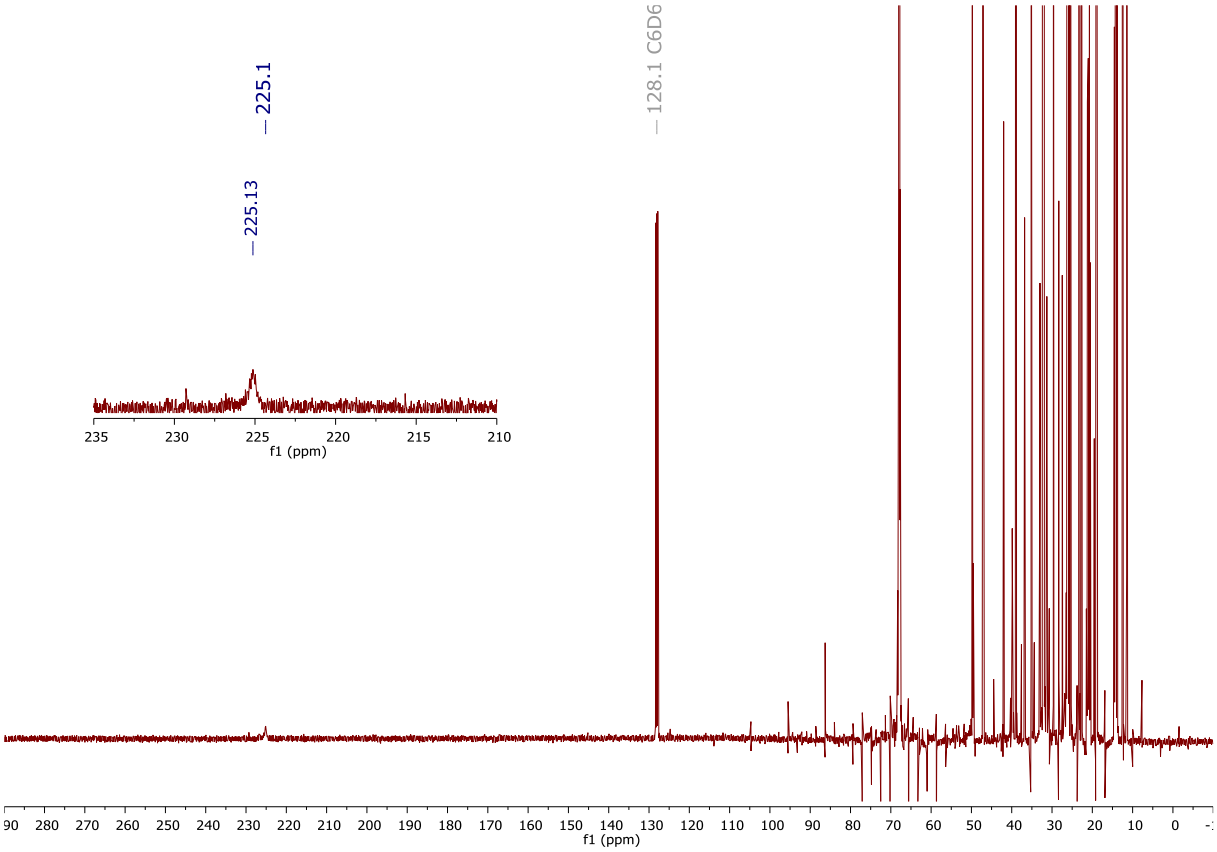
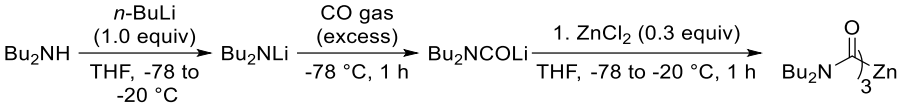


Figure 14. ^{13}C NMR of the sample prepared in THF (capillary C_6D_6) by addition of TMPLi into the mixture of $ZnCl_2$ (0.3 equiv) and *N*,*N*-dibutylformamide **86** showing a signal for tricarbamoylzincate **94**.



Scheme 78. Transmetalation of *N*,*N*-dibutylcarbamoyllithium with 0.3 equiv $ZnCl_2$.

Sample preparation:

Heat and vacuum dried two-necked Schlenk flask flushed with argon was filled with Bu_2NH (10.0 mmol, 1.0 equiv) as 0.5 M solution in THF and cooled to −78 °C. After dropwise addition of *n*-BuLi (10 mmol, 1.0 equiv) 1.6 M in hexane the mixture was allowed to slowly warm to −20 °C. The mixture was again cooled to −78 °C and CO gas was introduced (yellow color developed) into the flask *via* tubing through quick-fit attachment. CO atmosphere was maintained for 1 h and then $ZnCl_2$ (0.3 equiv) was added. The reaction mixture was stirred for 1 h (allowed to slowly warm up) to enable full transmetalation. Into the flame dried and argon flushed NMR tube equipped with capillary C_6D_6 1 mL of the solution was transferred.

CAUTION: Working with highly toxic CO gas should be done only with proper equipment, a validated CO-gas detector and by a trained chemist.

Note: Reaction of aliquots with allyl bromide in the presence of CuCN·2LiCl afforded **8a** as the sole product.

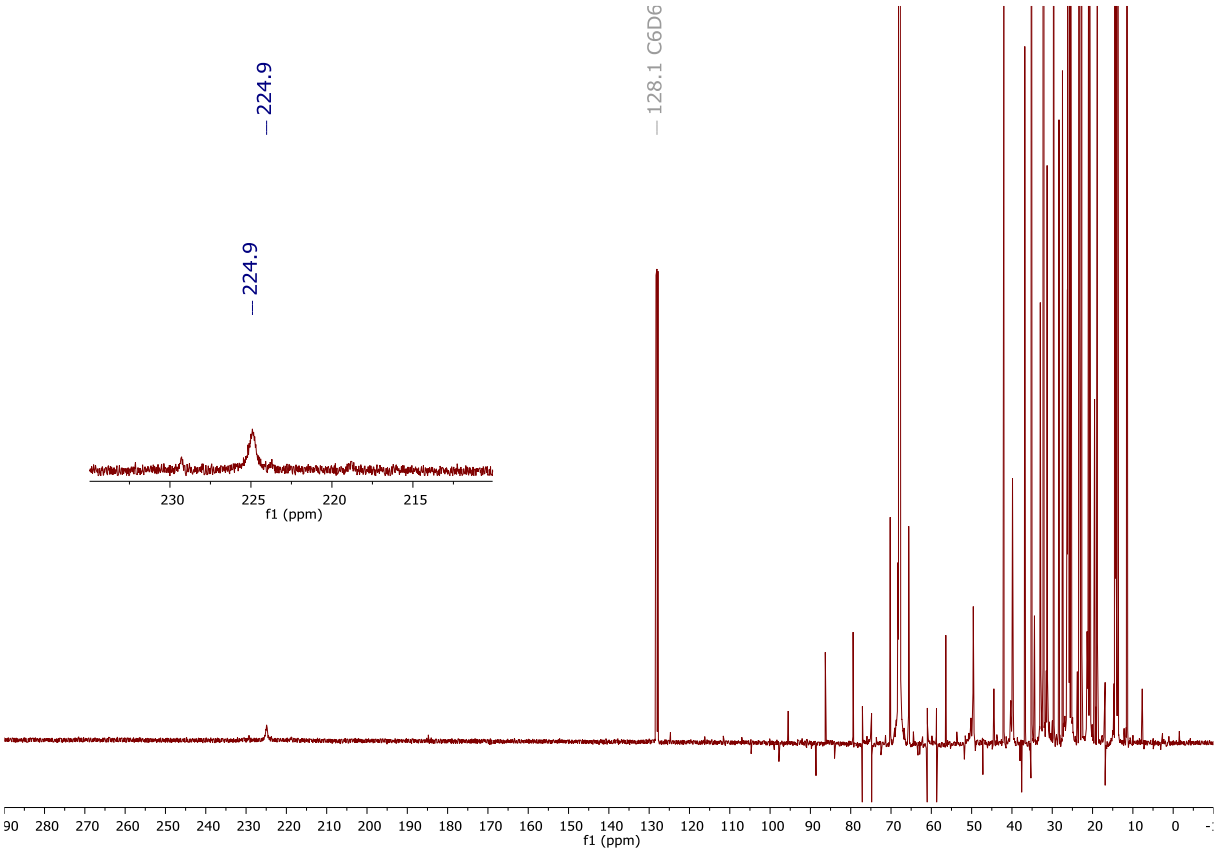
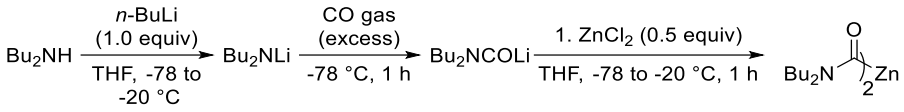


Figure 15. ^{13}C NMR of the tricarbamoylzincate **94** in THF (capillary C_6D_6) was obtained by transmetalation of *N*,*N*-dibutylcarbamoyllithium (**95**) with $ZnCl_2$ (0.3 equiv).



Scheme 79. Transmetalation of *N*,*N*-dibutylcarbamoyllithium with 0.5 equiv $ZnCl_2$.

Sample preparation:

Heat and vacuum dried two-necked Schlenk flask flushed with argon was filled with Bu_2NH (10.0 mmol, 1.0 equiv) as 0.5 M solution in THF and cooled to −78 °C. After dropwise addition of *n*-BuLi (10 mmol, 1.0 equiv) 1.6 M in hexane the mixture was allowed to slowly warm to −20 °C. The mixture was again cooled to −78 °C and CO gas was introduced (yellow color developed) into the flask *via* tubing through quick-fit attachment. CO atmosphere was maintained for 1 h and then $ZnCl_2$ (0.5 equiv) was added. The reaction mixture was stirred for 1 h (allowed to slowly warm up) to enable full transmetalation. Into the flame dried and argon flushed NMR tube equipped with capillary C_6D_6 1 mL of the solution was transferred.

CAUTION: Working with highly toxic CO gas should be done only with proper equipment, a validated CO-gas detector and by a trained chemist.

Note: Reaction of aliquots with allyl bromide in the presence of CuCN·2LiCl afforded **8a** as the sole product.

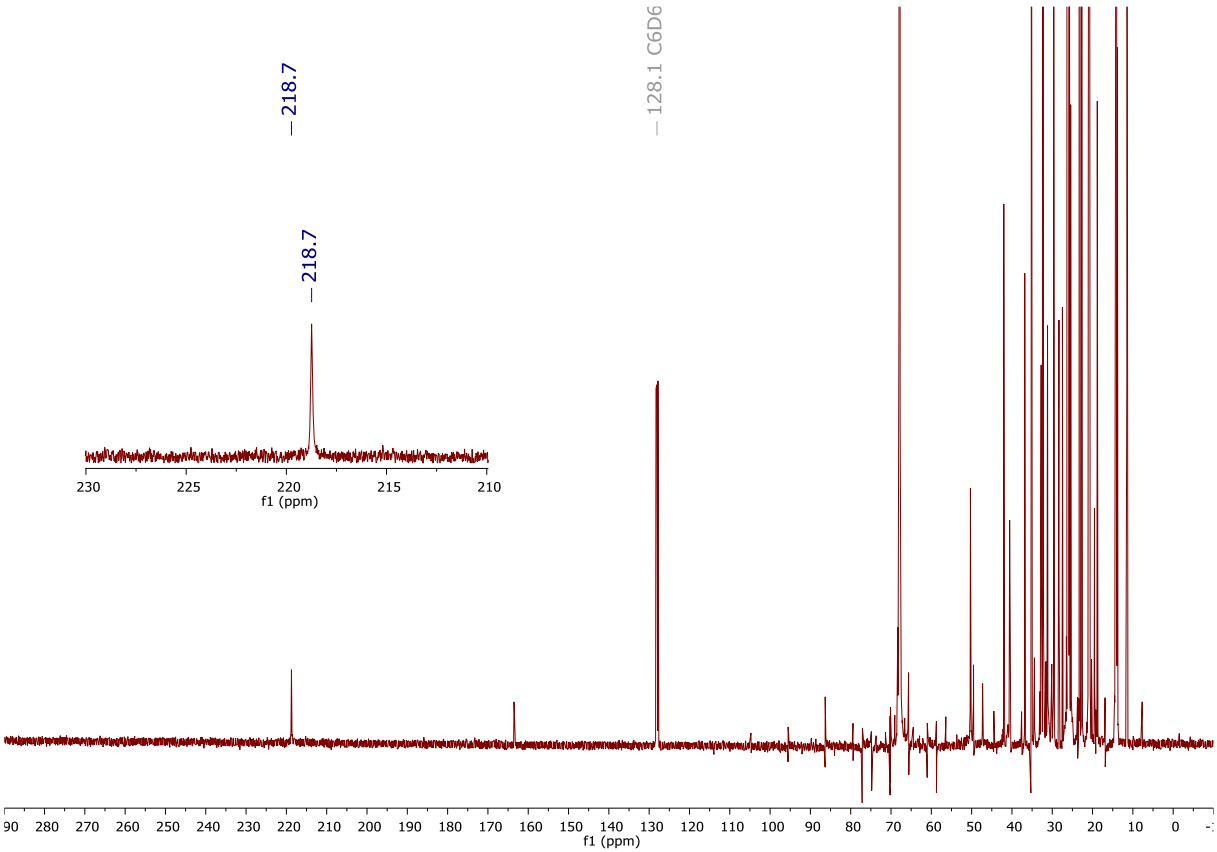
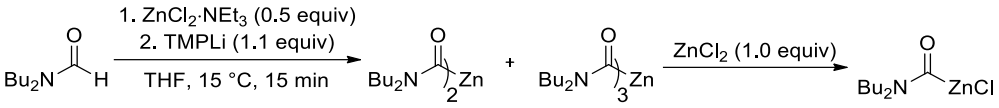


Figure 16. ^{13}C NMR of the dicarbamoylzinc **86a** in THF (capillary C_6D_6) was obtained by transmetalation of *N*,*N*-dibutylcarbamoyllithium (**95**) with $ZnCl_2$ (0.5 equiv).



Scheme 80. Formation of tentative monocarbamoylzinc reagent by addition of +1 equiv $ZnCl_2$ to the mixture of dicarbamoylzinc and tricarbamoylzinc.

Sample preparation:

In a clean, flame-dried, argon-filled flask was added *n*-BuLi 1.72 M in *n*-hexane (320 μL, 0.55 mmol). The high vacuum was slowly released (water bath at 25 °C). After ca. 2 h crystals of *n*-BuLi were observed on the walls of the flask. Flask was placed into a −78 °C acetone bath (stirring stopped due to freezing of *n*-BuLi slime on the bottom of the flask). d_8-THF ampule was opened and solvent was quickly taken into argon flushed syringe. d_8-THF was dropwise added to *n*-BuLi. To ensure stirring the flask was shaken gently outside of the acetone bath till the stirring bar was released from the bottom. When stirring was ensured, TMPH (72 mg, 0.5 mmol) was added in one portion and the mixture was stirred for 4 h to obtain white suspension of TMPLi. Then the flask was transferred into an ice/water bath and stirred for 15 min (yellowish solution obtained).

In another a clean, flame dried, argon filled flask was added $ZnCl_2$ 1M in THF (0.5 mL, 0.5 mmol) and the solvent was removed under a high vacuum (over 1 h). To the $ZnCl_2$ powder was added d8-THF (0.75 mL). To the solution was added Bu_2NCHO (64 mg, 0.4 mmol, 1.0 equiv) and the reaction mixture was tempered to 15 °C. The solution of TMPLi in d8-THF was dropwise added to the solution of $Bu_2NCHO/ZnCl_2$ in d8-THF at 15 °C and the reaction mixture was stirred for an additional 15 min.

The solution of carbamoylzinc reagent was transferred to the new flask containing dry $ZnCl_2$ powder (0.4 mmol, 0.4 equiv) (obtained by evaporating the THF solution of $ZnCl_2$ under a high vacuum). Into the flame dried and argon flushed NMR tube 1 mL of the solution was transferred.

Note: HMBC experiment was performed at 0 °C.

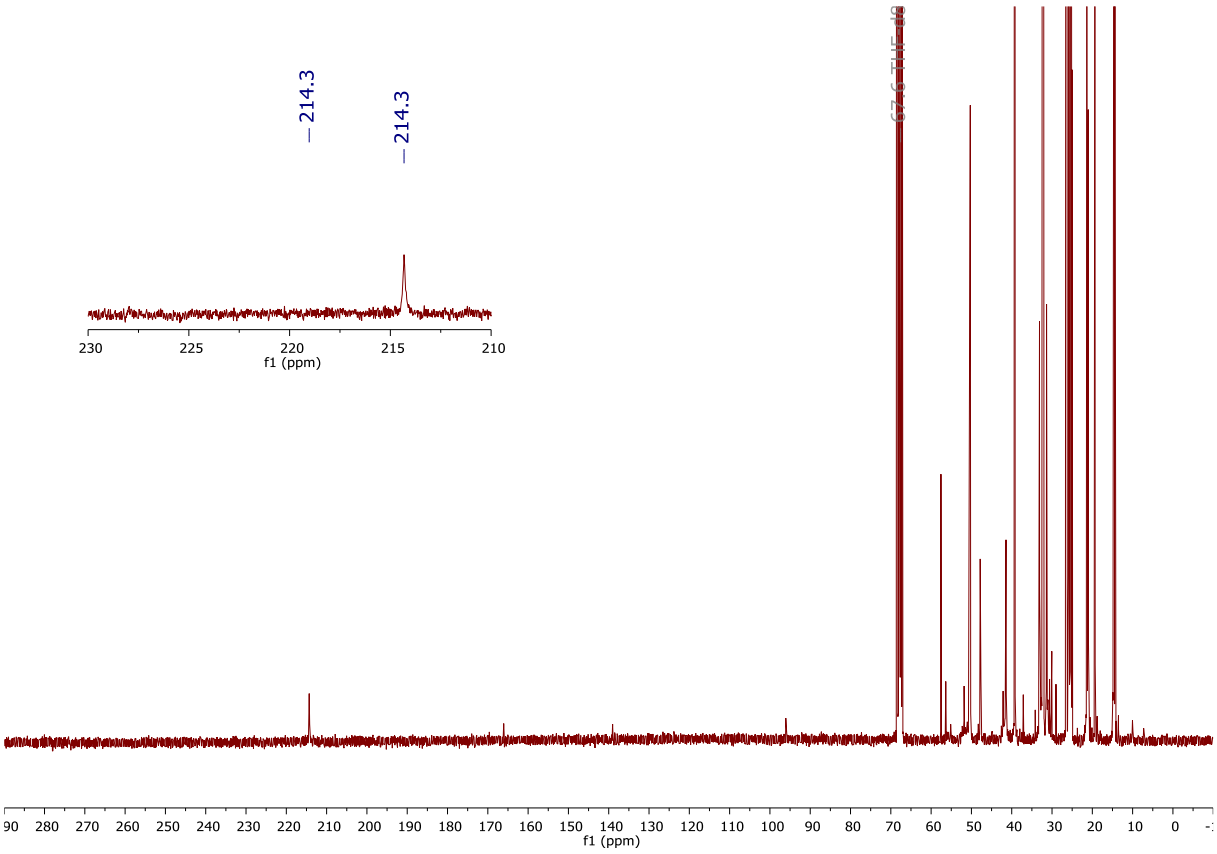


Figure 17. ^{13}C NMR spectra of tentative monocarbamoylzinc species $Bu_2NCOZnCl$ in d_8-THF.

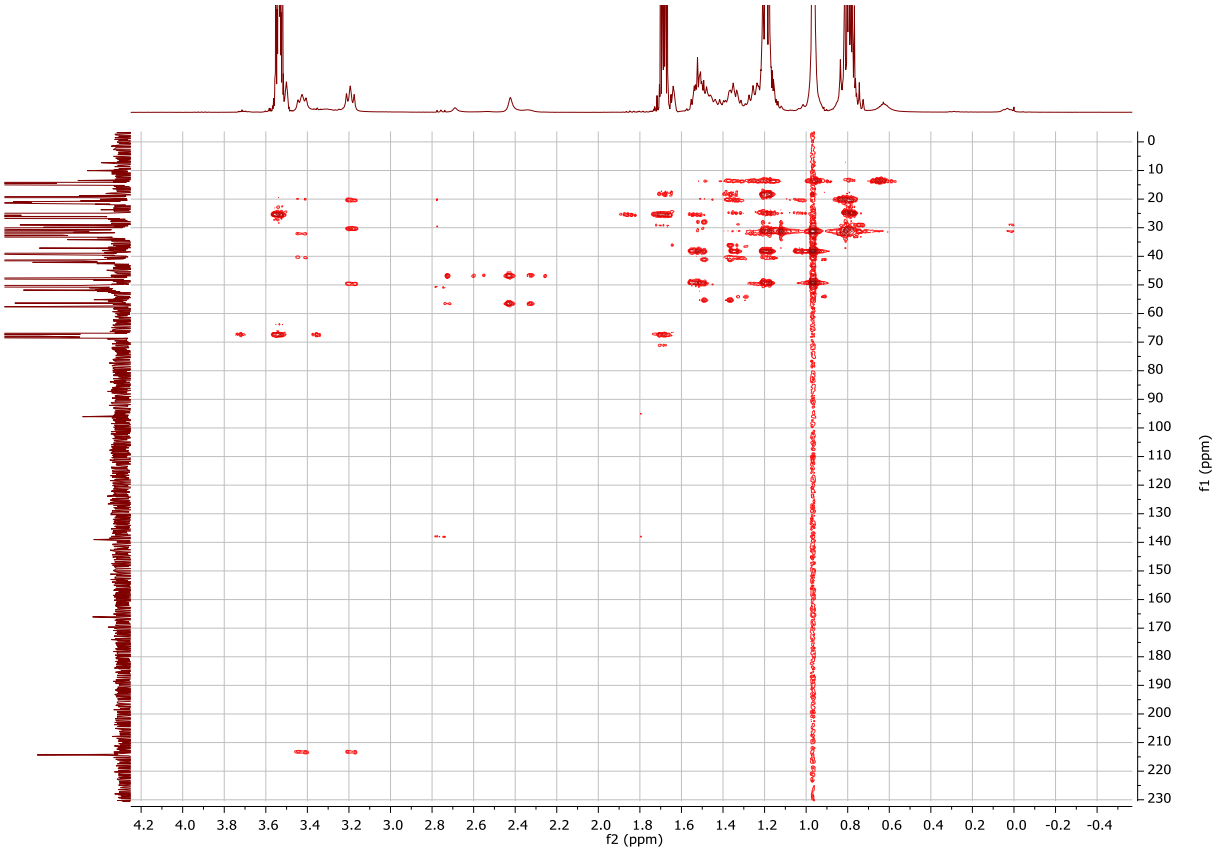


Figure 18. HMBC spectra of tentative monocarbamoylzinc species $Bu_2NCOZnCl$ in d_8-THF showing a correlation between carbonyl signal at 214 ppm and protons adjacent to nitrogen (3.2 and 3.4 ppm).

5.8 Single Crystal X-Ray Diffraction Studies

Single crystals of compound **86m**, suitable for X-ray diffraction, were obtained by slow evaporation of **ethyl acetate** solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[202] Absorption correction using the multiscan method[202] was applied. The structures were solved with SHELXS-97,[203] refined with SHELXL-97[204] and finally checked using PLATON.[205] Details for data collection and structure refinement are summarized in Table 37.

CCDC-**2164155** 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 **86m**.

	86m
Empirical formula	$C_{15}H_{18}N_2O_3$
Formula mass	274.31
T[K]	123(2)
Crystal size [mm]	0.40 × 0.30 × 0.25
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	8.0549(4)
b [Å]	16.1122(7)
c [Å]	11.0039(6)
α [°]	90.0
β [°]	103.830(5)
γ [°]	90.0
V [Å^3]	1386.71(12)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.314
μ [mm^{-1}]	0.092
F(000)	584
Θ range [°]	2.29 – 25.24
Index ranges	$-11 \leq h \leq 11$
	$-23 \leq k \leq 23$
	$-15 \leq l \leq 15$
Reflns. collected	28469
Reflns. obsd.	3488
Reflns. unique	4238
	(R_{int} = 0.0323)
R_1, wR_2 (2σ data)	0.0445, 0.1106
R_1, wR_2 (all data)	0.0553, 0.1179
GOOF on F^2	1.027
Peak/hole [e Å^{-3}]	0.392 / -0.181

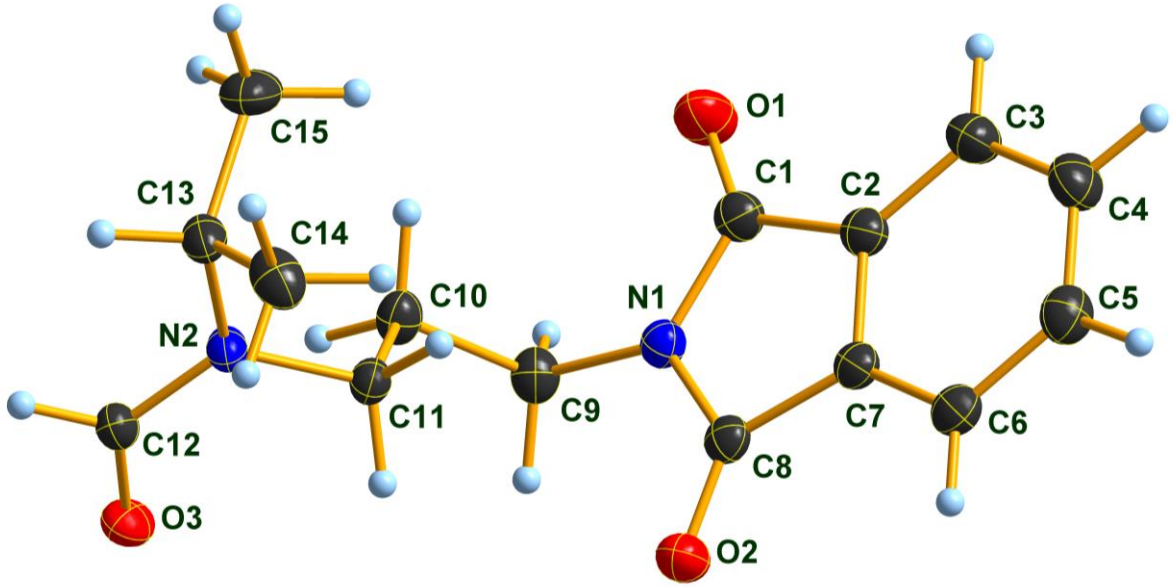


Figure 19. Molecular structure of compound **86m** in the crystal. DIAMOND[206] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 38. Selected bond lengths (Å) of compound **86m**.

O2 – C8	1.208(1)	C13 – C15	1.521(2)
N1 – C1	1.392(1)	C13 – C14	1.523(2)
N1 – C8	1.394(1)	C6 – C5	1.398(2)
N1 – C9	1.459(1)	C3 – C4	1.394(2)
C10 – C9	1.520(2)	C5 – C4	1.391(2)
C10 – C11	1.525(1)	C7 – C6	1.381(1)
N2 – C12	1.341(1)	C7 – C2	1.389(1)
N2 – C11	1.462(1)	C7 – C8	1.489(1)
N2 – C13	1.469(1)	O3 – C12	1.233(1)
C1 – O1	1.207(1)	C2 – C3	1.379(2)
C1 – C2	1.488(2)		

Table 39. Selected bond angles (°) of compound **86m**.

C1 – N1 – C8	112.0(1)	C7 – C6 – C5	117.0(1)
C1 – N1 – C9	123.6(1)	N2 – C11 – C10	112.5(1)
C8 – N1 – C9	124.3(1)	O3 – C12 – N2	124.6(1)
C9 – C10 – C11	112.3(1)	C2 – C3 – C4	117.4(1)

N1 – C9 – C10	113.5(1)	C4 – C5 – C6	121.2(1)
C12 – N2 – C11	118.7(1)	C5 – C4 – C3	121.2(1)
C12 – N2 – C13	120.6(1)	C3 – C2 – C1	130.5(1)
C11 – N2 – C13	120.6(1)	C7 – C2 – C1	108.2(1)
O1 – C1 – N1	124.5(1)	O2 – C8 – N1	124.6(1)
O1 – C1 – C2	129.6(1)	O2 – C8 – C7	129.4(1)
N1 – C1 – C2	105.9(1)	N1 – C8 – C7	106.0(1)
C6 – C7 – C2	121.9(1)	N2 – C13 – C15	111.1(1)
C6 – C7 – C8	130.2(1)	N2 – C13 – C14	111.3(1)
C2 – C7 – C8	107.9(1)	C15 – C13 – C14	111.7(1)
C3 – C2 – C7	121.4(1)		

Table 40. Selected torsion angles (°) of compound **86m**.

C1 – N1 – C9 – C10	-85.2(1)	C2 – C7 – C8 – O2	178.3(1)
C8 – N1 – C9 – C10	98.2(1)	C6 – C7 – C8 – N1	178.1(1)
C11 – C10 – C9 – N1	-61.3(1)	C2 – C7 – C8 – N1	-0.9(1)
C8 – N1 – C1 – O1	179.5(1)	C12 – N2 – C13 – C15	-120.8(1)
C9 – N1 – C1 – O1	2.5(2)	C11 – N2 – C13 – C15	62.3(1)
C8 – N1 – C1 – C2	0.0(1)	C12 – N2 – C13 – C14	114.1(1)
C9 – N1 – C1 – C2	-177.0(1)	C11 – N2 – C13 – C14	-62.9(1)
C6 – C7 – C2 – C3	1.0(2)	C2 – C7 – C6 – C5	-0.2(2)
C8 – C7 – C2 – C3	-179.9(1)	C8 – C7 – C6 – C5	-179.2(1)
C6 – C7 – C2 – C1	-178.2(1)	C12 – N2 – C11 – C10	79.5(1)
C8 – C7 – C2 – C1	0.9(1)	C13 – N2 – C11 – C10	-103.5(1)
O1 – C1 – C2 – C3	0.9(2)	C9 – C10 – C11 – N2	-168.4(1)
N1 – C1 – C2 – C3	-179.7(1)	C11 – N2 – C12 – O3	-1.6(2)
O1 – C1 – C2 – C7	180.0(1)	C13 – N2 – C12 – O3	-178.6(1)
N1 – C1 – C2 – C7	-0.6(1)	C7 – C2 – C3 – C4	-0.8(2)
C1 – N1 – C8 – O2	-178.7(1)	C1 – C2 – C3 – C4	178.2(1)
C9 – N1 – C8 – O2	-1.7(2)	C7 – C6 – C5 – C4	-0.6(2)
C1 – N1 – C8 – C7	0.6(1)	C6 – C5 – C4 – C3	0.8(2)

C9 – N1 – C8 – C7	177.5(1)	C2 – C3 – C4 – C5	0.0(2)
C6 – C7 – C8 – O2	-2.7(2)		

Single crystals of compound **86p**, suitable for X-ray diffraction, were obtained by slow evaporation of **$CDCl_3$** solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[202] Absorption correction using the multiscan method[202] was applied. The structures were solved with SHELXS-97,[203] refined with SHELXL-97[204] and finally checked using PLATON.[11] Details for data collection and structure refinement are summarized in Table 41.

CCDC-**2164152** 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 41. Details for X-ray data collection and structure refinement for compound **86p**.

	86p
Empirical formula	$C_{12}H_{13}N_3O$
Formula mass	215.25
T[K]	123(2)
Crystal size [mm]	0.40 × 0.40 × 0.05
Crystal description	colorless platelet
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	9.4066(5)
b [Å]	11.9350(5)
c [Å]	9.7498(5)
α [°]	90.0
β [°]	101.214(5)
γ [°]	90.0
V [Å^3]	1073.69(9)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.332
μ [mm^{-1}]	0.088
F(000)	456
Θ range [°]	2.21 – 25.24
Index ranges	$-12 \leq h \leq 12$
	$-15 \leq k \leq 15$
	$-12 \leq l \leq 12$
Reflns. collected	18754
Reflns. obsd.	2128
Reflns. unique	2660
	(R_{int} = 0.0355)
R_1, wR_2 (2σ data)	0.0400, 0.1028
R_1, wR_2 (all data)	0.0531, 0.1116
GOOF on F^2	1.043
Peak/hole [e Å^{-3}]	0.266 / -0.179

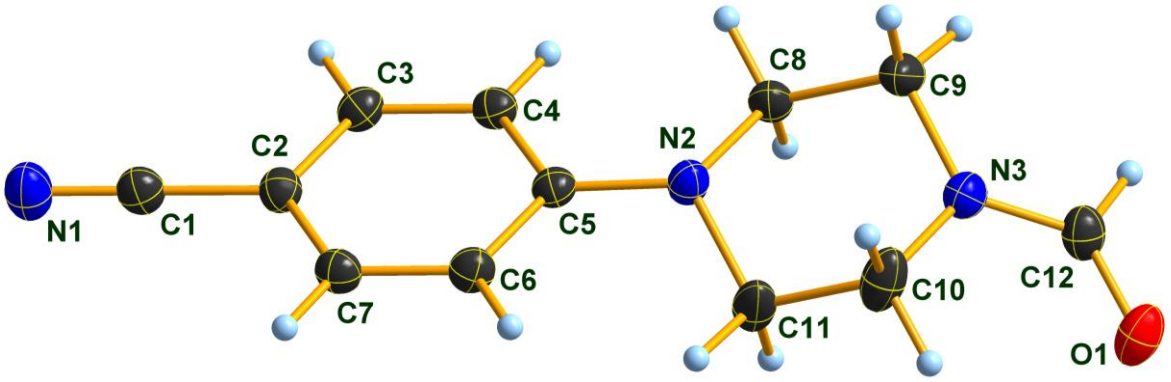


Figure 20. Molecular structure of compound **86p** in the crystal. DIAMOND[206] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 42. Selected bond lengths (Å) of compound **86p**.

C5 – N2	1.396(2)	C8 – N2	1.464(2)
C5 – C4	1.411(2)	C8 – C9	1.524(2)
C5 – C6	1.413(2)	N2 – C11	1.472(2)
C1 – N1	1.150(2)	C10 – C11	1.517(2)
C1 – C2	1.437(2)	N3 – C12	1.340(2)
O1 – C12	1.223(2)	N3 – C10	1.453(2)
C2 – C3	1.397(2)	N3 – C9	1.455(2)
C2 – C7	1.400(2)	C6 – C7	1.377(2)
C3 – C4	1.385(2)		

Table 43. Selected bond angles (°) of compound **86p**.

N2 – C5 – C4	121.8(1)	C5 – N2 – C8	118.5(1)
N2 – C5 – C6	120.4(1)	C5 – N2 – C11	117.6(1)
C4 – C5 – C6	117.8(1)	C8 – N2 – C11	111.2(1)
N1 – C1 – C2	178.2(1)	N3 – C10 – C11	109.9(1)
C3 – C2 – C7	119.1(1)	N3 – C9 – C8	111.3(1)
C3 – C2 – C1	120.8(1)	O1 – C12 – N3	125.8(1)
C7 – C2 – C1	120.1(1)	N2 – C11 – C10	111.0(1)
C4 – C3 – C2	120.5(1)	C7 – C6 – C5	121.1(1)

C12 – N3 – C10	122.1(1)	C6 – C7 – C2	120.7(1)
C12 – N3 – C9	123.1(1)	N2 – C8 – C9	110.4(1)
C10 – N3 – C9	114.5(1)	C3 – C4 – C5	120.9(1)

Table 44. Selected torsion angles (°) of compound **86p**.

C7 – C2 – C3 – C4	-0.6(2)	C6 – C5 – N2 – C11	37.8(2)
C1 – C2 – C3 – C4	179.4(1)	C9 – C8 – N2 – C5	162.4(1)
C2 – C3 – C4 – C5	-0.8(2)	C9 – C8 – N2 – C11	-56.6(1)
N2 – C5 – C4 – C3	-176.3(1)	C12 – N3 – C10 – C11	-120.4(1)
C6 – C5 – C4 – C3	1.9(2)	C9 – N3 – C10 – C11	53.3(1)
N2 – C5 – C6 – C7	176.8(1)	C12 – N3 – C9 – C8	120.9(1)
C4 – C5 – C6 – C7	-1.5(2)	C10 – N3 – C9 – C8	-52.7(2)
C5 – C6 – C7 – C2	0.1(2)	N2 – C8 – C9 – N3	53.0(1)
C3 – C2 – C7 – C6	1.0(2)	C10 – N3 – C12 – O1	-4.8(2)
C1 – C2 – C7 – C6	-179.0(1)	C9 – N3 – C12 – O1	-178.0(1)
C4 – C5 – N2 – C8	-5.6(2)	C5 – N2 – C11 – C10	-160.3(1)
C6 – C5 – N2 – C8	176.3(1)	C8 – N2 – C11 – C10	58.4(1)
C4 – C5 – N2 – C11	-144.1(1)	N3 – C10 – C11 – N2	-55.1(1)

Single crystals of compound **88j**, suitable for X-ray diffraction, were obtained by slow evaporation of **Et_2O** solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[202] Absorption correction using the multiscan method[202] was applied. The structures were solved with SHELXS-97,[203] refined with SHELXL-97[204] and finally checked using PLATON.[205] Details for data collection and structure refinement are summarized in Table 45.

CCDC-**2164153** 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 45. Details for X-ray data collection and structure refinement for compound **88j**.

	88j
Empirical formula	$C_{14}H_{17}NO_2$
Formula mass	231.28
T[K]	123(2)
Crystal size [mm]	0.40 × 0.35 × 0.30
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*n*
a [Å]	11.9110(8)
b [Å]	7.5895(3)
c [Å]	14.4486(9)
α [°]	90.0
β [°]	111.960(7)
γ [°]	90.0
V [Å^3]	1211.37(13)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.268
μ [mm^{-1}]	0.085
F(000)	496
Θ range [°]	2.79 – 25.24
Index ranges	$-15 \leq h \leq 15$
	$-10 \leq k \leq 10$
	$-19 \leq l \leq 19$
Reflns. collected	20442
Reflns. obsd.	2451
Reflns. unique	2990
	(R_{int} = 0.0391)
R_1, wR_2 (2σ data)	0.0442, 0.1043
R_1, wR_2 (all data)	0.0559, 0.1114
GOOF on F^2	1.017
Peak/hole [e Å^{-3}]	0.328 / -0.147

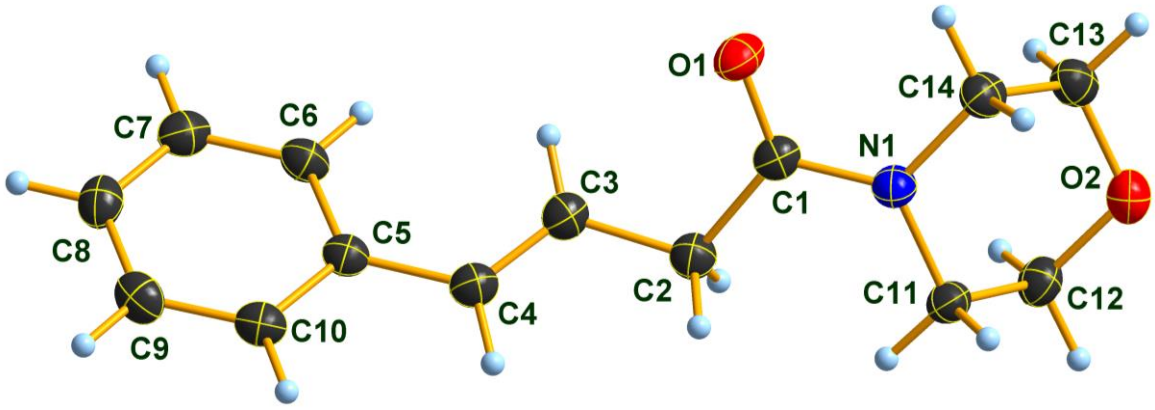


Figure 21. Molecular structure of compound **88j** in the crystal. DIAMOND[206] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 46. Selected bond lengths (Å) of compound **88j**.

C1 – O1	1.230(2)	C8 – C9	1.384(2)
C1 – N1	1.350(2)	C8 – C7	1.389(2)
C1 – C2	1.520(2)	C11 – C12	1.511(2)
N1 – C14	1.463(2)	C10 – C9	1.388(2)
N1 – C11	1.464(2)	C14 – C13	1.517(2)
C2 – C3	1.498(2)	C5 – C10	1.399(2)
O2 – C13	1.425(2)	C5 – C6	1.402(2)
O2 – C12	1.428(2)	C5 – C4	1.473(2)
C3 – C4	1.322(2)	C6 – C7	1.384(2)

Table 47. Selected bond angles (°) of compound **88j**.

O1 – C1 – N1	122.0(1)	C9 – C10 – C5	121.2(1)
O1 – C1 – C2	121.1(1)	C8 – C9 – C10	120.3(1)
N1 – C1 – C2	116.9(1)	C6 – C7 – C8	120.5(1)
C1 – N1 – C14	121.0(1)	N1 – C14 – C13	109.1(1)
C1 – N1 – C11	126.3(1)	O2 – C12 – C11	110.6(1)
C14 – N1 – C11	112.5(1)	O2 – C13 – C14	111.5(1)
C3 – C2 – C1	113.1(1)	C6 – C5 – C4	122.8(1)
C13 – O2 – C12	110.2(1)	C3 – C4 – C5	126.4(1)

C4 – C3 – C2	123.7(1)	C7 – C6 – C5	121.0(1)
C10 – C5 – C6	117.6(1)	C9 – C8 – C7	119.3(1)
C10 – C5 – C4	119.5(1)	N1 – C11 – C12	109.7(1)

Table 48. Selected torsion angles (°) of compound **88j**.

O1 – C1 – N1 – C14	-4.5(2)	C14 – N1 – C11 – C12	-54.7(1)
C2 – C1 – N1 – C14	175.1(1)	C6 – C5 – C10 – C9	-1.3(2)
O1 – C1 – N1 – C11	-178.5(1)	C4 – C5 – C10 – C9	179.3(1)
C2 – C1 – N1 – C11	1.1(2)	C7 – C8 – C9 – C10	0.9(2)
O1 – C1 – C2 – C3	-0.1(2)	C5 – C10 – C9 – C8	-0.1(2)
N1 – C1 – C2 – C3	-179.8(1)	C5 – C6 – C7 – C8	-1.3(2)
C1 – C2 – C3 – C4	-139.4(1)	C9 – C8 – C7 – C6	-0.2(2)
C2 – C3 – C4 – C5	-174.6(1)	C1 – N1 – C14 – C13	-121.1(1)
C10 – C5 – C4 – C3	-165.2(1)	C11 – N1 – C14 – C13	53.7(1)
C6 – C5 – C4 – C3	15.5(2)	C13 – O2 – C12 – C11	-60.5(1)
C10 – C5 – C6 – C7	2.0(2)	N1 – C11 – C12 – O2	57.2(1)
C4 – C5 – C6 – C7	-178.7(1)	C12 – O2 – C13 – C14	60.3(1)
C1 – N1 – C11 – C12	119.8(1)	N1 – C14 – C13 – O2	-56.0(1)

Single crystals of compound **91d**, suitable for X-ray diffraction, were obtained by slow evaporation of **Et_2O** solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[202] Absorption correction using the multiscan method[202] was applied. The structures were solved with SHELXS-97,[203] refined with SHELXL-97[204] and finally checked using PLATON.[205] Details for data collection and structure refinement are summarized in Table 49.

CCDC-**2164154** 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 49. Details for X-ray data collection and structure refinement for compound **91d**.

	91d
Empirical formula	$C_{17}H_{20}INO_2$
Formula mass	397.24
T[K]	123(2)
Crystal size [mm]	0.35 × 0.25 × 0.10
Crystal description	yellow block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	13.0951(7)
b [Å]	8.9157(6)
c [Å]	14.5136(9)
α [°]	90.0
β [°]	110.787(7)
γ [°]	90.0
V [Å^3]	1584.19(18)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.666
μ [mm^{-1}]	2.026
F(000)	792
Θ range [°]	2.83 – 25.24
Index ranges	$-17 \leq h \leq 17$
	$-11 \leq k \leq 11$
	$-19 \leq l \leq 19$
Reflns. collected	26840
Reflns. obsd.	3137
Reflns. unique	3914
	(R_{int} = 0.0430)
R_1, wR_2 (2σ data)	0.0274, 0.0612
R_1, wR_2 (all data)	0.0412, 0.0671
GOOF on F^2	1.034
Peak/hole [e Å^{-3}]	0.824 / -0.460

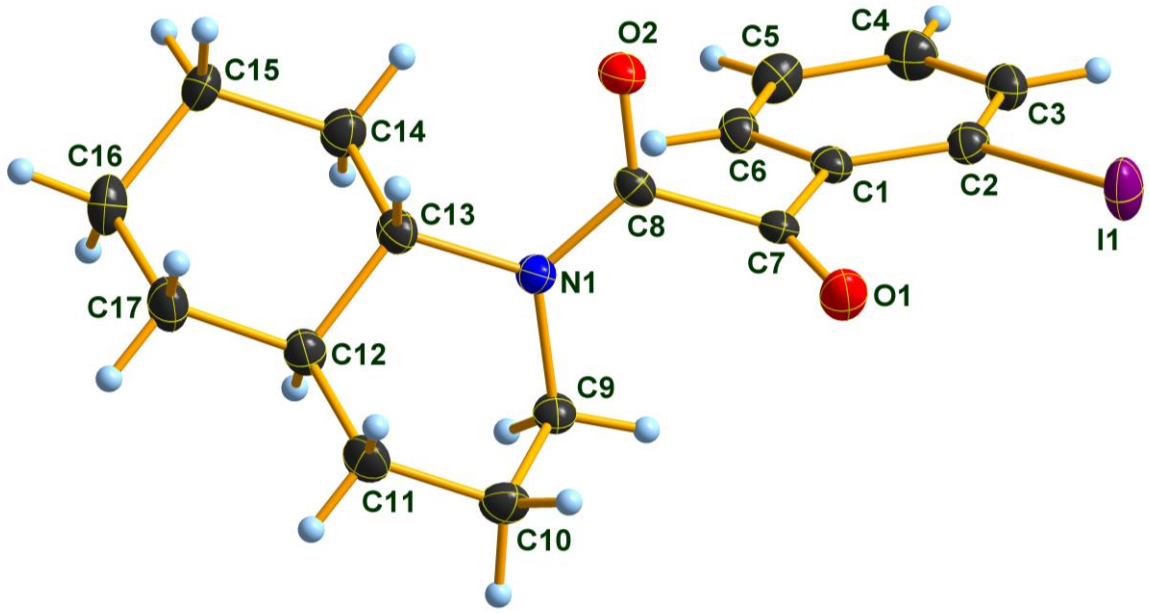


Figure 22. Molecular structure of compound **91d** in the crystal. DIAMOND[206] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 50. Selected bond lengths (Å) of compound **91d**.

I1 – C2	2.103(2)	C12 – C17	1.527(3)
O1 – C7	1.207(3)	C11 – C10	1.539(3)
N1 – C8	1.334(3)	C14 – C15	1.536(3)
N1 – C9	1.465(3)	C9 – C10	1.527(3)
N1 – C13	1.483(3)	C17 – C16	1.525(4)
C1 – C6	1.397(3)	C16 – C15	1.531(4)
C1 – C2	1.411(3)	C5 – C4	1.381(3)
C1 – C7	1.494(3)	C13 – C14	1.527(3)
O2 – C8	1.227(3)	C13 – C12	1.529(3)
C2 – C3	1.388(3)	C7 – C8	1.532(3)
C3 – C4	1.386(4)	C12 – C11	1.513(3)
C6 – C5	1.378(3)		

Table 51. Selected bond angles (°) of compound **91d**.

C8 – N1 – C9	124.7(2)	C13 – C14 – C15	111.0(2)
C8 – N1 – C13	118.4(2)	N1 – C9 – C10	109.9(2)

C9 – N1 – C13	116.7(2)	C16 – C17 – C12	111.4(2)
C6 – C1 – C2	117.8(2)	C17 – C16 – C15	111.9(2)
C6 – C1 – C7	117.3(2)	C16 – C15 – C14	111.9(2)
C2 – C1 – C7	124.9(2)	C9 – C10 – C11	111.6(2)
C3 – C2 – C1	120.0(2)	O1 – C7 – C1	125.0(2)
C3 – C2 – I1	116.4(2)	O1 – C7 – C8	120.5(2)
C1 – C2 – I1	123.7(2)	C1 – C7 – C8	114.2(2)
C4 – C3 – C2	120.6(2)	O2 – C8 – N1	125.4(2)
C5 – C6 – C1	121.9(2)	O2 – C8 – C7	115.1(2)
C6 – C5 – C4	119.5(2)	N1 – C8 – C7	119.4(2)
C5 – C4 – C3	120.1(2)	C11 – C12 – C17	114.4(2)
N1 – C13 – C14	112.4(2)	C11 – C12 – C13	111.0(2)
N1 – C13 – C12	110.1(2)	C17 – C12 – C13	107.8(2)
C14 – C13 – C12	110.5(2)	C12 – C11 – C10	112.2(2)

Table 52. Selected torsion angles (°) of compound **91d**.

C6 – C1 – C2 – C3	1.7(3)	C13 – N1 – C8 – C7	-177.8(2)
C7 – C1 – C2 – C3	178.4(2)	O1 – C7 – C8 – O2	100.9(3)
C6 – C1 – C2 – I1	-179.4(2)	C1 – C7 – C8 – O2	-73.3(3)
C7 – C1 – C2 – I1	-2.6(3)	O1 – C7 – C8 – N1	-79.0(3)
C1 – C2 – C3 – C4	-2.0(4)	C1 – C7 – C8 – N1	106.8(2)
I1 – C2 – C3 – C4	179.0(2)	N1 – C13 – C12 – C11	47.4(3)
C2 – C1 – C6 – C5	0.0(3)	C14 – C13 – C12 – C11	172.1(2)
C7 – C1 – C6 – C5	-177.0(2)	N1 – C13 – C12 – C17	173.4(2)
C1 – C6 – C5 – C4	-1.4(4)	C14 – C13 – C12 – C17	-61.9(3)
C6 – C5 – C4 – C3	1.1(4)	C17 – C12 – C11 – C10	180.0(2)
C2 – C3 – C4 – C5	0.6(4)	C13 – C12 – C11 – C10	-57.8(3)
C8 – N1 – C13 – C14	71.2(3)	N1 – C13 – C14 – C15	-178.2(2)
C9 – N1 – C13 – C14	-113.0(2)	C12 – C13 – C14 – C15	58.4(3)
C8 – N1 – C13 – C12	-165.2(2)	C8 – N1 – C9 – C10	116.6(2)
C9 – N1 – C13 – C12	10.6(3)	C13 – N1 – C9 – C10	-58.9(3)

C6 – C1 – C7 – O1	157.8(2)	C11 – C12 – C17 – C16	-175.7(2)
C2 – C1 – C7 – O1	-19.0(4)	C13 – C12 – C17 – C16	60.3(3)
C6 – C1 – C7 – C8	-28.3(3)	C12 – C17 – C16 – C15	-55.4(3)
C2 – C1 – C7 – C8	154.9(2)	C17 – C16 – C15 – C14	50.4(3)
C9 – N1 – C8 – O2	-173.1(2)	C13 – C14 – C15 – C16	-51.9(3)
C13 – N1 – C8 – O2	2.3(3)	N1 – C9 – C10 – C11	46.2(3)
C9 – N1 – C8 – C7	6.8(3)	C12 – C11 – C10 – C9	9.5(3)

Single crystals of compound **93g**, suitable for X-ray diffraction, were obtained by slow evaporation of **$CDCl_3$** solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[202] Absorption correction using the multiscan method[202] was applied. The structures were solved with SHELXS-97,[203] refined with SHELXL-97[204] and finally checked using PLATON.[205] Details for data collection and structure refinement are summarized in Table 53.

CCDC-**2164156** 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 53. Details for X-ray data collection and structure refinement for compound **93g**.

	93g
Empirical formula	$C_{21}H_{27}NO_3$
Formula mass	341.43
T[K]	123(2)
Crystal size [mm]	0.30 × 0.18 × 0.07
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*n*
a [Å]	8.4082(3)
b [Å]	9.9782(4)
c [Å]	22.7287(8)
α [°]	90.0
β [°]	94.143(3)
γ [°]	90.0
V [Å^3]	1901.93(12)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.192
μ [mm^{-1}]	0.079
F(000)	736
Θ range [°]	2.23 – 25.24
Index ranges	$-10 \leq h \leq 10$
	$-12 \leq k \leq 12$
	$-29 \leq l \leq 29$
Reflns. collected	30212
Reflns. obsd.	3245
Reflns. unique	4182
	(R_{int} = 0.0420)
R_1, wR_2 (2σ data)	0.0441, 0.1020
R_1, wR_2 (all data)	0.0610, 0.1114
GOOF on F^2	1.042
Peak/hole [e Å^{-3}]	0.257 / -0.198

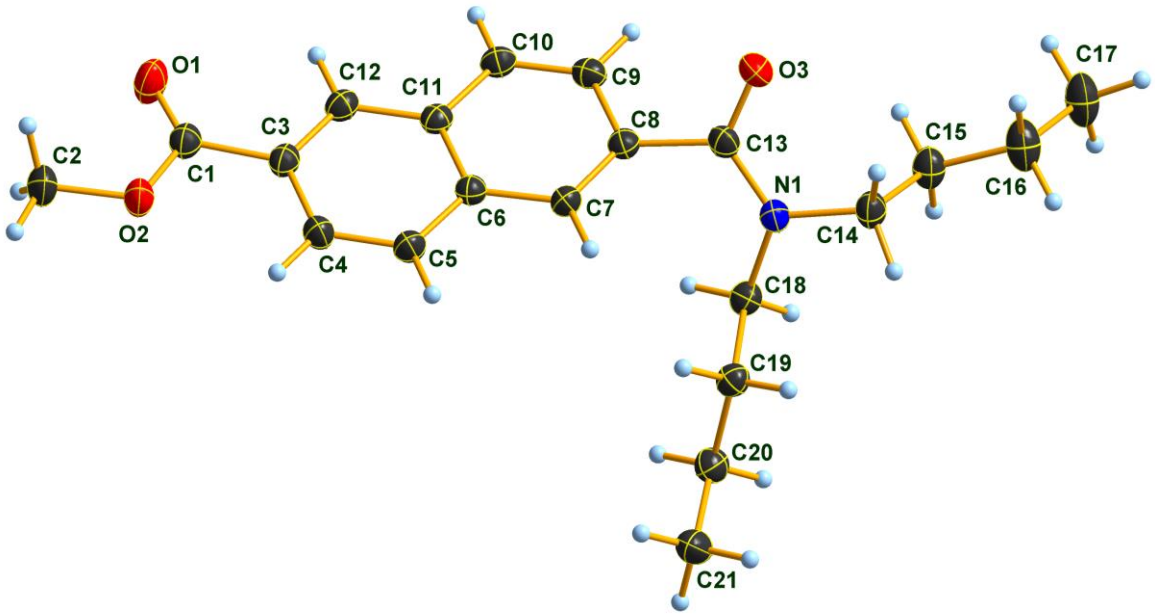


Figure 23. Molecular structure of compound **93g** in the crystal. DIAMOND[206] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 54. Selected bond lengths (Å) of compound **93g**.

C6 – C5	1.420(2)	C9 – C10	1.366(2)
C6 – C11	1.425(2)	C15 – C14	1.520(2)
C6 – C7	1.425(2)	C15 – C16	1.528(2)
C12 – C3	1.376(2)	C16 – C17	1.513(2)
C12 – C11	1.420(2)	C1 – O1	1.205(2)
C13 – O3	1.239(2)	C8 – C9	1.422(2)
C13 – N1	1.344(2)	C20 – C19	1.522(2)
C13 – C8	1.510(2)	C20 – C21	1.525(2)
N1 – C18	1.467(2)	C11 – C10	1.422(2)
N1 – C14	1.472(2)	C18 – C19	1.523(2)
C5 – C4	1.367(2)	C7 – C8	1.369(2)
C3 – C4	1.420(2)	O2 – C1	1.338(2)
C3 – C1	1.495(2)	O2 – C2	1.445(2)

Table 55. Selected bond angles (°) of compound **93g**.

C5 – C6 – C11	119.1(1)	C5 – C4 – C3	120.1(1)
C5 – C6 – C7	121.7(1)	C14 – C15 – C16	111.4(1)
C11 – C6 – C7	119.2(1)	C20 – C19 – C18	111.6(1)
C3 – C12 – C11	120.4(1)	N1 – C14 – C15	113.3(1)
O3 – C13 – N1	122.0(1)	C17 – C16 – C15	113.1(1)
O3 – C13 – C8	117.3(1)	N1 – C18 – C19	114.0(1)
N1 – C13 – C8	120.7(1)	C8 – C7 – C6	120.6(1)
C13 – N1 – C18	125.1(1)	C1 – O2 – C2	116.2(1)
C13 – N1 – C14	117.3(1)	O1 – C1 – O2	123.4(1)
C18 – N1 – C14	117.0(1)	O1 – C1 – C3	125.1(1)
C4 – C5 – C6	120.8(1)	O2 – C1 – C3	111.5(1)
C12 – C3 – C4	120.5(1)	C7 – C8 – C9	120.0(1)
C12 – C3 – C1	118.5(1)	C7 – C8 – C13	122.4(1)
C4 – C3 – C1	120.9(1)	C9 – C8 – C13	116.9(1)
C12 – C11 – C10	122.2(1)	C19 – C20 – C21	111.9(1)
C12 – C11 – C6	119.0(1)	C10 – C9 – C8	120.7(1)
C10 – C11 – C6	118.8(1)	C9 – C10 – C11	120.7(1)

Table 56. Selected torsion angles (°) of compound **93g**.

O3 – C13 – N1 – C18	-169.5(1)	C12 – C3 – C1 – O2	-177.7(1)
C8 – C13 – N1 – C18	11.4(2)	C4 – C3 – C1 – O2	1.3(2)
O3 – C13 – N1 – C14	1.8(2)	C6 – C7 – C8 – C9	-1.1(2)
C8 – C13 – N1 – C14	-177.3(1)	C6 – C7 – C8 – C13	168.7(1)
C11 – C6 – C5 – C4	-0.8(2)	O3 – C13 – C8 – C7	-118.4(2)
C7 – C6 – C5 – C4	177.3(1)	N1 – C13 – C8 – C7	60.7(2)
C11 – C12 – C3 – C4	-1.9(2)	O3 – C13 – C8 – C9	51.7(2)
C11 – C12 – C3 – C1	177.1(1)	N1 – C13 – C8 – C9	-129.2(1)
C3 – C12 – C11 – C10	-178.0(1)	C7 – C8 – C9 – C10	-0.1(2)
C3 – C12 – C11 – C6	0.4(2)	C13 – C8 – C9 – C10	-170.4(1)
C5 – C6 – C11 – C12	1.0(2)	C8 – C9 – C10 – C11	1.8(2)

C7 – C6 – C11 – C12	-177.2(1)	C12 – C11 – C10 – C9	175.9(1)
C5 – C6 – C11 – C10	179.4(1)	C6 – C11 – C10 – C9	-2.4(2)
C7 – C6 – C11 – C10	1.3(2)	C6 – C5 – C4 – C3	-0.7(2)
C13 – N1 – C18 – C19	-110.1(2)	C12 – C3 – C4 – C5	2.0(2)
C14 – N1 – C18 – C19	78.7(2)	C1 – C3 – C4 – C5	-176.9(1)
C5 – C6 – C7 – C8	-177.6(1)	C21 – C20 – C19 – C18	-177.2(1)
C11 – C6 – C7 – C8	0.5(2)	N1 – C18 – C19 – C20	-174.4(1)
C2 – O2 – C1 – O1	1.7(2)	C13 – N1 – C14 – C15	-83.6(2)
C2 – O2 – C1 – C3	-179.2(1)	C18 – N1 – C14 – C15	88.4(2)
C12 – C3 – C1 – O1	1.4(2)	C16 – C15 – C14 – N1	168.3(1)
C4 – C3 – C1 – O1	-179.6(1)	C14 – C15 – C16 – C17	-177.8(2)