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Continuous Flow Metalations of Arenes, Heteroarenes and Formamides Using Lithium and Zinc Reagents

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 Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, 16. September 2016

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Matthias Richard Becker

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1. Gutachter: Prof. Dr. Paul Knochel
2. Gutachter: Prof. Dr. Konstantin Karaghiosoff

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Parts of this PhD thesis have been published

Communications

1. Matthias R. Becker, Paul Knochel, "Practical Continuous-Flow Trapping Metalations of Functionalized Arenes and Heteroarenes Using TMPLi in the Presence of Mg, Zn, Cu, or La Halides", *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; *Angew. Chem.* **2015**, *127*, 12681.

2. Matthias R. Becker, Maximilian A. Ganiek, Paul Knochel, "Practical and economic lithiations of functionalized arenes and heteroarenes using Cy_2NLi in the presence of Mg, Zn or La halides in a continuous flow", *Chem. Sci.* **2015**, *6*, 6649.

3. Matthias R. Becker, Paul Knochel, "High-Temperature Continuous-Flow Zincations of Functionalized Arenes and Heteroarenes Using $(Cy_2N)_2Zn{\cdot}2LiCl$", *Org. Lett.* **2016**, *18*, 1462.

4. Maximilian A. Ganiek, Matthias R. Becker, Paul Knochel, "Continuous flow *in situ* trapping functionalizations of *N*,*N*-disubstituted formamides using LDA", *manuscript in preparation.*

Reviews

1. Andreas D. Benischke, Mario Ellwart, Matthias R. Becker, Paul Knochel, "Polyfunctional Zinc and Magnesium Organometallics for Organic Synthesis: Some Perspectives", *Synthesis* **2016**, *48*, 1101.

Patents

1. Matthias R. Becker, Paul Knochel, "Kontinuierliche Durchfluss-Metallierungen organischer Verbindungen mit Lewis-acidem Wasserstoff" **2015**, *patent pending*.

2. Matthias R. Becker, Paul Knochel, "Kontinuierliche Durchfluss-Zinkierungen organischer Verbindungen mit Lewis-acidem Wasserstoff unter Verwendung einer Bis(dicyclohexylamino)zink-Base" **2015**, *patent pending*.

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
c	*cyclo*
calcd	calculated
conc	concentrated
Cy	Cyclohexyl
dba	*trans*,*trans*-dibenzylideneacetone
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DPP	diphenylphosphine
E	electrophile
EI	electron ionization
equiv	equivalent
Et	ethyl
eV	electronvolt
FG	functional group
g	gram
GC	gas chromatography
h	hour
Hal	halogen

Het	heteroaryl
HRMS	high resolution mass spectrometry
i	*iso*
id	inner diameter
IR	infrared
J	coupling constant (NMR)
LDA	lithium diisopropylamide
M	mole/L
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mm	millimeter
mmol	millimole
mol%	mole percent
mp	melting point
MS	mass spectrometry
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
Oct	octyl
p	*para*
Pent	pentyl
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
PFA	perfluoroalkoxy alkane
Ph	phenyl
pin	pinacolate
piv	pivaloyl

ppm	parts per million
Pr	propyl
PTFE	polytetrafluoroethylene
R	organic substituent
rt	room temperature
s	second
sat	saturated
S-Phos	2-dicylohexylphosphino-2',6'-dimethoxybiphenyl
t	*tert*
TBAB	tetra-*n*-butylammonium bromide
TFA	trifluoroacetic acid
tfp	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
t_{met}	metalation time
T_{met}	metalation temperature
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
Ts	tosyl
UV	ultraviolet
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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A. Introduction

1. Overview

Since the discovery of diethyl zinc by *E. Frankland* in 1849,[1] organometallic chemistry has experienced a constant development and numerous discoveries, and today it exhibits a major field of organic chemistry. Organometallic reagents play an important role as catalysts, bases or nucleophiles, and their chemical behavior is decisively determined by the nature of their metal-nonmetal bond.[2] According to the common definitions of electronegativity by *Pauling*, *Allred-Rochow* or *Mulliken*, more electropositive metals like lithium and magnesium cause a bond polarization and a more distinct ionic character.[3] As a result, the important classes of organolithium and -magnesium reagents are highly reactive, but sometimes lack selectivity.[4] In order to increase the selectivity a more covalent but also less reactive metal-nonmetal bond is needed, which is commonly realized by the usage of more electronegative metals like zinc, copper or boron.[5]

However, considering the generally high reactivity of several organometallic compounds, certain precautions usually have to be taken for a successful reaction process like low temperatures, short reaction times or high dilution conditions. Therefore, performing organometallic reactions under continuous flow conditions is highly interesting, since this technique offers a number of advantages compared to conventional batch chemistry.[6] By conducting organometallic reactions in flow, a better heat transfer between the reaction system and the environment and a minimum amount of reactive intermediate per time permits the safe handling of highly exothermic or hazardous reactions. Furthermore, a high degree of automation, rapid mixing of reaction components, the prevention of hot spot formation and the precise control of reaction times by flow rates and reactor volumes enable the control of extremely fast reactions with formation of reactive intermediates. Finally, the automation in flow chemistry also facilitates the compliance of a set of reaction conditions, the reproducibility of experimental results and it offers a straightforward scalability of reactions.

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2. Preparation of organometallic reagents

2.1 Oxidative insertion

After *Franklands* discovery of diethyl zinc in 1849,[1] organozinc reagents were at the beginning only used for few synthetic applications like the *Reformatsky* reaction or the *Simmons-Smith* cyclopropanation, because of their low reactivity and the necessity of elevated temperatures and polar aprotic solvents.[7-9] In 1900 the French chemist *Victor Grignard* described the first synthesis of an organomagnesium reagent by reacting magnesium turnings with methyl iodide in diethyl ether.[10] Until today, the direct insertion of elemental metal via a radical pathway is considered to be one of the most convenient and straightforward approaches to prepare organometallics.[11,12] The preparation of these "*Grignard* reagents" via the insertion of elemental magnesium into a carbon-halogen bond also required elevated temperatures. But in contrast to the synthesis of organozinc reagents, this method showed a reduced tolerance towards functional groups. A possible solution to this limitation was found by *Rieke* et al. with the development of highly reactive metal powders like the so-called "*Rieke*-magnesium" (Mg*)[13] or "*Rieke*-zinc" (Zn*),[14] which were formed by the reduction of $MgCl_2$ or $ZnCl_2$ with lithium naphthalenide. The *in situ* prepared "*Rieke*-magnesium" allowed an oxidative insertion even at -78 °C (Scheme 1).[15] In this manner *Grignard* reagents with functional groups like nitriles, esters or halides were successfully prepared and *Rieke* expanded the method to more metals like manganese or copper.[16]

[7] a) S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210. b) S. Reformatsky, *Chem. Ber.* **1895**, *28*, 2842. c) R. Ocampo, *Tetrahedron* **2004**, *60*, 9325. d) A. Fürstner, *Angew. Chem. Int. Ed.* **1993**, *32*, 164.
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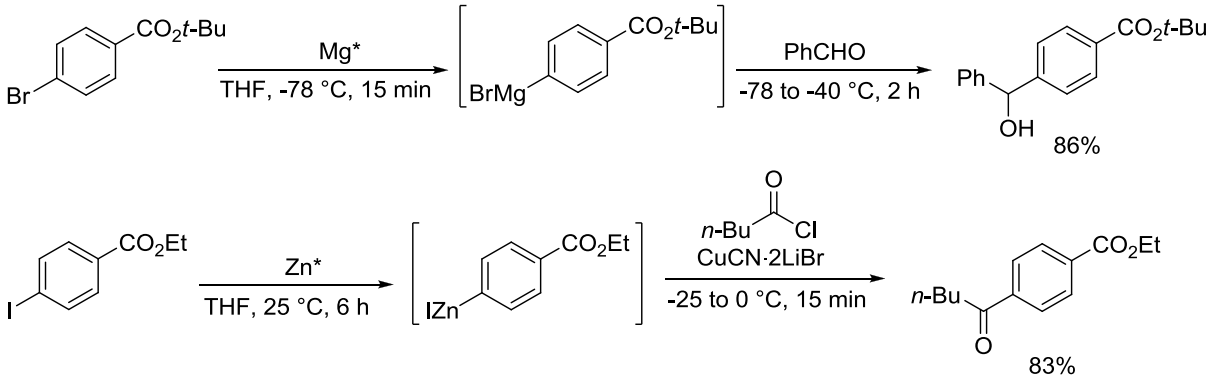

Scheme 1: Preparation of functionalized organometallic reagents according to *Rieke* et al.[14a,15b]

Rieke's approach offered an access to new organometallic reagents, but the method often required cryogenic reaction conditions. As a result, *Knochel* and co-workers developed a more convenient preparation of functionalized organometallics from a variety of iodides, bromides and even chlorides via oxidative insertion of elemental metals like Mg,[17] Zn,[18] Al,[19] In[20] or Mn[21] in the presence of LiCl (Scheme 2). The additional LiCl increased the solubility of the generated organometallic species and promoted the electron transfer to the aryl halide reactants.[22] Furthermore, the presence of additives like $ZnCl_2$ or $MnCl_2$ allowed *in situ* transmetalations to more covalent organometallics, which offered a better functional group tolerance and the possibility of subsequent reactions like transition metal-catalyzed cross-couplings.[23] Oxidative insertions in the presence of $Zn(OPiv)_2$ or $Mg(OPiv)_2$ were especially remarkable, since subsequent solvent evaporation afforded the corresponding solid organozinc reagents with an extraordinary stability towards air and moisture.[24]

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[23] a) A. O. King, N. Okukado, E.-I. Negishi, *J. Chem. Soc. Chem. Commun.* **1977**, *19*, 683. b) H. C. Brown, U. S. Racherla, *J. Org. Chem.* **1986**, *51*, 427. c) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824. d) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082. e) Z. Peng, N. Li, X. Sun, F. Wang, L. Xu, C. Jiang, L. Song, Z.-F. Yan, *Org. Biomol. Chem.* **2014**, *12*, 7800. f) P. Quinio, A. D. Benischke, A. Moyeux, G. Cahiez, P. Knochel, *Synlett* **2015**, *26*, 514. g) A. D. Benischke, A. J. A. Breuillac, A. Moyeux, G. Cahiez, P. Knochel, *Synlett* **2016**, *27*, 471. h) A. D. Benischke, I. Knoll, A. Rérat, C. Gosmini, P. Knochel, *Chem. Commun.* **2016**, *52*, 3171.
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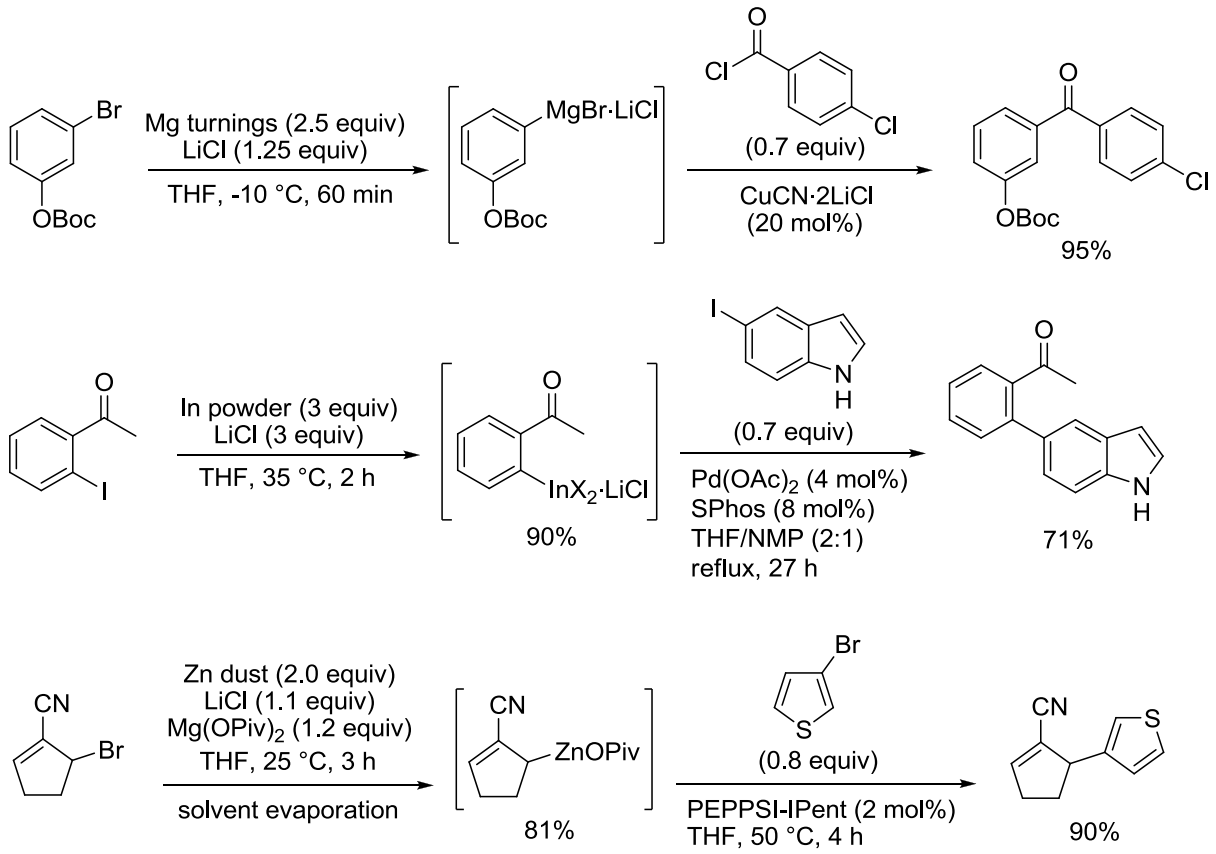
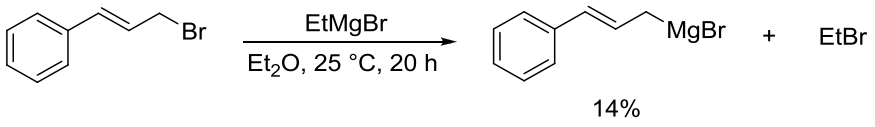


Scheme 2: Preparation of functionalized organometallic reagents via oxidative insertion of elemental metals in the presence of LiCl.[17a,20a,24b]

2.2 Halogen-metal exchange

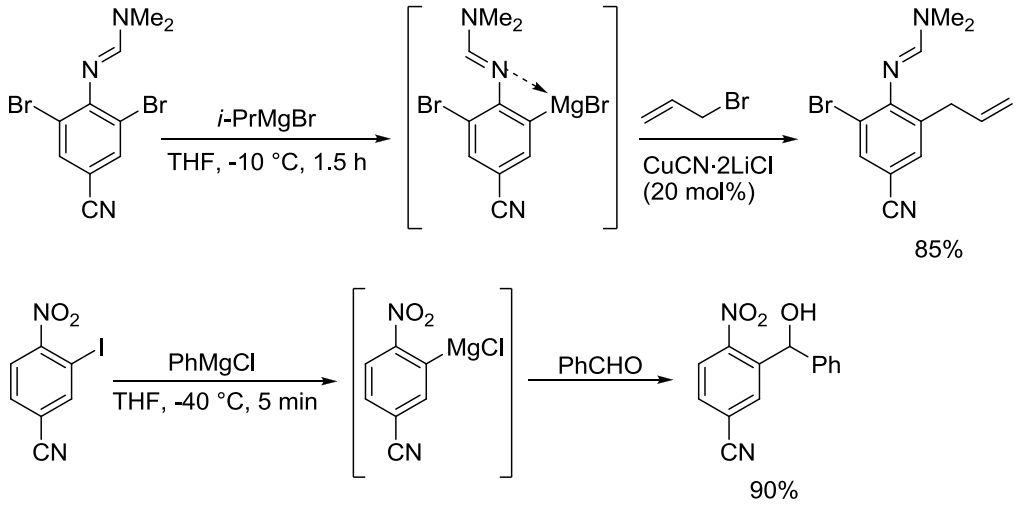
Organometallic reagents can also be generated from organic halides via an exchange reaction with another organometallic reagent. In 1931 *C. Prévost* published the first halogen-magnesium exchange between cinnamyl bromide and ethylmagnesium bromide (Scheme 3).[25] The fundamental driving force of this reaction is the formation of the more stable organometallic species ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec}$).[26]



Scheme 3: First example of a halogen-magnesium exchange.[25]

[25] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[26] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.

However, the cinnamylmagnesium bromide was only generated in a low yield of 14% and further developments in halogen-magnesium exchanges were limited to special synthetic applications.[27] Moreover, subsequent publications by *Wittig*[28] and *Gilman*[29] reported about halogen-lithium exchanges, which did not tolerate a large number of functional groups, and halogen-zinc exchanges suffered from drawbacks like a limited applicability, long reaction times and an excessive use of pyrophoric dialkyl zinc reagents.[30] As a consequence, the halogen-metal exchange only played a minor role for the preparation of highly functionalized organometallic compounds until *Knochel* et al. reported the conversion of aryl iodides or aryl bromides with chelating groups using *i*-PrMgBr or PhMgCl (Scheme 4).[4b,31] Now *Grignard* reagents with a broad range of functionalities like halides, esters, amides as well as cyano- or nitro-groups became accessible via an exchange reaction.



Scheme 4: Preparation of functionalized *Grignard* reagents via halogen-magnesium exchange with *i*-PrMgBr or PhMgCl.[31a,c]

[27] a) J. Villiéras, *Bull. Soc. Chim. Fr.* **1967**, 1520. b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* **1986**, 470. c) C. Tamborski, G. J. Moore, *J. Organomet. Chem.* **1971**, *26*, 153. d) N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett.* **1987**, *28*, 5845. e) D. J. Burton, Z.-Y. Yang, *Tetrahedron* **1992**, *48*, 189. f) G. Cahiez, D. Bernard, J. F. Normant, *J. Organomet. Chem.* **1976**, *113*, 107. g) C. Bolm, D. Pupowicz, *Tetrahedron Lett.* **1997**, *38*, 7349.

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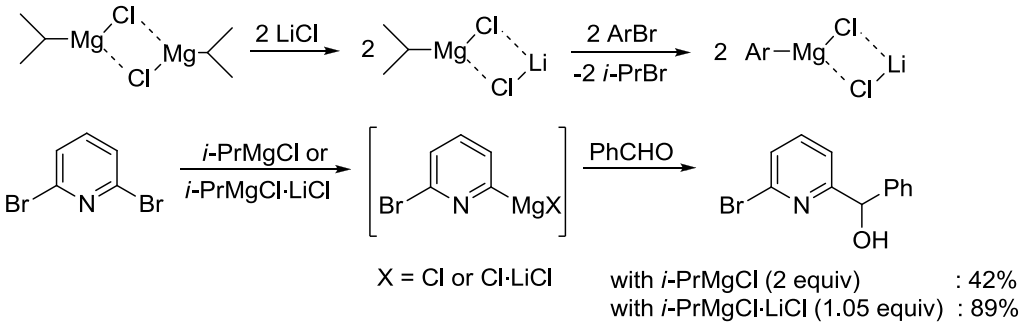
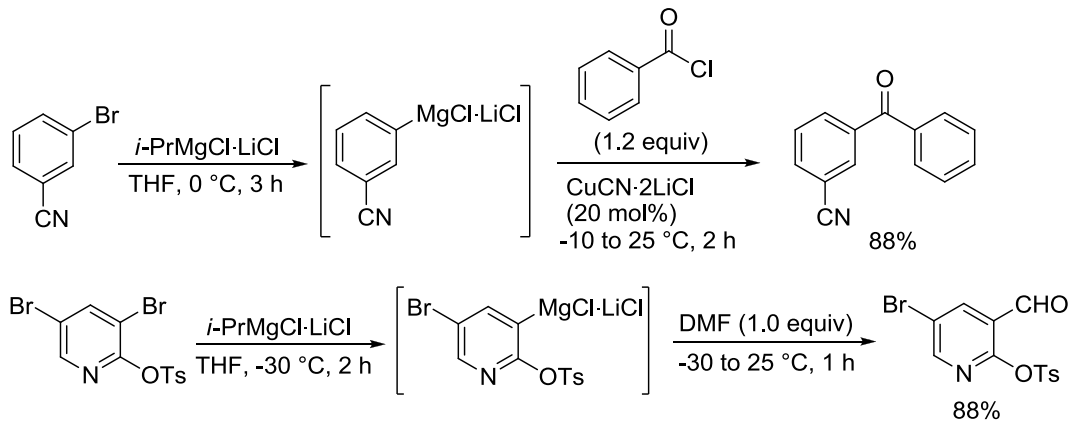
Without a chelating group in *ortho*-position to the halide substituent, the new exchange method was limited to the use of expensive and mostly sensitive iodides. Therefore a tremendous improvement was achieved, when *Knochel* and co-workers extended the halogen-magnesium exchange to organic bromides by adding a stoichiometric amount of LiCl to *i*-PrMgCl in THF.[32] The LiCl additive is supposed to disaggregate the polymeric structures of *i*-PrMgCl in solution leading to the more reactive, monomeric base *i*-PrMgCl·LiCl ("Turbo-*Grignard*") (Scheme 5). The salt additive also led to a better solubility and it allowed the convenient bromine-magnesium exchange in the presence of various sensitive functional groups (Scheme 6).



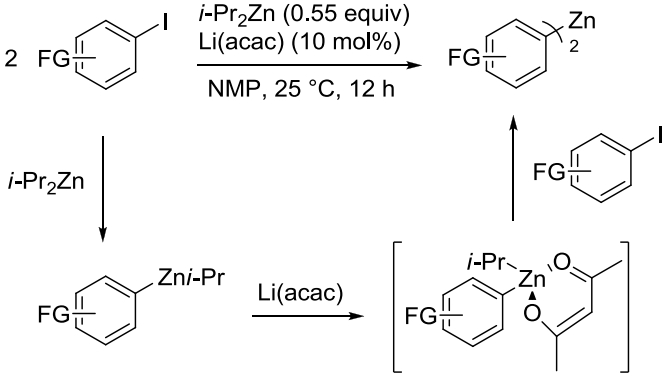
Scheme 5: Effect of LiCl on the Grignard reagent *i*-PrMgCl.[32a]



Scheme 6: Preparation of functionalized organomagnesium reagents via Br-Mg exchange with "Turbo-*Grignard*".[32a,c]

[32] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159. c) H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726. d) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543. e) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.

Concerning the halogen-zinc exchange, a similar breakthrough was accomplished in 2004 by the addition of a catalytic amount of Li(acac) (10 mol%) to *i*-Pr_2Zn in NMP.[33] The metal salt additive tremendously increased the reactivity by promoting a second exchange via the formation of an ate complex (Scheme 7). Thus, various aryl and heteroaryl iodides with sensitive functionalities like ketones, aldehydes, cyano or isothiocyanato groups could be successfully used as reactants for these exchange reactions.



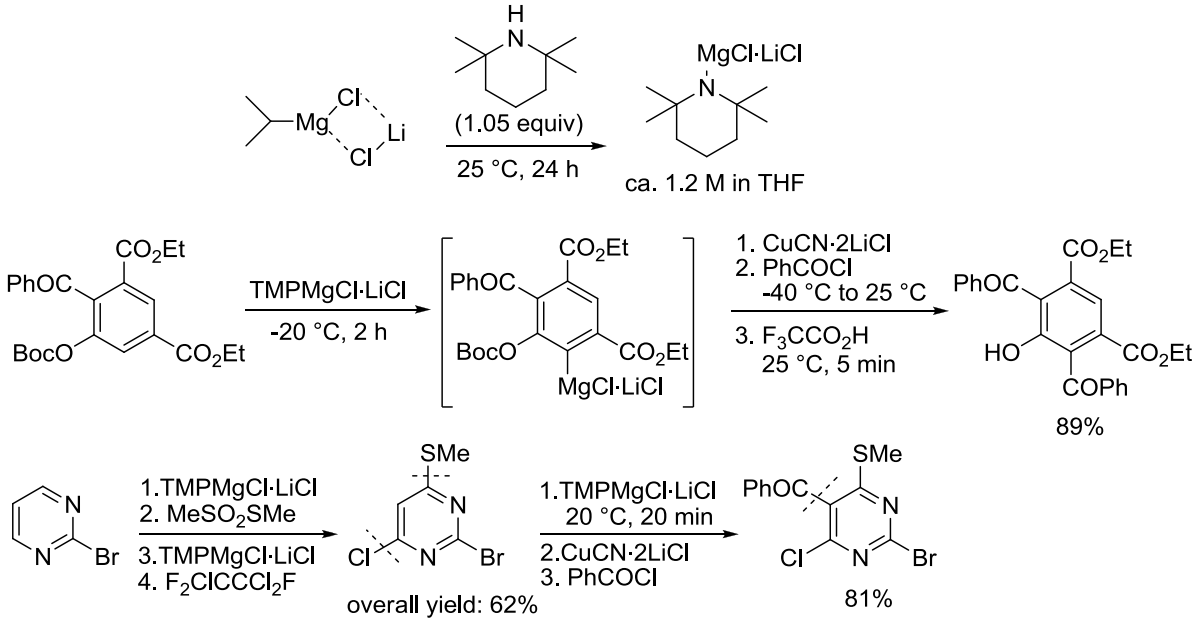
Scheme 7: Li(acac)-catalyzed iodine-zinc exchange.[33a]

2.3 Directed metalation

The directed metalation offers a particular useful method for the preparation of organometallic reagents, because the scope of potential reactants is not limited to expensive organic halides. For this method to be applicable to a broad range of substrates, a strong base is required. However, the high reactivity of alkyllithium[34] or lithium amide[35] bases raises problems regarding a limited functional group tolerance or unwanted side reactions. Furthermore, solutions of these bases in THF show a low stability at room temperature and the necessity for cryogenic temperatures complicates the scale-up of their reactions. Considering these facts, the directed metalation with magnesium amides emerged as a potential alternative to overcome these limitations, since *Hauser* showed the possible non-nucleophilic magnesiation for the self-condensation of esters using diethyl- or diisopropylaminomagnesium bromide.[36,37]

[33] a) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017. b) L.-Z. Gong, P. Knochel, *Synlett* **2005**, 267.
[34] for a review, see: V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.
[35] for a review, see: M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376.
[36] L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758.
[37] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295. b) F. C. Frostick, C. R. Hauser, *J. Am. Chem. Soc.* **1949**, *71*, 1350.

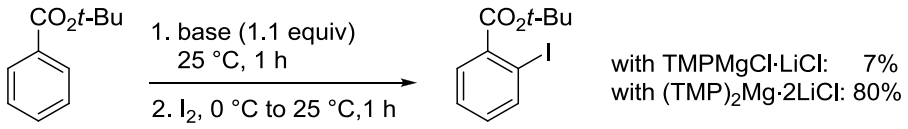
His work was extended by *Eaton*[38] and *Mulzer*[39] to directed magnesiations of benzenes, pyridines, and cyclopropanes with sterically more hindered amides like TMPMgCl, TMPMgBr or $(TMP)_2Mg$. However, these bases showed a low solubility and kinetic basicity, so bases and electrophiles were used in a large excess (2 – 8 equiv) and metalations had to be performed under harsh conditions (refluxing THF) in order to achieve good conversions. As a consequence, these bases were inappropriate for a large number of reactants and they did not find a more general application in organic synthesis. This changed in 2006, when *Knochel* reported the discovery of the mixed lithium magnesium amide base, TMPMgCl·LiCl, which was prepared by the mere reaction of *i*-PrMgCl·LiCl and TMPH (Scheme 8).[40,41] It offered an excellent solubility in THF, a good thermal stability and a high kinetic reactivity. Therefore it allowed the regioselective and efficient functionalization of various aromatic and heteroaromatic compounds.



Scheme 8: Directed magnesiations with the mixed lithium magnesium amide TMPMgCl·LiCl.[40a,b,e]

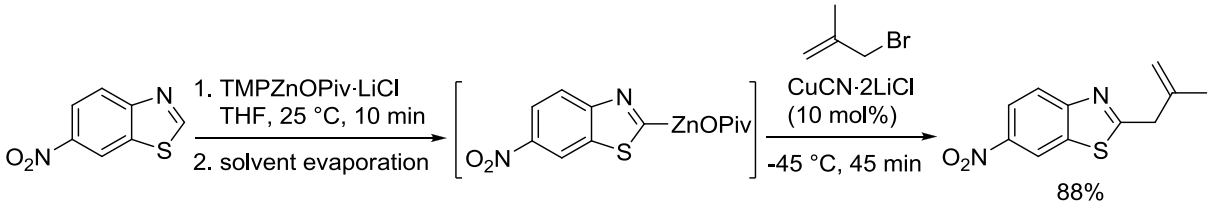
[38] a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016. b) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370. c) M.-X. Zhang, P. E. Eaton, *Angew. Chem. Int. Ed.* **2002**, *41*, 2169.
[39] a) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414. b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Liebigs Ann.* **1995**, 1441.
[40] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958. b) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673. c) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525. d) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113. e) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497. f) C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326.
[41] for the structural elucidation of TMPMgCl·LiCl, see: P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.

However, the reactivity of TMPMgCl·LiCl was too weak to metalate moderately activated aromatics. Therefore, *Knochel* and co-workers envisioned the stronger LiCl-complexed magnesium bisamide base $(TMP)_2Mg·2LiCl$, which e.g. successfully magnesiated *tert*-butyl benzoate (Scheme 9).[42]



Scheme 9: Directed magnesiation with the mixed lithium magnesium bisamide $(TMP)_2Mg·2LiCl$.[42a]

Nevertheless, the progress on the development of sterically hindered magnesium amide bases still left sensitive arenes and heteroarenes with functionalities like aldehydes or nitro groups inaccessible for directed metalations. Despite the discovery of various transition-metal TMP bases like $(TMP)_2Mn·2MgCl_2·4LiCl$,[43] $(TMP)_2Fe·2MgCl_2·4LiCl$,[44] or $(TMP)_3La·3MgCl_2·5LiCl$,[45] this problem was effectively solved with evolution of the TMP zinc bases TMPZnCl·LiCl[46] and $(TMP)_2Zn·2MgCl_2·2LiCl$.[47,48] They offered the possibility for smooth and chemoselective metalations and the opportunity for convenient cross-couplings increased the range of subsequent reaction pathways. In this context the recently developed TMPZnOPiv·LiCl[49] is particular remarkable, since it enabled the simple one-pot synthesis of the easy to handle, air and moisture resistant zinc pivalates (Scheme 10).

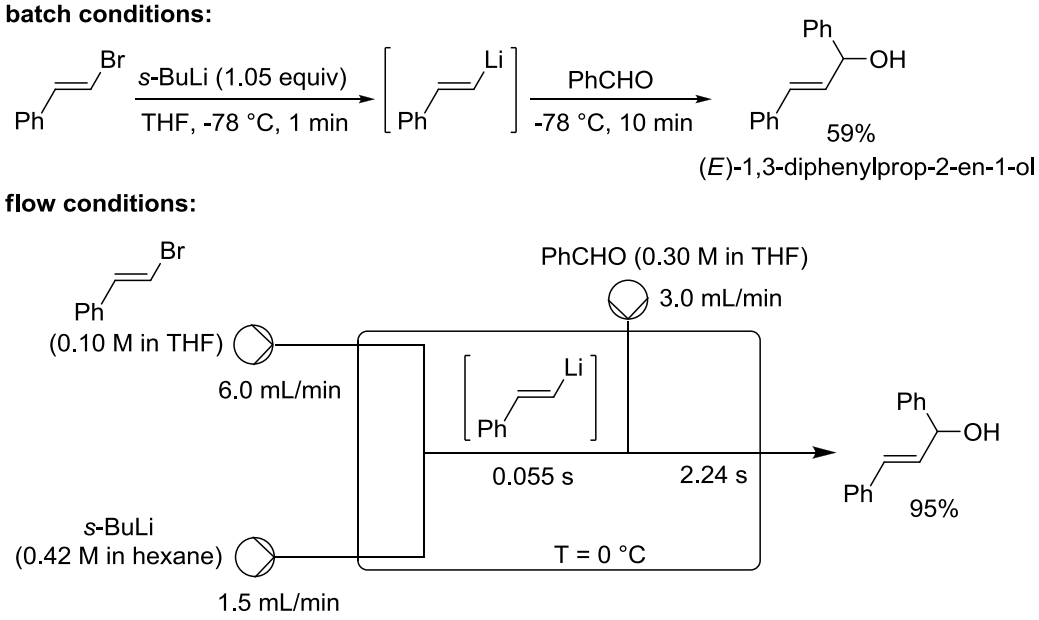


Scheme 10: Directed zincation using TMPZnOPiv·LiCl and subsequent Cu-mediated allylation.[49]

[42] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503. c) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237. d) C. J. Rohbogner, S. Wirth, P. Knochel, *Org. Lett.* **2010**, *12*, 1984.
[43] S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.
[44] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.
[45] S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3304.
[46] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837. b) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406. c) A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680. d) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584. e) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128.
[47] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705. c) S. H. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, *47*, 6387.
[48] for a review about metalations using hindered amide bases, see: B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[49] C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302.

3. Continuous flow reactions in organometallic chemistry

The numerous advantages of the continuous flow methodology have already found versatile applications in synthetic organic chemistry like for the preparation of natural products or pharmaceuticals.[50] Moreover, a variety of specialized equipment has been developed over the last decades such as high-pressure resistant microreactors or *in-line* monitoring or purification set-ups.[51] The possibility to conduct extremely fast and exothermic reactions in a highly controlled manner has also established the continuous flow mode as an important reaction technique in organometallic chemistry.[52] An impressive example for the exceptional opportunities was reported by *Yoshida* and co-workers with a bromine-lithium exchange between (*E*)-β-bromostyrene and *s*-BuLi followed by nucleophilic addition to benzaldehyde (Scheme 11).[53]

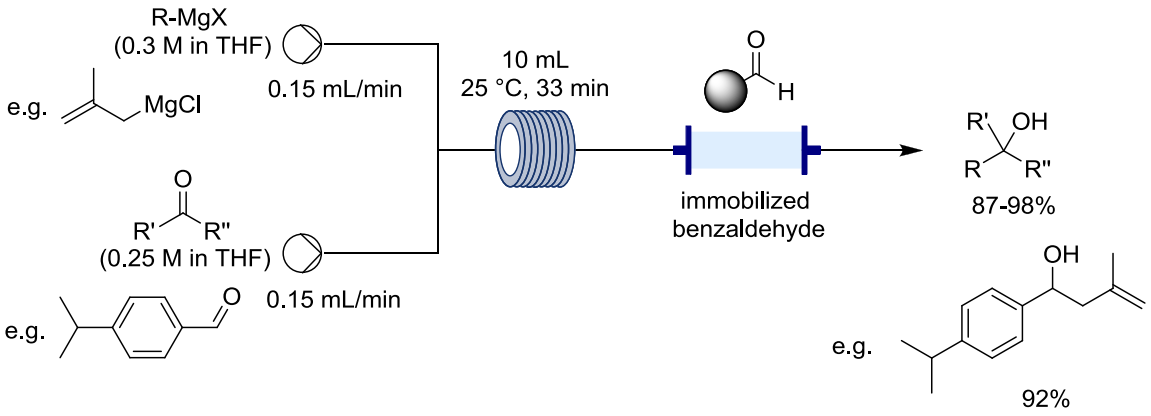


Scheme 11: Extremely fast bromine-lithium exchange with subsequent addition to benzaldehyde in a continuous flow reactor. Yields were determined by GC-analysis.[53]

[50] for reviews, see: a) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849. b) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11*, 1194. c) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688.
[51] for reviews, see: a) T. N. Glasnov, C. O. Kappe, *Chem. Eur. J.* **2011**, *17*, 11956. b) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17. c) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384. d) M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349. e) S. V. Ley, D. E. Fitzpatrick, R. J. Ingham, R. M. Myers, *Angew. Chem. Int. Ed.* **2015**, *54*, 3449.
[52] for a review about cross-couplings in flow, see: T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010.
[53] A. Nagaki, Y. Takahashi, S. Yamada, C. Matsuo, S. Haraki, Y. Moriwaki, S. Kim, J.-i. Yoshida, *J. Flow Chem.* **2012**, *2*, 70.

In batch, the stereoselective formation of terminal vinyllithiums via a bromine-lithium exchange generally requires a temperature of -120 °C and utilization of 2 equiv. *t*-BuLi, which are highly problematic conditions for any potential scale-up.[54] Conducting the bromine exchange of (*E*)-β-bromostyrene with the less reactive *s*-BuLi at -78 °C afforded the corresponding alcohol, (*E*)-1,3-diphenylprop-2-en-1-ol, after benzaldehyde addition only in a moderate yield of 59%, according to GC-analysis.[53] In contrast, the capability of an efficient heat transfer and the fast mixing in a flow reactor enabled the prevention of cryogenic temperatures. The metalated species was trapped after only 0.055 s to prevent the vinyllithium species from decomposing or conducting side reactions at this unusually high temperature. As a result, the corresponding alcohol was formed in an excellent GC-yield of 95%.

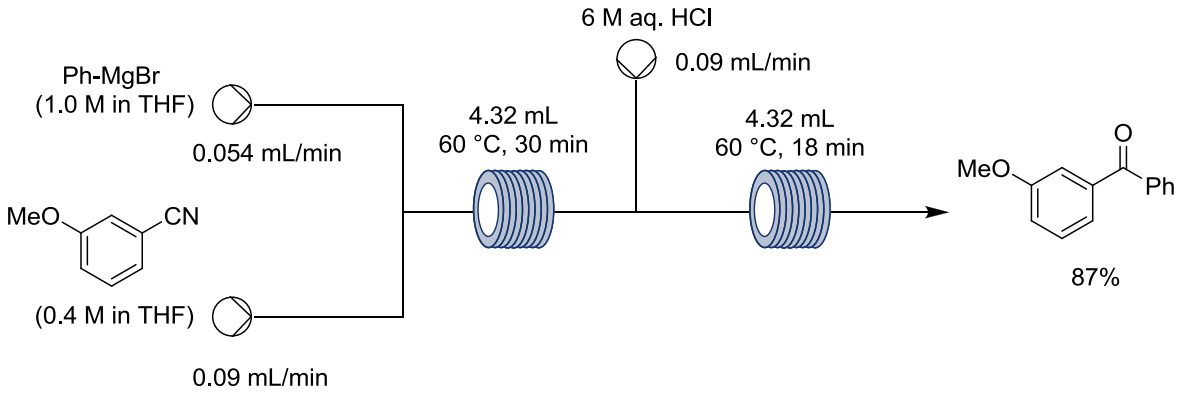
Rencurosi and co-workers recently demonstrated the easy set-up of a general and convenient reaction protocol for a broad range of substrates by performing the addition of different allyl, alkyl and aryl *Grignard* reagents to various carbonyl compounds in excellent yields within 33 min at room temperautre in a flow reactor (Scheme 12).[55] The shown reaction of (2-methylallyl)magnesium chloride (1.2 equiv) and 4-isopropylbenzaldehyde (1.0 equiv) afforded the corresponding alcohol in 92% yield. A similar yield in batch required the application of a lower temperature (-20 °C), a larger excess of nucleophile (2.0 equiv) and a longer reaction time (50 min). Furthermore, the same synthesis was easily scaled up in a flow reactor to prepare 2 g of the alcohol with an output of 0.9 g/h using the optimized conditions.



Scheme 12: Reaction set-up for the addition of organomagnesium reagents to carbonyl compounds to form secondary and tertiary alcohols. The immobilized benzaldehyde was utilized for scavenging unreacted *Grignard* reagent.[55]

[54] H. Neumann, D. Seebach, *Tetrahedron Lett.* **1976**, *17*, 4839.
[55] E. Riva, S. Gagliardi, M. Martinelli, D. Passarella, D. Vigo, A. Rencurosi, *Tetrahedron* **2010**, *66*, 3242.

Mateos et al. have reported an approach for the preparation of various ketones by nucleophilic addition of the corresponding *Grignard* reagents to nitriles followed by subsequent imine hydrolysis (Scheme 13).[56]

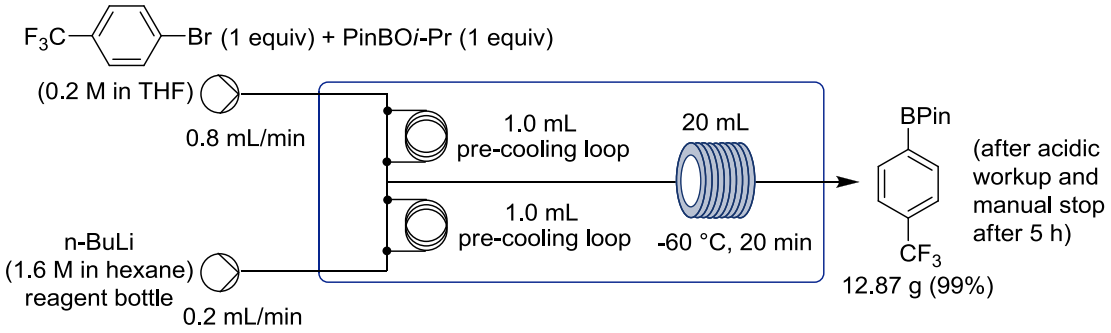


Scheme 13: Continuous flow synthesis of ketones by addition of *Grignard* reagents to nitriles with subsequent imine hydrolysis.[56]

The flow procedure was developed to have a convenient synthesis on a multi-gram scale, since the imine hydrolysis is highly exothermic and difficult to control under batch conditions. The efficient heat exchange enabled by the large surface-to-volume ratio of the set-up and the continuous conversion of reactants in flow mode allowed the safe preparation of the shown benzophenone derivative on a 12 g/day scale. Further optimizations offered the scale-up of the synthesis to 144 g/day.

Moreover, the growing interest in flow chemistry leads to constant innovation and introduction of new equipment. A remarkable example was set by the *Ley* group with their development of a novel and commercially available cryostatic flow reactor ("*Polar Bear*"), which enables the easy application of temperatures as far as -89 °C for several hours without the requirement for cryogenic consumables like dry ice or liquid nitrogen.[57] *Ley* et al. demonstrated the opportunities of the "*Polar Bear*" by efficiently preparing a number of arylboronic acid pinacol esters, which exhibit precious precursors for *Suzuki-Miyaura* cross-couplings,[58] on a multi-gram scale (Scheme 14).[59]

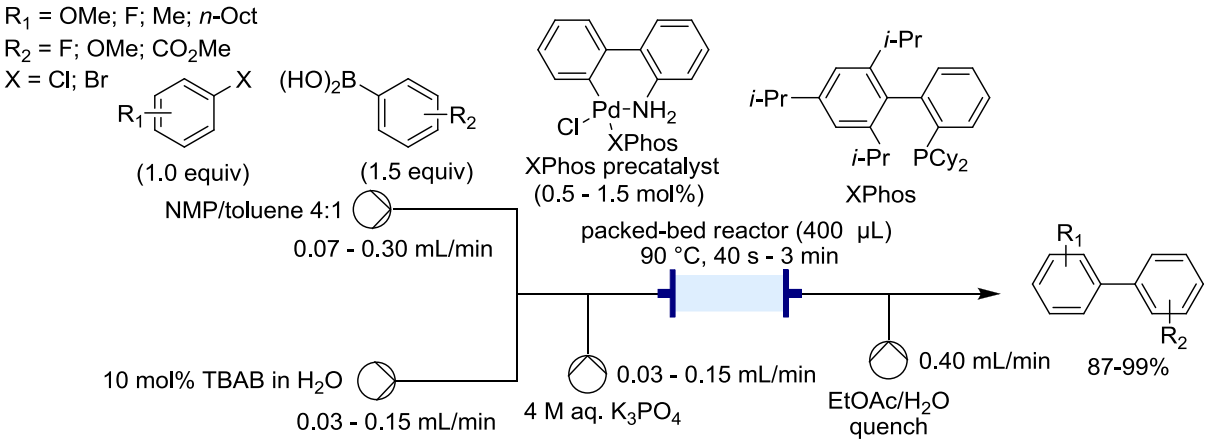
[56] C. Mateos, J. A. Rincón, J. Villanueva, *Tetrahedron Lett.* **2013**, *54*, 2226.
[57] D. L. Browne, B. H. Harji, S. V. Ley, *Chem. Eng. Technol.* **2013**, *36*, 959.
[58] a) N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, *19*, 866. b) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437.
[59] D. L. Browne, M. Baumann, B. H. Harji, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2011**, *13*, 3312.



Scheme 14: Multi-gram synthesis of arylboronic acid pinacol esters using a novel cryostatic flow reactor.[59]

The integrated pre-cooling loops guaranteed that the desired temperature was acquired by both stock solutions before mixing. Otherwise, the *in situ* generated aryllithium species could have decomposed.

Applications of continuous flow conditions in organometallic chemistry are not restricted to exchange and addition reactions or the syntheses of starting materials for cross-couplings. In fact a large number of different cross-coupling reactions have already been reported with partly vast modifications for a successful or even superior execution in a flow reactor compared to batch conditions.[52] A notable example for a homogeneous *Suzuki-Miyaura* Cross-coupling in flow mode was recently published by *Noël* and co-workers (Scheme 15).[60] They presented a general and efficient procedure for the conversion of various (hetero)arylboronic acids and (hetero)aryl halides in a biphasic solvent stream using one of *Buchwald's* precatalysts.[61]

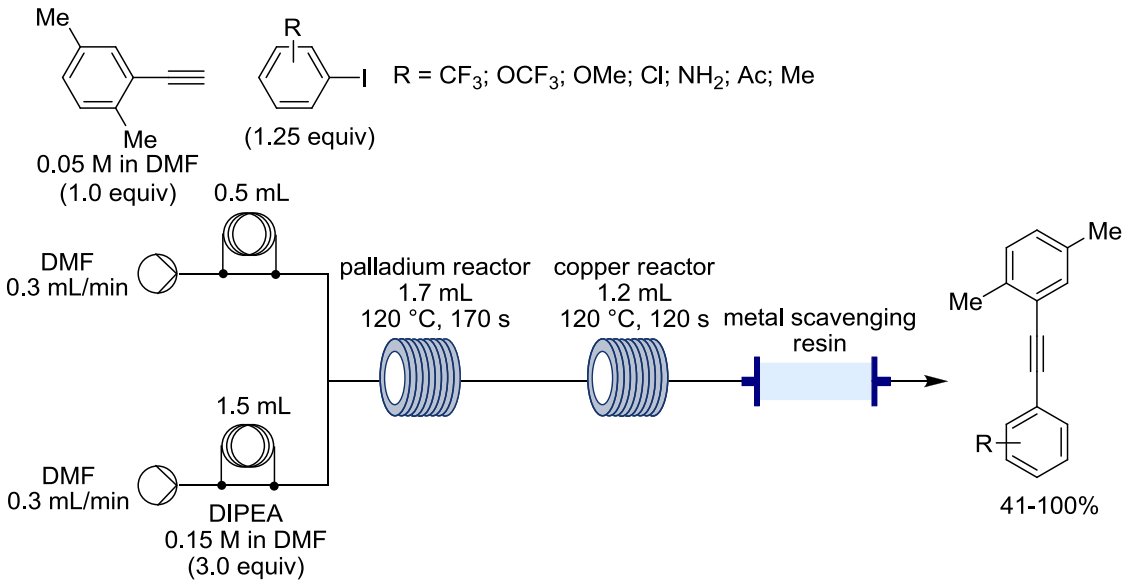


Scheme 15: *Suzuki-Miyaura* cross-couplings in a flow reactor.[60]

[60] T. Noël, A. J. Musacchio, *Org. Lett.* **2011**, *13*, 5180.
[61] T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14073.

The biphasic solvent system was necessary to ensure a good solubility of all reaction components. To provide a good mixing between the two immiscible phases, the reactant stream was directed through a packed-bed reactor with stainless steel spheres.[62] As a consequence, the cross-coupling occurred very fast with a residence time of up to three minutes, and the corresponding products were isolated in excellent yields.

The application of new equipment also facilitates the optimization of cross-coupling reactions. This was demonstrated by *Lee* and co-workers by performing heterogeneous catalyzed *Sonogashira* cross-couplings in a palladium-copper flow reactor (Scheme 16).[63]



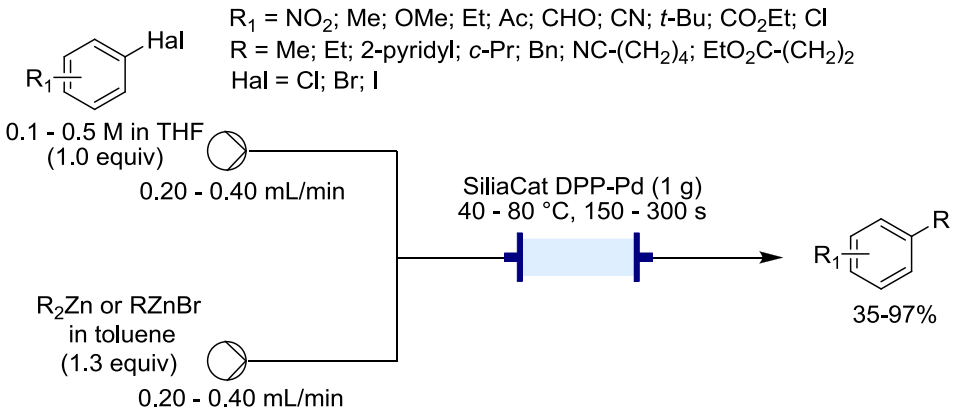
Scheme 16: Heterogeneous *Sonogashira* cross-coupling in a palladium-copper dual flow reactor. Yields were determined by GC-analysis.[63]

The reactant stream was directed through a palladium-coated copper and a subsequent neat copper flow reactor. The cross-couplings were not only conveniently conducted within a few minutes and mostly in very good GC-yields, but the utilization of the two reactors offered even more advantages. Considering the fact that the catalytically active palladium is a very expensive metal, a minimum use of it was strongly desired. By directing the reactant stream over the heterogeneous palladium, only a minimal amount was leached from the solid support and started the catalytic cycle in a quasi-homogeneous mechanism without the need of any additional promoters. The oxidatively inserted palladium was either deposited

[62] J. R. Naber, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2010**, *49*, 9469.
[63] L.-M. Tan, Z.-Y. Sem, W.-Y. Chong, X. Liu, W. L. Kwan, C.-L. K. Lee, *Org. Lett.* **2013**, *15*, 65.

on the copper reactor or caught by the metal scavenging resin after the reactors. These facts make the method very interesting for "*Green chemistry*" applications as well.[64] Furthermore, the minimum release of palladium turned the reactor into a quasi-unlimited source of catalyst, which still kept its efficiency after several tested catalyst cycles. Thus, it offers remarkable advantages over common immobilized palladium catalysts, whose performance gradually decreases.[65] However, the examined cross-couplings were only conducted on a small scale.

Despite versatile investigations on cross-couplings in continuous flow mode and its importance in batch chemistry, the *Negishi* cross-coupling has been completely neglected until *Alcázar* et al. recently published the first example of an alkyl-aryl *Negishi* cross-coupling in a flow reactor (Scheme 17).[66]



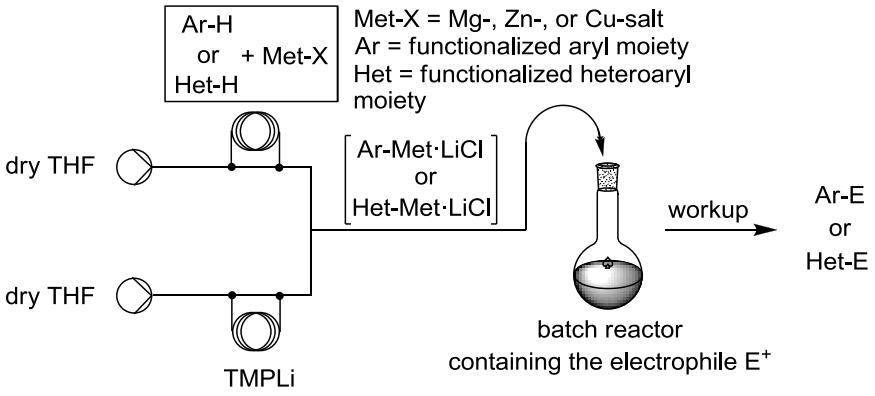
Scheme 17: First alkyl-aryl *Negishi* cross-couplings in a continuous flow reactor.[66]

The reactions were conducted under heterogeneous conditions with the catalyst immobilized on a silica matrix. Due to the high functional group tolerance of organozinc reagents, sensitive functionalities like aldehydes, esters, nitriles or nitro-groups were successfully used in various aryl halides or alkylzinc reactants. The cross-couplings occurred fast (residence time: 150 – 300 s) at elevated temperatures (40 – 80 °C) and the products were mostly isolated in very good yields up to 97%. Furthermore, numerous compounds were formed in high purity, which made it unnecessary to purify them via laborious methods like chromatography.

[64] B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300.
[65] C. G. Frost, L. Mutton, *Green Chem.* **2010**, *12*, 1687.
[66] B. Egle, J. d. M. Muñoz, N. Alonso, W. M. De Borggraeve, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar, *J. Flow Chem.* **2014**, *4*, 22.

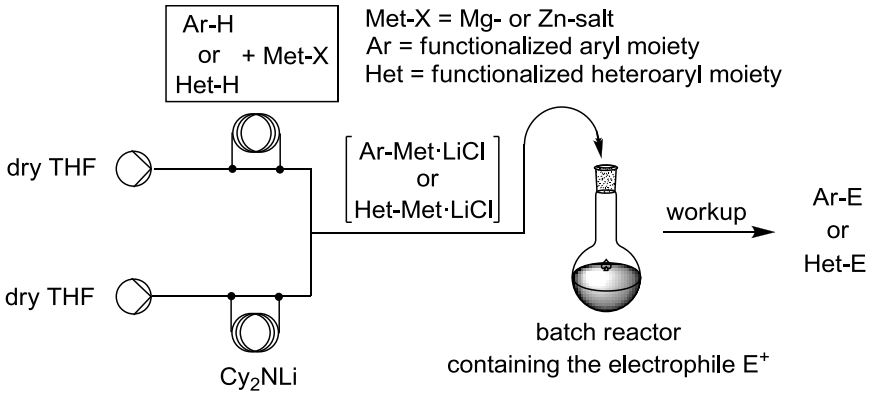
4. Objectives

At the beginning of this work, recently developed *in situ* trapping metalations with lithium 2,2,6,6,-tetramethylpiperidide (TMPLi) in the presence of metal salts such as $MgCl_2$, $ZnCl_2$ or CuCN should be transferred to a continuous flow system. Under batch conditions, this newly developed method gave access to the directed metalation of numerous functionalized arenes and heteroarenes within 5 min at -78 °C. Moreover, unusual metalation regioselectivities were observed in several cases compared to standard metalation procedures. However, the harsh reaction conditions and the difficult scalability excluded broader applications of this method so far. By using the flow methodology for these *in situ* trapping metalations, a convenient reaction protocol without the need of cryogenic temperatures and a straightforward scalability should be realized (Scheme 18).



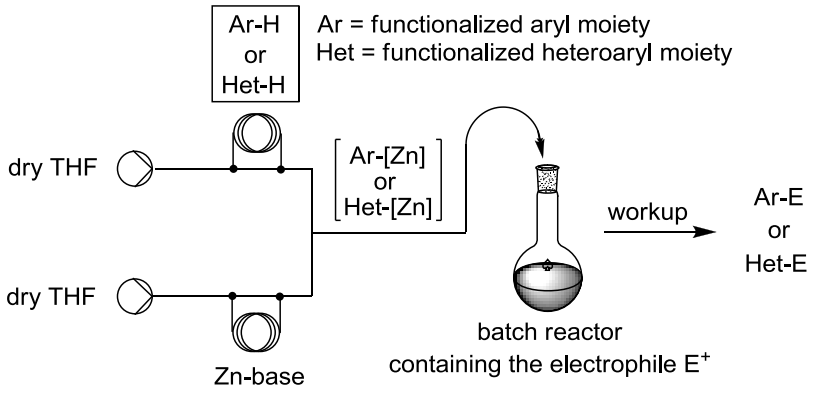
Scheme 18: Continuous flow *in situ* trapping metalations of functionalized arenes and heteroarenes using TMPLi followed by batch quenching with electrophiles.

Due to the high price of the corresponding amide 2,2,6,6-tetramethylpiperide, TMPLi should be substituted for the *in situ* trapping metalations in the framework of a second project. The cheaper replacement lithium dicyclohexylamide (Cy_2NLi) was supposed to be used in order to establish an overall efficient and economic metalation procedure for numerous functionalized aromatics and heteroaromatics in flow mode (Scheme 19).



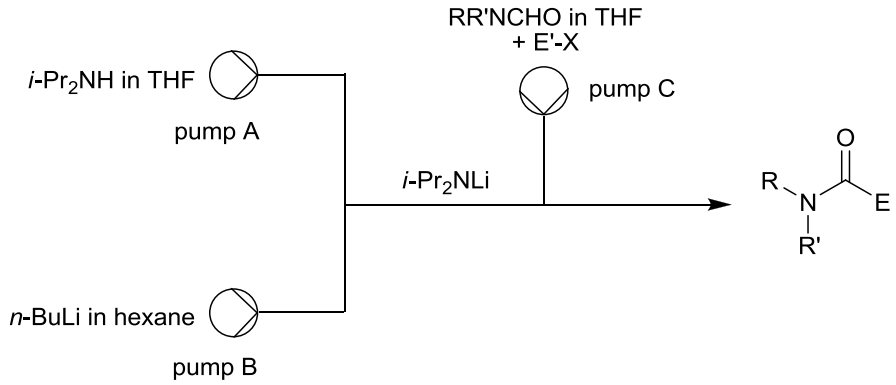
Scheme 19: Continuous flow *in situ* trapping metalations of functionalized aromatics and heteroaromatics using Cy_2NLi followed by batch quenching with electrophiles.

Despite the use of the continuous flow methodology and immediate transmetalations to more stable organometallic intermediates, the metalations with strong lithium bases under convenient conditions led in several cases to decomposition or poor metalation regioselectivities. Therefore, a mild, economic and storable zinc base should be developed for efficient functionalizations of particular sensitive aromatic and heteroaromatic substrates (Scheme 20).



Scheme 20: Continuous flow zincations of sensitive aromatic and heteroaromatic substrates followed by batch quenching with electrophiles.

In the last part of this work, a flow approach for the convenient generation of carbamoyllithium reagents from the corresponding formamides should be established (Scheme 21). These intermediates offer versatile applications in organic synthesis. However, the formation in batch suffers from the need of cryogenic temperatures and a moderate functional group tolerance.



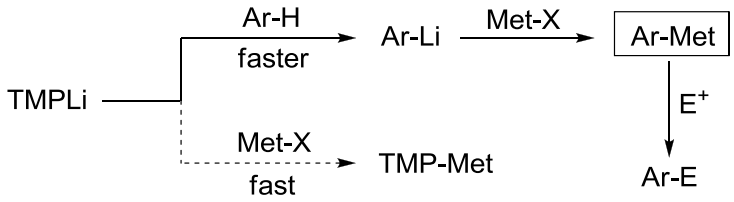
Scheme 21: Convenient continuous flow lithiations of formamides.

B. Results and discussion

1. Practical continuous flow trapping metalations of functionalized arenes and heteroarenes using TMPLi in the presence of Mg, Zn, Cu, or La halides

1.1 Introduction

The *ortho*-lithiation of arenes and heteroarenes is a powerful tool for the functionalization of unsaturated molecules.[67] TMPLi is an especially efficient base for such lithiations;[68] however, the high ionic character of the carbon–lithium bond in aryllithiums often precludes the presence of sensitive functionalities like esters, nitriles, and nitro groups. The use of highly sterically hindered silylated esters has recently solved this problem.[69] Furthermore, conducting lithiations under continuous flow conditions has increased the functional-group tolerance as well.[70] Recently, *Knochel* and co-workers have reported that *in situ* trapping transmetalations can be performed on various aromatic and heterocyclic substrates (Ar-H, Het-H).[71] In this procedure, the unsaturated substrate is mixed at -78 °C with a metal salt (Met-X) such as $ZnCl_2 \cdot 2LiCl$, $MgCl_2$, or $CuCN \cdot 2LiCl$ and treated with TMPLi. It was found that the lithiation of Ar-H (or Het-H) by TMPLi is faster than the transmetalation of TMPLi with the metal salt (Scheme 22).



Scheme 22: *In situ* trapping metalation of aromatic substrates.

Although this method can be used to perform a range of new regioselective lithiations, the

[67] a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**. b) J. Clayden, J. Dufour, D. M. Grainger, M. Helliwell, *J. Am. Chem. Soc.* **2007**, *129*, 7488. c) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879. d) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306. e) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206. f) M. Schlosser, *Organometallics in Synthesis*, *3rd ed.* (Ed.: M. Schlosser), Wiley, New York, **2013**, Chap. 1. g) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470. h) D. R. Armstrong, E. Crosbie, E. Hevia, R. E. Mulvey, D. L. Ramsay, S. D. Robertson, *Chem. Sci.* **2014**, *5*, 3031. i) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667. j) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, *37*, 2620. k) C. Unkelbach, D. F. O`Shea, C. Strohmann, *Angew. Chem. Int. Ed*. **2014**, *53*, 553. l) A. Salomone, F. M. Perna, A. Falcicchio, S. O. N. Lill, A. Moliterni, R. Michel, S. Florio, D. Stalke, V. Capriati, *Chem. Sci.* **2014**, *5*, 528.

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[70] a) A. Nagaki, Y. Takahashi, J.-i. Yoshida, *Chem. Eur. J.* **2014**, *20*, 7931. b) A. Nagaki, D. Ichinari, J.-i. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 12245. c) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914. d) L. Kupracz, A. Kirschning, *Adv. Synth. Catal.* **2013**, *355*, 3375. e) J. Wu, X. Yang, Z. He, X. Mao, T. A. Hatton, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *53*, 8416. f) T. Fukuyama, T. Totoki, I. Ryu, *Org. Lett.* **2014**, *16*, 5632. g) H. Kim, H.-J. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 1877.

[71] A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.

synthetic scope of such metalations is narrowed since cryogenic temperatures are required. Furthermore, it was noticed that the scale-up of these *in situ* trapping reactions proved to be difficult, requiring much optimization. Herein, it is shown that these problems can be solved by using continuous flow conditions[72] allowing the rapid mixing of the reaction components and avoiding the formation of hot spots. Furthermore, the *in situ* transmetalation with the metal salt present generates a more stable organometallic species. Thus the *in situ* trapping metalations can now be performed at 0 °C (instead of -78 °C). Moreover, these new reaction conditions considerably increase the reaction scope of this method and permit a straightforward scale-up of such metalations.

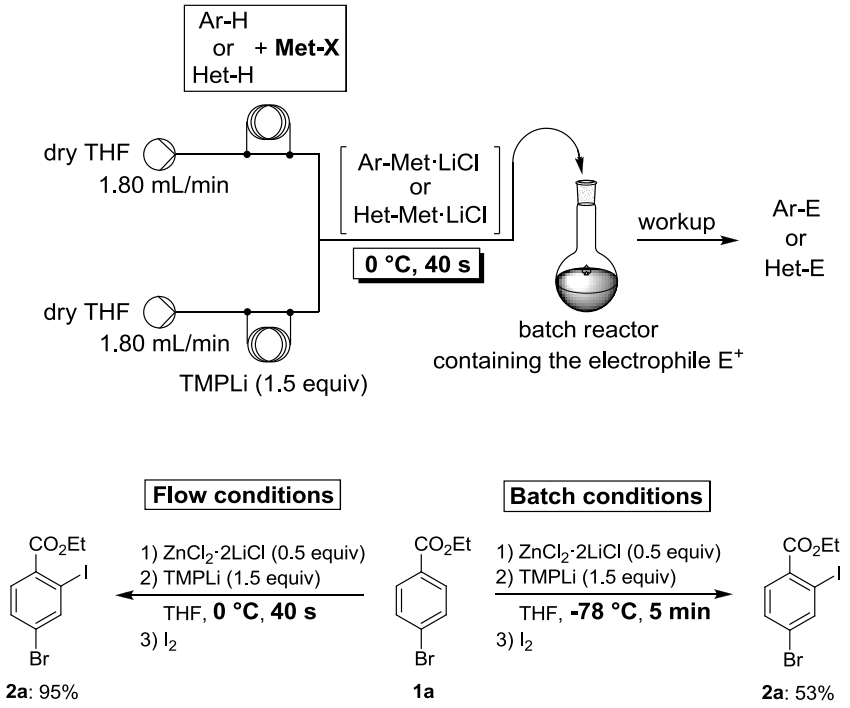
1.2 Continuous flow *in situ* trapping metalations of arenes

The use of a continuous flow set-up as described in Scheme 23 makes it possible to *in situ* transmetalate a broad range of unsaturated substrates at 0 °C within 40 s (instead at -78 °C under batch conditions). Thus, the mixing of a 1:2 mixture of the well-soluble $ZnCl_2$·2LiCl and ethyl 4-bromobenzoate (**1a**) in THF with TMPLi (1.5 equiv) in a flow apparatus[73] for 40 s at 0 °C produces after "batch iodolysis" the aryl iodide (**2a**) in 95% yield. In strong contrast, when this procedure was performed in a standard Schlenk flask (batch conditions) at -78 °C the desired iodide (**2a**) was produced only in 53% yield despite numerous optimization attempts. It should be noted that TMP_2Zn·2LiCl,[47a,b] which would be produced in the absence of ethyl 4-bromobenzoate (**1a**), does not metalate the aryl bromide (**1a**) under these reaction conditions, showing that the metalating agent of **1a** is TMPLi. After transmetalation with $ZnCl_2$·2LiCl the resulting arylzinc reagent is quenched with a range of electrophiles. Thus, a Pd-catalyzed *Negishi* cross-coupling[74] with aryl iodides having either electron-donating or

[72] for recent advances in flow chemistry, see: a) T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010. b) T. O. Painter, P. D. Thornton, M. Orestano, C. Santini, M. G. Organ, J. Aubé, *Chem. Eur. J.* **2011**, *17*, 9595. c) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102. d) M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 4247. e) M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 11628. f) Z. He, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *53*, 3353. g) Y. Zhang, S. C. Born, K. F. Jensen, *Org. Process Res. Dev.* **2014**, *18*, 1476. h) J. M. Sauks, D. Mallik, Y. Lawryshyn, T. Bender, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 1310. i) K. S. Nalivela, M. Tilley, M. A. McGuire, M. G. Organ, *Chem. Eur. J.* **2014**, *20*, 6603. j) K. Somerville, M. Tilley, G. Li, D. Mallik, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 1315. k) K. Gilmore, D. Kopetzki, J. W. Lee, Z. Horváth, D. T. McQuade, A. Seidel-Morgenstern, P. H. Seeberger, *Chem. Commun.* **2014**, *50*, 12652. l) D. B. Ushakov, K. Gilmore, D. Kopetzki, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2014**, *53*, 557. m) M. Chen, S. Ichikawa, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2015**, *54*, 263. n) R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed.* **2015**, *54*, 144. o) D. N. Tran, C. Battilocchio, S.-B. Lou, J. M. Hawkins, S. V. Ley, *Chem. Sci.* **2015**, *6*, 1120. p) D. R. Snead, T. F. Jamison, *Angew. Chem. Int. Ed.* **2015**, *54*, 983. q) S. V. Ley, D. E. Fitzpatrick, R. J. Ingham, R. M. Myers, *Angew. Chem. Int. Ed.* **2015**, *54*, 3449. r) D. Ghislieri, K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 678. s) M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828. t) A. K. Singh, D.-H. Ko, N. K. Vishwakarma, S. Jang, K.-I. Min, D.-P. Kim, *Nat. Commun.* **2016**, *7*, 10741. u) A. Adamo, R. L. Beingessner, M. Behnam, J. Chen, T. F. Jamison, K. F. Jensen, J.-C. M. Monbaliu, A. S. Myerson, E. M. Revalor, D. R. Snead, T. Stelzer, N. Weeranoppanant, S. Y. Wong, P. Zhang, *Science* **2016**, *352*, 61. v) H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691.

[73] flow reactions were performed with commercially available equipment from Uniqsis Ltd. (FlowSyn; http://www.uniqsis.com).

[74] a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340. b) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585.

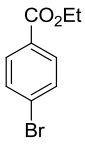
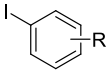
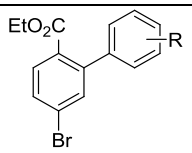
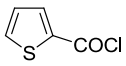
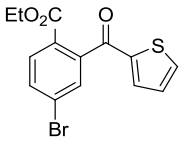
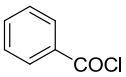
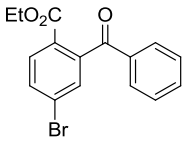
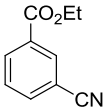
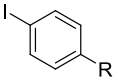
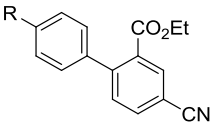
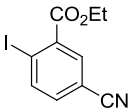
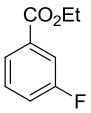
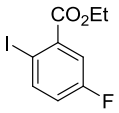


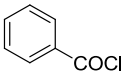
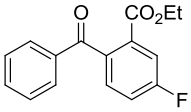
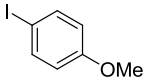
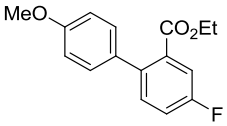
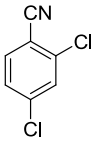
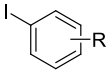
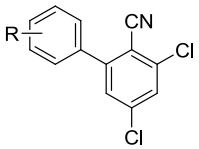
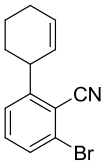
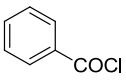
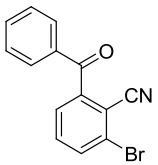
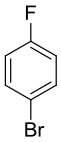
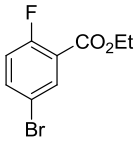
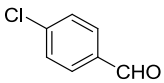
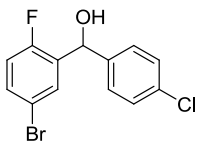
Scheme 23: Continuous flow set-up for *in situ* trapping metalations using TMPLi in the presence of metal salts (Met-X = $ZnCl_2$·2LiCl, $MgCl_2$, CuCN·2LiCl, $LaCl_3$·2LiCl) (top) and iodination of ethyl 4-bromobenzoate (**1a**) using flow and batch conditions for the *in situ* trapping metalation (bottom).

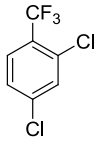
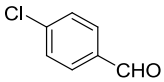
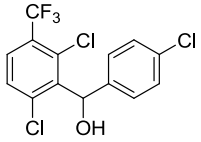
electron-withdrawing substituents produces the biphenyls (**2b**–**d**) in 70–78% yield (Table 1, entries 1–3). Moreover, Cu-mediated acylations afford the corresponding ketones (**2e**,**f**) in 53 and 54% yield, respectively (entries 4 and 5).

Remarkable regioselectivities are obtained in such *in situ* transmetalations. The most acidic hydrogen of the 3-substituted ethyl benzoates (**1b**,**c**) is at position 2. This position is therefore always deprotonated with standard bases such as TMPMgCl·LiCl[40] and $(TMP)_2Mn·2MgCl_2·4LiCl$.[43] However, under the kinetically controlled reaction conditions described herein, the strong TMPLi base is able to abstract the ring hydrogen at position 6, leading after *Negishi* cross-coupling, iodination or copper-mediated acylation to the trisubstituted arenes (**2g**–**m**) in 54–88% yield (entries 6–12). Such kinetic metalations resulting in unique metalation regioselectivities are not limited to benzoate derivatives. 2,4-Dichlorobenzonitrile (**1d**) is also *in situ* zincated at position 6, affording the cyano-substituted biphenyls (**2n**,**o**) in 83–92% yield after *Negishi* cross-coupling (entries 13 and 14). Also 2-bromobenzonitrile (**1e**) undergoes smooth flow metalation with TMPLi in the presence of $ZnCl_2$·2LiCl (0 °C, 40 s). Copper-mediated quenching with 3-bromocyclohexene (0.8 equiv)

Table 1. Continuous flow trapping-metalation of arenes **1** followed by reaction with electrophiles leading to products **2**.

Entry	Substrate	Electrophile	Product[a]
			
1	**1a**	R = *m*-OMe	**2b**: 78%[b,d]
2	**1a**	R= *p*-CO_2Et	**2c**: 77%[b,d]
3	**1a**	R= *m*-NO_2	**2d**: 70%[b,d]
			
4	**1a**		**2e**: 54%[b,e]
			
5	**1a**		**2f**: 53%[b,e]
			
6	**1b**	R = CN	**2g**: 76%[b,d]
7	**1b**	R = OMe	**2h**: 73%[b,d]
8	**1b**	R = CO_2Et	**2i**: 71%[b,d]
			
9	**1b**	I_2	**2j**: 54%[b]
			
10	**1c**	I_2	**2k**: 88%[b]

Entry	Substrate	Electrophile	Product[a]
			
11	**1c**		**2l**: 70%[b,e]
			
12	**1c**		**2m**: 63%[b,d]
			
13	**1d**	R = *p*-Cl	**2n**: 92%[b,d]
14	**1d**	R = *m*-OMe	**2o**: 83%[b,d]
			
15	**1e**		**2p**: 88%[b,f] (87%)[g]
			
16	**1e**		**2q**: 73%[b,e]
			
17	**1f**	NC-CO_2Et	**2r**: 84%[c]
			
18	**1f**		**2s**: 79%[c]

Entry	Substrate	Electrophile	Product[a]
19	 **1g**		 **2t**: 69%[c]

[a] Yield of isolated product. [b] $ZnCl_2 \cdot 2LiCl$ (0.5 equiv) was used. [c] $MgCl_2$ (0.5 equiv) was used. [d] Obtained using 2 mol% $[Pd(dba)_2]$ and 4 mol% P(2-furyl)$_3$. [e] Obtained by a Cu-mediated acylation. [f] Obtained by a Cu-catalyzed allylation. [g] Yield obtained on a 10 mmol scale.

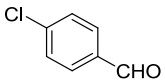
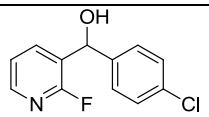
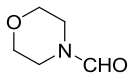
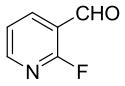
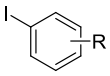
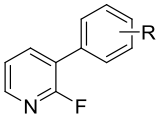
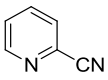
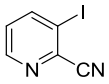
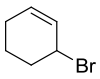
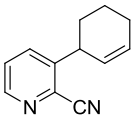
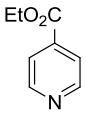
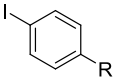
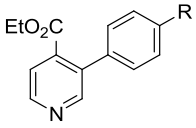
or benzoyl chloride (0.8 equiv) lead to the trisubstituted nitriles (**2p**,**q**) in 73–88% yield (entries 15 and 16). Most of the examples in Table 1 were performed on a 1.7 mmol scale. However, these metalations can be scaled up by simply extending the reaction time. Thus, the preparation of the trisubstituted nitrile (**2p**) on a 10 mmol scale in 87% yield is possible without further optimization, demonstrating the striking advantages of continuously processed reactions. Furthermore, the *ortho*-lithiation of haloarenes such as **1f** and **1g**, which are notoriously prone to decompose via benzyne formation,[75] undergo flow metalation with TMPLi in the presence of $MgCl_2$ (0.5 equiv) under standard conditions (0 °C, 40 s). Subsequent reactions with ethyl cyanoformate (1.5 equiv) or *p*-chlorobenzaldehyde (1.5 equiv) lead to the *o*-functionalized haloarenes (**2r**–**t**) in 69–84% yield (entries 17–19).

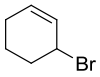
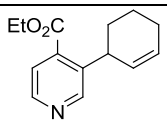
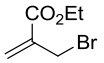
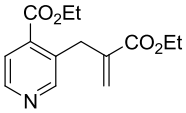
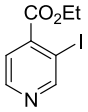
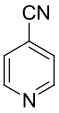
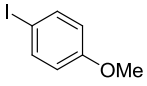
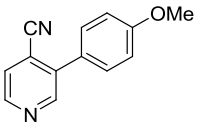
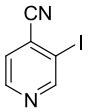
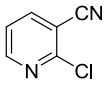
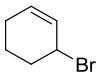
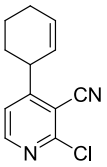
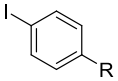
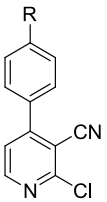
1.3 Continuous flow *in situ* trapping metalations of heteroarenes

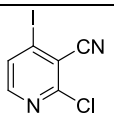
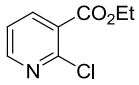
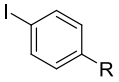
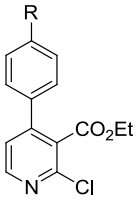
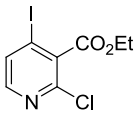
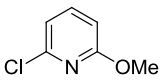
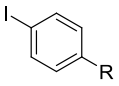
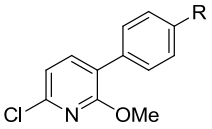
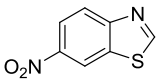
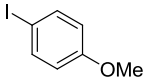
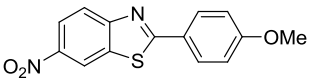
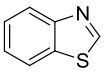
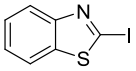
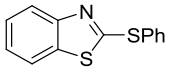
These *in situ* trapping flow metalations are readily extended to a range of highly sensitive, electron-deficient pyridines and benzothiazoles (**3a**–**i**), which are substituted with various electron-withdrawing groups such as a chloride, a fluoride, or a cyano, ester, or nitro group (Table 2). Thus, the 2-substituted pyridines (**3a**,**b**) react under flow conditions in the presence of $MgCl_2$ or $ZnCl_2 \cdot 2LiCl$ with TMPLi leading to the corresponding pyridyl-magnesium and -zinc species. These organometallic intermediates undergo various quenching reactions such as an addition to *p*-chlorobenzaldehyde, a formylation with 4-formylmorpholine, an iodination, a Pd-catalyzed *Negishi* cross-coupling, or a copper-catalyzed allylation providing the corresponding 2,3-disubstituted pyridines (**4a**–**h**) in 50–98% yield (entries 1–8).

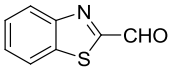
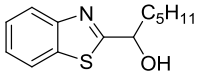
[75] H. Heaney, *Chem. Rev.* **1962**, *62*, 81.

Table 2. Continuous flow trapping-metalation of *N*-heterocycles **3** followed by reaction with electrophiles leading to products **4** and **5**.

Entry	Substrate	Electrophile	Product[a]
			
1	**3a**		**4a**: 96%[c] (84%)[h]
			
2	**3a**		**4b**: 50%[c]
			
3	**3a**	R = *p*-CF_3	**4c**: 98%[b,e]
4	**3a**	R = *m*-NO_2	**4d**: 90%[b,e]
5	**3a**	R = *p*-Cl	**4e**: 54%[b,e]
			
6	**3a**	I_2	**4f**: 64%[b]
			
7	**3b**	I_2	**4g**: 89%[b]
			
8	**3b**		**4h**: 80%[b,f]
			
9	**3c**	R = CO_2Et	**4i**: 90%[b,e]
10	**3c**	R = F	**4j**: 81%[b,e]

Entry	Substrate	Electrophile	Product[a]
			
11	**3c**		**4k**: 84%[d]
			
12	**3c**		**4l**: 79%[d]
			
13	**3c**	I_2	**4m**: 81%[b] (83%)[h]
			
14	**3d**		**4n**: 88%[b,e] (83%)[h]
			
15	**3d**	I_2	**4o**: 70%[b]
			
16	**3e**		**4p**: 89%[d]
			
17	**3e**	R = CO_2Me	**4q**: 83%[b,e]
18	**3e**	R = CF_3	**4r**: 72%[b,e]

Entry	Substrate	Electrophile	Product[a]
			
19	**3e**	I_2	**4s**: 79%[b]
			
20	**3f**	R = OMe	**4t**: 90%[b,e]
21	**3f**	R = CF_3	**4u**: 85%[b,e]
			
22	**3f**	I_2	**4v**: 93%[b]
			
23	**3g**	R = OMe	**4w**: 99%[b,e]
24	**3g**	R = CN	**4x**: 89%[b,e] (85%)[h]
			
25	**3h**		**4y**: 63%[b,g]
			
26	**3i**	I_2	**4z**: 98%[b]
			
27	**3i**	Ph-SO_2-SPh	**5a**: 92%[c]

Entry	Substrate	Electrophile	Product[a]
28	**3i**	DMF	 **5b**: 71%[c]
29	**3i**	C_5H_{11}-CHO	 **5c**: 63%[c]

[a] Yield of isolated product. [b] $ZnCl_2$·2LiCl (0.5-1.1 equiv) was used. [c] $MgCl_2$ (0.5 equiv) was used. [d] CuCN·2LiCl (1.1 equiv) was used. [e] Obtained using 2 mol% $[Pd(dba)_2]$ and 4 mol% P(2-furyl)$_3$. [f] Obtained by a Cu-catalyzed allylation. [g] Obtained using 5 mol% $[Pd(PPh_3)_4]$. [h] Yield obtained on a 8-12 mmol scale.

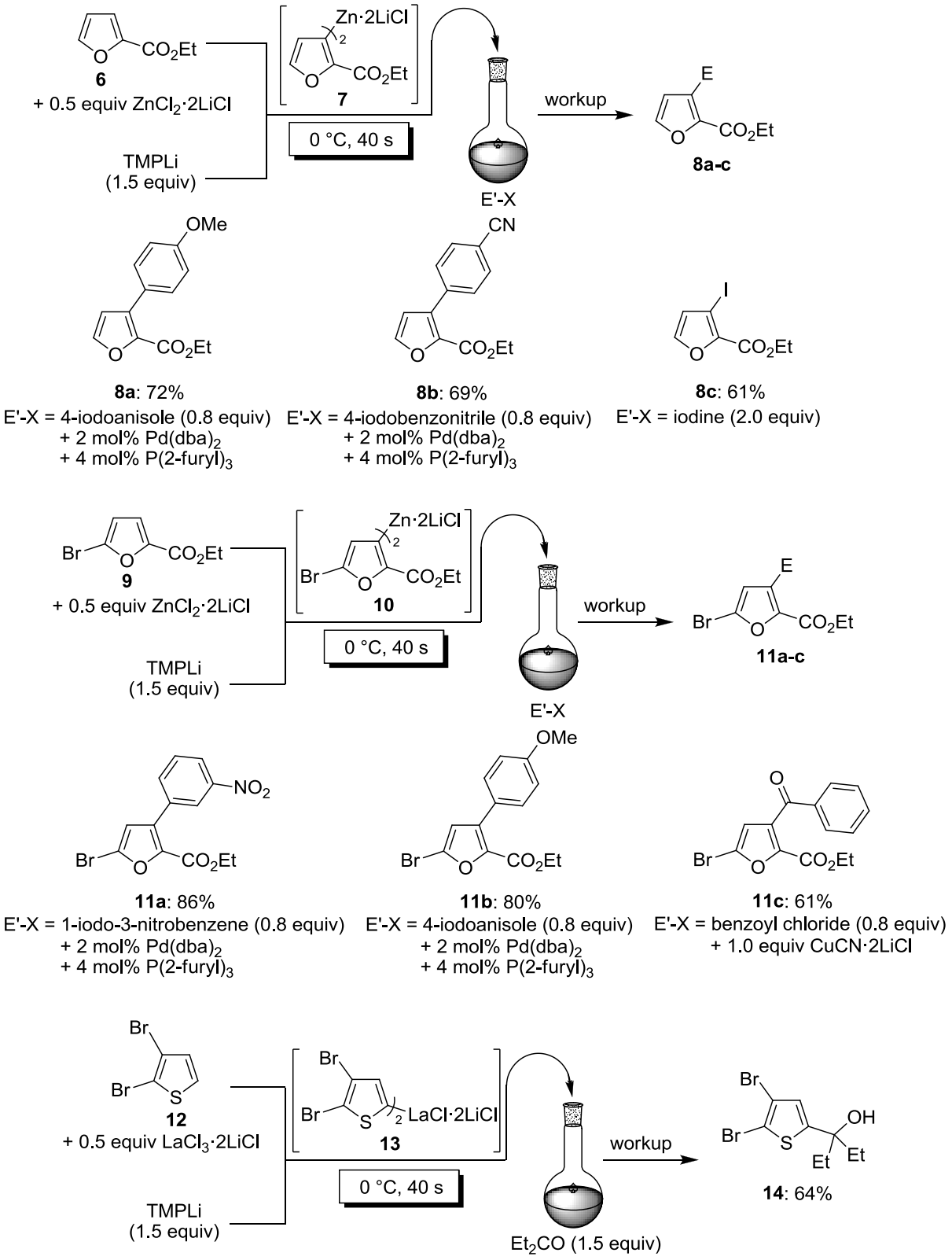
Whereas the metalation of 2-fluoropyridine (**3a**) failed using a standard batch *in situ* trapping protocol (TMPLi, $ZnCl_2$·2LiCl, -78 °C, 5 min),[71,76] the same metalation performed in a flow mode produces the alcohol (**4a**) on a 12 mmol scale in 84% yield. Previously known TMPMgCl·LiCl magnesiations of 4-functionalized pyridines such as **3c**,**d** in the presence of BF_3·OEt_2 lead to a selective metalation at position 3.[77] However, they require low temperatures as well as stoichiometric amounts of the Lewis acid. In contrast, these 4-functionalized pyridines (**3c**,**d**) are smoothly metalated at position 3 under continuous flow conditions using TMPLi and $ZnCl_2$·2LiCl or CuCN·2LiCl, leading after iodinations, *Negishi* cross-couplings or copper-mediated allylations to the 3,4-disubstituted pyridines (**4i**–**o**) in 70–90% yield (entries 9–15). Furthermore, the preparation of the ester (**4m**) and the nitrile (**4n**) on a 8 mmol scale in flow mode can be realized, affording the desired biaryls (**4m**,**n**) in 83% yield, respectively. Under the established standard conditions, the 2,3-disubstituted pyridines (**3 e**,**f**) are smoothly flow-metalated in position 4. Quenching with 3-bromocyclohexene (1.0 equiv), iodine (2.0 equiv) or aryl iodides (0.8 equiv) affords the trisubstituted pyridines (**4p**,**v**) in 72–93% yield (entries 16–22). Under these flow metalation conditions, 2-chloro-6-methoxypyridine (**3g**) is zincated in position 5 and *Negishi* cross-couplings with aryl iodides having either electron-donating or electron-withdrawing substituents afford the corresponding biaryls (**4w**,**x**) in 89–99% yield (entries 23 and 24). Interestingly, the metalation of 2-chloro-6-methoxypyridine (**3g**) with TMPLi and $ZnCl_2$·2LiCl failed at -78 °C in a batch reactor, but

[76] the metalation of 2-fluoropyridine using LDA (-78 °C, 4 h) and iodolysis afforded 2-fluoro-3-iodopyridine in 85% yield: L. Estel, F. Marsais, G. Quéguiner, *J. Org. Chem.* **1988**, *53*, 2740.
[77] M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.

the flow metalation of **3g** on a 10 mmol scale affords the desired product (**4x**) in 85 % yield. Also, the *in situ* trapping metalation of the sensitive 6-nitrobenzothiazole (**3h**) failed under batch conditions at -78 °C due to side reactions caused by the nitro group. However, the *in situ* zincation in a flow reactor at 0 °C within 40 s and subsequent *Negishi* cross-coupling with 4-iodoanisole (0.8 equiv) leads to the 2,6-disubstituted benzothiazole (**4y**) in 63% yield (entry 25). *In situ* magnesiations of unsubstituted benzothiazole (**3i**) and quenching with various electrophiles like iodine (2.0 equiv), *S*-phenyl benzenethiosulfonate (1.5 equiv), DMF (6.0 equiv) or hexanal (1.5 equiv) affords the corresponding products (**4z**–**5c**) in 63–98% yield (entries 26–29).

The metalation of ethyl 2-furoate (**6**) with TMPMgCl·LiCl proceeds at positions 3 and 5 in a 4:1 mixture,[78] but the use of ate bases[79] or *in situ* trapping[71] in batch provides the 3-metalated furan. The flow conditions lead to a practical metalation (0 °C, 40 s) of **6** in position 3, resulting in the formation of the furylzinc reagent **7** (Scheme 24). *Negishi* cross-couplings with 4-iodoanisole or 4-iodobenzonitrile and iodination furnish the 2,3-disubstituted furans **8a**–**c** in 61–72% yield. Similarly, the metalation of ethyl 5-bromo-2-furoate (**9**) is completed under flow conditions in 40 s at 0 °C leading to the zinc species **10**. Previously, such a metalation required 30 min at -50 °C.[78] Pd-catalyzed cross-couplings of the zincated furan **10** with 1-iodo-3-nitrobenzene or 4-iodoanisole and Cu-mediated acylation with benzoyl chloride furnish the trisubstituted furans **11a**–**c** in 61–86% yield (Scheme 24). Although all the previous flow metalations were performed by treating a mixture of the metalating substrate and $MgCl_2$, $ZnCl_2$·2LiCl, or CuCN·2LiCl with TMPLi, other valuable salts may be used instead of the above-mentioned Mg, Zn, and Cu halides. Of special interest are lanthanum halides such as $LaCl_3$·2LiCl[80] since organolanthanums display a higher reactivity towards carbonyl addition compared to *Grignard* reagents. Thus, a mixture of 2,3-dibromothiophene (**12**) with $LaCl_3$·2LiCl (0.5 equiv) was submitted to the flow metalation with TMPLi (0 °C, 40 s). The intermediate lanthanum derivative **13** was obtained in high conversion and reacted with diethyl ketone (1.5 equiv) providing the tertiary alcohol (**14**) in 64% yield (Scheme 24).

[78] F. M. Piller, P. Knochel, *Synthesis* **2011**, 1751.
[79] a) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539. b) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. c) S. E. Baillie, V. L. Blair, D. C. Blakemore, D. Hay, A. R. Kennedy, D. C. Pryde, E. Hevia, *Chem. Commun.* **2012**, *48*, 1985. d) K. Snégaroff, J.-M. L'Helgoual'ch, G. Bentabed-Ababsa, T. T. Nguyen, F. Chevallier, M. Yonehara, M. Uchiyama, A. Derdour, F. Mongin, *Chem. Eur. J.* **2009**, *15*, 10280. e) G. Dayaker, A. Sreeshailam, F. Chevallier, T. Roisnel, P. R. Krishna, F. Mongin, *Chem. Commun.* **2010**, *46*, 2862.
[80] a) G. A. Molander, *Chem. Rev.* **1992**, *92*, 29. b) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227. c) A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497. d) A. Metzger, A. Gavryushin, P. Knochel, *Synlett* **2009**, 1433. e) K. C. Nicolaou, A. Krasovskiy, V. É. Trépanier, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* **2008**, *47*, 4217.



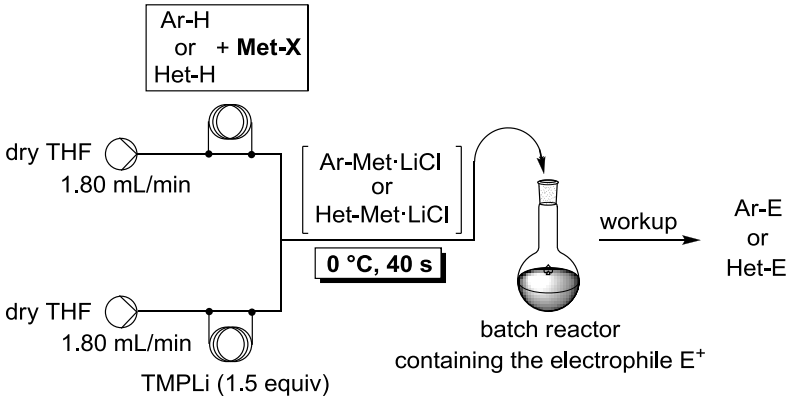
Scheme 24: *In situ* trapping zincation or lanthanation of functionalized furans or thiophenes using TMPLi and $ZnCl_2$·2LiCl or $LaCl_3$·2LiCl in flow mode.

2. Practical and economic lithiations of functionalized arenes and heteroarenes using Cy_2NLi in the presence of Mg, Zn or La halides in a continuous flow

2.1 Introduction

The lithiation of arenes and heteroarenes is a common method for the functionalization of unsaturated molecules.[67a,b,g,h,k,l] Pioneering work of *Snieckus*[67c-e] and others[67f,i,j,79b] have demonstrated the utility of aromatic lithiations for the preparation of pharmaceutical and agrochemical targets. Nevertheless, the use of powerful lithium bases has some drawbacks such as low metalation temperatures and a moderate functional group tolerance. Also, it requires a careful choice of the lithium base used for the metalation step.

It was shown that an *in situ* trapping metalation sequence using TMPLi allows the performance of selective lithiations of various arenes and heteroarenes at 0 °C within 40 s if conducted in a continuous flow system (Scheme 25, see chapter B.1). Under conventional batch conditions, these *in situ* trapping metalations require cryogenic temperatures (-78 °C) in order to avoid unwanted side reactions or decomposition of the organometallic intermediate.[71] Furthermore, the scale-up of these batch metalations proved to be difficult, requiring much optimization.



Scheme 25: Continuous flow set-up for *in situ* trapping metalations using TMPLi in the presence of metal salts (Met-X = $ZnCl_2$·2LiCl, $MgCl_2$, CuCN·2LiCl, $LaCl_3$·2LiCl) and subsequent batch quenching with electrophiles (E^+).

Despite the convenient reaction conditions in flow mode, the use of stoichiometric amounts of TMPLi makes this lithiation still expensive (TMPH = ca. 630 $/mol).[81] The steric hindrance

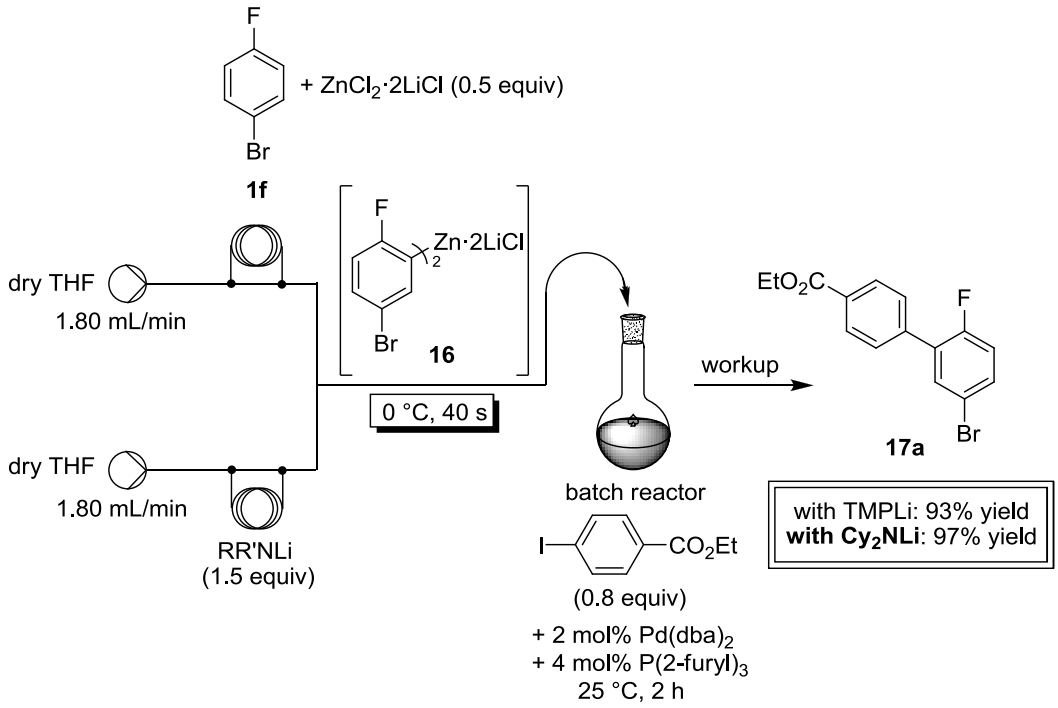
[81] the price of the corresponding amine TMPH from Sigma-Aldrich is ca. 630 $/mol for the largest package.

of the TMP-moiety was required in order to avoid side-reactions. Due to the fast mixing of the reaction components and the prevention of hot spot formation,[6] such highly sterically hindered bases may no longer be mandatory when using the flow methodology.[72] Preliminary experiments attempting to perform metalations of various aromatics using cheaper readily available lithium or other metallic amides R_2NMet (R = *i*-Pr, Cy, TMS; Met = Li, MgHal, ZnHal) were disappointing either due to insufficient reactivity or unwanted side-reactions. The *in situ* trapping methodology developed by *Knochel* and co-workers, in which the aromatic substrate is mixed with a metallic salt and TMPLi is added, proves to be compatible with the replacement of TMPLi with much cheaper bases, since this Barbier-type lithiation minimizes the contact time of the lithium base with the aromatic substrate. The replacement of TMPLi by Cy_2NLi is of special interest since the price of the corresponding amine Cy_2NH (ca. 6.40 $/mol) is only ca. 1% of TMPH.[81,82] Herein, the use of the economic amide base lithium dicyclohexylamide (Cy_2NLi) instead of TMPLi for *in situ* trapping metalations under continuous flow conditions is presented. Cy_2NLi has so far not yet been used for extensive lithiations of functionalized arenes and heteroarenes.[83]

2.2 Continuous flow *in situ* trapping metalations of arenes

In a first experiment, 1-bromo-4-fluorobenzene (**1f**) was metalated under flow conditions (Scheme 26). Thus, **1f** (1.0 equiv) was mixed with $ZnCl_2 \cdot 2LiCl$ (0.5 equiv) and submitted to flow metalation[73] (0 °C, 40 s) using respectively TMPLi and Cy_2NLi. The corresponding arylzinc intermediate (**16**) was quenched via a Pd-catalyzed *Negishi* cross-coupling[74a] in a batch reactor containing ethyl 4-iodobenzoate (0.8 equiv) and a standard Pd-catalytic system (2 mol% $Pd(dba)_2$ and 4 mol% $P(2\text{-furyl})_3$)[74b] providing the expected biphenyl (**17a**) in 93% (using TMPLi) and 97% (using Cy_2NLi) yield. Like for reactions with TMPLi, *in situ* trapping metalations with Cy_2NLi can be simply scaled up without further optimization just by running the reaction for a longer time. Therefore, the reaction of **16** with 3-iodoanisole (0.8 equiv) affords after a *Negishi* cross-coupling the expected product **17b** in 97% yield on

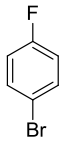
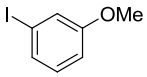
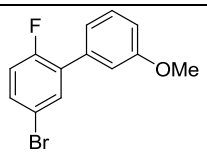
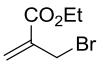
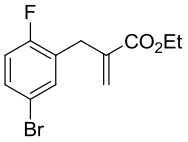
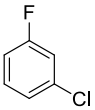
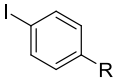
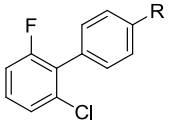
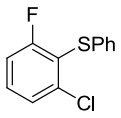
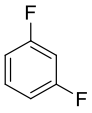
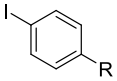
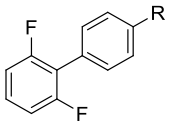
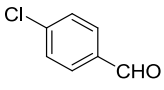
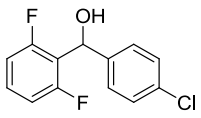
[82] the price of the corresponding amine Cy_2NH from Sigma-Aldrich is ca. 6.40 $/mol for the largest package.
[83] for the use of Cy_2N-bases for metalations, see: a) R. N. McDonald, H. E. Petty, N. L. Wolfe, J. V. Paukstelis, *J. Org. Chem.* **1974**, *39*, 1877. b) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 12557. c) A. Renaudat, L. Jean-Gérard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem. Int. Ed.* **2010**, *49*, 7261. d) T. Truong, J. Alvarado, L. D. Tran, O. Daugulis, *Org. Lett.* **2010**, *12*, 1200.

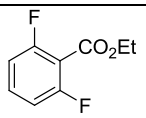
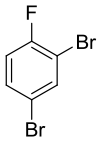
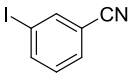
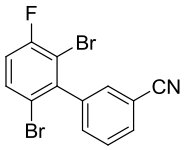
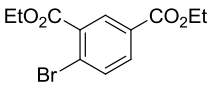
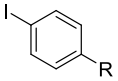
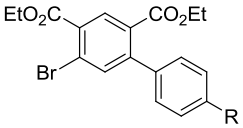
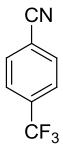
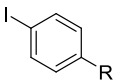
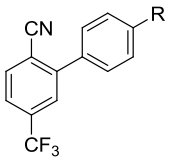
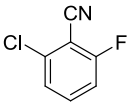
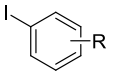
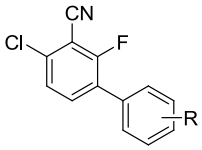


Scheme 26: Continuous flow ***in situ*** trapping zincation of 1-bromo-4-fluorobenzene (**1f**) using TMPLi and Cy_2NLi and subsequent Pd-catalyzed *Negishi* cross-coupling with ethyl 4-iodobenzoate in a batch reactor.

a 1.7 mmol scale and in 95% yield on a 11 mmol scale (Table 3, entry 1). A Cu-catalyzed allylation of **16** with ethyl 2-(bromomethyl)acrylate (0.8 equiv) furnishes the corresponding arene (**17c**) in 61% yield (entry 2). Using Cy_2NLi for the *ortho*-lithiation of 1,3-dihaloarenes (**15a**,**b**) abstracts under the standard reaction conditions (0 °C, 40 s) the most acidic hydrogen at position 2. *In situ* transmetalations with $ZnCl_2·2LiCl$ or $MgCl_2$ (0.5 equiv, respectively) generate the corresponding aryl-zinc and -magnesium species, which are quenched in subsequent batch reactions with aryl iodides (0.8 equiv), *S*-phenyl benzenethiosulfonate (0.8 equiv), *p*-chlorobenzaldehyde (0.8 equiv) and ethyl cyanoformate (0.8 equiv) leading to the trisubstituted arenes (**17d–j**) in 67–98% yield (entries 3–9). Moreover, 2,4-dibromo-1-fluorobenzene (**15c**) is flow metalated within 40 s at 0 °C and subsequent Pd-catalyzed cross-coupling with 3-iodobenzonitrile (0.8 equiv) results in the expected biaryl (**17k**) in 72% yield (entry 10). The *in situ* metalations with Cy_2NLi are not limited to haloarenes, and sensitive functionalities such as esters and nitriles are tolerated as well. Thus, diethyl 4-bromoisophthalate (**15d**) is smoothly flow-zincated in position 6 and a *Negishi* cross-coupling with ethyl 4-iodobenzoate (0.8 equiv) or 4-iodoanisole (0.8 equiv) produces the expected products (**17l**,**m**) in 61–72% yield (entries 11 and 12). Similarly, substituted

Table 3. Continuous flow trapping-metalation of arenes **1** and **15** followed by reaction with electrophiles leading to products **17**.

Entry	Substrate	Electrophile	Product[a]
			
1	**1f**		**17b**: 97%[b,d] (95%)[f]
			
2	**1f**		**17c**: 61%[b,e]
			
3	**15a**	R = OMe	**17d**: 98%[b,d]
4	**15a**	R = CO_2Et	**17e**: 91%[b,d]
			
5	**15a**	Ph-SO_2-SPh	**17f**: 75%[c]
			
6	**15b**	R = CO_2Et	**17g**: 94%[b,d]
7	**15b**	R = OMe	**17h**: 89%[b,d]
			
8	**15b**		**17i**: 74%[c]

Entry	Substrate	Electrophile	Product[a]
			
9	**15b**	NC-CO_2Et	**17j**: 67%[c]
			
10	**15c**		**17k**: 72%[b,d]
			
11	**15d**	R = CO_2Et	**17l**: 72%[b,d]
12	**15d**	R = OMe	**17m**: 61%[b,d]
			
13	**15e**	R = OMe	**17n**: 70%[b,d]
14	**15e**	R = CF_3	**17o**: 61%[b,d]
			
15	**15f**	R = *m*-OMe	**17p**: 97%[b,d]
16	**15f**	R = *p*-CN	**17q**: 73%[b,d]

[a] Yield of isolated product. [b] $ZnCl_2$·2LiCl (0.5 equiv) was used. [c] $MgCl_2$ (0.5 equiv) was used. [d] Obtained using 2 mol% [$Pd(dba)_2$] and 4 mol% P(2-furyl)$_3$. [e] Obtained by a Cu-catalyzed allylation. [f] Yield obtained on a 11 mmol scale.

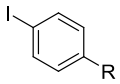
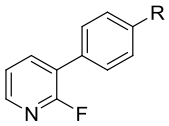
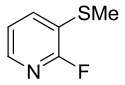
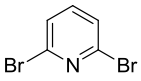
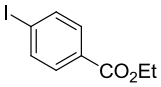
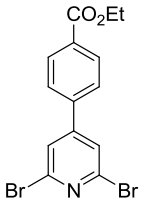
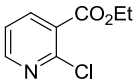
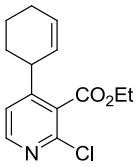
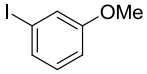
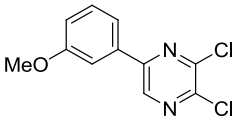
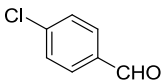
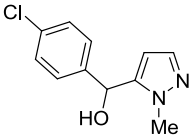
nitriles such as **15e** and **15f** are *in situ* metalated in the presence of $ZnCl_2$·2LiCl (0.5 equiv) within 40 s at 0 °C, and subsequent quenching reactions with aryl iodides

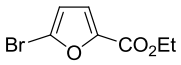
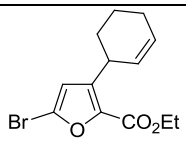
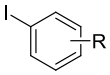
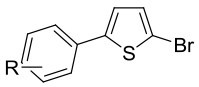
(0.8 equiv) having either electron-donating or electron-withdrawing substituents lead to the cyano-substituted biphenyls (**17n–q**) in 61–97% yield (entries 13–16).

2.3 Continuous flow *in situ* trapping metalations of heteroarenes

This *in situ* trapping methodology with Cy_2NLi in a flow reactor is not limited to functionalized arenes. In fact, it can be readily extended to a broad range of sensitive, electron-deficient heteroarenes (Table 4). Thus, 2-fluoropyridine (**3a**), which is notoriously difficult to metalate,[76] undergoes a smooth zincation or magnesiation in position 3 in the presence of $ZnCl_2 \cdot 2LiCl$ or $MgCl_2$ and quenching with ethyl 4-iodobenzoate (0.8 equiv), 4-iodobenzonitrile (0.8 equiv) or *S*-methyl methanethiosulfonate (0.8 equiv) produces the disubstituted pyridines (**19a**–**c**) in 75–94% yield (entries 1–3). However, using the standard conditions, 2,6-dibromopyridine (**18a**) is *in situ* metalated in position 4 and a subsequent *Negishi* cross-coupling with ethyl 4-iodobenzoate (0.8 equiv) affords the desired pyridine (**19d**) in 67% yield (entry 4). Similarly, ethyl 2-chloronicotinate (**3f**) is flow-zincated within 40 s at 0 °C in position 4 affording the trisubstituted pyridine (**19e**) in 88% yield after a Cu-catalyzed allylation with 3-bromocyclohexene (0.8 equiv; entry 5). The sensitive 2,3-dichloropyrazine (**18b**) is smoothly flow-metalated (0 °C, 40 s) in the presence of $ZnCl_2 \cdot 2LiCl$ (0.5 equiv) and quenching with 3-iodoanisole (0.8 equiv) leads to the pyrazine (**19f**) in 77% yield (entry 6). The *in situ* trapping metalations with Cy_2NLi can also be used for the functionalization of a broad range of substituted 5-membered ring heterocycles. Thus, the lanthanation of 1-methylpyrazole (**18c**) in the presence of $LaCl_3 \cdot 2LiCl$ (0.5 equiv) under standard conditions (0 °C, 40 s) produces the desired alcohol (**19g**) in 62% yield after addition to *p*-chlorobenzaldehyde (0.8 equiv; entry 7). Ethyl 5-bromo-2-furoate (**9**) is regioselectively flow metalated in position 3 and a subsequent Cu-catalyzed reaction with 3-bromocyclohexene (0.8 equiv) leads to the trisubstituted furan (**19h**) in 76% yield (entry 8). The *in situ* trapping zincation of 2-bromothiophene (**18d**) within 40 s at 0 °C abstracts the most acidic hydrogen at position 5 affording the 2,5-disubstituted thiophenes (**19i**,**j**) in 89–91% yield after *Negishi* cross-couplings with 4-iodobenzotrifluoride (0.8 equiv) and 1-iodo-3-nitrobenzene (0.8 equiv; entries 9 and 10).

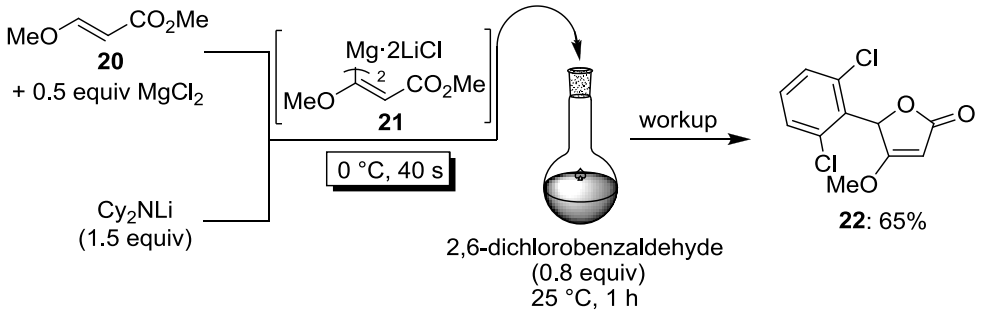
Table 4. Continuous flow trapping-metalation of heterocycles **3**,**9** and **18** followed by reaction with electrophiles leading to products **19**.

Entry	Substrate	Electrophile	Product[a]
			
1	**3a**	R = CO_2Et	**19a**: 94%[b,e]
2	**3a**	R = CN	**19b**: 80%[b,e]
			
3	**3a**	Me-SO_2-SMe	**19c**: 75%[c]
			
4	**18a**		**19d**: 67%[b,e]
			
5	**3f**		**19e**: 88%[b,f]
			
6	**18b**		**19f**: 77%[b,e]
			
7	**18c**		**19g**: 62%[d]

Entry	Substrate	Electrophile	Product[a]
			
8	**9**		**19h**: 76%[b,f]
			
9	**18d**	R = *p*-CF_3	**19i**: 91%[b,e]
10	**18d**	R = *m*-NO_2	**19j**: 89%[b,e]

[a] Yield of isolated product. [b] $ZnCl_2$·2LiCl (0.5 equiv) was used. [c] $MgCl_2$ (0.5 equiv) was used. [d] $LaCl_3$·2LiCl (0.5 equiv) was used. [e] Obtained using 2 mol% $[Pd(dba)_2]$ and 4 mol% P(2-furyl)$_3$. [f] Obtained by a Cu-catalyzed allylation.

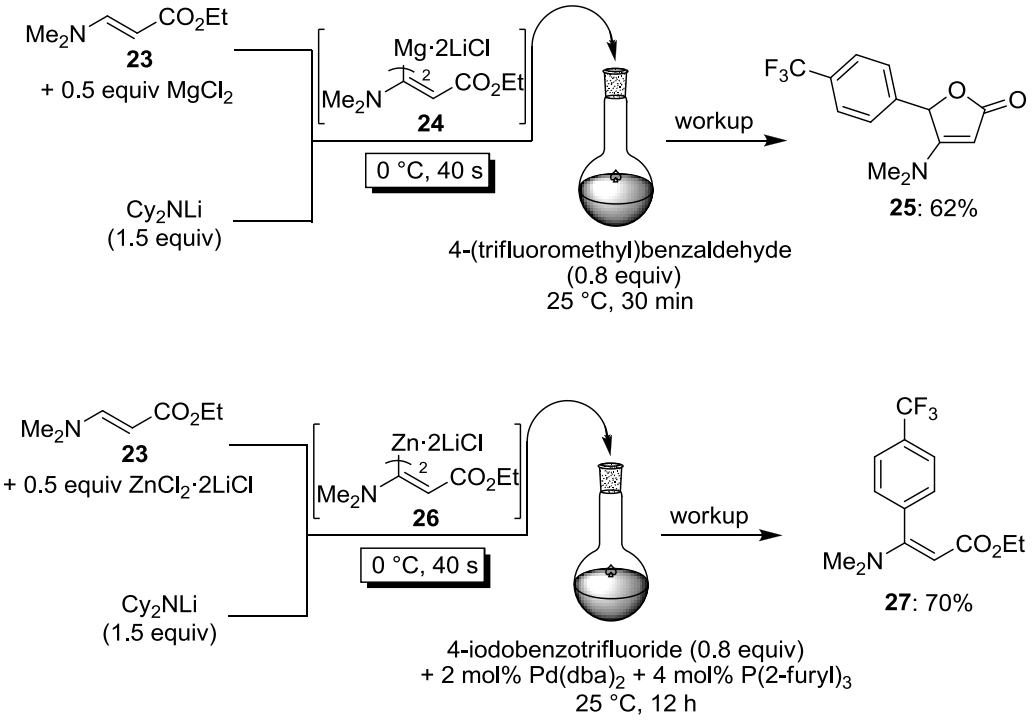
To demonstrate the broad practicability of the *in situ* trapping metalations with Cy_2NLi, the functionalization of acyclic acrylate derivatives has been investigated, which are prone to polymerize. However, submitting a mixture of (*E*)-methyl 3-methoxyacrylate (**20**) with $MgCl_2$ (0.5 equiv) to the flow metalation with Cy_2NLi (1.5 equiv) for 40 s at 0 °C leads to the formation of the magnesium intermediate **21** in high conversion (Scheme 27). Subsequent reaction of **21** with 2,6-dichlorobenzaldehyde (0.8 equiv) produces the lactone **22** in 65% yield.



Scheme 27: *In situ* trapping magnesiation of (*E*)-methyl 3-methoxyacrylate (**20**) using Cy_2NLi in a flow reactor.

Similarly, (*E*)-ethyl 3-(dimethylamino)acrylate (**23**) is *in situ* metalated (0 °C, 40 s) in the presence of $MgCl_2$ or $ZnCl_2$·2LiCl (Scheme 28). The corresponding magnesium (**24**) and zinc (**26**) organometallic intermediates undergo various quenching reactions, such as an addition to 4-(trifluoromethyl)benzaldehyde (0.8 equiv) and a *Negishi* cross-coupling with 4-

iodobenzotrifluoride (0.8 equiv), providing the corresponding lactone (**25**) and the ester **27** in 62–70% yield.

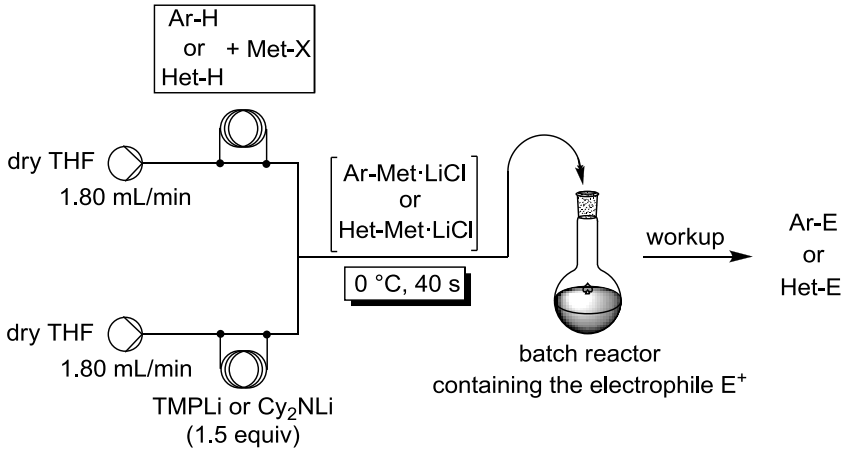


Scheme 28: *In situ* trapping magnesiation and zincation of (*E*)-ethyl 3-(dimethylamino)acrylate (**23**) using Cy_2NLi in a flow reactor.

3. High temperature continuous flow zincations of functionalized arenes and heteroarenes using $(Cy_2N)_2Zn \cdot 2LiCl$

3.1 Introduction

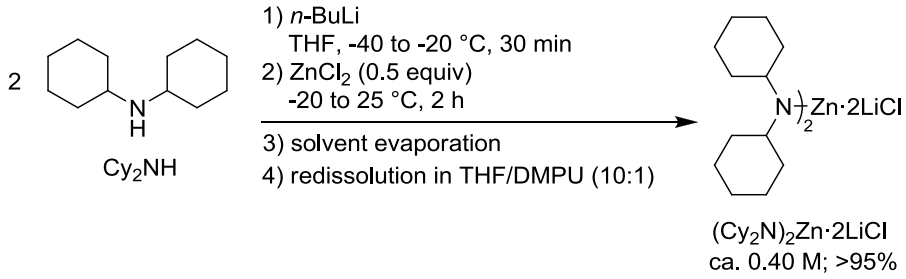
The directed metalation of unsaturated substrates with lithium, magnesium, or zinc bases allows the preparation of polyfunctional aryl- and heteroaryl organometallics, which are key intermediates in organic synthesis.[2,4,67] Therefore, various ate bases[79] or, more recently, LiCl-activated amides[4c,48] have been developed for their preparation. Furthermore, lithiation[70] in a continuous flow reactor[72] has led to significant improvements and expanded the scope of potential applications. As part of this work, the *in situ* trapping metalation of various aromatic and heteroaromatic substrates (Ar-H, Het-H) in the presence of metal salts (Met-X) such as $ZnCl_2 \cdot 2LiCl$, $MgCl_2$, $CuCN \cdot 2LiCl$, or $LaCl_3 \cdot 2LiCl$ using either TMPLi or Cy_2NLi has been demonstrated (see chapter B.1 and B.2). Running the reactions in a continuous flow system allows the completion of these *in situ* trapping metalations within 40 s at 0 °C due to the fast mixing of the reaction components and the prevention of hot-spot formation (Scheme 29).



Scheme 29: Continuous flow set-up for *in situ* trapping metalations using TMPLi or Cy_2NLi in the presence of metal salts (Met-X = $ZnCl_2 \cdot 2LiCl$, $MgCl_2$, $CuCN \cdot 2LiCl$, $LaCl_3 \cdot 2LiCl$) and subsequent batch quenching with electrophiles (E^+).

Although this method permits the immediate transmetalation to more stable organometallic intermediates, the use of powerful lithium bases still precludes the successful chemo- and regioselective functionalization of a range of sensitive substrates. Attempts to perform metalations of such aromatics with less reactive, readily available, and economic magnesium or zinc amides R_2NMet (R = *i*-Pr, Cy, TMS; Met = MgHal, ZnHal) were disappointing either because of insufficient reactivity or extensive side reactions. However, these limitations can

be overcome by using the new zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ made from Cy_2NLi and $ZnCl_2$ in >95% yield (Scheme 30).



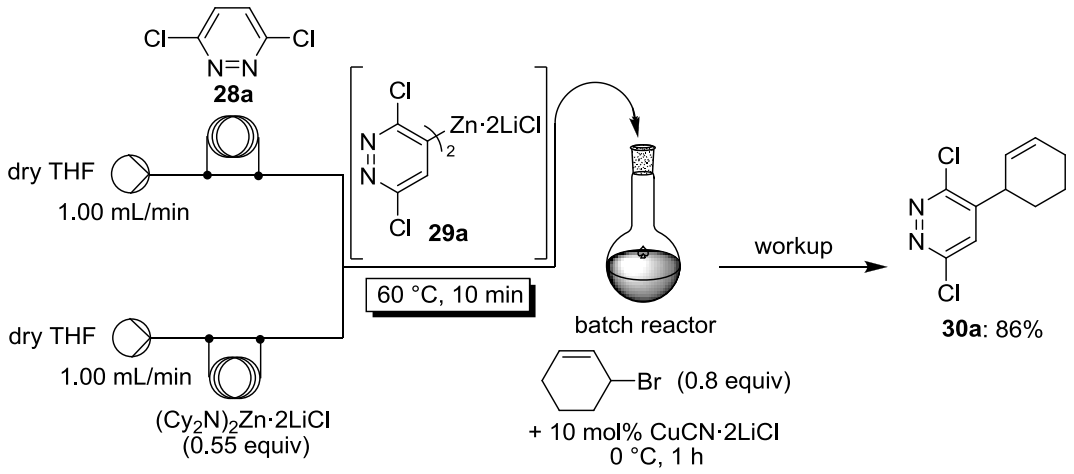
Scheme 30: Preparation of the zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ in THF/DMPU (10:1).

Remarkably, by redissolving $(Cy_2N)_2Zn{\cdot}2LiCl$ after solvent evaporation in the binary cosolvent system THF/DMPU (10:1), a higher solubility and an increased reactivity is achieved.[84] Furthermore, this base can be stored for, at least, several weeks at 25 °C without any decomposition under argon. The use of Cy_2NH is particularly desirable, since its price is only ca. 1% of the commonly utilized TMPH.[81,82] The zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ has so far not yet been used extensively for the metalation of functionalized unsaturated substrates.[83] Herein, the selective and highly efficient continuous flow zincation of various functionalized arenes and heteroarenes with $(Cy_2N)_2Zn{\cdot}2LiCl$ (in THF/DMPU = 10:1) is presented, resulting in the preparation of polyfunctional zinc reagents for organic synthesis.

3.2 High temperature zincations of functionalized heteroarenes

In a first experiment, the flow metalation[73] of 3,6-dichloropyridazine (**28a**) was investigated, which cannot be performed via an *in situ* trapping zincation with TMPLi or Cy_2NLi in the presence of $ZnCl_2{\cdot}2LiCl$ (see chapter B.1 and B.2). However, the zincation of **28a** proceeds smoothly within 10 min at 60 °C using $(Cy_2N)_2Zn{\cdot}2LiCl$ (0.55 equiv). Subsequent batch quenching of the organozinc intermediate **29a** with 3-bromocyclohexene (0.8 equiv), in the presence of 10 mol% of $CuCN{\cdot}2LiCl$, affords the expected product (**30a**) in 86% yield (Scheme 31). Furthermore, *Negishi* cross-coupling reactions[74a] of **29a** with aryl iodides (0.8 equiv) and a standard Pd-catalyst system (2 mol% $Pd(dba)_2$ and 4 mol% P(2-furyl)$_3$)[74b] lead to the corresponding biaryls (**30b**,**c**) in 64–72% yield (Table 5, entries 1 and 2).

[84] the reactivity of different solvent systems for the zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ was studied for the zincation of 3,6-dichloropyridazine (**28a**; metalation temperature: 60 °C, metalation time: 10 min). The progress of metalation was checked by iodolysis of reaction aliquots and subsequent GC-analysis. 91% conversion of **28a** for THF/DMPU (10:1; 0.36 M), 63% conversion of **28a** for THF/TMU (10:1; 0.34 M; TMU = tetramethylurea) and 38% conversion of **28a** for THF (0.08 M) has been observed.

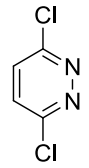
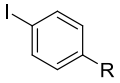
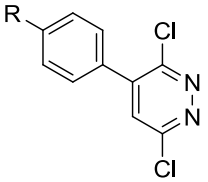
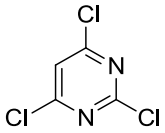
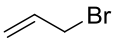
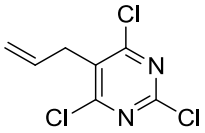
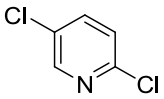
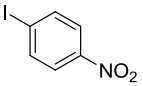
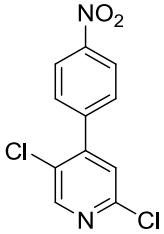
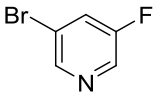
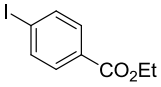
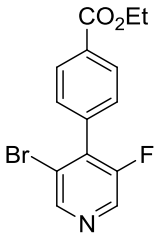
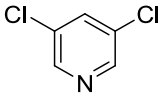
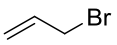
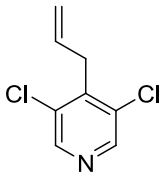


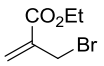
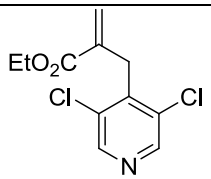
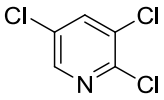
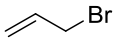
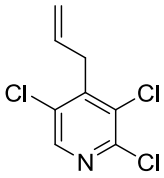
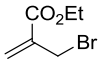
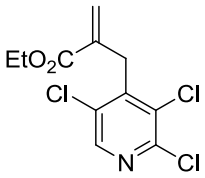
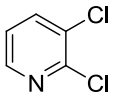
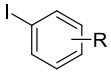
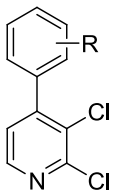
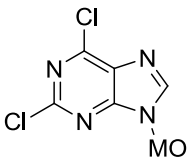
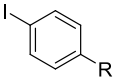
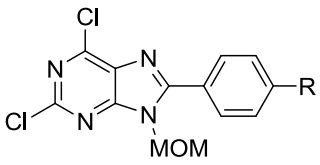
Scheme 31: Continuous flow zincation of 3,6-dichloropyridazine (**28a**) using $(Cy_2N)_2Zn{\cdot}2LiCl$ and subsequent Cu-catalyzed allylation with 3-bromocyclohexene in a batch reactor.

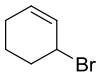
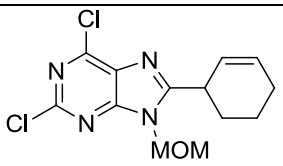
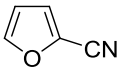
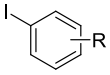
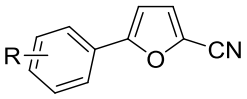
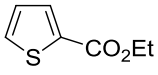
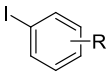
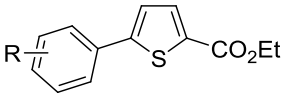
Similarly, the flow zincation of 2,4,6-trichloropyrimidine (**28b**) occurrs in 98% conversion at 50 °C within 10 min. Subsequent quenching with allyl bromide (0.8 equiv) furnishes the fully functionalized pyrimidine (**30d**) in 92% yield (entry 3). Remarkable regioselectivities are obtained when $(Cy_2N)_2Zn{\cdot}2LiCl$ is used for such flow zincations. The metalation of substituted pyridines like **28c**–**f** with LiCl-activated TMP bases such as TMPMgCl·LiCl or TMPZnCl·LiCl preferentially proceeds under kinetic reaction conditions at position 2 or position 6, respectively, due to a distinct substrate–base interaction via a metal–nitrogen coordination.[4c,48,85,86] However, thermodynamically controlled zincations of **28c**–**f** with $(Cy_2N)_2Zn{\cdot}2LiCl$ (0.55 equiv) in a flow reactor (60 °C, 10 min) proceed regioselectively at position 4 (Scheme 32). Quenching of the corresponding organozinc intermediates with various allylic bromides (0.8 equiv) or aryl iodides (0.8 equiv) furnishes the expected pyridines (**30e**–**k**) in 60–97% yield (entries 4–9). 2,3-Dichloropyridine (**28g**) is also zincated at position 4 within 10 min at 60 °C. *Negishi* cross-couplings with ethyl 4-iodobenzoate (0.8 equiv) or 3-iodonitrobenzene (0.8 equiv) give the trisubstituted pyridines (**30l**,**m**) in 62–66% yield (entries 10 and 11). The MOM-protected (MOM = methoxymethyl) purine (**28h**) is smoothly flow-metalated (25 °C, 10 min) with the zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ (0.55 equiv). Subsequent Pd-catalyzed *Negishi* cross-coupling reactions or Cu-catalyzed allylation lead to the fully functionalized purines (**30n**–**p**) in 61–98% yield (entries 12–14).

[85] T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933.
[86] a) K. Snégaroff, T. T. Nguyen, N. Marquise, Y. S. Halauko, P. J. Harford, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Chevallier, A. E. H. Wheatley, P. C. Gros, F. Mongin, *Chem. Eur. J.* **2011**, *17*, 13284. b) A. J. Martínez-Martínez, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834.

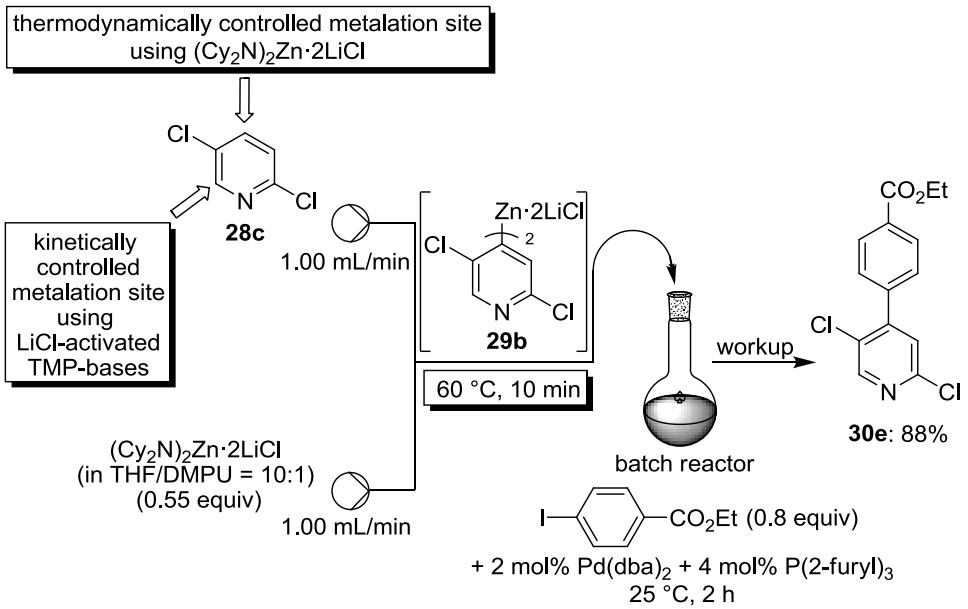
Table 5. Continuous flow zincation of heterocycles **28** followed by reaction with electrophiles leading to products **30**.

Entry	Substrate [metalation conditions]	Electrophile	Product[a]
			
1	**28a** [60 °C, 10 min]	R = CO_2Et	**30b**: 72%[b]
2	**28a**	R = CF_3	**30c**: 64%[b]
			
3	**28b** [50 °C, 10 min]		**30d**: 92%[c]
			
4	**28c** [60 °C, 10 min]		**30f**: 78%[b]
			
5	**28d** [60 °C, 10 min]		**30g**: 60%[b]
			
6	**28e** [60 °C, 10 min]		**30h**: 87%[c]

Entry	Substrate [metalation conditions]	Electrophile	Product[a]
			
7	**28e**		**30i**: 74%[c]
			
8	**28f** [60 °C, 10 min]		**30j**: 97%[c]
			
9	**28f**		**30k**: 64%[c]
			
10	**28g** [60 °C, 10 min]	R = *p*-CO_2Et	**30l**: 66%[b]
11	**28g**	R = *m*-NO_2	**30m**: 62%[b]
			
12	**28h** [25 °C, 10 min]	R = OMe	**30n**: 98%[b]
13	**28h**	R = NO_2	**30o**: 61%[b]

Entry	Substrate [metalation conditions]	Electrophile	Product[a]
			
14	**28h**		**30p**: 78%[c]
			
15	**28i** [80 °C, 10 min]	R = *m*-OMe	**30q**: 70%[b]
16	**28i**	R = *p*-CF_3	**30r**: 64%[b]
			
17	**28j** [100 °C, 10 min]	R = *p*-CO_2Et	**30s**: 68%[b]
18	**28j**	R = *m*-OMe	**30t**: 64%[b]

[a] Yield of isolated product. [b] Obtained using 2 mol% [$Pd(dba)_2$] and 4 mol% P(2-furyl)$_3$. [c] Obtained by a Cu-catalyzed allylation.

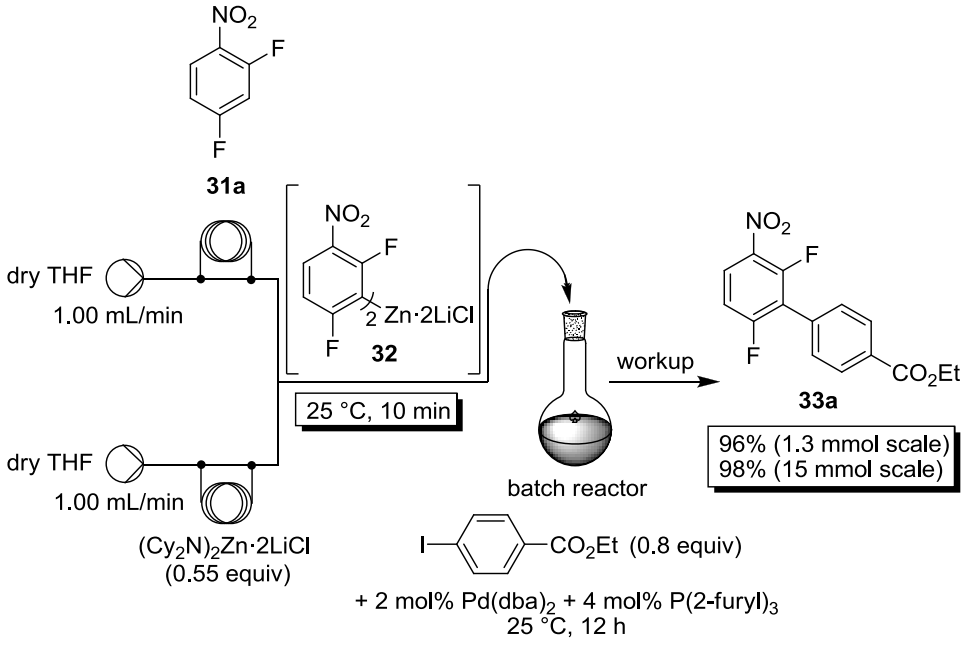


Scheme 32: Switching metalation regioselectivity for the continuous flow zincation of 2,5-dichloropyridine (**28c**) using $(Cy_2N)_2Zn{\cdot}2LiCl$ and subsequent Pd-catalyzed *Negishi* cross-coupling with ethyl 4-iodobenzoate in a batch reactor.

Moreover, conducting these zincations at elevated temperatures (between 60–100 °C) in a continuous flow apparatus allows the convenient and safe handling of such unconventional reaction conditions. Thus, 2-furonitrile (**28i**) is metalated with $(Cy_2N)_2Zn{\cdot}2LiCl$ (0.55 equiv) at 80 °C within 10 min at position 5. *Negishi* cross-couplings with aryl iodides (0.8 equiv) having either electron-withdrawing or electron-donating substituents provide the corresponding 2,5-disubstituted furans (**30q**,**r**) in 64–70% yield (entries 15 and 16). $(Cy_2N)_2Zn{\cdot}2LiCl$ can be used for high-temperature metalations up to 100 °C, and ethyl 2-thiophenecarboxylate (**28j**) is zincated in 90% conversion within 10 min at 100 °C. Quenching with aryl iodides (0.8 equiv) in the presence of a Pd-catalyst furnishes the expected 2,5-disubstituted thiophenes (**30s**,**t**) in 64–68% yield (entries 17 and 18).

3.3 High temperature zincations of functionalized arenes

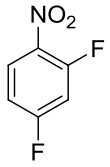
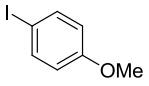
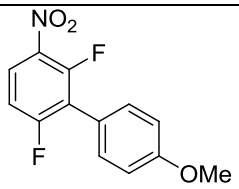
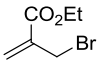
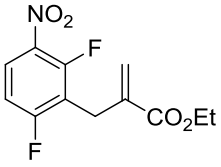
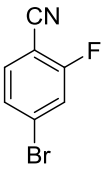
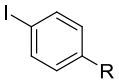
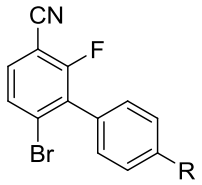
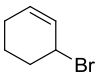
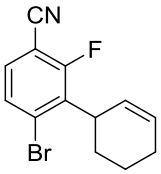
The efficient and economic functionalization of sensitive substrates with the zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ is not limited to heteroarenes. In fact, the base can be used for the smooth flow zincation (25 °C, 10 min) of 2,4-difluoronitrobenzene (**31a**), which is notoriously difficult to metalate because of the nitro group (Scheme 33).[46a,47a,87]



Scheme 33: Continuous flow zincation of 2,4-difluoronitrobenzene (**31a**) using $(Cy_2N)_2Zn{\cdot}2LiCl$ and subsequent Pd-catalyzed *Negishi* cross-coupling with ethyl 4-iodobenzoate on a 1.3 and 15 mmol scale.

[87] T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914.

Table 6. Continuous flow zincation of arenes **31** followed by reaction with electrophiles leading to products **33**.

Entry	Substrate [metalation conditions]	Electrophile	Product[a]
			
1	**31a** [25 °C, 10 min]		**33b**: 76%[b]
			
2	**31a**		**33c**: 71%[d]
			
3	**31b** [60 °C, 10 min]	R = OMe	**33d**: 85%[c]
4	**31b**	R = CO_2Et	**33e**: 77%[c]
			
5	**31b**		**33f**: 79%[d]

[a] Yield of isolated product. [b] Obtained using 2 mol% [$Pd(dba)_2$] and 4 mol% P(2-furyl)$_3$. [c] Obtained using 5 mol% [$Pd(PPh_3)_4$]. [d] Obtained by a Cu-catalyzed allylation.

Batch quenching of the zinc intermediate **32** with ethyl 4-iodobenzoate (0.8 equiv) leads to formation of the biphenyl (**33a**) in 96% yield on a 1.3 mmol scale. Furthermore, this reaction is readily scaled up to 15 mmol without further optimization just by running it for a longer time (55 min) to afford **33a** in 98% yield. Further trapping of **32** with 4-iodoanisole (0.8 equiv) and a Pd-catalyst or ethyl 2-(bromomethyl)acrylate (0.8 equiv) in the presence of

10 mol% of CuCN·2LiCl provides the corresponding products (**33b**,**c**) in 71–76% yield (Table 6, entries 1 and 2). The sensitive nitrile (**31b**) is efficiently zincated by $(Cy_2N)_2Zn·2LiCl$ (0.55 equiv) within 10 min at 60 °C. Subsequent quenching via Cu-catalyzed allylation or Pd-catalyzed *Negishi* cross-coupling affords the expected bicyclic products (**33d**–**f**) in 77–85% yield (entries 3–5). Alternative metalations of **31b** using *in situ* trapping zincations (TMPLi/$ZnCl_2$·2LiCl; $Cy_2NLi/ZnCl_2·2LiCl$) or a magnesiation with TMPMgCl·LiCl followed by a transmetalation with $ZnCl_2$ lead to decomposition.

4. Convenient *in situ* trapping functionalizations of *N,N*-disubstituted formamides using LDA in the presence of electrophiles in a continuous flow

4.1 Introduction

The carbonyl group displays a major functionality in organic chemistry and its potential use as anionic reagent for synthetic applications has been extensively studied.[88,89] However, the high reactivity of carbonyl anions complicates their direct use and alternative strategies like an umpolung of reactivity by *Corey* and *Seebach* have been developed.[90] In this approach, aldehydes or acetals are converted to the corresponding 1,3-dithianes, lithiated with *n*-BuLi and trapped with various electrophiles. Despite their synthetic value as acyl anion equivalents, the preparation of such reagents suffers from tedious protection-deprotection steps and a poor atom economy.[91]

Compared to aldehydes, formamides display more suitable reactants for the formation of anionic intermediates due to their higher stability and broader applicability in organic synthesis.[88g] In 1967, the first preparation of a carbamoyllithium species via a mercury-lithium exchange of bis(diethylcarbamoyl)mercury and *n*-butyllithium has been reported by *Schöllkopf* and *Gerhart*.[92] The generated diethylcarbamoyllithium intermediate was stable at -78 °C and could be reacted with numerous electrophiles. However, the use of toxic mercury as well as the need of cryogenic temperatures exhibit major drawbacks for broader synthetic applications, which could also not be completely overcome by alternative strategies like reductive lithiations[93] of carbamoyl chlorides or directed metalations[94] of formamides.

Recently, *Yoshida* and co-workers established a flow protocol for the rapid formation of carbamoyllithium compounds from the corresponding carbamoyl chlorides via a reductive metal insertion with lithium naphtalenide.[95] Despite the short reaction times and the successful synthesis of synthetically valuable products like functionalized α-ketoamides, the

[88] for reviews, see: a) D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 639. b) D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **1974**, *7*, 147. c) O. W. Lever, *Tetrahedron* **1976**, *32*, 1943. d) B. T. Gröbel, D. Seebach, *Synthesis* **1977**, 357. e) D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239. f) S. F. Martin, *Synthesis* **1979**, 633. g) C. Nájera, M. Yus, *Org. Prep. Proc. Int.* **1995**, *27*, 383.

[89] 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. c) C. S. Shiner, A. H. Berks, A. M. Fisher, *J. Am. Chem. Soc.* **1988**, *110*, 957.

[90] a) E. J. Corey, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075. b) E. J. Corey, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1077. c) D. Seebach, E. J. Corey, A. K. Beck, *Chem. Ber.* **1974**, *107*, 367. d) D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 231.

[91] a) B. M. Trost, *Science* **1991**, *254*, 1471. b) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40.

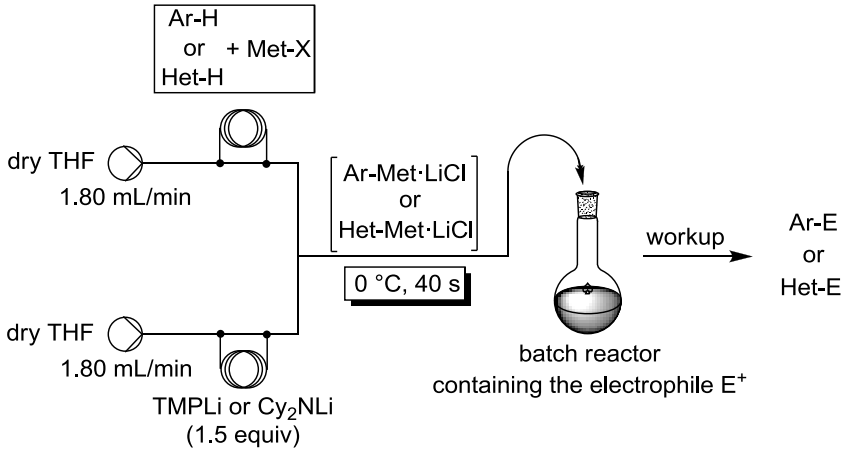
[92] U. Schöllkopf, F. Gerhart, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 805.

[93] a) D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1993**, *34*, 7115. b) D. J. Ramón, M. Yus, *Tetrahedron* **1996**, *52*, 13739.

[94] a) B. Bánhidai, U. Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 836. b) R. F. Cunico, J. Chen, *Synth. Commun.* **2003**, *33*, 1963.

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

method still requires low temperatures (-78 °C) and the use of expensive starting materials. As part of this work, an *in situ* trapping procedure for the metalation of various aromatic and heteroaromatic substrates (Ar-H, Het-H) in the presence of metal salts (Met-X) using either TMPLi or Cy_2NLi has been established (see chapter B.1 and B.2). Running the reactions in a continuous flow system allows the completion of these *in situ* trapping metalations within 40 s at 0 °C due to the fast mixing of the reaction components and the prevention of hot-spot formation (Scheme 34).



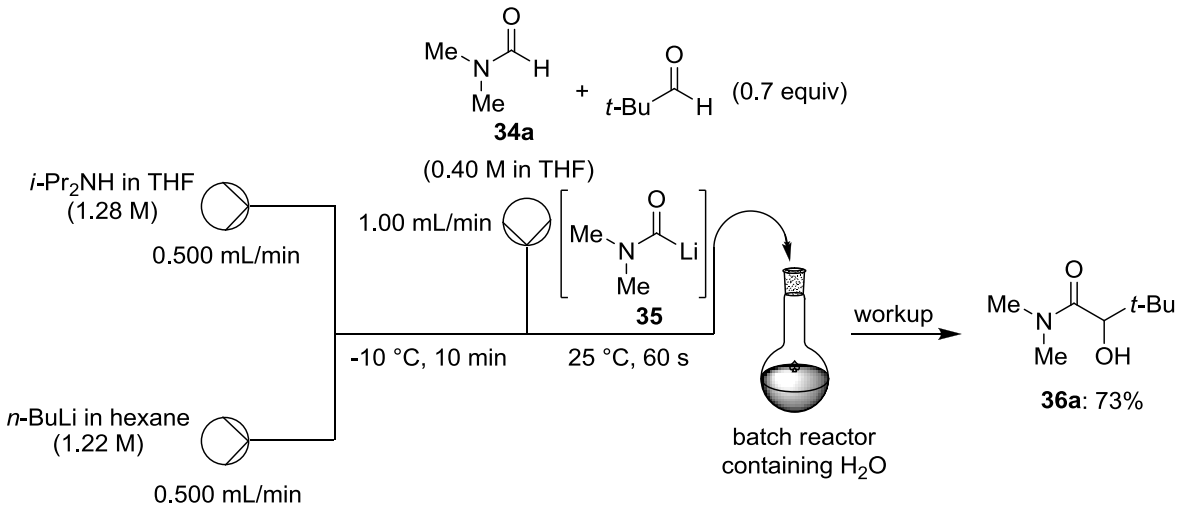
Scheme 34: Continuous flow set-up for *in situ* trapping metalations using TMPLi or Cy_2NLi in the presence of metal salts (Met-X = $ZnCl_2$·2LiCl, $MgCl_2$, CuCN·2LiCl, $LaCl_3$·2LiCl) and subsequent batch quenching with electrophiles (E^+).

Concerning the advantages of our newly developed method, we envisioned a continuous flow *in situ* trapping approach for the metalation of *N*,*N*-disubstituted formamides in the presence of electrophiles. Considering the lower price and simple preparation[96] of formamides compared to the corresponding carbamoyl chlorides, their use in synthesis is highly desirable. Moreover, the immediate trapping of the carbamoyllithium intermediates offers the chance of more convenient reaction conditions.

4.2 Functionalizations of *N*,*N*-disubstituted formamides

In a first experiment, the *in situ* trapping functionalization of *N*,*N*-dimethylformamide (**34a**) was investigated in a continuous flow system (Scheme 35).[97] Due to technical limitations, the metalating base LDA (1.5 equiv) had to be prepared *in flow*[98] from *n*-BuLi and *i*-Pr_2NH

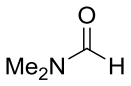
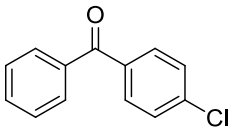
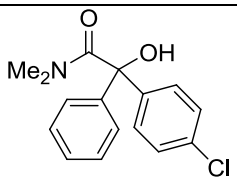
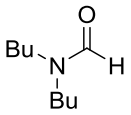
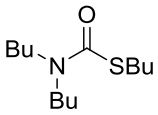
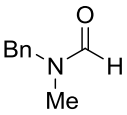
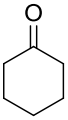
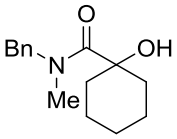
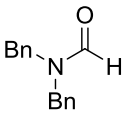
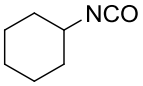
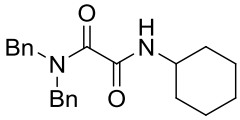
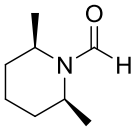
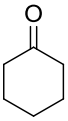
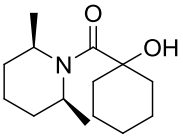
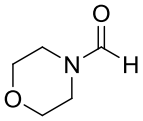
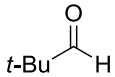
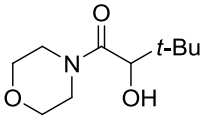
[96] for the preparation of formamides from amines, see: C. J. Gerack, L. McElwee-White, *Molecules* **2014**, *19*, 7689.
[97] flow reactions were performed with commercially available equipment from Vapourtec Ltd. (E-series easy-Medchem; http://www.vapourtec.com).
[98] Conditions for the preparation of LDA and the set-up *in flow* were established by Maximilian A. Ganiek.

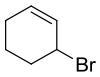
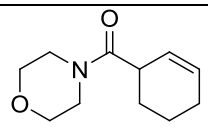
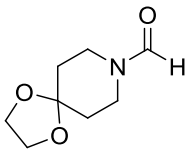
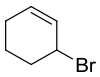
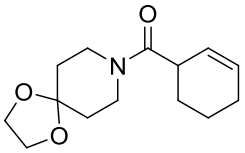


Scheme 35: Continuous flow set-up for the *in situ* trapping metalation of dimethylformamide (**34a**) using LDA in the presence of trimethylacetaldehyde.

within 10 min at -10 °C. Then, the stream was combined with a solution of **34a** and trimethylacetaldehyde (0.7 equiv) and submitted to the flow functionalization within 60 s at 25 °C. The generated dimethylcarbamoyllithium intermediate (**35**) was *in situ* quenched with the electrophile affording the corresponding alcohol (**36a**) in 73% yield. Further reaction of **35** with 4-chlorobenzophenone (0.7 equiv) leads to the formation of the expected product (**36b**) in 79% yield (Table 7, entry 1). Reactions of carbamoyllithium species were not limited to additions to aldehydes or ketones. In fact, *N*,*N*-dibutylformamide (**34b**) was successfully metalated with LDA (1.5 equiv) within 60 s at 25 °C in the presence of dibutyl disulfide (0.7 equiv) resulting in the thiocarbamate (**36c**) in 88% yield (entry 2). Interestingly, no addition of LDA to dibutyl disulfide was observed. Remarkable electrophiles could be used for such *in situ* trapping functionalizations. Cyclohexanone is notoriously prone to enolization when treated with bases due to its acidic α-hydrogens. However, the continuously processed reaction with LDA and *N*-benzyl-*N*-methylformamide (**34c**) affords after 60 s at 25 °C the desired tertiary alcohol (**36d**) in 63% yield (entry 3). *N*,*N*-Dibenzylformamide (**34d**) reacts under the same conditions (25 °C, 60 s) with cyclohexyl isocyanate (0.7 equiv) to the corresponding product (**36e**) in 54% yield (entry 4) and the *in situ* trapping functionalization of the cyclic formamide (**34e**) and cyclohexanone (0.7 equiv) gives the expected alcohol (**36f**) in 72% yield (entry 5). 4-Formylmorpholine (**34f**) could not only be reacted with LDA and trimethylacetaldehyde (0.7 equiv) to afford the desired product (**36g**) in 64% yield after 60 s at 25 °C (entry 6). Moreover, a Cu-catalyzed allylation of the lithiated intermediate with 3-

Table 7. Continuous flow trapping-functionalization of formamides **34** leading to products **36**.

Entry	Substrate	Electrophile	Product[a]
			
1	**34a**		**36b**: 79%
			
2	**34b**	Bu_2S_2	**36c**: 88%
			
3	**34c**		**36d**: 63%
			
4	**34d**		**36e**: 54%
			
5	**34e**		**36f**: 72%
			
6	**34f**		**36g**: 64%

Entry	Substrate	Electrophile	Product[a]
7	**34f**		 **36h**: 60%[b]
8	 **34g**		 **36i**: 54%[b]

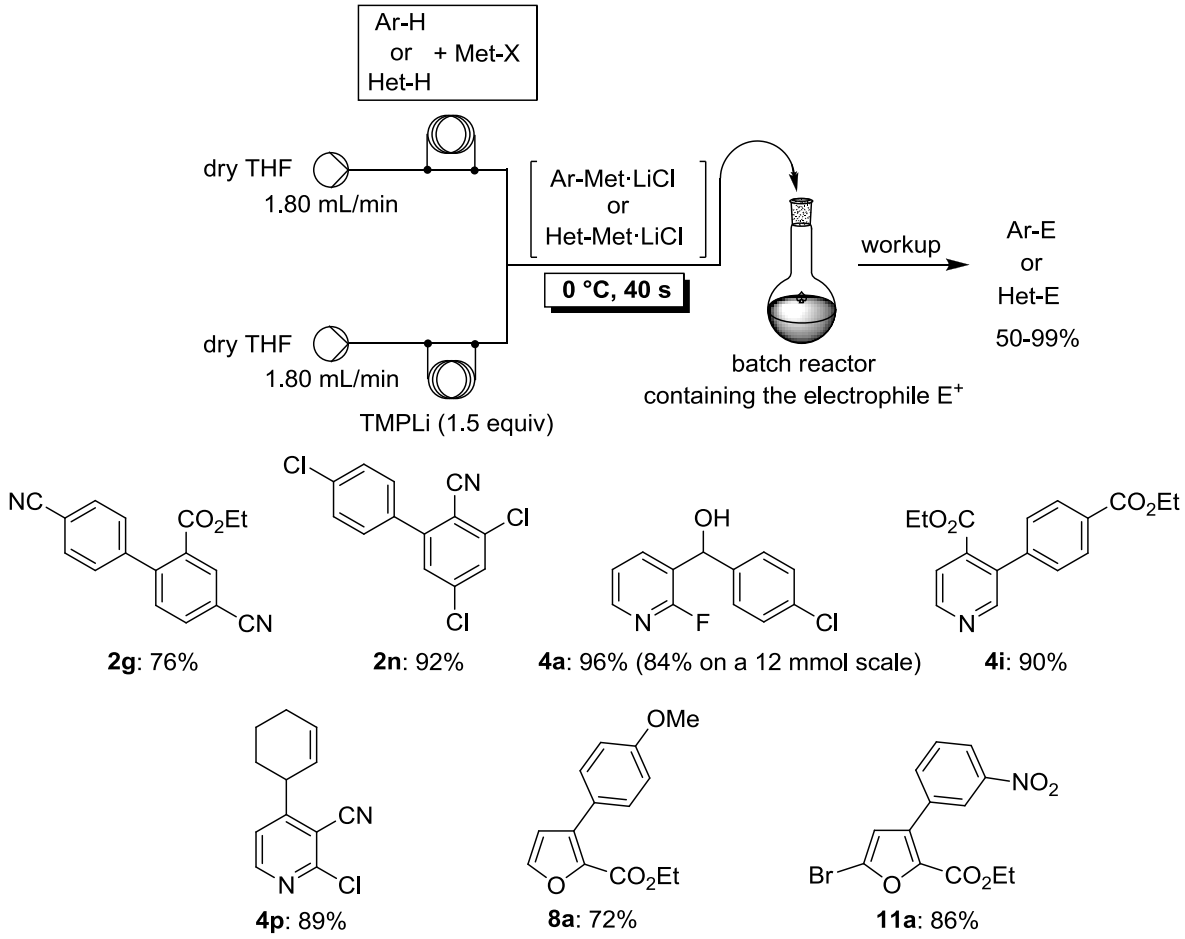
[a] Yield of isolated product. [b] Obtained by a Cu-catalyzed allylation.

bromocyclohexene (0.7 equiv) results in the formation of the corresponding amide (**36h**) in 60% yield (entry 7). Similarly, the acetal-protected formamide (**34g**) affords after lithiation with LDA in the presence of 10 mol% CuCN·2LiCl and 3-bromocyclohexene (0.7 equiv) the allylated product (**36i**) in 54% yield (entry 8).

5. Summary

5.1 Practical continuous flow trapping metalations of functionalized arenes and heteroarenes using TMPLi in the presence of Mg, Zn, Cu, or La halides

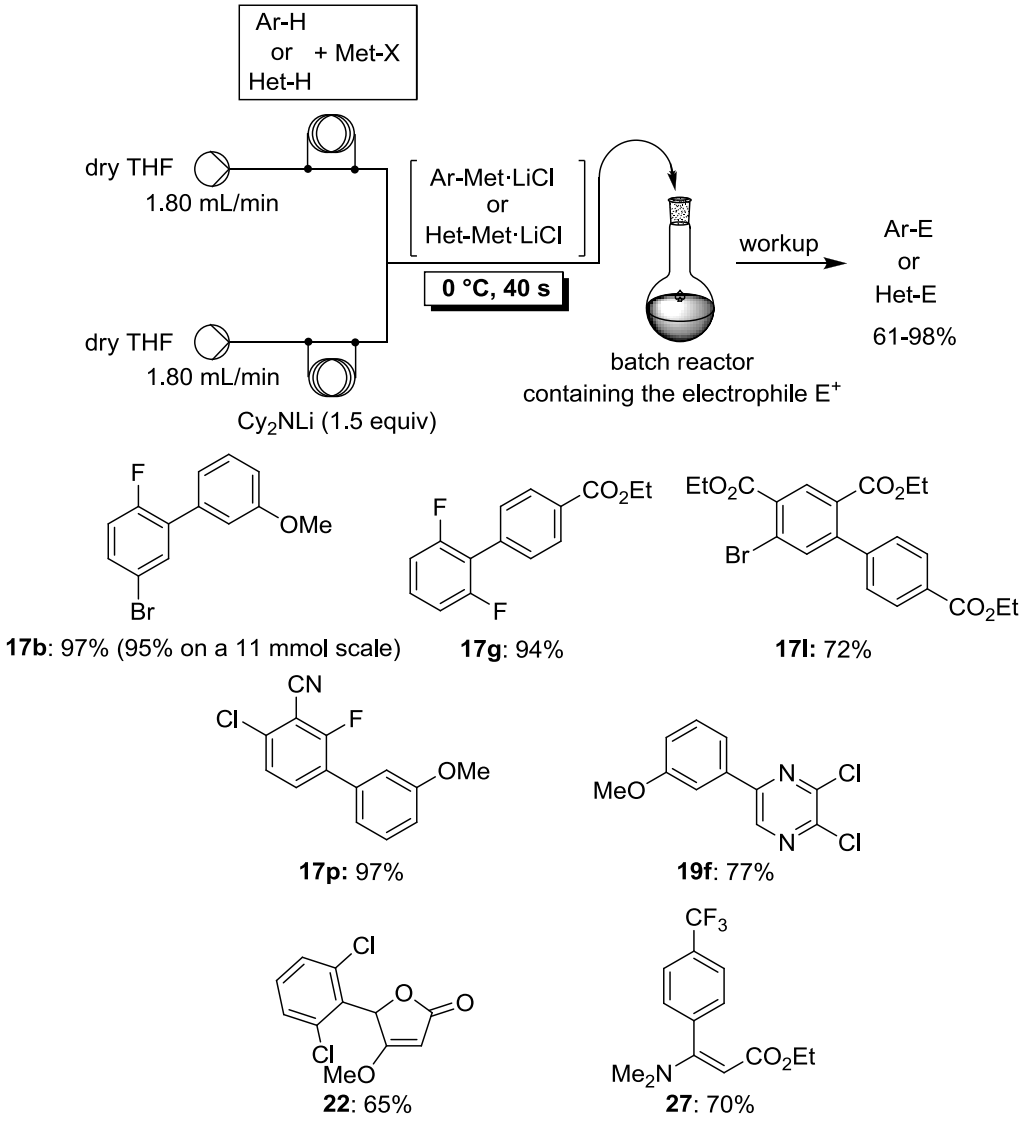
In summary, it has been shown that the flow metalation of arenes and heteroarenes with TMPLi involving an *in situ* trapping with various metal salts ($ZnCl_2$·2LiCl, $MgCl_2$, CuCN·2LiCl, $LaCl_3$·2LiCl) proceeds under very convenient conditions (0 °C, 40 s; Scheme 36). The resulting Mg, Zn, Cu, or La organic species are trapped with various electrophiles in high yields. In several cases, unusual kinetically controlled regioselectivities are obtained. All these flow metalations are scaled-up simply by extending the reaction time and no special optimization is required. The reaction scope of these flow *in situ* trapping metalations is considerably broader than that of the batch procedures.



Scheme 36: Continuous flow *in situ* trapping metalations of functionalized arenes and heteroarenes using TMPLi in the presence of metal salts (Met-X = $ZnCl_2$·2LiCl, $MgCl_2$, CuCN·2LiCl, $LaCl_3$·2LiCl).

5.2 Practical and economic lithiations of functionalized arenes and heteroarenes using Cy_2NLi in the presence of Mg, Zn or La halides in a continuous flow

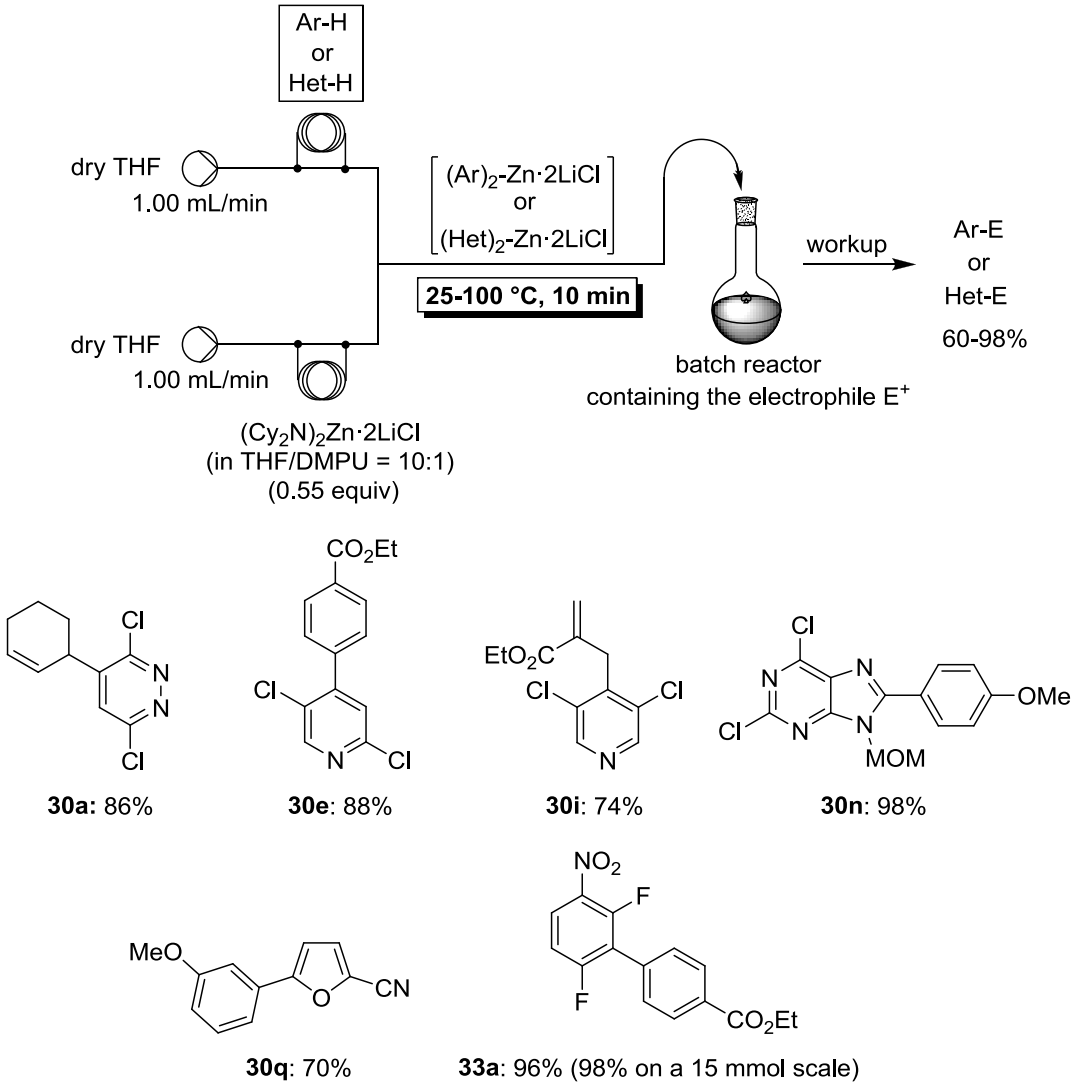
In summary, the economic amide base lithium dicyclohexylamide (Cy_2NLi) undergoes fast and convenient (40 s, 0 °C; Scheme 37) *in situ* trapping flow metalations of a broad range of functionalized arenes, heteroarenes and acrylate derivatives in the presence of various metal salts ($ZnCl_2 \cdot 2LiCl$, $MgCl_2$, $LaCl_3 \cdot 2LiCl$). The resulting Zn-, Mg- or La-organometallic intermediates are trapped with numerous electrophiles in high yields. These flow-metalations are easily scaled-up without further optimization simply by running the reaction for a longer time.



Scheme 37: Continuous flow *in situ* trapping metalations of functionalized arenes and heteroarenes using Cy_2NLi in the presence of metal salts (Met-X = $ZnCl_2 \cdot 2LiCl$, $MgCl_2$, $LaCl_3 \cdot 2LiCl$).

5.3 High temperature continuous flow zincations of functionalized arenes and heteroarenes using $(Cy_2N)_2Zn{\cdot}2LiCl$

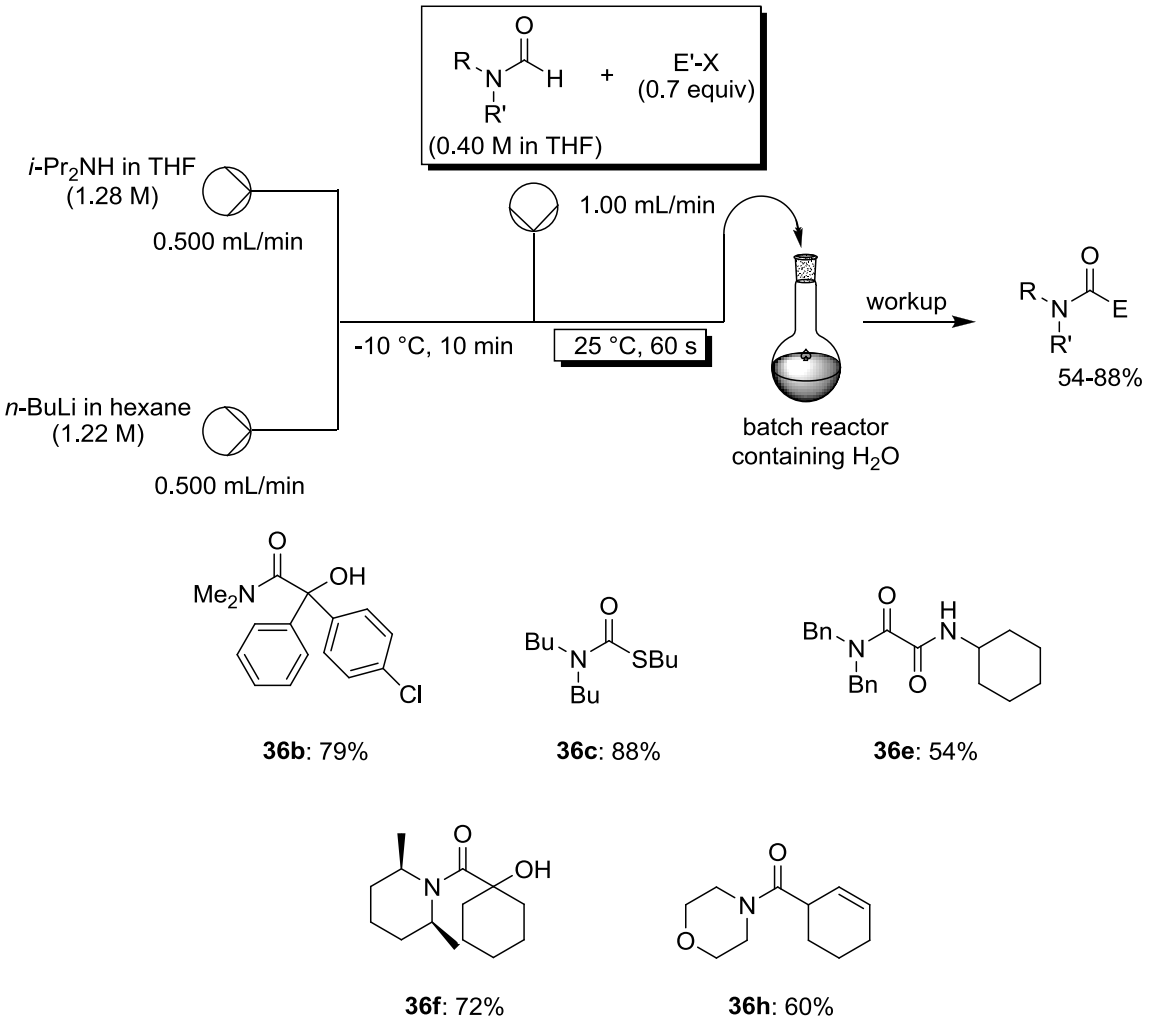
In summary, the use of the economic zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ (in THF/DMPU = 10:1) for fast (10 min) and highly efficient (0.55 equiv base) flow zincations of sensitive arenes and heteroarenes is reported (Scheme 38). Metalations between 60 and 100 °C, which are problematic under batch conditions, can be conveniently realized using flow methodology, and a simple scale-up of the zincations without further optimization can be readily achieved. Moreover, complementary metalation regioselectivities are obtained for several substituted pyridines, compared to commonly used LiCl-activated TMP-zinc and -magnesium bases.



Scheme 38: Continuous flow zincations of functionalized arenes and heteroarenes using $(Cy_2N)_2Zn{\cdot}2LiCl$.

5.4 Convenient *in situ* trapping functionalizations of *N*,*N*-disubstituted formamides using LDA in the presence of electrophiles in a continuous flow

In summary, the fast (60 s) and convenient (25 °C) continuous flow *in situ* trapping functionalization of various *N*,*N*-disubstituted formamides has been demonstrated (Scheme 39). By using LDA as metalating reagent and formamides as starting materials, this method is considerably more economical than previously reported procedures. Moreover, quenching the generated organolithium intermediates under flow conditions allows the reaction with sensitive electrophiles, offering a broad range of potential functionalities.



Scheme 39: Continuous flow *in situ* trapping metalations of *N*,*N*-disubstituted formamides using LDA in the presence of electrophiles.

C. Experimental part

1. General considerations

In situ trapping metalations with TMPLi or Cy_2NLi and metalations with $(Cy_2N)_2Zn{\cdot}2LiCl$ were carried out with a FlowSyn system purchased from Uniqsis. Metalations of *N*-substituted formamides were carried out with an E-series easy-Medchem system purchased from Vapourtec. *In situ* trapping metalations were performed in a coiled reactor and a tube (1.0 mm id; 2.0 and 0.4 mL) and reactant solutions were pre-cooled in 1.0 mL loops (1.0 mm id) made from PFA or PTFE Teflon. Metalations with $(Cy_2N)_2Zn{\cdot}2LiCl$ were performed in a coiled reactor and a tube (1.0 mm id; 20 and 0.4 mL) made from PFA, PTFE Teflon or stainless steel. The continuous flow preparation of LDA and the metalation of *N*-substituted formamides followed by *in situ* trapping reactions with electrophiles were performed in coiled reactors (1.0 mm id; 2.0 and 10 mL) made from PFA or PTFE Teflon. Carrier solvents as well as reactant solutions were stored under argon. Concerning *in situ* trapping metalations with TMPLi or Cy_2NLi and metalations with $(Cy_2N)_2Zn{\cdot}2LiCl$, reactions with electrophiles were carried out under batch conditions with magnetic stirring and in flame-dried glassware under argon. Syringes, which were used to transfer reagents and solvents, were purged with argon prior to use.

Solvents

Solvents were dried according to standard methods by distillation from drying agents as stated below and were stored under argon. Otherwise they were obtained from commercial sources and used without further purification.

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

DMPU was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Solvents for column chromatography were distilled prior to use.

Reagents

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

Cy_2NH was distilled prior to use and stored under argon.

***i*-Pr_2NH** was distilled prior to use and stored under argon.

TMPH was distilled prior to use and stored under argon.

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

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

$LaCl_3$·2LiCl solution (0.50 M in THF) was purchased from Rockwood Lithium.

$MgCl_2$ solution (0.50 M in THF) was prepared by suspending Mg turnings (2.55 g; 105 mmol) in dry THF (200 mL) in a flame-dried and argon flushed Schlenk flask. Then 1,2-dichloroethane (9.90 g; 100 mmol; 7.92 mL) was carefully added over 15 min and the reaction mixture was stirred overnight at 25 °C until gas evolution was complete.

$ZnCl_2$ solution (1.00 M in THF) was prepared by drying $ZnCl_2$ (27.3 g; 200 mmol) in a Schlenk flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (200 mL) was added and stirred until the salt was dissolved.

$ZnCl_2$·2LiCl solution (1.00 M in THF) was prepared by drying $ZnCl_2$ (27.3 g; 200 mmol) and LiCl (17.0 g; 400 mmol) in a Schlenk flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (200 mL) was added and stirred until the salts were dissolved.

Cy_2NLi solution in THF was prepared by slow addition of *n*-BuLi (8.2 mL; 20 mmol; 2.5 M in hexane) to a solution of Cy_2NH (3.7 g; 4.1 mL; 20 mmol) in THF (20 mL) at -40 °C and stirred for 30 min at -40 °C. The concentration was determined by titration against *N*-benzylbenzamide in THF.

TMPLi solution in THF was prepared by slow addition of *n*-BuLi (8.2 mL; 20 mmol; 2.5 M in hexane) to a solution of TMPH (2.9 g; 3.4 mL; 20 mmol) in THF (20 mL) at -40 °C and stirred for 30 min at -40 °C. The concentration was determined by titration against *N*-benzylbenzamide in THF.

$(Cy_2N)_2Zn$·2LiCl (solution in THF/DMPU = 10:1) was prepared by slow addition of *n*-BuLi (32.8 mL; 80 mmol; 2.5 M in hexane) to a solution of Cy_2NH (14.8 g; 16.4 mL; 80 mmol) in THF (80 mL) at -40 °C and slowly warmed to -20 °C within 30 min. $ZnCl_2$ (40 mL; 40 mmol; 1.00 M in THF) was added at -20 °C and the solution was slowly warmed to 25 °C within 2 h. All solvents were removed *in vacuo* and the remaining residue was dissolved under vigorous stirring in freshly distilled THF and 10 vol% DMPU until a clear solution was obtained. The

concentration was determined by titration against benzoic acid in THF using 4-(phenylazo)diphenylamine as indicator.

Chromatography

Flash column chromatography was performed using SiO_2 60 (0.040-0.063 mm, 230-400 mesh ASTM) from Merck.

Thin layer chromatography (TLC) was performed using aluminium plates covered with SiO_2 (Merck 60, F-254). Spots were visualized under UV light and/or by staining of the TLC plate with one of the solutions below, followed by heating with a heat gun:

- $KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g) in water (300 mL).
- Neat iodine absorbed on silica gel.
- Phosphor molybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12.0 mL) in water (230 mL).

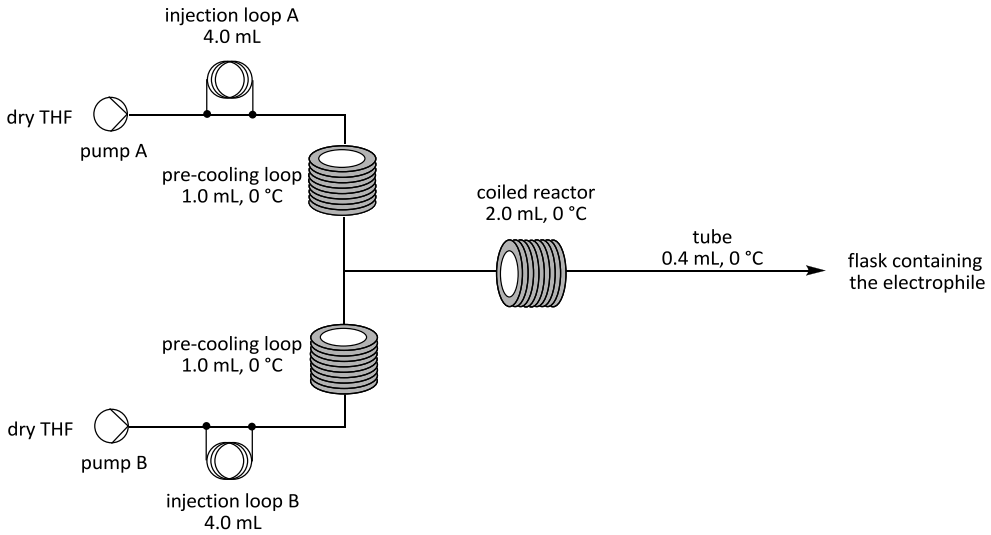
Analytical data

NMR spectra were recorded on *Bruker* ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δ_H: 7.26; δ_C: 77.16). For the observation of the observed signal multiplicities, the following abbreviations were used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quint (quintet), sext (sextet), m (multiplet) and br (broad). If not otherwise noted, the coupling constants given are H-H-coupling constants for proton signals and C-F-coupling constants for carbon signals. Melting points are uncorrected and were measured on a *Büchi* B.540 apparatus. Infrared spectra were recorded from 4000-400 cm^{-1} on a *Nicolet* 510 FT-IR or a *Perkin-Elmer* 281 IR spectrometer. Samples were measured neat (*Smiths Detection* DuraSampl *IR* II Diamond ATR). The absorption bands are reported in wavenumbers (cm^{-1}). Gas chromatography (GC) was performed with instruments of the type *Hewlett-Packard* 6890 or 5890 Series II, using a column of the type HP 5 (*Hewlett-Packard,* 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm, film thickness: 0.25 μm). The detection was accomplished using a flame ionization detector. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a *Finnigan* MAT95Q or *Finnigan* MAT90 instrument for electron impact ionization (EI) and electrospray ionization (ESI). For the combination of gas chromatography with mass spectroscopic detection, a GC-MS of the

type *Hewlett-Packard* 6890 / MSD 5793 networking was used (column: HP 5-MS, *Hewlett-Packard*; 5% phenylmethylpolysiloxane; length: 15 m, diameter 0.25 mm; film thickness: 0.25 μm).

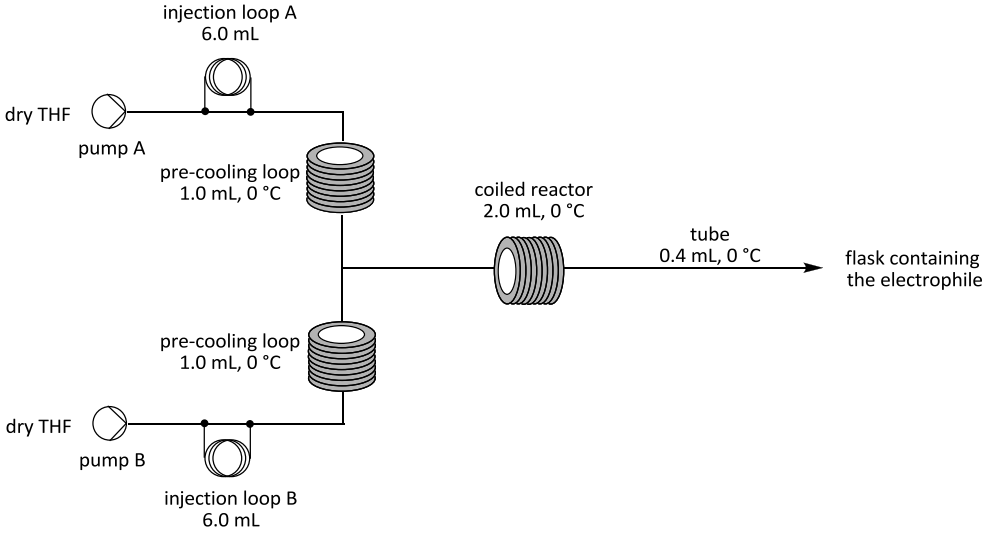
2. Typical procedures (TP)

Typical procedure for the *in situ* trapping metalation with TMPLi in flow followed by the reaction with an electrophile in batch (TP1):



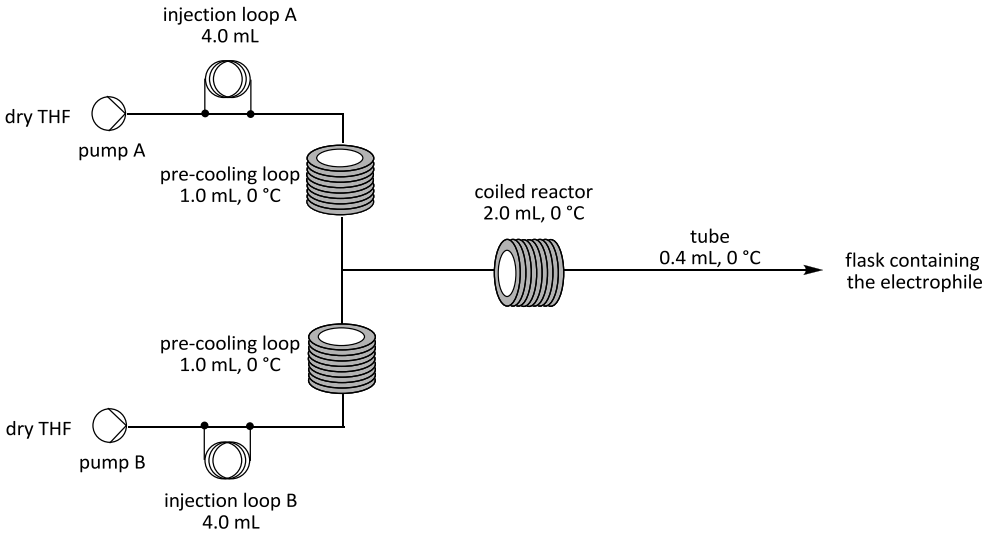
The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL/min; run-time: 30 min). Injection loop A (4.0 mL) was loaded with the reactant solution (0.40 – 0.42 M in dry THF containing 0.5 – 1.1 equiv metal salt additive; 5.0 mL) and injection loop B (4.0 mL) was loaded with TMPLi (0.59 – 0.64 M in dry THF; 1.5 equiv; 5.0 mL). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.80 mL/min), which passed a pre-cooling loop (1.0 mL; residence time: 33 s; 0 °C) respectively, before they were mixed in a coiled reactor followed by a tube (2.4 mL in total; residence time: 40 s; 0 °C). The combined streams were collected in a flame-dried, argon flushed 25 mL flask equipped with a magnetic stirrer and a septum containing the electrophile (0.7 – 6 equiv) dissolved in 2 mL dry THF. Then the reaction mixture was further stirred for the indicated time at the indicated temperature. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with concentrated aqueous NH_4Cl or $Na_2S_2O_3$ solutions and using undecane as an internal standard.

Typical procedure for the scale-up *in situ* trapping metalation with TMPLi in flow followed by the reaction with an electrophile in batch (TP2):



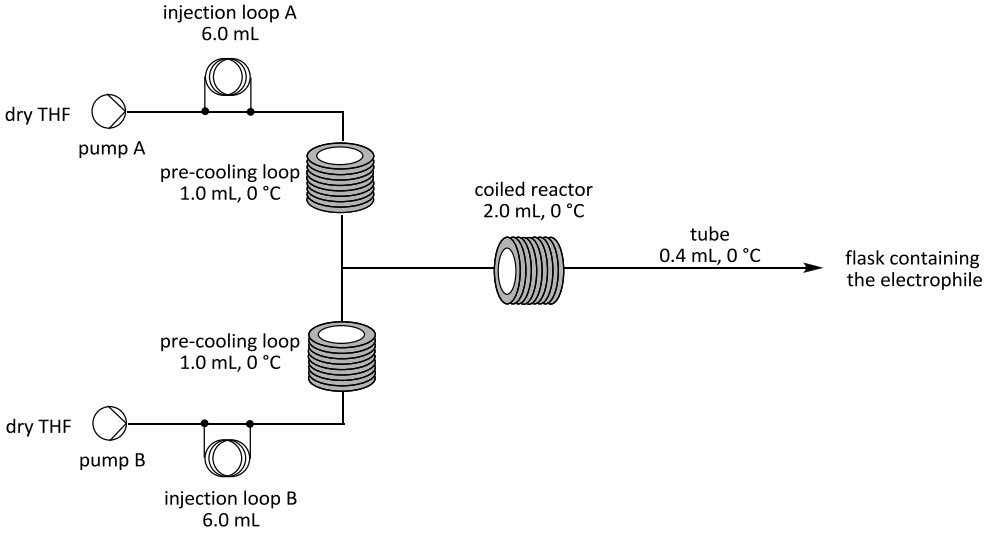
The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL/min; run-time: 30 min). Injection loop A (6.0 mL) was loaded with the reactant solution (0.40 – 0.43 M in dry THF containing 0.5 – 1.1 equiv metal salt additive; 7.0 mL) and injection loop B (6.0 mL) was loaded with TMPLi (0.61 – 0.64 M in dry THF; 1.5 equiv; 7.0 mL). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.80 mL/min), which passed a pre-cooling loop (1.0 mL; residence time: 33 s; 0 °C) respectively, before they were mixed in a coiled reactor followed by a tube (2.4 mL in total; residence time: 40 s; 0 °C). The combined streams were collected in a flame-dried, argon flushed 250 or 500 mL flask equipped with a magnetic stirrer and a septum containing the electrophile (0.8 – 2.0 equiv) dissolved in 20 mL dry THF. After 4.5 min, the injection loops were reloaded with the reactant solution and TMPLi, injected into the separate THF streams again and collected in the same flask as well. The number of reloads was depending on the desired reaction scale. Then the reaction mixture was further stirred for the indicated time at the indicated temperature. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with concentrated aqueous NH_4Cl or $Na_2S_2O_3$ solutions and using undecane as an internal standard.

Typical procedure for the *in situ* trapping metalation with Cy_2NLi in flow followed by the reaction with an electrophile in batch (TP3):



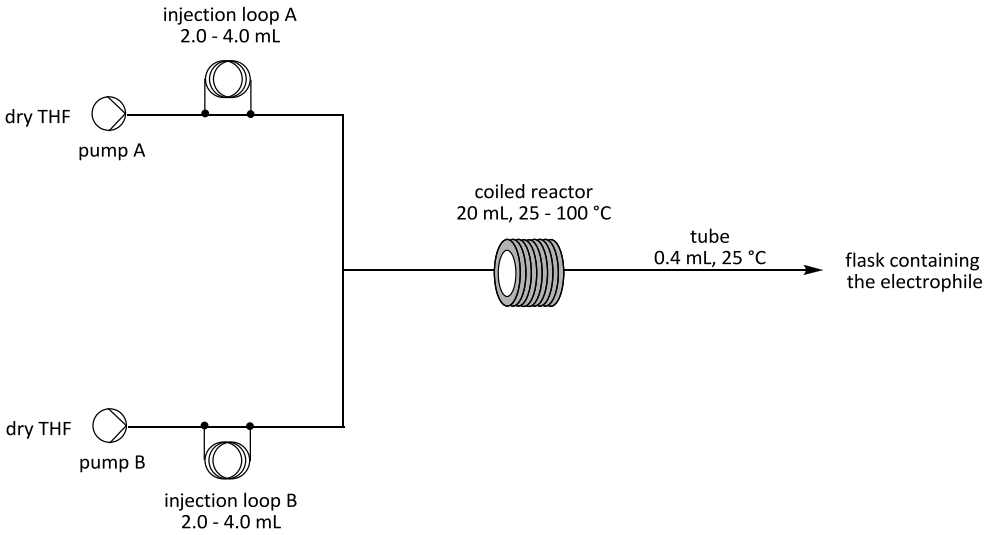
The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL/min; run-time: 30 min). Injection loop A (4.0 mL) was loaded with the reactant solution (0.43 – 0.45 M in dry THF containing 0.5 equiv metal salt additive; 5.0 mL) and injection loop B (4.0 mL) was loaded with Cy_2NLi (0.65 – 0.69 M in dry THF; 1.5 equiv; 5.0 mL). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.80 mL/min), which passed a pre-cooling loop (1.0 mL; residence time: 33 s; 0 °C) respectively, before they were mixed in a coiled reactor followed by a tube (2.4 mL in total; residence time: 40 s; 0 °C). The combined streams were collected in a flame-dried, argon flushed 25 mL flask equipped with a magnetic stirrer and a septum containing the electrophile (0.8 equiv) dissolved in dry THF (2 mL). Then the reaction mixture was further stirred for the indicated time at the indicated temperature. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with concentrated aqueous NH_4Cl solution and using undecane as an internal standard.

Typical procedure for the scale-up *in situ* trapping metalation with Cy_2NLi in flow followed by the reaction with an electrophile in batch (TP4):



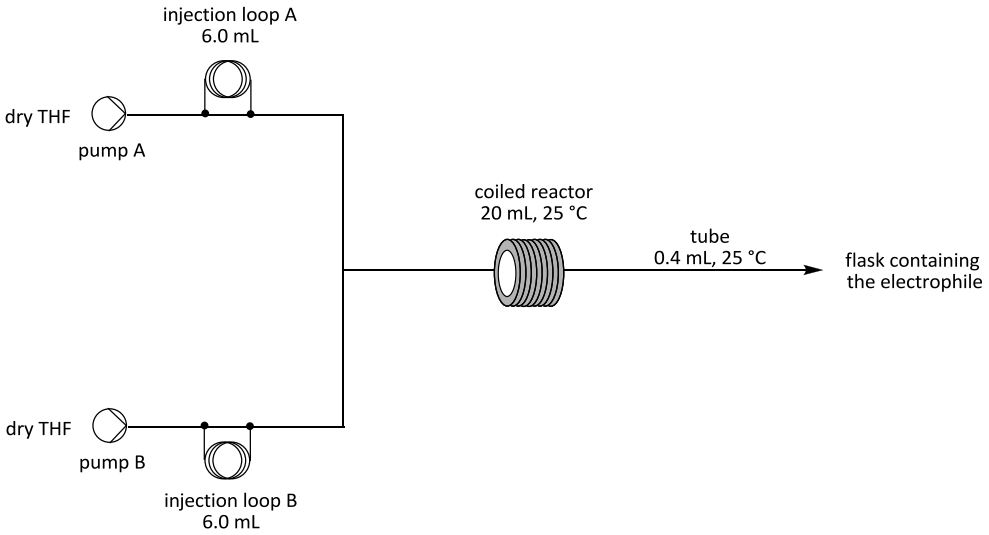
The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL/min; run-time: 30 min). Injection loop A (6.0 mL) was loaded with the reactant solution (0.45 M in dry THF containing 0.5 equiv metal salt additive; 7.0 mL) and injection loop B (6.0 mL) was loaded with Cy_2NLi (0.68 M in dry THF; 1.5 equiv; 7.0 mL). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.80 mL/min), which passed a pre-cooling loop (1.0 mL; residence time: 33 s; 0 °C) respectively, before they were mixed in a coiled reactor followed by a tube (2.4 mL in total; residence time: 40 s; 0 °C). The combined streams were collected in a flame-dried, argon flushed 250 mL flask equipped with a magnetic stirrer and a septum containing the electrophile (0.8 equiv) dissolved in dry THF (20 mL). After 4.5 min, the injection loops were reloaded with the reactant solution and Cy_2NLi, injected into the separate THF streams again and collected in the same flask as well. The number of reloads was depending on the desired reaction scale. Then the reaction mixture was further stirred for the indicated time at the indicated temperature. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with concentrated aqueous NH_4Cl solution and using undecane as an internal standard.

Typical procedure for the zincation in flow using $(Cy_2N)_2Zn{\cdot}2LiCl$ followed by the reaction with an electrophile in batch (TP5):



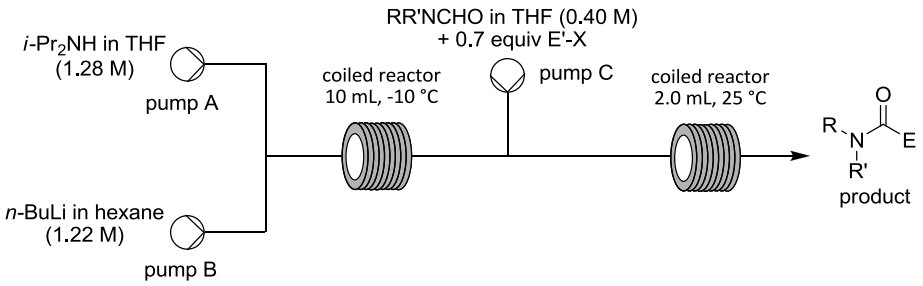
The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL/min; run-time: 30 min). Injection loop A (2.0 or 4.0 mL) was loaded with the reactant solution (0.36 – 0.78 M in dry THF; 3.0 or 5.0 mL) and injection loop B (2.0 or 4.0 mL) was loaded with $(Cy_2N)_2Zn{\cdot}2LiCl$ (0.20 – 0.43 M in dry THF + 10 vol% dry DMPU; 0.55 equiv; 3.0 or 5.0 mL). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.00 mL/min) respectively, before they were mixed in a coiled reactor followed by a tube (20.4 mL in total; residence time: 10 min; 25 - 100 °C). The combined streams were collected in a flame-dried, argon flushed 25 mL flask equipped with a magnetic stirrer and a septum containing the electrophile (0.8 equiv) dissolved in dry THF (2 mL). Then the reaction mixture was further stirred for the indicated time at the indicated temperature. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with concentrated aqueous NH_4Cl solution and using undecane as an internal standard.

Typical procedure for the scale-up zincation in flow using $(Cy_2N)_2Zn{\cdot}2LiCl$ followed by the reaction with an electrophile in batch (TP6):



The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL/min; run-time: 30 min). Injection loop A (6.0 mL) was loaded with the reactant solution (0.49 M in dry THF; 7.0 mL) and injection loop B (6.0 mL) was loaded with $(Cy_2N)_2Zn{\cdot}2LiCl$ (0.27 M in dry THF + 10 vol% dry DMPU; 0.55 equiv; 7.0 mL). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.00 mL/min) respectively, before they were mixed in a coiled reactor followed by a tube (20.4 mL in total; residence time: 10 min; 25 °C). The combined streams were collected in a flame-dried, argon flushed 250 mL flask equipped with a magnetic stirrer and a septum containing the electrophile (0.8 equiv) dissolved in dry THF (20 mL). After 7 min, the injection loops were reloaded with the reactant solution and $(Cy_2N)_2Zn{\cdot}2LiCl$, injected into the separate THF streams again and collected in the same flask as well. The number of reloads was depending on the desired reaction scale. Then the reaction mixture was further stirred for the indicated time at the indicated temperature. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with concentrated aqueous NH_4Cl solution and using undecane as an internal standard.

Typical procedure for the one stream continuous flow functionalization of *N,N*-disubstituted formamides via metalation with LDA and subsequent reaction with an electrophile (TP7):

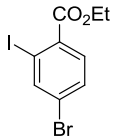


The flow system (Vapourtec E-series) was dried by flushing it with dry THF and dry hexane (flow rate of all pumps: 1.00 mL/min; run-time: 15 min). Solutions of *i*-Pr_2NH (1.28 M in THF; 4.0 mL) and *n*-BuLi (1.22 M in hexane; 4.0 mL) were pumped into the system (pump A and B; flow rates: 0.500 mL/min) and mixed in a coiled reactor (10 mL; residence time: 10 min; -10 °C). The combined stream of *in situ* prepared LDA (1.5 equiv) was mixed with a solution (pump C; flow rate: 1.00 mL/min) of the *N*-substituted formamide (0.40 M in THF; 5.0 mL) and the electrophile (E'-X; 0.7 equiv) followed by a coiled reactor (2.0 mL; residence time: 60 s; 25 °C). The crude product solution was collected in a flask containing water (20 mL) and the reaction progress was checked via GC analysis of reaction aliquots using undecane as an internal standard.

3. Preparation of products

3.1 Continuous flow *in situ* trapping metalations using TMPLi

Synthesis of ethyl 4-bromo-2-iodobenzoate (**2a**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 4-bromobenzoate (**1a**; 0.42 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.64 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (853 mg; 3.36 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (20 mL).

The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **2a** as a yellow oil (566 mg; 1.59 mmol; 95%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.12 (d, J = 1.9 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.49 (dd, J = 8.3 Hz, J = 1.9 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H).

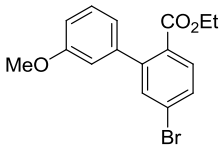
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.6, 143.4, 133.9, 131.8, 131.1, 126.4, 94.8, 61.9, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3081, 2979, 2934, 2902, 2364, 1721, 1567, 1544, 1457, 1388, 1365, 1279, 1242, 1171, 1145, 1105, 1082, 1025, 871, 852, 830, 786, 765, 729, 676.

MS (EI, 70 eV): m/z (%) = 356 (54), 355 (10, M^+), 354 (54), 328 (36), 326 (36), 312 (13), 311 (100), 310 (14), 309 (96), 283 (16), 281 (16), 156 (14), 154 (16), 75 (30), 74 (19).

HRMS (EI): calcd. for [$C_9H_8BrIO_2$]: 353.8752; found: 353.8748 (M^+).

Synthesis of ethyl 5-bromo-3'-methoxybiphenyl-2-carboxylate (**2b**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 4-bromobenzoate (**1a**; 0.42 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.64 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-iodoanisole (314 mg; 1.34 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **2b** as a yellow oil (348 mg; 1.04 mmol; 78%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.69 – 7.66 (m, 1H), 7.54 – 7.50 (m, 2H), 7.30 – 7.25 (m, 1H), 6.91 – 6.81 (m, 3H), 4.07 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H).

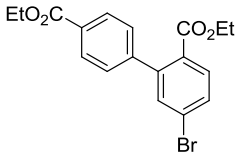
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.9, 159.4, 144.1, 141.5, 133.5, 131.2, 130.3, 130.2, 129.1, 125.5, 120.8, 113.8, 113.3, 61.1, 55.3, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2936, 2834, 1712, 1602, 1581, 1555, 1464, 1428, 1384, 1364, 1280, 1265, 1242, 1209, 1171, 1132, 1096, 1049, 1028, 995, 870, 830, 775, 746, 695.

MS (EI, 70 eV): m/z (%) = 337 (10), 336 (84), 335 (12, M^+), 334 (100), 292 (26), 290 (21), 289 (62), 262 (45), 259 (10), 246 (10), 211 (18), 210 (30), 182 (13), 167 (14), 152 (17), 139 (52).

HRMS (EI): calcd. for [$C_{16}H_{15}BrO_3$]: 334.0205; found: 334.0198 (M^+).

Synthesis of diethyl 5-bromobiphenyl-2,4'-dicarboxylate (**2c**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 4-bromobenzoate (**1a**; 0.42 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.64 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (370 mg; 1.34 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **2c** as a yellow oil (387 mg; 1.03 mmol; 77%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.05 (m, 2H), 7.74 (d, J = 8.3 Hz, 1H), 7.55 (dd, J = 8.3 Hz, J = 2.0 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.33 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H).

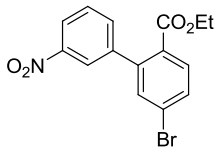
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.2, 166.3, 144.8, 143.5, 133.4, 131.7, 130.9, 129.7, 129.3, 128.3 125.9, 61.2, 61.0, 14.3, 13.7. (One signal not observed; possible coincidental isochronicity.)

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2936, 2905, 1711, 1610, 1585, 1553, 1464, 1445, 1407, 1385, 1366, 1267, 1241, 1178, 1132, 1096, 1029, 1013, 858, 834, 797, 771, 700, 667.

MS (EI, 70 eV): m/z (%) = 379 (15), 378 (68), 377 (18, M^+), 376 (62), 350 (11), 348 (11), 334 (18), 332 (21), 331 (100), 261 (37), 260 (13), 196 (10), 180 (24), 179 (10), 168 (19), 152 (37), 151 (37), 150 (31), 139 (11).

HRMS (EI): calcd. for [$C_{18}H_{17}BrO_4$]: 376.0310; found: 376.0317 (M^+).

Synthesis of ethyl 5-bromo-3'-nitrobiphenyl-2-carboxylate (**2d**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 4-bromobenzoate (**1a**; 0.42 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.64 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 1-iodo-3-nitrobenzene (334 mg; 1.34 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **2d** as a yellow solid (329 mg; 0.94 mmol; 70%).

m.p. (°C): 102.4 – 103.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.25 – 8.21 (m, 1H), 8.16 – 8.14 (m, 1H), 7.85 – 7.82 (m, 1H), 7.63 – 7.53 (m, 3H), 7.50 – 7.49 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 1.05 (t, J = 7.1 Hz, 3H).

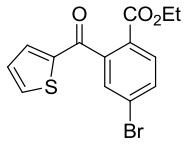
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 147.9, 142.2, 141.9, 134.5, 133.7, 132.1, 131.5, 129.2, 128.9, 126.4, 123.4, 122.5, 61.4, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3092, 2981, 2904, 1935, 1717, 1583, 1554, 1520, 1486, 1469, 1390, 1365, 1346, 1311, 1285, 1264, 1243, 1171, 1146, 1106, 1091, 1080, 1040, 1023, 932, 910, 891, 871, 851, 842, 808, 791, 777, 739, 711, 700, 680.

MS (EI, 70 eV): m/z (%) = 352 (10), 351 (56), 350 (9, M^+), 349 (58), 323 (30), 307 (19), 306 (100), 305 (24), 304 (92), 290 (26), 276 (26), 274 (27), 260 (27), 259 (26), 258 (25), 257 (17), 248 (11), 246 (13), 231 (20), 230 (15), 229 (17), 168 (23), 152 (25), 151 (73), 150 (73), 140 (14), 139 (34), 75 (14).

HRMS (EI): calcd. for [$C_{15}H_{12}BrNO_4$]: 348.9950; found: 348.9960 (M^+).

Synthesis of ethyl 4-bromo-2-(thiophene-2-carbonyl)benzoate (**2e**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 4-bromobenzoate (**1a**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 2-thiophenecarbonyl chloride (192 mg; 1.31 mmol; 0.8 equiv) and CuCN·2LiCl (1.6 mL; 1.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **2e** as an orange solid (242 mg; 0.71 mmol; 54%).

m.p. (°C): 90.1 – 91.6.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.91 – 7.88 (m, 1H), 7.70 – 7.66 (m, 2H), 7.58 – 7.57 (m, 1H), 7.27 – 7.25 (m, 1H), 7.07 – 7.04 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 1.09 (t, J = 7.1 Hz, 3H).

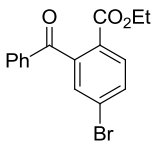
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 187.3, 165.2, 144.1, 142.5, 134.8, 134.6, 133.0, 131.9, 130.6, 128.2, 128.1, 127.1, 61.8, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3096, 2982, 1719, 1643, 1584, 1556, 1519, 1448, 1414, 1381, 1364, 1352, 1287, 1267, 1246, 1235, 1152, 1127, 1096, 1081, 1050, 1008, 924, 905, 881, 851, 786, 756, 740, 692, 677, 649, 585, 566.

MS (EI, 70 eV): m/z (%) = 340 (21), 339 (4, M^+), 338 (22), 296 (15), 295 (26), 294 (16), 293 (26), 229 (10), 187 (15), 158 (13), 111 (100).

HRMS (EI): calcd. for [$C_{14}H_{11}BrO_3S$]: 337.9612; found: 337.9610 (M^+).

Synthesis of ethyl 2-benzoyl-4-bromobenzoate (**2f**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 4-bromobenzoate (**1a**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After

injection and *in situ* trapping metalation the combined streams were collected in a flask containing benzoyl chloride (184 mg; 1.31 mmol; 0.8 equiv) and CuCN·2LiCl (1.6 mL; 1.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **2f** as an orange solid (229 mg; 0.69 mmol; 53%).

m.p. (°C): 89.1 – 90.5.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.93 – 7.90 (m, 1H), 7.75 – 7.72 (m, 2H), 7.69 – 7.66 (m, 1H), 7.58 – 7.50 (m, 2H), 7.45 – 7.39 (m, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.02 (t, *J* = 7.1 Hz, 3H).

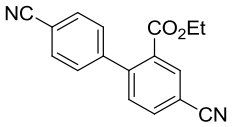
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 195.1, 165.1, 143.2, 136.6, 133.4, 132.7, 131.7, 130.6, 129.4, 128.6, 128.1, 127.4, 61.7, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2982, 2908, 1712, 1677, 1598, 1583, 1556, 1472, 1450, 1383, 1363, 1318, 1282, 1243, 1178, 1136, 1098, 1074, 1020, 965, 948, 898, 858, 842, 805, 778, 759, 712, 697, 689, 681, 641, 604.

MS (EI, 70 eV): m/z (%) = 334 (11), 333 (2, M^+), 332 (11), 289 (17), 287 (16), 257 (21), 255 (22), 229 (28), 227 (29), 152 (17), 105 (100), 77 (33).

HRMS (EI): calcd. for [$C_{16}H_{13}BrO_3$]: 332.0048; found: 332.0039 (M^+).

Synthesis of ethyl 4,4'-dicyanobiphenyl-2-carboxylate (**2g**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 3-cyanobenzoate (**1b**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.62 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzonitrile (263 mg; 1.15 mmol; 0.7 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 4 h at 25 °C before it was quenched with water (20 mL) and sat. aq. NH_4Cl (10 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash

column chromatography (silica gel; *i*-hexane:EtOAc = 4:1) afforded **2g** as a colorless solid (239 mg; 0.87 mmol; 76%).

m.p. (°C): 129.7 – 130.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.21 (d, J = 1.7 Hz, 1H), 7.82 (dd, J = 8.2 Hz, J = 1.9 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.08 (t, J = 7.1 Hz, 3H).

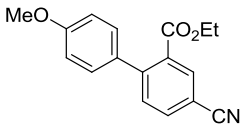
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.5, 145.1, 144.4, 134.6, 134.1, 132.0, 131.7, 131.4, 129.0, 118.4, 117.4, 112.7, 112.2, 61.9, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2854, 2224, 1725, 1604, 1482, 1412, 1400, 1364, 1314, 1295, 1245, 1188, 1142, 1116, 1100, 1016, 921, 868, 830, 791, 747, 628, 573, 566.

MS (EI, 70 eV): m/z (%) = 276 (33, M^+), 248 (25), 232 (19), 231 (100), 204 (10), 203 (18), 202 (14), 176 (23).

HRMS (EI): calcd. for [$C_{17}H_{12}N_2O_2$]: 276.0899; found: 276.0894 (M^+).

Synthesis of ethyl 4-cyano-4'-methoxybiphenyl-2-carboxylate (**2h**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 3-cyanobenzoate (**1b**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.62 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (269 mg; 1.15 mmol; 0.7 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 4 h at 25 °C before it was quenched with water (20 mL) and sat. aq. NH_4Cl (10 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1) afforded **2h** as a yellow oil (235 mg; 0.84 mmol; 73%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.04 (d, J = 1.8 Hz, 1H), 7.73 (dd, J = 8.0 Hz, J = 1.8 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H).

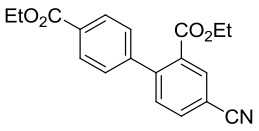
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.0, 159.9, 146.3, 134.0, 133.5, 132.4, 131.8, 131.5, 129.4, 118.0, 113.8, 110.8, 61.6, 55.3, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2938, 2839, 2231, 1716, 1607, 1578, 1552, 1519, 1482, 1464, 1443, 1419, 1406, 1389, 1366, 1289, 1239, 1178, 1145, 1112, 1087, 1035, 1016, 1000, 912, 850, 827, 792, 676, 631, 606, 571.

MS (EI, 70 eV): m/z (%) = 282 (21), 281 (100, M^+), 253 (23), 237 (13), 236 (66), 194 (10), 193 (19), 166 (10), 165 (20), 164 (25).

HRMS (EI): calcd. for [$C_{17}H_{15}NO_3$]: 281.1052; found: 281.1048 (M^+).

Synthesis of diethyl 4-cyanobiphenyl-2,4'-dicarboxylate (**2i**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 3-cyanobenzoate (**1b**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.62 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (317 mg; 1.15 mmol; 0.7 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 4 h at 25 °C before it was quenched with water (20 mL) and sat. aq. NH_4Cl (10 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1) afforded **2i** as a yellow solid (265 mg; 0.82 mmol; 71%).

m.p. (°C): 62.7 – 64.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.14 (d, J = 1.7 Hz, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.78 (dd, J = 8.0 Hz, J = 1.8 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H).

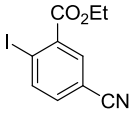
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.6, 166.1, 145.9, 144.1, 134.3, 133.8, 132.2, 131.5, 130.2, 129.5, 128.1, 117.6, 112.1, 69.2, 59.1, 21.3, 16.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 2936, 2233, 1713, 1606, 1573, 1476, 1447, 1403, 1367, 1272, 1243, 1187, 1146, 1100, 1024, 1005, 914, 865, 840, 791, 774, 739, 703, 675, 635, 612, 576.

MS (EI, 70 eV): m/z (%) = 324 (11), 323 (42, M^+), 295 (15), 279 (21), 278 (100), 267 (12), 250 (32), 206 (37), 178 (13), 177 (27), 176 (15), 166 (12), 151 (17), 150 (11), 89 (16), 75 (12), 43 (10).

HRMS (EI): calcd. for [$C_{19}H_{17}NO_4$]: 323.1158; found: 323.1152 (M^+).

Synthesis of ethyl 5-cyano-2-iodobenzoate (**2j**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 3-cyanobenzoate (**1b**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (833 mg; 3.28 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. NH_4Cl (10 mL) and sat. aq. $Na_2S_2O_3$ (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **2j** as a colorless solid (268 mg; 0.89 mmol; 54%).

m.p. (°C): 98.7 – 100.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.11 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.36 (dd, J = 8.2 Hz, J = 2.1 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H).

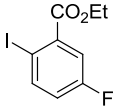
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.7, 142.5, 136.6, 134.5, 133.9, 117.3, 112.4, 100.2, 62.5, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2968, 2926, 2232, 1736, 1586, 1549, 1460, 1396, 1368, 1295, 1244, 1192, 1154, 1099, 1022, 969, 912, 866, 832, 778, 756, 676, 579, 567.

MS (EI, 70 eV): m/z (%) = 301 (63, M^+), 273 (86), 256 (100), 228 (17), 149 (51), 111 (12), 101 (29), 95 (30), 85 (19), 83 (22), 57 (24), 71 (29), 70 (15), 55 (29), 43 (27), 43 (30), 41 (28).

HRMS (EI): calcd. for [$C_{10}H_8INO_2$]: 300.9600; found: 300.9579 (M^+).

Synthesis of ethyl 5-fluoro-2-iodobenzoate (**2k**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 3-fluorobenzoate (**1c**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask

containing I_2 (812 mg; 3.20 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **2k** as a yellow oil (412 mg; 1.40 mmol; 88%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.53 – 7.50 (m, 1H), 7.37 – 7.30 (m, 1H), 7.18 – 7.12 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

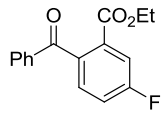
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.0 (d, *J* = 2.6 Hz), 162.0 (d, *J* = 245.1 Hz), 138.1 (d, *J* = 1.4 Hz), 129.7 (d, *J* = 8.2 Hz), 126.3 (d, *J* = 3.2 Hz), 117.9 (d, *J* = 25.4 Hz), 82.6 (d, *J* = 27.3 Hz), 62.0, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2360, 1725, 1566, 1458, 1427, 1392, 1367, 1286, 1265, 1247, 1181, 1140, 1113, 1086, 1065, 1020, 942, 862, 802, 754, 688, 579.

MS (EI, 70 eV): m/z (%) = 294 (56, M^+), 266 (26), 250 (13), 249 (100), 221 (24), 68 (11).

HRMS (EI): calcd. for [$C_9H_8FIO_2$]: 293.9553; found: 293.9549 (M^+).

Synthesis of ethyl 2-benzoyl-5-fluorobenzoate (**2l**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 3-fluorobenzoate (**1c**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing benzoyl chloride (180 mg; 1.28 mmol; 0.8 equiv) and CuCN·2LiCl (1.6 mL; 1.0 equiv) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1.5 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 15 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **2l** as a yellow oil (242 mg; 0.89 mmol; 70%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.10 – 8.08 (m, 1H), 7.74 – 7.73 (m, 2H), 7.56 – 7.53 (m, 1H), 7.43 – 7.41 (m, 2H), 7.22 – 7.20 (m, 1H), 7.07 – 7.05 (m, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.02 (t, *J* = 7.1 Hz, 3H).

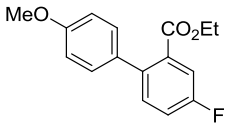
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 195.2, 165.7, 164.8 (d, J = 256.3 Hz), 144.4 (d, J = 6.9 Hz), 136.6, 133.4, 133.0 (d, J = 8.9 Hz), 129.3, 128.6, 125.3, 116.5 (d, J = 21.5 Hz), 115.1 (d, J = 23.5 Hz), 61.6, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 2984, 1717, 1674, 1606, 1597, 1581, 1489, 1476, 1450, 1410, 1391, 1367, 1274, 1213, 1176, 1114, 1080, 1016, 1002, 978, 933, 861, 837, 780, 698, 686, 650, 624, 616, 600.

MS (EI, 70 eV): m/z (%) = 272 (21, M^+), 228 (14), 227 (35), 199 (10), 195 (30), 170 (15), 167 (51), 105 (100), 77 (44), 42 (10).

HRMS (EI): calcd. for [$C_{16}H_{13}FO_3$]: 272.0849; found: 272.0847 (M^+).

Synthesis of ethyl 4-fluoro-4'-methoxybiphenyl-2-carboxylate (**2m**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 3-fluorobenzoate (**1c**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (300 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **2m** as a colorless oil (219 mg; 0.80 mmol; 63%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.64 – 7.61 (m, 1H), 7.41 – 7.24 (m, 3H), 6.95 – 6.85 (m, 3H), 4.06 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 0.98 (t, J = 7.1 Hz, 3H).

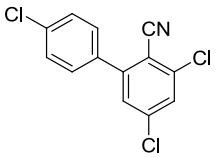
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.4 (d, J = 3.1 Hz), 159.6 (d, J = 246.3 Hz), 159.2, 135.4, 134.0 (d, J = 2.8 Hz), 128.9, 125.2 (d, J = 3.7 Hz), 121.8 (d, J = 1.1 Hz), 118.6 (d, J = 23.5 Hz), 114.9 (d, J = 1.1 Hz), 113.5, 61.1, 55.2, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2836, 1715, 1601, 1582, 1494, 1456, 1444, 1428, 1391, 1367, 1285, 1243, 1210, 1175, 1138, 1092, 1048, 1021, 952, 869, 856, 809, 782, 758, 741, 715, 697, 648, 567.

MS (EI, 70 eV): m/z (%) = 275 (17), 274 (100, M^+), 246 (10), 229 (67), 202 (75), 186 (28), 172 (13), 159 (11), 158 (16).

HRMS (EI): calcd. for [$C_{16}H_{15}FO_3$]: 274.1005; found: 274.1001 (M^+).

Synthesis of 3,4',5-trichlorobiphenyl-2-carbonitrile (**2n**)



According to **TP1**, injection loop A and B were loaded with solutions of 2,4-dichlorobenzonitrile (**1d**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.62 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 1-chloro-4-iodobenzene (312 mg; 1.31 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 1.5 h at 25 °C before it was quenched with water (15 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 40:1) afforded **2n** as a colorless solid (342 mg; 1.21 mmol; 92%).

m.p. (°C): 151.5 – 152.6.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 7.52 (d, J = 1.9 Hz, 1H), 7.47 – 7.43 (m, 4H), 7.36 (d, J = 2.0 Hz, 1H).

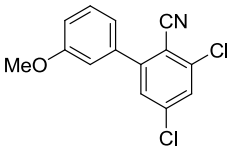
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 147.5, 139.6, 139.0, 136.1, 134.6, 129.9, 129.3, 128.8, 128.5, 114.8, 110.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 2230, 1734, 1596, 1580, 1543, 1494, 1435, 1407, 1387, 1290, 1194, 1105, 1092, 1056, 1014, 910, 868, 849, 829, 719, 706, 656, 635, 622, 586.

MS (EI, 70 eV): m/z (%) = 285 (35), 284 (15), 283 (93, M^+), 282 (14), 281 (100), 246 (20), 213 (18), 211 (52), 176 (10), 175 (17).

HRMS (EI): calcd. for [$C_{13}H_6Cl_3N$]: 280.9566; found: 280.9569 (M^+).

Synthesis of 3,5-dichloro-3'-methoxybiphenyl-2-carbonitrile (**2o**)



According to **TP1**, injection loop A and B were loaded with solutions of 2,4-dichlorobenzonitrile (**1d**; 0.40 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-iodoanisole (300 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 3 h at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **2o** as a colorless solid (294 mg; 1.06 mmol; 83%).

m.p. (°C): 157.3 – 157.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.51 – 7.50 (m, 1H), 7.41 – 7.37 (m, 2H), 7.08 – 7.06 (m, 1H), 7.02 – 6.99 (m, 2H), 3.85 (s, 3H).

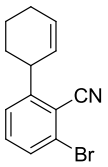
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.8, 148.7, 139.4, 138.9, 137.6, 130.1, 128.6, 128.6, 121.0, 115.5, 115.0, 114.2, 111.0, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 2970, 2229, 1739, 1600, 1575, 1548, 1495, 1470, 1426, 1388, 1327, 1301, 1258, 1229, 1200, 1181, 1162, 1108, 1088, 1071, 1028, 994, 911, 890, 865, 845, 781, 768, 740, 700, 668, 646, 612, 582, 565.

MS (EI, 70 eV): m/z (%) = 281 (11), 280 (12), 279 (67), 278 (23, M^+), 277 (100), 250 (23), 248 (31), 247 (16), 212 (12), 211 (14), 208 (10), 198 (14), 177 (21), 164 (38).

HRMS (EI): calcd. for [$C_{14}H_9Cl_2NO$]: 277.0061; found: 277.0047 (M^+).

Synthesis of 2-bromo-6-(cyclohex-2-enyl)benzonitrile (**2p**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-bromobenzonitrile (**1e**; 0.40 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (206 mg; 1.28 mmol; 0.8 equiv) and $CuCN \cdot 2LiCl$ (0.16 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous

Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1) afforded **2p** as a colorless oil (293 mg; 1.12 mmol; 88%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.49 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.29 (dd, J = 7.9 Hz, J = 1.4 Hz, 1H), 6.02 – 5.95 (m, 1H), 5.61 – 5.55 (m, 1H), 3.89 – 3.83 (m, 1H), 2.16 – 2.05 (m, 3H), 1.74 – 1.57 (m, 2H), 1.55 – 1.43 (m, 1H).

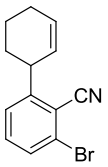
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.2, 133.3, 130.6, 130.4, 127.5, 126.9, 125.8, 116.2, 115.4, 40.6, 31.3, 24.7, 20.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 3022, 2931, 2859, 2836, 2228, 1699, 1650, 1587, 1557, 1448, 1433, 1344, 1308, 1251, 1237, 1224, 1202, 1155, 1137, 1125, 1069, 1058, 1042, 986, 936, 912, 896, 883, 854, 839, 799, 783, 740, 723, 703, 693.

MS (EI, 70 eV): m/z (%) = 263 (75), 262 (100, M^+), 261 (76), 260 (82), 246 (25), 245 (18), 182 (29), 181 (20), 180 (19), 167 (37), 166 (24), 165 (60), 154 (91), 153 (33), 141 (44), 140 (26), 128 (24), 127 (40), 115 (18), 77 (20).

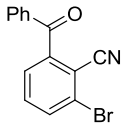
HRMS (EI): calcd. for [$C_{13}H_{11}BrN$]: 260.0075; found: 260.0074 (M^+ - H).

Scale-up synthesis of 2-bromo-6-(cyclohex-2-enyl)benzonitrile (**2p**)



According to **TP2**, injection loop A and B were loaded with solutions of 2-bromobenzonitrile (**1e**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (1.27 g; 7.87 mmol; 0.8 equiv) and CuCN·2LiCl (0.99 mL; 10 mol%) dissolved in THF (20 mL) and cooled to 0 °C. The injection loops were reloaded three times and the reaction mixture was stirred for further 1 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 50 mL). The aq. layer was extracted with EtOAc (3×200 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1) afforded **2p** as a colorless oil (1.79 g; 6.83 mmol; 87%).

Synthesis of 2-benzoyl-6-bromobenzonitrile (**2q**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-bromobenzonitrile (**1e**; 0.40 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing benzoyl chloride (180 mg; 1.28 mmol; 0.8 equiv) and CuCN·2LiCl (1.6 mL; 1.0 equiv) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C and overnight at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 15 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1) afforded **2q** as a yellow solid (266 mg; 0.93 mmol; 73%).

m.p. (°C): 113.8 – 115.2.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.88 – 7.82 (m, 1H), 7.79 – 7.76 (m, 2H), 7.66 – 7.61 (m, 1H), 7.56 – 7.45 (m, 4H).

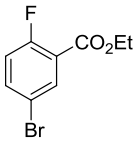
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 192.7, 144.3, 135.4, 135.1, 134.3, 132.9, 130.4, 128.8, 128.0, 127.6, 115.2, 114.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2854, 2231, 1732, 1661, 1593, 1582, 1554, 1448, 1427, 1312, 1269, 1209, 1180, 1157, 1122, 1073, 1000, 974, 951, 814, 783, 753, 730, 700, 683, 652, 605, 572.

MS (EI, 70 eV): m/z (%) = 286 (1, M^+), 206 (45), 105 (100), 77 (48), 51 (29), 50 (10).

HRMS (EI): calcd. for [$C_{14}H_8BrNO$]: 284.9789; found: 284.9795 (M^+).

Synthesis of ethyl 5-bromo-2-fluorobenzoate (**2r**)



According to **TP1**, injection loop A and B were loaded with solutions of 1-bromo-4-fluorobenzene (**1f**; 0.41 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl cyanoformate (244 mg; 2.46 mmol; 1.5 equiv) dissolved in THF (2 mL). The reaction

mixture was stirred for further 30 min at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **2r** as a yellow oil (339 mg; 1.37 mmol; 84%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.01 – 7.98 (m, 1H), 7.58 – 7.53 (m, 1H), 7.02 – 6.96 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

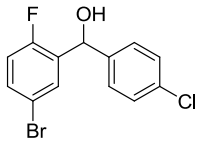
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.9 (d, *J* = 3.8 Hz), 160.9 (d, *J* = 261.1 Hz), 137.0 (d, *J* = 9.1 Hz), 134.6 (d, *J* = 0.8 Hz), 120.7 (d, *J* = 11.3 Hz), 118.8 (d, *J* = 24.1 Hz), 116.3 (d, *J* = 3.8 Hz), 61.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3105, 2983, 2939, 2907, 2874, 1732, 1716, 1606, 1578, 1479, 1446, 1405, 1390, 1366, 1292, 1268, 1239, 1173, 1137, 1091, 1076, 1016, 950, 890, 862, 820, 779, 694, 670, 622.

MS (EI, 70 eV): m/z (%) = 248 (24), 246 (21), 220 (42), 218 (38), 203 (94), 201 (100), 175 (23), 173 (22), 167 (21), 111 (17), 97 (22), 95 (16), 93 (15), 85 (18), 83 (24), 81 (20), 71 (28), 69 (37), 57 (45), 56 (14), 55 (35), 45 (22), 44 (15), 43 (30), 43 (28), 41 (28).

HRMS (EI): calcd. for [$C_9H_8BrFO_2$]: 245.9692; found: 245.9689 (M^+).

Synthesis of (5-bromo-2-fluorophenyl)(4-chlorophenyl)methanol (**2s**)



According to **TP1**, injection loop A and B were loaded with solutions of 1-bromo-4-fluorobenzene (**1f**; 0.41 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-chlorobenzaldehyde (346 mg; 2.46 mmol; 1.5 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **2s** as a yellow solid (411 mg; 1.30 mmol; 79%).

m.p. (°C): 111.0 – 112.2.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.66 – 7.63 (m, 1H), 7.38 – 7.32 (m, 1H), 7.30 (s, 4H), 6.92 – 6.85 (m, 1H), 6.04 – 6.03 (m, 1H), 2.34 – 2.33 (m, 1H).

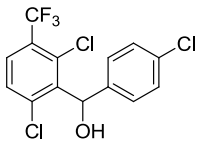
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.6 (d, J = 246.7 Hz), 140.5 (d, J = 0.8 Hz), 133.9, 132.7 (d, J = 14.3 Hz), 132.2 (d, J = 8.3 Hz), 130.3 (d, J = 3.8 Hz), 128.8, 127.7 (d, J = 0.8 Hz), 117.3 (d, J = 23.4 Hz), 117.2, 69.1 (d, J = 3.0 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3314, 2922, 1705, 1596, 1579, 1478, 1403, 1332, 1238, 1188, 1164, 1109, 1091, 1072, 1030, 1013, 943, 883, 813, 795, 760, 733, 624, 596, 566.

MS (EI, 70 eV): m/z (%) = 316 (41, M^+), 314 (33), 204 (14), 203 (100), 202 (12), 201 (95), 183 (27), 143 (13), 139 (66), 123 (14), 115 (11), 113 (38), 112 (46), 111 (19), 105 (13), 96 (26), 95 (19), 94 (27), 77 (79), 76 (16), 75 (42), 74 (12), 51 (19), 50 (20), 43 (13).

HRMS (EI): calcd. for [$C_{13}H_9BrClFO$]: 313.9509; found: 313.9500 (M^+).

Synthesis of (4-chlorophenyl)(2,6-dichloro-3-(trifluoromethyl)phenyl)methanol (**2t**)



According to **TP1**, injection loop A and B were loaded with solutions of 2,4-dichlorobenzotrifluoride (**1g**; 0.40 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-chlorobenzaldehyde (337 mg; 2.40 mmol; 1.5 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 40:1 → 10:1) afforded **2t** as a yellow oil (391 mg; 1.10 mmol; 69%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.20 – 7.17 (m, 2H), 6.71 (d, J = 10.3 Hz, 1H), 3.33 (d, J = 10.3 Hz, 1H).

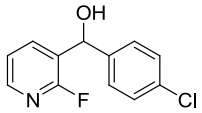
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 139.8, 139.2, 139.1, 133.7, 133.4, 129.3, 128.8 (q, J = 31.2 Hz), 128.7, 127.8 (q, J = 6.0 Hz), 126.7, 122.4 (q, J = 273.6 Hz), 71.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3417, 3087, 2929, 1904, 1586, 1568, 1491, 1454, 1388, 1314, 1255, 1176, 1144, 1115, 1090, 1038, 1013, 904, 858, 825, 775, 758, 721, 673, 617, 577, 569.

MS (EI, 70 eV): m/z (%) = 356 (32, M^+), 354 (25), 321 (31), 243 (59), 241 (100), 143 (14), 141 (15), 139 (21), 77 (10), 43 (29).

HRMS (EI): calcd. for [$C_{14}H_8Cl_3F_3O$]: 353.9593; found: 353.9579 (M^+).

Synthesis of (4-chlorophenyl)(2-fluoropyridin-3-yl)methanol (**4a**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.42 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-chlorobenzaldehyde (354 mg; 2.52 mmol; 1.5 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 2:1 + 0.5 vol% NEt_3) afforded **4a** as a colorless solid (382 mg; 1.61 mmol; 96%).

m.p. (°C): 111.8 – 113.3.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.00 – 7.90 (m, 2H), 7.26 (s, 4H), 7.17 – 7.13 (m, 1H), 5.96 (s, 1H), 3.47 (br, 1H).

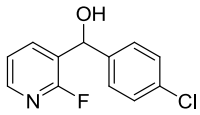
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2 (d, J = 239.5 Hz), 146.3 (d, J = 14.3 Hz), 140.4, 138.3 (d, J = 4.8 Hz), 133.8, 128.8, 127.8 (d, J = 1.1 Hz), 126.0 (d, J = 27.5 Hz), 121.8 (d, J = 4.5 Hz), 68.8 (d, J = 2.5 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3310, 2927, 1733, 1710, 1606, 1580, 1490, 1434, 1411, 1376, 1329, 1303, 1244, 1189, 1166, 1110, 1091, 1039, 1013, 947, 875, 829, 788, 758, 717, 693, 666.

MS (EI, 70 eV): m/z (%) = 239 (16), 237 (50, M^+), 202 (69), 185 (10), 184 (11), 154 (12), 139 (20), 126 (13), 125 (24), 124 (100), 113 (27), 112 (27), 111 (13), 106 (18), 98 (18), 97 (73), 96 (15), 78 (20), 77 (56), 75 (13), 57 (11), 51 (22).

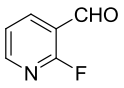
HRMS (EI): calcd. for [$C_{12}H_9ClFNO$]: 237.0357; found: 237.0351 (M^+).

Scale-up synthesis of (4-chlorophenyl)(2-fluoropyridin-3-yl)methanol (**4a**)



According to **TP2**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.40 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-chlorobenzaldehyde (2.53 g; 18.0 mmol; 1.5 equiv) dissolved in THF (20 mL). The injection loops were reloaded four times and the reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (200 mL). The aq. layer was extracted with EtOAc (3×300 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 2:1 + 0.5 vol% NEt_3) afforded **4a** as a colorless solid (2.41 g; 10.1 mmol; 84%).

Synthesis of 2-fluoronicotinaldehyde (**4b**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.42 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-formylmorpholine (387 mg; 3.36 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 4:1 + 0.5 vol% NEt_3) afforded **4b** as a colorless oil (105 mg; 0.84 mmol; 50%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.29 (s, 1H), 8.45 – 8.43 (m, 1H), 8.31 – 8.25 (m, 1H), 7.37 – 7.32 (m, 1H).

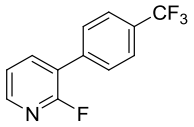
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 186.2, 163.9 (d, J = 248.5 Hz), 153.3 (d, J = 16.2 Hz), 139.5 (d, J = 2.9 Hz), 122.3 (d, J = 4.5 Hz), 118.5 (d, J = 22.2 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2922, 2853, 1705, 1601, 1575, 1462, 1435, 1392, 1377, 1294, 1272, 1246, 1204, 1174, 1095, 974, 891, 866, 802, 755, 722, 667.

MS (EI, 70 eV): m/z (%) = 126 (15), 125 (80, M^+), 96 (47), 85 (14), 70 (14), 69 (12), 43 (23), 43 (28).

HRMS (EI): calcd. for [C_6H_3FNO]: 124.0199; found: 124.0184 (M^+ - H).

Synthesis of 2-fluoro-3-(4-(trifluoromethyl)phenyl)pyridine (**4c**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzotrifluoride (348 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **4c** as a colorless solid (301 mg; 1.25 mmol; 98%).

m.p. (°C): 80.9 – 82.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.25 – 8.22 (m, 1H), 7.90 – 7.84 (m, 1H), 7.73 – 7.65 (m, 4H), 7.33 – 7.28 (m, 1H).

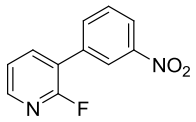
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.3 (d, J = 240.7 Hz), 147.3 (d, J = 14.9 Hz), 140.7 (d, J = 3.9 Hz), 137.5 (d, J = 5.1 Hz), 130.5 (q, J = 32.8 Hz), 129.2 (d, J = 3.3 Hz), 125.7 (q, J = 3.9 Hz), 122.5 (d, J = 28.1 Hz), 122.1, 122.0 (d, J = 4.5 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 2924, 2854, 1936, 1743, 1616, 1606, 1580, 1566, 1525, 1495, 1447, 1401, 1324, 1287, 1248, 1200, 1168, 1112, 1096, 1066, 1024, 1005, 986, 974, 956, 844, 832, 798, 780, 762, 740, 715.

MS (EI, 70 eV): m/z (%) = 241 (100, M^+), 222 (12), 172 (10).

HRMS (EI): calcd. for [$C_{12}H_7F_4N$]: 241.0515; found: 241.0507 (M^+).

Synthesis of 2-fluoro-3-(3-nitrophenyl)pyridine (**4d**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.40 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 1-iodo-3-nitrobenzene (319 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **4d** as a colorless solid (251 mg; 1.15 mmol; 90%).

m.p. (°C): 109.2 – 110.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.42 (s, 1H), 8.28 – 8.24 (m, 2H), 7.95 – 7.89 (m, 2H), 7.68 – 7.62 (m, 1H), 7.36 – 7.32 (m, 1H).

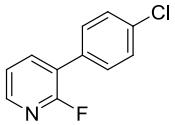
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2 (d, J = 240.7 Hz), 148.6, 147.7 (d, J = 15.2 Hz), 140.7 (d, J = 3.6 Hz), 135.6 (d, J = 5.3 Hz), 134.8 (d, J = 3.7 Hz), 129.8, 123.7 (d, J = 3.1 Hz), 123.3, 122.2 (d, J = 4.5 Hz), 121.5 (d, J = 28.0 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3096, 3067, 3034, 2927, 2856, 1986, 1931, 1806, 1749, 1608, 1568, 1531, 1490, 1462, 1447, 1420, 1348, 1320, 1290, 1244, 1209, 1180, 1120, 1102, 1075, 1028, 1002, 982, 936, 904, 882, 841, 812, 801, 762, 753, 732, 683, 667.

MS (EI, 70 eV): m/z (%) = 219 (13), 218 (100, M^+), 172 (63), 171 (15), 160 (12), 152 (20), 145 (35), 125 (22), 50 (10).

HRMS (EI): calcd. for [$C_{11}H_7FN_2O_2$]: 218.0492; found: 218.0483 (M^+).

Synthesis of 3-(4-chlorophenyl)-2-fluoropyridine (**4e**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.40 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.59 M). After injection and *in situ*

trapping metalation the combined streams were collected in a flask containing 1-chloro-4-iodobenzene (305 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (15 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **4e** as a yellow solid (143 mg; 0.69 mmol; 54%).

m.p. (°C): 88.9 – 90.5.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.20 – 8.17 (m, 1H), 7.85 – 7.79 (m, 1H), 7.50 – 7.40 (m, 4H), 7.28 – 7.24 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2 (d, J = 240.4 Hz), 146.7 (d, J = 14.6 Hz), 140.5 (d, J = 4.2 Hz), 134.7, 132.3 (d, J = 5.1 Hz), 130.1 (d, J = 3.1 Hz), 129.0, 122.7 (d, J = 28.1 Hz), 121.9 (d, J = 4.5 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3053, 2956, 2924, 2854, 2362, 1961, 1910, 1887, 1780, 1739, 1607, 1597, 1578, 1563, 1498, 1454, 1438, 1393, 1308, 1270, 1247, 1209, 1120, 1106, 1090, 1020, 1004, 982, 964, 946, 849, 829, 796, 760, 748, 712, 656.

MS (EI, 70 eV): m/z (%) = 209 (29), 208 (13, M^+), 207 (100).

HRMS (EI): calcd. for [$C_{11}H_7ClFN$]: 207.0251; found: 207.0255 (M^+).

Synthesis of 2-fluoro-3-iodopyridine (**4f**)

According to **TP1**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (812 mg; 3.20 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (15 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1 + 0.5 vol% NEt_3) afforded **4f** as a colorless solid (228 mg; 1.02 mmol; 64%).

m.p. (°C): 41.7 – 43.0.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.17 – 8.11 (m, 2H), 6.95 – 6.91 (m, 1H).

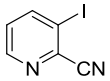
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.0 (d, J = 235.1 Hz), 150.2 (d, J = 2.8 Hz), 147.2 (d, J = 13.1 Hz), 122.7 (d, J = 4.5 Hz), 76.0 (d, J = 43.5 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2932, 1730, 1576, 1558, 1445, 1423, 1407, 1373, 1288, 1254, 1216, 1155, 1124, 1066, 1018, 976, 877, 844, 793, 737.

MS (EI, 70 eV): m/z (%) = 223 (100, M^+), 96 (71), 76 (21).

HRMS (EI): calcd. for [C_5H_3FIN]: 222.9294; found: 222.9296 (M^+).

Synthesis of 3-iodopicolinonitrile (**4g**)



According to **TP1**, injection loop A and B were loaded with solutions of picolinonitrile (**3b**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (812 mg; 3.20 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (15 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 4:1 + 0.5 vol% NEt_3) afforded **4g** as a colorless solid (328 mg; 1.43 mmol; 89%).

m.p. (°C): 103.8 – 105.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.65 (dd, J = 4.6 Hz, J = 1.1 Hz, 1H), 8.22 (dd, J = 8.2 Hz, J = 1.0 Hz, 1H), 7.25 (dd, J = 8.2 Hz, J = 4.7 Hz, 1H).

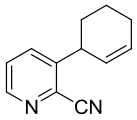
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.5, 146.7, 139.5, 127.5, 117.5, 97.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3108, 3056, 2922, 2853, 2238, 1936, 1549, 1462, 1434, 1409, 1258, 1246, 1192, 1129, 1060, 1012, 951, 796, 744.

MS (EI, 70 eV): m/z (%) = 230 (100, M^+), 125 (10), 123 (17), 111 (22), 109 (23), 103 (70), 99 (10), 97 (28), 95 (25), 85 (24), 83 (29), 81 (24), 76 (24), 71 (31), 70 (10), 69 (35), 67 (11), 57 (35), 55 (28), 43 (21), 43 (11), 41 (12).

HRMS (EI): calcd. for [$C_6H_3IN_2$]: 229.9341; found: 229.9334 (M^+).

Synthesis of 3-(cyclohex-2-enyl)picolinonitrile (**4h**)



According to **TP1**, injection loop A and B were loaded with solutions of picolinonitrile (**3b**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (206 mg; 1.28 mmol; 0.8 equiv) and CuCN·2LiCl (0.16 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1.5 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **4h** as a yellow oil (189 mg; 1.03 mmol; 80%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.52 (dd, J = 4.6 Hz, J = 1.6 Hz, 1H), 7.70 (dd, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.43 (dd, J = 8.1 Hz, J = 4.6 Hz, 1H), 6.03 – 6.00 (m, 1H), 5.57 – 5.55 (m, 1H), 3.89 – 3.85 (m, 1H), 2.16 – 2.08 (m, 3H), 1.70 – 1.63 (m, 2H), 1.52 – 1.46 (m, 1H).

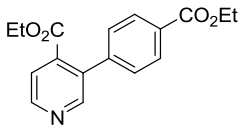
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 148.6, 146.7, 136.2, 133.4, 131.1, 126.8, 126.7, 116.2, 38.3, 31.3, 24.7, 20.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 2931, 2860, 2233, 1736, 1651, 1564, 1450, 1425, 1345, 1301, 1248, 1230, 1216, 1192, 1162, 1137, 1098, 1037, 984, 932, 899, 881, 851, 813, 801, 773, 724, 681, 660, 609, 593, 570.

MS (EI, 70 eV): m/z (%) = 184 (59, M^+), 183 (100), 169 (30), 168 (14), 166 (13), 157 (10), 156 (22), 155 (39), 130 (20), 129 (14), 116 (10).

HRMS (EI): calcd. for [$C_{12}H_{11}N_2$]: 183.0922; found: 183.0920 (M^+ - H).

Synthesis of ethyl 3-(4-(ethoxycarbonyl)phenyl)isonicotinate (**4i**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl isonicotinate (**3c**; 0.40 M containing 1.1 equiv $ZnCl_2$·2LiCl) and TMPLi (0.61 M). After injection and *in*

situ trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (353 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 3:1 + 0.5 vol% NEt_3) afforded **4i** as an orange oil (343 mg; 1.15 mmol; 90%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.71 (d, J = 5.0 Hz, 1H), 8.64 (d, J = 0.7 Hz, 1H), 8.10 – 8.06 (m, 2H), 7.65 (dd, J = 5.0 Hz, J = 0.8 Hz, 1H), 7.39 – 7.35 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H).

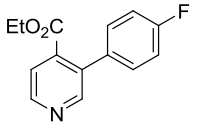
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 166.2, 151.0, 149.5, 142.0, 137.9, 135.3, 130.1, 129.5, 128.7, 122.7, 61.8, 61.1, 14.3, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2361, 1711, 1610, 1584, 1568, 1464, 1445, 1412, 1395, 1365, 1311, 1268, 1214, 1176, 1097, 1074, 1022, 1000, 862, 850, 794, 770, 704, 669, 675.

MS (EI, 70 eV): m/z (%) = 299 (53, M^+), 271 (14), 255 (16), 254 (100), 226 (21), 182 (22), 126 (10).

HRMS (EI): calcd. for $[C_{17}H_{17}NO_4]$: 299.1158; found: 299.1148 (M^+).

Synthesis of ethyl 3-(4-fluorophenyl)isonicotinate (**4j**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl isonicotinate (**3c**; 0.40 M containing 1.1 equiv $ZnCl_2$·2LiCl) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 1-fluoro-4-iodobenzene (284 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×90 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel;

i-hexane:EtOAc = 4:1 + 0.5 vol% NEt_3) afforded **4j** as a yellow oil (255 mg; 1.04 mmol; 81%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.68 (d, J = 5.0 Hz, 1H), 8.63 (s, 1H), 7.62 (d, J = 5.0 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.14 – 7.06 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.06 (t, J = 7.1 Hz, 3H).

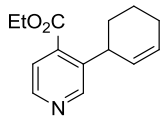
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.8, 162.7 (d, J = 247.6 Hz), 151.3, 149.1, 138.1, 135.1, 133.4 (d, J = 3.7 Hz), 130.4 (d, J = 8.1 Hz), 122.6, 115.3 (d, J = 21.7 Hz), 61.7, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3042, 2982, 2937, 1722, 1607, 1596, 1583, 1550, 1512, 1479, 1445, 1413, 1396, 1314, 1280, 1245, 1222, 1178, 1159, 1095, 1075, 1046, 1015, 1003, 938, 876, 835, 819, 791, 758, 734, 714, 672.

MS (EI, 70 eV): m/z (%) = 246 (13), 245 (79, M^+), 217 (24), 216 (10), 201 (20), 200 (100), 173 (13), 172 (41), 145 (28), 144 (13), 125 (21), 71 (10), 69 (11), 57 (13), 42 (15).

HRMS (EI): calcd. for [$C_{14}H_{12}FNO_2$]: 245.0852; found: 245.0846 (M^+).

Synthesis of ethyl 3-(cyclohex-2-enyl)isonicotinate (**4k**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl isonicotinate (**3c**; 0.40 M containing 1.1 equiv CuCN·2LiCl) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (283 mg; 1.76 mmol; 1.1 equiv) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1.5 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 8:1 + 0.5 vol% NEt_3) afforded **4k** as an orange oil (312 mg; 1.35 mmol; 84%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.61 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.51 (d, J = 5.0 Hz, 1H), 5.96 – 5.89 (m, 1H), 5.65 – 5.59 (m, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.15 – 4.07 (m, 1H), 2.15 – 2.03 (m, 3H), 1.74 – 1.42 (m, 3H), 1.35 (t, J = 7.1 Hz, 3H).

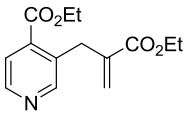
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 151.3, 147.6, 140.2, 137.2, 129.4, 128.6, 122.6, 61.6, 36.2, 31.9, 24.8, 21.0, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 3031, 2924, 2860, 1730, 1647, 1496, 1454, 1436, 1361, 1253, 1188, 1164, 1094, 1065, 1028, 944, 904, 871, 837, 736, 698, 673.

MS (EI, 70 eV): m/z (%) = 231 (16, M^+), 186 (16), 185 (100), 184 (51), 167 (19), 166 (20), 156 (21).

HRMS (EI): calcd. for [$C_{14}H_{17}NO_2$]: 231.1259; found: 231.1255 (M^+).

Synthesis of ethyl 3-(2-(ethoxycarbonyl)allyl)isonicotinate (**4l**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl isonicotinate (**3c**; 0.42 M containing 1.1 equiv CuCN·2LiCl) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 2-(bromomethyl)acrylate (357 mg; 1.85 mmol; 1.1 equiv) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 2 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 3:1 + 0.5 vol% NEt_3) afforded **4l** as a colorless oil (347 mg; 1.32 mmol; 79%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.53 (d, J = 5.0 Hz, 1H), 8.50 (s, 1H), 7.61 (d, J = 5.0 Hz, 1H), 6.15 (d, J = 1.1 Hz, 1H), 5.17 (d, J = 1.0 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.93 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H).

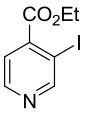
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 165.8, 152.9, 148.5, 139.4, 137.5, 133.4, 126.0, 123.3, 61.6, 60.8, 32.9, 14.1, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 2938, 2907, 2362, 2340, 1713, 1632, 1589, 1557, 1466, 1446, 1407, 1368, 1312, 1268, 1206, 1173, 1132, 1098, 1062, 1020, 948, 878, 854, 830, 816, 785, 721, 689, 671.

MS (EI, 70 eV): m/z (%) = 263 (2, M^+), 218 (13), 217 (37), 190 (33), 189 (100), 162 (24), 161 (88), 146 (33), 145 (24), 144 (19), 132 (13), 118 (10), 117 (29), 116 (19), 91 (10), 90 (13), 89 (22), 63 (18).

HRMS (EI): calcd. for [$C_{14}H_{18}NO_4$]: 264.1236; found: 264.1227 (M^+ + H).

Synthesis of ethyl 3-iodoisonicotinate (**4m**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl isonicotinate (**3c**; 0.40 M containing 1.1 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (812 mg; 3.20 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (20 mL). The aq. layer was extracted with EtOAc (3×40 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **4m** as a yellow oil (357 mg; 1.29 mmol: 81%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.04 (d, J = 0.6 Hz, 1H), 8.56 (d, J = 4.9 Hz, 1H), 7.58 (dd, J = 4.9 Hz, J = 0.7 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H).

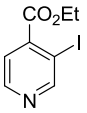
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.9, 159.5, 149.0, 142.4, 124.4, 92.4, 62.4, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3037, 2979, 2935, 1726, 1574, 1526, 1464, 1443, 1393, 1365, 1298, 1259, 1208, 1177, 1111, 1077, 1010, 871, 841, 776, 699, 662.

MS (EI, 70 eV): m/z (%) = 277 (100, M^+), 249 (49), 232 (61), 204 (22), 177 (21), 122 (16), 94 (24), 78 (15), 50 (29).

HRMS (EI): calcd. for [$C_8H_8INO_2$]: 276.9600; found: 276.9599 (M^+).

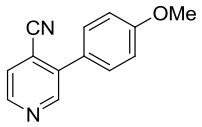
Scale-up synthesis of ethyl 3-iodoisonicotinate (**4m**)



According to **TP2**, injection loop A and B were loaded with solutions of ethyl isonicotinate (**3c**; 0.43 M containing 1.1 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.64 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (3.93 g; 15.5 mmol; 2.0 equiv) dissolved in THF (20 mL). The injection loops were reloaded twice and the reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (90 mL). The aq. layer was extracted with EtOAc (3×150 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in*

vacuo. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **4m** as a yellow oil (1.78 g; 6.42 mmol: 83%).

Synthesis of 3-(4-methoxyphenyl)isonicotinonitrile (**4n**)



According to **TP1**, injection loop A and B were loaded with solutions of isonicotinonitrile (**3d**; 0.42 M containing 1.1 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.64 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (314 mg; 1.34 mmol; 0.8 equiv), $Pd(dba)_2$ (19 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 3:1 + 0.5 vol% NEt_3) afforded **4n** as a colorless solid (249 mg; 1.18 mmol; 88%).

m.p. (°C): 143.0 – 144.5.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.82 (s, 1H), 8.67 (d, J = 5.0 Hz, 1H), 7.57 (d, J = 5.0 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.07 – 7.02 (m, 2H), 3.86 (s, 3H).

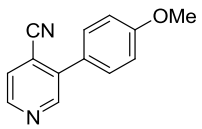
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.7, 150.9, 148.1, 138.4, 130.1, 126.7, 126.0, 118.4, 116.6, 114.6, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3088, 3065, 3041, 3023, 3006, 2971, 2939, 2840, 2230, 1959, 1733, 1611, 1575, 1544, 1516, 1482, 1466, 1455, 1439, 1425, 1401, 1325, 1314, 1296, 1254, 1202, 1184, 1150, 1118, 1082, 1028, 1014, 998, 981, 964, 948, 935, 915, 841, 830, 818, 784, 758, 724, 709, 666.

MS (EI, 70 eV): m/z (%) = 210 (60, M^+), 195 (11), 167 (21), 140 (15), 43 (13).

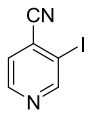
HRMS (EI): calcd. for [$C_{13}H_{10}N_2O$]: 210.0793; found: 210.0784 (M^+).

Scale-up synthesis of 3-(4-methoxyphenyl)isonicotinonitrile (**4n**)



According to **TP2**, injection loop A and B were loaded with solutions of isonicotinonitrile (**3d**; 0.43 M containing 1.1 equiv $ZnCl_2$·2LiCl) and TMPLi (0.64 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (1.45 g; 6.20 mmol; 0.8 equiv), $Pd(dba)_2$ (89 mg; 2 mol%) and tfp (72 mg; 4 mol%) dissolved in THF (20 mL). The injection loops were reloaded twice and the reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (100 mL). The aq. layer was extracted with EtOAc (3×150 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 3:1 + 0.5 vol% NEt_3) afforded **4n** as a colorless solid (1.08 g; 5.15 mmol; 83%).

Synthesis of 3-iodoisonicotinonitrile (**4o**)



According to **TP1**, injection loop A and B were loaded with solutions of isonicotinonitrile (**3d**; 0.42 M containing 1.1 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (853 mg; 3.36 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 6:1 + 0.5 vol% NEt_3) afforded **4o** as a colorless solid (268 mg; 1.17 mmol; 70%).

m.p. (°C): 99.0 – 100.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.09 (s, 1H), 8.70 (d, J = 4.9 Hz, 1H), 7.49 (d, J = 4.9 Hz, 1H).

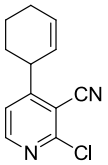
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.0, 148.9, 128.0, 127.1, 117.0, 96.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3099, 3069, 3003, 2923, 2234, 1915, 1732, 1698, 1606, 1568, 1524, 1509, 1460, 1399, 1301, 1282, 1269, 1247, 1212, 1198, 1162, 1147, 1102, 1083, 1036, 1015, 947, 930, 915, 846, 831, 779, 730, 685.

MS (EI, 70 eV): m/z (%) = 230 (9, M^+), 103 (10), 57 (17), 55 (10), 43 (13), 43 (19).

HRMS (EI): calcd. for [$C_6H_3IN_2$]: 229.9341; found: 229.9336 (M^+).

Synthesis of 2-chloro-4-(cyclohex-2-enyl)nicotinonitrile (**4p**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-chloronicotinonitrile (**3e**; 0.40 M containing 1.1 equiv CuCN·2LiCl) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (258 mg; 1.60 mmol; 1.0 equiv) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 6:1 + 0.5 vol% NEt_3) afforded **4p** as a yellow oil (312 mg; 1.43 mmol; 89%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.43 (d, J = 5.2 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 6.08 – 6.02 (m, 1H), 5.58 – 5.52 (m, 1H), 3.84 – 3.78 (m, 1H), 2.19 – 2.07 (m, 3H), 1.72 – 1.43 (m, 3H).

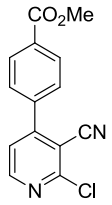
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.9, 153.3, 151.9, 131.7, 125.5, 121.5, 113.8, 110.4, 40.2, 30.6, 24.6, 20.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3025, 2933, 2861, 2837, 2229, 1650, 1575, 1542, 1450, 1433, 1394, 1370, 1307, 1258, 1239, 1203, 1162, 1136, 1076, 1060, 1046, 940, 908, 890, 842, 805, 777, 751, 731, 717, 699, 636, 609, 588.

MS (EI, 70 eV): m/z (%) = 220 (23), 219 (40, M^+), 218 (75), 217 (100), 203 (31), 202 (12), 201 (10), 200 (13), 191 (12), 190 (12), 189 (16), 183 (10), 181 (13), 167 (10), 166 (15), 165 (10), 155 (20), 153 (13), 141 (11), 128 (11), 127 (11), 81 (10), 77 (11), 54 (20), 43 (12), 41 (17).

HRMS (EI): calcd. for $[C_{12}H_{10}ClN_2]$: 217.0533; found: 217.0516 (M^+ - H).

Synthesis of methyl 4-(2-chloro-3-cyanopyridin-4-yl)benzoate (**4q**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-chloronicotinonitrile (**3e**; 0.40 M containing 1.1 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing methyl 4-iodobenzoate (335 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 4:1 + 0.5 vol% NEt_3) afforded **4q** as a colorless solid (289 mg; 1.06 mmol; 83%).

m.p. (°C): 189.9 – 191.3.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.60 (d, J = 5.2 Hz, 1H), 8.19 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 5.2 Hz, 1H), 3.94 (s, 3H).

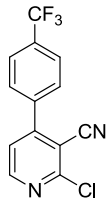
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.0, 155.0, 154.4, 152.1, 139.0, 132.1, 130.4, 128.5, 122.6, 114.2, 109.3, 52.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079, 2952, 2227, 2020, 1962, 1728, 1712, 1611, 1570, 1531, 1455, 1431, 1404, 1362, 1306, 1290, 1210, 1186, 1115, 1105, 1059, 1014, 967, 877, 853, 836, 808, 793, 777, 755, 703, 682, 666.

MS (EI, 70 eV): m/z (%) = 272 (23; M^+), 243 (31), 242 (13), 241 (100), 178 (18), 177 (36), 151 (10), 44 (29), 43 (26).

HRMS (EI): calcd. for $[C_{14}H_9ClN_2O_2]$: 272.0353; found: 272.0335 (M^+).

Synthesis of 2-chloro-4-(4-(trifluoromethyl)phenyl)nicotinonitrile (**4r**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-chloronicotinonitrile (**3e**; 0.40 M containing 1.1 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzotrifluoride (348 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 1.5 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 6:1 + 0.5 vol% NEt_3) afforded **4r** as a yellow solid (260 mg; 0.92 mmol; 72%).

m.p. (°C): 124.8 – 126.7.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.62 (d, J = 5.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 5.2 Hz, 1H).

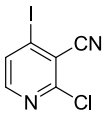
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.5, 152.2, 138.3, 132.6 (q, J = 33.2 Hz), 128.9, 126.2 (q, J = 3.8 Hz), 125.3, 122.5, 121.7, 114.1, 109.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2230, 1714, 1621, 1573, 1530, 1454, 1412, 1373, 1321, 1231, 1204, 1192, 1160, 1111, 1072, 1050, 1014, 960, 866, 845, 835, 767, 758, 740, 669.

MS (EI, 70 eV): m/z (%) = 284 (29), 283 (13, M^+), 282 (100), 247 (27), 246 (58), 227 (18), 220 (10), 196 (11), 131 (14), 111 (11), 97 (20), 85 (22), 83 (17), 71 (28), 69 (22), 57 (37), 55 (22), 44 (28), 43 (26), 43 (62), 41 (12).

HRMS (EI): calcd. for $[C_{13}H_6ClF_3N_2]$: 282.0172; found: 282.0161 (M^+).

Synthesis of 2-chloro-4-iodonicotinonitrile (**4s**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-chloronicotinonitrile (**3e**; 0.40 M containing 1.1 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (812 mg; 3.20 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (20 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were

dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:Et_2O = 4:1 + 0.5 vol% NEt_3) afforded **4s** as a colorless solid (334 mg; 1.26 mmol; 79%).

m.p. (°C): 149.8 – 151.2.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.16 (d, J = 5.3 Hz, 1H), 7.81 (d, J = 5.3 Hz, 1H).

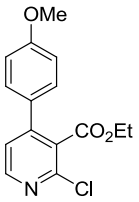
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.4, 151.4, 132.7, 119.0, 115.8, 112.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2230, 1957, 1678, 1550, 1527, 1515, 1437, 1366, 1281, 1247, 1230, 1211, 1128, 1098, 1077, 965, 840, 800, 741, 666.

MS (EI, 70 eV): m/z (%) = 266 (25), 264 (100; M^+), 231 (16), 139 (14), 137 (46), 127 (40), 83 (13), 76 (37), 75 (51), 71 (16), 70 (14), 69 (24), 59 (24), 57 (27), 55 (35), 45 (13), 45 (11), 44 (52), 43 (27), 43 (20), 41 (46).

HRMS (EI): calcd. for [$C_6H_2ClIN_2$]: 263.8951; found: 263.8931 (M^+).

Synthesis of ethyl 2-chloro-4-(4-methoxyphenyl)nicotinate (**4t**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 2-chloronicotinate (**3f**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (307 mg; 1.31 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (15 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **4t** as a yellow oil (343 mg; 1.18 mmol; 90%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.38 (d, J = 5.1 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.22 (d, J = 5.1 Hz, 1H), 6.95 – 6.90 (m, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H).

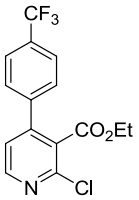
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.0, 160.6, 150.0, 149.6, 147.9, 129.3, 129.1, 129.0, 123.0, 114.3, 62.1, 55.3, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2936, 2839, 2361, 1730, 1608, 1576, 1535, 1515, 1454, 1417, 1378, 1362, 1250, 1215, 1196, 1179, 1131, 1114, 1095, 1056, 1026, 854, 827, 776, 742, 642, 604, 574.

MS (EI, 70 eV): m/z (%) = 293 (42), 292 (20, M^+), 291 (100), 263 (13), 248 (27), 247 (13), 246 (84), 211 (15), 210 (72), 203 (11), 183 (10), 140 (21), 113 (10), 63 (10), 41 (22).

HRMS (EI): calcd. for [$C_{15}H_{14}ClNO_3$]: 291.0662; found: 291.0660 (M^+).

Synthesis of ethyl 2-chloro-4-(4-(trifluoromethyl)phenyl)nicotinate (**4u**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 2-chloronicotinate (**3f**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzotrifluoride (356 mg; 1.31 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (15 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **4u** as a yellow solid (367 mg; 1.11 mmol; 85%).

m.p. (°C): 83.0 – 83.9.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.47 (d, J = 5.1 Hz, 1H), 7.70 – 7.67 (m, 2H), 7.52 – 7.49 (m, 2H), 7.24 (d, J = 5.1 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.09 (t, J = 7.1 Hz, 3H).

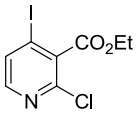
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.2, 150.0, 148.8, 148.2, 140.3, 131.4 (q, J = 32.4 Hz), 129.2, 128.5, 125.7 (q, J = 3.8 Hz), 123.7 (q, J = 272.4 Hz), 122.8, 62.3, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2989, 1727, 1621, 1583, 1536, 1474, 1456, 1410, 1384, 1361, 1325, 1286, 1268, 1225, 1200, 1162, 1145, 1132, 1109, 1076, 1064, 1049, 1019, 974, 860, 841, 826, 785, 768, 747, 722, 659, 612, 599, 578.

MS (EI, 70 eV): m/z (%) = 329 (21, M^+), 301 (20), 300 (11), 286 (45), 285 (18), 284 (100), 256 (15), 248 (13), 221 (10), 43 (22).

HRMS (EI): calcd. for [$C_{15}H_{11}ClF_3NO_2$]: 329.0430; found: 329.0420 (M^+).

Synthesis of ethyl 2-chloro-4-iodonicotinate (**4v**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 2-chloronicotinate (**3f**; 0.41 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (833 mg; 3.28 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **4v** as a yellow solid (472 mg; 1.52 mmol; 93%).

m.p. (°C): 85.0 – 86.7.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.03 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 5.2 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H).

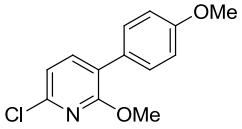
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.3, 149.6, 147.0, 136.4, 132.7, 104.7, 62.8, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 1732, 1552, 1530, 1456, 1432, 1379, 1357, 1265, 1217, 1204, 1147, 1113, 1088, 1056, 1012, 870, 854, 818, 780, 742, 692, 578.

MS (EI, 70 eV): m/z (%) = 313 (15), 311 (41, M^+), 285 (17), 283 (51), 268 (32), 267 (10), 266 (100), 239 (11), 238 (19).

HRMS (EI): calcd. for [$C_8H_7ClINO_2$]: 310.9210; found: 310.9203 (M^+).

Synthesis of 6-chloro-2-methoxy-3-(4-methoxyphenyl)pyridine (**4w**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-chloro-6-methoxypyridine (**3g**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.59 M). After

injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (300 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **4w** as a yellow oil (317 mg; 1.27 mmol; 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.52 – 7.50 (m, 1H), 7.47 – 7.43 (m, 2H), 6.97 – 6.93 (m, 3H), 3.96 (s, 3H), 3.83 (s, 3H).

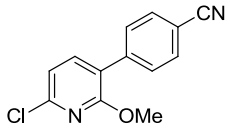
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3, 159.3, 146.3, 140.2, 130.2, 127.8, 122.7, 116.6, 113.8, 55.3, 54.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2997, 2951, 2903, 2861, 2836, 1890, 1610, 1581, 1560, 1514, 1461, 1422, 1370, 1298, 1242, 1178, 1141, 1110, 1036, 1020, 1013, 995, 958, 888, 836, 810, 801, 769, 713, 678.

MS (EI, 70 eV): m/z (%) = 251 (36), 250 (21, M^+), 249 (100), 248 (16), 234 (17), 214 (15), 206 (11), 199 (10), 145 (21).

HRMS (EI): calcd. for [$C_{13}H_{12}ClNO_2$]: 249.0557; found: 249.0549 (M^+).

Synthesis of 4-(6-chloro-2-methoxypyridin-3-yl)benzonitrile (**4x**)



According to **TP1**, injection loop A and B were loaded with solutions of 2-chloro-6-methoxypyridine (**3g**; 0.40 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.59 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzonitrile (293 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **4x** as a colorless solid (279 mg; 1.14 mmol; 89%).

m.p. (°C): 138.0 – 139.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.70 – 7.67 (m, 2H), 7.63 – 7.60 (m, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 3.96 (s, 3H).

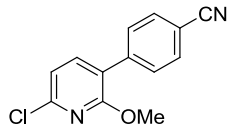
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.1, 148.4, 140.7, 140.3, 132.0, 129.7, 121.0, 118.7, 116.9, 111.4, 54.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3002, 2959, 2922, 2855, 1939, 1738, 1606, 1585, 1572, 1543, 1506, 1458, 1422, 1408, 1370, 1310, 1300, 1283, 1259, 1202, 1181, 1146, 1110, 1026, 1018, 998, 952, 892, 847, 806, 784, 768, 727, 703.

MS (EI, 70 eV): m/z (%) = 246 (35), 245 (38, M^+), 244 (100), 243 (83), 225 (12), 215 (19), 214 (10), 209 (22), 180 (13), 179 (30), 165 (17), 152 (14), 140 (38), 139 (21), 97 (10), 83 (10), 81 (13), 69 (15), 57 (11).

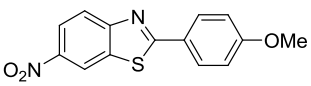
HRMS (EI): calcd. for [$C_{13}H_9ClN_2O$]: 244.0403; found: 244.0397 (M^+).

Scale-up synthesis of 4-(6-chloro-2-methoxypyridin-3-yl)benzonitrile (**4x**)



According to **TP2**, injection loop A and B were loaded with solutions of 2-chloro-6-methoxypyridine (**3g**; 0.42 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzonitrile (1.85 g; 8.08 mmol; 0.8 equiv), $Pd(dba)_2$ (115 mg; 2 mol%) and tfp (93 mg; 4 mol%) dissolved in THF (20 mL). The injection loops were reloaded three times and the reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (150 mL). The aq. layer was extracted with EtOAc (3×200 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **4x** as a colorless solid (1.67 g; 6.83 mmol; 85%).

Synthesis of 2-(4-methoxyphenyl)-6-nitrobenzothiazole (**4y**)



According to **TP1**, injection loop A and B were loaded with solutions of 6-nitrobenzothiazole (**3h**; 0.42 M containing 1.1 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After injection and *in*

situ trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (314 mg; 1.34 mmol; 0.8 equiv) and $Pd(PPh_3)_4$ (97 mg; 5 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (40 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **4y** as an orange solid (241 mg; 0.84 mmol; 63%).

m.p. (°C): 200.1 – 201.5.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.77 (dd, J = 2.3 Hz, J = 0.4 Hz, 1H), 8.32 (dd, J = 9.0 Hz, J = 2.3 Hz, 1H), 8.06 – 8.01 (m, 3H), 7.03 – 6.98 (m, 2H), 3.89 (s, 3H).

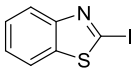
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 173.5, 162.9, 158.1, 144.6, 135.1, 129.7, 125.5, 122.7, 121.9, 118.0, 114.6, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3103, 2924, 2842, 1597, 1572, 1509, 1472, 1441, 1419, 1332, 1304, 1283, 1252, 1171, 1118, 1030, 965, 896, 878, 845, 829, 810, 790, 751, 720, 694, 662, 623, 580.

MS (EI, 70 eV): m/z (%) = 287 (16), 286 (100, M^+), 256 (20), 240 (24), 225 (12), 197 (11), 107 (22), 63 (66).

HRMS (EI): calcd. for [$C_{14}H_{10}N_2O_3S$]: 286.0412; found: 286.0400 (M^+).

Synthesis of 2-iodobenzothiazole (**4z**)



According to **TP1**, injection loop A and B were loaded with solutions of benzothiazole (**3i**; 0.42 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.63 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (853 mg; 3.36 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (15 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **4z** as an orange solid (431 mg; 1.65 mmol; 98%).

m.p. (°C): 87.8 – 88.9.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.97 – 7.94 (m, 1H), 7.78 – 7.74 (m, 1H), 7.38 – 7.29 (m, 2H).

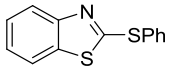
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.3, 139.2, 126.4, 126.7, 122.6, 120.5, 105.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 3025, 2956, 2924, 2853, 2830, 1588, 1557, 1450, 1435, 1415, 1361, 1339, 1307, 1272, 1227, 1167, 1156, 1150, 1125, 1089, 1078, 1064, 1009, 948, 847, 835, 748, 721, 702, 666.

MS (EI, 70 eV): m/z (%) = 261 (100, M^+), 134 (67), 125 (11), 121 (15), 111 (31), 109 (28), 97 (39), 95 (19), 91 (14), 85 (22), 83 (41), 81 (22), 77 (25), 71 (34), 70 (30), 70 (15), 69 (68), 63 (12), 57 (55), 56 (17), 55 (64), 43 (66), 43 (25), 41 (26).

HRMS (EI): calcd. for [C_7H_4INS]: 260.9109; found: 260.9106 (M^+).

Synthesis of 2-(phenylthio)benzothiazole (**5a**)



According to **TP1**, injection loop A and B were loaded with solutions of benzothiazole (**3i**; 0.40 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing *S*-phenyl benzenethiosulfonate (601 mg; 2.40 mmol; 1.5 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (15 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1 + 0.5 vol% NEt_3) afforded **5a** as a yellow oil (357 mg; 1.47 mmol; 92%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.90 – 7.87 (m, 1H), 7.75 – 7.72 (m, 2H), 7.67 – 7.63 (m, 1H), 7.50 – 7.44 (m, 3H), 7.43 – 7.38 (m, 1H), 7.29 – 7.24 (m, 1H).

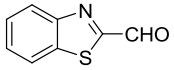
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 169.6, 153.9, 135.6, 135.3, 130.5, 130.0, 129.9, 126.2, 124.3, 122.0, 120.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2920, 2248, 1941, 1902, 1581, 1558, 1473, 1455, 1439, 1423, 1308, 1273, 1236, 1174, 1157, 1124, 1080, 1067, 1019, 1006, 998, 981, 934, 850, 746, 724, 703, 665.

MS (EI, 70 eV): m/z (%) = 244 (13), 243 (61, M^+), 242 (100).

HRMS (EI): calcd. for [$C_{13}H_8NS_2$]: 242.0098; found: 242.0092 (M^+ - H).

Synthesis of benzothiazole-2-carbaldehyde (**5b**)



According to **TP1**, injection loop A and B were loaded with solutions of benzothiazole (**3i**; 0.40 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing DMF (0.72 mL; 0.70 g; 9.6 mmol; 6.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (15 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **5b** as an orange solid (185 mg; 1.13 mmol; 71%).

m.p. (°C): 83.9 – 85.3.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.15 (s, 1H), 8.25 – 8.21 (m, 1H), 8.01 – 7.97 (m, 1H), 7.63 – 7.53 (m, 2H).

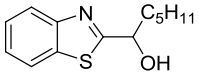
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 185.4, 165.3, 153.6, 136.4, 128.4, 127.4, 125.8, 122.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3372, 3056, 2924, 2847, 2819, 1982, 1942, 1857, 1692, 1590, 1551, 1503, 1485, 1462, 1427, 1321, 1233, 1202, 1176, 1121, 1061, 1013, 954, 912, 863, 770, 734, 703.

MS (EI, 70 eV): m/z (%) = 163 (31, M^+), 162 (51), 135 (27), 134 (60), 108 (17), 90 (12).

HRMS (EI): calcd. for [C_8H_4NOS]: 162.0014; found: 162.0000 (M^+ - H).

Synthesis of 1-(benzothiazol-2-yl)hexan-1-ol (**5c**)



According to **TP1**, injection loop A and B were loaded with solutions of benzothiazole (**3i**; 0.40 M containing 0.5 equiv $MgCl_2$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing hexanal (0.30 mL; 0.24 g; 2.4 mmol; 1.5 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (15 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column

chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **5c** as a yellow solid (235 mg; 1.00 mmol; 63%).

m.p. (°C): 48.1 – 49.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.95 – 7.92 (m, 1H), 7.85 – 7.82 (m, 1H), 7.45 – 7.40 (m, 1H), 7.36 – 7.31 (m, 1H), 5.06 (s, 1H), 3.75 (br, 1H), 2.05 – 1.83 (m, 2H), 1.54 – 1.20 (m, 6H), 0.87 – 0.83 (m, 3H).

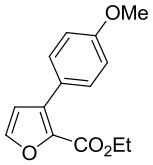
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 176.7, 152.7, 134.7, 126.0, 124.9, 122.8, 121.8, 72.3, 38.1, 31.6, 24.8, 22.5, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3258, 3065, 2954, 2926, 2857, 1788, 1666, 1594, 1560, 1513, 1456, 1438, 1378, 1314, 1240, 1174, 1156, 1125, 1058, 1014, 969, 935, 866, 756, 728, 666.

MS (EI, 70 eV): m/z (%) = 235 (27, M^+), 191 (14), 190 (16), 178 (24), 166 (12), 165 (100), 164 (65), 162 (29), 162 (16), 136 (26), 135 (26), 134 (16), 109 (19), 108 (10).

HRMS (EI): calcd. for [$C_{13}H_{17}NOS$]: 235.1031; found: 235.1019 (M^+).

Synthesis of ethyl 3-(4-methoxyphenyl)furan-2-carboxylate (**8a**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl furan-2-carboxylate (**6**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (300 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1) afforded **8a** as a yellow oil (227 mg; 0.92 mmol; 72%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.56 – 7.51 (m, 3H), 6.94 – 6.89 (m, 2H), 6.58 – 6.57 (m, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

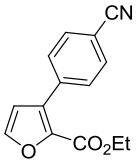
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.7, 159.2, 144.8, 138.6, 134.4, 130.6, 124.1, 114.3, 113.4, 60.8, 55.3, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2936, 2838, 1708, 1612, 1588, 1572, 1515, 1487, 1464, 1443, 1424, 1402, 1385, 1290, 1242, 1176, 1130, 1103, 1069, 1021, 964, 922, 892, 865, 833, 782, 758, 727, 679, 634, 603.

MS (EI, 70 eV): m/z (%) = 247 (17), 246 (100, M^+), 218 (40), 203 (16), 201 (25), 174 (35), 159 (10), 145 (20), 131 (21), 91 (13), 77 (10), 71 (17), 69 (11), 58 (25), 56 (11).

HRMS (EI): calcd. for [$C_{14}H_{14}O_4$]: 246.0892; found: 246.0883 (M^+).

Synthesis of ethyl 3-(4-cyanophenyl)furan-2-carboxylate (**8b**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl furan-2-carboxylate (**6**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzonitrile (293 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1) afforded **8b** as a yellow solid (212 mg; 0.88 mmol; 69%).

m.p. (°C): 95.1 – 96.9.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.67 (s, 4H), 7.59 (d, J = 1.8 Hz, 1H), 6.61 (d, J = 1.8 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H).

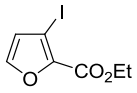
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.7, 145.4, 136.7, 132.6, 131.8, 130.1, 125.1, 118.7, 114.0, 111.9, 61.3, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3130, 3108, 2989, 2926, 2224, 1713, 1610, 1583, 1556, 1508, 1483, 1418, 1385, 1374, 1302, 1283, 1218, 1190, 1149, 1134, 1124, 1112, 1101, 1078, 1060, 1018, 972, 962, 944, 921, 894, 863, 851, 832, 798, 761, 680, 664, 608, 584, 558.

MS (EI, 70 eV): m/z (%) = 242 (14), 241 (68, M^+), 213 (54), 212 (25), 197 (16), 196 (100), 169 (52), 141 (11), 140 (69), 114 (17), 113 (20).

HRMS (EI): calcd. for [$C_{14}H_{11}NO_3$]: 241.0739; found: 241.0735 (M^+).

Synthesis of ethyl 3-iodofuran-2-carboxylate (**8c**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl furan-2-carboxylate (**6**; 0.40 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing I_2 (812 mg; 3.20 mmol; 2.0 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1) afforded **8c** as a colorless oil (261 mg; 0.98 mmol; 61%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.48 (d, J = 1.8 Hz, 1H), 6.67 (d, J = 1.9 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).

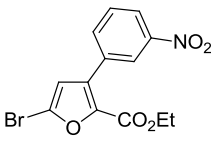
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.2, 146.5, 144.1, 121.4, 73.7, 61.4, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3123, 2982, 2936, 1712, 1555, 1479, 1445, 1376, 1274, 1186, 1164, 1116, 1065, 1018, 973, 886, 862, 827, 772, 621, 601.

MS (EI, 70 eV): m/z (%) = 266 (78, M^+), 238 (76), 222 (28), 221 (100), 125 (10), 111 (18), 99 (11), 97 (24), 95 (14), 85 (30), 83 (25), 83 (10), 71 (50), 70 (14), 69 (35), 67 (14), 66 (26), 57 (83), 56 (15), 55 (45), 55 (15), 42 (19), 40 (25), 38 (59), 38 (23).

HRMS (EI): calcd. for [$C_7H_7IO_3$]: 265.9440; found: 265.9437 (M^+).

Synthesis of ethyl 5-bromo-3-(3-nitrophenyl)furan-2-carboxylate (**11a**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 5-bromofuran-2-carboxylate (**9**; 0.40 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 1-iodo-3-nitrobenzene (319 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and

the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **11a** as a yellow solid (373 mg; 1.10 mmol; 86%).

m.p. (°C): 127.6 – 129.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.42 (dd, J = 2.3 Hz, J = 1.3 Hz, 1H), 8.22 (ddd, J = 8.2 Hz, J = 2.3 Hz, J = 1.1 Hz, 1H), 7.88 (ddd, J = 7.9 Hz, J = 2.1 Hz, J = 1.1 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 6.61 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H).

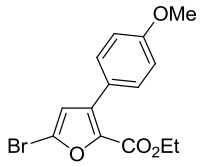
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.7, 148.0, 141.5, 135.3, 134.0, 132.5, 129.1, 127.5, 124.4, 123.5, 115.6, 61.5, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3125, 2992, 1711, 1579, 1524, 1492, 1468, 1438, 1402, 1383, 1350, 1308, 1289, 1272, 1245, 1177, 1163, 1139, 1105, 1094, 1085, 1026, 1000, 937, 896, 874, 840, 806, 769, 737, 729, 688, 676, 652, 624, 590.

MS (EI, 70 eV): m/z (%) = 342 (11), 341 (77), 340 (17, M^+), 339 (84), 313 (33), 311 (31), 296 (34), 294 (40), 269 (88), 267 (96), 114 (30), 113 (100), 102 (42), 101 (33), 87 (29), 75 (22), 63 (71), 62 (24).

HRMS (EI): calcd. for [$C_{13}H_{11}BrNO_5$]: 339.9821; found: 339.9737 (M^+ + H).

Synthesis of ethyl 5-bromo-3-(4-methoxyphenyl)furan-2-carboxylate (**11b**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 5-bromofuran-2-carboxylate (**9**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (300 mg; 1.28 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **11b** as a red solid (334 mg; 1.03 mmol; 80%).

m.p. (°C): 78.5 – 81.9.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.53 – 7.48 (m, 2H), 6.94 – 6.89 (m, 2H), 6.52 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).

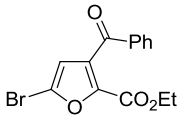
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.0, 158.2, 140.5, 136.6, 130.6, 126.6, 123.0, 115.9, 113.5, 61.0, 55.3, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3117, 2982, 1711, 1608, 1588, 1567, 1515, 1482, 1443, 1422, 1394, 1374, 1314, 1300, 1268, 1252, 1224, 1185, 1174, 1144, 1117, 1083, 1017, 968, 931, 825, 796, 765, 671, 640, 623, 610, 570.

MS (EI, 70 eV): m/z (%) = 327 (20), 326 (98), 325 (22, M^+), 324 (100), 225 (30), 223 (27), 201 (17), 189 (15), 161 (12), 145 (38), 144 (28), 132 (15), 129 (11), 115 (15), 102 (22), 101 (41), 89 (12), 75 (35), 74 (18), 63 (16).

HRMS (EI): calcd. for [$C_{14}H_{13}BrO_4$]: 323.9997; found: 323.9988 (M^+).

Synthesis of ethyl 3-benzoyl-5-bromofuran-2-carboxylate (**11c**)



According to **TP1**, injection loop A and B were loaded with solutions of ethyl 5-bromofuran-2-carboxylate (**9**; 0.40 M containing 0.5 equiv $ZnCl_2$·2LiCl) and TMPLi (0.61 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing benzoyl chloride (180 mg; 1.28 mmol; 0.8 equiv) and CuCN·2LiCl (1.6 mL; 1.0 equiv) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C and overnight at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **11c** as a yellow solid (252 mg; 0.78 mmol; 61%).

m.p. (°C): 96.1 – 97.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.85 – 7.82 (m, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.42 (m, 2H), 6.59 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 0.95 (t, *J* = 7.1 Hz, 3H).

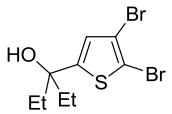
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 189.5, 156.7, 143.3, 136.7, 134.0, 132.8, 129.5, 128.6, 127.7, 114.4, 61.6, 13.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3116, 3066, 2982, 2936, 1720, 1669, 1596, 1574, 1478, 1449, 1400, 1382, 1303, 1249, 1177, 1153, 1100, 1073, 1016, 934, 917, 864, 840, 830, 800, 770, 716, 688, 668, 613, 573.

MS (EI, 70 eV): m/z (%) = 324 (51), 323 (10, M^+), 322 (53), 280 (16), 279 (17), 278 (17), 277 (15), 252 (16), 250 (27), 248 (16), 219 (32), 217 (31), 170 (15), 143 (15), 115 (12), 114 (10), 105 (100), 77 (86), 51 (22).

HRMS (EI): calcd. for [$C_{14}H_{11}BrO_4$]: 321.9841; found: 321.9836 (M^+).

Synthesis of 3-(4,5-dibromothiophen-2-yl)pentan-3-ol (**14**)



According to **TP1**, injection loop A and B were loaded with solutions of 2,3-dibromothiophene (**12**; 0.40 M containing 0.5 equiv $LaCl_3$·2LiCl) and TMPLi (0.60 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-pentanone (207 mg; 2.40 mmol; 1.5 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **14** as a colorless oil (334 mg; 1.02 mmol; 64%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 6.88 (s, 1H), 2.24 (sext, J = 7.5 Hz, 2H), 2.09 (s, 1H), 1.77 (sext, J = 7.3 Hz, 2H), 0.84 (t, J = 7.4 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.0, 133.9, 110.1, 102.3, 78.6, 32.8, 7.7.

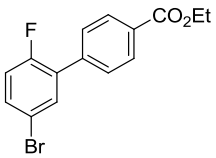
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3584, 3481, 3095, 2968, 2934, 2878, 2853, 1515, 1456, 1438, 1377, 1352, 1301, 1262, 1160, 1098, 1076, 1034, 977, 954, 930, 864, 818, 758, 684, 644, 625, 577, 561.

MS (EI, 70 eV): m/z (%) = 301 (54), 300 (10), 299 (100), 297 (54), 177 (16), 175 (17), 57 (15).

HRMS (EI): calcd. for [$C_9H_{12}Br_2OS$]: 325.8976; found: 325.8965 (M^+).

3.2 Continuous flow *in situ* trapping metalations using Cy_2NLi

Synthesis of ethyl 5'-bromo-2'-fluorobiphenyl-4-carboxylate (**17a**)



According to **TP3**, injection loop A and B were loaded with solutions of 1-bromo-4-fluorobenzene (**1f**; 0.44 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (389 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 40:1) afforded **17a** as a colorless solid (443 mg; 1.37 mmol; 97%).

m.p. (°C): 73.8 – 75.7.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.12 – 8.08 (m, 2H), 7.59 – 7.54 (m, 3H), 7.45 – 7.41 (m, 1H), 7.07 – 7.01 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

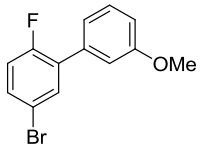
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.2, 158.7 (d, *J* = 249.7 Hz), 138.7 (d, *J* = 1.5 Hz), 133.2 (d, *J* = 3.0 Hz), 132.4 (d, *J* = 8.3 Hz), 130.2, 130.1 (d, *J* = 15.1 Hz), 129.7, 128.9 (d, *J* = 3.0 Hz), 118.0 (d, *J* = 24.1 Hz), 116.9 (d, *J* = 3.8 Hz), 61.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2993, 2978, 2931, 2869, 1885, 1713, 1611, 1576, 1558, 1513, 1473, 1465, 1443, 1415, 1386, 1378, 1366, 1318, 1274, 1254, 1218, 1210, 1185, 1120, 1102, 1080, 1031, 1016, 943, 901, 870, 861, 854, 775, 755, 742, 720, 702, 654.

MS (EI, 70 eV): m/z (%) = 324 (32), 322 (32), 296 (23), 294 (24), 279 (62), 278 (12), 277 (65), 171 (15), 170 (100), 169 (15), 85 (33).

HRMS (EI): calcd. for $[C_{15}H_{12}BrFO_2]$: 322.0005; found: 321.9999 (M^+).

Synthesis of 5-bromo-2-fluoro-3'-methoxybiphenyl (**17b**)



According to **TP3**, injection loop A and B were loaded with solutions of 1-bromo-4-fluorobenzene (**1f**; 0.44 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-iodoanisole (330 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at

25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **17b** as a yellow oil (384 mg; 1.37 mmol; 97%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.58 – 7.55 (m, 1H), 7.40 – 7.37 (m, 1H), 7.35 – 7.32 (m, 1H), 7.11 – 7.07 (m, 1H), 7.05 – 6.99 (m, 2H), 6.95 – 6.91 (m, 1H), 3.84 (s, 3H).

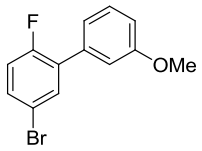
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.6, 158.8 (d, J = 248.2 Hz), 135.7 (d, J = 1.5 Hz), 133.4 (d, J = 3.0 Hz), 131.7 (d, J = 8.3 Hz), 131.0 (d, J = 15.1 Hz), 129.6, 121.3 (d, J = 3.0 Hz), 117.9 (d, J = 24.9 Hz), 116.7 (d, J = 3.8 Hz), 114.6 (d, J = 3.0 Hz), 113.8, 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3001, 2935, 2835, 1873, 1745, 1599, 1582, 1565, 1495, 1470, 1430, 1389, 1380, 1292, 1263, 1251, 1224, 1205, 1171, 1119, 1076, 1052, 1029, 995, 939, 872, 857, 812, 779, 723, 712, 692.

MS (EI, 70 eV): m/z (%) = 281 (38, M^+), 252 (31), 239 (38), 237 (45), 186 (22), 172 (25), 171 (25), 170 (61), 169 (12), 158 (62), 157 (100), 152 (12), 140 (12), 138 (13), 132 (20), 85 (20), 75 (10), 74 (12), 63 (14), 50 (11), 43 (11), 41 (11).

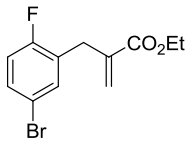
HRMS (EI): calcd. for [$C_{13}H_{11}BrFO$]: 280.9977; found: 280.9969 (M^+ + H).

Scale-up synthesis of 5-bromo-2-fluoro-3'-methoxybiphenyl (**17b**)



According to **TP4**, injection loop A and B were loaded with solutions of 1-bromo-4-fluorobenzene (**1f**; 0.45 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.68 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-iodoanisole (2.02 g; 8.64 mmol; 0.8 equiv), $Pd(dba)_2$ (124 mg; 2 mol%) and tfp (100 mg; 4 mol%) dissolved in THF (20 mL). The injection loops were reloaded three times and the reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (100 mL). The aq. layer was extracted with EtOAc (3×200 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **17b** as a yellow oil (2.31 g; 8.22 mmol; 95%).

Synthesis of ethyl 2-(5-bromo-2-fluorobenzyl)acrylate (**17c**)



According to **TP3**, injection loop A and B were loaded with solutions of 1-bromo-4-fluorobenzene (**1f**; 0.44 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 2-(bromomethyl)acrylate (272 mg; 1.41 mmol; 0.8 equiv) and CuCN·2LiCl (0.18 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1.5 h at 0 °C and 1 h at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 15 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 50:1) afforded **17c** as a colorless oil (248 mg; 0.86 mmol; 61%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.26 (m, 2H), 6.91 – 6.87 (m, 1H), 6.26 (s, 1H), 5.48 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.60 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

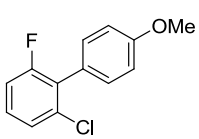
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.4, 160.2 (d, *J* = 246.4 Hz), 138.0, 133.9 (d, *J* = 5.0 Hz), 131.1 (d, *J* = 8.0 Hz), 128.2 (d, *J* = 17.1 Hz), 126.8, 117.1 (d, *J* = 24.1 Hz), 116.4 (d, *J* = 4.0 Hz), 61.0, 30.9 (d, *J* = 3.0 Hz), 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2932, 1713, 1633, 1578, 1483, 1433, 1401, 1368, 1327, 1301, 1281, 1254, 1235, 1196, 1171, 1137, 1103, 1073, 1025, 949, 931, 891, 866, 811, 779, 725, 685.

MS (EI, 70 eV): m/z (%) = 288 (24), 286 (25), 243 (12), 241 (13), 240 (14), 179 (20), 178 (22), 135 (23), 134 (85), 133 (100), 108 (15), 107 (18), 67 (24).

HRMS (EI): calcd. for $[C_{12}H_{12}BrFO_2]$: 286.0005; found: 285.9994 (M^+).

Synthesis of 2-chloro-6-fluoro-4'-methoxybiphenyl (**17d**)



According to **TP3**, injection loop A and B were loaded with solutions of 1-chloro-3-fluorobenzene (**15a**; 0.43 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.65 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask

containing 4-iodoanisole (323 mg; 1.38 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 50:1) afforded **17d** as a colorless oil (320 mg; 1.35 mmol; 98%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.28 (m, 3H), 7.27 – 7.20 (m, 1H), 7.10 – 7.04 (m, 1H), 7.03 – 6.99 (m, 2H), 3.87 (s, 3H).

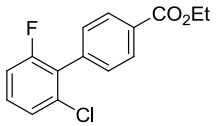
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.5 (d, J = 247.5 Hz), 159.5, 134.6 (d, J = 3.8 Hz), 131.4 (d, J = 1.5 Hz), 128.7 (d, J = 18.9 Hz), 128.7 (d, J = 9.8 Hz), 125.4 (d, J = 3.8 Hz), 124.7, 114.2 (d, J = 23.4 Hz), 113.6, 55.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3003, 2936, 2837, 1892, 1602, 1579, 1565, 1518, 1445, 1410, 1293, 1244, 1177, 1109, 1074, 1036, 1020, 1002, 964, 936, 889, 828, 805, 780, 738, 717.

MS (EI, 70 eV): m/z (%) = 238 (32), 237 (15, M^+), 236 (100), 221 (12), 195 (12), 193 (34), 167 (12), 158 (10).

HRMS (EI): calcd. for [$C_{13}H_{10}ClFO$]: 236.0404; found: 236.0399 (M^+).

Synthesis of ethyl 2'-chloro-6'-fluorobiphenyl-4-carboxylate (**17e**)



According to **TP3**, injection loop A and B were loaded with solutions of 1-chloro-3-fluorobenzene (**15a**; 0.43 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.65 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (381 mg; 1.38 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 50:1) afforded **17e** as a colorless oil (348 mg; 1.25 mmol; 91%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.15 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.12 – 7.05 (m, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

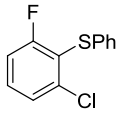
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.2, 160.1 (d, J = 249.0 Hz), 137.1, 134.1 (d, J = 3.8 Hz), 130.3, 130.3 (d, J = 1.5 Hz), 129.6 (d, J = 9.1 Hz), 129.3, 128.1 (d, J = 18.9 Hz), 125.5 (d, J = 3.0 Hz), 114.3 (d, J = 23.4 Hz), 61.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 1714, 1612, 1564, 1514, 1447, 1402, 1367, 1270, 1243, 1177, 1146, 1099, 1073, 1027, 1007, 964, 895, 855, 784, 772, 757, 727, 704, 680.

MS (EI, 70 eV): m/z (%) = 278 (33), 250 (31), 235 (30), 234 (14), 233 (100), 231 (12), 171 (12), 170 (73), 169 (12), 153 (15), 125 (13), 111 (20), 109 (15), 97 (32), 95 (19), 85 (25), 85 (17), 83 (26), 81 (19), 71 (34), 69 (31), 67 (14), 57 (48), 55 (30), 39 (24), 29 (16).

HRMS (EI): calcd. for [$C_{15}H_{12}ClFO_2$]: 278.0510; found: 278.0506 (M^+).

Synthesis of (2-chloro-6-fluorophenyl)(phenyl)sulfane (**17f**)



According to **TP3**, injection loop A and B were loaded with solutions of 1-chloro-3-fluorobenzene (**15a**; 0.44 M containing 0.5 equiv $MgCl_2$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing *S*-phenyl benzenethiosulfonate (353 mg; 1.41 mmol; 0.8 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 50:1) afforded **17f** as a colorless oil (253 mg; 1.06 mmol; 75%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.36 – 7.15 (m, 7H), 7.12 – 7.05 (m, 1H).

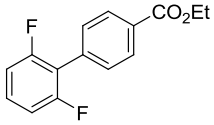
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.8 (d, J = 250.5 Hz), 140.7 (d, J = 0.8 Hz), 135.2 (d, J = 1.5 Hz), 131.0 (d, J = 9.8 Hz), 129.0, 128.4, 126.4, 126.0 (d, J = 3.0 Hz), 120.9 (d, J = 21.1 Hz), 114.8 (d, J = 24.1 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 2925, 2853, 1584, 1565, 1477, 1444, 1327, 1301, 1266, 1248, 1177, 1156, 1102, 1081, 1068, 1050, 1024, 999, 966, 888, 834, 778, 734, 711, 686.

MS (EI, 70 eV): m/z (%) = 240 (34), 239 (14, M^+), 238 (86), 204 (16), 203 (100), 202 (74), 126 (14), 109 (11), 101 (22), 77 (36), 65 (17), 57 (11), 51 (50), 50 (13).

HRMS (EI): calcd. for [$C_{12}H_8ClFS$]: 238.0019; found: 238.0036 (M^+).

Synthesis of ethyl 2',6'-difluorobiphenyl-4-carboxylate (**17g**)



According to **TP3**, injection loop A and B were loaded with solutions of 1,3-difluorobenzene (**15b**; 0.44 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (389 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 50:1) afforded **17g** as a colorless oil (350 mg; 1.33 mmol; 94%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.13 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.36 – 7.26 (m, 1H), 7.04 – 6.95 (m, 2H), 4.41 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

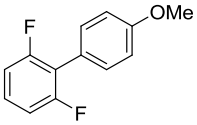
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.2, 159.9 (dd, J = 249.7 Hz, J = 6.8 Hz), 133.8, 130.8 (t, J = 2.3 Hz), 130.2, 129.6 (t, J = 10.6 Hz), 129.4, 117.6 (t, J = 18.9 Hz), 111.7 (dd, J = 18.1 Hz, J = 8.3 Hz), 61.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 2983, 2935, 2906, 1935, 1714, 1625, 1612, 1588, 1578, 1566, 1519, 1466, 1404, 1368, 1314, 1266, 1230, 1183, 1101, 1070, 1028, 1009, 997, 858, 787, 771, 723, 702.

MS (EI, 70 eV): m/z (%) = 262 (23, M^+), 234 (35), 218 (14), 217 (73), 189 (33), 188 (29), 123 (14), 111 (23), 109 (18), 97 (40), 95 (23), 85 (40), 83 (36), 82 (14), 81 (28), 71 (57), 70 (14), 69 (48), 67 (24), 57 (100), 56 (20), 55 (68), 44 (30), 43 (78), 43 (14), 41 (46).

HRMS (EI): calcd. for [$C_{15}H_{12}F_2O_2$]: 262.0805; found: 262.0803 (M^+).

Synthesis of 2,6-difluoro-4'-methoxybiphenyl (**17h**)



According to **TP3**, injection loop A and B were loaded with solutions of 1,3-difluorobenzene (**15b**; 0.44 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-

iodoanisole (330 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 70:1) afforded **17h** as a colorless oil (276 mg; 1.25 mmol; 89%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.44 – 7.40 (m, 2H), 7.29 – 7.20 (m, 1H), 7.03 – 6.93 (m, 4H), 3.86 (s, 3H).

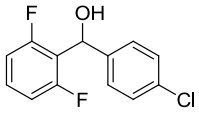
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2 (dd, J = 247.5 Hz, J = 6.8 Hz), 159.5, 131.5 (t, J = 2.3 Hz), 128.3 (t, J = 10.6 Hz), 121.3, 118.2 (t, J = 18.1 Hz), 113.8, 111.6 (dd, J = 18.1 Hz, J = 8.3 Hz), 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 3013, 2962, 2938, 2840, 1919, 1745, 1611, 1586, 1566, 1523, 1462, 1441, 1412, 1373, 1298, 1282, 1267, 1250, 1228, 1177, 1154, 1108, 1069, 1033, 1020, 1004, 991, 960, 936, 880, 838, 822, 807, 783, 754, 734, 713.

MS (EI, 70 eV): m/z (%) = 221 (15), 220 (100, M^+), 206 (12), 205 (33), 178 (13), 177 (83), 157 (13), 151 (40), 97 (13), 95 (13), 83 (17), 81 (14), 74 (10), 71 (16), 69 (21), 67 (14), 57 (28), 55 (35), 43 (28), 41 (31).

HRMS (EI): calcd. for $[C_{13}H_{10}F_2O]$: 220.0700; found: 220.0684 (M^+).

Synthesis of (4-chlorophenyl)(2,6-difluorophenyl)methanol (**17i**)



According to **TP3**, injection loop A and B were loaded with solutions of 1,3-difluorobenzene (**15b**; 0.45 M containing 0.5 equiv $MgCl_2$) and Cy_2NLi (0.67 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-chlorobenzaldehyde (202 mg; 1.44 mmol; 0.8 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1) afforded **17i** as an orange oil (269 mg; 1.06 mmol; 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35 – 7.26 (m, 5H), 6.95 – 6.88 (m, 2H), 6.22 – 6.20 (m, 1H), 2.80 – 2.78 (m, 1H).

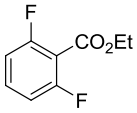
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.7 (dd, J = 248.4 Hz, J = 8.0 Hz), 140.6, 133.3, 129.8 (t, J = 11.1 Hz), 128.5, 126.9 (t, J = 1.0 Hz), 119.0 (t, J = 16.1 Hz), 112.0 (dd, J = 20.1 Hz, J = 7.0 Hz), 66.9 (t, J = 4.0 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3386, 2927, 1712, 1624, 1592, 1490, 1469, 1405, 1268, 1232, 1198, 1185, 1172, 1090, 1037, 1013, 993, 945, 864, 844, 782, 737, 722, 673, 578.

MS (EI, 70 eV): m/z (%) = 256 (28), 254 (38), 237 (18), 220 (18), 219 (100), 201 (32), 143 (26), 142 (24), 125 (30), 123 (24), 123 (27), 113 (36), 112 (22), 111 (37), 109 (20), 107 (16), 105 (20), 99 (16), 97 (33), 96 (17), 95 (44), 85 (29), 83 (24), 82 (17), 81 (46), 77 (25), 75 (20), 71 (43), 70 (16), 69 (32), 67 (28), 57 (66), 56 (17), 55 (29), 42 (20), 40 (20).

HRMS (EI): calcd. for [$C_{13}H_9ClF_2O$]: 254.0310; found: 254.0309 (M^+).

Synthesis of ethyl 2,6-difluorobenzoate (**17j**)



According to **TP3**, injection loop A and B were loaded with solutions of 1,3-difluorobenzene (**15b**; 0.45 M containing 0.5 equiv $MgCl_2$) and Cy_2NLi (0.67 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl cyanoformate (143 mg; 1.44 mmol; 0.8 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **17j** as a yellow oil (178 mg; 0.96 mmol; 67%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41 – 7.33 (m, 1H), 6.94 – 6.89 (m, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H).

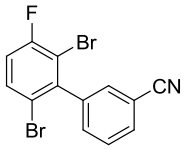
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5 (t, J = 1.0 Hz), 160.6 (dd, J = 256.4 Hz, J = 6.0 Hz), 132.4 (t, J = 11.1 Hz), 111.9 (dd, J = 21.1 Hz, J = 5.0 Hz), 111.5 (t, J = 18.1 Hz), 62.0, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2986, 2937, 1730, 1625, 1595, 1469, 1392, 1368, 1287, 1262, 1235, 1174, 1107, 1058, 1006, 856, 796, 767, 701, 583, 564.

MS (EI, 70 eV): m/z (%) = 186 (33, M^+), 159 (11), 158 (100), 142 (38), 114 (12), 113 (72), 63 (43).

HRMS (EI): calcd. for [$C_9H_8F_2O_2$]: 186.0492; found: 186.0490 (M^+).

Synthesis of 2',6'-dibromo-3'-fluorobiphenyl-3-carbonitrile (**17k**)



According to **TP3**, injection loop A and B were loaded with solutions of 2,4-dibromo-1-fluorobenzene (**15c**; 0.45 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.67 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-iodobenzonitrile (330 mg; 1.44 mmol; 0.8 equiv), $Pd(dba)_2$ (21 mg; 2 mol%) and tfp (17 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 60:1) afforded **17k** as a colorless solid (368 mg; 1.04 mmol; 72%).

m.p. (°C): 151.6 – 152.9.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.78 – 7.77 (m, 1H), 7.73 – 7.68 (m, 3H), 7.59 – 7.55 (m, 1H), 7.47 – 7.45 (m, 1H).

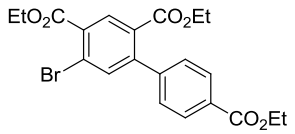
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.3 (d, J = 249.4 Hz), 135.8, 135.0 (d, J = 1.0 Hz), 133.2 (d, J = 3.0 Hz), 132.4 (d, J = 3.0 Hz), 132.3 (d, J = 2.0 Hz), 132.2, 129.7 (d, J = 15.1 Hz), 129.7, 118.2, 117.3 (d, J = 5.0 Hz), 113.2, 111.4 (d, J = 24.1 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 2228, 1982, 1918, 1728, 1592, 1578, 1554, 1482, 1459, 1442, 1405, 1393, 1381, 1324, 1291, 1276, 1251, 1235, 1201, 1163, 1097, 1056, 993, 932, 899, 886, 870, 857, 830, 801, 738, 723, 695, 678.

MS (EI, 70 eV): m/z (%) = 357 (49), 356 (12), 355 (100, M^+), 353 (47), 196 (11), 195 (68), 168 (11), 98 (10).

HRMS (EI): calcd. for [$C_{13}H_6Br_2FN$]: 352.8851; found: 352.8835 (M^+).

Synthesis of triethyl 5-bromobiphenyl-2,4,4'-tricarboxylate (**17l**)



According to **TP3**, injection loop A and B were loaded with solutions of diethyl 4-bromoisophthalate (**15d**; 0.45 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.68 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (398 mg; 1.44 mmol; 0.8 equiv), $Pd(dba)_2$ (21 mg; 2 mol%) and tfp (17 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **17l** as an orange solid (463 mg; 1.03 mmol; 72%).

m.p. (°C): 89.2 – 91.6.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.29 (s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.65 (s, 1H), 7.34 (d, J = 8.1 Hz, 2H), 4.45 – 4.33 (m, 4H), 4.08 (q, J = 7.1 Hz, 2H), 1.43 – 1.37 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H).

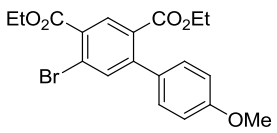
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 166.1, 165.0, 145.4, 143.7, 136.3, 133.0, 131.7, 130.1, 129.9, 129.4, 128.2, 125.0, 62.0, 61.5, 61.1, 14.3, 14.2, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 2980, 2938, 2907, 2872, 1709, 1594, 1535, 1466, 1445, 1405, 1392, 1365, 1353, 1309, 1270, 1228, 1175, 1098, 1012, 931, 888, 864, 853, 839, 773, 720, 705, 696, 666.

MS (EI, 70 eV): m/z (%) = 451 (17), 450 (74), 449 (21, M^+), 448 (73), 406 (21), 405 (100), 404 (23), 403 (99), 377 (28), 376 (12), 375 (28), 349 (12), 347 (12), 331 (18), 166 (10), 165 (10), 150 (16).

HRMS (EI): calcd. for $[C_{21}H_{21}BrO_6]$: 448.0522; found: 448.0508 (M^+).

Synthesis of diethyl 5-bromo-4'-methoxybiphenyl-2,4-dicarboxylate (**17m**)



According to **TP3**, injection loop A and B were loaded with solutions of diethyl 4-bromoisophthalate (**15d**; 0.45 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.67 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (337 mg; 1.44 mmol; 0.8 equiv), $Pd(dba)_2$ (21 mg; 2 mol%) and tfp (17 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **17m** as an orange solid (357 mg; 0.88 mmol; 61%).

m.p. (°C): 84.6 – 85.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (s, 1H), 7.66 (s, 1H), 7.23 – 7.19 (m, 2H), 6.94 – 6.90 (m, 2H), 4.41 (q, J = 7.1 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H).

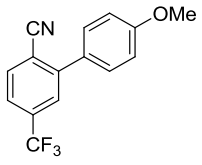
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.4, 165.2, 159.8, 146.0, 136.5, 132.8, 131.4, 130.4, 130.2, 129.5, 124.7, 113.8, 61.9, 61.4, 55.4, 14.2, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 3030, 2982, 2958, 2935, 2905, 2872, 2836, 1728, 1700, 1605, 1593, 1535, 1514, 1461, 1444, 1415, 1390, 1377, 1365, 1354, 1282, 1228, 1177, 1109, 1041, 1020, 1006, 939, 930, 891, 862, 835, 812, 793, 776, 756, 735, 704, 675.

MS (EI, 70 eV): m/z (%) = 409 (21), 408 (92), 407 (14, M^+), 406 (100), 380 (13), 378 (14), 363 (53), 362 (17), 361 (54), 335 (22), 333 (18), 331 (11), 328 (10), 210 (10), 209 (10), 137 (10), 82 (10), 80 (10).

HRMS (EI): calcd. for [$C_{19}H_{19}BrO_5$]: 406.0416; found: 406.0403 (M^+).

Synthesis of 4'-methoxy-5-(trifluoromethyl)biphenyl-2-carbonitrile (**17n**)



According to **TP3**, injection loop A and B were loaded with solutions of 4-(trifluoromethyl)benzonitrile (**15e**; 0.44 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (330 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred

overnight at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 40:1) afforded **17n** as a colorless solid (274 mg; 0.99 mmol; 70%).

m.p. (°C): 128.0 – 129.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.85 (d, J = 8.1 Hz, 1H), 7.73 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.05 – 7.01 (m, 2H), 3.86 (s, 3H).

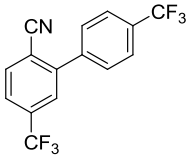
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.7, 146.1, 134.5 (q, J = 33.2 Hz), 134.3, 130.1, 129.1, 126.7 (q, J = 4.0 Hz), 123.7 (q, J = 4.0 Hz), 123.1 (q, J = 273.6 Hz), 117.7, 114.5, 114.5, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 3002, 2947, 2847, 2227, 1900, 1719, 1607, 1576, 1519, 1491, 1465, 1454, 1447, 1423, 1407, 1338, 1313, 1293, 1265, 1256, 1249, 1183, 1161, 1132, 1108, 1074, 1037, 1019, 972, 944, 909, 853, 932, 818, 793, 754, 737, 726, 713, 697, 663.

MS (EI, 70 eV): m/z (%) = 278 (19), 277 (100, M^+), 234 (38).

HRMS (EI): calcd. for [$C_{15}H_{10}F_3NO$]: 277.0714; found: 277.0712 (M^+).

Synthesis of 4',5-bis(trifluoromethyl)biphenyl-2-carbonitrile (**17o**)



According to **TP3**, injection loop A and B were loaded with solutions of 4-(trifluoromethyl)benzonitrile (**15e**; 0.44 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzotrifluoride (384 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 50:1) afforded **17o** as a colorless solid (272 mg; 0.86 mmol; 61%).

m.p. (°C): 135.8 – 137.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 – 7.92 (m, 1H), 7.80 – 7.75 (m, 4H), 7.70 – 7.67 (m, 2H).

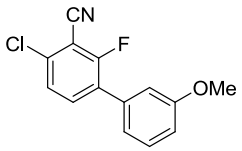
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 144.8, 140.1, 134.9 (q, J = 34.2 Hz), 134.4, 131.6 (q, J = 33.2 Hz), 129.2, 126.9 (q, J = 4.0 Hz), 126.0 (q, J = 4.0 Hz), 125.1 (q, J = 3.0 Hz), 123.7 (q, J = 272.5 Hz), 122.9 (q, J = 273.5 Hz), 116.9, 114.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 2230, 1932, 1618, 1524, 1493, 1426, 1413, 1401, 1323, 1297, 1265, 1249, 1202, 1161, 1112, 1070, 1030, 1014, 967, 917, 848, 841, 777, 756, 743, 733, 712, 662, 655.

MS (EI, 70 eV): m/z (%) = 316 (19), 315 (100, M^+), 296 (21), 246 (11), 226 (23), 177 (10).

HRMS (EI): calcd. for [$C_{15}H_7F_6N$]: 315.0483; found: 315.0477 (M^+).

Synthesis of 4-chloro-2-fluoro-3'-methoxybiphenyl-3-carbonitrile (**17p**)



According to **TP3**, injection loop A and B were loaded with solutions of 2-chloro-6-fluorobenzonitrile (**15f**; 0.45 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.67 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-iodoanisole (337 mg; 1.44 mmol; 0.8 equiv), $Pd(dba)_2$ (21 mg; 2 mol%) and tfp (17 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **17p** as a yellow solid (365 mg; 1.39 mmol; 97%).

m.p. (°C): 103.8 – 105.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.62 – 7.58 (m, 1H), 7.40 – 7.35 (m, 2H), 7.06 – 7.03 (m, 1H), 7.00 – 6.95 (m, 2H), 3.84 (s, 3H).

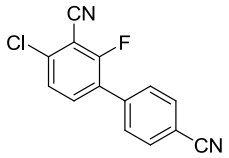
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.7 (d, J = 263.5 Hz), 159.9, 136.5 (d, J = 2.0 Hz), 135.4 (d, J = 5.0 Hz), 134.0 (d, J = 1.0 Hz), 130.0, 128.7 (d, J = 12.1 Hz), 125.8 (d, J = 5.0 Hz), 121.1 (d, J = 3.0 Hz), 114.6 (d, J = 3.0 Hz), 114.4, 111.4, 104.0 (d, J = 19.1 Hz), 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3107, 3049, 3007, 2945, 2893, 2837, 2239, 1652, 1608, 1579, 1561, 1492, 1463, 1406, 1339, 1313, 1289, 1273, 1228, 1216, 1175, 1150, 1114, 1095, 1076, 994, 930, 906, 885, 872, 826, 794, 777, 744, 718, 694, 684.

MS (EI, 70 eV): m/z (%) = 263 (33), 262 (15, M^+), 261 (100), 231 (25), 218 (24), 195 (10), 182 (11).

HRMS (EI): calcd. for [$C_{14}H_9ClFNO$]: 261.0357; found: 261.0352 (M^+).

Synthesis of 4-chloro-2-fluorobiphenyl-3,4'-dicarbonitrile (**17q**)



According to **TP3**, injection loop A and B were loaded with solutions of 2-chloro-6-fluorobenzonitrile (**15f**; 0.45 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.67 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzonitrile (330 mg; 1.44 mmol; 0.8 equiv), $Pd(dba)_2$ (21 mg; 2 mol%) and tfp (17 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1) afforded **17q** as a colorless solid (269 mg; 1.05 mmol; 73%).

m.p. (°C): 223.0 – 224.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.78 – 7.76 (m, 2H), 7.63 – 7.59 (m, 3H), 7.45 – 7.43 (m, 1H).

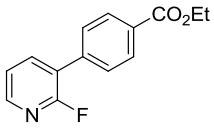
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.5 (d, J = 264.5 Hz), 138.0 (d, J = 2.0 Hz), 137.2 (d, J = 4.0 Hz), 135.0 (d, J = 5.0 Hz), 132.7, 129.5 (d, J = 3.0 Hz), 126.9 (d, J = 12.1 Hz), 126.3 (d, J = 4.0 Hz), 118.2, 113.0, 110.9, 104.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3083, 2925, 2235, 1940, 1660, 1609, 1570, 1459, 1430, 1395, 1307, 1282, 1266, 1229, 1208, 1183, 1157, 1115, 1079, 1016, 969, 914, 885, 859, 854, 834, 823, 794, 770, 751, 693, 667.

MS (EI, 70 eV): m/z (%) = 258 (32), 257 (15, M^+), 256 (100), 220 (11), 194 (10).

HRMS (EI): calcd. for [$C_{14}H_6ClFN_2$]: 256.0204; found: 256.0191 (M^+).

Synthesis of ethyl 4-(2-fluoropyridin-3-yl)benzoate (**19a**)



According to **TP3**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.44 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (389 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×50 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **19a** as a yellow oil (327 mg; 1.33 mmol; 94%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.22 – 8.20 (m, 1H), 8.13 – 8.09 (m, 2H), 7.91 – 7.84 (m, 1H), 7.64 – 7.59 (m, 2H), 7.30 – 7.26 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

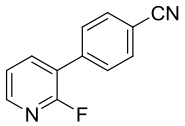
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.1, 160.3 (d, *J* = 240.7 Hz), 147.1 (d, *J* = 15.1 Hz), 140.7 (d, *J* = 4.5 Hz), 138.2 (d, *J* = 5.3 Hz), 130.4, 129.9, 128.7 (d, *J* = 3.0 Hz), 122.9 (d, *J* = 28.7 Hz), 121.9 (d, *J* = 4.5 Hz), 61.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 2982, 2933, 2907, 2874, 1712, 1611, 1603, 1577, 1562, 1514, 1476, 1438, 1397, 1367, 1314, 1269, 1246, 1204, 1183, 1101, 1025, 1003, 855, 845, 805, 773, 757, 731, 702, 645, 634, 616, 608, 591, 570.

MS (EI, 70 eV): m/z (%) = 245 (35, M^+), 217 (31), 201 (17), 200 (100), 172 (30), 145 (16), 125 (10).

HRMS (EI): calcd. for [$C_{14}H_{12}FNO_2$]: 245.0802; found: 245.0840 (M^+).

Synthesis of 4-(2-fluoropyridin-3-yl)benzonitrile (**19b**)



According to **TP3**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.44 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.66 M). After injection and *in situ*

trapping metalation the combined streams were collected in a flask containing 4-iodobenzonitrile (323 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **19b** as a colorless solid (224 mg; 1.13 mmol; 80%).

m.p. (°C): 143.4 – 145.2.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.27 – 8.24 (m, 1H), 7.90 – 7.83 (m, 1H), 7.77 – 7.73 (m, 2H), 7.68 – 7.65 (m, 2H), 7.34 – 7.29 (m, 1H).

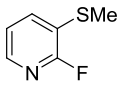
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.1 (d, J = 240.7 Hz), 147.7 (d, J = 14.3 Hz), 140.6 (d, J = 3.8 Hz), 138.5 (d, J = 5.3 Hz), 132.5, 129.5 (d, J = 3.8 Hz), 122.1 (d, J = 4.5 Hz), 122.0 (d, J = 27.9 Hz), 118.4, 112.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2228, 1603, 1574, 1512, 1438, 1399, 1317, 1277, 1246, 1205, 1184, 1112, 1078, 1008, 974, 842, 800, 781, 763, 727, 672, 647, 574, 562.

MS (EI, 70 eV): m/z (%) = 198 (100, M^+), 197 (17), 123 (16), 97 (10), 83 (18), 77 (12), 71 (12), 69 (24), 57 (17), 55 (18), 44 (46), 43 (26), 41 (13).

HRMS (EI): calcd. for [$C_{12}H_7FN_2$]: 198.0593; found: 198.0589 (M^+).

Synthesis of 2-fluoro-3-(methylthio)pyridine (**19c**)



According to **TP3**, injection loop A and B were loaded with solutions of 2-fluoropyridine (**3a**; 0.44 M containing 0.5 equiv $MgCl_2$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing *S*-methyl methanethiosulfonate (178 mg; 1.41 mmol; 0.8 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **19c** as an orange oil (152 mg; 1.06 mmol; 75%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.96 – 7.93 (m, 1H), 7.62 – 7.55 (m, 1H), 7.14 – 7.09 (m, 1H), 2.45 (s, 3H).

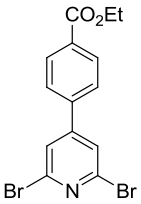
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.1 (d, J = 236.2 Hz), 143.2 (d, J = 14.3 Hz), 137.5 (d, J = 3.8 Hz), 122.1 (d, J = 33.2 Hz), 121.7 (d, J = 4.5 Hz), 14.8 (d, J = 1.5 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 2959, 2925, 2855, 1585, 1559, 1446, 1408, 1322, 1303, 1289, 1233, 1189, 1141, 1082, 1047, 971, 959, 921, 901, 840, 789, 742, 708, 678, 620, 554.

MS (EI, 70 eV): m/z (%) = 143 (100, M^+), 110 (12).

HRMS (EI): calcd. for [C_6H_6FNS]: 143.0205; found: 143.0193 (M^+).

Synthesis of ethyl 4-(2,6-dibromopyridin-4-yl)benzoate (**19d**)



According to **TP3**, injection loop A and B were loaded with solutions of 2,6-dibromopyridine (**18a**; 0.45 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.67 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (398 mg; 1.44 mmol; 0.8 equiv), $Pd(dba)_2$ (21 mg; 2 mol%) and tfp (17 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1 + 0.5 vol% NEt_3) afforded **19d** as a colorless solid (371 mg; 0.96 mmol; 67%).

m.p. (°C): 114.9 – 116.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 – 8.12 (m, 2H), 7.65 (s, 2H), 7.63 – 7.60 (m, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H).

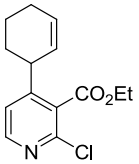
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.8, 152.1, 141.5, 139.5, 132.0, 130.5, 127.2, 125.1, 61.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 3066, 2983, 2931, 2910, 2866, 1714, 1664, 1613, 1575, 1515, 1482, 1467, 1439, 1407, 1358, 1314, 1276, 1221, 1183, 1168, 1154, 1119, 1106, 1092, 1063, 1025, 1018, 979, 883, 850, 817, 800, 774, 758, 718, 701, 670.

MS (EI, 70 eV): m/z (%) = 387 (22), 385 (44, M^+), 383 (23), 359 (30), 357 (59), 355 (29), 342 (54), 341 (17), 340 (100), 338 (50), 233 (30), 231 (30), 153 (29), 152 (48), 151 (23), 126 (18), 125 (15), 76 (10).

HRMS (EI): calcd. for [$C_{14}H_{11}Br_2NO_2$]: 382.9157; found: 382.9150 (M^+).

Synthesis of ethyl 2-chloro-4-(cyclohex-2-enyl)nicotinate (**19e**)



According to **TP3**, injection loop A and B were loaded with solutions of ethyl 2-chloronicotinate (**3f**; 0.43 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.65 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (222 mg; 1.38 mmol; 0.8 equiv) and CuCN·2LiCl (0.17 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1.5 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1 + 0.5 vol% NEt_3) afforded **19e** as a colorless oil (321 mg; 1.21 mmol; 88%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.29 (d, J = 5.2 Hz, 1H), 7.15 (d, J = 5.2 Hz, 1H), 5.99 – 5.92 (m, 1H), 5.56 – 5.52 (m, 1H), 4.50 – 4.33 (m, 2H), 3.45 – 3.38 (m, 1H), 2.08 – 1.98 (m, 3H), 1.75 – 1.43 (m, 3H), 1.40 – 1.35 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.9, 155.6, 149.7, 147.4, 130.5, 129.8, 127.1, 121.8, 62.1, 39.2, 31.2, 24.6, 20.8, 14.0.

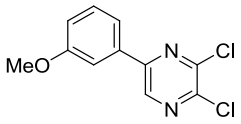
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2982, 2932, 2861, 2838, 1730, 1650, 1579, 1546, 1447, 1393, 1379, 1363, 1309, 1270, 1226, 1215, 1180, 1119, 1095, 1061, 1044, 1012, 938, 910, 890, 852, 841, 803, 736, 724, 694.

MS (EI, 70 eV): m/z (%) = 267 (15), 265 (43), 236 (19), 222 (16), 221 (39), 220 (58), 219 (100), 218 (44), 203 (14), 202 (24), 201 (41), 200 (40), 190 (13), 184 (23), 183 (25), 182 (83),

166 (36), 156 (16), 155 (14), 154 (42), 128 (28), 127 (24), 116 (10), 115 (12), 77 (17), 41 (11).

HRMS (EI): calcd. for [$C_{14}H_{16}ClNO_2$]: 265.0870; found: 265.0862 (M^+).

Synthesis of 2,3-dichloro-5-(3-methoxyphenyl)pyrazine (**19f**)



According to **TP3**, injection loop A and B were loaded with solutions of 2,3-dichloropyrazine (**18b**; 0.44 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-iodoanisole (330 mg; 1.44 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1 + 0.5 vol% NEt_3) afforded **19f** as a yellow solid (275 mg; 1.08 mmol; 77%).

m.p. (°C): 111.0 – 112.7.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.67 (s, 1H), 7.53 – 7.51 (m, 2H), 7.41 – 7.37 (m, 1H), 7.03 – 7.00 (m, 1H), 3.87 (s, 3H).

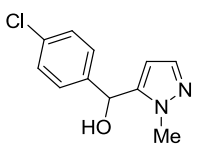
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.4, 150.7, 146.8, 145.4, 138.5, 135.1, 130.3, 119.3, 116.6, 112.4, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 2938, 2840, 1715, 1607, 1580, 1545, 1506, 1491, 1465, 1451, 1434, 1415, 1351, 1323, 1300, 1273, 1220, 1207, 1196, 1175, 1161, 1065, 1035, 925, 887, 859, 786, 753, 694, 677, 659.

MS (EI, 70 eV): m/z (%) = 257 (10), 256 (63), 254 (100), 253 (21), 226 (11), 225 (11), 224 (15), 211 (11); 162 (10), 133 (13), 114 (10), 103 (19), 90 (10), 89 (19), 63 (23).

HRMS (EI): calcd. for [$C_{11}H_8Cl_2N_2O$]: 254.0014; found: 254.0014 (M^+).

Synthesis of (4-chlorophenyl)(1-methyl-1H-pyrazol-5-yl)methanol (**19g**)



According to **TP3**, injection loop A and B were loaded with solutions of 1-methylpyrazole (**18c**; 0.43 M containing 0.5 equiv $LaCl_3 \cdot 2LiCl$) and Cy_2NLi (0.65 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-chlorobenzaldehyde (194 mg; 1.38 mmol; 0.8 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 1 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3 → EtOAc + 0.5 vol% NEt_3) afforded **19g** as an orange oil (192 mg; 0.86 mmol; 62%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.26 (m, 5H), 5.96 (s, 1H), 5.83 (s, 1H), 3.70 (s, 3H), 3.32 (br, 1H).

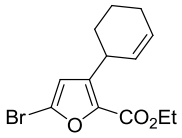
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 143.8, 139.5, 137.8, 133.9, 128.7, 127.8, 105.9, 67.6, 37.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3215, 2944, 2858, 1596, 1578, 1488, 1397, 1326, 1282, 1199, 1087, 1052, 1013, 936, 853, 841, 799, 777, 764, 725, 709, 686, 672.

MS (EI, 70 eV): m/z (%) = 224 (32), 223 (18, M^+), 222 (100), 221 (12), 207 (20), 205 (50), 141 (17), 139 (46), 112 (17), 111 (34), 111 (20), 110 (19), 109 (97), 105 (18), 95 (10), 83 (64), 82 (11), 77 (35), 75 (14), 56 (11), 42 (14).

HRMS (EI): calcd. for [$C_{11}H_{11}ClN_2O$]: 222.0560; found: 222.0553 (M^+).

Synthesis of ethyl 5-bromo-3-(cyclohex-2-enyl)furan-2-carboxylate (**19h**)



According to **TP3**, injection loop A and B were loaded with solutions of ethyl 5-bromofuran-2-carboxylate (**9**; 0.45 M containing 0.5 equiv $ZnCl_2 \cdot 2LiCl$) and Cy_2NLi (0.68 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (232 mg; 1.44 mmol; 0.8 equiv) and CuCN·2LiCl (0.18 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash

column chromatography (silica gel; *i*-hexane:EtOAc = 100:1) afforded **19h** as a colorless oil (327 mg; 1.09 mmol; 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.33 (s, 1H), 5.83 – 5.78 (m, 1H), 5.54 – 5.50 (m, 1H), 4.34 – 4.28 (m, 2H), 4.05 – 4.00 (m, 1H), 2.04 – 1.93 (m, 3H), 1.73 – 1.42 (m, 3H), 1.35 – 1.31 (m, 3H).

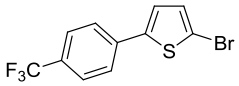
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.3, 142.3, 141.2, 128.9, 128.3, 126.2, 114.7, 60.8, 32.3, 30.0, 24.8, 21.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 1705, 1591, 1476, 1446, 1398, 1383, 1308, 1258, 1143, 1094, 1068, 1037, 1015, 979, 933, 896, 881, 865, 814, 762, 724, 678.

MS (EI, 70 eV): m/z (%) = 300 (49), 298 (51), 271 (45), 269 (43), 254 (29), 253 (91), 252 (32), 251 (100), 225 (32), 223 (28), 145 (21), 144 (23), 117 (56), 116 (29), 115 (60), 91 (53), 89 (21), 81 (28), 79 (34), 78 (22), 77 (43), 67 (19), 65 (24), 63 (26), 51 (33), 41 (41).

HRMS (EI): calcd. for [$C_{13}H_{15}BrO_3$]: 298.0205; found: 298.0198 (M^+).

Synthesis of 2-bromo-5-(4-(trifluoromethyl)phenyl)thiophene (**19i**)



According to **TP3**, injection loop A and B were loaded with solutions of 2-bromothiophene (**18d**; 0.44 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzotrifluoride (384 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane) afforded **19i** as a colorless solid (396 mg; 1.29 mmol; 91%).

m.p. (°C): 96.0 – 97.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.62 – 7.57 (m, 4H), 7.12 (d, J = 3.9 Hz, 1H), 7.05 (d, J = 3.9 Hz, 1H).

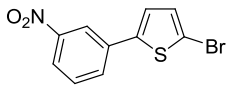
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 144.0, 136.9, 131.2, 129.7 (q, J = 33.2 Hz), 126.1 (q, J = 4.0 Hz), 125.7, 124.7, 124.0 (q, J = 271.6 Hz), 133.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 1914, 1759, 1612, 1571, 1506, 1429, 1411, 1324, 1283, 1245, 1209, 1191, 1161, 1127, 1109, 1071, 1059, 1017, 1008, 979, 944, 880, 834, 799, 775, 735, 696.

MS (EI, 70 eV): m/z (%) = 309 (12), 308 (96), 307 (10, M^+), 306 (100), 183 (67), 133 (10), 97 (10), 83 (12), 71 (17), 69 (16), 57 (25), 55 (16), 43 (18), 43 (27), 41 (18).

HRMS (EI): calcd. for [$C_{11}H_6BrF_3S$]: 305.9326; found: 305.9323 (M^+).

Synthesis of 2-bromo-5-(3-nitrophenyl)thiophene (**19j**)



According to **TP3**, injection loop A and B were loaded with solutions of 2-bromothiophene (**18d**; 0.44 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 1-iodo-3-nitrobenzene (351 mg; 1.41 mmol; 0.8 equiv), $Pd(dba)_2$ (20 mg; 2 mol%) and tfp (16 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred for further 2 h at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 80:1) afforded **19j** as a yellow solid (354 mg; 1.25 mmol; 89%).

m.p. (°C): 114.5 – 116.7.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.32 (t, J = 2.0 Hz, 1H), 8.10 (ddd, J = 8.1 Hz, J = 2.1 Hz, J = 1.0 Hz, 1H), 7.77 (ddd, J = 7.9 Hz, J = 1.9 Hz, J = 1.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 3.9 Hz, 1H), 7.06 (d, J = 3.9 Hz, 1H).

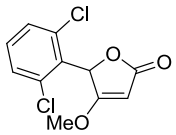
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.8, 142.8, 135.2, 131.3, 131.1, 130.0, 125.0, 122.2, 120.1, 113.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3096, 3063, 2921, 1762, 1575, 1537, 1516, 1480, 1437, 1418, 1346, 1287, 1244, 1209, 1102, 1077, 996, 962, 911, 886, 877, 862, 790, 732, 660.

MS (EI, 70 eV): m/z (%) = 285 (72), 283 (69), 239 (15), 237 (14), 159 (12), 158 (100), 114 (21), 79 (14).

HRMS (EI): calcd. for [$C_{10}H_6BrNO_2S$]: 282.9303; found: 282.9299 (M^+).

Synthesis of 5-(2,6-dichlorophenyl)-4-methoxyfuran-2(5H)-one (**22**)



According to **TP3**, injection loop A and B were loaded with solutions of (E)-methyl 3-methoxyacrylate (**20**; 0.45 M containing 0.5 equiv $MgCl_2$) and Cy_2NLi (0.68 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 2,6-dichlorobenzaldehyde (252 mg; 1.44 mmol; 0.8 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 1 h at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 3:1) afforded **22** as a colorless solid (241 mg; 0.93 mmol; 65%).

m.p. (°C): 134.0 – 136.2.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.30 (m, 1H), 7.23 – 7.19 (m, 2H), 6.50 (d, J = 1.5 Hz, 1H), 5.22 (d, J = 1.5 Hz, 1H), 3.82 (s, 3H).

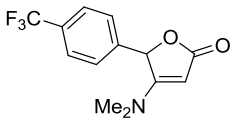
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 180.0, 172.3, 137.4, 136.2, 131.1, 130.3, 128.7, 127.8, 90.6, 76.3, 59.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3117, 2925, 1747, 1628, 1580, 1563, 1436, 1346, 1283, 1246, 1189, 1148, 1094, 1035, 988, 941, 888, 836, 769, 734, 674.

MS (EI, 70 eV): m/z (%) = 260 (23), 258 (31), 175 (13), 173 (15), 85 (100).

HRMS (EI): calcd. for [$C_{11}H_8Cl_2O_3$]: 257.9851; found: 257.9842 (M^+).

Synthesis of 4-(dimethylamino)-5-(4-(trifluoromethyl)phenyl)furan-2(5H)-one (**25**)



According to **TP3**, injection loop A and B were loaded with solutions of (E)-ethyl 3-(dimethylamino)acrylate (**23**; 0.44 M containing 0.5 equiv $MgCl_2$) and Cy_2NLi (0.66 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-(trifluoromethyl)benzaldehyde (246 mg; 1.41 mmol; 0.8 equiv) dissolved in THF (2 mL). The reaction mixture was stirred for further 30 min at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the

combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; EtOAc) afforded **25** as a yellow solid (238 mg; 0.88 mmol; 62%).

m.p. (°C): 146.5 – 148.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 5.76 (s, 1H), 4.79 (s, 1H), 2.79 (br, 6H).

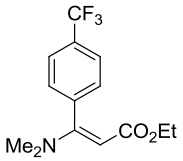
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.5, 169.7, 139.1, 131.8 (q, J = 33.2 Hz), 128.3, 126.2 (q, J = 3.0 Hz), 123.7 (q, J = 272.6 Hz), 83.3, 79.2, 40.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3116, 2925, 2855, 1811, 1779, 1714, 1617, 1518, 1478, 1443, 1425, 1411, 1331, 1306, 1272, 1201, 1163, 1106, 1068, 1009, 973, 903, 872, 850, 839, 786, 769, 753, 718, 678.

MS (EI, 70 eV): m/z (%) = 272 (12), 271 (84, M^+), 97 (11), 69 (100).

HRMS (EI): calcd. for [$C_{13}H_{12}F_3NO_2$]: 271.0820; found: 271.0821 (M^+).

Synthesis of (E)-ethyl 3-(dimethylamino)-3-(4-(trifluoromethyl)phenyl)acrylate (**27**)



According to **TP3**, injection loop A and B were loaded with solutions of (E)-ethyl 3-(dimethylamino)acrylate (**23**; 0.45 M containing 0.5 equiv $ZnCl_2$·2LiCl) and Cy_2NLi (0.69 M). After injection and *in situ* trapping metalation the combined streams were collected in a flask containing 4-iodobenzotrifluoride (392 mg; 1.44 mmol; 0.8 equiv), $Pd(dba)_2$ (21 mg; 2 mol%) and tfp (17 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with water (25 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1) afforded **27** as a yellow solid (291 mg; 1.01 mmol; 70%).

m.p. (°C): 83.1 – 84.7.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 4.80 (s, 1H), 3.87 (q, J = 7.1 Hz, 2H), 2.76 (s, 6H), 1.04 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.7, 161.9, 140.7, 130.4 (q, J = 32.2 Hz), 128.7, 125.3 (q, J = 4.0 Hz), 124.1 (q, J = 272.6 Hz), 87.7, 58.6, 40.3, 14.3.

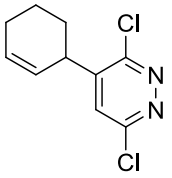
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 2933, 1680, 1618, 1563, 1519, 1481, 1448, 1401, 1351, 1320, 1243, 1210, 1145, 1116, 1090, 1061, 1043, 1015, 998, 911, 856, 840, 796, 755, 721, 687.

MS (EI, 70 eV): m/z (%) = 287 (57, M^+), 286 (100), 268 (11), 258 (30), 242 (98), 240 (14), 215 (23), 214 (70), 212 (19), 199 (16), 184 (14), 173 (33), 171 (24), 151 (22), 145 (15), 72 (18), 44 (32), 42 (11).

HRMS (EI): calcd. for [$C_{14}H_{15}F_3NO_2$]: 286.1055; found: 286.1043 (M^+ - H).

3.3 High temperature continuous flow zincations using $(Cy_2N)_2Zn{\cdot}2LiCl$

Synthesis of 3,6-dichloro-4-(cyclohex-2-enyl)pyridazine (**30a**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 3,6-dichloropyridazine (**28a**; 3.0 mL; 0.67 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.37 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing 3-bromocyclohexene (172 mg; 1.07 mmol; 0.8 equiv) and CuCN·2LiCl (0.13 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C and 30 min at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1 + 0.5 vol% NEt_3) afforded **30a** as a colorless oil (211 mg; 0.92 mmol; 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 (s, 1H), 6.12 – 6.07 (m, 1H), 5.55 – 5.50 (m, 1H), 3.72 – 3.68 (m, 1H), 2.11 – 2.07 (m, 3H), 1.67 – 1.44 (m, 3H).

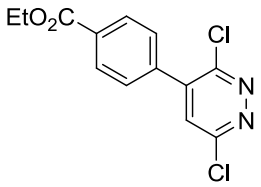
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.6, 156.1, 147.7, 132.6, 128.8, 124.8, 37.4, 28.4, 24.7, 19.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3025, 2930, 2862, 2836, 1651, 1559, 1509, 1446, 1431, 1393, 1356, 1342, 1312, 1293, 1275, 1252, 1227, 1212, 1191, 1127, 1100, 1058, 1047, 1038, 995, 921, 910, 880, 863, 851, 814, 764, 754, 723, 686, 666.

MS (EI, 70 eV): m/z (%) = 230 (24), 228 (35), 193 (10), 157 (24), 142 (21), 139 (17), 137 (55), 129 (20), 111 (23), 104 (14), 103 (12), 102 (35), 101 (14), 89 (13), 81 (100), 79 (14), 77 (32), 75 (19), 67 (41), 65 (12), 63 (17), 54 (24), 53 (23), 51 (40), 50 (16), 41 (42).

HRMS (EI): calcd. for [$C_{10}H_{10}Cl_2N_2$]: 228.0221; found: 228.0203 (M^+).

Synthesis of ethyl 4-(3,6-dichloropyridazin-4-yl)benzoate (**30b**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 3,6-dichloropyridazine (**28a**; 3.0 mL; 0.67 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.37 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing ethyl 4-iodobenzoate (295 mg; 1.07 mmol; 0.8 equiv), $Pd(dba)_2$ (15 mg; 2 mol%) and tfp (12 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred for 2 h at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 7:1 + 0.5 vol% NEt_3) afforded **30b** as a yellow solid (229 mg; 0.77 mmol; 72%).

m.p. (°C): 94.5 – 96.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.50 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H).

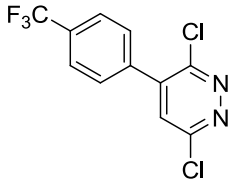
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.6, 156.1, 154.4, 141.8, 137.2, 132.1, 130.0, 129.6, 129.0, 61.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3048, 2980, 2905, 2872, 2244, 1713, 1612, 1561, 1508, 1476, 1464, 1446, 1407, 1367, 1352, 1327, 1313, 1271, 1183, 1135, 1101, 1056, 1040, 1018, 908, 860, 840, 774, 752, 730, 703.

MS (EI, 70 eV): m/z (%) = 298 (37), 297 (M^+, 15), 296 (48), 270 (28), 268 (49), 254 (13), 253 (62), 252 (14), 251 (100), 188 (11), 160 (13), 153 (22), 126 (18), 99 (10).

HRMS (EI): calcd. for [$C_{13}H_{10}Cl_2N_2O_2$]: 296.0119; found: 296.0116 (M^+).

Synthesis of 3,6-dichloro-4-(4-(trifluoromethyl)phenyl)pyridazine (**30c**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 3,6-dichloropyridazine (**28a**; 3.0 mL; 0.67 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.37 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing 4-iodobenzotrifluoride (291 mg; 1.07 mmol; 0.8 equiv), $Pd(dba)_2$ (15 mg; 2 mol%) and tfp (12 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **30c** as a colorless solid (202 mg; 0.69 mmol; 64%).

m.p. (°C): 117.7 – 119.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.79 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.49 (s, 1H).

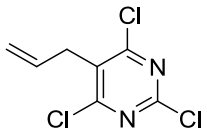
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.2, 154.4, 141.3, 136.7, 132.4 (q, J = 33.2 Hz), 129.6, 129.4, 126.0 (q, J = 4.0 Hz), 123.6 (q, J = 272.6 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3108, 3062, 3033, 2927, 2855, 1619, 1555, 1492, 1459, 1409, 1380, 1351, 1324, 1284, 1234, 1216, 1193, 1172, 1145, 1136, 1120, 1106, 1071, 1055, 1040, 1014, 975, 961, 920, 852, 845, 836, 773, 760, 741, 706, 658.

MS (EI, 70 eV): m/z (%) = 294 (24), 292 (38), 266 (58), 265 (11), 264 (78), 231 (20), 229 (66), 216 (18), 214 (28), 209 (14), 206 (30), 204 (100), 195 (17), 194 (50), 193 (19), 176 (11), 175 (11), 170 (25), 169 (39), 154 (28), 145 (18), 144 (21), 143 (10), 126 (12), 125 (19), 120 (10), 99 (22), 95 (16), 75 (22), 74 (13).

HRMS (EI): calcd. for [$C_{11}H_5Cl_2F_3N_2$]: 291.9782; found: 291.9763 (M^+).

Synthesis of 5-allyl-2,4,6-trichloropyrimidine (**30d**)



According to **TP5**, injection loop A and B (4.0 mL) were loaded with solutions of 2,4,6-trichloropyrimidine (**28b**; 5.0 mL; 0.49 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (5.0 mL; 0.27 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 50 °C) the combined streams were collected in a flask containing allyl bromide (190 mg; 1.57 mmol; 0.8 equiv) and CuCN·2LiCl (0.20 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C and 30 min at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 100:1 + 0.5 vol% NEt_3) afforded **30d** as a yellow oil (324 mg; 1.45 mmol; 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.84 – 5.74 (m, 1H), 5.16 – 5.06 (m, 2H), 3.60 – 3.58 (m, 2H).

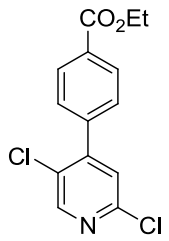
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.0, 157.1, 130.2, 129.3, 118.5, 33.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3086, 2985, 1640, 1538, 1497, 1432, 1415, 1333, 1311, 1213, 1184, 1172, 1116, 1094, 989, 928, 908, 870, 834, 791, 741, 730.

MS (EI, 70 eV): m/z (%) = 310 (17), 286 (19), 284 (27), 228 (18), 226 (27), 224 (91), 222 (100), 201 (22), 189 (26), 188 (34), 187 (36), 186 (34), 153 (26), 152 (32), 151 (69), 150 (47), 126 (27), 125 (33), 90 (44), 83 (17), 57 (22), 55 (45), 44 (30), 43 (17), 43 (39), 41 (47).

HRMS (EI): calcd. for $[C_7H_5Cl_3N_2]$: 221.9518; found: 221.9517 (M^+).

Synthesis of ethyl 4-(2,5-dichloropyridin-4-yl)benzoate (**30e**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,5-dichloropyridine (**28c**; 3.0 mL; 0.78 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.43 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing ethyl 4-iodobenzoate (345 mg; 1.25 mmol; 0.8 equiv), $Pd(dba)_2$ (18 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred for 2 h at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1 + 0.5 vol% NEt_3) afforded **30e** as a colorless solid (327 mg; 1.10 mmol; 88%).

m.p. (°C): 111.8 – 113.2.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.45 (s, 1H), 8.14 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.31 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H).

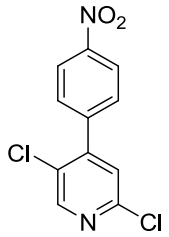
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 149.9, 149.7, 149.5, 139.6, 131.4, 129.8, 129.1, 128.9, 125.4, 61.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3075, 3045, 2993, 2983, 2938, 2911, 2870, 1711, 1665, 1646, 1611, 1573, 1519, 1508, 1480, 1468, 1448, 1422, 1406, 1365, 1337, 1314, 1278, 1213, 1182, 1146, 1127, 1119, 1102, 1081, 1026, 940, 915, 907, 875, 860, 828, 773, 750, 738, 726, 703, 655.

MS (EI, 70 eV): m/z (%) = 295 (10), 269 (12), 267 (20), 252 (23), 250 (32), 70 (14), 61 (18), 45 (16), 43 (100).

HRMS (EI): calcd. for $[C_{14}H_{11}Cl_2NO_2]$: 295.0167; found: 295.0158 (M^+).

Synthesis of 2,5-dichloro-4-(4-nitrophenyl)pyridine (**30f**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,5-dichloropyridine (**28c**; 3.0 mL; 0.78 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.43 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and

metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing 4-iodonitrobenzene (311 mg; 1.25 mmol; 0.8 equiv), $Pd(dba)_2$ (18 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred for 2 h at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **30f** as a yellow solid (264 mg; 0.98 mmol; 78%).

m.p. (°C): 158.3 – 160.1.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.49 (s, 1H), 8.34 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 8.9 Hz, 2H), 7.33 (s, 1H).

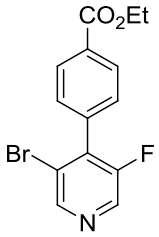
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.1, 149.9, 148.4, 148.1, 141.5, 130.0, 128.9, 125.3, 123.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3106, 3056, 2930, 2851, 1740, 1651, 1621, 1602, 1573, 1513, 1495, 1446, 1422, 1397, 1351, 1336, 1319, 1294, 1281, 1251, 1239, 1213, 1190, 1143, 1116, 1047, 1024, 1009, 985, 925, 919, 894, 857, 826, 759, 735, 727, 715, 696, 659.

MS (EI, 70 eV): m/z (%) = 270 (80), 268 (100), 241 (18), 140 (33), 240 (24), 238 (35), 224 (12), 222 (23), 212 (26), 196 (17), 195 (14), 189 (26), 187 (56), 168 (37), 167 (30), 166 (48), 162 (12), 160 (29), 140 (13), 74 (14), 61 (15), 45 (17), 44 (63), 43 (87).

HRMS (EI): calcd. for $[C_{11}H_6Cl_2N_2O_2]$: 267.9806; found: 267.9808 (M^+).

Synthesis of ethyl 4-(3-bromo-5-fluoropyridin-4-yl)benzoate (**30g**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 3-bromo-5-fluoropyridine (**28d**; 3.0 mL; 0.56 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.31 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing ethyl 4-iodobenzoate (248 mg; 0.90 mmol; 0.8 equiv), $Pd(dba)_2$ (13 mg; 2 mol%) and tfp (10 mg; 4 mol%) dissolved in THF (2 mL). The reaction

mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1 + 0.5 vol% NEt_3) afforded **30g** as a yellow solid (175 mg; 0.54 mmol; 60%).

m.p. (°C): 72.4 – 74.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.66 (s, 1H), 8.47 (s, 1H), 8.15 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).

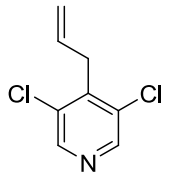
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 156.3 (d, J = 261.5 Hz), 148.2 (d, J = 5.0 Hz), 137.2 (d, J = 15.1 Hz), 137.1 (d, J = 25.1 Hz), 135.9, 131.4, 129.7, 129.5 (d, J = 1.0 Hz), 121.2 (d, J = 2.0 Hz), 61.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 2980, 2930, 2872, 1715, 1612, 1585, 1572, 1533, 1453, 1398, 1367, 1312, 1261, 1214, 1180, 1137, 1099, 1031, 1012, 964, 882, 854, 774, 754, 740, 702, 668.

MS (EI, 70 eV): m/z (%) = 325 (27), 323 (26), 297 (49), 295 (53), 280 (95), 279 (16), 278 (100), 171 (51), 144 (37).

HRMS (EI): calcd. for [$C_{14}H_{11}BrFNO_2$]: 322.9957; found: 322.9952 (M^+).

Synthesis of 4-allyl-3,5-dichloropyridine (**30h**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 3,5-dichloropyridine (**28e**; 3.0 mL; 0.78 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.43 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing allyl bromide (151 mg; 1.25 mmol; 0.8 equiv) and CuCN·2LiCl (0.16 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 30 min at 0 °C and 30 min at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel;

i-hexane:EtOAc = 200:1 + 0.5 vol% NEt_3) afforded **30h** as a colorless oil (205 mg; 1.09 mmol; 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.42 (s, 2H), 5.89 – 5.79 (m, 1H), 5.12 – 5.03 (m, 2H), 3.67 – 3.64 (m, 2H).

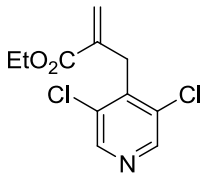
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.6, 144.2, 132.8, 131.1, 117.8, 34.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3083, 3048, 3014, 2983, 2927, 2854, 1740, 1638, 1615, 1560, 1529, 1435, 1403, 1390, 1295, 1270, 1239, 1213, 1188, 1167, 1147, 1087, 1047, 1011, 989, 920, 886, 838, 826, 811, 792, 739, 689, 661.

MS (EI, 70 eV): m/z (%) = 191 (10), 189 (58), 188 (M^+, 15), 187 (100), 186 (10), 155 (12), 153 (39), 152 (17), 151 (11), 117 (60), 116 (53), 115 (13), 89 (33), 63 (13), 43 (25).

HRMS (EI): calcd. for [$C_8H_7Cl_2N$]: 186.9956; found: 186.9950 (M^+).

Synthesis of ethyl 2-((3,5-dichloropyridin-4-yl)methyl)acrylate (**30i**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 3,5-dichloropyridine (**28e**; 3.0 mL; 0.78 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.43 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing ethyl 2-(bromomethyl)acrylate (241 mg; 1.25 mmol; 0.8 equiv) and CuCN·2LiCl (0.16 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 30 min at 0 °C and 30 min at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1 + 0.5 vol% NEt_3) afforded **30i** as a colorless solid (242 mg; 0.93 mmol; 74%).

m.p. (°C): 67.9 – 69.4.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (s, 2H), 6.20 (s, 1H), 4.98 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

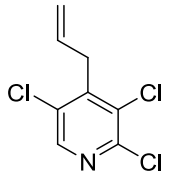
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.1, 147.6, 143.6, 134.9, 133.4, 125.0, 61.3, 32.3, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3049, 2984, 2961, 2928, 2855, 2360, 1708, 1673, 1634, 1562, 1528, 1476, 1446, 1426, 1411, 1395, 1368, 1345, 1281, 1223, 1213, 1189, 1162, 1136, 1113, 1088, 1026, 953, 895, 870, 844, 819, 806, 792, 749, 675.

MS (EI, 70 eV): m/z (%) = 226 (33), 225 (12), 224 (94), 216 (12), 214 (17), 198 (32), 197 (12), 196 (100), 151 (15), 150 (21), 43 (23).

HRMS (EI): calcd. for [$C_{11}H_{11}Cl_2NO_2$]: 259.0167; found: 259.0165 (M^+).

Synthesis of 4-allyl-2,3,5-trichloropyridine (**30j**)



According to **TP5**, injection loop A and B (4.0 mL) were loaded with solutions of 2,3,5-trichloropyridine (**28f**; 5.0 mL; 0.49 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (5.0 mL; 0.27 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing allyl bromide (190 mg; 1.57 mmol; 0.8 equiv) and CuCN·2LiCl (0.20 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 30 min at 0 °C and 1 h at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 100:1 + 0.5 vol% NEt_3) afforded **30j** as a colorless oil (338 mg; 1.52 mmol; 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.24 (s, 1H), 5.86 – 5.76 (m, 1H), 5.14 – 5.06 (m, 2H), 3.71 – 3.68 (m, 2H).

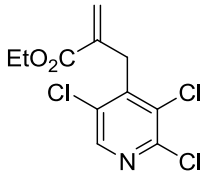
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.2, 147.2, 146.0, 131.6, 131.3, 130.5, 118.3, 36.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 2929, 1639, 1550, 1417, 1342, 1219, 1181, 1119, 1092, 1040, 989, 923, 888, 844, 808, 752, 718, 678.

MS (EI, 70 eV): m/z (%) = 225 (22), 223 (M^+, 67), 221 (67), 188 (27), 187 (12), 186 (45), 185 (11), 153 (13), 152 (33), 151 (38), 150 (100), 123 (18), 114 (18), 63 (10).

HRMS (EI): calcd. for [$C_8H_6Cl_3N$]: 220.9566; found: 220.9568 (M^+).

Synthesis of ethyl 2-((2,3,5-trichloropyridin-4-yl)methyl)acrylate (**30k**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,3,5-trichloropyridine (**28f**; 3.0 mL; 0.78 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.43 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing ethyl 2-(bromomethyl)acrylate (241 mg; 1.25 mmol; 0.8 equiv) and CuCN·2LiCl (0.16 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 30 min at 0 °C and 1 h at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 100:1 + 0.5 vol% NEt_3) afforded **30k** as a colorless oil (236 mg; 0.80 mmol; 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.29 (s, 1H), 6.21 (s, 1H), 4.99 (s, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.96 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H).

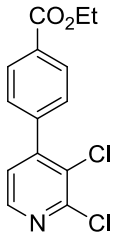
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 148.4, 146.6, 146.1, 134.5, 132.2, 132.0, 125.1, 61.4, 33.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2936, 2907, 2360, 1712, 1634, 1552, 1527, 1465, 1421, 1368, 1343, 1278, 1252, 1216, 1191, 1173, 1133, 1094, 1024, 952, 905, 862, 813, 756, 694.

MS (EI, 70 eV): m/z (%) = 260 (49), 259 (10), 258 (73), 250 (14), 248 (13), 234 (11), 232 (66), 231 (12), 230 (100), 186 (13), 185 (12), 184 (18), 150 (12), 43 (46).

HRMS (EI): calcd. for [$C_{11}H_{10}Cl_3NO_2$]: 292.9777; found: 292.9769 (M^+).

Synthesis of ethyl 4-(2,3-dichloropyridin-4-yl)benzoate (**30l**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,3-dichloropyridine (**28g**; 3.0 mL; 0.78 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.43 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing ethyl 4-iodobenzoate (345 mg; 1.25 mmol; 0.8 equiv), $Pd(dba)_2$ (18 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred for 2 h at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **30l** as a colorless solid (242 mg; 0.82 mmol; 66%).

m.p. (°C): 117.9 – 119.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.32 (d, J = 4.9 Hz, 1H), 8.13 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 4.9 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).

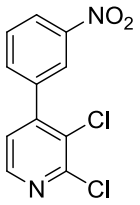
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 150.7, 150.1, 146.7, 140.9, 131.2, 129.7, 128.8, 128.8, 124.3, 61.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 2988, 2964, 2925, 2854, 1938, 1711, 1671, 1651, 1611, 1574, 1515, 1470, 1453, 1443, 1397, 1360, 1312, 1287, 1278, 1246, 1196, 1184, 1154, 1137, 1128, 1101, 1063, 1035, 1018, 964, 876, 867, 850, 801, 770, 748, 703, 671.

MS (EI, 70 eV): m/z (%) = 297 (18), 295 (28), 267 (60), 254 (14), 253 (11), 252 (66), 251 (16), 250 (100), 224 (10), 222 (16), 189 (10), 187 (28), 152 (10), 151 (10), 61 (11), 45 (12), 43 (59).

HRMS (EI): calcd. for $[C_{14}H_{11}Cl_2NO_2]$: 295.0167; found: 295.0157 (M^+).

Synthesis of 2,3-dichloro-4-(3-nitrophenyl)pyridine (**30m**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,3-dichloropyridine (**28g**; 3.0 mL; 0.78 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.43 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing 3-iodonitrobenzene (311 mg; 1.25 mmol; 0.8 equiv), $Pd(dba)_2$ (18 mg; 2 mol%) and tfp (14 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred for 2 h at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **30m** as a yellow solid (209 mg; 0.78 mmol; 62%).

m.p. (°C): 165.8 – 167.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.38 (d, J = 4.9 Hz, 1H), 8.34 – 8.30 (m, 2H), 7.79 – 7.76 (m, 1H), 7.70 – 7.66 (m, 1H), 7.23 (d, J = 4.9 Hz, 1H).

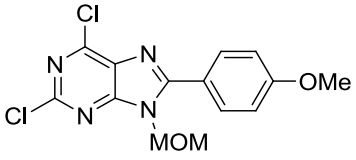
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.0, 148.4, 148.3, 147.1, 138.1, 134.8, 129.7, 128.9, 124.2, 124.1, 123.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 2924, 2860, 2360, 2340, 1614, 1572, 1520, 1483, 1443, 1427, 1367, 1344, 1310, 1302, 1276, 1251, 1222, 1196, 1175, 1143, 1119, 1105, 1093, 1065, 1039, 1024, 999, 972, 951, 917, 894, 850, 843, 813, 808, 766, 751, 736, 689, 682.

MS (EI, 70 eV): m/z (%) = 272 (11), 270 (66), 268 (100), 224 (24), 222 (35), 189 (17), 187 (53), 186 (11), 160 (11), 152 (14), 151 (16), 126 (12), 125 (14), 42 (32).

HRMS (EI): calcd. for $[C_{11}H_6Cl_2N_2O_2]$: 267.9806; found: 267.9811 (M^+).

Synthesis of 2,6-dichloro-9-(methoxymethyl)-8-(4-methoxyphenyl)-9H-purine (**30n**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,6-dichloro-9-(methoxymethyl)-9H-purine (**28h**; 3.0 mL; 0.69 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.38 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 25 °C) the combined streams were collected in a flask containing 4-iodoanisole (257 mg; 1.10 mmol; 0.8 equiv), $Pd(dba)_2$ (16 mg; 2 mol%) and tfp (13 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **30n** as a yellow solid (366 mg; 1.08 mmol; 98%).

m.p. (°C): 163.8 – 165.6.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 5.55 (s, 2H), 3.87 (s, 3H), 3.56 (s, 3H).

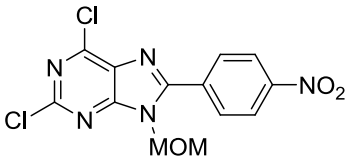
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.5, 157.6, 155.8, 152.2, 150.1, 131.6, 130.4, 120.0, 114.6, 74.0, 57.8, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 3014, 2923, 2851, 1609, 1563, 1526, 1478, 1462, 1449, 1437, 1425, 1399, 1366, 1353, 1313, 1297, 1259, 1219, 1198, 1179, 1157, 1117, 1081, 1042, 1019, 963, 954, 882, 839, 801, 782, 773, 742, 707, 677, 665.

MS (EI, 70 eV): m/z (%) = 340 (45), 339 (M^+, 13), 338 (68), 310 (24), 309 (22), 308 (37), 307 (27), 295 (12), 293 (12), 133 (15), 45 (100).

HRMS (EI): calcd. for $[C_{14}H_{12}Cl_2N_4O_2]$: 338.0337; found: 338.0332 (M^+).

Synthesis of 2,6-dichloro-9-(methoxymethyl)-8-(4-nitrophenyl)-9H-purine (**30o**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,6-dichloro-9-(methoxymethyl)-9H-purine (**28h**; 3.0 mL; 0.69 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.38 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 25 °C) the combined streams were collected in a flask containing 4-iodonitrobenzene (274 mg;

1.10 mmol; 0.8 equiv), $Pd(dba)_2$ (16 mg; 2 mol%) and tfp (13 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **30o** as a yellow solid (236 mg; 0.67 mmol; 61%).

m.p. (°C): 189.2 – 192.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.41 – 8.32 (m, 4H), 5.61 (s, 2H), 3.60 (s, 3H).

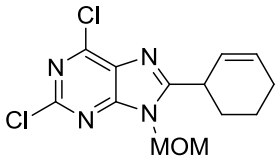
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.4, 154.9, 153.6, 152.0, 149.6, 133.6, 131.0, 130.2, 124.2, 74.0, 58.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3092, 3038, 3011, 2938, 2850, 2823, 1601, 1581, 1564, 1518, 1506, 1482, 1447, 1403, 1367, 1341, 1318, 1300, 1260, 1223, 1202, 158, 1146, 1107, 1086, 1032, 1010, 967, 885, 868, 855, 808, 787, 752, 715, 708, 688, 678, 663.

MS (EI, 70 eV): m/z (%) = 353 (14), 325 (18), 324 (11), 323 (29), 322 (12), 45 (100).

HRMS (EI): calcd. for [$C_{13}H_9Cl_2N_5O_3$]: 353.0082; found: 353.0084 (M^+).

Synthesis of 2,6-dichloro-8-(cyclohex-2-enyl)-9-(methoxymethyl)-9H-purine (**30p**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,6-dichloro-9-(methoxymethyl)-9H-purine (**28h**; 3.0 mL; 0.56 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.31 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 25 °C) the combined streams were collected in a flask containing 3-bromocyclohexene (145 mg; 0.90 mmol; 0.8 equiv) and CuCN·2LiCl (0.11 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C and overnight at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 5:1 + 0.5 vol% NEt_3) afforded **30p** as a yellow solid (220 mg; 0.70 mmol; 78%).

m.p. (°C): 97.1 – 99.1.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.02 – 5.97 (m, 1H), 5.75 – 5.72 (m, 1H), 5.58 (s, 2H), 3.93 – 3.86 (m, 1H), 3.37 (s, 3H), 2.23 – 2.10 (m, 3H), 2.03 – 1.92 (m, 2H), 1.74 – 1.63 (m, 1H).

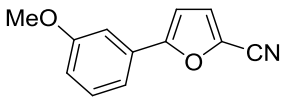
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.5, 155.1, 152.4, 150.2, 130.8, 130.0, 124.3, 73.2, 57.4, 35.6, 28.1, 24.5, 21.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3030, 2935, 2836, 1734, 1591, 1560, 1503, 1465, 1448, 1435, 1390, 1355, 1314, 1294, 1266, 1239, 1224, 1196, 1181, 1139, 1126, 1084, 1044, 995, 970, 916, 902, 876, 847, 792, 749, 722, 682.

MS (EI, 70 eV): m/z (%) = 314 (14), 312 (20), 284 (14), 283 (16), 282 (19), 281 (21), 271 (13), 267 (22), 253 (14), 216 (12), 45 (100).

HRMS (EI): calcd. for [$C_{13}H_{14}Cl_2N_4O$]: 312.0545; found: 312.0540 (M^+).

Synthesis of 5-(3-methoxyphenyl)furan-2-carbonitrile (**30q**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2-furonitrile (**28i**; 3.0 mL; 0.69 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.38 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 80 °C) the combined streams were collected in a flask containing 3-iodoanisole (257 mg; 1.10 mmol; 0.8 equiv), $Pd(dba)_2$ (16 mg; 2 mol%) and tfp (13 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **30q** as a yellow solid (153 mg; 0.77 mmol; 70%).

m.p. (°C): 86.5 – 88.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.36 – 7.25 (m, 2H), 7.23 – 7.22 (m, 1H), 7.14 (d, J = 3.7 Hz, 1H), 6.93 – 6.90 (m, 1H), 6.69 (d, J = 3.7 Hz, 1H), 3.85 (s, 3H).

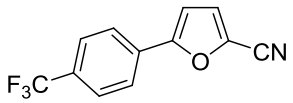
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.1, 158.5, 130.1, 129.9, 125.1, 123.9, 117.4, 115.5, 111.9, 110.1, 106.3, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3123, 3006, 2943, 2913, 2836, 2221, 1747, 1615, 1590, 1572, 1515, 1486, 1453, 1435, 1358, 1338, 1318, 1286, 1249, 1231, 1208, 1177, 1154, 1102, 1061, 1044, 1031, 994, 964, 896, 868, 836, 823, 796, 775, 688, 676, 622, 596, 568, 559.

MS (EI, 70 eV): m/z (%) = 200 (11), 199 (M^+, 100), 156 (11).

HRMS (EI): calcd. for [$C_{12}H_9NO_2$]: 199.0633; found: 199.0628 (M^+).

Synthesis of 5-(4-(trifluoromethyl)phenyl)furan-2-carbonitrile (**30r**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2-furonitrile (**28i**; 3.0 mL; 0.69 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.38 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 80 °C) the combined streams were collected in a flask containing 4-iodobenzotrifluoride (299 mg; 1.10 mmol; 0.8 equiv), $Pd(dba)_2$ (16 mg; 2 mol%) and tfp (13 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1) afforded **30r** as a yellow solid (167 mg; 0.70 mmol; 64%).

m.p. (°C): 89.3 – 90.9.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.81 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 3.7 Hz, 1H), 6.83 (d, J = 3.7 Hz, 1H).

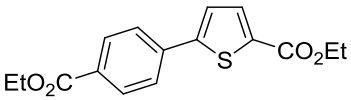
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.9, 131.7, 131.2 (q, J = 33.2 Hz), 127.4, 126.1 (q, J = 4.0 Hz), 125.0, 123.9, 123.8 (q, J = 272.3 Hz), 111.5, 107.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3135, 2934, 2230, 1618, 1592, 1574, 1532, 1489, 1418, 1392, 1364, 1318, 1277, 1235, 1218, 1167, 1111, 1070, 1052, 1025, 967, 926, 895, 880, 846, 830, 797, 774, 741, 694, 670, 629, 593.

MS (EI, 70 eV): m/z (%) = 238 (11), 237 (M^+, 100), 183 (26), 140 (22).

HRMS (EI): calcd. for [$C_{12}H_6F_3NO$]: 237.0401; found: 237.0397 (M^+).

Synthesis of ethyl 5-(4-(ethoxycarbonyl)phenyl)thiophene-2-carboxylate (**30s**)



According to **TP5**, injection loop A and B (4.0 mL) were loaded with solutions of ethyl 2-thiophenecarboxylate (**28j**; 5.0 mL; 0.36 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (5.0 mL; 0.20 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 100 °C) the combined streams were collected in a flask containing ethyl 4-iodobenzoate (317 mg; 1.15 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (13 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **30s** as a yellow solid (236 mg; 0.78 mmol; 68%).

m.p. (°C): 105.8 – 107.2.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 3.9 Hz, 1H), 7.67 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 3.9 Hz, 1H), 4.40 – 4.32 (m, 4H), 1.40 – 1.35 (m, 6H).

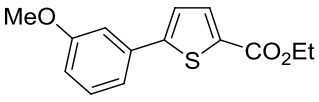
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.0, 162.1, 149.4, 137.5, 134.2, 133.9, 130.4, 130.4, 125.9, 124.8, 61.3, 61.2, 14.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2987, 2976, 2928, 2905, 2870, 1699, 1605, 1566, 1536, 1507, 1476, 1449, 1410, 1388, 1362, 1342, 1314, 1288, 1268, 1250, 1212, 1184, 1112, 1095, 1052, 1012, 959, 904, 882, 856, 845, 818, 769, 746, 717, 694, 666.

MS (EI, 70 eV): m/z (%) = 305 (16), 304 (M^+, 100), 276 (22), 260 (15), 259 (82), 233 (11), 232 (13), 158 (11), 115 (13).

HRMS (EI): calcd. for $[C_{16}H_{16}O_4S]$: 304.0769; found: 304.0759 (M^+).

Synthesis of ethyl 5-(3-methoxyphenyl)thiophene-2-carboxylate (**30t**)



According to **TP5**, injection loop A and B (4.0 mL) were loaded with solutions of ethyl 2-thiophenecarboxylate (**28j**; 5.0 mL; 0.36 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (5.0 mL; 0.20 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and

metalation (residence time: 10 min; metalation temperature: 100 °C) the combined streams were collected in a flask containing 3-iodoanisole (269 mg; 1.15 mmol; 0.8 equiv), $Pd(dba)_2$ (17 mg; 2 mol%) and tfp (13 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 50:1) afforded **30t** as a yellow oil (193 mg; 0.74 mmol; 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.72 (d, J = 3.9 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.25 (d, J = 3.9 Hz, 1H), 7.21 – 7.19 (m, 1H), 7.14 – 7.13 (m, 1H), 6.89 – 6.86 (m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

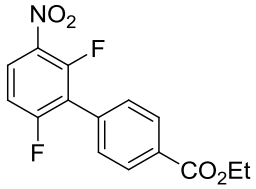
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.3, 160.1, 150.9, 134.8, 134.1, 132.6, 130.1, 123.8, 118.7, 114.3, 111.8, 61.2, 55.3, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3081, 2980, 2938, 2906, 2836, 1700, 1598, 1579, 1537, 1493, 1459, 1438, 1392, 1367, 1344, 1273, 1242, 1218, 1167, 1090, 1041, 1013, 994, 906, 864, 839, 814, 774, 746, 684.

MS (EI, 70 eV): m/z (%) = 263 (18), 262 (M^+, 100), 234 (45), 218 (15), 217 (80), 190 (17), 145 (23), 102 (11).

HRMS (EI): calcd. for [$C_{14}H_{14}O_3S$]: 262.0664; found: 262.0659 (M^+).

Synthesis of ethyl 2',6'-difluoro-3'-nitrobiphenyl-4-carboxylate (**33a**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,4-difluoronitrobenzene (**31a**; 3.0 mL; 0.67 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.37 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 25 °C) the combined streams were collected in a flask containing ethyl 4-iodobenzoate (295 mg; 1.07 mmol; 0.8 equiv), $Pd(dba)_2$ (15 mg; 2 mol%) and tfp (12 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were

dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **33a** as an orange solid (315 mg; 1.03 mmol; 96%).

m.p. (°C): 85.0 – 86.9.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 8.4 Hz, 2H), 8.14 – 8.09 (m, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.16 – 7.11 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

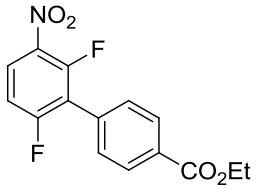
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 162.5 (dd, *J* = 260.4 Hz, *J* = 6.0 Hz), 153.8 (dd, *J* = 267.5 Hz, *J* = 8.0 Hz), 134.7, 131.3, 130.2 (t, *J* = 2.0 Hz), 129.7, 126.6 (dd, *J* = 11.1 Hz, *J* = 2.0 Hz), 120.3 (dd, *J* = 20.1 Hz, *J* = 18.1 Hz), 112.2 (dd, *J* = 24.1 Hz, *J* = 4.0 Hz), 61.3, 14.3. (One signal not observed; possible coincidental isochronicity.)

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3101, 2984, 2904, 1891, 1712, 1619, 1589, 1567, 1536, 1510, 1472, 1405, 1367, 1342, 1304, 1286, 1269, 1214, 1184, 1148, 1127, 1103, 1070, 1021, 1010, 948, 879, 857, 824, 777, 757, 713, 702, 667.

MS (EI, 70 eV): m/z (%) = 307 (M^+, 24), 279 (41), 263 (16), 262 (100), 216 (32), 188 (32), 187 (10).

HRMS (EI): calcd. for [$C_{15}H_{11}F_2NO_4$]: 307.0656; found: 307.0643 (M^+).

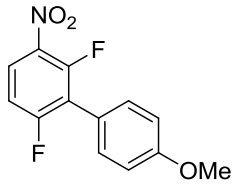
Scale-up synthesis of ethyl 2',6'-difluoro-3'-nitrobiphenyl-4-carboxylate (**33a**)



According to **TP6**, injection loop A and B (6.0 mL) were loaded with solutions of 2,4-difluoronitrobenzene (**31a**; 7.0 mL; 0.49 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (7.0 mL; 0.27 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 25 °C) the combined streams were collected in a flask containing ethyl 4-iodobenzoate (3.26 g; 11.8 mmol; 0.8 equiv), $Pd(dba)_2$ (169 mg; 2 mol%) and tfp (137 mg; 4 mol%) dissolved in THF (20 mL). The reaction loops were reloaded four times and the reaction mixture was further stirred overnight at 25 °C before it was quenched with water (150 mL). The aq. layer was extracted with EtOAc (3×200 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography

(silica gel; *i*-hexane:EtOAc = 30:1) afforded **33a** as an orange solid (3.56 g; 11.6 mmol; 98%).

Synthesis of 2,6-difluoro-4'-methoxy-3-nitrobiphenyl (**33b**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 2,4-difluoronitrobenzene (**31a**; 3.0 mL; 0.67 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.37 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 25 °C) the combined streams were collected in a flask containing 4-iodoanisole (250 mg; 1.07 mmol; 0.8 equiv), $Pd(dba)_2$ (15 mg; 2 mol%) and tfp (12 mg; 4 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×80 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **33b** as a yellow solid (216 mg; 0.81 mmol; 76%).

m.p. (°C): 104.5 – 106.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 – 8.00 (m, 1H), 7.37 (d, J = 8.9 Hz, 2H), 7.11 – 7.06 (m, 1H), 7.00 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H).

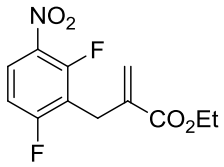
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.8 (dd, J = 258.5 Hz, J = 7.0 Hz), 160.3, 153.9 (dd, J = 265.5 Hz, J = 8.0 Hz), 134.9, 131.5 (t, J = 2.0 Hz), 125.5 (dd, J = 11.1 Hz, J = 1.0 Hz), 121.0 (dd, J = 20.1 Hz, J = 18.1 Hz), 118.9, 114.2, 112.0 (dd, J = 25.1 Hz, J = 4.0 Hz), 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 2940, 2843, 1893, 1613, 1587, 1576, 1532, 1516, 1468, 1438, 1411, 1347, 1305, 1282, 1256, 1212, 1179, 1146, 1117, 1073, 1017, 1007, 954, 938, 876, 840, 822, 806, 765, 730, 689.

MS (EI, 70 eV): m/z (%) = 266 (14), 265 (M^+, 100), 219 (38), 204 (21), 188 (21), 176 (39), 175 (48).

HRMS (EI): calcd. for $[C_{13}H_9F_2NO_3]$: 265.0551; found: 265.0542 (M^+).

Synthesis of ethyl 2-(2,6-difluoro-3-nitrobenzyl)acrylate (**33c**)



According to **TP5**, injection loop A and B (4.0 mL) were loaded with solutions of 2,4-difluoronitrobenzene (**31a**; 5.0 mL; 0.49 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (5.0 mL; 0.27 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 25 °C) the combined streams were collected in a flask containing ethyl 2-(bromomethyl)acrylate (303 mg; 1.57 mmol; 0.8 equiv) and CuCN·2LiCl (0.20 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C and overnight at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **33c** as a yellow oil (301 mg; 1.11 mmol; 71%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 – 7.98 (m, 1H), 7.03 – 6.98 (m, 1H), 6.28 (s, 1H), 5.43 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.74 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H).

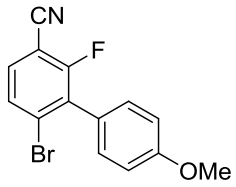
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 164.3 (dd, J = 259.5 Hz, J = 8.0 Hz), 155.3 (dd, J = 267.5 Hz, J = 9.1 Hz), 136.2, 134.4, 126.7, 125.7 (dd, J = 11.1 Hz, J = 1.0 Hz), 117.7 (dd, J = 20.1 Hz, J = 18.1 Hz), 111.6 (dd, J = 24.1 Hz, J = 4.0 Hz), 61.2, 25.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3107, 2984, 2908, 2876, 1714, 1624, 1596, 1534, 1476, 1455, 1434, 1408, 1348, 1319, 1300, 1275, 1257, 1213, 1174, 1136, 1096, 1036, 951, 885, 859, 823, 765, 739, 715, 680.

MS (EI, 70 eV): m/z (%) = 271 (M^+, 23), 226 (58), 225 (52), 223 (15), 206 (12), 198 (12), 197 (40), 179 (15), 172 (13), 152 (21), 151 (100), 148 (23), 140 (10), 133 (12), 126 (14), 125 (14), 55 (11).

HRMS (EI): calcd. for $[C_{12}H_{11}F_2NO_4]$: 271.0656; found: 271.0645 (M^+).

Synthesis of 6-bromo-2-fluoro-4'-methoxybiphenyl-3-carbonitrile (**33d**)



According to **TP5**, injection loop A and B (4.0 mL) were loaded with solutions of 4-bromo-2-fluorobenzonitrile (**31b**; 5.0 mL; 0.36 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (5.0 mL; 0.20 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing 4-iodoanisole (269 mg; 1.15 mmol; 0.8 equiv) and $Pd(PPh_3)_4$ (83 mg; 5 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (20 mL). The aq. layer was extracted with EtOAc (3×60 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 20:1) afforded **33d** as a colorless solid (299 mg; 0.98 mmol; 85%).

m.p. (°C): 87.8 – 89.6.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.59 – 7.56 (m, 1H), 7.44 – 7.41 (m, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H).

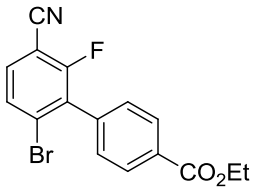
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.6 (d, *J* = 260.5 Hz), 160.1, 132.3 (d, *J* = 17.1 Hz), 132.1 (d, *J* = 1.0 Hz), 131.2 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 2.0 Hz), 129.4 (d, *J* = 4.0 Hz), 124.5, 114.0, 113.6, 101.1 (d, *J* = 18.1 Hz), 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3071, 3004, 2949, 2844, 2240, 1904, 1722, 1666, 1642, 1609, 1597, 1578, 1564, 1554, 1514, 1471, 1451, 1440, 1423, 1406, 1300, 1278, 1242, 1180, 1132, 1115, 1088, 1062, 1028, 916, 887, 858, 834, 827, 816, 810, 782, 756, 723.

MS (EI, 70 eV): m/z (%) = 308 (17), 307 (100), 306 (M^+, 16), 264 (19), 262 (21), 183 (28), 182 (26).

HRMS (EI): calcd. for [$C_{14}H_9BrFNO$]: 306.9831; found: 306.9816 (M^+).

Synthesis of ethyl 6'-bromo-3'-cyano-2'-fluorobiphenyl-4-carboxylate (**33e**)



According to **TP5**, injection loop A and B (4.0 mL) were loaded with solutions of 4-bromo-2-fluorobenzonitrile (**31b**; 5.0 mL; 0.36 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (5.0 mL; 0.20 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing ethyl 4-iodobenzoate (317 mg; 1.15 mmol; 0.8 equiv) and $Pd(PPh_3)_4$ (83 mg; 5 mol%) dissolved in THF (2 mL). The reaction mixture was further stirred overnight at 25 °C before it was quenched with water (30 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 15:1) afforded **33e** as a yellow oil (310 mg; 0.89 mmol; 77%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (d, J = 8.6 Hz, 2H), 7.62 – 7.60 (m, 1H), 7.51 – 7.48 (m, 1H), 7.37 (d, J = 8.4 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H).

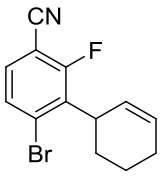
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.0, 160.2 (d, J = 261.5 Hz), 136.8, 132.9 (d, J = 1.0 Hz), 131.7 (d, J = 17.1 Hz), 131.2, 130.3 (d, J = 3.0 Hz), 129.9 (d, J = 1.0 Hz), 129.8, 129.6 (d, J = 5.0 Hz), 113.2, 101.3 (d, J = 17.1 Hz), 61.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 2982, 2937, 2906, 2238, 1713, 1612, 1599, 1572, 1558, 1513, 1476, 1453, 1428, 1403, 1367, 1310, 1270, 1245, 1196, 1179, 1102, 1086, 1020, 964, 889, 854, 836, 817, 773, 751, 708, 696.

MS (EI, 70 eV): m/z (%) = 349 (26), 347 (25), 321 (53), 319 (54), 305 (20), 304 (99), 303 (19), 302 (100), 196 (16), 195 (95), 168 (13), 97 (19).

HRMS (EI): calcd. for $[C_{16}H_{11}BrFNO_2]$: 346.9957; found: 346.9960 (M^+).

Synthesis of 4-bromo-3-(cyclohex-2-enyl)-2-fluorobenzonitrile (**33f**)



According to **TP5**, injection loop A and B (2.0 mL) were loaded with solutions of 4-bromo-2-fluorobenzonitrile (**31b**; 3.0 mL; 0.67 M) and $(Cy_2N)_2Zn{\cdot}2LiCl$ (3.0 mL; 0.37 M in THF + 10 vol% DMPU; 0.55 equiv). After injection (flow rate of pump A and B: 1.00 mL/min) and metalation (residence time: 10 min; metalation temperature: 60 °C) the combined streams were collected in a flask containing 3-bromocyclohexene (172 mg; 1.07 mmol; 0.8 equiv) and CuCN·2LiCl (0.13 mL; 10 mol%) dissolved in THF (2 mL) and cooled to 0 °C. The reaction mixture was stirred for further 1 h at 0 °C and 30 min at 25 °C before it was quenched with sat. aq. NH_4Cl/NH_3 (10 vol%; 20 mL). The aq. layer was extracted with EtOAc (3×70 mL), the combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 30:1) afforded **33f** as a colorless oil (238 mg; 0.85 mmol; 79%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.44 (m, 1H), 7.31 – 7.27 (m, 1H), 5.85 – 5.79 (m, 1H), 5.57 – 5.54 (m, 1H), 4.01 – 3.98 (m, 1H), 2.18 – 2.02 (m, 2H), 1.92 – 1.58 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.1 (d, J = 264.5 Hz), 134.8 (d, J = 13.1 Hz), 131.1, 131.1 (d, J = 1.0 Hz), 129.6 (d, J = 4.0 Hz), 127.8 (d, J = 2.0 Hz), 127.2 (d, J = 1.0 Hz), 113.6 (d, J = 1.0 Hz), 101.6 (d, J = 17.1 Hz), 27.7, 27.7, 24.4, 22.5.

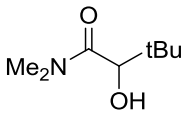
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3084, 3025, 2933, 2837, 2860, 2238, 1651, 1597, 1558, 1454, 1419, 1344, 1315, 1300, 1264, 1246, 1225, 1213, 1196, 1184, 1140, 1127, 1063, 1047, 1016, 946, 930, 898, 875, 858, 814, 754, 719, 644, 632, 612, 580, 557.

MS (EI, 70 eV): m/z (%) = 61 (13), 45 (13), 43 (100).

HRMS (EI): calcd. for $[C_{13}H_{11}BrFN]$: 279.0059; found: 279.0057 (M^+).

3.4 Continuous flow metalations of *N,N*-disubstituted formamides using LDA

Synthesis of 2-hydroxy-*N*,*N*,3,3-tetramethylbutanamide (**36a**)



According to **TP7**, a solution of *N*,*N*-dimethylformamide (**34a**; 0.40 M in THF; 1.0 equiv; 5.0 mL) and trimethylacetaldehyde (0.7 equiv) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane → EtOAc) afforded **36a** as a colorless solid (162 mg; 1.02 mmol; 73%).

m.p. (°C): 126.1 – 127.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.18 (s, 1H), 3.03 (s, 3H), 2.99 (s, 3H), 0.95 (s, 9H).

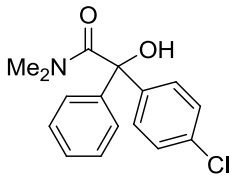
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.8, 73.9, 37.9, 36.6, 35.8, 25.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3319, 2977, 2951, 2867, 1738, 1625, 1506, 1478, 1460, 1432, 1394, 1380, 1362, 1314, 1252, 1195, 1141, 1076, 1022, 960, 933, 894, 840, 794, 706.

MS (EI, 70 eV): m/z (%) = 103 (81), 102 (43), 87 (26).

HRMS (EI): calcd. for [$C_8H_{17}NO_2$]: 159.1259; found: 159.1250 (M^+).

Synthesis of 2-(4-chlorophenyl)-2-hydroxy-N,N-dimethyl-2-phenylacetamide (**36b**)



According to **TP7**, a solution of *N*,*N*-dimethylformamide (**34a**; 0.40 M in THF; 1.0 equiv; 5.0 mL) and 4-chlorobenzophenone (0.7 equiv) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×60 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 2:1) afforded **36b** as a colorless solid (319 mg; 1.10 mmol; 79%).

m.p. (°C): 143.7 – 145.1.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 – 7.21 (m, 9H), 5.90 (br, 1H), 3.09 (br, 3H), 2.57 (br, 3H).

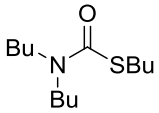
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.0, 141.3, 140.4, 133.8, 129.6, 128.5, 128.4, 128.1, 127.9, 80.3, 39.3, 38.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3278, 2931, 1739, 1625, 1600, 1577, 1488, 1451, 1398, 1364, 1257, 1208, 1158, 1089, 1061, 1032, 1013, 987, 945, 920, 865, 844, 812, 765, 746, 726, 709, 704, 655, 641.

MS (EI, 70 eV): m/z (%) = 218 (24), 217 (100), 165 (10), 141 (24), 139 (84), 111 (21), 105 (50), 77 (26), 72 (22).

HRMS (EI): calcd. for [$C_{16}H_{16}ClNO_2$]: 289.0870; found: 289.0859 (M^+).

Synthesis of *S*-butyl dibutylcarbamothioate (**36c**)



According to **TP7**, a solution of *N*,*N*-dibutylformamide (**34b**; 0.40 M in THF; 1.0 equiv; 5.0 mL) and dibutyl disulfide (0.7 equiv) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×60 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane → *i*-hexane:EtOAc = 50:1) afforded **36c** as a colorless oil (302 mg; 1.23 mmol; 88%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.32 – 3.26 (m, 4H), 2.89 – 2.84 (m, 2H), 1.61 – 1.52 (m, 6H), 1.44 – 1.24 (m, 6H), 0.94 – 0.85 (m, 9H).

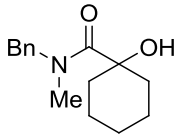
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.8, 47.7, 47.3, 32.3, 32.2, 30.4, 30.0, 29.8, 22.1, 20.6, 20.1, 13.8, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2931, 2873, 1647, 1464, 1405, 1377, 1313, 1282, 1204, 1123, 1101, 1052, 1038, 954, 916, 875, 837, 821, 784, 745, 710, 664.

MS (EI, 70 eV): m/z (%) = 245 (38, M^+), 202 (36), 189 (16), 174 (67), 157 (64), 156 (67), 156 (100), 84 (18), 57 (86), 55 (17), 41 (49).

HRMS (EI): calcd. for [$C_{13}H_{27}NOS$]: 245.1813; found: 245.1810 (M^+).

Synthesis of *N*-benzyl-1-hydroxy-*N*-methylcyclohexanecarboxamide (**36d**)



According to **TP7**, a solution of *N*-benzyl-*N*-methylformamide (**34c**; 0.40 M in THF; 1.0 equiv; 5.0 mL) and cyclohexanone (0.7 equiv) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×60 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 3:1) afforded **36d** as a yellow oil (218 mg; 0.88 mmol; 63%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 – 7.30 (m, 2H), 7.27 – 7.23 (m, 1H), 7.19 – 7.16 (m, 2H), 4.72 (br, 2H), 3.56 (br, 1H), 3.03 (br, 1H), 1.96 – 1.89 (m, 2H), 1.74 – 1.58 (m, 8H), 1.28 – 1.17 (m, 1H).

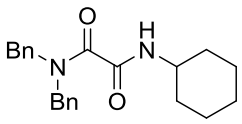
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 176.1, 137.0, 128.7, 127.4, 127.2, 74.6, 53.6, 36.1, 34.7, 25.2, 21.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3357, 2947, 2932, 2850, 1608, 1493, 1452, 1430, 1393, 1356, 1315, 1291, 1256, 1207, 1195, 1164, 1129, 1048, 1036, 1027, 988, 942, 912, 902, 847, 829, 818, 737, 711, 697, 656.

MS (EI, 70 eV): m/z (%) = 150 (17), 149 (100), 148 (51), 121 (17), 120 (33), 99 (62), 97 (13), 92 (17), 91 (76), 85 (13), 83 (16), 71 (21), 69 (17), 65 (11), 57 (25), 55 (22), 43 (19), 40 (17).

HRMS (EI): calcd. for [$C_{15}H_{21}NO_2$]: 247.1572; found: 247.1574 (M^+).

Synthesis of *N*,*N*-dibenzyl-*N'*-cyclohexyloxalamide (**36e**)



According to **TP7**, a solution of *N*,*N*-dibenzylformamide (**34d**; 0.40 M in THF; 1.0 equiv; 5.0 mL) and cyclohexyl isocyanate (0.7 equiv) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 10:1 + 0.5 vol% NEt_3) afforded **36e** as a colorless oil (266 mg; 0.76 mmol; 54%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31 – 7.17 (m, 10H), 4.91 (s, 2H), 4.46 (s, 2H), 3.75 – 3.66 (m, 1H), 1.90 – 1.84 (m, 2H), 1.70 – 1.65 (m, 2H), 1.59 – 1.52 (m, 1H), 1.36 – 1.07 (m, 6H).

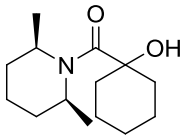
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.0, 160.4, 136.6, 136.1, 128.7, 128.7, 128.4, 127.9, 127.7, 127.7, 50.7, 48.8, 48.6, 32.6, 25.4, 24.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3286, 3064, 3029, 2930, 2854, 1737, 1672, 1619, 1585, 1545, 1517, 1495, 1465, 1450, 1363, 1329, 1305, 1257, 1241, 1206, 1151, 1091, 1078, 1045, 1029, 1002, 968, 945, 891, 844, 822, 809, 785, 752, 732, 697.

MS (EI, 70 eV): m/z (%) = 260 (14), 259 (100), 224 (10), 196 (31), 106 (61), 91 (82), 83 (12), 55 (13).

HRMS (EI): calcd. for [$C_{22}H_{26}N_2O_2$]: 350.1994; found: 350.1989 (M^+).

Synthesis of (2,6-dimethylpiperidin-1-yl)(1-hydroxycyclohexyl)methanone (**36f**)



According to **TP7**, a solution of 2,6-dimethylpiperidine-1-carbaldehyde (**34e**; 0.40 M in THF; 1.0 equiv; 5.0 mL) and cyclohexanone (0.7 equiv) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×70 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 6:1) afforded **36f** as a colorless solid (228 mg; 1.01 mmol; 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.68 (s, 2H), 4.38 (s, 1H), 1.91 – 1.45 (m, 15H), 1.35 – 1.13 (m, 7H).

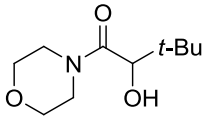
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 175.6, 74.6, 46.9, 35.1, 30.1, 25.3, 21.9, 21.5, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3381, 2962, 2929, 2850, 1598, 1446, 1415, 1363, 1342, 1315, 1303, 1274, 1257, 1242, 1189, 1163, 1150, 1122, 1094, 1076, 1046, 1034, 1016, 990, 980, 950, 932, 910, 889, 857, 832, 760, 735, 696, 677.

MS (EI, 70 eV): m/z (%) = 142 (13), 141 (52), 140 (20), 126 (100), 112 (15), 99 (48), 98 (57), 97 (11), 81 (41), 55 (54), 43 (13), 41 (23).

HRMS (EI): calcd. for [$C_{14}H_{25}NO_2$]: 239.1885; found: 239.1876 (M^+).

Synthesis of 2-hydroxy-3,3-dimethyl-1-morpholinobutan-1-one (**36g**)



According to **TP7**, a solution of *N*-formylmorpholine (**34f**; 0.40 M in THF; 1.0 equiv; 5.0 mL) and trimethylacetaldehyde (0.7 equiv) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×70 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 1:1) afforded **36g** as a colorless oil (181 mg; 0.90 mmol; 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.14 (s, 1H), 3.80 – 3.65 (m, 5H), 3.60 – 3.50 (m, 3H), 0.96 (s, 9H).

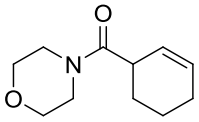
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.6, 73.7, 66.9, 66.4, 46.9, 42.8, 36.5, 26.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3337, 2959, 2919, 2849, 1736, 1616, 1511, 1467, 1426, 1388, 1363, 1325, 1294, 1261, 1235, 1181, 1111, 1085, 1065, 1032, 961, 932, 914, 886, 847, 822, 793, 717.

MS (EI, 70 eV): m/z (%) = 145 (100), 144 (60), 116 (27), 115 (35), 114 (29), 88 (26), 87 (48), 86 (13), 70 (18), 69 (12), 57 (21), 41 (10).

HRMS (EI): calcd. for [$C_{10}H_{19}NO_3$]: 201.1365; found: 201.1366 (M^+).

Synthesis of cyclohex-2-enyl(morpholino)methanone (**36h**)



According to **TP7**, a solution of *N*-formylmorpholine (**34f**; 0.40 M in THF; 1.0 equiv; 5.0 mL), 3-bromocyclohexene (0.7 equiv) and CuCN·2LiCl (1.0 M in THF; 10 mol%) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×60 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 1:1) afforded **36h** as a yellow oil (164 mg; 0.84 mmol; 60%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 5.88 – 5.85 (m, 1H), 5.58 – 5.55 (m, 1H), 3.67 – 3.52 (m, 6H), 3.32 – 3.28 (m, 1H), 2.11 – 1.98 (m, 2H), 1.89 – 1.75 (m, 3H), 1.60 – 1.54 (m, 1H), 1.30 – 1.11 (m, 1H), 0.92 – 0.85 (m, 1H).

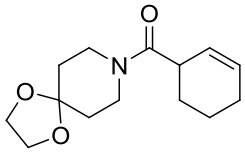
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 173.3, 129.8, 124.7, 67.0, 66.8, 46.2, 42.1, 38.5, 25.7, 24.6, 21.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 2925, 2856, 1734, 1635, 1426, 1391, 1360, 1328, 1299, 1269, 1249, 1221, 1194, 1180, 1156, 1136, 1112, 1068, 1052, 1034, 1019, 998, 954, 934, 897, 888, 874, 849, 821, 801, 728, 703, 666.

MS (EI, 70 eV): m/z (%) = 195 (25), 194 (21), 114 (100), 107 (12), 97 (14), 95 (13), 88 (11), 86 (31), 85 (14), 83 (13), 81 (32), 80 (15), 79 (24), 77 (14), 71 (20), 70 (72), 69 (21), 67 (17), 57 (29), 56 (29), 55 (19), 53 (11), 43 (23), 42 (20), 41 (28).

HRMS (EI): calcd. for [$C_{11}H_{17}NO_2$]: 195.1259; found: 195.1254 (M^+).

Synthesis of cyclohex-2-enyl(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)methanone (**36i**)



According to **TP7**, a solution of 1,4-dioxa-8-azaspiro[4.5]decane-8-carbaldehyde (**34g**; 0.40 M in THF; 1.0 equiv; 5.0 mL), 3-bromocyclohexene (0.7 equiv) and CuCN·2LiCl (1.0 M in THF; 10 mol%) was pumped into the system. The combined streams were collected in a flask containing water (20 mL) and the aq. layer was extracted with EtOAc (3×70 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel; *i*-hexane:EtOAc = 1:1) afforded **36i** as a colorless oil (191 mg; 0.76 mmol; 54%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.86 – 5.81 (m, 1H), 5.58 – 5.54 (m, 1H), 3.95 (s, 4H), 3.68 (t, J = 6.0 Hz, 2H), 3.57 (t, J = 5.9 Hz, 2H), 3.36 – 3.32 (m, 1H), 2.06 – 1.98 (m, 2H), 1.87 – 1.62 (m, 7H), 1.59 – 1.51 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.0, 129.5, 125.1, 106.9, 64.4, 43.6, 40.0, 38.7, 35.9, 34.8, 25.9, 24.6, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2877, 1634, 1433, 1360, 1338, 1266, 1216, 1142, 1101, 1084, 1053, 1032, 999, 944, 925, 900, 866, 825, 800, 729, 660.

MS (EI, 70 eV): m/z (%) = 251 (45, M^+), 171 (10), 170 (98), 142 (100), 108 (12), 99 (32), 98 (12), 81 (21), 79 (14), 56 (10), 42 (12).

HRMS (EI): calcd. for [$C_{14}H_{21}NO_3$]: 251.1521; found: 251.1513 (M^+).