Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

METALATIONS, IN SITU TRAPPING METALATIONS, AND IN SITU TRAPPING HALOGEN-LITHIUM EXCHANGES IN CONTINUOUS FLOW USING LITHIUM AND SODIUM REAGENTS

von

Marthe Ketels

aus

Hamburg

2018

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, 3. April 2018

……
(Marthe Ketels)

Dissertation eingereicht am:	3. April 2018
1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Oliver Trapp
Mündliche Prüfung am:	22. Mai 2018

This work was carried out from June 2015 to March 2018 under the guidance of Prof. Dr. Paul Knochel at the Department of Chemistry of the Ludwig-Maximilians-Universität, Munich.

Firstly, I would like to express my appreciation and thanks to Prof. Dr. Paul Knochel for giving me the great opportunity to do my Ph.D. in his group and for his guidance in the course of my scientific research.

I would also like to express my gratitute to Prof. Dr. Oliver Trapp for agreeing to be second reviewer of my thesis, as well as Prof. Dr. Franz Bracher, Prof. Dr. Manfred Heuschmann and Dr. Henry Dube for their interest shown in this manuscript by accepting to be members of my defense committee. In addition, special thanks go to Prof. Dr. Konstantin Karaghiosoff for his great support during my whole Ph.D. and his interest in this manuscript.

Moreover, I would like to thank the "Stiftung der Deutschen Wirtschaft" for supporting me financially through a scholarship during my Ph.D.

I really would like to thank Dorothée S. Ziegler, Meike Simon, Moritz Balkenhohl, Niels Weidmann and Maximilian A. Ganiek for careful correction of this manuscript as well as Simon Grassl for helpful advice.

Furthermore, I would like to thank all past and present members I have met in the Knochel group for all the moments and acitivities inside and outside the lab and for making my three years in the group a great experience. Especially I want to mention all my former and current lab mates of F2.004, Dr. Mario Ellwart, Dr. Daniela Sustac Roman, Dr. Yi-Hung Chen, Niels Weidmann, Simon Grassl, Peter J. Dowling and Lena Hausner, who gave me the best working and living atmosphere one can imagine.

In addition, I would like to thank the flow team – Dr. Matthias R. Becker, Maximilian A. Ganiek and Niels Weidmann – for numerous scientific discussions and the productive collaborations. Furthermore, thanks go to David B. Konrad for fruitful discussions and strong collaborations on the azobenzene project. I thank my former students Julian Feilner, Martin Daiger, and Jerome Ring for their excellent contributions in the course of their internships.

Morevoer, I would like to thank Peter Dowling, Sophie Hansen, Dr. Vladimir Malakhov and Yulia Tsvik for their help organizing everyday life in the lab and the office, as well as the analytical team of the LMU for their invaluable help.

Very special thanks go to Dorothée S. Ziegler for being an invaluable discussion partner for all kinds of questions during my whole Ph.D. and for just being my friend for the past nine years.

I would like to thank my whole family, especially my parents, and my friends for every possible support, for their love, patience and believe in me.

Finally, I thank Josef for his love and always being there for me.

Parts of this Ph.D. Thesis have been published

A) Communications

1) "Selective Lithiation, Magnesiation, and Zincation of Unsymmetrical Azobenzenes Using Continuous Flow"
M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.* **2017**, *19*, 1666.

2) "Selective Zincation of 1,2-Dicyanobenzene and Related Benzonitriles in Continuous Flow Using In Situ Trapping Metalations"
M. Ketels, D. S. Ziegler, P. Knochel, *Synlett* **2017**, *28*, 2817.

3) "Synthesis of Polyfunctional Diorganomagnesium and Diorganozinc Reagents through In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuous Flow"
M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770; *Angew. Chem.* **2017**, *129*, 12944.

4) "Sodiation of Arenes and Heteroarenes in Continuous Flow"
N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, DOI: 10.1002/anie.201803961.

B) Posters

"Selective Metalation of Unsymmetrical Azobenzenes Using Continuous Flow"
M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *OMCOS conference* **2017**, Jeju, South Korea.

“After climbing a great hill, one only finds that there are many more hills to climb”

Nelson Mandela

Abbreviations

Ac	acetyl
aq.	aq.
Ar	undefined aryl substituent
ATR	attenuated total reflection
Bn	benzyl
BPR	back pressure regulator
bpy	2,2'-bipyridine
Bu	butyl
calcd.	calculated
CCDC	Cambridge Crystallographic Data Center
Cy	cylohexyl
d	doublet (NMR)
Davephos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	*trans*,*trans*-dibenzylideneacetone
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMEA	dimethylethylamine
DMF	*N*,*N*-dimethylformamide
d.r.	diastereomeric ratio
E^+	electrophile
e.g.	for example
EI	electron ionization (MS)
equiv.	equivalents
ESI	electrospray ionization (MS)
Et	ethyl
FG	functional group
GC	gas chromatography
Het	undefined heteroaryl substituent
Hex	hexyl
HRMS	high resolution mass spectroscopy
i	*iso*
I.D.	inner diameter
inj.	injection
IR	infrared
J	coupling constant (NMR)
LDA	lithium diisopropylamide

LED	light-emittig diode
M	mol L^{-1}
M	metal
Me	methyl
Mes	mesityl
MOM	methoxymethyl
M.p.	melting point
MS	mass spectrometry
NaDA	sodium diisopropylamide
NMR	nuclear magnetic resonance
o	*ortho*
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
PFA	perfluoroalkoxy alkane
Ph	phenyl
Piv	pivaloyl
PMDTA	*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
PTFE	polytetrafluoroethylene
q	quartet (NMR)
R	undefined organic substituent
s	*sec*
s	singulet (NMR)
sat.	saturated
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	*tert*
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
Vol	volume

TABLE OF CONTENTS

A. INTRODUCTION 2

1 Overview 3

2 Organometallic Chemistry in Continuous Flow 5

2.1 Preparation of Organometallic Reagents in Continuous Flow 5

2.1.1 Oxidative Insertions 6

2.1.2 Halogen-Metal Exchange 8

2.1.3 Directed Metalation 10

2.1.4 Transmetalation 12

2.2 Organometallic Reactions in Continuous Flow 14

3 Objectives 18

B. RESULTS AND DISCUSSION 20

1 Selective Lithiation, Magnesiation and Zincation of Unsymmetrical Azobenzenes Using Continuous Flow 21

1.1 Introduction 21

1.2 Lithiation of Methoxy-Substituted Azobenzenes 23

1.3 In Situ Trapping Metalation of Functionalized Azobenzenes 25

2 Selective Zincation of 1,2-Dicyanobenzene and Related Benzonitriles in Continuous Flow Using In Situ Trapping Metalations 29

2.1 Introduction 29

2.2 Zincation of 1,2-Dicyanobenzenes 30

2.3 Functionalization of 1,2-Dicyano-3-iodobenzene Using Continuous Flow 34

3 Preparation of Polyfunctional Diorgano-Magnesium and -Zinc Reagents Using In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuous Flow 35

3.1 Introduction 35

3.2 Optimization of Reaction Conditions 36

3.3 In Situ Trapping Halogen-Lithium Exchange on Sensitive Substrates 37

3.4 In Situ Trapping Halogen-Lithium Exchange on Highly Sensitive Substrates 40

3.5 In Situ Trapping Halogen-Lithium Exchange on Heterocycles 43

4 Sodiation of Arenes and Heteroarenes in Continuous Flow 46

4.1 Introduction 46

4.2 Optimization of Reaction Conditions 47

4.3 Sodiation of Arenes and Heteroarenes 48

4.4 Sodiation of Sensitive Arenes and Heteroarenes 51

4.5 Sodiation of Acrylonitriles 54

5 Summary 56

5.1 Selective Lithiation, Magnesiation and Zincation of Unsymmetrical Azobenzenes Using Continuous Flow 56

5.2 Selective Zincation of 1,2-Dicyanobenzene and Related Benzonitriles in Continuous Flow Using In Situ Trapping Metalations 57

5.3 Preparation of Polyfunctional Diorgano-Magnesium and –Zinc Reagents using In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuous Flow 58

5.4 Sodiation of Arenes and Heteroarenes in Continuous Flow 59

C. EXPERIMENTAL PART 60

1 General Considerations 61

1.1 Solvents 61

1.2 Reagents 61

1.3 Chromatography 62

1.4 Analytical Data 63

2 Selective Lithiation, Magnesiation and Zincation of Unsymmetrical Azobenzenes Using Continuos Flow 64

2.1 Typical Procedures (TP) 64

2.2 Preparation of the Products 66

3 Selective Zincation of 1,2-Dicyanobenzene and Related Benzonitriles in Continuous Flow Using In Situ Trapping Metalations 87

3.1 Typical Procedures (TP) 87

3.2 Preparation of the Products 88

4 Preparation of Polyfunctional Diorgano-Magnesium and –Zinc Reagents Using In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuos Flow 101

4.1 Typical Procedure (TP 8) 101

4.2 Preparation of the products 102

5 Sodiation of Arenes and Heteroarenes in Continuous Flow 138

5.1 Typical Procedure (TP 9) 138

5.2 Attempted Batch Sodiation 138

5.3 Preparation of the Products 139

6 Crystallographic Data 168

A. INTRODUCTION

1 Overview

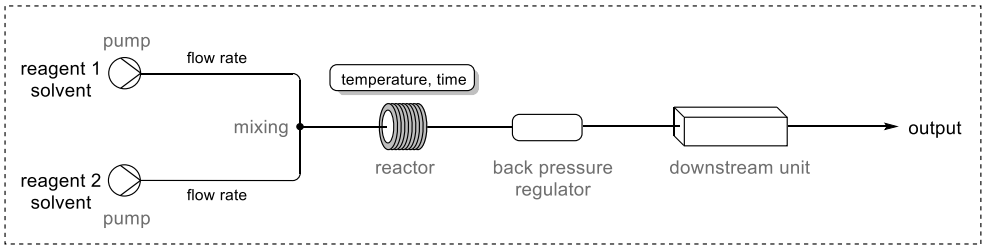
According to predictions of the United Nations Population Fund the world population of today 7.55 billion will grow to over 11.1 billion people by 2100.[1] Increasing population, rising age of the population as well as a claim for high living standards all over the world create a demand for safe supply in food, pharmaceuticals and new materials. Major contributions to the development and progress in all of these fields are provided by organic chemists.[2] As an example over 95% of the top 200 prescribed drugs in the United States in 2016 contain small organic molecules as the active pharmaceutical ingredient.[3] Thus, organic chemistry is constantly facing the challenge of developing new efficient methods for the synthesis of fine chemicals and related products. A broad entry for the synthesis of organic molecules is offered by organometallic chemistry.[4] With their reactivity depending on the polarity of the nonmetal-metal bond, organometallic reagents can be employed as bases, nucleophiles and catalysts. Highly reactive and often unstable organometallic compounds containing lithium, sodium or magnesium show a distinct ionic bond character due to a high difference in electronegativity between the metal and the adjacent atom. In contrast, milder and less reactive organometallic compounds containing for example zinc or boron with a more covalent metal-nonmetal bond offer a higher stability and functional group compatibility. With its broad variety in reactivity the organometallic toolbox thus offers suitable reagents for many synthetic tasks.

In addition to the task of synthesizing new molecules, demand for environmentally friendly and efficient methods has increased dramatically.[5] Thus, the utilization of continuous flow setups for the laboratory scale marked a disruptive breakthrough in organic chemistry.[6]

In flow chemistry, reagents are pumped in a continuously flowing stream through a reactor zone allowing an efficient and safe handling of reactions. Flow systems exist in all levels of complexity from being able to perform a single step reaction to advanced reaction sequences including several steps and workups (Scheme 1).

---

[1] United Nations, Department of Economic and Social Affairs, Population Division, *World Population Prosepects: The 2017 Revision, Key Findings and Advance Table*, ESA/P/WP/248.
[2] a) M. MacCoss, T. A. Baillie, *Science* **2004**, *303*, 5665; b) D. P. Rotella, *ACS Chem. Neurosci*. **2016**, *7*, 1315.
[3] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Ed.* **2010**, 87, 1348.
[4] *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.
[5] 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; c) C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197; d) C. A. Kuttruff, M. D. Eastgate, P. S. Baran, *Nat. Prod. Rep.* **2014**, *31*, 419.
[6] For an introduction and overview, see: a) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688; b) T. Glasnov, *Continuous-Flow Chemistry in the Research Laboratory*, Springer, Cham, **2016**; c) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.



Scheme 1: Schematic representation of a typical continuous flow setup.[7]

In a basic setup, pumps deliver reagents and solvents at a fixed flow rate and quantity to the reactor. While in most cases liquids are pumped, advanced setups allow the feed of gases and slurries thus expanding the range of possible reactions. Reagents are combined and mixed in a mixing device. While in a simple setup mixing is achieved by diffusion of the reagent streams after a Y- or T-piece in a laminar flow or a vortex,[8] highly sophisticated micromixers accelerate this process immensly. Mixing efficiency plays a crucial role for continuous flow reactions when using highly reactive compounds, for which reaction rates are typically faster than conventional mixing times in batch reactors.[9] A variety of reactors can be connected to the mixing unit.[10] Basic setups contain coiled or chip reactors that can be heated or cooled. Column reactors offer the possibility to lead the reaction stream over a solid phase containing for example a catalyst or scavengers. In addition, photochemical reactors allow light-induced reactions in flow with a high photonic efficiency.[11] Furthermore, ultrasound, microwave or electrochemical reactors can be introduced into flow systems expanding the reaction scope. After the reactor, a back pressure regulator (BPR) controls the upstream system pressure allowing for example to process reactions in the liquid phase above the boiling point of the reaction media. Moreover, different analytical devices like inline IR or NMR-monitoring can be added to the flowsystems allowing efficient monitoring and screening of the reaction conditions.[12] Additionally, work-up operations can be included in the flow system. By connecting more pumps and reactors, complete reaction sequences can be conducted in one setup allowing highly efficient preparations of synthetic targets.[13]

---

[7] *Flow Chemistry, Vol. 1, Fundamentals* (Eds.: F. v. Darvas, V. Hessel, G. Dorman), De Gruyter, Berlin, **2014**.
[8] S. Schwolow, J. Hollmann, B. Schenkel, T. Röder, *Org. Process Res. Dev.* **2012**, *16*, 1513; and references therein.
[9] a) E. A. Mansur, M. Ye, Y. Wang, Y. Dai, *Chin. J. Chem. Eng.* **2008**, *16*, 503; b) J. Aubin, M. Ferrando, V. Jiricny, *Chem. Eng. Sci.* **2010**, *65*, 2065; c) L. Capretto, W. Cheng, M. Hill, X. Zhang in *Microfluidics: Technologies and Applications* (Ed.: B. Lin), Springer, Berlin, **2011**; d) C.-Y. Lee, C.-L. Chang, Y.-N. Wang, L.-M. Fu, *Int. J. Mol. Sci.* **2011**, *12*, 3263; e) J. M. Reckamp, A. Bindels, S. Duffield, Y. C. Liu, E. Bradford, E. Ricci, F. Susanne, A. Rutter, *Org. Process Res. Dev.* **2017**, *21*, 816.
[10] a) T. Wirth, *Mircroreactors in Organic Synthesis and Catalysis*, Wiley-VCH, Weihnheim, **2008**; b) P. Watts, C. Wiles, *Micro Reaction Technology in Organic Synthesis*, CRC Press, New York, **2011**.
[11] a) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025; b) C. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noel, *Chem. Rev.* **2016**, *116*, 10276.
[12] a) J. Yue, J. C. Schouten, T. A. Nijhuis, *Ind. Eng. Chem. Res.* **2012**, *51*, 14583; b) J. Reizmann, K. F. Jensen, *Acc. Chem. Res.* **2016**, *49*, 1786; c) V. Sans, L. Cronin, *Chem. Soc. Rev.* **2016**, *45*, 2032; d) D. C. Fabry, E. Sugiono, M. Rueping, *React. Chem. Eng.* **2016**, *1*, 129.
[13] J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849.

Overall, the advances in continuous flow chemistry allow a transformation of past organic synthetic approaches of all kinds into a more rapid automated set of synthetic operations providing an entry into a more sustainable future.[14]

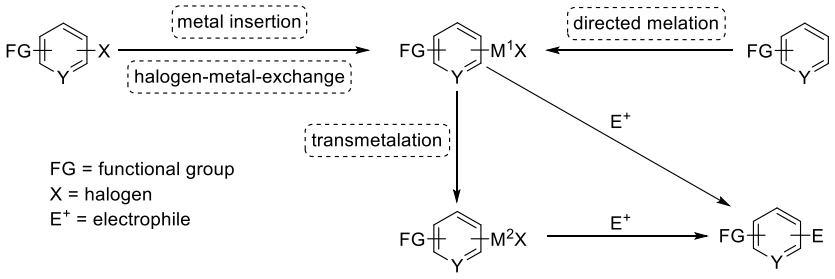
2 Organometallic Chemistry in Continuous Flow

Especially in the field of organometallic chemistry, continuous flow offers numerous advantages compared to classical batch approaches to control highly reactive reagents.[15] Foremost, only a minimal amount of highly reactive intermediate is present at any time of the reaction, allowing a safer handling of hazardous intermediates.[16] Secondly, performing the reaction in a flow setup enables a better heat transfer between the reaction system and the environment, providing a narrow temperature profile and thus preventing the formation of hot spots and thermal runaways. Moreover, fast reactions with highly reactive organometallic intermediates can be conducted in a controlled manner through precise residence time control by defined flow rates, reactor volumes and rapid mixing of reaction streams. By using advanced setups with several pumps and reactors, multipstep reaction sequences can be performed without the exposure of any reactive or hazardous organometallic intermediates to the environment. Finally, scale-up, which is often limited under batch conditions for organometallic reactions, is possible without further optimization by simply extending the run time of a reaction. In addition, reproducibility of experimental conditions and results is ensured through the precise control and automation of continuous flow setups.

2.1 Preparation of Organometallic Reagents in Continuous Flow

Since the first synthesis of an organometallic reagent by *de Gassicourt*[17] in 1760 and pioneering contributions by *Frankland*[18] and *Grignard*[19] various entries to polyfunctional organometallic compounds have been found. The three most commonly used strategies include oxidative insertion, halogen-metal exchange and directed metalation (Scheme 2). In addition, transmetalation opens the way to a broad range of other organometallic compounds.

[14] *Sustainable Flow Chemistry: Methods and Applications* (Ed.: L. Vaccaro), Wiley-VCH, Weinheim, **2017**.
[15] *Flash Chemistry, Fast Organic Synthesis in Microsystems* (Ed.: J.-i. Yoshida), Wiley, Chichester, **2008**.
[16] M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892.
[17] D. Seyferth, *Organometallics* **2001**, *20*, 1488.
[18] a) E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171; b) D. Seyferth, *Organometallics* **2001**, *20*, 2940.
[19] a) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322; b) D. Seyferth, *Organometallics* **2009**, *28*, 1598.



Scheme 2: Preparation of organometallic reagents *via* different pathways.

All of these preparation methods have been transferred to continuous flow in recent years taking advantage of the above described features of flow setups.

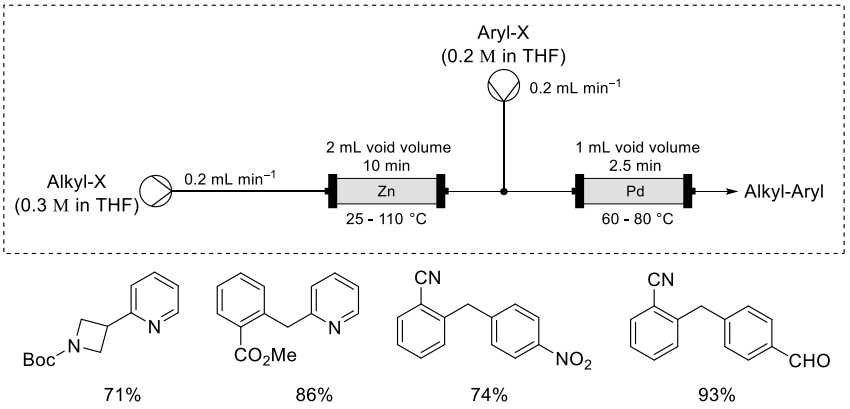
2.1.1 Oxidative Insertions

Direct insertion of elemental metal is one of the most convenient and straightforward methods to prepare organometallics.[20] This method was first described in 1849 by *Frankland* who reacted ethyliodide with zinc leading to diethylzinc.[18a] In 1900, the French chemist *Grignard* reacted magnesium turnings with methyl iodide in diethyl ether yielding the first organomagnesium compounds and thus marking a breakthrough for organometallic chemistry.[19] The direct insertion of zinc into carbon-halogen bonds proceeds with a high functional group tolerance but requires elevated temperatures and long reaction times. In contrast, direct insertions of magnesium display a much narrower functional group tolerance but take place in shorter times. In addition, elemental magnesium easily adopts a passivation layer of magnesium oxide or magnesium hydroxide upon storage. Thus, activation with additives like iodine,[21] 1,2-dibromoethane,[22] or DIBAL-H[23] is required to facilitate insertion. To achieve a high functional group tolerance, *Knochel* and coworkers developed an oxidative insertion in the presence of LiCl for a variety of metals including zinc,[24] magnesium,[25] manganese,[26] aluminum,[27] and indium[28] under mild conditions.

---

[20] a) *Handbook of Grignard Reagents* (Eds.: G. S. Silvermann, P.E. Rakita), Marcel Dekker, New York, **1996**; b) *Grignard Reagents, New Developments* (Ed.: H. G. Richey jr.), Wiley & Sons, New York, **2000**.
[21] H. Gold, M. Larhed, P. Nilsson, *Synlett* **2005**, 1596.
[22] W. E. Lindsell in *Comprehensive Organometallic Chemistry I, Vol 1* (Eds.: G. Wilkinson, F. G. S. Stone, G. E. Ebel) Pergamon Press, Oxford, **1982**.
[23] U. Tilstam, H. Weinmann, *Org. Process Res. Dev*. **2002**, *6*, 906.
[24] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.
[25] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
[26] Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198.
[27] a) T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313; b) T. D. Blümke, T. Klatt, K. Koszinowski, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9926.
[28] a) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; b) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236.

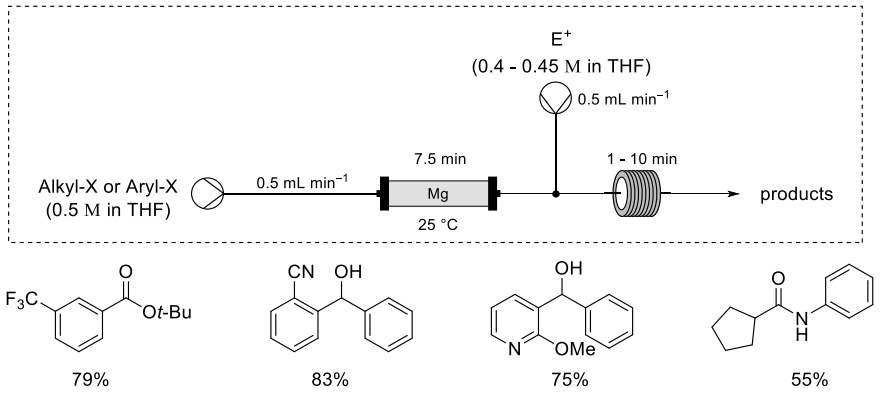
Conducting oxidative insertions in continuous flow allows a safer handling of the exothermic reaction conditions and a higher process intensity due to shorter reaction times. *Alcázar* and coworkers reported an oxidative insertion of zinc into alkyl and benzylic halides with subsequent *Negishi*[29] cross-coupling (Scheme 3).[30] A solution of an organohalide is passed over a packed bed of zinc particles which are activated prior to insertion with TMSCl and 1,2-dibromoethane. The reaction is finished within 10 min and gives a steady concentration of the organozinc reagent over a long period of time tolerating sensitive groups like nitriles and esters.



Scheme 3: Continuous synthesis of organozinc halides and subsequent *Negishi* cross-couplings.[30]

Similar setups have been reported for the oxidative insertion of magnesium into aryl and alkyl halides.[31] After activation of granulated magnesium in a packed bed reactor with DIBAL-H, TMSCl and 1-bromo-2-chloroethane, magnesium reagents can be generated in a constant concentration at ambient temperature and subsequently reacted with a variety of electrophiles (Scheme 4). Conducting oxidative insertions in continuous flow allows an on-demand preparation of the metalorganic reagents in a controlled and reproducible reaction setup under mild conditions.

[29] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[30] a) N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737; b) M. Berton, L. Huck, J. Alcázar, *Nat. Protoc.* **2018**, *13*, 324.
[31] a) A. A. Grachev, A. O. Klochkov, V. I. Shiryaev, *Russ. J. Appl. Chem.* **2012**, *85*, 629; b) P. A. Storozhenko, A. A. Grachev, A. O. Klochkov, V. I. Shiryaev, *Russ. J. Appl. Chem.* **2013**, *86*, 397; c) M. Goldbach, E. Danieli, J. Perlo, B. Kaptein, V. M. Litvinov, B. Blümich, F. Casanova, A. L. L. Duchateau, *Tetrahedron Lett.* **2016**, *57*, 122; d) L. Huck, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar, *Org. Lett.* **2017**, *19*, 3747.



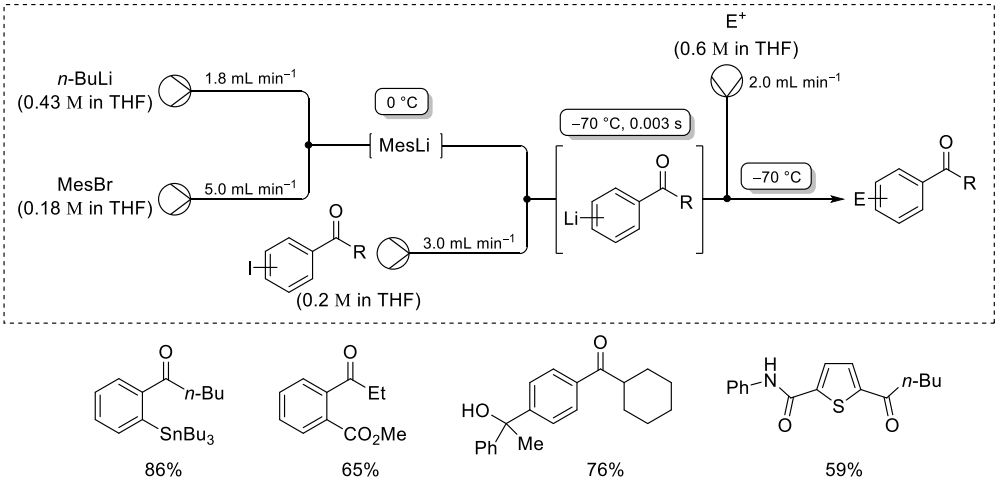
Scheme 4: Oxidative insertion of magnesium into alkyl and aryl halides using continuous flow.[31d]

2.1.2 Halogen-Metal Exchange

Another commonly used method for preparing organometallic reagents is the halogen-metal exchange. Driving force of this reaction is the formation of the more stable organometallic species ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec} > sp^3_{tert}$).[32] Under optimized batch conditions, halogen-lithium exchange reactions have to be conducted at temperatures down to −100 °C to permit a moderate functional group tolerance.[33] The high reactivity and instability of organolithium compounds originates from the strongly ionic character of the newly formed carbon-lithium bond. In contrast, magnesium-halogen exchanges generate more stable organometallic intermediates. After pioneering work of *Prévost*[34] and *Villieras*[35], *Knochel* demonstrated the potential of the iodine-magnesium exchange using *i*-PrMgCl and PhMgCl on substrates bearing sensitive functionalities like ester or nitro groups.[36] A major improvement was the addition of one equivalent LiCl, leading to the so called "*Turbo-Grignard*", a reagent with remarkably higher reactivity allowing a bromine-magnesium exchange.[37]

[32] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.
[33] a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704; b) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187; c) M. Yus, F. Foubelo in *Handbook of Functionalized Organometallics: Applications in Synthesis, 1* (Ed.: P. Knochel), Wiley-VCH, Berlin, **2005**; d) *Lithium Compounds in Organic Synthesis* (Eds.: R. Luisi, V. Capriati), Wiley-VCH, Weinheim, **2014**.
[34] C. Prévost, *Bull. Soc. Chem. Fr.* **1931**, *49*, 1372.
[35] a) J. Villieras, *Bull. Soc. Chim. Fr.* **1967**, *5*, 1520; b) J. Villieras, B. Kirschleger, R. Tarhouni, M. Rambauf, *Bull. Soc. Chim. Fr.* **1986**, *24*, 470.
[36] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) W. Dohle, D. M. Lindsay, P. Knochel, *Org. Lett.* **2001**, *3*, 2871 c) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; d) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565; e) G. Varchi, C. Kofink, D. M. Lindsay, A. Ricci, P. Knochel, *Chem. Commun.* **2003**, 396.
[37] 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) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; d) C. Sämann, B. Haag, P. Knochel, *Chem. Eur. J.* **2012**, *18*, 16145; e) N. M. Barl, V. Werner, C. Sämann, P. Knochel, *Heterocycles* **2014**, *88*, 827.

A major breakthrough in halogen-metal exchanges was made by *Yoshida* and coworkers employing continuous flow technology.[38] By precise time control using highly advanced flow systems with reaction times down to 0.002 s it was possible to tolerate even nitro or nitrile groups at moderate temperatures of −20 °C.[38i] In addition, this setup enabled halogen-lithium exchanges that are not possible under batch conditions at all. Thus, for example, a ketone containing arylhalide could be subjected to a halogen-lithium exchange with in flow generated mesityl lithium without attack at the functional group.[38e] After subsequent electrophilic quench in flow of the highly reactive intermediate polyfunctional arenes could be isolated in high yields without the need to protect the ketone functionality (Scheme 5).

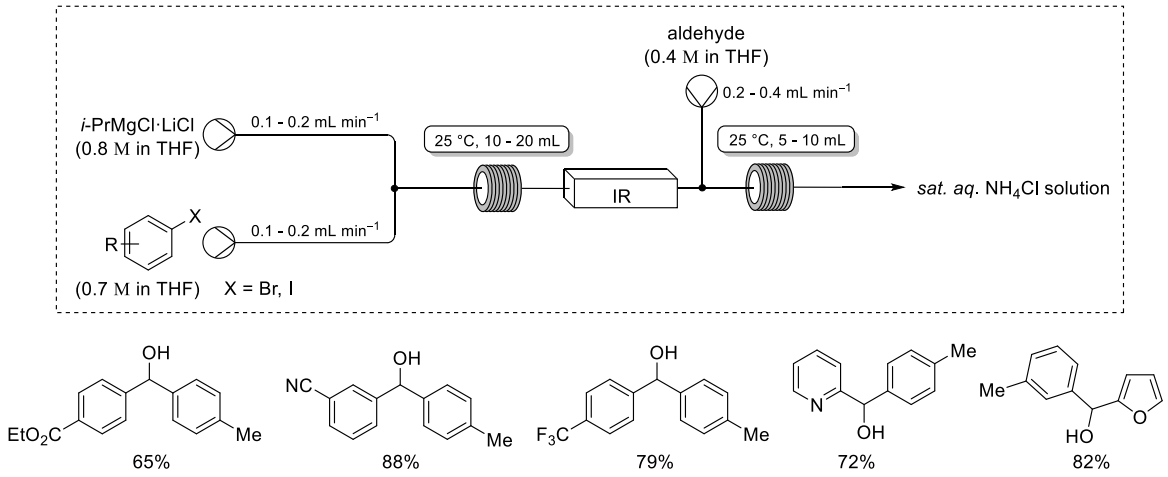


Scheme 5: Ultrafast iodine-lithium exchange using MesLi in continuous flow with subsequent electrophilic quench.[38g]

Ley and coworkers transferred the halogen-magnesium exchange using *i*-PrMgCl·LiCl to a continuous flow setup, thereby allowing the preparation of a wide range of organomagnesium reagents at room temperature without the need for energy-intensive cryogenic conditions as employed in batch mode and significantly shortening the reaction time (Scheme 6).[39] Formation of the *Grignard* reagent could be monitored inline by an IR device. The metalorganic intermediates were quenched inline with aldehydes providing diarylmethanols in high yields.

[38] a) A. Nagaki, Y. Tomida, H. Usutani, H. Kim, N. Takabayashi, T. Nokami, H. Okamoto, J.-i. Yoshida, *Chem. Asian J.* **2007**, *2*, 1513; b) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J.-i. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046A; c) A. Nagaki, H. Kim, H. Usutani, C. Matsuo, J.-i. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; d) A. Nagaki, S. Yamada, M. Doi, Y. Tomida, N. Takabayashi, J.-i. Yoshida, *Green Chem.* **2011**, *13*, 1110; e) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; f) Y. Tomida, A. Nagaki, J.-i. Yoshida *J. Am. Chem. Soc.* **2011**, *133*, 3744; g) A. Nagaki, Y. Takahashi, S. Yamada, C. Matsuo, S. Haraki, Y. Moriwaki, S. Kim, J.-i. Yoshida, *J. Flow Chem.* **2012**, *2*, 70; h) J.-i. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896; i) A. Nagaki, Y. Takahashi, J.-i. Yoshida, *Chem. Eur. J.* **2014**, *20*, 7931; j) Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; k) A. Nagaki, Y. Tsuchihashi, S. Haraki, J.-i. Yoshida, *Org. Biomol. Chem.* **2015**, *13*, 7140.

[39] a) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2011**, *16*, 1102; b) P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1192.



Scheme 6: Halogen-magnesium exchange in continuous flow at ambient temperature and subsequent quench with aldehydes.[39b]

2.1.3 Directed Metalation

While for oxidative insertion or halogen-metal exchange a halogen-carbon bond needs to be present in the molecule, in directed metalation the organometallic compound is formed directly from a hydrogen-carbon bond. Alkyl-lithium bases as *n*-BuLi, *s*-BuLi or *t*-BuLi and strong lithium amides like lithium diisopropylamide (LDA) or TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) are commonly used for these metalations.[40] To enhance functional group tolerance a range of TMP bases including TMPZnCl·LiCl,[41] $(TMP)_2Zn·2MgCl_2·2LiCl$,[42] TMPZnOPiv·LiCl,[43] TMPMgCl·LiCl,[44] $(TMP)_2Mg·2LiCl$,[45]

[40] For an overview, see: a) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306; b) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356; c) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; d) L. Green, B. Chauder, V. Snieckus, *J. Heterocyclic Chem.* **1999**, *36*, 1453; e) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; f) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; g) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161; h) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069.

[41] a) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; b) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; c) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584; d) A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680; e) D. Haas, D. Sustac-Roman, S. Schwarz, P. Knochel, *Org. Lett.* **2016**, *18*, 6380.

[42] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, *47*, 6387; c) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.

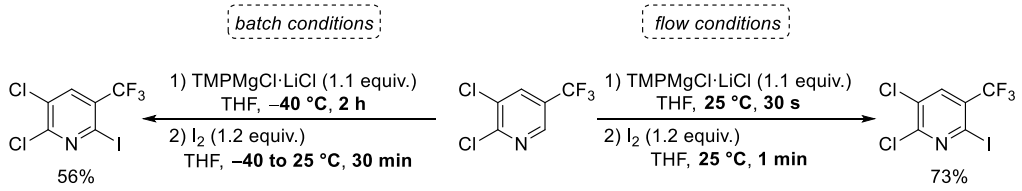
[43] a) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302; b) Y.-H. Chen, M. Ellwart, G. Toupalas, Y. Ebe, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 4612; c) Y.-H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 9236.

[44] 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) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497; e) 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; f) C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326; g) M. Balkenhohl, C. François, D. Sustac-Roman, P. Quinio, P. Knochel, *Org. Lett.* **2017**, *19*, 536.

[45] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; b) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237; c) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; d) C. J. Rohbogner, S. Wirth, P. Knochel, *Org. Lett.* **2010**, *12*, 1984.

$(TMP)_2Fe\cdot 2MgCl_2\cdot 4LiCl$,[46] $(TMP)_2Mn\cdot 2MgCl_2\cdot 4LiCl$,[47] $(TMP)_4Zr\cdot 4MgCl_2\cdot 6LiCl$,[48] and $(TMP)_3La\cdot 3MgCl_2\cdot 5LiCl$[49] were developed. These bases differ in reactivity and regioselectivity and thus offer a broad toolbox for the metalation of organic substrates and subsequent reactions with electrophiles.[50]

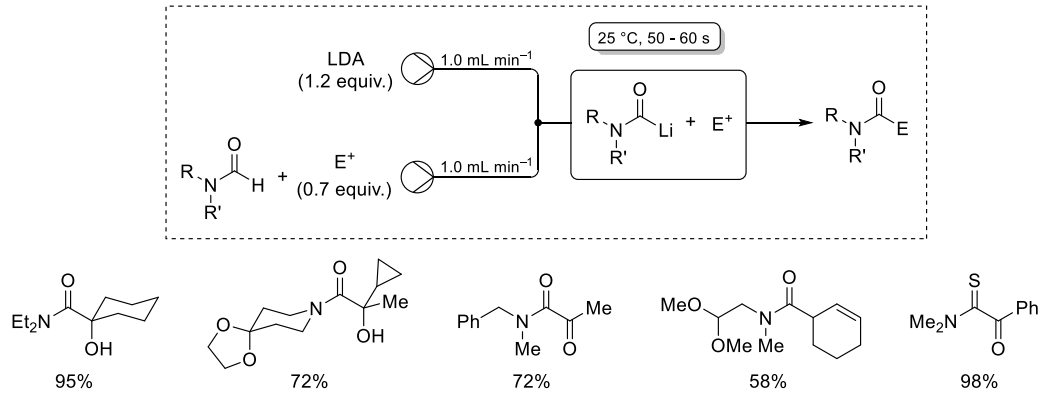
While strong lithium and magnesium bases display high reactivity and thus need to be conducted at cryogenic temperatures, milder bases containing for example zinc as a metal often require elevated temperatures and long reaction times. Both of these problems can be overcome by using continuous flow chemistry. For instance, functionalized heterocycles and acrylates could be metalated using TMPMgCl·LiCl under convenient conditions (30 s, 25 °C) in continuous flow avoiding cryogenic temperatures and achieving higher yields than in a comparable batch procedure (Scheme 7).[51]



Scheme 7: Metalation of 2,3-dichloro-5-(trifluoromethyl)pyridine in the presence of TMPMgCl·LiCl and subsequent iodolysis in continuous flow and batch.[51a]

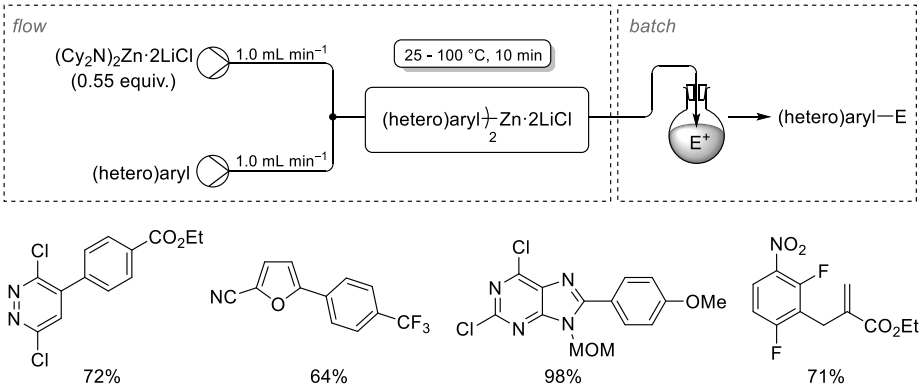
Furthermore, highly reactive LDA could be employed for a Barbier lithiation generating unstable carbamoyllithium intermediates which could be trapped in situ with various electrophiles including carbonyl compounds leading for example to α-hydroxy amides in high yields (Scheme 8).[52] The metalation proceeds at ambient temperature and is easily scaled up. In addition to this nucleophilic amidation, thioamidation is described for similar conditions (25 °C, 48 s).

[46] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.
[47] S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.
[48] M. Jeganmohan, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8520.
[49] S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3304.
[50] For reviews on metalations using TMP-bases, see: a) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794; b) M. Balkenhohl, P. Knochel, *SynOpen* **2018**, *2*, 78.
[51] a) T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933; b) M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828.
[52] M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280.



Scheme 8: Continuous flow generation of carbamoyllithium intermediates in the presence of various electrophiles at ambient temperature.[52]

On the other hand, zincations of sensitive arenes and heteroarenes could be achieved using $(Cy_2N)_2Zn{\cdot}2LiCl$ in a continuous flow setup at temperatures between 25 and 100 °C within relatively short reaction times of 10 min (Scheme 9).[53] The use of a back pressure regulator permits to run reactions at temperatures above the boiling point of the solvent thus allowing zincations that would be hard to conduct under batch conditions. The resulting organozinc reagents could be trapped with various allylic bromides in the presence of a copper catalyst and aryl iodides in the presence of a palladium catalyst in high yields.



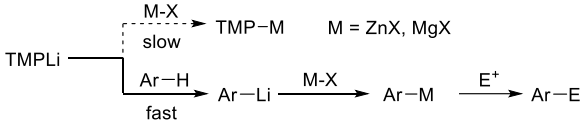
Scheme 9: Continuous flow zincations of sensitive (hetero)arenes followed by reaction with electrophiles leading to functionalized (hetero)aromatic compounds.

2.1.4 Transmetalation

Organometallic compounds bearing a carbon-metal bond are easily transmetalated into another organometallic compound by addition of a metal salt. Driving forces are the formation of a more covalent bond between the new metal and the carbon as well as the lattice energy of the product metal halide. The transmetalation leads to a modification in selectivity and reactivity of the newly formed

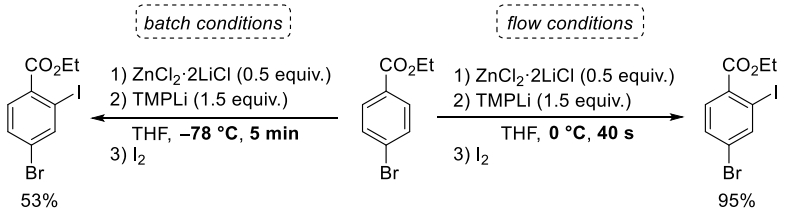
[53] M. R. Becker, P. Knochel, *Org. Lett.* **2016**, *18*, 1462.

carbon-metal bond. While lithium bases offer a broad entry into organometallic chemistry, the high reactivity of the generated lithium intermediates limits their application and requires harsh reaction conditions such as cryogenic temperatures. Transmetalation to less reactive organometallic compounds containing for example magnesium, zinc, boron, aluminum or copper leads to a reduced basicity of the organometallic species bearing a more covalent carbon-metal bond and thus to a more stable organometallic species.



Scheme 10: In situ trapping metalation of aromatic substrates.[54]

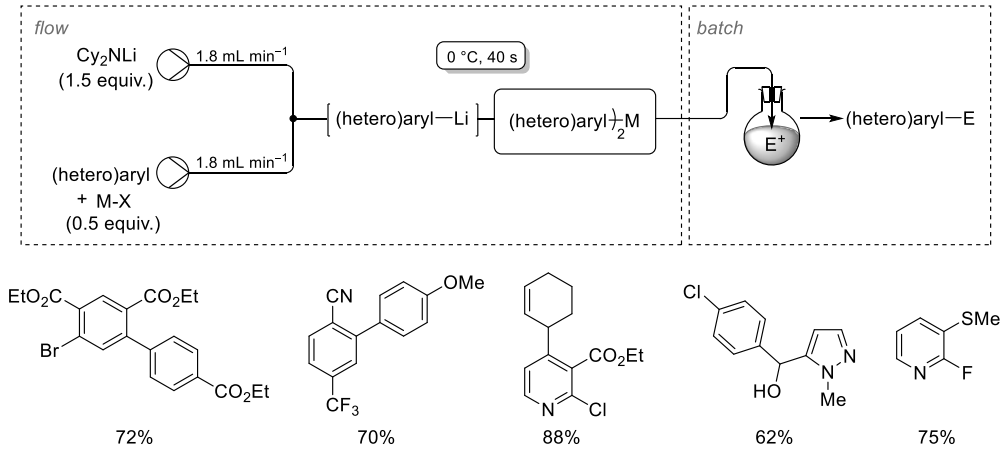
Knochel and coworkers developed an in situ trapping metalation, in which metalation of an aromatic substrate with TMPLi is conducted in the presence of a THF-soluble metal salt such as $MgCl_2$, $ZnCl_2$ or CuCN·2LiCl.[54] The reaction of TMPLi with the aromatic substrate is more than six times faster than the reaction of TMPLi with the metal salt (Scheme 10). The lithiated intermediate is directly transmetalated to the more stable organometallic species. Reactivity of TMPLi under batch conditions is only efficiently controlled at −78 °C. Cryogenic temperatures could be avoided transferring this procedure to continuous flow. It was shown, that in situ trapping metalations using TMPLi in the presence of various metal salts could be conducted at 0 °C within 40 s using a commercially available flow setup tolerating sensitive functional groups (Scheme 11).[55] Efficient mixing and control of reaction heat inhibit side reactions that occur under conventional batch conditions.



Scheme 11: In situ trapping metalation in continuous flow and batch of ethyl 4-bromobenzoate using TMPLi in the presence of $ZnCl_2$·2LiCl.[55]

Furthermore, an in situ trapping flow metalation of a broad range of functionalized arenes, heteroarenes and arylate derivatives using the economic amide base lithium dicyclohexylamide (Cy_2NLi) is possible under flow conditions in 40 s at 0 °C (Scheme 12).[56] All of these metalations are easily scaled up without further optimization.

[54] 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.
[55] M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501.
[56] M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649.

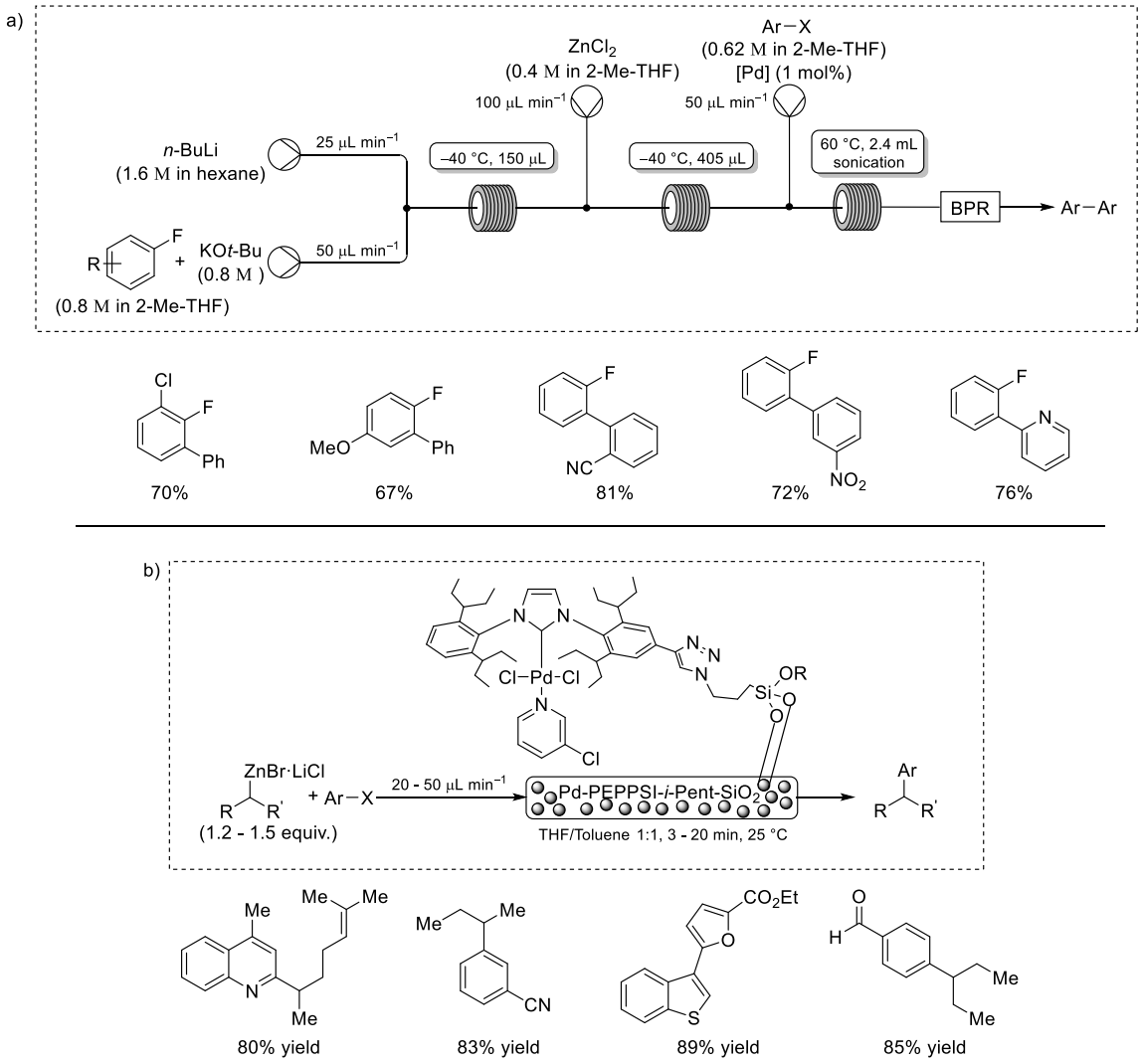


Scheme 12: Continuous flow in situ trapping metalation of (hetero)arenes followed by reaction with electrophiles leading to functionalized (hetero)arenes.[56]

2.2 Organometallic Reactions in Continuous Flow

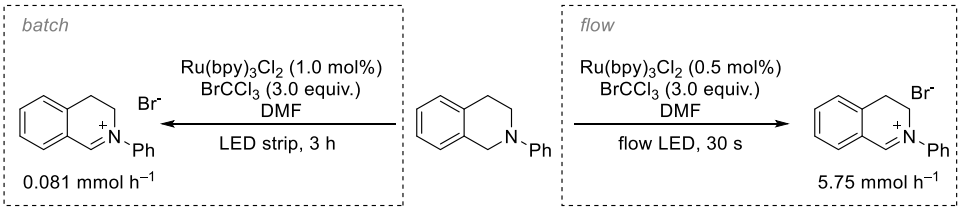
In addition to the advantageous preparation of organometallic reagents in continuous flow, other organometallic reactions benefit from being conducted in flow. For instance, different cross-couplings, both hetero- and homogenous, are reported under flow conditions.[57] *Buchwald* and coworkers report the synthesis of biaryls by *Negishi* cross-couplings[29] of fluoro- and trifluoromethyl-susbtituted arenes and heteroarenes (Scheme 13a).[58] In addition to convenient metalation conditions in continuous flow, good cross-coupling yields are achieved in short residence times. A heterogenous approach is reported by *Organ* and coworkers using an immobilized palladium precatalyst in a packed bed reactor (Scheme 13b).[59] The silica-supported Pd-PEPPSI-*i*-Pr enables *Negishi* cross-couplings[29] at room temperature within 10 min of aryl halides with alkylzinc reagents with a minor decay in activity of the catalyst over 15 h of continuous reaction being observed. *Buchwald* and coworkers developed an advanced setup for *Suzuki-Miyaura* cross-couplings[60] allowing an automatic optimization of reaction conditions due to included analytical and feedback devices in the continuous flow setup.[61] Reaction optimization with screening of palladium source, ligand and continuous variables was completed within 96 experiments.

[57] T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010.
[58] S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463.
[59] G. A. Price, A. R. Bogdan, A. L. Aguirre, T. Iwa, S. W. Djuric, M. G. Organ, *Catal. Sci. Technol.* **2016**, *6*, 4733.
[60] a) N. Miyaura, A. Suzuki, *Chem. Commun.* **1979**, *19*, 866; b) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437.
[61] B. J. Reizman, Y.-M. Wang, S. L. Buchwald, K. F. Jensen, *React. Chem. Eng.* **2016**, *1*, 658.



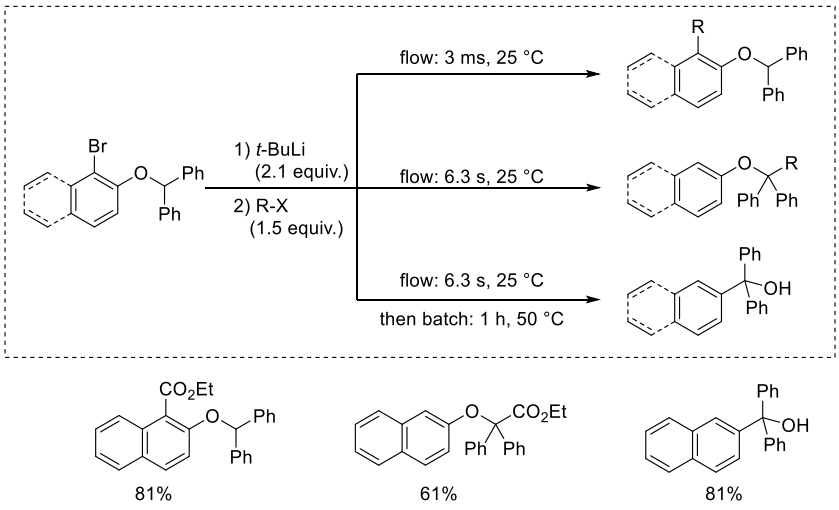
Scheme 13: a) Homogeneous[58] and b) heterogenuos[59] *Negishi* cross-couplings[29] in continuous flow.

Conducting photoredox catalysis using organometallic catalysts in continuous flow allows direct irradiation of the reaction medium leading to a higher photonic effiency and thus to shorter reaction times. In addition, reactions can be scaled up without a limit which is reached quickly under batch conditions. For instance, reaction time of Ru-catalyzed oxidation of tetrahydroisoquinolines through iminium formation could be reduced from 3 h to 30 s by conducting it in flow (Scheme 14).[62]



Scheme 14: Oxidation of tetrahydroisoquinoline in batch and flow.[62]

Precise reaction times in continuous flow setups enable to control tandem chemical transformations that are often difficult to control under batch conditions because they proceed rapidly through multiple unstable reactive intermediates. For example, *Yoshida* and coworkers designed a flow microreactor platdorm controlling tandem isomerizations of *o*-lithiated aryl benzyl ethers (Scheme 15).[63] Depending on the reaction time, three intermediates can be selectively trapped to obtain the desired products.

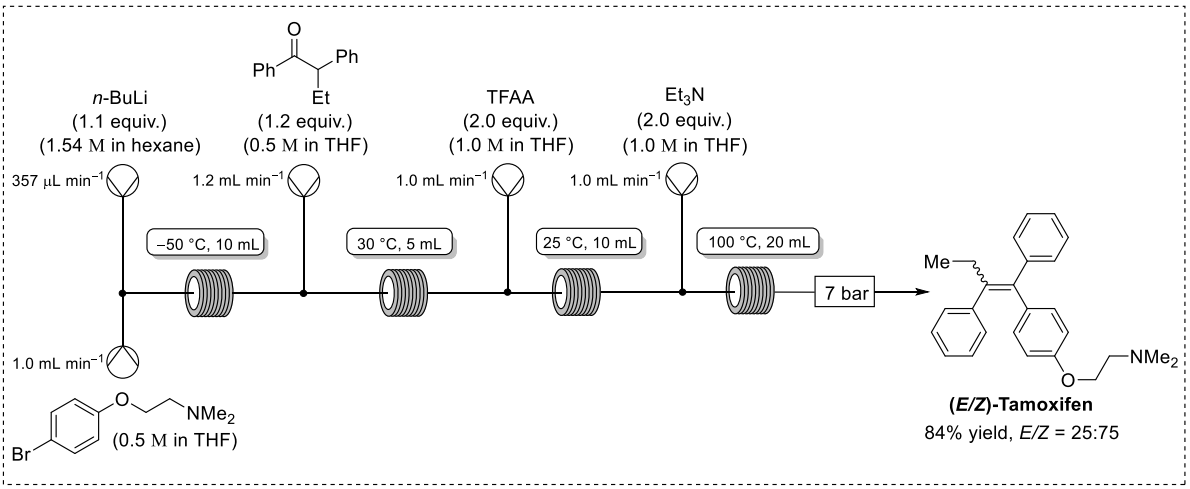


Scheme 15: Control of tandem isomerization of *o*-lithiated aryl benzyl ethers in continuous flow.[63]

Highly advanced flow platforms combining multiple reaction steps and inline workups have been developed to allow the synthesis of important pharmaceuticals minimizing labor-intensive and repetitive operations. Many of these setups incorporate organometallic reactions which can be safely conducted without exposure of highly reactive and hazardous reagents under controlled and

[62] J. W. Tucker, Y. Zhang, T. F. Jamison, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2012**, *51*, 4144.
[63] H.-J. Lee, H. Kim, J.-i. Yoshida, D.-P. Kim, *Chem. Commun.* **2018**, *54*, 547.

reproducible conditions.[64] For example, an efficient flow synthesis of the breast cancer drug tamoxifen is described by *Ley* and coworkers, yielding after 80 min of continuous collection tamoxifen in 84% yield which is enough material for over 900 days of treatment for one patient (Scheme 16).[65] Key step in the flow setup is the generation of a highly reactive organolithiumspecies.

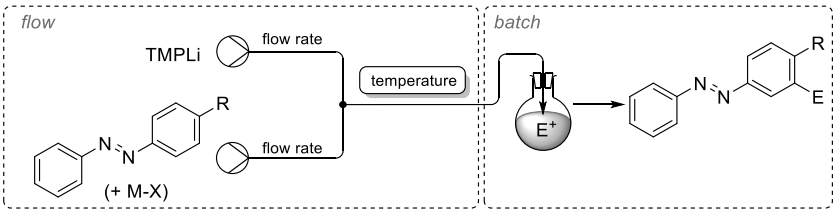


Scheme 16 Continuous-flow telescoped synthesis of (*E/Z*)-tamoxifen.[65] Intermediate cooling or heating loops for reagents are left out for clarity.

[64] For a highly advanced platform for the on-demand production of pharmaceuticals, see: 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.
[65] P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1192.

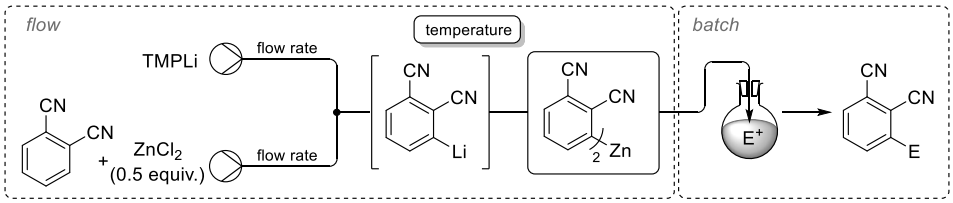
3 Objectives

Based on previous results of directed metalations and in situ trapping metalations of aromatic substrates in continuous flow, the metalation and in situ trapping metalation of substituted azobenzenes in continuous flow should be investigated. It was envisioned that under flow conditions the metalation of substituted azobenzenes would be possible without attack of the nitrogen double bond and would not require cryogenic temperatures allowing a late stage functionalization of photoswitches based on azobenzene cores (Scheme 17).



Scheme 17: Continuous flow metalation and in situ trapping metalation of substituted azobenzenes.

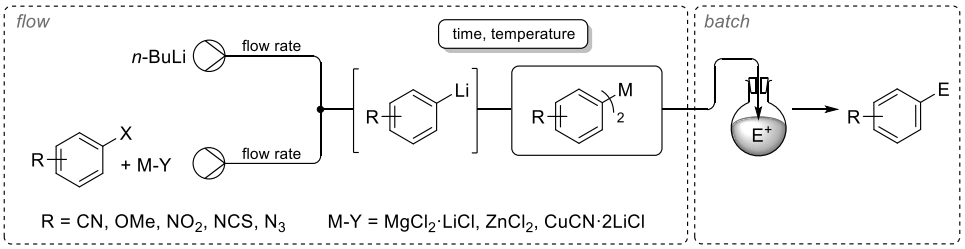
Furthermore, the in situ trapping metalation in continuous flow at mild temperatures should be extended to the functionalization of 1,2-dicyanobenzenes and related benzonitriles giving access to functionalized building blocks for the synthesis of phthalocyanines. Particularly, a scale-up procedure needed to be developed to overcome scale-up problems when executing the reaction under batch conditions (Scheme 18).[66]



Scheme 18: Continuous flow in situ trapping metalation of 1,2-dicyanobenzene.

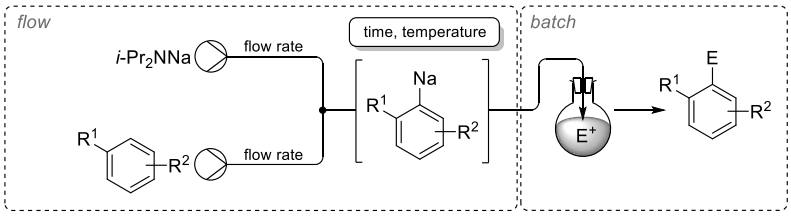
Moreover, it was proposed to transfer the concept of in situ trapping metalations to an in situ trapping halogen-lithium exchange in continuous flow where halogen-lithium exchange is faster than transmetalation of the exchange reagent with a metal salt additive. Especially aromatic compounds containing highly sensitive groups such as isothiocyanates or azides that are not tolerated under batch halogen-lithium exchange conditions should be investigated (Scheme 19).[67]

[66] This project was developed in cooperation with Dorothée S. Ziegler, see: D. S. Ziegler, Dissertation, LMU München.
[67] This project was developed in cooperation with Maximilian A. Ganiek and Niels Weidmann, see: M. A. Ganiek, Dissertation, LMU München and N. Weidmann, Dissertation, LMU München.



Scheme 19: In situ trapping halogen-metal exchange of highly sensitive (hetero)arenes using continuous flow.

Finally, a flow procedure for the sodiation of arenes and heteroarenes using the soluble base sodium diisopropylamide should be developed. It was anticipated that precise time control and efficient mixing enabled by continuous flow would allow sodiation of (hetero)arenes that decompose upon batch sodiation and thus broaden the scope of sodiation chemistry, which is a promising alternative to commonly used lithiations (Scheme 20).[68]



Scheme 20: Sodiation of arenes and heteroarenes in continuous flow.

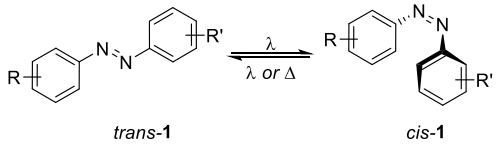
[68] This project was developed in cooperation with Niels Weidmann, see: N. Weidmann, Dissertation, LMU München.

B. RESULTS AND DISCUSSION

1 Selective Lithiation, Magnesiation and Zincation of Unsymmetrical Azobenzenes Using Continuous Flow

1.1 Introduction

Azobenzenes (**1**) function as versatile photoswitches that can be cycled between their *cis*- and *trans*-configuration with light (Scheme 21).[69] Their synthetic accessibility,[70] small size and robust switching, paired with a low rate of photobleaching makes them excellent building blocks for the incorporation into more complex optical devices.[71] Photopharmaceuticals, for instance, contain azobenzene units as on- and off-switches which allow the control of biological functions with a high spatiotemporal resolution of light.[72]



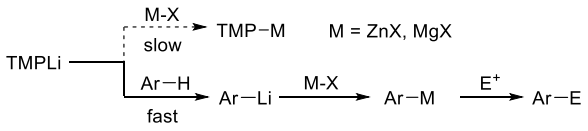
Scheme 21: Isomerization of azobenzenes (**1**).[69]

It is noteworthy, that the switching-wavelengths, the stability of the *cis*- and *trans*-isomers, and the switching kinetics are strongly influenced by the substitution pattern of the azobenzene core.[73] Therefore, the syntheses of elaborate photopharmaceuticals and the fine-tuning of the desired photoswitching properties rely on the availability of efficient synthetic methods for the direct functionalization of azobenzenes (**1**).[74] One approach for preparing functionalized azobenzenes (**1**) is their metalation with strong bases. Thus, lithiation under standard conditions with TMPLi is reported at cryogenic temperatures of −78 °C using a large excess TMPLi and subsequent quenching with CO_2

[69] H. M. D. Bandara, S. C. Burdette, *Chem. Soc. Rev.* **2012**, *41*, 1809.
[70] E. Merino, *Chem. Soc. Rev.* **2011**, *40*, 3835.
[71] M.-M. Russew, S. Hecht, *Adv. Mater.* **2010**, *22*, 3348.
[72] a) A. A. Beharry, G. A. Woolley, *Chem. Soc. Rev.* **2011**, *40*, 4422; b) T. Fehrentz, M. Schönberger, D. Trauner, *Angew. Chem. Int. Ed.* **2011**, *50*, 12156; c) C. Brieke, F. Rohrbach, A. Gottschalk, G. Mayer, A. Heckel, *Angew. Chem. Int. Ed.* **2012**, *51*, 8446; d) W. Szymański, J. M. Beierle, H. A. V. Kistemaker, W. A. Velema, B. L. Feringa, *Chem. Rev.* **2013**, *113*, 6114; e) W. A. Velema, W. Szymanski, B. L. Feringa, *J. Am. Chem. Soc.* **2014**, *136*, 2178; f) J. Broichhagen, J. A. Frank, D. Trauner, *Acc. Chem. Res.* **2015**, *48*, 1947.
[73] a) D. Bléger, S. Hecht, *Angew. Chem. Int. Ed.* **2015**, *54*, 11338; b) M. Dong, A. Babalhavaeji, S. Samanta, A. A. Beharry, G. A. Woolley, *Acc. Chem. Res.* **2015**, *48*, 2662; c) D. B. Konrad, J. A. Frank, D. Trauner, *Chem. Eur. J.* **2016**, *22*, 4364; d) M. Hammerich, C. Schütt, C. Stähler, P. Lentes, F. Röhricht, R. Höppner, R. Herges, *J. Am. Chem. Soc.* **2016**, *138*, 13111; e) M. J. Hansen, M. M. Lerch, W. Szymanski, B. L. Feringa, *Angew. Chem. Int. Ed.* **2016**, *55*, 13514; f) J. Calbo, C. E. Weston, A. J. P. White, H. S. Rzepa, J. Contreras-García, M. J. Fuchter, *J. Am. Chem. Soc.* **2017**, *139*, 1261; g) J. B. Trads, J. Burgstaller, L. Laprell, D. B. Konrad, L. de la Osa de la Rosa, C. D. Weaver, H. Baier, D. Trauner, D. M. Barber, *Org. Biomol. Chem.* **2017**, *15*, 76.
[74] E. Leonard, F. Mangin, C. Villette, M. Billamboz, C. Len, *Catal. Sci. Tech.* **2016**, *6*, 379.

or TMSCl.[75] Alternatively, the selective lithiation of unsymmetrical azobenzenes (**1**) was only realized using a halogen-lithium or a tin-lithium exchange.[76]

The generation of reactive organometallic intermediates can be greatly improved using continuous flow.[77] Recently, *Knochel* and coworkers have shown that the metalation of polyfunctional aromatics can be advantageously realized using a continuous flow setup. Especially practical was the use of in situ trapping metalation procedures where a mixture of the aromatic substrate and $ZnCl_2$ or $MgCl_2$ was treated in a commercial flow reactor with TMPLi at 0 °C.[78] The success of this procedure relies on the fact that the lithiation of the aromatic substrate with TMPLi is faster than the transmetalation of TMPLi with $MgCl_2$ or $ZnCl_2$ (Scheme 22).[79] Both approaches, the direct metalation as well as the in situ trapping metalation provide entries to the functionalization of unsymmetrical azobenzenes (**1**).



Scheme 22: In situ trapping metalation of aromatic substrates.

[75] T. T. T. Nguyen, A. Boussonniere, E. Banaszak, A.-S. Castanet, K. P. P. Nguyen, J. Mortier, *J. Org. Chem.* **2014**, *79*, 2775.

[76] a) T. Kozlecki, L. Syper, K. A. Wilk, *Synthesis* **1997**, 681; b) F. A. Garlichs-Zschoche, K. H. Doetz, *Organometallics* **2007**, *26*, 4535; c) M. D. Segarra-Maset, P. W. N. M. van Leeuwen, Z. Freixa, *Eur. J. Inorg. Chem.* **2010**, 2075; d) M. Unno, K. Kakiage, M. Yamamura, T. Kogure, T. Kyomen, M. Hanaya, *Appl. Organomet. Chem.* **2010**, *24*, 247; e) T. Soga, Y. Jimbo, K. Suzuki, D. Citterio, *Anal. Chem. (Washington, DC, U. S.)* **2013**, *85*, 8973; f) J. Strueben, M. Lipfert, J.-O. Springer, C. A. Gould, P. J. Gates, F. D. Soennichsen, A. Staubitz, *Chem. Eur. J.* **2015**, *21*, 11165.

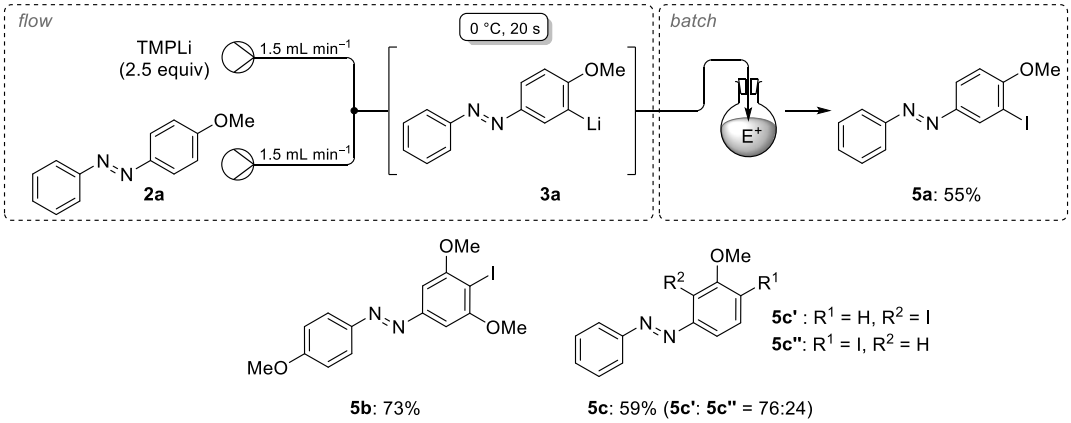
[77] For recent advances in flow chemistry and reviews see: a) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675; b) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; c) T. Noel, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010; d) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102; e) T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933; f) J. Hartwig, J. B. Metternich, N. Nikbin, A. Kirschning, S. V. Ley, *Org. Biomol. Chem.* **2014**, *12*, 3611; g) K. Somerville, M. Tilley, G. Li, D. Mallik, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 1315; h) Z. He, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *53*, 3353; i) D. B. Ushakov, K. Gilmore, D. Kopetzki, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2014**, *53*, 557; A. Hafner, V. Mancino, M. Meisenbach, N. Schenkel, J. Sedelmeier, *Org. Lett.* **2017**, *19*, 786; j) M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349; k) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; l) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; m) M. R. Becker, P. Knochel, *Org. Lett.* **2016**, *18*, 1462; n) M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2016**, *18*, 828; o) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892; p) P. D. Morse, R. L. Beingessner, T. F. Jamison, *Isr. J. Chem.* **2017**, *57*, 218.

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

[79] Experimental evidence suggests that the metalation of the aromatic substrate by TMPLi at −78 °C proceeds at least six times faster than the transmetalation of TMPLi with a metal salt additive, see: 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.

1.2 Lithiation of Methoxy-Substituted Azobenzenes

First, the attention was turned to the less sensitive 4-methoxyphenyl-2-phenyldiazene (**2a**). Its reaction with TMPLi, completed within 20 s at 0 °C in THF using a flow rate of 3 mL min^{-1}, produced the aryllithium **3a** and afforded after an iodine (**4a**) quench 1-(3-iodo-4-methoxyphenyl)-2-phenyldiazene (**5a**) in 55% yield (Scheme 23). In contrast, adding TMPLi at 0 °C under batch conditions to azobenzene **2a** lead mostly to decomposition and a mixture of products as indicated by GC-analysis. Similarly, 1-(3,5-dimethoxyphenyl)-2-(4-methoxy-phenyl)-diazene (**2b**) was lithiated under the same conditions providing after iodolysis the corresponding iodo-substituted azobenzene **5b** in 73% yield. In the case of 3-methoxyphenyl-2-phenyldiazene (**2c**), the lithiation with TMPLi is only moderately selective furnishing after iodolysis two easily separable *ortho*-substituted products (**5c'** and **5c''**) in a 3:1 ratio and 59% yield.

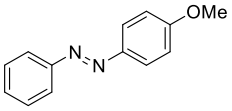
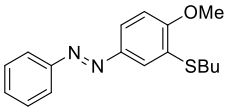
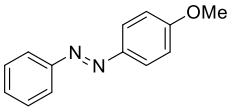
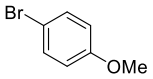
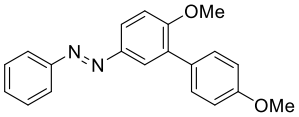
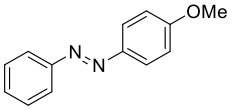
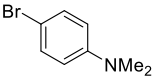
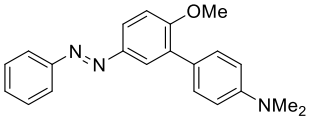
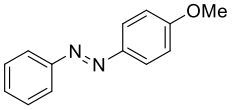
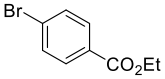
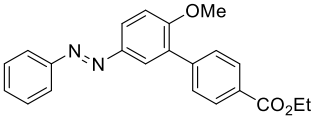
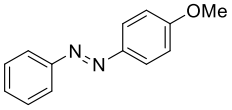
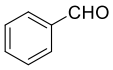
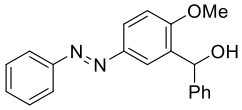
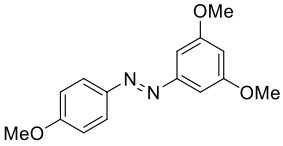
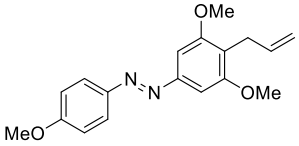
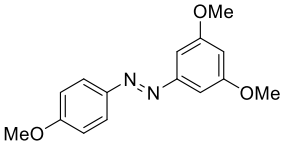
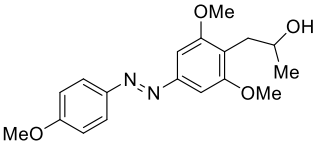
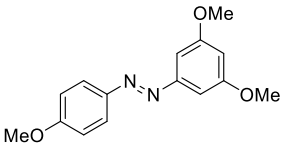
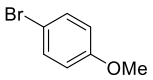
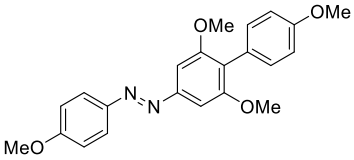


Scheme 23: Lithiation of methoxy-substituted azobenzenes (**2**) in continuous flow.

In addition to iodine, various other electrophiles were used successfully such as Bu_2S_2 (**4b**) leading to azobenzene **5d** (Table 1, entry 1). Aryl bromides **4c – e** afforded in the presence of a palladium catalyst (4 mol % $Pd(dba)_2$, 8 mol % DavePhos) after transmetalation of the lithiated azobenzene to the corresponding zinc reagent with $ZnCl_2$ diazenes **5e – g** and **5k** (entries 2 – 4 and 8). Furthermore, quenching with benzaldehyde (**4f**) or allyl bromide (**4g**) in the presence of 10% CuCN·2LiCl[80] lead to azobenzenes **5h – i** (entry 5 – 6). Reaction with propylene oxide (**4h**) afforded after transmetalation to the corresponding *Grignard* reagent, using $MgCl_2$·LiCl and 10% CuI as catalyst, diazene **5j** (entry 7). The structure of compound **5g** was confirmed by X-ray analysis.[81]

[80] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[81] CCDC 1532299 (**5g**) contains the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

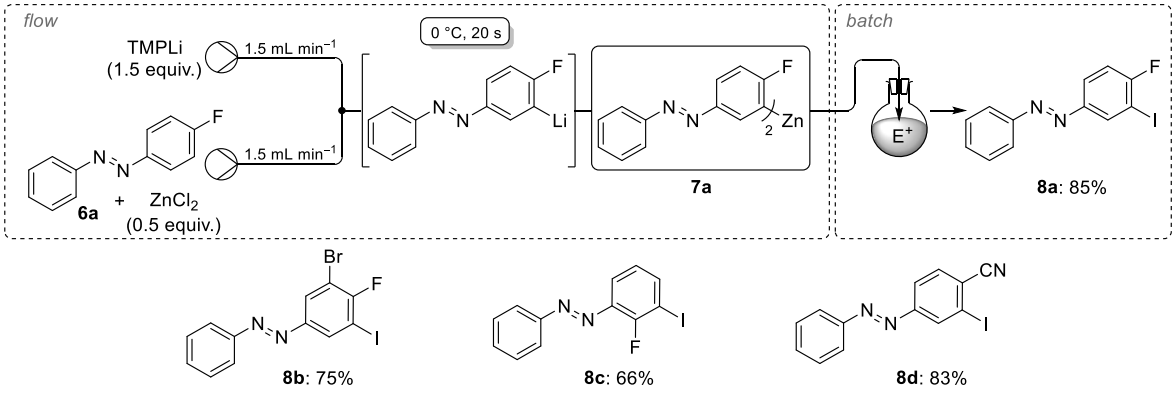
Table 1: Functionalized methoxy-substituted azobenzenes of type **5** obtained *via* lithiation in continuous flow and subsequent trapping with an electrophile (E^+) in batch.

Entry	Azobenzene	Electrophile (E^+)[a]	Product/Yield[b]
1	 **2a**	Bu_2S_2 **4b**	 **5d**: 83%[c]
2	 **2a**	 **4c**	 **5e**: 63%[e],[f]
3	 **2a**	 **4d**	 **5f**: 69%[e],[f]
4	 **2a**	 **4e**	 **5g**: 83%[g]
5	 **2a**	 **4f**	 **5h**: 58%[c],[h],[i]
6	 **2b**	 **4g**	 **5i**: 90%[c],[j]
7	 **2b**	 **4h**	 **5j**: 78%[c],[h],[k]
8	 **2b**	 **4c**	 **5k**: 90%[c],[f]

[a] Yield based on electrophile used as limiting reagent. [b] Yield of isolated, analytically pure product. [c] 0.8 equiv. E^+. [d] 0 °C, 10 min. [e] 0.7 equiv. E^+. [f] 1.1 equiv. $ZnCl_2$, 4 mol% $Pd(dba)_2$, 8 mol% DavePhos, 25 °C, 12 h. [g] 1.1 equiv. $ZnCl_2$, 0 °C, 15 min; then 0.8 equiv. E^+, 4 mol% Pd $(dba)_2$, 8 mol% DavePhos, 25 °C, 12 h. [h] 1.1 equiv. $MgCl_2$·LiCl. [i] 0 °C, 5 h. [j] 10 mol% CuCN·2LiCl, 25 °C, 1 h. [k] 10 mol% CuI, 25 °C, 12 h.

1.3 In Situ Trapping Metalation of Functionalized Azobenzenes

Although the lithiation with TMPLi under flow conditions was satisfactory with the relatively low functionalized diaryl diazenes **2a** – **c** the use of more sensitive azobenzenes bearing a fluoro-, bromo- or cyano-substituent required an in situ trapping metalation procedure using $ZnCl_2$.



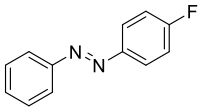
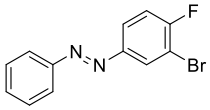
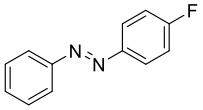
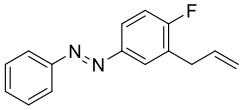
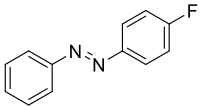
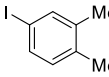
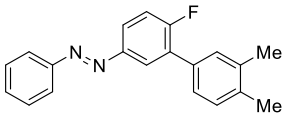
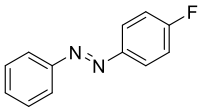
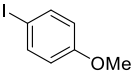
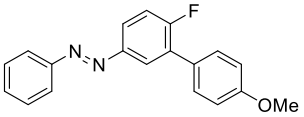
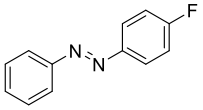
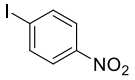
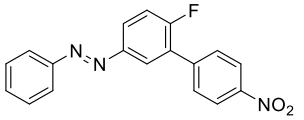
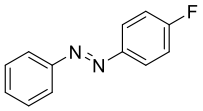
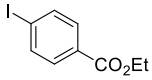
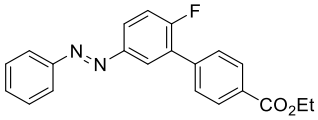
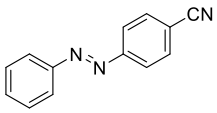
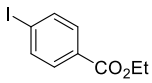
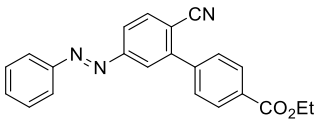
Scheme 24: In situ trapping procedure allowing the zincation and iodolysis of various unsymmetrical azobenzenes of type **6** in continuous flow.

Thus, the treatment of a mixture of 4-fluorophenyl-2-phenyldiazene (**6a**) (1.0 equiv.) and $ZnCl_2$ (0.5 equiv.) with TMPLi (1.5 equiv.) under flow conditions (3.0 mL min^{-1}, 0 °C, 20 s) led to a highly regioselective lithiation of **6a** in *ortho*-position to the fluoro-substituent giving after transmetalation with $ZnCl_2$ the corresponding arylzinc reagent **7a** which was quenched with iodine (**4a**) providing the desired azobenzene **8a** in 85% yield. Similarly, the fluoro-, bromo- and cyano-substituted diazenes **6b**, **6c** and **6d** were regioselectively lithiated, transmetalated to the zinc species and iodinated affording the unsymmetrically azobenzenes **8b, c** and **d** in 66 – 83% yield (Scheme 24). The structure of compound **8d** was confirmed by X-ray analysis.[82] This procedure was extended to a range of other electrophiles. Thus, a bromination of **6a** directly performed with Br_2 (**4i**) on a gram scale provided the bromo-derivative **8e** in 74% isolated yield without further optimization (Table 2, entry 1). A copper-catalyzed[83] allylation with allyl bromide (**4g**) provided the 3-allylated azobenzene **8f** in 85% yield (entry 2). The zinc intermediate **7a** undergoes various *Negishi* cross-couplings[84] with aryl iodides using 2 mol% $Pd(OAc)_2$ and 4 mol% SPhos[85] leading to the unsymmetrical azobenzenes **8g** – **j** in 69 – 83% yield (entries 3 – 6).

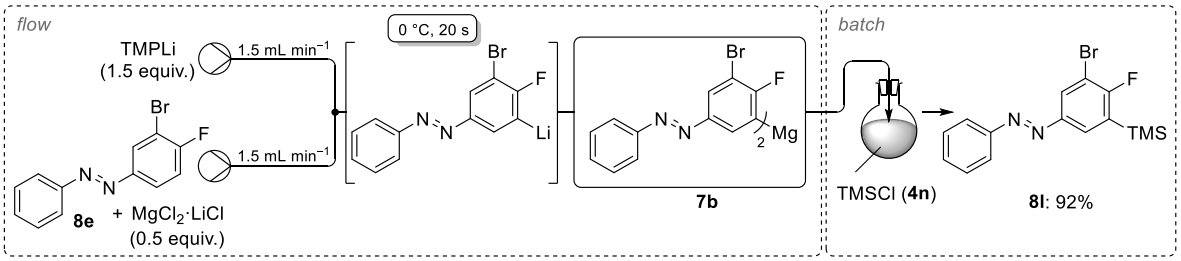
[82] CCDC 1532300 (**8d**) contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[83] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[84] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[85] R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.

Similarly, the cyano-substituted azobenzene **6d** was zincated under the same conditions in *ortho*-position to the cyano-substituent and arylated *via* a *Negishi* cross-coupling[84] providing azobenzene **8k** in 67% yield (entry 7).

Table 2: Functionalized fluoro- and cyano-substituted azobenzenes of type **6** obtained *via* an in situ trapping procedure in continuous flow using $ZnCl_2$ and subsequent trapping with an electrophile (E^+) in batch.

Entry	Azobenzene	Electrophile (E^+)	Product/Yield[a]
			
1	**6a**	**4i**	**8e**: 74%[b]
			
2	**6a**	**4g**	**8f**: 85%[c],[d] 83%[d],[e]
			
3	**6a**	**4j**	**8g**: 73%[c],[f]
			
4	**6a**	**4k**	**8h**: 76%[c],[f]
			
5	**6a**	**4l**	**8i**: 69%[c],[f]
			
6	**6a**	**4m**	**8j**: 83%[c],[f]
			
7	**6d**	**4m**	**8k**: 67%[f],[g]

[a] Yield of isolated, analytically pure product. [b] 3.0 equiv. E^+, on a gram scale, 0 °C, 1 h. [c] 1.1 equiv. E^+. [d] 10 mol% CuCN·2LiCl, 0 °C, 1 h. [e] 2.0 equiv. E^+, on a gram scale, 0 °C, 1 h. [f] 2 mol% $Pd(OAc)_2$, 4 mol% SPhos, 25 °C, 3 h. [g] 0.8 equiv. E^+, yield based on electrophile used as limiting reagent.



Scheme 25: In situ trapping procedure allowing the magnesiation of unsymmetrical azobenzenes and subsequent electrophilic quench in continuous flow.

This in situ trapping metalation procedure was extended for preparing *Grignard* reagents which are more reactive than organozinc species and are much better suited for reactions with aldehydes or acyl chlorides. Thus, the azobenzene **8e** was mixed with $MgCl_2 \cdot LiCl$ (0.5 equiv.) and reacted with TMPLi (1.5 equiv.) in a continuous flow setup (3 mL min^{-1}, 0 °C, 20 s) providing magnesium intermediate **7b**. After quenching in batch with TMSCl (**4n**) the silylated azobenzene **8l** was obtained in 92% yield (Scheme 25).

Table 3: Functionalized fluoro-substituted azobenzenes of type **8** obtained *via* an in situ trapping procedure in continuous flow using $MgCl_2 \cdot LiCl$ and subsequent trapping with an electrophile (E^+) in batch.

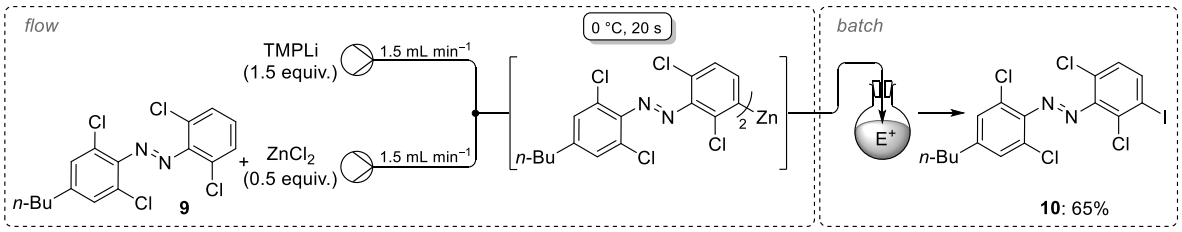
Entry	Azobenzene	Electrophile (E^+)[a]	Product/Yield[b]
1	**6a**	**4f**	**8m**: 77%[c]
2	**6a**	**4o**	**8n**: 74%[c]
3	**6a**	**4p**	**8o**: 81%[d]
4	**6a**	**4q**	**8p**: 78%[d]

[a] Yield based on electrophile used as limiting reagent. [b] Yield of isolated, analytically pure product. [c] 0.8 equiv. E^+, 0 °C, 3 – 5 h. [d] 0.8 equiv. E^+, 1.1 equiv. CuCN·2LiCl, 0 °C, 2 h.

This procedure was extended for performing quenching reactions with benzaldehyde (**4f**) or acyl chlorides using azobenzene **6a** as starting material. Thus, quenching of the corresponding magnesiated azobenzene **7c** with benzaldehyde (**4f**) or 4-fluoro-benzaldehyde (**4o**) provided the hydroxy-azobenzene

derivatives **8m** and **8n** in 77% and 74% yield, respectively (Table 3, entries 1 – 2). Similarly, quenching reactions with acid chlorides **4p** and **4q** in the presence of CuCN·2LiCl (1.1 equiv.) furnished the corresponding acyl-substituted azobenzenes **8o** and **8p** in 81% and 78% yield (entries 3 – 4).

This method was further applied to the highly functionalized azobenzene **9**. Its tetra-*ortho*-chloro substitution pattern enables visible-light photoswitching which makes it a valuable synthetic intermediate for photopharmaceuticals that target complex animal tissues.[73] This additional functionalization proceeded smoothly through an in situ trapping zincation using TMPLi followed by a batch-iodination and afforded the selectively iodinated azobenzene **10** in 65% yield (Scheme 26). The structure of compound **10** was confirmed by X-ray analysis.[86]



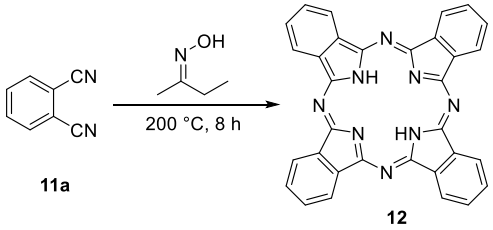
Scheme 26: In situ trapping metalation procedure allowing the zincation and iodolysis of the tetra-*ortho*-chloro-substituted azobenzene **9** in continuous flow.

[86] CCDC 1532301 (**10**) contains the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

2 Selective Zincation of 1,2-Dicyanobenzene and Related Benzonitriles in Continuous Flow Using In Situ Trapping Metalations

2.1 Introduction

The metalation of polyfunctionalized aromatics and heterocycles pioneered among others by *Snieckus*[87] is a key reaction of the expedited functionalization of these unsaturated building blocks for applications in pharmacy, agrochemistry and material science.[88] Of special importance is the functionalization of 1,2-dicyanobenzenes (**11a**) since derivatives of such scaffolds may be used for heterocyclic syntheses and for the elaboration of phthalocyanines (**12**) with potential applications in solar cells (Scheme 27).[89]



Scheme 27: Example synthesis of the phthalocyanine scaffold (**12**) starting from 1,2-dicyanobenzene (**11a**).[90]

Recently, *Knochel* and coworkers have shown that the performance of the so called in situ trapping metalations[91] for polyfunctionalized aromatics can be advantageous since the produced lithium intermediate is immediately trapped with metallic salts such as $MgCl_2 \cdot 2LiCl$, $ZnCl_2$, $CuCN \cdot 2LiCl$ or

[87] a) V. Snieckus, *Heterocycles* **1980**, *14***,** 1649; b) M. Watanabe, V. Snieckus, *J. Am. Chem. Soc.* **1980**, *102,* 1457; c) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982,** *15,* 306; d) V. Snieckus, *Chem. Rev*. **1990**, *90*, 879; e) F. Beaulieu, V. Snieckus, *Synthesis* **1991**, *2*, 112; f) B. A. Chauder, A. V. Kalinin, V. Snieckus, *Synthesis* **2001**, *1*, 140; g) C. Schneider, E. David, A. A. Toutov, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 2722; h) Y. Zhao, V. Snieckus, *J. Am. Chem. Soc.*, **2014**, *136*, 11224; i) M. A. Fuentes, A. R. Kennedy, R. E. Mulvey, J. A. Parkinson, T. Rantanen, S. D. Robertson, V. Snieckus, *Chem. Eur. J.* **2015**, *21*, 14812; j) Y. Zhao, V. Snieckus, *Chem. Commun.*, **2016**, *52*, 1681.

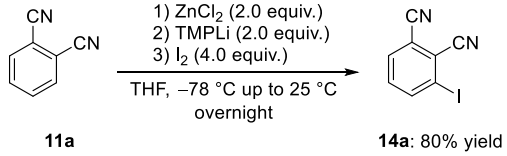
[88] a) L. Maat in *Classics in Total Synthesis* (Eds.: K. C. Nicolaou, E. J. Sorensen), Wiley-VCH, Weinheim, **1996**; b) *Classics in Total Synthesis II* (Eds.: K. C. Nicolaou, S. A. Snyder), Wiley-VCH, Weinheim, **2003**; c) R. Chinchilla, C. Nájera, M. Yus, *Tetrahedron* **2005**, *61*, 3139; d) J. Y. Kim, K. Lee, N. E. Coates, D. Moses, T.-Q. Nguyen, M. Dante, A. J. Heeger, *Science* **2007**, *317*, 222; e) K. C. Nicolaou, J. S. Chen, D. J. Edmonds, A. A. Estrada, *Angew. Chem. Int. Ed*. **2009**, *48*, 660; f) T. Clarke, A. Ballantyne, F. Jamieson, C. Brabec, J. Nelson, J. Durrant, *Chem. Commun*. **2009**, 89; g) J. Nafe, P. Knochel, *Synthesis* **2016**, *48*, 103; g) K. Moriya, K. Schwaerzer, K. Karaghiosoff, P. Knochel, *Synthesis* **2016**, *48*, 3141; h) F. Lima, M. A. Kabeshov, D. N. Tran, C. Battilocchio, J. Sedelmeier, G. Sedelmeier, B. Schenkel, S. V. Ley, *Angew. Chem. Int. Ed.* **2016**, *55*, 14085; i) A. B. Bellan, O. M. Kuzmina, V. A. Vetsova, P. Knochel, *Synthesis* **2017**, *49*, 188.

[89] a) M. O. Senge, N. N. Sergeeva in *The Chemistry of Organozinc Compounds* (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons, Chichester, **2006**, 395; b) H. Xu, W.-K. Chan, D. K. P. Ng, *Synthesis* **2009**, 1791; c) L. Tejerina, M. V. Martínez-Díaz, M. K. Nazeeruddin, T. Torres, *Chem. Eur. J.* **2016**, *22*, 4369; d) S. Yamamoto, A. Zhang, M. J. Stillmann, N. Kobayashi, M. Kimura, *Chem. Eur. J.* **2016**, *22*, 18760.

[90] M. N. Kopylovich, V. Y. Kukushkin, M. Haukka, K. V. Luzyanin, A. J. L. Pombeiro, *J. Am. Chem. Soc.* **2004**, *126*, 15040.

[91] 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.

$LaCl_3 \cdot 2LiCl$.[92] Preliminary experiments with 1,2-dicyanobenzene (**11a**) have shown that the addition of TMPLi[93] (1.2 equiv.) to a mixture of **11a** with the metal salt $ZnCl_2$ at −78 °C first lead to the lithiation of the arene followed by transmetalation with the metal salt to afford an *ortho*-zincated intermediate **13a** and provided after iodolysis the desired 3-iodo derivative (**14a**) in 80% yield. Further experiments showed that the generation of the lithium species and in situ trapping with $ZnCl_2$ required a temperature of −78 °C in batch and cannot be scaled-up without further optimization (Scheme 28).



Scheme 28: Batch-conditions for the functionalization of 1,2-dicyanobenzene (**11a**).

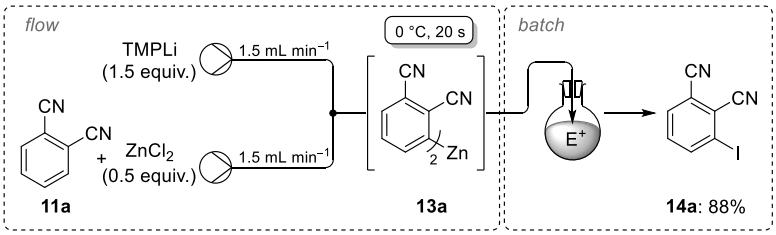
Recently, *Knochel* and coworkers reported that in situ trapping metalations can be performed at mild conditions using a continuous flow setup.[94] In this procedure, the substrate, here 1,2-dicyanobenzene (**11a**) is mixed with $ZnCl_2$ (0.5 equiv.) in THF and this solution is mixed in continuous flow with a THF solution of TMPLi (ca. 0.6 M, 1.5 equiv.). Such a mixing is done at 0 °C (and not cryogenic temperatures as for the batch procedure) and requires only 20 s reaction time. Herein, the successful use of this setup to prepare a range of functionalized 1,2-dicyanobenzenes of type **14** as well as some related polyfunctionalized benzonitriles of type **15** is reported.

2.2 Zincation of 1,2-Dicyanobenzenes

The treatment of a mixture of 1,2-dicyanobenzene (**11a**, 1.0 equiv.) and $ZnCl_2$ (0.5 equiv.) with TMPLi (1.5 equiv.) under flow conditions[95] (3.0 mL min^{-1}, 0 °C, 20 s) led to a regioselective lithiation of **11a**, giving after transmetalation with $ZnCl_2$ the corresponding diarylzinc reagent (**13a**), which was quenched with iodine (**16a**), providing 3-iodo-1,2-dicyanobenzene (**14a**) in 88% yield (Scheme 29). Using the same stoichiometry in a batch reaction lead to a lower conversion and poorer yields were obtained.

---

[92] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
[93] a) M. W. Rathke, R. Kow, *J. Am. Chem. Soc.* **1972**, *94*, 6854; b) C. L. Kissel, B. Rickborn, *J. Org. Chem.* **1972**, *37*, 2060; c) R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95*, 581; d) R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95*, 582; e) M. Uzelac, A. R. Kennedy, E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2016**, *55*, 13147.
[94] a) T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933; b) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; c) M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org Lett.* **2016**, *18*, 828; d) M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.* **2017**, *19*, 1666.
[95] Flow reactions were performed with commercially available equipment from Uniqsis Ltd (FlowSyn; http://www.uniqsis.com). See experimental part for details.



Scheme 29: Continuous flow setup for in situ trapping metalations of 1,2-dicyanobenzene (**11a**) using TMPLi in the presence of $ZnCl_2$.

This in situ generation of a zincated dicyanobenzene such as **13a** can be used to perform reactions with various classes of organic electrophiles. Thus, collecting the flow stream in a flask containing an allylic bromide such as 3-bromocyclohexene (**16b**) or ethyl 2-(bromomethyl)acrylate (**16c**) and 10 mol% CuCN·2LiCl[96] on an approximately 0.5 mmol scale gave the allylated products **14b** and **c** in 81% and 76% yield (Table 4, entries 1 – 2).

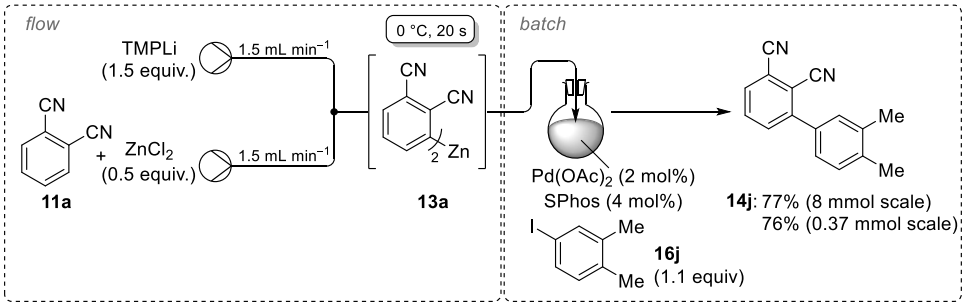
Table 4: Functionalized 1,2-dicyanobenzenes of type **14** obtained *via* an in situ trapping procedure in continuous flow using $ZnCl_2$ and subsequent trapping with an electrophile (E^+) in batch.

Entry	Electrophile (E^+)[a]	Product/Yield[b]	Entry	Electrophile (E^+)[a]	Product/Yield[b]
1	**16b**	**14b**: 81%[c]	5	**16f**	**14f**: 78%[d]
2	**16c**	**14c**: 76%[c]	6	**16g**	**14g**: 76%[d]
3	**16d**	**14d**: 57%[d]	7	**16h**	**14h**: 87%[e]
4	**16e**	**14e**: 74%[d]	8	**16i**	**14i**: 82%[e]

[a] 1.1 equiv. of E^+ were used. [b] Yield of isolated, analytically pure product. [c] Obtained in the presence of 10 mol% CuCN·2LiCl, 0 °C, 2 h. [d] Obtained after transmetalation with 1.1 equiv. of CuCN·2LiCl, 0 °C, 2 h. [e] Obtained using 2 mol% $Pd(OAc)_2$ and 4 mol% SPhos, 25 °C, overnight.

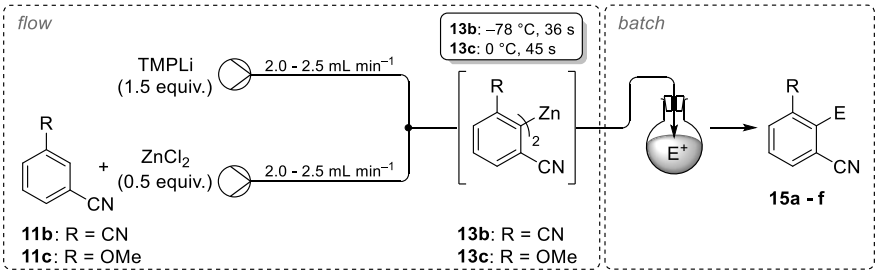
[96] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

Similarly, copper-mediated acylations with 3-chlorobenzoyl chloride (**16d**) or 2,4-dichlorobenzoyl chloride (**16e**) afforded the functionalized 1,2-dicyanobenzene derivatives (**14d** – **e**) in 57% and 74% yield (entries 3 – 4). Ketones **14f** – **g** were obtained in 76 – 78% yield after transmetalation of zincated intermediate **13a** to the corresponding copper derivative using CuCN·2LiCl[96] and acylation with cyclopropanecarbonyl chloride (**16f**) or thiophene-2-carbonyl chloride (**16g**, entries 5 – 6). Zinc intermediate **13a** underwent various *Negishi* cross-couplings[97] with 4-iodoanisole (**16h**) or ethyl 4-iodobenzoate (**16i**) using 2 mol% $Pd(OAc)_2$ and 4 mol% SPhos[98], leading to the desired products **14h** – **i** in 76 – 87% yield (entries 7 and 8).



Scheme 30: 8 mmol scale-up for the in situ trapping metalation of 1,2-dicyanobenzene (**11a**).

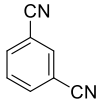
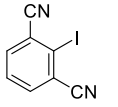
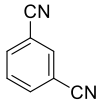
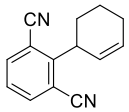
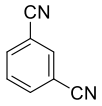
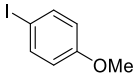
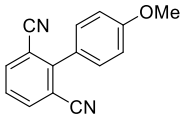
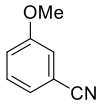
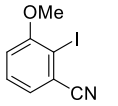
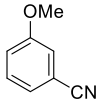
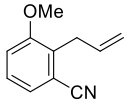
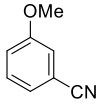
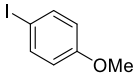
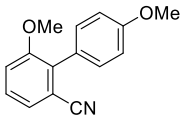
The scale-up of these in situ trapping metalations in flow is readily performed and does not require further optimization. It is realized by simply extending the collection time of the metalated species in batch. Thus, the flow metalation of 1,2-dicyanobenzene (**11a**) was performed on a 8 mmol scale for the *Negishi* cross-coupling[97] with 4-iodo-1,2-dimethylbenzene (**16j**, 2 mol% $Pd(OAc)_2$, 4 mol% SPhos,[98] Scheme 30) leading to the biphenyl **14j** in 77% yield. In addition, a 10 mmol scale-up for the reaction of the zincated 1,2-dicyanobenzene (**13a**) with iodine (**16a**) led to **14a** in 87% yield.



Scheme 31: Continuous flow setup for the in situ trapping procedure of related functionalized benzonitriles **11b** and **11c**.

[97] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[98] R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.

Table 5: Related functionalized benzonitriles of type **15** obtained *via* an in situ trapping procedure in continuous flow using $ZnCl_2$ and subsequent trapping with an electrophile (E^+) in batch.

Entry	Benzonitrile	Electrophile (E^+)	Product/Yield[a]
1	 **11b**	**16a**	 **15a**: 79%[b]
2	 **11b**	 **16b**	 **15b**: 88%[c],[d]
3	 **11b**	 **16h**	 **15c**: 80%[d],[e]
4	 **11c**	**16a**	 **15d**: 82%[b]
5	 **11c**	**16c**	 **15e**: 58%[c],[d]
6	 **11c**	 **16h**	 **15f**: 80%[d],[e]

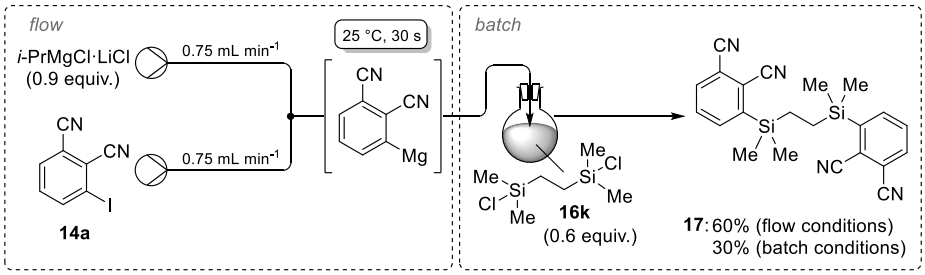
[a] Yield of isolated, analytically pure product. [b] 1.1 equiv. of E^+ was used. [c] Obtained in the presence of 10 mol% CuCN·2LiCl, 0 °C, 2 h. [d] 0.8 equiv. of E^+ was used. [e] Obtained using 2 mol% $Pd(OAc)_2$ and 4 mol% SPhos, 25 °C, overnight.

Furthermore, the in situ trapping metalation procedure was extended for the zincation of 1,3-dicyanobenzene (**11b**) and 3-methoxybenzonitrile (**11c**) (Scheme 31). Thus, the treatment of a mixture of 1,3-dicyanobenzene (**11b**, 1.0 equiv.) and $ZnCl_2$ (0.5 equiv.) with TMPLi (1.5 equiv.) under flow conditions (5.0 mL min^{-1}, −78 °C, 45 s) led to a regioselective lithiation of **11b** in 2-position, giving after transmetalation with $ZnCl_2$ the corresponding diarylzinc reagent (**13b**), which was quenched with iodine (**16a**), providing the desired product **15a** in 79% yield (Table 5, entry 1). A copper-catalyzed allylation[96] with 3-bromocyclohex-1-ene (**16b**) provided the 2-allylated 1,3-dicyanobenzene (**15b**) in 88% yield (entry 2). Pd-catalyzed *Negishi* cross-coupling[97] (2 mol% $Pd(OAc)_2$ and 4 mol% SPhos[98]) with 4-iodoanisole (**16h**) furnished the arylated 1,3-dicyanobenzene (**15c**) in 80% yield (entry 3). Similiary, 3-methoxybenzonitrile (**11c**) was regioselectively lithiated and transmetalated to the zinc species (**13c**) in continuous flow (4.0 mL min^{-1},

0 °C, 45 s), and iodinated, allylated, and cross-coupled, leading to the desired products **15d** – **f** in 58 – 82% yield (entries 4 – 6).

2.3 Functionalization of 1,2-Dicyano-3-iodobenzene Using Continuous Flow

The iodinated dicyanobenzene (**14a**) can be further modified to extend the variety of precursors for phthalocyanines. Thus, an iodine-magnesium exchange reaction in continuous flow (1.5 mL min^{-1}, 25 °C, 20 s) was realized by the reaction of **14a** with *i*-PrMgCl·LiCl (0.9 equiv.).[99] Subsequent quenching with 1,2-bis(chlorodimethylsilyl)ethane (**16k**, 0.6 equiv.) produces the desired product **17**, which could act as an interesting precursor for the synthesis of bridged phthalocyanines (**12**)[100], in 60% yield while in batch only 30% was isolated. (Scheme 32).



Scheme 32: Iodine-magnesium exchange by the reaction of **14a** with *i*-PrMgCl·LiCl.

[99] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.
[100] a) D. M. Drew, C. C. Leznoff, *Synlett* **1994**, 623; b) C. C. Leznoff, D. M. Drew, *Can. J. Chem.* **1996**, *74*, 307.

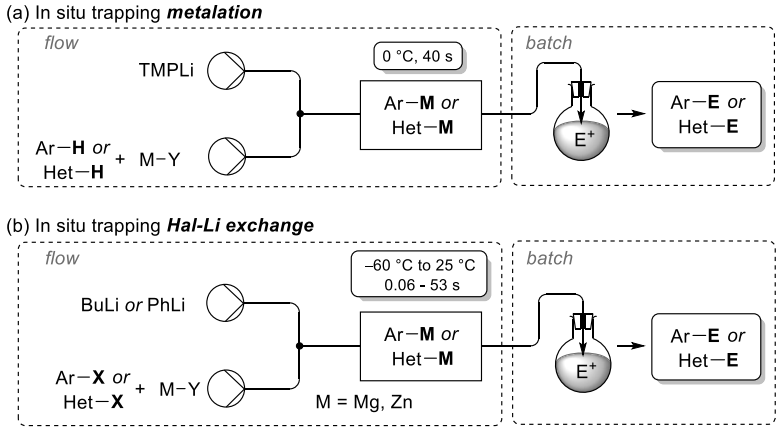
3 Preparation of Polyfunctional Diorgano-Magnesium and -Zinc Reagents Using In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuous Flow

3.1 Introduction

Organolithiums are key organometallic intermediates in organic synthesis.[101] The halogen-lithium exchange reaction is a standard preparation of organolithium compounds[102] and provides access after transmetalation to a broad variety of other useful organometallic species.[103] The scope of halogen-lithium exchange reactions is limited by the presence of sensitive functional groups in these unsaturated substrates,[102c,103d] precluding the presence of an ester, a nitro, an azide or an isothiocyanato group.[104] These drawbacks were avoided to some extent by the use of cryogenic temperatures[102c], special protecting groups[105] or by fast consecutive transmetalations to less reactive organometallics.[101f,106] Continuous flow setups have emerged as a powerful tool for solving synthetic problems.[107] Thus, *Yoshida* and others have utilized ultra-fast mixing and precise reaction time control of custom-made flow setups for achieving the generation of lithiated arenes bearing ester, isothiocyanate, cyano or nitro groups.[108] Recently, *Knochel* and coworkers have shown that the scope of metalations of arenes (Ar – H) with a strong base like TMPLi is dramatically increased by performing these metalations in

[101] a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; b) *The Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**; c) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; d) D. B. Collum, A. J. McNeil, A. Ramirez, *Angew. Chem. Int. Ed.* **2007**, *46*, 3002; e) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, *37*, 2620; f) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463.
[102] a) W. E. Parham, L. D. Jones, Y. Sayed, *J. Org. Chem.* **1975**, *40*, 2394; b) W. E. Parham, C. K. Bradscher, *Acc. Chem. Res.* **1982**, *15*, 300; c) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1.
[103] a) A. Boudier, L. A. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; b) D. R. Armstrong, E. Crosbie, E. Hevia, R. E. Mulvey, D. L. Ramsay, S. D. Robertson, *Chem. Sci.* **2014**, *5*, 3031; c) K. Moriya, M. Simon, R. Mose, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10963; d) M. Uzelac, A. R. Kennedy, E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2016**, *55*, 13147.
[104] a) S. Cook, B. J. Wakefield, *J. Chem. Soc. Perkin Trans. 1*, **1980**, 2392; b) M. Hatano, S. Suzuki, K. Ishihara, *Synlett* **2010**, 321; c) T. Kim, K. Kim, *J. Heterocyclic Chem.* **2010**, *47*, 98; d) K. Kobayashi, Y. Yokoi, T. Nakahara, N. Matsumoto, *Tetrahedron* **2013**, *69*, 10304; e) K. N. Plessel, A. C. Jones, D. J. Wherritt, R. M. Maksymowicz, E. T. Poweleit, H. J. Reich, *Org. Lett.* **2015**, *17*, 2310; f) A. Matsuzawa, S. Takeuchi, K. Sugita, *Chem. Asian J.* **2016**, *11*, 2863; g) K. Kobayashi, Y. Chikazawa, *Helv. Chim. Acta* **2016**, *99*, 33.
[105] S. Oda, H. Yamamoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 8165.
[106] a) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983; b) I. Klement, M. Rottlaender, C. E. Tucker, T. N. Majid, P. Knochel, P. Venegas, G. Cahiez, *Tetrahedron* **1996**, *52*, 7201.
[107] For general advances in flow chemistry, see: a) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102; b) D. Ghislieri, K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 678; c) M. Teci, M. Tilley, M. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967; d) C. Battilocchio, F. Feist, A. Hafner, M. Simon, D. N. Tran, D. M. Allwood, D. C. Blakemore, S. V. Ley, *Nat. Chem.* **2016**, *8*, 360; e) H. Seo, M. H. Katcher, T. F. Jamison, *Nat. Chem.* **2017**, *9*, 453.
[108] a) A. Nagaki, H. Kim, H. Usutani, C. Matsuo J.-i. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; b) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun*. **2011**, *2*, 264; c) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; d) H. Kim, H. J. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 1877.

the presence of metallic salts (M – Y).[109] The resulting organometallics (Ar – M) are much more stable than the initially generated lithium reagents and can be broadly functionalized with a variety of electrophiles (E^+). The scope and reaction conditions of this in situ trapping procedure are further improved by switching from a batch to a continuous flow setup (Scheme 33a).[110] Aware of the fast rate of the halogen-lithium exchange,[111] an analogous in situ trapping exchange procedure was envisioned (Scheme 33b). Herein, a halogen-lithium exchange performed in the presence of metallic salts for the convenient functionalization of sensitive (hetero)arenes using continuous flow technology is reported (Scheme 33b).



Scheme 33: (a) In situ trapping metalation and (b) in situ trapping exchange using commercially available continuous flow setups.

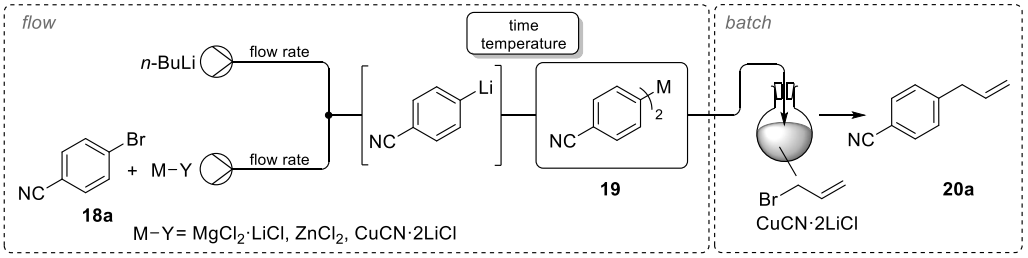
3.2 Optimization of Reaction Conditions

First, the reaction conditions of the bromine-lithium exchange for 4-bromobenzonitrile (**18a**) using *n*-BuLi as exchange reagent were optimized (Table 6). Optimized flow conditions without the addition of a metal salt led after quenching with allyl bromide (**21a**, 2.5 equiv.) and CuCN·2LiCl[112] (10 mol%) to the allylated arene **20a** in 17% GC-yield (entry 1). This low yield may be due to the competitive addition of the newly generated aryllithium or *n*-BuLi to the cyano group. Addition of the well-soluble $MgCl_2$·LiCl to the aryl bromide **18a** and further optimization of the flow rate, reaction time and temperature led to the magnesiated species **19a** and increased the GC-yield of the allylated product **20a** to 85% (entries 2 – 7). Instead of $MgCl_2$·LiCl, also $ZnCl_2$ or CuCN·2LiCl were used as in situ transmetalating agents leading to **20a** in 71 – 82% GC-yield (entries 8 – 9). To confirm the order of

[109] A. Frischmuth, M. Fernández, N. M. Barl, F. Achreiner, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53,* 7928.
[110] a) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed*. **2015**, *54*, 12501; b) M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.*, **2017**, *19*, 1666.
[111] a) W. F. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861; b) S. Goto, J. Velder, S. El Sheikh, Y. Sakamoto, M. Mitani, S. Elmas, A. Adler, A. Becker, J. Neudörfl, J. Lex, H. G. Schmalz, *Synlett* **2008**, 1361.
[112] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

exchange and transmetalation the metal salts (M – Y) were premixed with *n*-BuLi in batch at −78 °C for 20 min. The resulting zinc- or magnesium base was injected in flow using the established conditions. In the case of the zinc species no reaction occurred (entry 10)[113] and in the case of the magnesium species only 26% GC-yield of the allylated arene **20a** were obtained (entry 11) confirming the reaction order of the halogen-lithium exchange with *n*-BuLi and subsequent transmetalation with the premixed metal salt.

Table 6: Optimization of the in situ trapping bromine-lithium exchange for 4-bromobenzonitrile (**18a**) using *n*-BuLi as exchange reagent leading to allylated benzonitrile **20a**.



Entry	M–Y (equiv.)	*n*-BuLi equiv.	Temperature [°C]	Flow rate [mL min^{-1}]	Time [s]	Yield of 20a [%][a]
1	–	1.5	0	6.0	2.50	17
2	$MgCl_2$·LiCl (1.1)	1.5	0	6.0	2.50	57
3	$MgCl_2$·LiCl (0.5)	1.1	0	6.0	2.50	62
4	$MgCl_2$·LiCl (0.5)	1.5	0	1.0	15.0	68
5	$MgCl_2$·LiCl (0.5)	1.5	0	16.0	0.94	78
6	$MgCl_2$·LiCl (0.5)	1.5	25	6.0	2.50	38
7	$MgCl_2$·LiCl (0.5)	1.5	0	6.0	2.50	85
8	$ZnCl_2$ (0.5)	1.5	0	6.0	2.50	82
9	CuCN·2LiCl (1.1)	1.5	0	6.0	2.50	71
10	$ZnCl_2$ (0.5)[b]	1.5	0	6.0	2.50	0
11	$MgCl_2$·LiCl (0.5)[b]	1.5	0	6.0	2.50	26

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

3.3 In Situ Trapping Halogen-Lithium Exchange on Sensitive Substrates

The intermediate magnesium species **19a** was used in various quenching reactions with electrophiles. Thus, an iodolysis led to aryl iodide **20b** in 70% isolated yield (Table 7, entry 1). The addition of

[113] Compare: a) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017; b) E. Gioria, J. M. Martínez-Ilarduya, P. Espinet, *Organometallics* **2014**, *33*, 4394.

diarylmagnesium **19a** to benzaldehyde (**21c**) provided benzylic alcohol **20c** in 83% yield (entry 2). Batch acylation of the magnesium reagent **19a** in the presence of CuCN·2LiCl with acyl chlorides such as 3-chlorobenzoyl chloride (**21d**) and pivaloyl chloride (**21e**) led to the expected ketones **20d** and **e** in 85% and 78% yield (entries 3 – 4). Alternatively, an in situ trapping bromine-lithium exchange in the presence of CuCN·2LiCl (instead of $MgCl_2$·LiCl) produced arylcopper **19b** which reacted similarly with benzoyl chloride (**21f**) providing benzophenone **20f** in 80% yield (entry 5). The range of substrates was extended to various other sensitive bromobenzonitriles **18b** and **18c** which were converted in a comparable way to the corresponding diarylmagnesium species (**19c** and **19d**) under appropriate conditions (0 °C, 9 mL min^{-1}, 1.7 s). Thus, after batch-quenching with ketones, allyl bromides or acyl chlorides in the presence of CuCN·2LiCl the corresponding products **20g – l** were obtained in 68 – 78% yield (entries 6 – 11).

Table 7: In situ exchange transmetalation for sensitive aryl iodides and bromides of type **18** leading *via* intermediate diorganozincs or -magnesiums of type **19** to polyfunctional arenes of type **20**.

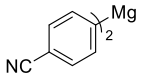
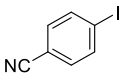
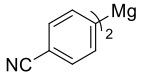
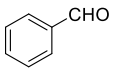
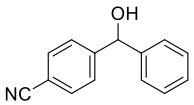
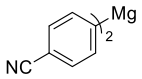
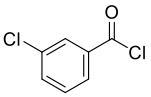
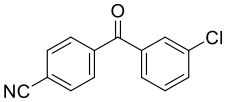
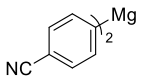
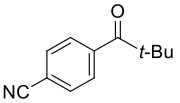
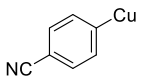
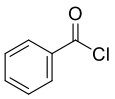
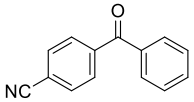
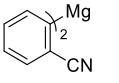
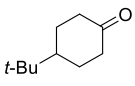
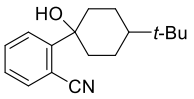
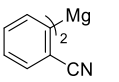
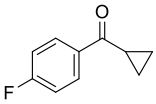
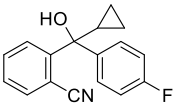
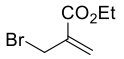
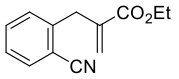
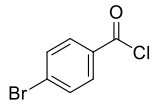
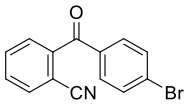
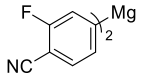
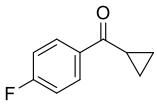
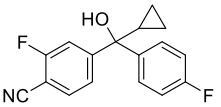
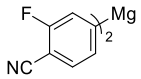
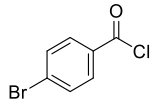
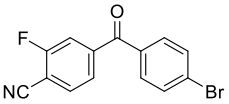
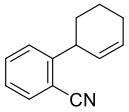
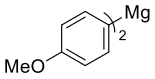
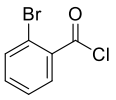
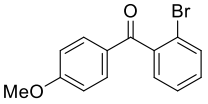
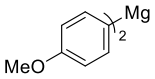
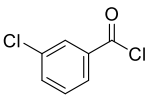
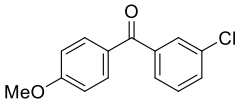
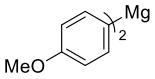
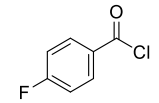
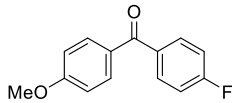
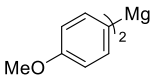
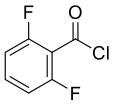
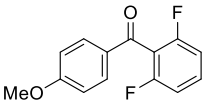
Entry	Metal species [T, flow rate, t]	Electrophile (E^+)	Product/Yield[a]
			
1	**19a** (0 °C, 6 mL min^{-1}, 2.5 s)[b]	**21b**[c]	**20b**: 83%
			
2	**19a** (0 °C, 6 mL min^{-1}, 2.5 s)[b]	**21c**[d]	**20c**: 70%
			
3	**19a** (0 °C, 6 mL min^{-1}, 2.5 s)[b]	**21d**[e],[f]	**20d**: 85%
			
4	**19a** (0 °C, 6 mL min^{-1}, 2.5 s)[b]	**21e**[e],[f]	**20e**: 78%
			
5	**19b** (0 °C, 6 mL min^{-1}, 2.5 s)[b]	**21f**[f]	**20f**: 80%
			
6	**19c** (0 °C, 9 mL min^{-1}, 1.7 s)[b]	**21g**[d]	**20g**: 73% (d.r. = 84:16)
			
7	**19c** (0 °C, 9 mL min^{-1}, 1.7 s)[b]	**21h**[d]	**20h**: 70%

Table 7 continued

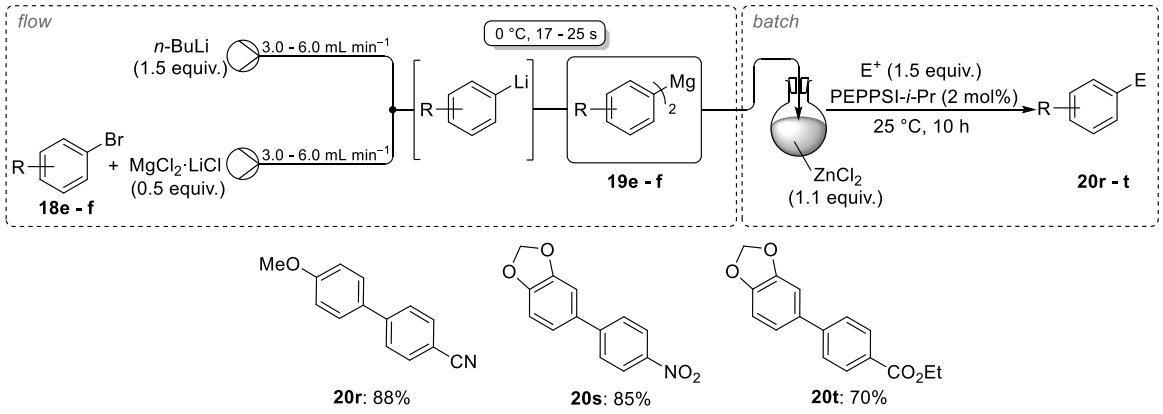
			
8	**19c** (0 °C, 9 mL min^{-1}, 1.7 s)[b]	**21i**[g]	**20i**: 68%
			
9	**19c** (0 °C, 9 mL min^{-1}, 1.7 s)[b]	**21j**[e],[f]	**20j**: 78%
			
10	**19d** (0 °C, 9 mL min^{-1}, 1.7 s)[b]	**21h**[d]	**20k**: 74%
			
11	**19d** (0 °C, 9 mL min^{-1}, 1.7 s)[b]	**21j**[d]	**20l**: 74% (76%)[h]
			
12	**19e** (0 °C, 9 mL min^{-1}, 1.7 s)[i]	**21k**[g]	**20m**: 80%
			
13	**19f** (0 °C, 12 mL min^{-1}, 25 s)[b]	**21l**[e],[f]	**20n**: 68%
			
14	**19f** (0 °C, 12 mL min^{-1}, 25 s)[b]	**21d**[e],[f]	**20o**: 56%
			
15	**19f** (0 °C, 12 mL min^{-1}, 25 s)[b]	**21m**[e],[f]	**20p**: 67%
			
16	**19f** (0 °C, 12 mL min^{-1}, 25 s)[b]	**21n**[e],[f]	**20q**: 61%

[a] Yield of analytically pure isolated product. [b] Metal species prepared from the corresponding aryl bromide. [c] 2.0 equiv., 10 min, 25 °C. [d] 1.1 – 1.5 equiv., 1 – 2 h, 0 °C. [e] 1.1 equiv. CuCN·2LiCl was added. [f] 1.5 equiv., 1 – 2 h, 0 °C. [g] 2.5 equiv., 10 mol% CuCN·2LiCl, 30 min, 0 °C. [h] Reaction performed on 10 mmol scale, 3 h, 0 °C. [i] Metal species prepared from the corresponding aryl iodide.

While most examples were performed on a 0.5 mmol scale, these in situ trapping exchange reactions can be conveniently scaled up by simply extending the runtime. Thus, benzophenone **20l** was prepared on a 10 mmol scale in 76% yield (entry 11) without further optimization.[114] It was also possible to

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

perform an iodine-lithium exchange on 2-iodobenzonitrile (**18d**) using similar conditions (0.5 equiv. $ZnCl_2$, 0 °C, 6 mL min^{-1}, 2.5 s), providing the diarylzinc species **19e**. Allylation with 3-bromocyclohexene (**21k**) afforded 1,2-disubstituted benzonitrile **20m** in 80% yield (entry 12). Remarkably, these exchange reactions proceed at 0 °C in contrast to the standard halogen-lithium exchanges in batch which are performed at −78 °C.[102,106] Also, electron-rich aryl bromides like 4-bromoanisole (**18e**) were in situ transmetalated in the presence of $MgCl_2$·LiCl and quenched with various acyl chlorides **21l – n** in batch leading to ketones **20n – q** in 56 – 68% yield (entries 13 – 16). Furthermore, electron-rich aryl bromides **18e** and **18f** furnished diarylmagnesiums **19f** and **19g** under the established conditions, which after batch-transmetalation with $ZnCl_2$ underwent *Negishi* cross-couplings[115] with a range of aryl iodides **20b**, **21o**, and **21p** in the presence of *Organ's* catalyst PEPPSI-*i*-Pr[116] leading to polyfunctional biphenyls **20r – t** in 70 – 88% yield (Scheme 34).



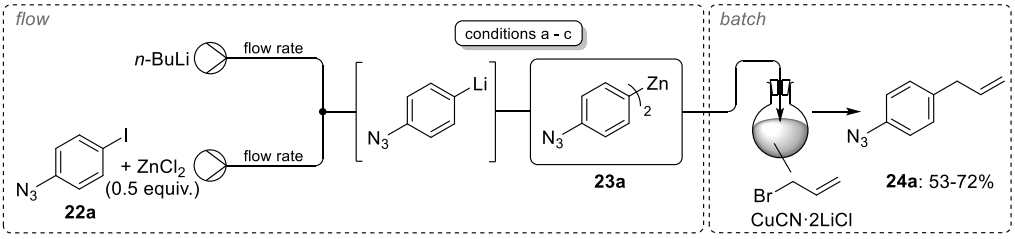
Scheme 34: In situ exchange transmetalation and *Negishi* cross-couplings[115] for biphenyl synthesis (**20r – t**).

3.4 In Situ Trapping Halogen-Lithium Exchange on Highly Sensitive Substrates

To further demonstrate the broad applicability of in situ trapping exchange reactions in flow, the compatibility of these exchanges with aryl halides bearing challenging functional groups such as an ester, a ketone, a nitro, and heterocumulene groups e.g. an azide or isothiocyanate was investigated.[102 – 106] Notably, only halogen-lithium exchanges of *ortho*-nitroarenes[102,106] and an alkenyl iodide containing an aliphatic azide[106] at −100 °C under batch conditions are known, as well as several flow protocols for ester-, ketone- and nitro-containing arenes applying ultrafast micromixing and residence times down to 0.0015 s.[108]

[115] E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298.
[116] N. Hadei, E. A. B. Kantchev, C. J. O'Brie, J. Christopher, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805.

Again, it was found that in the absence of a metal salt 4-iodophenyl azide[117] (**22a**) decomposes completely performing the reaction in flow. However, screening of various in situ trapping exchange conditions, e.g. addition of soluble metal salts, flow rate and temperature, led to the zincated arene **23a** and after a batch quench with allyl bromide (**21a**) to the desired allylated phenyl azide **24a** in 72% isolated yield (Scheme 35). Scale-up of this reaction from 1 to 5 mmol provided aryl azide **24a** in 60% yield. The analogous *meta*-allyl azidobenzene (**24b**) was obtained in 83% yield (Table 8, entry 1).



Scheme 35: Iodine-lithium exchange in presence of an azide group under various reaction conditions a – c: [a] In situ exchange, 0 °C, 2.5 s, 6 mL min^{-1}; **24a**: 53% yield. [b] 0 °C, 2.5 s; no salt additive: no product and decomposition of reagents. [c] In situ exchange, 40 °C, 1.25 s, 12 mL min^{-1}; **24a**: 72% yield (1 mmol); 60% (5 mmol).

Furthermore, nitro-, ketone- and ester-groups were tested because of their pivotal role in organic synthesis and well known challenges in organometallic chemistry due to competitive electron transfer and nucleophilic addition reactions.[104,105] In order to access aryl organometallics with such functional groups, the best lithiation exchange reagent was found to be PhLi instead of *n*-BuLi. Interestingly, also with PhLi, the exchange is faster than a competitive transmetalation of PhLi therefore allowing an efficient generation of diarylzincs and -magnesiums (**23c** – **h**). Thus, bis-(nitroaryl)zincs and -magnesiums **23c** – **f** were generated from the corresponding aryl halides **22c** – **f**. Allylation, acylation and addition to indole aldehyde **21r** or ketone **21h** in batch furnished the desired functionalized nitro arenes **24c** – **h** in 60 – 93% yield (entries 2 – 7). Similarly, aryl bromide **22g**, containing a ketone was functionalized by in situ trapping exchange reactions at −40 °C in the presence of $ZnCl_2$. Typical quenching conditions led to the allylated products **24i** – **j** from the diarylzinc **23g** in 65 – 78% yield (entries 8 and 9). Furthermore, ethyl 4-iodobenzoate (**22h**) led to ketones **24k** – **l** and to the secondary alcohol **24m** *via* the diarylmagnesium **23h** in 70 – 78% (entries 10 – 12). It was further possible to perform a bromine-lithium exchange on aryl bromides bearing a *para*-, *meta*-, and *ortho*-isothiocyanate moiety without subsequent additions to the electrophilic isothiocyanate.[104] After various copper mediated allylations or acylations,[112] the desired products **24n** – **r** were obtained in 60 – 68% yield (entries 13 – 17).

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

Table 8: In situ exchange transmetalation for highly sensitive aryl iodides and bromides of type **22** leading *via* intermediate diorganozincs or -magnesiums of type **23** to polyfunctional arenes of type **24**.

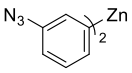
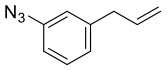
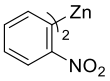
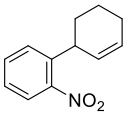
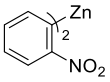
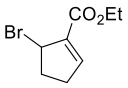
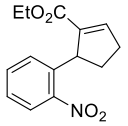
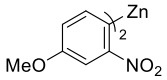
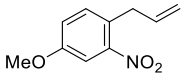
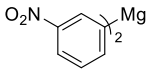
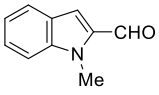
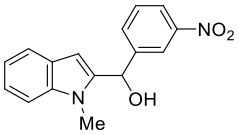
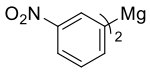
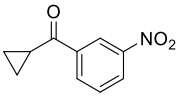
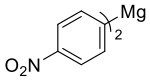
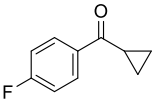
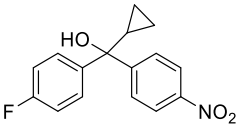
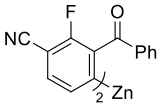
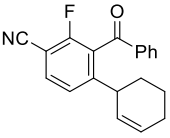
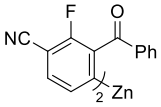
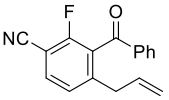
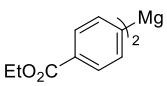
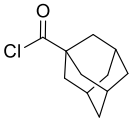
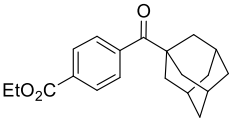
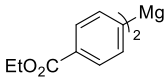
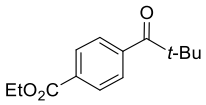
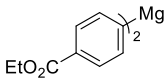
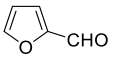
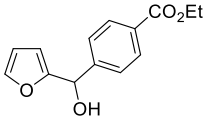
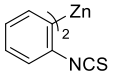
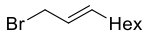
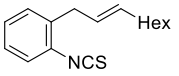
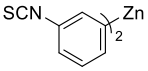
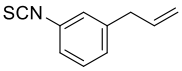
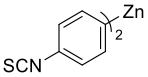
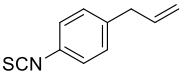
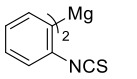
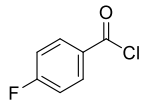
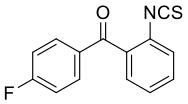
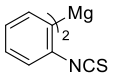
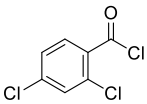
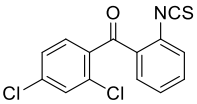
Entry	Metal species [T, flow rate, t]	Electrophile (E^+)	Product/Yield[a]
			
1	**23b** (−40 °C, 12 mL min^{-1}, 1.25 s)[b]	**21a**[c]	**24b**: 83%
			
2	**23c** (−20 °C, 12 mL min^{-1}, 1.25 s)[d]	**21k**[d]	**24c**: 93%
			
3	**23c** (−20 °C, 12 mL min^{-1}, 1.25 s)[d]	**21q**[c]	**24d**: 78%
			
4	**23d** (−20 °C, 12 mL min^{-1}, 0.10 s)[d]	**21a**[c]	**24e**: 73%
			
5	**23e** (−20 °C, 20 mL min^{-1}, 0.06 s)[b]	**21r**[e]	**24f**: 60%
			
6	**23e** (−20 °C, 20 mL min^{-1}, 0.06 s)[b]	**21s**[f]	**24g**: 63%
			
7	**23f** (−60 °C, 16 mL min^{-1}, 0.08 s)[b]	**21h**[e]	**24h**: 73%
			
8	**23g** (−40 °C, 20 mL min^{-1}, 0.06 s)[d]	**21k**[c]	**24i**: 78%
			
9	**23g** (−40 °C, 20 mL min^{-1}, 0.06 s)[d]	**21a**[c]	**24j**: 65%
			
10	**23h** (−40 °C, 16 mL min^{-1}, 0.94 s)[b]	**21t**[f]	**24k**: 70%

Table 8 continued

11	 **23h** (−40 °C, 16 mL min^{-1}, 0.94 s)[b]	 **21e**[f]	 **24l**: 78%
12	 **23h** (−40 °C, 16 mL min^{-1}, 0.94 s)[b]	 **21u**[e]	 **24m**: 75%
13	 **23i** (−20 °C, 12 mL min^{-1}, 1.25 s)[d]	 **21v**[c]	 **24n**: 68%
14	 **23j** (−60 °C, 18 mL min^{-1}, 0.07 s)[d]	 **21a**[c]	 **24o**: 65%
15	 **23k** (−60 °C, 9 mL min^{-1}, 0.15 s)[d]	 **21a**[c]	 **24p**: 67%
16	 **23l** (−20 °C, 16 mL min^{-1}, 0.94 s)[d]	 **21m**[f]	 **24q**: 63%
17	 **23l** (−20 °C, 16 mL min^{-1}, 0.94 s)[d]	 **21w**[f]	 **24r**: 60%

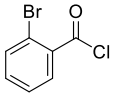
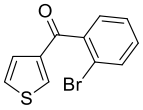
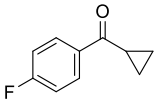
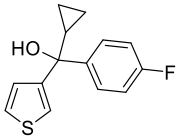
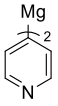
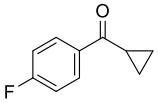
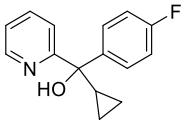
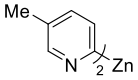
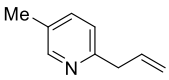
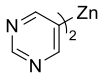
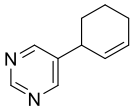
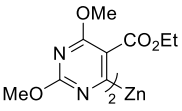
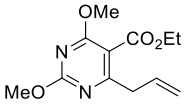
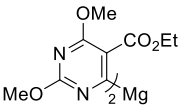
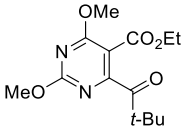
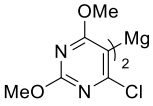
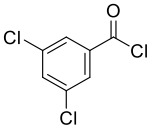
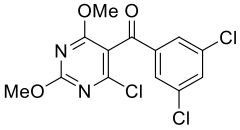
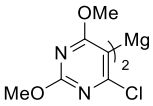
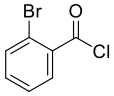
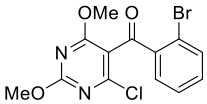
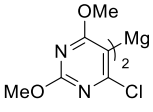
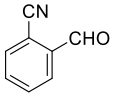
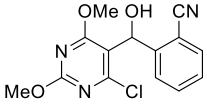
[a] Yield of analytically pure isolated product. [b] Metal species prepared from the corresponding aryl iodide. [c] 2.5 equiv., 10 mol% CuCN·2LiCl, 30 min, 0 °C. [d] Metal species prepared from the corresponding aryl bromide. [e] 1.1 – 1.5 equiv., 1 – 2 h, 0 °C. [f] 1.5 equiv., 1.1 equiv. CuCN·2LiCl, 1 – 2 h, 0 °C., 30 min, 0 °C.

3.5 In Situ Trapping Halogen-Lithium Exchange on Heterocycles

The preparation of polyfunctional heterocyclic organometallics is of key importance for the pharmaceutical and agrochemical industry.[118,119] Thus, sulfur- and nitrogen-containing heterocyclic halides were subjected to in situ trapping exchange reactions. For instance, 3-bromothiophene (**25a**) was converted to the reactive diheteroarylmagnesium species **26a**. Further copper-mediated batch acylation[112] with 2-bromobenzoyl chloride (**21l**) led to the heterocyclic bisaryl ketone **27a** in 72% yield (Table 9, entry 1) and batch addition to ketone **21h** led to tertiary alcohol **27b** in 77% yield (entry 2).

[118] a) *Comprehensive Heterocyclic Chemistry II* (Eds.: C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**; b) T. Eicher, S. Hauptmann, A. Speicher, *The Chemistry of Heterocycles, 2nd Ed*, Wiley, Weinheim, **2003**.
[119] a) R. E. Miller, T. Rantanen, K. A. Ogilvie, U. Groth, V. Snieckus, *Org. Lett.* **2010**, *12*, 2198; b) C. Schneider, E. David, A. A. Toutov, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 2722; c) J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2012**, *14*, 5400; d) F. Sandfort, M. J. O'Neill, J. Cornella, L. Wimmer, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3319.

Table 9: In situ exchange transmetalation for highly sensitive aryl iodides and bromides of type **25** leading *via* intermediate diorganozincs or -magnesiums of type **26** to polyfunctional arenes of type **27**.

Entry	Metal species [T, flow rate, t]	Electrophile (E^+)	Product/Yield[a]
			
1	**26a** (0 °C, 6 mL min^{-1}, 10 s)[b]	**21l**[c]	**27a**: 72%
			
2	**26a** (0 °C, 6 mL min^{-1}, 10 s)[b]	**21h**[d]	**27b**: 77%
			
3	**26b** (0 °C, 18 mL min^{-1}, 0.83 s)[e]	**21h**[d]	**27c**: 62%
			
4	**26c** (0 °C, 6 mL min^{-1}, 53 s)[b]	**21a**[f]	**27d**: 63%
			
5	**26d** (0 °C, 12 mL min^{-1}, 1.25 s)[b]	**21k**[f]	**27e**: 68%
			
6	**26e** (−40 °C, 16 mL min^{-1}, 0.08 s)[e]	**21a**[f]	**27f**: 70%
			
7	**26f** (−40 °C, 20 mL min^{-1}, 0.06 s)[e]	**21e**[c]	**27g**: 68%
			
8	**26g** (−20 °C, 9 mL min^{-1}, 1.7 s)[e]	**21x**[c]	**27h**: 72%
			
9	**26g** (−20 °C, 9 mL min^{-1}, 1.7 s)[e]	**21l**[c]	**27i**: 63%
			
10	**26g** (−20 °C, 9 mL min^{-1}, 1.7 s)[e]	**21y**[d]	**27j**: 59%

[a] Yield of analytically pure isolated product. [b] Metal species prepared from the corresponding aryl bromide. [c] 1.5 equiv., 1.1 equiv. CuCN·2LiCl, 1 – 2 h, 0 °C. [d] 1.1 equiv., 1 – 2 h, 0 °C. [e] Metal species prepared from the corresponding aryl iodide. [f] 2.5 equiv., 10 mol% CuCN·2LiCl, 30 min, 0 °C.

To expand the range of substrates, different pyridines and pyrimidines were subjected successfully to the bromine-lithium exchange. Thus, pyridine derivatives **25b** and **25c** underwent the in situ trapping exchange (entries 3 – 4). Quenching of the bispyridyl-zinc and -magnesium reagents **26b** and **26c** in batch led to the tertiary alcohol **27c** and allylated picoline **27d** in 62 – 63% yield (entries 3 – 4). Furthermore, 5-bromopyrimidine (**25d**) and the fully substituted iodopyrimidines such as **25e** and **25f** were transmetalated in situ using short reaction times (0.06 – 1.25 s) at −40 to 0 °C (entries 4 – 10). By using PhLi, an ester was tolerated providing the allylated and acylated[112] pyrimidines **27e** and **27f** in 68 – 70% yield (entries 6 – 7). Interestingly, uracil derived, electron-rich iodopyrimidine **25f** underwent an efficient exchange using the same method and the reactive metal species **26g** was quenched with different benzoyl chlorides **21x** and **21l** and aldehyde **21y** in subsequent batch reactions leading to benzophenones **27h** and **27i** and alcohol **27j** in 59 – 72% yield (entries 8 – 10).

4 Sodiation of Arenes and Heteroarenes in Continuous Flow

4.1 Introduction

The functionalization of aromatics and heteroaromatics is a central synthetic task especially for the elaboration of pharmaceuticals and agrochemicals.[120] Lithium bases have been extensively used for the metalation of (hetero)arenes and offer broad synthetic possibilities for their subsequent functionalization.[121] In addition, other milder magnesium and zinc bases have been developed in order to achieve a higher functional group tolerance allowing the preparation of polyfunctional aromatics.[122] In the course of these studies, it was realized by *Yoshida*,[123] *Knochel*[124] and others[125] that a high compatibility with sensitive functional groups can be achieved by performing these metalations under flow conditions.[126] Such setups have multiple advantages, such as mild reaction conditions (ambient temperature metalations), short reaction times and scale-ups without the need of further optimization.[127] In contrast to the use of lithium bases, corresponding sodium bases have not received great attention due to the ionic C – Na bond and poor solubility. Since sodium is ca. 1500 times more abundant than lithium in the earth crust and lithium demand and prices are increasing in recent years,[128] the use of

---

[120] a) *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**; b) N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348; c) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2013**, *9*, 2265.

[121] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; c) *Science of Synthesis, Vols. 8a-b* (Eds.: V. Snieckus, M. Majewski), Georg Thieme Verlag, Stuttgart, **2005**.

[122] *Handbook of Functionalized Organometallics* (Ed.: Paul Knochel), Wiley-VCH, Weinheim, **2005**.

[123] a) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun*. **2011**, *2*, 264; b) A. Nagaki, J.-i. Yoshida in *Organometallic Flow Chemistry, Vol. 57* (Ed.: T. Noël), Springer, Cham, **2015**; b) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; c) H. Kim, H.-J. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 1877; d) A. Nagaki, Y. Takahashi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2016**, *55*, 5327.

[124] a) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; b) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; c) M. Ketels, M. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770; d) M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.* **2017**, *19*, 1666; e) M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280.

[125] a) W. Shu, L. Pellegatti, M. A. Oberli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 10665; b) J. A. Newby, D. W. Blaylock, P. M. Witt, R. M. Turner, P. L. Heider, B. H. Harji, D. L. Browne, S. V. Ley, *Org. Process Res. Dev.* **2014**, *18*, 1221; c) C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4945; d) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463.

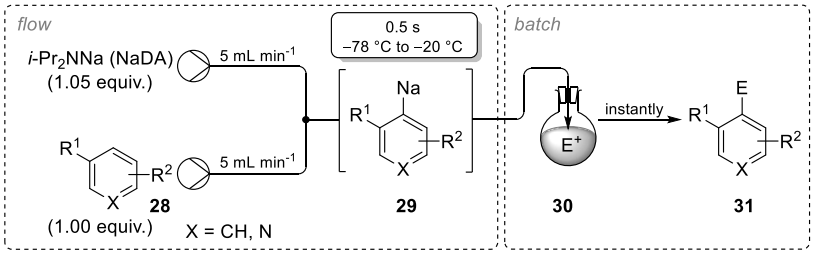
[126] For recent advances in organometallic flow chemistry, see: a) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102; b) D. Ghislieri, K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 678; c) G. A. Price, A. R. Bogdan, A. L. Aguirre, T. Iwai, S. W. Djuric, M. G. Organ, *Catal. Sci. Technol.* **2016**, *6*, 4733; d) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967; e) C. Battilocchio, F. Feist, A. Hafner, M. Simon, D. N. Tran, D. M. Allwood, D. C. Blakemore, S. V. Ley, *Nat. Chem.* **2016**, *8*, 360; f) A. Greb, J.-S. Poh, S. Greed, C. Battilocchio, P. Pasau, D. C. Blakemore, S. V. Ley, *Angew. Chem. Int. Ed.* **2017**, *56*, 16602; g) H.-J. Lee, H. Kim, J.-i. Yoshida, D.-P. Kim, *Chem. Commun.* **2018**, *54*, 547.

[127] For recent general reviews on flow chemistry, see: a) *Microreactors in Organic Synthesis and Catalysis, 2nd ed.* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2013**; b) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796; c) B. Gutmann, C. O. Kappe, *J. Flow. Chem.* **2017**, *7*, 65; d) J. Britton, T. F. Jamison, *Nat. Protoc.* **2017**, *12*, 2423.

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

sodium compounds is certainly underexploited in organic synthesis. Already, *Schlosser* and *Mordini*,[129] *Mulvey*,[130] and *Mioskowski*[131] have demonstrated the high potential of sodium organometallic chemistry. Recently, *Collum*[132] reported sodiations of aromatic and heterocyclic substrates using sodium diisopropylamide (NaDA) as a soluble highly reactive base in dimethylethylamine (DMEA) at cryogenic temperatures.

Herein, the first sodiation of arenes and heteroarenes of type **28** in a microflow reactor setup producing a broad range of aryl- and heteroaryl-sodium intermediates of type **29** is reported. These organosodium reagents react instantly in batch with various electrophiles (E^+) of type **30** forming functionalized arenes and heteroarenes of type **31** (Scheme 36). The scope of this sodiation in flow is significantly broader compared to batch reactions.



Scheme 36: General setup for the sodiation of arenes and heteroarenes of type **28** with NaDA in a microflow reactor and subsequent trapping with electrophiles in batch.

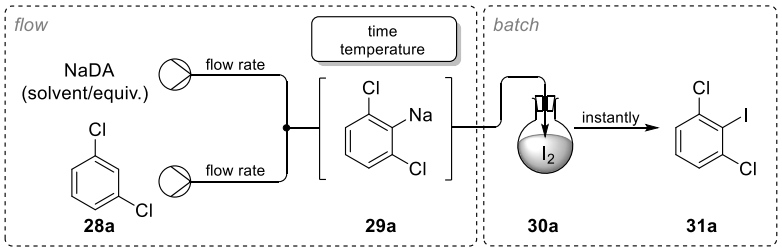
4.2 Optimization of Reaction Conditions

NaDA was prepared according to a slightly modified procedure by *Collum* using less equivalents of sodium in DMEA and diluted to a 0.2 M solution.[132b,133] This concentration was ideal for sodiation performed in flow avoiding any precipitation. The reaction conditions were optimized with 1,3-dichlorobenzene (**28a**) as a substrate. The sodiated intermediate **29a** was instantly quenched with iodine in batch at 0 °C. Conversion and product yield were determined by gas chromatography (GC) using an internal standard. Using a flow rate of 10 mL min^{-1}, it was possible to achieve full sodiation of **28a** within 0.5 s at −20 °C (Table 10, entry 4), compared to batch sodiation at −78 °C.[132b] While the

[129] a) M. Stähle, R. Lehmann, J. Kramar, M. Schlosser, *Chimia* **1985**, *39*, 229; b) M. Schlosser, J. Hartmann, M. Stähle, J. Kramar, A. Walde, A. Mordini, *Chimia* **1986**, *40*, 306; c) A. Mordini, M. Schlosser, *Chimia* **1986**, *40*, 309.
[130] a) P. C. Andrews, N. D. R. Barnett, R. E. Mulvey, W. Clegg, P. A. O'Neil, D. Barr, L. Cowton, A. J. Dawson, B. J. Wakefield, *J. Organomet. Chem.* **1996**, *518*, 85; b) J. A. Garden, D. R. Armstrong, W. Clegg, J. Garcia-Alvarez, E. Hevia, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, L. Russo, *Organometallics.* **2013**, *32*, 5481; c) A. J. Martínez-Martínez, A. R. Kenneddy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834.
[131] A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 340.
[132] a) Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312; b) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197; c) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 7921; d) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544.
[133] See experimental part for optimized preparation of NaDA.

flow rate did not have an effect on the yield (entry 6), changing the reactor diameter during the reaction led to more efficient mixing and thus better yields (entry 4 – 5). A longer reactor (0.25 mL, entry 1) or higher temperatures (0 °C, entry 2) led to decomposition of the starting material and low product yields. Using higher concentrations of NaDA and 1,3-dichlorobenzene (**28a**) led to blockage of the reactor during the reaction (entry 3). Changing the solvent for NaDA from DMEA to PMDTA led to a lower GC-yield of 72% (entry 7). Solubility of NaDA in trimethylamine was not high enough to conduct the sodiation (entry 8).

Table 10: Optimization of flow conditions for the sodiation of 1,3-dichlorobenzene (**28a**)



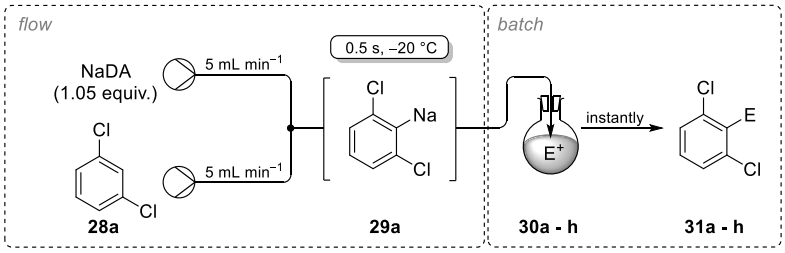
Entry	Base/solvent (equiv.)	Flow Conditions (temperature, flow rate, reactor size)	Result
1	NaDA in DMEA (0.21 M, 1.2 equiv.)	0 °C, 10 mL min^{-1} 0.25 mL reactor	Decomposition
2	NaDA in DMEA (0.21 M, 1.05 equiv.)	0 °C, 10 mL min^{-1} 0.08 mL reactor with changing diameter	30% GC-yield
3	NaDA in DMEA (0.50 M, 1.05 equiv.)	−20 °C, 10 mL min^{-1} 0.08 mL reactor with changing diameter	Blockage
4	NaDA in DMEA (0.21 M, 1.05 equiv.)	−20 °C, 10 mL min^{-1} 0.08 mL reactor with changing diameter	89% GC-yield (84% isolated yield)
5	NaDA in DMEA (0.21 M, 1.05 equiv.)	−20 °C, 10 mL min^{-1} 0.08 mL reactor	84% GC-yield
6	NaDA in DMEA (0.21 M, 1.2 equiv.)	−20 °C, 16 mL min^{-1} 0.08 mL reactor with changing diameter	89% GC-yield
7	NaDA in PMDTA (0.21 M, 1.05 equiv.)	−20 °C, 10 mL min^{-1} 0.08 mL reactor with changing diameter	72% GC-yield
8	NaDA in Et_3N	–	Solubility not high enough

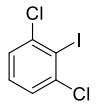
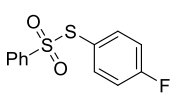
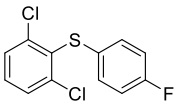
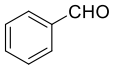
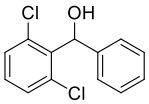
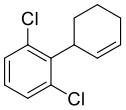
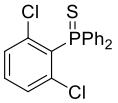
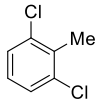
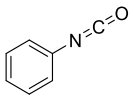
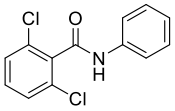
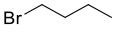
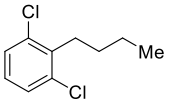
4.3 Sodiation of Arenes and Heteroarenes

2,6-Dichlorophenylsodium (**28a**) was quenched in batch with iodine (**30a**) at 0 °C providing aryl iodide **31a** in 84% isolated yield (Table 11, entry 1). Similarly, **29a** was quenched in batch with benzaldehyde (**30b**), PPh_2Cl (**30c**, followed by the addition of sulfur), phenylisocyanate (**30d**), and

S-(4-fluorophenyl)benzene-sulfonothioate (**30e**) affording the expected products **31b – e** in 64 – 95% yield (entries 2 – 5). Remarkably, no benzyne formation was observed under these flow conditions. In addition, substitution reactions (*Wurtz-Fittig*-couplings) were examined.[134] Whereas the use of an allylic bromide such as cyclohexenyl bromide (**30f**) required copper-catalysis,[135] methyl iodide (**30g**) and *n*-butyl bromide (**30h**) reacted at −40 °C instantly in the absence of any transition metal catalyst with the in flow generated arylsodium **29a** affording the cross-coupling products **31f** – **h** in 53 – 75% yield (entries 6 – 8).

Table 11: Sodiation of 1,3-dichlorobenzene (**28a**) using a microflow reactor and subsequent batch quench of the intermediate organosodium **29a** with various electrophiles of type **30** leading to functionalized dichlorobenzenes of type **31**.



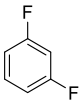
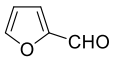
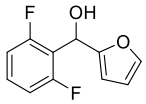
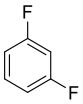
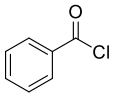
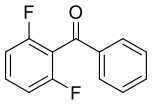
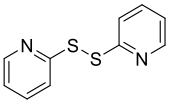
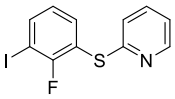
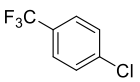
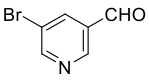
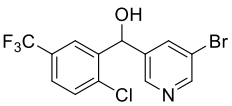
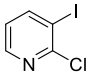
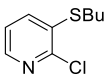
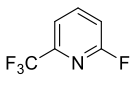
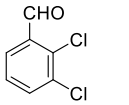
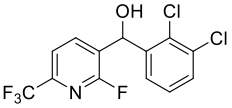
Entry	Electrophile (E^+)	Product[a]	Entry	Electrophile (E^+)	Product[a]
	I_2				
1	**30a**[b]	**31a**: 84%	5	**30e**[b]	**31e**: 75%
					
2	**30b**[c]	**31b**: 95%	6	**30f**[e]	**31f**: 75%
	$PPh_2Cl + S_8$			MeI	
3	**30c**[d]	**31c**: 74%	7	**30g**[f]	**31g**: 53%
					
4	**30d**[b]	**31d**: 64%	8	**30h**[g]	**31h**: 53%

[a] Yield of analytically pure isolated product. [b] 2.5 equiv. E^+. [c] 1.5 equiv. E^+. [d] 2.5 equiv. PPh_2Cl, then 10.0 equiv. S_8, overnight. [e] 5 mol% CuCN·2LiCl, 2.5 equiv. E^+. [f] 5.0 equiv. E^+. [g] 10 equiv. E^+.

[134] a) A. Wurtz, *Liebigs Ann. Chem.* **1855**, *96*, 364; b) B. Tollens, R. Fittig, *Liebigs Ann. Chem.* **1864**, *131*, 303; c) P. F. Hudrlik, W. D. Arasho, A. M. Hudrlik, *J. Org. Chem.* **2007**, *72*, 8107; d) A. S. Jeevan Chakravarthy, M. S. Krishnamurthy, Noor Shahina Begum, S. Hari Prasad, *Tetrahedron Lett.* **2016**, *57*, 3231; e) J. B. Campbell, R. F. Dedinas, S. Trumbower-Walsh, *Synlett* **2010**, 3008.
[135] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

Furthermore, related arenes bearing chloro-, iodo-, fluoro- or trifluoromethyl-substituents were subjected to the optimized flow conditions. Thus, 1,3-difluorobenzene (**28b**) was sodiated at −40 °C providing the corresponding arylsodium **29b** which was subsequently quenched in batch with furan-2-carbaldehyde (**30i**) providing alcohol **31i** in 88% yield (Table 12, entry 1). Alternatively, arylsodium **29b** was trapped with benzoyl chloride (**30j**) in the absence of any transition metal catalyst leading to benzophenone derivate **31j** in 71% yield (entry 2). Flow-sodiation of 2-fluoroiodobenzene (**28c**) and subsequent quench with aldrithiol (**30k**) led to the corresponding thioether **31k** in 62% yield (entry 3). In addition, trifluoromethyl-substituted arene **28d** was sodiated at −40 °C and quenched with 5-bromonicotinaldehyde (**30l**) leading to alcohol **31l** in 85% yield (entry 4).

Table 12: Sodiation of arenes and heteroarenes of type **28** leading *via* intermediate organosodiums of type **29** to polyfunctional arenes and heteroarenes of type **31**.

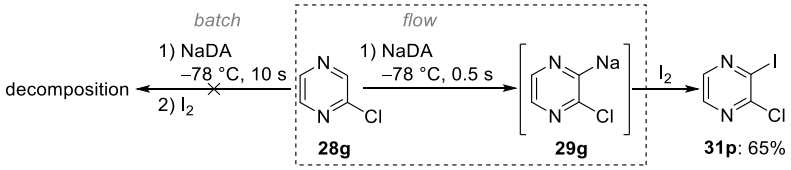
Entry	Substrate (sodiation temperature)	Electrophile (E^+)	Product[a]
			
1	**28b** (−40 °C)	**30i**[b]	**31i**: 88%
			
2	**28b** (−40 °C)	**30j**[c]	**31j**: 71%
			
3	**28c** (−40 °C)	**30k**[c]	**31k**: 62%
			
4	**28d** (−40 °C)	**30l**[b]	**31l**: 85%
		I_2	
5	**28e** (−20 °C)	**30a**[c]	**31m**: 53%
		Bu_2S_2	
6	**28e** (−20 °C)	**30m**[c]	**31n**: 89%
			
7	**28f** (−40 °C)	**30n**[b]	**31o**: 68%

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

Furthermore, the optimized flow conditions were applied to the sodiation of heteroarenes. Thus, 2-chloropyridine (**28e**) was sodiated in flow at convenient conditions (−20 °C, 0.5 s at a flow rate of 10 mL min^{-1}; compared to −78 °C in batch) and the intermediate 2-chloro-3-pyridyl sodium (**29e**) was subsequently trapped with iodine (**30a**) and dibutyl disulfide (**30m**) leading to the functionalized pyridines **31m** and **31n** in 53 – 89% yield (entries 5 – 6). Trifluoromethyl-substituted pyridine **28f** was sodiated in flow and trapped with aldehyde **30n** yielding the secondary alcohol **31o** in 68% yield (entry 7).

4.4 Sodiation of Sensitive Arenes and Heteroarenes

This flow sodiation procedure extends considerably the reaction scope of such metalations and applies to sensitive substrates that decompose under batch sodiation conditions.[132b,136] Thus, for example, 2-chloropyrazine (**28g**) cannot be sodiated in batch with NaDA at −78 °C, however under optimized flow conditions (−78 °C, 0.5 s using a flow rate of 10 mL min^{-1}) a complete consumption of the starting material takes place affording after iodolysis the pyrazine **31p** in 65% yield (Scheme 37).

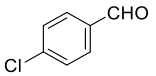
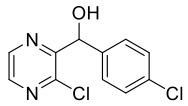
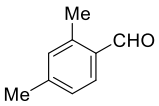
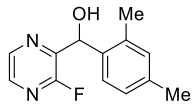
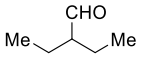
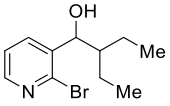
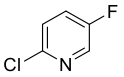
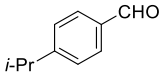
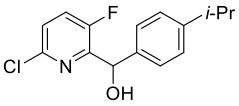
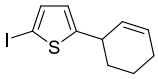
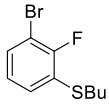
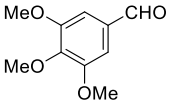
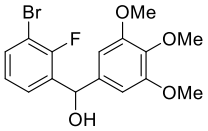
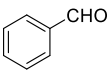
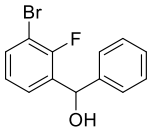


Scheme 37: Sodiation of sensitive heteroarene 2-chloropyrazine (**28g**) in a microflow reactor and under batch conditions and subsequent trapping with iodine (**30a**) leading to functionalized heteroarene **31p** or decomposition.

In addition to 2-chloropyrazine (**28g**), 2-fluoropyrazine (**28h**) and substituted pyridines **28i** and **28j** that decompose upon batch sodiation were successfully sodiated under flow conditions and trapped with aldehydes **30o – r** yielding functionalized heteroarenes **31q – t** in 65 – 97% yield (Table 13, entries 1 – 4). Copper-catalyzed[135] batch allylation under flow-conditions of sodiated 2-iodothiophene (**28k**) led to functionalized thiophene **31u** in 76% yield (entry 5). At −60 °C it was possible to sodiate 2-bromofluorbenzene (**28l**) without aryne-formation. Instant reaction of the sodiated intermediate **29l** with dimethyldisulfide (**30s**) or benzaldehydes **30t** and **30b** furnished functionalized arenes **31v – x** in 70 – 81% yield (entries 6 – 8).

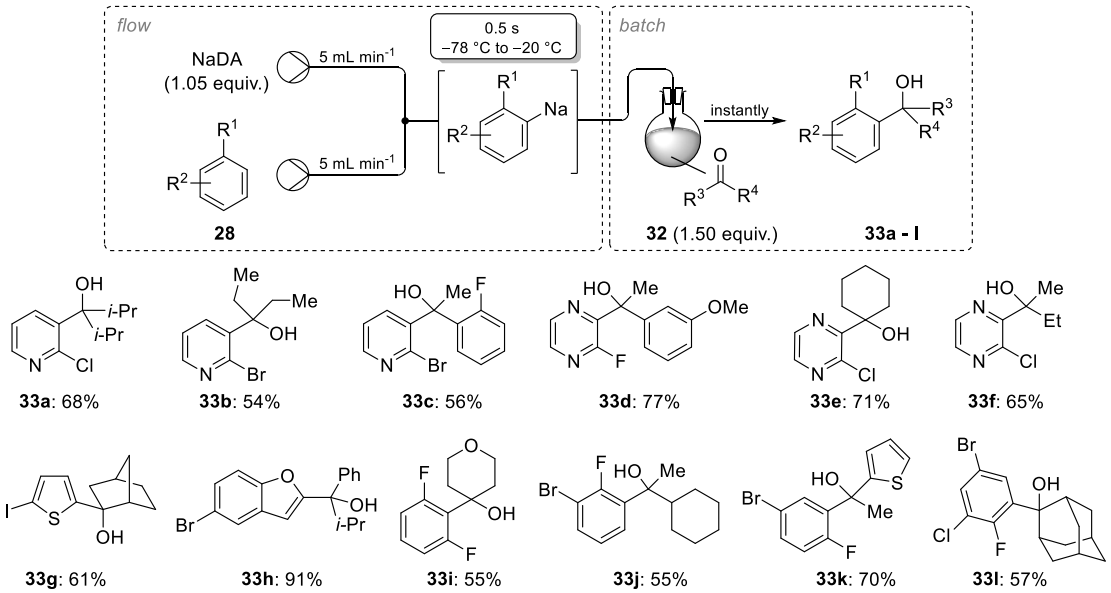
[136]See experimental part for attempted batch sodiation reaction.

Table 13: Sodiation of sensitive arenes and heteroarenes of type **28** leading *via* intermediate organosodiums of type **29** to polyfunctional arenes and heteroarenes of type **31**.

Entry	Substrate (sodiation temperature)	Electrophile (E^+)	Product[a]
			
1	**28g** (−78 °C)	**30o**[b]	**31q**: 79%
			
2	**28h** (−60 °C)	**30p**[b]	**31r**: 97%
			
3	**28i** (−78 °C)	**30q**[b]	**31s**: 65%
			
4	**28j** (−78 °C)	**30r**[b]	**31t**: 77%
			
5	**28k** (−78 °C)	**30f**[c]	**31u**: 76%
		Bu_2S_2	
6	**28l** (−60 °C)	**30s**[d]	**31v**: 70%
			
7	**28l** (−60 °C)	**30t**[b]	**31w**: 80%
			
8	**28l** (−60 °C)	**30b**[b]	**31x**: 81%

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

Addition of organometallics to ketones is always subject to side reactions.[137][138] Remarkably, the in flow generated sodium derivatives of type **29** underwent reactions with ketones of type **32**, leading to tertiary alcohols of type **33**. Thus, polyfunctional arenes and heteroarenes **33a – l** were obtained in up to 91% yield (Scheme 38).

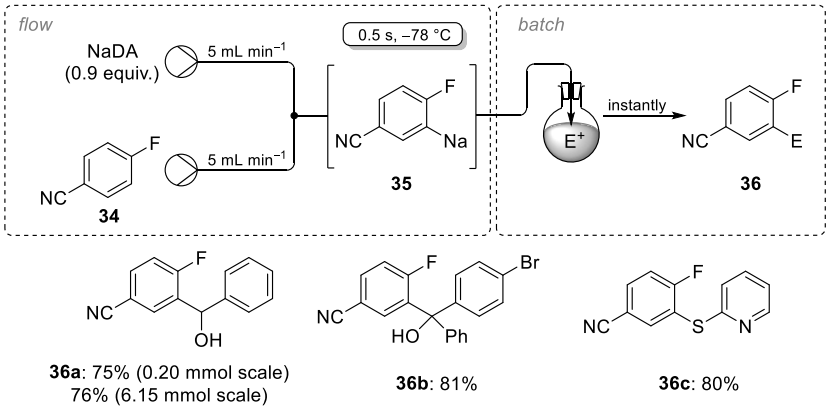


Scheme 38: Sodiation of (hetero)arenes of type **28** and subsequent batch quench with ketones of type **32** leading to tertiary alcohols of type **33**.

[137] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998; c) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *J. Org. Chem.* **2010**, *75*, 5008;

[138] noteworthy exceptions: a) C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy, E. Hevia, *Angew. Chem. Int. Ed.* **2014**, *53*, 5969; b) L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salmone, S. Florio, V. Capriati, *Chem. Sci.* **2016**, *7*, 1192.

Noteworthy, sodiation of 4-fluorobenzonitrile **34** at −78 °C led to the desired sodium arene **35** without the attack at the nitrile functionality. To inhibit double metalation 0.9 equiv. of NaDA were used as the limiting reagent. Batch quench of sodiated intermediate **35** with benzaldehyde (**30b**), ketone **32n** and disulfide **30k** led instantly to functionalized benzonitriles **36a – c** in 75 – 81% yield (Scheme 39). Additionally, a scale-up[139] was possible without any further optimization by simply extending the running time. Thus, a scale-up by factor 30 was conducted and functionalized benzonitrile **36a** was obtained in 76% yield (Scheme 39).



Scheme 39: Sodiation of highly sensitive 4-fluorobenzonitrile (**34**) and subsequent batch quench with electrophiles yielding functionalized benzonitriles **36a** – **c**.

4.5 Sodiation of Acrylonitriles

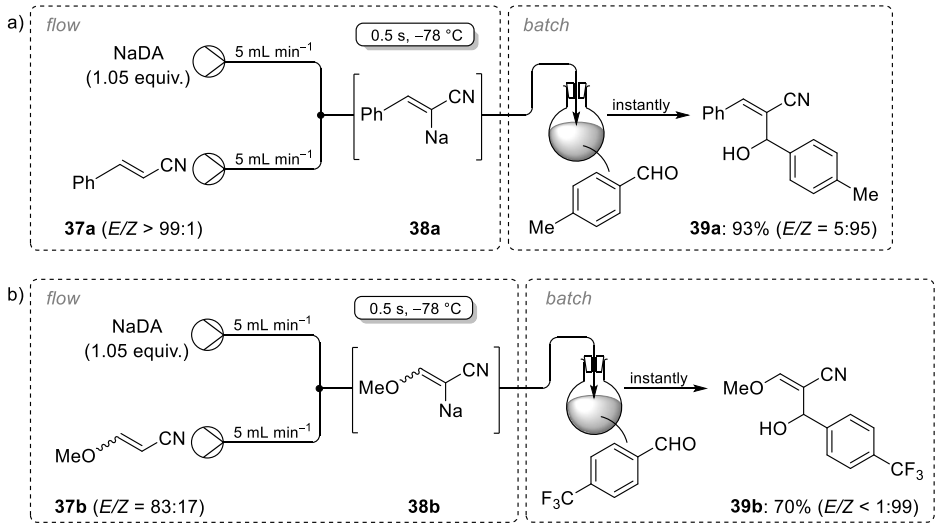
Finally, the attention was turned to the sodiation of α,β-unsaturated nitrile derivatives as these compounds are useful building blocks for the synthesis of natural products and heterocycles.[140] Using the established flow conditions it was possible to sodiate acrylonitriles of type **37** without polymerization or other side reactions. Thus, cinnamonitrile (**37a**) and methoxyacrylonitrile (**37b**) were sodiated at −78 °C in 0.5 s in flow. The sodiated intermediates **38a – b** were subsequently quenched with aldehydes yielding functionalized acrylonitriles **39a – b** in 70 – 93% yield and high selectivity up to *E*:*Z* < 1:99 (Scheme 39).[141]

---

[139] For large-scale (micro)flow reactions, see: a) F. Ullah, T. Samarakoon, A. Rolfe, R. D. Kurtz, P. R. Hanson, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10959; b) J. A. Newby, L. Huck, D. W. Blaylock, P. M. Witt, S. V. Ley, D. L. Browne, *Chem. Eur. J.* **2014**, *20*, 263; c) D. A. Thaisrivongs, J. R. Naber, N. J. Rogus, G. Spencer, *Org. Process Res. Dev.* **2018**, *22*, 403.

[140] a) R. R. Schmidt in *Natural Product Chemistry* (Ed.: A. Rahman), Springer, Berlin, **1986**; b) *Name Reactions in Heterocyclic Chemistry* (Eds.: J. J. Li, E. J. Corey), Wiley, Hoboken, **2005**.

[141] Configuration of the double bond was determined by X-Ray crystallography. CCDC 1831884 (**39a**) and CCDC 1831885 (**39b**) contain the supplementary crystallographic data for these compounds. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.



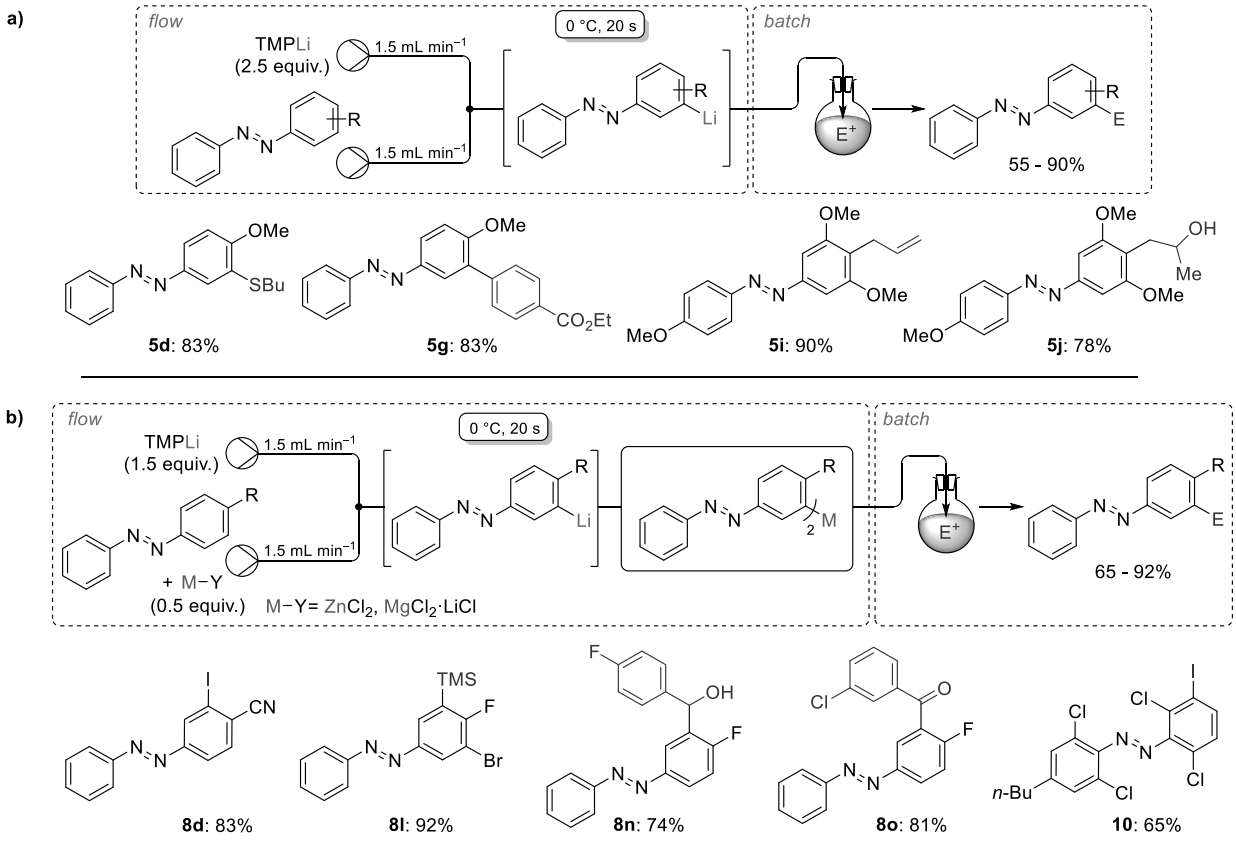
Scheme 40: Flow-sodiation of a) cinnamonitrile (**37a**) and b) methoxyacrylonitrile (**37b**) and subsequent batch quench with aldehydes yielding functionalized acrylonitriles **39**.

5 Summary

This work focused on exploiting the advantages of continuous flow setups for sensitive organometallic reactions. First, unsymmetrical azobenzenes were metalated with TMPLi under mild conditions (0 °C, 20 s) without attack of the nitrogen-nitrogen double bond. For sensitive azobenzenes, in situ trapping metalations using TMPLi in the presence of $ZnCl_2$ or $MgCl_2 \cdot LiCl$ provided the metalated intermediate which could subsequently be quenched with various electrophiles, affording functionalized azobenzenes that are important building blocks for photoswitches. In addition, 1,2-dicyanobenzene and related benzonitriles were metalated with TMPLi in the presence of $ZnCl_2$ under convenient flow conditions (0 °C, 20 s). Whereas scaling up the reaction in batch proved to be difficult, under flow conditions a scale-up was possible without any need of further optimization. Furthermore, the concept of in situ trapping metalations was successfully transferred to an in situ trapping halogen-lithium exchange. Under flow conditions it was possible to tolerate highly sensitive moieties such as isothiocyanats, nitriles, azides and nitro groups at temperatures up to 0 °C which decompose under batch halogen-lithium exchange conditions. Finally, a flow procedure for the sodiation of (hetero)arenes and acrylonitriles using the diethylmethylamine soluble base sodium diisopropylamide was developed. Using precise time control and efficient mixing in continuous flow, (hetero)arenes and acrylonitriles which decompose under batch sodiation conditions were sodiated and subsequently quenched with a variety of electrophiles, providing after workup functionalized (hetero)arenes and acrylonitriles. This sodiation procedure offers an alternative to commonly used lithiation strategies.

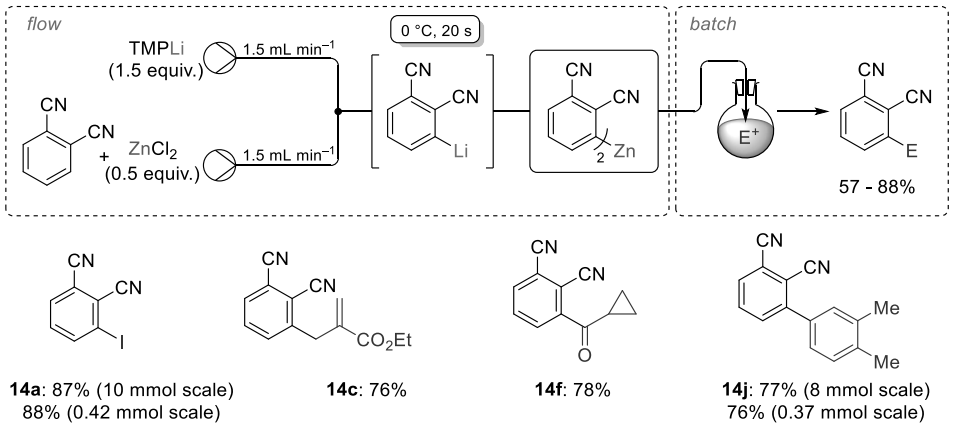
5.1 Selective Lithiation, Magnesiation and Zincation of Unsymmetrical Azobenzenes Using Continuous Flow

A general method for the late-stage-functionalization of unsymmetrical azobenzenes in continuous flow was developed. Methoxy-substituted azobenzenes could be metalated at convenient conditions (0 °C, 20 s) using TMPLi (Scheme 41a), while for azobenzenes containing more sensitive functional groups an in situ trapping metalation using $ZnCl_2$ or $MgCl_2 \cdot LiCl$ was very effective (Scheme 41b). The metalated azobenzenes reacted with a variety of electrophiles, providing functionalized azobenzenes in high yields. A simple scale-up was possible without further optimization of the reaction conditions. It was demonstrated, that even a highly functionalized tetra-*ortho*-chloro azobenzene that is of interest for the preparation of elaborate photopharmaceuticals could be further functionalized by this in situ trapping procedure.



Scheme 41: a) Metalation and b) in situ trapping metalation of unsymmetrical azobenzenes at mild conditions using continuous flow.

5.2 Selective Zincation of 1,2-Dicyanobenzene and Related Benzonitriles in Continuous Flow Using In Situ Trapping Metalations



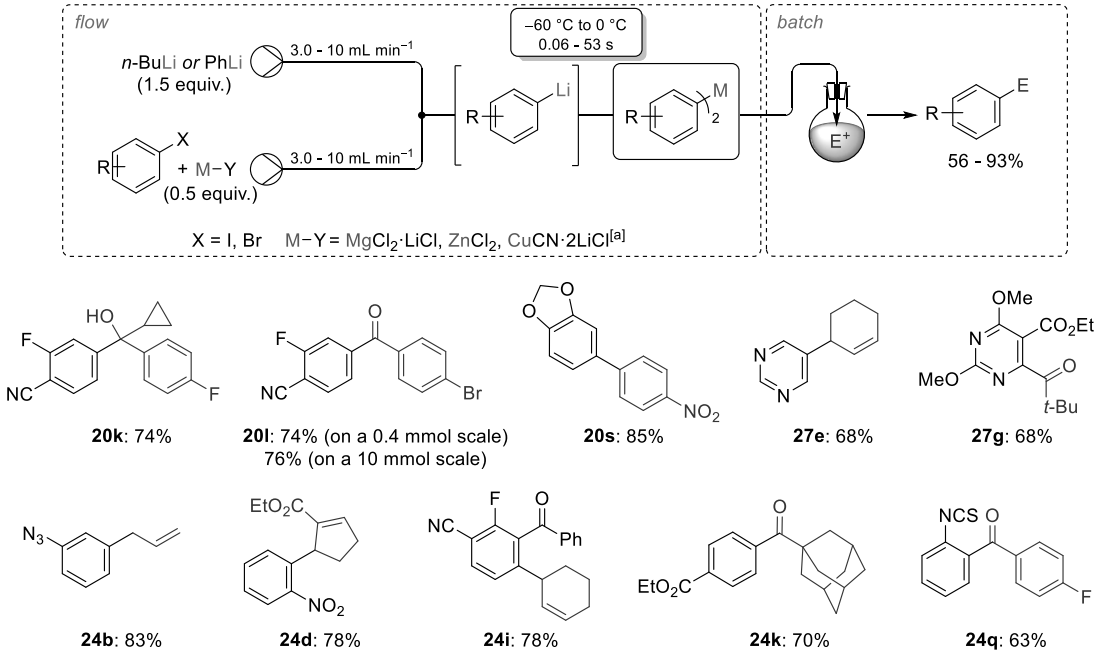
Scheme 42: In situ trapping metalation of 1,2-dicyanobenzene (**11a**) in continuous flow providing polyfunctional benzonitriles (**14**).

A general continuous flow method for the functionalization of 1,2-dicyanobenzene and related benzonitriles using in situ trapping metalations with TMPLi in the presence of $ZnCl_2$ under convenient conditions (0 °C, 20 s) was developed (Scheme 42). The resulting zinc organometallics were trapped

with various classes of electrophiles, providing functionalized benzonitriles in high yields. A simple scale-up was possible without further optimization of the reaction conditions. The reaction scope of these in situ trapping metalations in flow is broader and needs less equivalents of the base and the metal salt than the batch procedures.

5.3 Preparation of Polyfunctional Diorgano-Magnesium and –Zinc Reagents using In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuous Flow

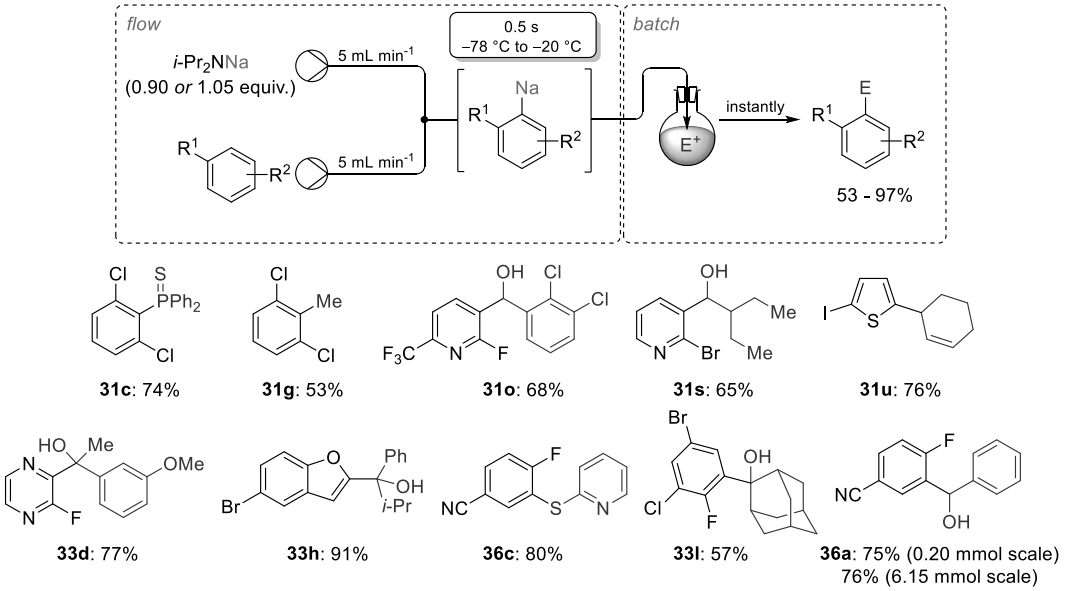
The concept of in situ trapping metalations was successfully transferred to an in situ trapping halogen-lithium exchange. The exchange was performed using *n*-butyllithium or phenyllithium on a broad range of bromo- or iodo(hetero)arenes in the presence of various metal salts ($ZnCl_2$, $MgCl_2 \cdot LiCl$, $CuCN \cdot 2LiCl$) in a commercially available continuous flow setup. The resulting diarylmetal species were trapped with various electrophiles, resulting in the formation of polyfunctional (hetero)arenes in high yields (Scheme 43). This method enabled the functionalization of (hetero)arenes containing highly sensitive moieties such as an isothiocyanate, nitro, azide or ester group. A straightforward scale-up was possible without further optimization.



Scheme 43: In situ trapping halogen-lithium exchange for highly sensitive (hetero)aryl halides leading *via* intermediate diorganozinc or diorganomagnesium species to polyfunctional (hetero)arenes. [a] 1.1 equiv. $CuCN \cdot 2LiCl$ was used, leading to the monoarylcopper intermediate.

5.4 Sodiation of Arenes and Heteroarenes in Continuous Flow

The first sodiation in continuous flow of arenes and heteroarenes using the in diethylmethylamine soluble base sodium diisopropylamide was developed. This procedure allows sodiation of arenes and heteroarenes containing sensitive functional groups that decompose under batch-sodiation conditions. Sodiated intermediates reacted instantly with various electrophiles leading to polyfunctional (hetero)arenes in high yields. A scale-up was possible without further optimization. As lithium demand and prices have increased in the past years, this method offers an alternative to the commonly used and extensively researched lithium bases.



Scheme 44: Sodiation of arenes and heteroarenes in continuous flow using the in DMEA soluble base NaDA.

C. EXPERIMENTAL PART

1 General Considerations

Metalations and in situ trapping metalations with TMPLi and NaDA were carried out with a FlowSyn system purchased from Uniqsis. In situ trapping halogen-lithium exchange reactions were carried out with a FlowSyn system purchase from Uniqsis or with an E-series easy Medchem systems purchased from Vapourtec. Reactor sizes and diameters are specified in the relevant typical procedures. Carrier solvents as well as reactant solutions were stored under argon. Quench 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 anhydrous solvents or reagents were purged with argon prior to use. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC.

1.1 Solvents

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

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and then stored over molecular sieves.
***n*-hex** 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.
DMEA was heated to reflux for 1 h over sodium benzophenone ketyl and freshly distilled under argon and stored under argon.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acyl chlorides were distilled prior to use.
***n*-BuLi** solution in hexane was purchased from Albemarle and the concentration was determined by titration against 1,10-phenanthroline in THF with *i*-PrOH.[142]
PhLi solution in dibutyl ether was purchased from Sigma Aldrich and the concentration was determined by titration against 1,10-phenanthroline in THF with *i*-PrOH.[142]

[142] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.

***i*-Pr$_2$NH** was heated to reflux for 14 h over CaH_2, distilled and stored under argon.

TMPH was distilled prior to use and stored under argon.

***i*-PrMgCl·LiCl** solution in THF was obtained from Albemarle.

CuCN·2LiCl[143] 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.

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 salts were dissolved.

MgCl$_2$·LiCl solution (0.5 M in THF) was prepared by drying LiCl (4.24 g, 100 mmol) in a *Schlenk*-flask equipped with a magnetic stirrer and a septum under vacuum for 5 h at 150 °C. After cooling to 25 °C Mg turnings (2.55 g, 105 mmol) and THF (200 mL) were added. 1,2-Dichloroethane (9.90 g, 100 mmol, 7.92 mL) was added dropwise over 1 h. The reaction mixture was stirred at 25 °C until gas evolution was complete.

TMPLi solution in THF was prepared by slow addition of *n*-BuLi (4 mL, 10 mmol, 2.5 M in hexane) to a solution of TMPH (1.7 mL, 10 mmol) in THF (10 mL) at −40 °C and stirred for 30 min at −40 °C. The concentration was determined by titration against *N*-benzylbenzamide in THF. The solution was warmed to 0 °C before use. The solution could be stored for one day at −40 °C.

Azobenzenes were prepared according to literature procedures.[144].

NaDA solution (1.00 M in DMEA) was prepared according to a slightly modified procedure reported by *Collum*.[145] It was demonstrated that a quantity reduction of sodium dispersion did not influence the concentration of resulting NaDA solution. Sodium dispersion (5 mL, 58.3 mmol, 30 wt% in toluene, <0.1 mm particle size) was washed with dry DMEA (3×2 mL). Then, dry DMEA (14.4 mL) and dry diisopropylamine (4.2 mL, 29.8 mmol) were added. After cooling the solution to 0 °C, isoprene (1.52 mL, 15.0 mmol) was added dropwise and the solution was allowed to warm to room temperature over 2 h. The concentration of the resulting yellow NaDA solution was determined by titration with diphenyl acetic acid. Prior to use the solution was diluted to a concentration close to 0.2 M.

1.3 Chromatography

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

[143] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[144] E. Merino, *Chem. Soc. Rev.* **2011**, *40*, 3835.
[145] F. R. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197.

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

- $KMnO_4$ stain: $KMnO_4$ (3.0 g), K_2CO_3 (20 g), 5% NaOH solution (5 mL), water (300 mL).
- Seebach's stain (aka "Magic"): Phosphomolybdic acid (2.5 g), $Ce(SO_4)_2$ (1.0 g), conc. H_2SO_4 (6 mL), H_2O (94 mL).
- Neat iodine absorbed on silica gel.

1.4 Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments in $CDCl_3$. Chemical shifts are reported as δ-values in parts per million (ppm) relative to the residual solvent peak $CDCl_3$ (δH: 7.26; δC: 77.16) or CD_3CN (δH: 1.94; δC: 118.26 and 1.32). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; 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. Due the photochemical properties of azobenzenes, the NMR spectra contain mixtures of *trans*- and *cis*-isomers. The ratio is reported in the analytical section for each compound. The ratio can be altered by irradiation of the compound with light at specific wavelengths or thermal relaxation to the *trans*-isomer in the dark.

High resolution **Mass spectroscopy** (HR-MS) electron impact ionization (EI) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. EI was conducted with an electron energy of 70 eV. Electrospray ionization (ESI) spectra were recorded on a FINNIGAN LTQ FTICR instrument.

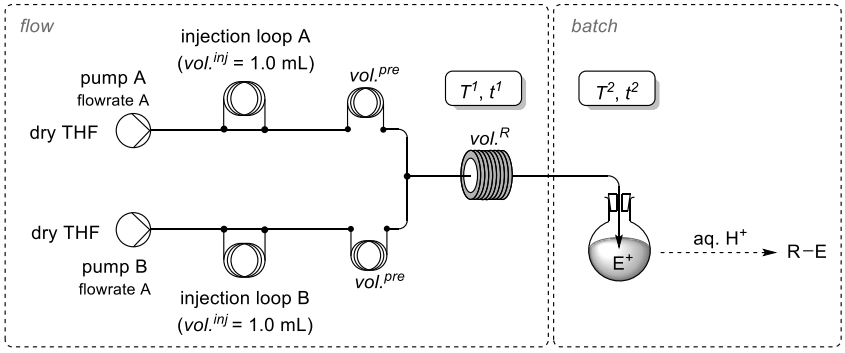
Gas chromatography (GC) was performed on machines of the types Hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm). The detection was accomplished using a flame ionization detector.

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

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

2 Selective Lithiation, Magnesiation and Zincation of Unsymmetrical Azobenzenes Using Continuos Flow

2.1 Typical Procedures (TP)



Scheme 45: General flow setup for the selective lithiation, magnesiation and zincation of unsymmetrical azobenzenes.

Typical Procedure for the lithiation of methoxy-substituted azobenzenes in flow followed by the reaction with an electrophile in batch (TP 1):

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A ($vol.^{inj}$ = 1.0 mL) was loaded with TMPLi (0.54 – 0.64 M in dry THF, 2.5 equiv.) and injection loop B ($vol.^{inj}$ = 1.0 mL) was loaded with the reactant solution (0.22 – 0.26 M in dry THF, 1.0 equiv.). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.50 mL min^{-1}), which passed a pre-cooling loop ($vol.^{pre}$ = 1 mL, residence time: 40 s, 0 °C) respectively, before they were mixed in a coiled reactor ($vol.^{R}$ = 1 mL, residence time: t^1 = 20 s, T^1 = 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 – 2.0 equiv.) dissolved in dry THF (1 mL). Then the reaction mixture was further stirred for the indicated time (t^2) at the indicated temperature (T^2). The completion of the reaction was checked by GC analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution and using dodecane or hexadecane as an internal standard.

Typical Procedure for the in situ trapping metalation with $ZnCl_2$ of unsymmetrical azobenzenes in flow followed by the reaction with an electrophile in batch (TP 2):

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A ($vol.^{inj}$ = 1.0 mL) was loaded with TMPLi (0.30 – 0.61 M in dry THF, 1.5 equiv.) and injection loop B ($vol.^{inj}$ = 1.0 mL) was loaded with the reactant solution (0.20 – 0.41 M in dry THF containing 0.5 equiv. of $ZnCl_2$, 1.0 equiv.). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.50 mL min^{-1}),

which passed a pre-cooling loop (vol.^{pre} = 1 mL, residence time: 40 s, 0 °C) respectively, before they were mixed in a coiled reactor (vol.^{R} = 1 mL, residence time: 20 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 – 2.0 equiv.) dissolved in dry THF (1 mL). Then the reaction mixture was further stirred for the indicated time (t^2) at the indicated temperature (T^2). The completion of the reaction was checked by GC-analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution and using dodecane or hexadecane as an internal standard.

Typical Procedure for the in situ trapping metalation with $MgCl_2$·LiCl of unsymmetrical azobenzenes in flow followed by the reaction with an electrophile in batch (TP 3):

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A (vol.^{inj} = 1.0 mL) was loaded with TMPLi (0.52 – 0.59 M in dry THF, 1.5 equiv.) and injection loop B (vol.^{inj} = 1.0 mL) was loaded with the reactant solution (0.35 – 0.39 M in dry THF containing 0.5 equiv. of $MgCl_2$·LiCl, 1.0 equiv.). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.50 mL min^{-1}), which passed a pre-cooling loop (vol.^{pre} = 1 mL, residence time: 40 s, 0 °C) respectively, before they were mixed in a coiled reactor (vol.^{R} = 1 mL, residence time: t^1 = 20 s, T^1 = 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 (1 mL). Then the reaction mixture was further stirred for the indicated time (t^2) at the indicated temperature (T^2). The completion of the reaction was checked by GC-analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution and using dodecane or hexadecane as an internal standard.

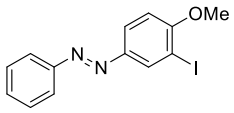
Typical Procedure for the scale-up of the in situ trapping metalation of unsymmetrical azobenzenes in flow followed by the reaction with an electrophile in batch (TP 4):

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A (vol.^{inj} = 6.0 mL) was loaded with TMPLi (0.58 M in dry THF, 1.5 equiv.) and injection loop B (vol.^{inj} = 6.0 mL) was loaded with the reactant solution (0.39 M in dry THF containing 0.5 equiv. $ZnCl_2$, 1.0 equiv.). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.50 mL min^{-1}), which passed a pre-cooling loop (vol.^{pre} = 1 mL, residence time: 40 s, 0 °C) respectively, before they were mixed in a coiled reactor (vol.^{R} = 1 mL, residence time: t^1 = 20 s, T^1 = 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 (2.0 – 3.0 equiv.) dissolved in dry THF (10 mL). After 4 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 (t^2) at the indicated temperature

(T^2). The completion of the reaction was checked by GC analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution and using dodecane or hexadecane as an internal standard.

2.2 Preparation of the Products

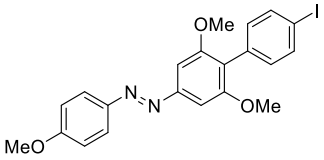
(*E*)-1-(3-Iodo-4-methoxyphenyl)-2-phenyldiazene (5a)



According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(4-methoxyphenyl)-2-phenyldiazene (**2a**, 0.22 M, 1.0 equiv., 1 mL) and TMPLi (0.54 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask containing iodine (**4a**, 122 mg, 0.44 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:DCM = 19:1) afforded **5a** as a red solid (41 mg, 0.12 mmol, 55%). ^{1}H-NMR analysis indicated that the sample contains a 10:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.41 (d, *J* = 2.3 Hz, 1H), 7.97 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.53 – 7.48 (m, 2H), 7.47 – 7.44 (m, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 3.97 (s, 3H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 160.2, 152.6, 147.7, 132.6, 130.9, 129.2, 126.7, 122.9, 110.4, 86.7, 56.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3067, 2937, 2838, 1586, 1564, 1476, 1436, 1388, 1307, 1270, 1251, 1169, 1133, 1070, 1040, 1014, 921, 895, 813, 765, 688, 666.
MS (EI, 70 eV): *m/z* (%) = 339 (13), 338 (100), 261 (36), 233 (79), 218 (17), 203 (15), 105 (11), 78 (17), 77 (53), 76 (17), 63 (13).
HRMS (EI): *m/z* calcd. for [$C_{13}H_{11}IN_2O$]: 337.9916, found 337.9911 (M^+).
M.p. (°C): 88.5 – 89.2.

(*E*)-1-(4-Iodo-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)diazene (5b)



According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)diazene (**2b**, 0.26 M, 1.0 equiv., 1 mL) and TMPLi (0.64 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask containing iodine (**4a**, 132 mg, 0.52 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further

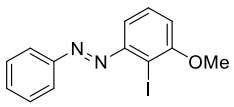
10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:DCM = 9:1) afforded **5b** as a yellow-orange solid (76 mg, 0.19 mmol, 73%). ^{1}H-NMR analysis indicated that the sample contains a 15:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (d, *J* = 9.1 Hz, 2H), 7.10 (s, 2H), 7.02 (d, *J* = 9.1 Hz, 2H), 3.99 (s, 6H), 3.89 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.5, 159.9, 154.5, 146.8, 125.0, 114.4, 98.5, 80.4, 56.8, 55.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3001, 2954, 2934, 2908, 2832, 2168, 2158, 1726, 1601, 1585, 1499, 1466, 1399, 1321, 1244, 1220, 1212, 1180, 1117, 1031, 1017, 967, 931, 894, 834, 791, 723, 653.
MS (EI, 70 eV): *m/z* (%) = 399 (14), 398 (100), 262 (10), 135 (22), 107 (44), 92 (11), 77 (12).
HRMS (EI): *m/z* calcd. for [$C_{15}H_{15}IN_2O_3$]: 398.0127; found 398.0124 (M^+).
M.p. (°C): 80.1 – 82.1.

(*E*)-1-(2-Iodo-3-methoxyphenyl)-2-phenyldiazene (5c') and (*E*)-1-(4-iodo-3-methoxyphenyl)-2-phenyldiazene (5c'')

According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(3-methoxyphenyl)-2-phenyldiazene (**2c**, 0.22 M, 1.0 equiv., 1 mL) and TMPLi (0.56 M, 2.5 equiv., 1 mL). After injection and metalation, which was carried out at −20 °C in this case, the combined streams were collected in a flask containing iodine (**4a**, 112 mg, 0.44 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:DCM = 4:1) afforded **5c**' and **5c**'' in a ratio of 74:26 as two orange solids (44 mg, 0.13 mmol, 59%).

(*E*)-1-(2-Iodo-3-methoxyphenyl)-2-phenyldiazene (5c')



^{1}H-NMR analysis indicated that the sample contains a 3:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 – 8.01 (m, 2H), 7.61 – 7.48 (m, 3H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.30 – 7.22 (m, 1H), 6.92 (dd, *J* = 8.0, 1.4 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.3, 153.2, 152.5, 131.7, 129.6, 129.3, 123.7, 112.5, 110.2, 94.5, 56.9.

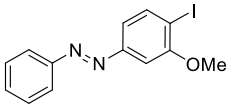
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 3013, 2976, 2940, 1577, 1565, 1457, 1424, 1297, 1264, 1184, 1150, 1100, 1057, 1015, 1003, 930, 873, 851, 782, 705, 684.

MS (EI, 70 eV): *m/z* (%) = 339 (14), 338 (93), 233 (12), 218 (22), 203 (27), 106 (17), 105 (49), 78 (20), 77 (100), 76 (21), 71 (11), 57 (11), 51 (17), 44 (18), 43 (44).

HRMS (EI): *m/z* calcd. for [$C_{13}H_{11}IN_2O$]: 337.9916; found 337.9910 (M^+).

M.p. (°C): 101.6 – 103.3.

(*E*)-1-(4-Iodo-3-methoxyphenyl)-2-phenyldiazene (5c'')



^{1}H-NMR analysis indicated that the sample contains a 5:1.0 mixture of *trans*- and *cis*-isomers.

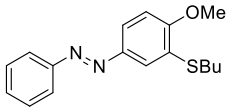
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 (d, *J* = 8.1 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.56 – 7.48 (m, 3H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.34 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.00 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.9, 154.0, 152.6, 139.9, 131.5, 129.3, 123.1, 118.8, 103.3, 89.9, 56.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3094, 3041, 2977, 2919, 2849, 1901, 1571, 1484, 1463, 1386, 1304, 1261, 1245, 1188, 1124, 1073, 1034, 1012, 1000, 982, 928, 860, 828, 772, 757, 685, 672.

M.p. (°C): 100.5 – 101.0.

(*E*)-1-(3-(Butylthio)-4-methoxyphenyl)-2-phenyldiazene (5d)



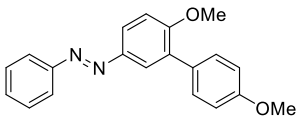
According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(4-methoxyphenyl)-2-phenyldiazene (**2a**, 0.24 M, 1.0 equiv., 1 mL) and TMPLi (0.59 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask at 0 °C containing Bu_2S_2 (**4b**, 34 mg, 0.19 mmol, 0.8 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min at 0 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **5d** as red oil (48 mg, 0.16 mmol, 83%). ^{1}H-NMR analysis indicated that the sample contains a 6.4:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 – 7.85 (m, 3H), 7.78 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.52 – 7.43 (m, 3H), 6.96 (d, *J* = 8.7 Hz, 1H), 3.98 (s, 3H), 3.00 (t, *J* = 7.4 Hz, 2H), 1.71 (quint, *J* = 7.4 Hz, 2H), 1.52 (sext, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.0, 152.9, 147.2, 130.6, 129.2, 127.5, 123.2, 122.7, 120.8, 110.1, 56.4, 31.3, 30.9, 22.3, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 2956, 2930, 2871, 2860, 2734, 2558, 1574, 1474, 1435, 1394, 1304, 1268, 1244, 1169, 1134, 1059, 1020, 954, 919, 876, 810, 764, 687, 662.
MS (EI, 70 eV): *m/z* (%) = 301 (11), 300 (64), 196 (11), 195 (100), 139 (11), 77 (56).
HRMS (EI): *m/z* calcd. for [$C_{17}H_{20}N_2OS$]: 300.1296; found 300.1296 (M^+).

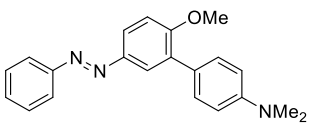
(*E*)-1-(4,6-Dimethoxy-[1,1'-biphenyl]-3-yl)-2-phenyldiazene (5e)



According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(4-methoxyphenyl)-2-phenyldiazene (**2a**, 0.25 M, 1.0 equiv., 1 mL) and TMPLi (0.62 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask containing $ZnCl_2$ (0.28 mL, 1.0 M in THF, 0.28 mmol, 1.1 equiv.), 4-bromoanisole (**4c**, 33 mg, 0.175 mmol, 0.7 equiv.), $Pd(dba)_2$ (5.8 mg, 4 mol%) and DavePhos (7.9 mg, 8 mol%) dissolved in THF (1 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **5e** as an orange solid (35 mg, 0.11 mmol, 63%). ^{1}H-NMR analysis indicated that the sample contains a 9:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.97 – 7.87 (m, 4H), 7.56 – 7.44 (m, 5H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.02 – 6.95 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.1, 153.0, 147.0, 131.1, 130.8, 130.5, 130.3, 129.2, 129.2, 124.7, 124.5, 122.7, 113.7, 111.2, 56.1, 55.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3001, 2937, 2836, 1609, 1595, 1516, 1486, 1463, 1440, 1420, 1398, 1262, 1248, 1179, 1125, 1071, 1030, 1024, 907, 833, 769, 690.
MS (EI, 70 eV): *m/z* (%) = 319 (22), 318 (87), 317 (12), 214 (20), 213 (100), 198 (34), 182 (12), 155 (10), 127 (10), 77 (25).
HRMS (EI): *m/z* calcd. for [$C_{20}H_{18}N_2O_2$]: 318.1368; found 318.1360 (M^+).
M.p. (°C): 91.9 – 92.9.

(*E*)-2'-Methoxy-*N*,*N*-dimethyl-5'-(phenyldiazenyl)-[1,1'-biphenyl]-4-amine (5f)

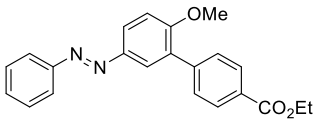


According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(4-methoxyphenyl)-2-phenyldiazene (**2a**, 0.25 M, 1.0 equiv., 1 mL) and TMPLi (0.62 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask containing $ZnCl_2$ (0.26 mL, 1.0 M in THF, 0.26 mmol, 1.1 equiv.), 4-bromo-*N*,*N*-dimethylaniline (**4d**, 34 mg, 0.17 mmol, 0.7 equiv.),

$Pd(dba)_2$ (5.5 mg, 4 mol%) and DavePhos (7.6 mg, 8 mol%) dissolved in THF (1 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:DCM = 9:1) afforded **5f** as a brown solid (39 mg, 0.12 mmol, 69%). ^{1}H-NMR analysis indicated that the sample contains a 10:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 2.5 Hz, 1H), 7.93 – 7.87 (m, 3H), 7.55 – 7.49 (m, 4H), 7.45 – 7.42 (m, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 6.84 – 6.80 (m, 2H), 3.91 (s, 3H), 3.01 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.2, 153.0, 150.0, 147.0, 131.5, 130.4, 130.4, 129.1, 125.7, 124.5, 123.8, 122.7, 112.3, 111.1, 56.0, 40.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3329, 2934, 2834, 1599, 1584, 1500, 1463, 1406, 1320, 1243, 1204, 1134, 1105, 1029, 1003, 940, 874, 840, 819, 765, 689.
MS (EI, 70 eV): *m/z* (%) = 332 (23), 331 (100), 330 (10), 227 (12), 226 (65), 77 (14).
HRMS (EI): *m/z* calcd. for $[C_{21}H_{21}N_3O]$: 331.1685; found 331.1681 (M^+).
M.p. (°C): 105.6 – 108.1.

(*E*)-Ethyl 2'-methoxy-5'-(phenyldiazene)-[1,1'-biphenyl]-4-carboxylate (5g)



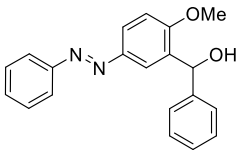
According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(4-methoxyphenyl)-2-phenyldiazene (**2a**, 0.24 M, 1.0 equiv., 1 mL) and TMPLi (0.59 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask at 0 °C containing $ZnCl_2$ (0.26 mL of a 1.0 M in THF, 0.26 mmol, 1.1 equiv.) and stirred for 15 min. Then ethyl 4-bromo-benzoate (**4e**, 44 mg, 0.19 mmol, 0.8 equiv.), $Pd(dba)_2$ (5.5 mg, 4 mol%) and DavePhos (7.6 mg, 8 mol%) dissolved in THF (1 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:DCM = 9:1) afforded **5g** as an orange solid (56 mg, 0.16 mmol, 83%). ^{1}H-NMR analysis indicated that the sample contains a 11:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 – 8.10 (m, 2H), 8.02 – 7.97 (m, 2H), 7.92 – 7.87 (m, 2H), 7.70 – 7.64 (m, 2H), 7.54 – 7.48 (m, 2H), 7.48 – 7.44 (m, 1H), 7.14 – 7.10 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.7, 159.0, 152.8, 147.0, 142.6, 130.7, 130.4, 129.7, 129.4, 129.4, 129.2, 125.4, 124.9, 122.8, 111.4, 61.1, 56.1, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2964, 2837, 1708, 1597, 1575, 1490, 1481, 1459, 1452, 1367, 1336, 1271, 1260, 1240, 1224, 1178, 1099, 1017, 930, 863, 824, 766, 689, 662.
MS (EI, 70 eV): *m/z* (%) = 360 (100), 283 (96), 255 (49), 165 (32), 100 (22).
HRMS (EI): *m/z* calcd. for [$C_{22}H_{20}N_2O_3$]: 360.1474; found 360.1479 (M^+).
M.p. (°C): 135.3 – 136.7.

The structure was confirmed by Single-Crystal X-Ray diffraction studies. For detailed information see Crystallographic Data section.

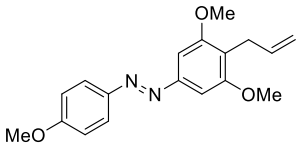
(*E*)-(2-Methoxy-5-(phenyldiazenyl)phenyl)(phenyl)methanol (5h)



According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(4-methoxyphenyl)-2-phenyldiazene (**2a**, 0.24 M, 1.0 equiv., 1 mL) and TMPLi (0.60 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask at 0 °C containing benzaldehyde (**4f**, 20 mg, 0.19 mmol, 0.8 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 5 h at 0 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 7:3) afforded **5h** as an orange solid (35 mg, 0.11 mmol, 58%). ^{1}H-NMR analysis indicated that the sample contains a 7.4:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 2.4 Hz, 1H), 7.93 – 7.86 (m, 3H), 7.52 – 7.43 (m, 5H), 7.38 – 7.32 (m, 3H), 7.30 – 7.24 (m, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.14 (s, 1H), 4.69 (s, 1H), 3.87 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.0, 152.9, 147.0, 143.1, 132.9, 130.5, 129.1, 128.4, 127.5, 126.8, 124.3, 122.7, 122.3, 110.9, 72.0, 55.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 3031, 2939, 2837, 1597, 1486, 1453, 1439, 1419, 1303, 1250, 1180, 1154, 1098, 1072, 1021, 965, 923, 832, 816, 759, 751, 736, 688, 668, 660.
MS (EI, 70 eV): *m/z* (%) = 319 (23). 318 (100), 316 (10), 213 (22), 211 (11), 197 (12), 196 (13), 195 (86), 180 (15), 165 (31), 153 (12), 152 (16), 107 (18), 105 (16), 79 (11), 77 (55), 44 (11).
HRMS (EI): *m/z* calcd. for [$C_{20}H_{18}N_2O_2$]: 318.1368; found 318.1362 (M^+).
M.p. (°C): 54.5 – 56.8.

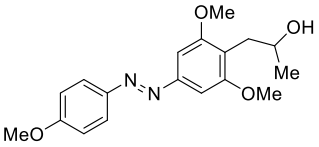
(*E*)-1-(4-Allyl-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)diazene (5i)



According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)diazene (**2b**, 0.25 M, 1.0 equiv., 1 mL) and TMPLi (0.63 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask containing containing allyl bromide (**4g**, 24 mg, 0.2 mmol, 0.8 equiv.) and CuCN·2LiCl solution (0.03 mL, 1.0 M in THF, 10 mol%) dissolved in THF (1 mL). The reaction mixture was stirred 1 h at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex: DCM = 19:1) afforded **5i** as an orange solid (57 mg, 0.18 mmol, 90%). ^{1}H-NMR analysis indicated that the sample contains a 34:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92 (d, *J* = 9.0 Hz, 2H), 7.16 (s, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.05 – 5.89 (m, 1H), 5.03 – 4.91 (m, 2H), 3.92 (s, 6H), 3.90 (s, 3H), 3.51 – 3.42 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.1, 158.6, 152.5, 147.1, 136.4, 124.8, 119.4, 114.4, 114.4, 98.9, 56.1, 55.7, 27.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2996, 2963, 2926, 2835, 1634, 1597, 1581, 1500, 1461, 1404, 1343, 1292, 1253, 1209, 1136, 1078, 1029, 1001, 910, 840, 832, 818, 799, 788, 723.
MS (EI, 70 eV): *m/z* (%) = 312 (27), 177 (18), 135 (41), 108 (10), 107 (100), 92 (15), 77 (28).
HRMS (EI): *m/z* calcd. for [$C_{18}H_{20}N_2O_3$]: 312.1474; found 312.1461 (M^+).
M.p. (°C): 89.2 – 91.0.

(*E*)-1-(2,6-Dimethoxy-4-((4-methoxyphenyl)diazenyl)phenyl)propan-2-ol (5j)

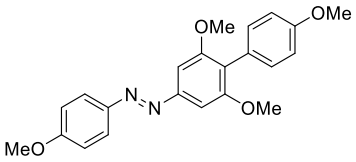


According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)diazene (**2b**, 0.24 M, 1.0 equiv., 1 mL) and TMPLi (0.59 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask at 0 °C containing propylene oxide (**4h**, 11 mg, 0.19 mmol, 0.8 equiv.) and CuI (4.6 mg, 10 mol%) dissolved in THF (1 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc:MeOH = 8:1.5:0.5) afforded **5j** as a red solid

(49 mg, 0.15 mmol, 78%). ^{1}H-NMR analysis indicated that the sample contains a 5.1:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92 (d, *J* = 8.8 Hz, 2H), 7.17 (s, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.06 (sept, *J* = 6.7 Hz, 1H), 3.92 (s, 6H), 3.90 (s, 3H), 3.00 – 2.83 (m, 2H), 1.23 (d, *J* = 6.2 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.2, 158.9, 152.6, 147.0, 124.8, 118.2, 114.4, 98.8, 68.6, 56.0, 55.7, 33.0, 23.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3328, 3068, 3042, 2931, 2886, 2835, 1712, 1610, 1598, 1592, 1485, 1463, 1441, 1406, 1251, 1322, 1260, 1241, 1202, 1123, 1039, 1022, 940, 923, 840, 818, 765, 689.
MS (EI, 70 eV): *m/z* (%) = 330 (43), 287 (10), 286 (57), 285 (100), 135 (26), 107 (54), 77 (18).
HRMS (EI): *m/z* calcd. for [$C_{18}H_{22}N_2O_4$]: 330.1568; found 330.1568 (M^+).
M.p. (°C): 108.1 – 108.5.

(*E*)-1-(4-Methoxyphenyl)-2-(2,4',6-trimethoxy-[1,1'-biphenyl]-4-yl)diazene (5k)

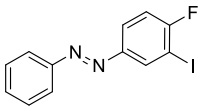


According to **TP 1**, injection loop A and B were loaded with solutions of (*E*)-1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)diazene (**2b**, 0.25 M, 1.0 equiv., 1 mL) and TMPLi (0.61 M, 2.5 equiv., 1 mL). After injection and metalation the combined streams were collected in a flask containing $ZnCl_2$ (0.28 mL, 1.0 M in THF, 0.28 mmol, 1.1 equiv.), 4-bromoanisole (**4c**, 37 mg, 0.20 mmol, 0.8 equiv.), $Pd(dba)_2$ (5.8 mg, 4 mol%) and DavePhos (7.9 mg, 8 mol%) dissolved in THF (1 mL). The reaction mixture was stirred overnight at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **5k** as an orange solid (68 mg, 0.18 mmol, 90%). ^{1}H-NMR analysis indicated that the sample contains only the *trans*-isomer.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 – 7.92 (m, 2H), 7.38 – 7.32 (m, 2H), 7.25 (s, 2H), 7.05 – 7.01 (m, 2H), 7.00 – 6.96 (m, 2H), 3.90 (s, 3H), 3.85 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.2, 158.7, 158.2, 153.1, 147.1, 132.1, 125.8, 124.9, 121.3, 114.4, 113.4, 99.2, 56.2, 55.7, 55.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3000, 2934, 2837, 1595, 1582, 1500, 1460, 1396, 1322, 1295, 1243, 1141, 1123, 1106, 1030, 998, 830, 790, 757, 725, 698, 659.
MS (EI, 70 eV): *m/z* (%) = 379 (33), 378 (100), 282 (15), 244 (13), 243 (19), 207 (21), 135 (35), 107 (80), 77 (24), 73 (28), 44 (23), 43 (26).

HRMS (EI): *m/z* calcd. for [$C_{22}H_{22}N_2O_4$]: 378.1580; found 378.1573 (M^+).
M.p. (°C): 152.4 – 153.9.

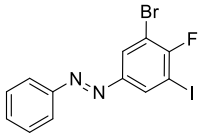
(*E*)-1-(4-Fluoro-3-iodophenyl)-2-phenyldiazene (8a)



According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.40 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.60 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing iodine (**4a**, 203 mg, 0.80 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8a** as an orange solid (111 mg, 0.34 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.37 – 8.32 (m, 1H), 7.97 – 7.92 (m, 1H), 7.92 – 7.89 (m, 2H), 7.55 – 7.48 (m, 3H), 7.23 – 7.19 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.2 (d, *J* = 250.9 Hz), 152.4, 150.0 (d, *J* = 3.3 Hz), 133.1 (d, *J* = 2.5 Hz), 131.6, 129.3, 126.0 (d, *J* = 8.0 Hz), 123.1, 116.0 (d, *J* = 25.5 Hz), 82.0 (d, *J* = 27.5 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 1700, 1654, 1577, 1507, 1474, 1463, 1445, 1386, 1241, 1166, 1116, 1030, 922, 893, 823, 766, 686, 668.
MS (EI, 70 eV): *m/z* (%) = 326 (43), 249 (12), 221 (41), 105 (50), 94 (64), 78 (11), 77 (100), 51 (40), 50 (16).
HRMS (EI): *m/z* calcd. for [$C_{12}H_8FIN_2$]: 325.9716; found 325.9711 (M^+).
M.p. (°C): 59.6 – 60.7.

(*E*)-1-(3-Bromo-4-fluoro-5-iodophenyl)-2-phenyldiazene (8b)

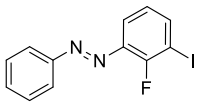


According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(3-bromo-4-fluorophenyl)-2-phenyldiazene (**6b**, 0.40 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.60 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing iodine (**4a**, 203 mg, 0.80 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*.

Purification by flash column chromatography (silica gel, *i*-hex) afforded **8b** as a light orange solid (121 mg, 0.30 mmol, 75%). ^{1}H-NMR analysis indicated that the sample contains a 25:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.28 (dd, *J* = 5.3, 2.3 Hz, 1H), 8.13 (dd, *J* = 6.0, 2.3 Hz, 1H), 7.92 – 7.88 (m, 2H), 7.55 – 7.50 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.4 (d, *J* = 249.5 Hz), 152.1, 149.8 (d, *J* = 4.0 Hz), 133.3 (d, *J* = 1.7 Hz), 132.0, 129.4, 128.2, 123.3, 109.3 (d, *J* = 25.5 Hz), 82.0 (d, *J* = 28.9 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 3055, 1562, 1470, 1449, 1437, 1387, 1306, 1253, 1166, 1158, 1144, 1022, 887, 874, 785, 767, 726, 696, 684, 661.
MS (EI, 70 eV): *m/z* (%) = 406 (25), 404 (21), 301 (13), 299 (15), 105 (47), 42 (100).
HRMS (EI): *m/z* calcd. for [$C_{12}H_7FBrIN_2$]: 403.8821; found 403.8818 (M^+).
M.p. (°C): 108.2 – 109.2.

(*E*)-1-(2-Fluoro-3-iodophenyl)-2-phenyldiazene (8c)

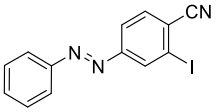


According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(2-fluorophenyl)-2-phenyldiazene (**6c**, 0.38 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.56 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation, which for this case was carried out at −20 °C for 60 seconds, the combined streams were collected in a flask containing iodine (**4a**, 203 mg, 0.80 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8c** as an orange solid (81 mg, 0.25 mmol, 66%). ^{1}H-NMR analysis indicated that the sample a 67:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 – 7.92 (m, 2H), 7.89 – 7.81 (m, 1H), 7.75 – 7.68 (m, 1H), 7.57 – 7.50 (m, 3H), 7.00 (td, *J* = 8.0, 1.1 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.1 (d, *J* = 256.3 Hz), 152.8, 141.5 (d, *J* = 1.8 Hz), 141.1 (d, *J* = 9.1 Hz), 132.0, 129.3, 126.0 (d, *J* = 4.5 Hz), 123.4, 118.3, 83.0 (d, *J* = 24.4 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 1888, 1694, 1586, 1574, 1487, 1449, 1301, 1291, 1231, 1149, 1070, 1018, 926, 852, 782, 718, 685.
MS (EI, 70 eV): *m/z* (%) = 327 (10), 326 (78), 249 (11), 221 (34), 105 (61), 94 (28), 77 (100), 44 (10), 43 (10).
HRMS (EI): *m/z* calcd. for [$C_{12}H_8FIN_2$]: 325.9716; found 325.9710 (M^+).

M.p. (°C): 70.8 – 71.9.

(*E*)-2-Iodo-4-(phenyldiazenyl)benzonitrile (8d)

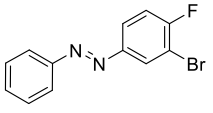


According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-(4-phenyldiazenyl)benzonitrile (**6d**, 0.41 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.61 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing iodine (**4a**, 208 mg, 0.82 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:DCM = 9:1) afforded **8d** as an orange solid (113 mg, 0.34 mmol, 83%). ^{1}H-NMR analysis indicated that the sample contains a 14:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.39 (d, *J* = 1.8 Hz, 1H), 7.96 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.95 – 7.92 (m, 2H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.53 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.4, 152.3, 135.0, 132.9, 132.8, 129.5, 123.6, 123.5, 121.9, 119.2, 99.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3083, 2230, 1584, 1558, 1458, 1440, 1374, 1310, 1283, 1254, 1156, 1145, 1070, 1029, 1020, 926, 892, 836, 769, 685, 668, 652.
MS (EI, 70 eV): *m/z* (%) = 333 (40), 228 (19), 105 (33), 101 (15), 77 (100).
HRMS (EI): *m/z* calcd. for [$C_{13}H_8IN_2$]: 332.9763; found 332.9759 (M^+).
M.p. (°C): 123.1 – 123.9.

The structure was confirmed by Single-Crystal X-Ray diffraction studies. For detailed information see Crystallographic Data section.

(*E*)-1-(3-Bromo-4-fluorophenyl)-2-phenyldiazene (8e)

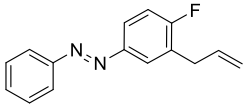


According to **TP 4**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.39 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 6 mL) and TMPLi (0.58 M, 1.5 equiv., 6 mL). After injection and in situ trapping metalation the combined streams were collected at 0 °C in a flask containing bromine (**4i**, 1.79 mL, 35 mmol, 3 equiv.) dissolved in THF (12 mL). This procedure was repeated 5 times for a total amount of 11.7 mmol. The reaction mixture was stirred for

further 1 h at 0 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (100 mL). The aq. layer was extracted with EtOAc (3×150 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8e** as an orange solid (2.428 g, 8.7 mmol, 74%). ^{1}H-NMR analysis indicated that the sample contains a 13:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 (dd, *J* = 6.5, 2.4 Hz, 1H), 7.91 (m, 3H), 7.56 – 7.49 (m, 3H), 7.27 (t, *J* = 8.0 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.6 (d, *J* = 252.8 Hz), 152.4, 150.0 (d, *J* = 3.5 Hz), 131.7, 129.32, 127.1 (d, *J* = 1.1 Hz), 125.1 (d, *J* = 7.8 Hz), 123.2 , 117.0 (d, *J* = 23.7 Hz), 110.2 (d, *J* = 22.6 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3088, 3054, 1590, 1580, 1492, 1476, 1462, 1442, 1388, 1305, 1252, 1241, 1162, 1156, 1113, 1032, 887, 783, 772, 704, 684.
MS (EI, 70 eV): *m/z* (%) = 280 (27), 278 (32), 175 (33), 172 (35), 105 (29), 94 (28), 77 (100), 71 (15), 57 (23), 43 (13).
HRMS (EI): *m/z* calcd. for [$C_{12}H_8FBrN_2$]: 277.9855; found 277.9852 (M^+).
M.p. (°C): 80.1 – 81.3.

(*E*)-1-(3-Allyl-4-fluorophenyl)-2-phenyldiazene (8f)



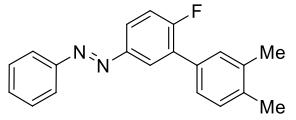
According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.41 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.61 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask at 0 °C containing allyl bromide (**4g**, 54 mg, 0.45 mmol, 1.1 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 10 mol%) dissolved in THF (1 mL). The reaction mixture was stirred for further 1 h at 0 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:Et_2O = 100:1) afforded **8f** as an orange liquid (84 mg, 0.35 mmol, 85%). ^{1}H-NMR analysis indicated that the sample contains a 6.2:1.0 mixture of *trans*- and *cis*-isomers.

scale-up:
According to **TP 4**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.40 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 6 mL) and TMPLi (0.60 M, 1.5 equiv., 6 mL). After injection and in situ trapping metalation the combined streams were collected at 0 °C in a flask containing allyl bromide (**4g**, 2.904 g, 24 mmol, 2 equiv.) and CuCN·2LiCl solution

(1.20 mL, 1.0 M in THF, 10 mol%) dissolved in THF (12 mL). This procedure was repeated 5 times for a total amount of 12.0 mmol. The reaction mixture was stirred for further 1 h at 0 °C before it was quenched with sat. aq. NH_4Cl solution (100 mL). The aq. layer was extracted with EtOAc (3×150 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8f** as an orange liquid (2.381 g, 9.91 mmol, 83%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 7.94 – 7.89 (m, 2H), 7.88 – 7.78 (m, 2H), 7.54 – 7.50 (m, 2H), 7.49 – 7.46 (m, 1H), 7.17 (t, *J* = 8.8 Hz, 1H), 6.07 – 5.99 (m, 1H), 5.22 – 5.12 (m, 2H), 3.51 (d, *J* = 7.0 Hz, 2H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 162.7 (d, *J* = 251.9 Hz), 152.7, 149.2, 135.3, 131.1, 129.2, 128.1 (d, *J* = 17.5 Hz),125.4 (d, *J* = 6.2 Hz), 123.0, 122.9, 117.0, 116.0 (d, *J* = 23.8 Hz), 33.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079, 2981, 2915, 1641, 1584, 1485, 1557, 1434, 1266, 1243, 1108, 1084, 1071, 994, 920, 824, 766, 688, 661.
MS (EI, 70 eV): *m/z* (%) = 326 (43), 249 (12), 221 (41), 105 (50), 94 (64), 78 (11), 77 (100), 51 (40), 50 (16).
HRMS (EI): *m/z* calcd. for [$C_{12}H_8FIN_2$]: 325.9716; found 325.9711 (M^+).

(*E*)-1-(6-Fluoro-3',4'-dimethyl-[1,1'biphenyl]-3-yl)-2-phenyldiazene (8g)



According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.41 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.61 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 4-iodo-1,2-dimethylbenzene (**4j**, 105 mg, 0.45 mmol, 1.1 equiv.), $Pd(OAc)_2$ (1.8 mg, 2 mol%) and SPhos (6.7 mg, 4 mol%) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8g** as a light orange solid (91 mg, 0.30 mmol, 73%). ^{1}H-NMR analysis indicated that the sample contains a 12:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.07 (dd, *J* = 7.4, 2.5 Hz, 1H), 7.95 – 7.92 (m, 2H), 7.92 – 7.88 (m, 1H), 7.56 – 7.52 (m, 2H), 7.51 – 7.47 (m, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.31 – 7.25 (m, 2H), 2.36 (s, 3H), 2.34 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 161.26 (d, *J* = 253.6 Hz), 152.46 , 149.13 , 137.83 – 135.26 (d, *J* = 19.8 Hz), 132.53 , 130.95 , 130.09 , 129.76 , 129.04 , 126.37 , 125.57 , 122.88 (d, *J* = 8.9 Hz), 122.75 , 116.69 (d, *J* = 24.8 Hz), 19.82 , 19.50.

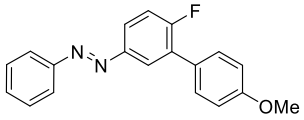
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 3023, 2940, 2920, 2859, 1583, 1481, 1447, 1384, 1248, 1226, 1156, 1107, 1020, 922, 886, 826, 766, 688, 668.

MS (EI, 70 eV): *m/z* (%) = 305 (15), 304 (78), 303 (70), 293 (10), 288 (17), 200 (15), 199 (100), 188 (11), 184 (46), 183(52), 105(28), 77 (91).

HRMS (EI): *m/z* calcd. for [$C_{20}H_{17}FN_2$]: 304.1376; found 304.1368 (M^+).

M.p. (°C): 89.5 – 90.9.

(*E*)-1-(6-Fluoro-4'-methoxy-[1,1'-biphenyl]-3-yl)-2-phenyldiazene (8h)



According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.41 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.61 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (**4k**, 106 mg, 0.45 mmol, 1.1 equiv.), $Pd(OAc)_2$ (1.8 mg, 2 mol%) and SPhos (6.7 mg, 4 mol%) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8h** as an orange solid (95 mg, 0.31 mmol, 76%). ^{1}H-NMR analysis indicated that the sample contains a 20:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.06 (dd, *J* = 7.4, 2.5 Hz, 1H), 7.96 – 7.92 (m, 2H), 7.90 – 7.87 (m, 1H), 7.62 – 7.58 (m, 2H), 7.56 – 7.51 (m, 2H), 7.51 – 7.47 (m, 1H), 7.31 – 7.26 (m, 1H), 7.05 – 7.01 (m, 2H), 3.88 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 161.2 (d, *J* = 253.2 Hz), 159.5, 152.4, 149.1, 131.0, 130.1, 129.3 (d, *J* = 15.6 Hz), 129.0, 127.4, 125.2, 122.9, 122.8, 122.7, 116.7 (d, *J* = 24.8 Hz), 114.0, 55.3.

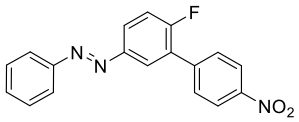
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3002, 2935, 2836, 1609, 1518, 1481, 1464, 1442, 1399, 1296, 1246, 1180, 1107, 1040, 1026, 922, 902, 832, 766, 688.

MS (EI, 70 eV): *m/z* (%) = 307 (18), 306 (100), 303 (13), 217 (10), 202 (15), 201 (97), 186 (27), 170 (21), 158 (42), 157 (19), 105 (22), 78 (10), 57 (12), 44 (63), 43 (21).

HRMS (EI): *m/z* calcd. for [$C_{19}H_{15}FN_2O$]: 306.1168; found 306.1158 (M^+).

M.p. (°C): 78.2 – 79.5.

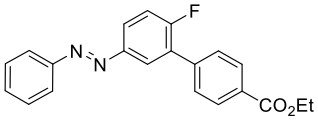
(*E*)-1-(6-Fluoro-4'-nitro-[1,1'-biphenyl]-3-yl]-2-phenyldiazene (8i)



According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.41 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.61 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 1-iodo-4-nitrobenzene (**4l**, 112 mg, 0.45 mmol, 1.1 equiv.), $Pd(OAc)_2$ (1.8 mg, 2 mol%) and SPhos (6.7 mg, 4 mol%) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8i** as an orange solid (90 mg, 0.28 mmol, 69%). ^{1}H-NMR analysis indicated that the sample contains a 14:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.33 (d, *J* = 8.8 Hz, 2H), 8.07 (dd, *J* = 7.3, 2.4 Hz, 1H), 8.03 – 7.99 (m, 1H), 7.93 (d, *J* = 7.1 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 282.9 Hz, 3H), 7.35 (d, *J* = 9.3 Hz, 1H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 161.1 (d, *J* = 255.4 Hz), 152.4, 149.4, 147.6, 141.7, 131.6, 130.0, 129.3, 127.6 (d, *J* = 14.2 Hz), 125.3 (d, *J* = 9.6 Hz), 125.2, 123.9, 123.1, 117.4 (d, *J* = 24.3 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3073, 2942, 2852, 1599, 1515, 1478, 1394, 1342, 1310, 1249, 1215, 1157, 1106, 1071, 1014, 1001, 906, 851, 767, 756, 688.
MS (EI, 70 eV): *m/z* (%) = 322 (14), 321 (42), 291 (42), 244 (16), 216 (34), 187 (14), 186 (54), 185 (25), 171 (10), 170 (61), 169 (30), 105 (42), 78 (12), 77 (100), 57 (18), 44 (68), 43 (28).
HRMS (EI): *m/z* calcd. for $[C_{18}H_{12}FN_3O_2]$: 321.0914; found 321.0904 (M^+).
M.p. (°C): 126.9 – 130.3.

(*E*)-Ethyl 2'-fluoro-5'-(phenyldiazene)-[1,1'-biphenyl]-4-carboxylate (8j)

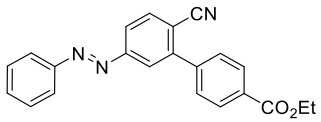


According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.41 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.61 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (**4m**, 124 mg, 0.45 mmol, 1.1 equiv.), $Pd(OAc)_2$ (1.8 mg, 2 mol%) and SPhos (6.7 mg, 4 mol%) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4,

filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8j** as a light orange solid (118 mg, 0.34 mmol, 83%). ^{1}H-NMR analysis indicated that the sample contains only the *trans*-isomers.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.19 – 8.14 (m, 2H), 8.08 (dd, *J* = 7.3, 2.5 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.94 – 7.91 (m, 2H), 7.74 – 7.70 (m, 2H), 7.55 – 7.51 (m, 2H), 7.51 – 7.47 (m, 1H), 7.33 – 7.29 (m, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 166.4, 161.3 (d, *J* = 254.8 Hz), 152.5, 149.4, 139.6, 131.4, 130.1, 129.9, 129.3, 129.1, 128.9 (d, *J* = 14.2 Hz), 125.5, 124.3 (d, *J* = 8.6 Hz), 123.0, 117.2 (d, *J* = 24.5 Hz), 61.2, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 2982, 1714, 1684, 1611, 1582, 1481, 1396, 1367, 1272, 1248, 1215, 1184, 1101, 1019, 905, 859, 771, 688, 668.
MS (EI, 70 eV): *m/z* (%) = 349 (23), 348 (82), 303 (19), 244 (18), 243 (87), 198 (20), 171 (33), 170 (82), 105 (31), 77 (100), 44 (13).
HRMS (EI): *m/z* calcd. for [$C_{21}H_{17}FN_2O_2$]: 348.1274; found 348.1264.
M.p. (°C): 112.0 – 115.0.

(*E*)-Ethyl 2'-cyano-5'-(phenyldiazene)-[1,1'-biphenyl]-4-carboxylate (8k)



According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.33 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.50 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (**4m**, 73 mg, 0.26 mmol, 0.8 equiv.), $Pd(OAc)_2$ (1.5 mg, 2 mol%) and SPhos (5.8 mg, 4 mol%) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 25 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 98:2) afforded **8k** as an orange solid (57 mg, 0.16 mmol, 67%). ^{1}H-NMR analysis indicated that the sample contains only the *trans*-isomer.

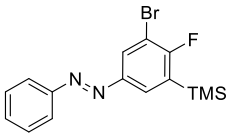
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.24 – 8.18 (m, 2H), 8.04 (d, *J* = 1.8 Hz, 1H), 8.00 – 7.92 (m, 4H), 7.75 – 7.69 (m, 2H), 7.56 – 7.53 (m, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.2, 154.6, 152.5, 145.7, 141.9, 135.0, 132.5, 131.1, 130.2, 129.4, 129.0, 124.3, 123.5, 122.2, 118.2, 112.8, 61.4, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 2224, 1715, 1682, 1602, 1474, 1462, 1441, 1417, 1311, 1283, 1274, 1183, 1126, 1102, 1016, 1000, 856, 850, 774, 704, 682, 666.

MS (EI, 70 eV): *m/z* (%) = 356 (24), 355 (88), 310 (18), 250 (34), 205 (20), 178 (23), 177 (36), 151 (10), 105 (33), 77 (100).

HRMS (EI): *m/z* calcd. for [$C_{22}H_{17}N_3O_2$]: 355.1321; found 355.1318 (M^+).

M.p. (°C): 151.9 – 153.9.

(*E*)-1-(3-Bromo-4-fluoro-5-(trimethylsilyl)phenyl)-2-phenyldiazene (8l)



According to **TP 3**, injection loop A and B were loaded with solutions of (*E*)-1-(3-bromo-4-fluorophenyl)-2-phenyldiazene (**8e**, 0.35 M containing 0.5 equiv. $MgCl_2 \cdot LiCl$, 1.0 equiv., 1 mL) and TMPLi (0.52 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask at 0 °C containing TMSCl (34 mg, 0.31 mmol, 0.9 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 0 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **8l** as a red oil (102 mg, 0.29 mmol, 92%). ^{1}H-NMR analysis indicated that the sample contains a 9:1 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.12 (dd, *J* = 6.7, 2.4 Hz, 1H), 7.97 – 7.93 (m, 1H), 7.92 – 7.89 (m, 2H), 7.54 – 7.49 (m, 3H), 0.41 (s, 9H).

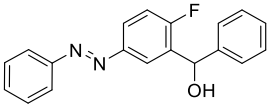
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.2 (d, *J* = 246.9 Hz), 152.5, 149.3, 131.5, 131.2 (d, *J* = 11.8 Hz), 129.3, 129.0, 128.6, 126.9, 123.1, 110.3 (d, *J* = 27.5 Hz), −1.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 2956, 2900, 1589, 1560, 1487, 1445, 1424, 1387, 1286, 1265, 1250, 1238, 1200, 1272, 1065, 1036, 957, 838, 763, 686, 662.

MS (EI, 70 eV): *m/z* (%) = 352 (20), 350 (15), 335 (11), 333 (14), 247 (13), 245 (10), 165 (13), 105 (18), 85 (11), 77 (56), 74 (12), 73 (100), 71 (38), 57 (28), 44 (12), 43 (25).

HRMS (EI): *m/z* calcd. for [$C_{15}H_{16}FBrN_2Si$]: 350.0250; found 350.0253 (M^+).

(*E*)-(2-Fluoro-5-(phenyldiazenyl)phenyl)(phenyl)methanol (8m)

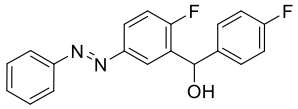


According to **TP 3**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.35 M containing 0.5 equiv. $MgCl_2 \cdot LiCl$, 1.0 equiv., 1 mL) and TMPLi (0.52 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask at 0 °C containing benzaldehyde (**4f**, 33 mg, 0.31 mmol, 0.9 equiv.) dissolved in THF (1 mL).

The reaction mixture was stirred for further 5 h at 0 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex: DCM = 2:1 → 1:2) afforded **8m** as an orange-red solid (83 mg, 0.27 mmol, 77%). ^{1}H-NMR analysis indicated that the sample contains only the *trans*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.95 – 7.89 (m, 2H), 7.89 – 7.83 (m, 1H), 7.56 – 7.44 (m, 5H), 7.40 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 7.19 – 7.11 (m, 1H), 6.19 (d, *J* = 2.8 Hz, 1H), 2.50 (d, *J* = 2.8 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.4 (d, *J* = 252.5 Hz), 152.6 , 149.4 (d, *J* = 3.1 Hz), 132.1 (d, *J* = 14.7 Hz), 131.2, 129.2, 128.8, 128.1, 126.6 (d, *J* = 0.8 Hz), 123.6 (d, *J* = 9.1 Hz), 123.0, 122.9 (d, *J* = 5.1 Hz), 116.3 (d, *J* = 23.4 Hz), 70.3 (d, *J* = 2.8 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3379, 3062, 1584, 1481, 1449, 1418, 1302, 1239, 1187, 1136, 1138, 1092, 1018, 924, 834, 766, 695, 686, 659.
MS (EI, 70 eV): *m/z* (%) = 307 (21), 306 (91), 229 (12), 201 (13), 184 (20), 183 (98), 152 (15), 107 (16), 105 (29), 95 (16), 79 (19), 77 (100), 51 (10), 43 (20).
HRMS (EI): *m/z* calcd. for [$C_{19}H_{15}FN_2O$]: 306.1168; found 306.1167 (M^+).
M.p. (°C): 96.0 – 96.9.

(*E*)-(2-Fluoro-5-(phenyldiazenyl)phenyl)(4-fluorophenyl)methanol (8n)



According to **TP 3**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.39 M containing 0.5 equiv. $MgCl_2$·LiCl, 1.0 equiv., 1 mL) and TMPLi (0.59 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask at 0 °C containing 4-fluoro-benzaldehyde (**4o**, 53 mg, 0.43 mmol, 1.1 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 0 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex: DCM = (8:2 → 1:2) afforded **8n** as an orange solid (94 mg, 0.29 mmol, 74%).^{1}H-NMR analysis indicated that the sample contains only the *trans*-isomer.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.18 (dd, *J* = 6.9, 2.5 Hz, 1H), 7.94 – 7.83 (m, 3H), 7.56 – 7.47 (m, 3H), 7.46 – 7.39 (m, 2H), 7.19 – 7.11 (m, 1H), 7.08 – 7.00 (m, 2H), 6.17 (d, *J* = 3.8 Hz, 1H), 2.47 (d, *J* = 3.8 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.5 (d, *J* = 246.5 Hz), 160.0 (d, *J* = 252.8 Hz), 152.6, 149.4 (d, *J* = 3.0 Hz), 138.3 (d, *J* = 3.1 Hz), 132.0 (d, *J* = 14.7 Hz), 131.3, 129.3, 128.4 (d, *J* = 9.0 Hz), 123.8 (d, *J* = 9.6 Hz), 123.0, 122.6 (d, *J* = 5.1 Hz), 116.4 (d, *J* = 23.3 Hz), 115.7 (d, *J* = 21.5 Hz), 69.7 (d, *J* = 2.8 Hz).

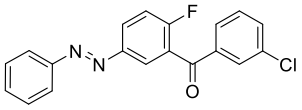
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3238, 3068, 1603, 1584, 1509, 1480, 1464, 1444, 1414, 1341, 1304, 1237, 1223, 1162, 1136, 1037, 1020, 911, 861, 839, 825, 766, 683.

MS (EI, 70 eV): *m/z* (%) = 325 (17), 324 (88), 219 (14), 202 (11), 201 (83), 171 (13), 125 (29), 123 (12), 105 (25), 97 (17), 95 (35), 77 (100), 57 (12).

HRMS (EI): *m/z* calcd. for [$C_{19}H_{14}F_2N_2O$]: 306.1168; found 324.1072 (M^+).

M.p. (°C): 110.3 – 110.6.

(*E*)-(3-Chlorophenyl)(2-fluoro-5-(phenyldiazenyl)phenyl)methanone (8o)



According to **TP 3**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.33 M containing 0.5 equiv. $MgCl_2$·LiCl, 1.0 equiv., 1 mL) and TMPLi (0.50 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask at 0 °C containing 3-chlorobenzoyl chloride (**4p**, 52 mg, 0.30 mmol, 0.9 equiv.) and CuCN·2LiCl solution (0.36 mL, 1.0 M in THF, 1.1 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 0 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 49:1) afforded **8o** as an orange solid (81 mg, 0.24 mmol, 81%). ^{1}H-NMR analysis indicated that the sample contains a 50:1 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 – 8.12 (m, 2H), 7.95 – 7.90 (m, 2H), 7.88 (s, 1H), 7.77 – 7.72 (m, 1H), 7.63 – 7.58 (m, 1H), 7.55 – 7.49 (m, 3H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.36 – 7.30 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.5, 161.4 (d, *J* = 258.2 Hz), 152.4, 149.0 (d, *J* = 3.3 Hz), 138.8, 135.1, 133.7, 131.7, 130.1, 129.7 (d, *J* = 1.0 Hz), 129.3, 128.1 (d, *J* = 1.0 Hz), 127.8 (d, *J* = 9.2 Hz), 127.1 (d, *J* = 16.4 Hz), 125.5 (d, *J* = 3.7 Hz), 123.2, 117.4 (d, *J* = 23.4 Hz).

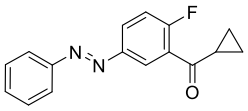
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 1668, 1589, 1577, 1573, 1480, 1426, 1307, 1281, 1270, 1227, 1209, 1174, 1088, 1069, 905, 828, 754, 682, 671.

MS (EI, 70 eV): *m/z* (%) = 340 (19), 339 (19), 338 (67), 235 (14), 233 (51), 198 (17), 141 (16), 139 (47), 111 (27), 105 (39), 77 (100), 75 (10), 57 (16).

HRMS (EI): *m/z* calcd. for [$C_{19}H_{12}FClN_2O$]: 338.0622; found 338.0616 (M^+).

M.p. (°C): 105.2 – 107.1.

(*E*)-Cyclopropyl-(2-fluoro-5-(phenyldiazenyl)phenyl)methanone (8p)



According to **TP 3**, injection loop A and B were loaded with solutions of (*E*)-1-(4-fluorophenyl)-2-phenyldiazene (**6a**, 0.33 M containing 0.5 equiv. $MgCl_2 \cdot LiCl$, 1.0 equiv., 1 mL) and TMPLi (0.50 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask at 0 °C containing cyclopropanecarbonyl chloride (**4q**, 31 mg, 0.30 mmol, 0.9 equiv.) and CuCN·2LiCl solution (0.36 mL, 1.0 M in THF, 1.1 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 3 h at 0 °C before it was quenched with sat. aq. NH_4Cl solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 49:1) afforded **8p** as an orange solid (62 mg, 0.23 mmol, 78%). ^{1}H-NMR analysis indicated that the sample contains a 8.7:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.35 (dd, *J* = 6.7, 2.4 Hz, 1H), 8.12 – 8.06 (m, 1H), 7.95 – 7.90 (m, 2H), 7.55 – 7.49 (m, 3H), 7.33 – 7.27 (m, 1H), 2.81 – 2.61 (m, 1H), 1.38 – 1.33 (m, 2H), 1.16 – 1.09 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.1, 162.8 (d, *J* = 259.2 Hz), 152.4, 149.0 (d, *J* = 3.1 Hz), 131.6, 129.3, 127.9 (d, *J* = 14.5 Hz), 127.6 (d, *J* = 9.8 Hz), 125.7 , 123.1, 117.7 (d, *J* = 25.1 Hz), 21.6, 12.9.

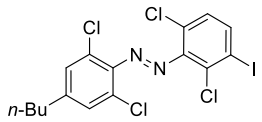
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3005, 2958, 2920, 1755, 1664, 1610, 1578, 1480, 1413, 1375, 1269, 1256, 1230, 1197, 1142, 1091, 1037, 1013, 970, 919, 883, 828, 766, 685, 656.

MS (EI, 70 eV): *m/z* (%) = 269 (19), 268 (99), 163 (59), 105 (29), 94 (15), 77 (100), 69 (42), 41 (11).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{13}FN_2O$]: 268.1012; found 268.1001 (M^+).

M.p. (°C): 63.1 – 64.4.

(*E*)-1-(4-Butyl-2,6-dichlorophenyl)-2-(2,6-dichloro-3-iodophenyl)diazene (10)



According to **TP 2**, injection loop A and B were loaded with solutions of (*E*)-1-(4-butyl-2,6-dichlorophenyl)-2-(2,6-dichlorophenyl)diazene (**9**, 0.20 M containing 0.5 equiv. $ZnCl_2$, 1.0 equiv., 1 mL) and TMPLi (0.30 M, 1.5 equiv., 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing iodine (**4a**, 102 mg, 0.40 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min at 25 °C before it was quenched with sat. aq. $Na_2S_2O_3$ solution (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated, and the solvent was

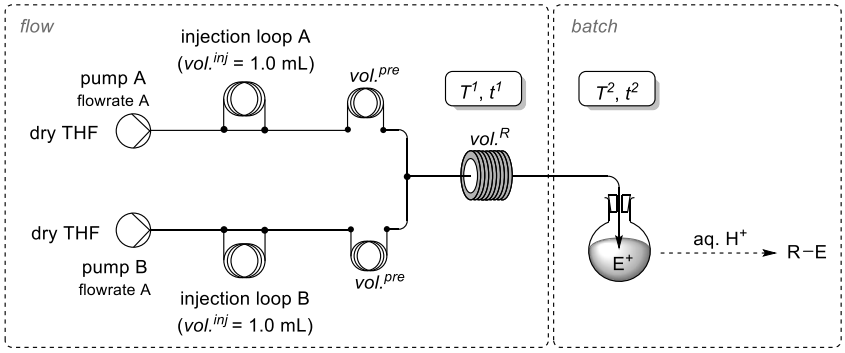
removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex) afforded **10** as an orange solid (65 mg, 0.13 mmol, 65%). ^{1}H-NMR analysis indicated that the sample contains a 3.3:1.0 mixture of *trans*- and *cis*-isomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (d, *J* = 8.6 Hz, 1H), 7.48 (s, 2H), 7.38 (d, *J* = 8.6 Hz, 1H), 2.83 (d, *J* = 7.2 Hz, 2H), 1.83 (p, *J* = 7.6 Hz, 2H), 1.58 (h, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 149.2, 146.5, 144.6, 139.2, 130.3, 129.7, 129.3, 128.1, 126.2, 98.4, 35.1, 33.1, 22.3, 14.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2932, 2858, 1592, 1551, 1542, 1491, 1464, 1447, 1435, 1424, 1401, 1362, 1274, 1239, 1208, 1184, 1170, 1117, 1096, 1080, 1004, 932, 912, 898, 870, 859, 801, 746, 726, 711, 691, 680, 668, 658, 651.
MS (EI, 70 eV): *m/z* (%) = 504 (18), 502 (39), 500 (30), 299 (14), 273 (18), 271 (29), 233 (10), 231 (65), 230 (13), 229 (100), 203 (21), 201 (34), 161 (40), 159 (61), 146 (13), 144 (19), 123 (15).
HRMS (EI): *m/z* calcd. for [$C_{16}H_{13}Cl_4IN_2$]: 499.8878; found 499.8872 (M^+).
M.p. (°C): 68.2 – 69.3.

The structure was confirmed by Single-Crystal X-Ray diffraction studies. For detailed information see Crystallographic Data Section.

3 Selective Zincation of 1,2-Dicyanobenzene and Related Benzonitriles in Continuous Flow Using In Situ Trapping Metalations

3.1 Typical Procedures (TP)



Scheme 46: General flow setup for the selective zincation of 1,2-dicyanobenzene and related benzonitriles.

Typical procedure for the in situ trapping metalation of 1,2-dicyanobenzene in flow followed by the reaction with an electrophile in batch (TP 5):

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A ($vol.^{inj}$ = 1.0 mL) was loaded with TMPLi (0.60 – 0.64 M in dry THF, 1.5 equiv.) and injection loop B ($vol.^{inj}$ = 1.0 mL) was loaded with the reactant solution (0.40 – 0.43 M in dry THF containing 0.5 equiv. $ZnCl_2$ additive). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.50 mL min^{-1}), which passed a pre-cooling loop ($vol.^{pre}$ = 1 mL, residence time: 40 s, 0 °C) respectively, before they were mixed in a coiled reactor ($vol.^{R}$ = 1 mL, residence time: t^1 = 20 s, T^1 = 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 (1.1 equiv.) dissolved in dry THF (1 mL). Then, the reaction mixture was further stirred for the indicated time (t^2) at the indicated temperature (T^2). The completion of the reaction was checked by GC analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution and using dodecane or hexadecane as an internal standard.

Typical procedure for the in situ trapping metalation in flow of 1,3-dicyanobenzene followed by the reaction with an electrophile in batch (TP 6):

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A ($vol.^{inj}$ = 1.0 mL) was loaded with TMPLi (0.51 – 0.66 M in dry THF, 1.5 equiv.) and injection loop B ($vol.^{inj}$ = 1.0 mL) was loaded with the reactant solution (0.34 – 0.38 M in dry THF containing 0.5 equiv. $ZnCl_2$ additive). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 2.50 mL min^{-1}), which

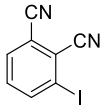
passed a pre-cooling loop (vol.^{pre} = 1 mL, residence time: 24 s, −78 °C) respectively, before they were mixed in a coiled reactor (vol.^{R} = 1 mL, residence time: t^1 = 36 s, T^1 = −78 °C). The combined streams were collected in a flame-dried, argon flushed 25 mL flask equipped with a magnetic stirrer and a septum containing the electrophile (0.8 – 1.2 equiv.) dissolved in dry THF (1 mL). Then, the reaction mixture was further stirred for the indicated time (t^2) at the indicated temperature (T^2). The completion of the reaction was checked by GC analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution and using dodecane or hexadecane as an internal standard.

Typical procedure for the in situ trapping metalation in flow of 3-methoxybenzonitrile followed by the reaction with an electrophile in batch (TP 7):

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A (vol.^{inj} = 1.0 mL) was loaded with TMPLi (0.52 – 0.56 M in dry THF, 1.5 equiv.) and injection loop B (vol.^{inj} = 1.0 mL) was loaded with the reactant solution (0.34 – 0.38 M in dry THF containing 0.5 equiv. $ZnCl_2$ additive). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 2.0 mL min^{-1}), which passed a pre-cooling loop (vol.^{pre} = 1 mL, residence time: 30 s, 0 °C) respectively, before they were mixed in a coiled reactor (vol.^{R} = 3 mL, residence time: t^1 = 45 s, T^1 = 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 – 1.2 equiv.) dissolved in dry THF (1 mL). Then the reaction mixture was further stirred for the indicated time (t^2) at the indicated temperature (T^2). The completion of the reaction was checked by GC-analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution and using dodecane or hexadecane as an internal standard.

3.2 Preparation of the Products

3-Iodophthalonitrile (14a)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.42 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.63 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing I_2 (**16a**, 197 mg, 0.84 mmol, 2.0 equiv.) dissolved in THF (1 mL). The reaction mixture was stirred for further 2 h at 0 °C before it was quenched with sat. aq. $Na_2S_2O_3$ (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 8:2) afforded **14a** as a white powder (93 mg, 0.37 mmol, 88%).

scale-up:

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A (6.0 mL) was loaded with TMPLi (0.63 M in dry THF, 1.5 equiv.) and injection loop B (6.0 mL) was loaded with 1,2-dicyanobenzene solution (**11a**, 0.42 M in dry THF containing 0.5 equiv. $ZnCl_2$ additive). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.50 mL min^{-1}), which passed a pre-cooling loop (1 mL, residence time: 40 s, 0 °C) respectively, before they were mixed in a coiled reactor (1 mL, residence time: 20 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 I_2 (**16a**, 10.15 g, 40.00 mmol, 4.0 equiv.) dissolved in THF (20 mL) at 25 °C. After 4 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. This procedure was repeated 4 times for a total amount of 10.08 mmol. The reaction mixture was stirred overnight before it was quenched with sat. aq. NH_4Cl (60 mL). The aq. layer was extracted with EtOAc (3×100 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = (8:2) afforded **14a** as a light brown solid (2.228 g, 8.77 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 143.6, 133.5, 132.8, 123.7, 118.0, 116.5, 114.8, 100.0.

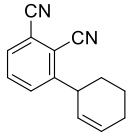
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 2230, 1570, 1552, 1448, 1426, 1206, 1126, 820, 804, 726.

MS (EI, 70 eV): *m/z* (%) = 253 (100), 155 (34), 127 (13), 100 (14).

HRMS (EI): *m/z* calcd. for [$C_8H_3IN_2$]: 253.9341; found: 253.9335.

M.p. (°C): 156.0 – 160.0.

1',2',3',4'-Tetrahydro-[1,1'-biphenyl]-2,3-dicarbonitrile (14b)

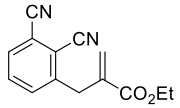


According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.42 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.63 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (**16b**, 74 mg, 0.46 mmol, 1.1 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 10 mol%) dissolved in THF (1 mL) at 0 °C. The reaction mixture was stirred for further 2 h at 0 °C before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed

in vacuo. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 1:4) afforded **14b** as a white powder (71 mg, 0.34 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.65 (s, 2H), 6.09 – 6.04 (m, 1H), 5.61 – 5.59 (m, 1H), 3.96 – 3.89 (m, 1H), 2.21 – 2.11, 3H), 1.75 – 1.67 (m, 2H), 1.55 – 1.47 (m, 1H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 152.6, 132.9, 132.7, 131.4, 131.3, 126.8, 116.6, 116.0, 115.4, 114.7, 40.4, 31.6, 24.8, 20.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2936, 2863, 2233, 2224, 1585, 1466, 1446, 1433, 1257, 1232, 1184, 1137, 1047, 945, 892, 807, 746, 732, 724.
MS (EI, 70 eV): *m/z* (%) = 209 (10), 208 (69), 207 (100), 193 (34), 192 (17), 191 (18), 190 (19), 181 (11), 180 (26), 179 (28), 167 (10), 165 (12), 153 (19), 152 (13), 141 (11), 140 (19), 54 (16), 43 (13).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{12}N_2$]: 208.1000; found: 207.0917 (M^+).
M.p. (°C): 117.3 – 118.4.

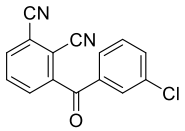
Ethyl 2-(2,3-dicyanobenzyl)acrylate (14c)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.42 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.63 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing ethyl 2-(bromomethyl)acrylate (**16c**, 89 mg, 0.46 mmol, 1.1 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 10 mol%) dissolved in THF (1 mL) at 0 °C. The reaction mixture was stirred for further 2 h at 0 °C before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 9:1) afforded **14c** as a colorless liquid (77 mg, 0.32 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.69 – 7.62 (m, 3H), 6.57 (s, 1H), 5.72 (s, 1H), 4.18 – 4.13 (q, *J* = 8 Hz, 2H) 3.9 (s, 2H), 1.26 – 1.22 (t, *J* = 8 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.8, 145.0, 137.0, 134.5, 132.9, 131.7, 128.8, 116.5, 116.1, 115.7, 114.7, 61.3, 37.0, 14.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 2984, 2930, 2854, 2362, 2236, 1711, 1632, 1586, 1465, 1447, 1408, 1369, 1329, 1300, 1255, 1200, 1175, 1139, 1096, 1024, 959, 858, 809, 792, 753, 733, 715.
MS (EI, 70 eV): *m/z* (%) = 212 (37), 195 (20), 194 (12), 168 (14), 167 (31), 166 (100), 165 (12), 141 (13), 140 (21).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{12}N_2O_2$]: 240.0899; found: 240.0883 (M^+).

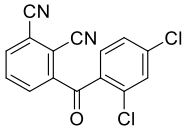
3-(3-Chlorobenzoyl)phthalonitrile (14d)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.44 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.66 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 3-chlorobenzoyl chloride (**16d**, 84 mg, 0.48 mmol, 1.1 equiv.) and CuCN·2LiCl solution (0.48 mL, 1.0 M in THF, 0.48 mmol, 1.1 equiv.) dissolved in THF (1 mL) at 0 °C. The reaction mixture was stirred for further 8 h at 0 °C before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 9:1) afforded **14d** as a pale brown solid (66 mg, 0.25 mmol, 57%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 – 7.97 (m, 1H), 7.93 – 7.86 (m, 2H), 7.76 (t, *J* = 1.7 Hz, 1H), 7.69 – 7.59 (m, 2H), 7.48 (t, *J* = 7.9 Hz, 1H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 190.7, 142.6, 136.6, 135.6, 135.5, 134.7, 133.7, 133.3, 133.3, 133.0, 130.5, 130.1, 128.6, 118.3, 115.3, 114.9, 113.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3086, 2925, 2242, 2234, 1667, 1590, 1570, 1468, 1441, 1422, 1401, 1292, 1276, 1207, 1166, 1074, 1015, 998, 896, 833, 799, 758, 727, 702, 672, 658.
MS (EI, 70 eV): *m/z* (%) = 268 (17), 266 (39), 231 (50), 155 (26), 141 (34), 139 (100), 127 (19), 111 (29), 75 (18), 44 (10).
HRMS (EI): *m/z* calcd. for $[C_{16}H_{12}N_2]$: 266.0247; found: 266.0240 (M^+).
M.p. (°C): 115.9 – 120.1.

1-(2,4-Dichlorobenzoyl)phthalonitrile (14)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.42 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.63 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 2,4-dichlorobenzoyl chloride (**16e**, 97 mg, 0.46 mmol, 1.1 equiv.) and CuCN·2LiCl solution (0.46 mL, 1.0 M in THF, 0.46 mmol, 1.1 equiv.) dissolved in THF (1.0 mL) at 0 °C. The reaction mixture was stirred for further 8 h at −20 °C before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 8:2) afforded **14e** as a light yellow powder (93 mg, 0.31 mmol, 74%).

^{1}H-NMR (4599 MHz, $CDCl_3$): δ / ppm = 8.01 (s, 1H), 7.86 (s, 2H), 7.58 – 7.38 (m, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 190.4, 141.6, 139.6, 136.5, 134.2, 133.4, 133.3, 132.1, 130.7, 128.2, 118.7, 115.0, 113.7.

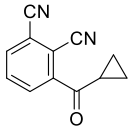
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3096, 2234, 1680, 1579, 1553, 1467, 1444, 1375, 1309, 1286, 1244, 1205, 1180, 1171, 1148, 1103, 1078, 1062, 1008, 991, 962, 940, 860, 832, 819, 800, 767, 729, 703, 670.

MS (EI, 70 eV): *m/z* (%) = 300 (11), 264 (78), 173 (100).

HRMS (EI): *m/z* calcd. for [$C_{15}H_6ON_2Cl_2$]: 299.9857; found: 299.9849 (M^+).

M.p. (°C): 145.0.

3-(Cyclopropanecarbonyl)phthalonitrile (14f)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.42 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.63 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing cyclopropanecarbonyl chloride (**16f**, 48 mg, 0.46 mmol, 1.1 equiv.) and CuCN·2LiCl solution (0.46 mL, 1.0 M in THF, 0.46 mmol, 1.1 equiv.) dissolved in THF (1 mL) at 0 °C. The reaction mixture was stirred for further 2 h at 0 °C before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 8:2) afforded **14f** as a light yellow powder (64 mg, 0.33 mmol, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 – 8.14 (m, 1H), 7.96 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.85 (td, *J* = 7.9, 0.9 Hz, 1H), 2.57 (tt, *J* = 7.7, 4.5, 1H), 1.45 (m, *J* = 3.6 Hz, 2H), 1.27 (dq, *J* = 7.6, 3.7 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 198.4, 143.5, 135.8, 133.1, 132.7, 118.6, 115.1, 114.5, 114.3, 20.3, 14.4.

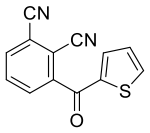
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3083, 2235, 2229, 1668, 1632, 1570, 1444, 1413, 1383, 1293, 1249, 1237, 1188, 1174, 1114, 1076, 1059, 1033, 954, 891, 821, 801, 773, 757, 718, 695.

MS (EI, 70 eV): *m/z* (%) = 196 (32), 156 (33), 127 (100).

HRMS (EI): *m/z* calcd. for [$C_{12}H_8N_2O$]: 196.0637; found: 196.0627 (M^+).

M.p. (°C): 173.0 – 175.0.

3-(Thiophene-2-carbonyl)phthalonitrile (14)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.42 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.63 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing thiophene-2-carbonyl chloride (**16g**, 67 mg, 0.46 mmol, 1.1 equiv.) and CuCN·2LiCl solution (0.46 mL, 1.0 M in THF, 0.46 mmol, 1.1 equiv.) dissolved in THF (1.0 mL) at 0 °C. The reaction mixture was stirred for further 8 h at −20 °C before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 8:2) afforded **14g** as a light yellow powder (76 mg, 0.32 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (d, *J* = 8.0 Hz, 2H), 7.91 – 7.82 (m, 2H), 7.50 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.21 (dd, *J* = 4.9, 3.9 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 183.5, 143.6, 141.8, 137.5, 136.6, 135.2, 132.8, 132.6, 128.9, 118.2, 115.1, 115.0, 113.6.

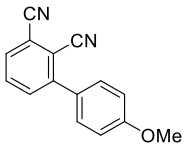
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079, 2237, 2230, 1635, 1574, 1511, 1438, 1405, 1352, 1302, 1289, 1231, 1203, 1164, 1075, 1063, 1034, 1000, 954, 946, 918, 866, 822, 799, 762, 752, 720, 676.

MS (EI, 70 eV): *m/z* (%) = 238 (51), 210 (35), 111 (100), 83 (11).

HRMS (EI): *m/z* calcd. for [$C_{13}H_6N_2OS$]: 238.0201; found: 238.0194 (M^+).

M.p. (°C): 160.0 – 163.0.

4'-Methoxy-[1,1'-biphenyl],-2,3-dicarbonitrile (14h)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.44 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.66 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (**16h**, 113 mg, 0.49 mmol, 1.1 equiv.), $Pd(OAc)_2$ (2.0 mg, 2 mol%) and SPhos (7.2 mg, 4 mol%) dissolved in THF (1 mL) at 25 °C. The reaction mixture was stirred overnight before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 9:1) afforded **14h** as a pale brown solid (89 mg, 0.38 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.76 – 7.72 (m, 3H), 7.55 – 7.49 (m, 2H), 7.06 – 7.02 (m, 2H), 3.88 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.8, 147.1, 134.0, 132.8, 131.5, 130.1, 128.7, 117.3, 115.8, 115.5, 114.6, 114.1, 55.5.

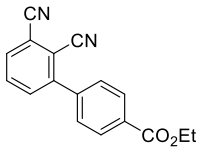
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2225, 1608, 1580, 1523, 1514, 1460, 1442, 1308, 1298, 1249, 1178, 1117, 1082, 1026, 991, 861, 840, 820, 802, 783, 769, 743, 725, 683.

MS (EI, 70 eV): *m/z* (%) = 235 (18), 234 (100), 219 (6), 191 (28), 165 (10), 164 (10), 138 (5), 43 (6).

HRMS (EI): *m/z* calcd. for [$C_{15}H_{10}N_2O$]: 234.0793; found: 234.0783 (M^+).

M.p. (°C): 200.3 – 201.5.

Ethyl 2',3'-dicyano-[1,1'-biphenyl]-4-carboxylate (14)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.44 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.66 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing ethyl 4-iodobenzoate (**16i**, 134 mg, 0.48 mmol, 1.1 equiv.), $Pd(OAc)_2$ (2.0 mg, 2 mol%) and SPhos (7.2 mg, 4 mol%) dissolved in THF (1 mL) at 25 °C. The reaction mixture was stirred overnight before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 9:1 → 7:3) afforded **14i** as a light brown solid (99 mg, 0.36 mmol, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 – 8.18 (d, *J* = 8.4 Hz, 2H), 7.86 – 7.77 (m, 3H), 7.63 – 7.61 (d, *J* = 8.4 Hz, 2H), 4.44 – 4.39 (q, *J* = 7 Hz, 2H), 1.44 – 1.40 (t, *J* = 7 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 146.4, 140.6, 134.1, 133.3, 132.7, 131.8, 130.4, 128.9, 117.6, 115.6, 115.0, 114.7, 61.5, 14.4.

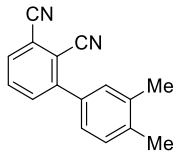
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2230, 1716, 1613, 1582, 1456, 1400, 1370, 1312, 1296, 1282, 1188, 1128, 1102, 1024, 1016, 863, 845, 814, 768, 743, 704.

MS (EI, 70 eV): *m/z* (%) = 276 (21), 248 (45), 232 (20), 230 (100), 204 (24), 203 (32), 202 (12), 176 (28).

HRMS (EI): *m/z* calcd. for [$C_{17}H_{12}N_2O_2$]: 276.0899; found: 276.0893 (M^+).

M.p. (°C): 168.4 – 171.6.

3',4'-Dimethyl-[1,1'-biphenyl]-2,3-dicarbonitrile (14j)



According to **TP 5**, injection loop A and B were loaded with solutions of 1,2-dicyanobenzene (**11a**, 0.37 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.56 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 4-iodo-1,2-dimethylbenzene (**16l**, 95 mg, 0.41 mmol, 1.1 equiv.), $Pd(OAc)_2$ (1.7 mg, 2 mol%) and SPhos (6.1 mg, 4 mol%) dissolved in THF (1 mL) at 25 °C. The reaction mixture was stirred overnight before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 7:3) afforded **14j** as a light brown solid (65 mg, 0.28 mmol, 76%).

scale-up:

The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A (4.0 mL) was loaded with TMPLi (0.6 M in dry THF, 1.5 equiv.) and injection loop B (4.0 mL) was loaded with the reactant solution (**11a**, 0.40 M in dry THF containing 0.5 equiv. $ZnCl_2$ additive). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.50 mL min^{-1}), which passed a pre-cooling loop (1 mL, residence time: 40 s, 0 °C) respectively, before they were mixed in a coiled reactor (1 mL, residence time: 20 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 4-iodo-1,2-dimethylbenzene (**16m**, 2.04 g, 8.80 mmol, 1.1 equiv.), $Pd(OAc)_2$ (36 mg, 2 mol%) and SPhos (131 mg, 4 mol%) dissolved in THF (20 mL) at 25 °C. After 3 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. This procedure was repeated 5 times for a total amount of 8 mmol. The reaction mixture was stirred overnight before it was quenched with sat. aq. NH_4Cl (60 mL). The aq. layer was extracted with EtOAc (3×100 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 9:1) afforded **14j** as a light brown solid (1.43 g, 6.16 mmol, 77%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 – 7.72 (m, 3H), 7.31 – 7.29 (m, 3H), 2.35 (s, 3H), 2.34 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 147.7, 138.7, 137.6, 134.2, 134.1, 132.9, 131.8, 130.4, 129.9, 126.2, 117.4, 116.0, 115.6, 114.4, 20.0, 19.8.

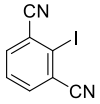
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3067, 2968, 2918, 2856, 1612, 1584, 1506, 1459, 1394, 1379, 1276, 1198, 1028, 995, 909, 838, 816, 800, 772, 744, 740, 716.

MS (EI, 70 eV): *m/z* (%) = 233 (17), 232 (100), 231 (69), 218 (10), 217 (66), 204 (11), 190 (29).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{12}N_2$]: 232.1000; found: 232.0996 (M^+).

M.p. (°C): 185.6 – 286.1.

2-Iodoisophthalonitrile (15a)



According to **TP 6**, injection loop A and B were loaded with solutions of 1,3-dicyanobenzene (**11b**, 0.34 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.51 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing I_2 (**16a**, 104 mg, 0.41 mmol, 1.2 equiv. dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min before it was quenched with sat. aq. $Na_2S_2O_3$ (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 19:1) afforded **15a** as a light brown solid (68 mg, 0.27 mmol, 79%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.80 – 7.78 (d, *J* = 8 Hz, 2H), 7.64 – 7.60 (t, *J* = 8 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 137.3, 129.2, 123.6, 118.3, 103.8.

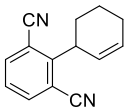
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3133, 3092, 3055, 3002, 2925, 2854, 2238, 2232, 1743, 1569, 1451, 1404, 1271, 1237, 1106, 1024, 879, 804, 704.

MS (EI, 70 eV): *m/z* (%) = 255 (9), 254 (100), 127 (9).

HRMS (EI): *m/z* calcd. for [$C_8H_3IN_2$]: 253.9341; found: 253.9351 (M^+).

M.p. (°C): 208.4 – 211.4.

1',2',3',4'-Tetrahydro-[1,1'-biphenyl]-2,6-dicarbonitrile (15b)

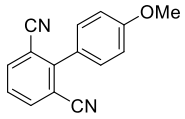


According to **TP 6**, injection loop A and B were loaded with solutions of 1,3-dicyanobenzene (**11b**, 0.38 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.56 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 3-bromocyclohexene (**16b**, 48 mg, 0.30 mmol, 0.8 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 10 mol%) dissolved in THF (1 mL) at 0 °C. The reaction mixture was stirred for further 2 h at 0 °C before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed

in vacuo. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 19:1) afforded **15b** as a white solid (56 mg, 0.27 mmol, 88%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.86 – 7.84 (d, *J* = 8 Hz, 2H), 7.46 – 7.42 (t, *J* = 8 Hz, 1H), 6.10 – 6.05 (m, 1H), 5.58 – 5.55 (m, 1H), 4.18 – 4.11 (m, 1H), 2.33 – 2.22 (m, 1H), 2.19 – 2.04 (m, 2H), 1.99 – 1.89 (m, 2H), 1.81 – 1.70 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.2, 138.0, 131.9, 127.6, 125.3, 116.4, 114.2, 41.8, 29.9, 24.4, 22.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 3025, 2933, 2861, 2836, 2230, 1580, 1457, 1442, 1265, 1222, 1136, 982, 916, 898, 847, 806, 748, 723, 709.
MS (EI, 70 eV): *m/z* (%) = 209 (11), 208 (92), 207 (100), 192 (23), 191 (44), 190 (33), 180 (22), 179 (27), 167 (11), 153 (13), 140 (11).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{12}N_2$]: 208.1000; found: 207.0925 (M^+).
M.p. (°C): 106.2 – 106.9.

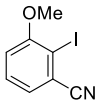
4'-Methoxy-[1,1'-biphenyl]-2,6-dicarbonitrile (15c)



According to **TP 6**, injection loop A and B were loaded with solutions of 1,3-dicyanobenzene (**11b**, 0.38 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.56 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (**16h**, 70 mg, 0.30 mmol, 0.8 equiv.), $Pd(OAc)_2$ (1.7 mg, 2 mol%) and SPhos (6.1 mg, 4 mol%) dissolved in THF (1 mL). The reaction mixture was stirred overnight before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 9:1) afforded **15c** as colorless crystals (56 mg, 0.24 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.96 – 7.94 (d, *J* = 8 Hz, 2H), 7.57 – 7.53 (t, *J* = 8 Hz, 1H), 7.50 – 7.47 (m, 2H), 7.09 – 7.05 (m, 2H), 3.89 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.2, 148.9, 137.3, 130.9, 128.0, 126.4, 117.1, 114.6, 114.5, 55.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 3007, 2932, 2840, 2233, 1729, 1608, 1582, 1517, 1449, 1440, 1299, 1252, 1180, 1153, 1033, 1017, 911, 834, 807, 755.
MS (EI, 70 eV): *m/z* (%) = 235 (18), 234 (100), 203 (8), 191 (23), 165 (9), 164 (10).
HRMS (EI): *m/z* calcd. for [$C_{15}H_{10}N_2O$]: 234.0793; found: 234.0800 (M^+).
M.p. (°C): 174.4 – 176.1.

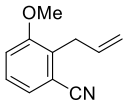
2-Iodo-3-methoxybenzonitrile (15d)



According to the **TP 7**, injection loop A and B were loaded with solutions of 3-methoxybenzonitrile (**11c**, 0.34 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.52 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing I_2 (**16a**, 104 mg, 0.41 mmol, 1.2 equiv. dissolved in THF (1 mL). The reaction mixture was stirred for further 10 min before it was quenched with sat. aq. $Na_2S_2O_3$ (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 19:1) afforded **15d** as colorless crystals (72 mg, 0.28 mmol, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 – 7.38 (t, *J* = 8 Hz, 1H), 7.23 – 7.20 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.00 – 6.98 (dd, *J* = 8.0, 1.4 Hz, 1H), 3.92 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.3, 130.1, 126.5, 122.3, 119.5, 114.6, 91.2, 56.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3131, 3080, 2969, 2941, 1926, 1836, 2228, 1579, 1562, 1462, 1420, 1408, 1290, 1269, 1190, 1063, 1024, 1013, 896, 798, 791, 704.
MS (EI, 70 eV): *m/z* (%) = 260 (7), 259 (100), 244 (15), 216 (6), 117 (13), 102 (5).
HRMS (EI): *m/z* calcd. for [C_8H_6INO]: 258.9494; found: 258.9495 (M^+).
M.p. (°C): 127.1 – 127.9.

2-Allyl-3-methoxybenzonitrile (15e)



According to **TP 7**, injection loop A and B were loaded with solutions of 3-methoxybenzonitrile (**11c**, 0.38 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.56 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing allylbromide (**16c**, 36 mg, 0.30 mmol, 0.8 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 10 mol%) dissolved in THF (1 mL) at 0 °C. The reaction mixture was stirred for further 2 h at 0 °C before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 19:1) afforded **15e** as a colorless liquid (30 mg, 0.17 mmol, 58%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.24 – 7.22 (m, 1H), 7.19 – 7.17 (m, 1H), 7.05 – 7.02 (m, 1H), 5.93 – 5.85 (m, 1H), 5.07 – 4.99 (m, 2H), 3.83 (s, 3H), 3.59 – 3.56 (d, 2H).

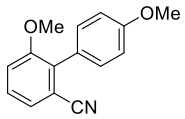
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.6, 134.6, 132.8, 128.2, 124.6, 118.0, 116.3, 114.9, 113.8, 56.0, 33.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3081, 3010, 2943, 2840, 2227, 1638, 1580, 1469, 1439, 1321, 1289, 1268, 1238, 1211, 1112, 1059, 993, 863, 786, 740, 690, 683.

MS (EI, 70 eV): *m/z* (%) = 173 (52), 159 (20), 158 (29), 140 (29), 130 (100), 116 (80), 115 (20), 103 (35), 89 (25).

HRMS (EI): *m/z* calcd. for [$C_{11}H_{11}NO$]: 173.0841; found: 173.0841 (M^+).

4'-6-Dimethoxy-[1,1'-biphenyl]-2-carbonitrile (15f)



According to **TP 7**, injection loop A and B were loaded with solutions of 3-methoxybenzonitrile (**11c**, 0.38 M containing 0.5 equiv. $ZnCl_2$, 1 mL) and TMPLi (0.56 M, 1 mL). After injection and in situ trapping metalation the combined streams were collected in a flask containing 4-iodoanisole (**16h**, 70 mg, 0.30 mmol, 0.8 equiv.), $Pd(OAc)_2$ (1.7 mg, 2 mol%) and SPhos (6.1 mg, 4 mol%) dissolved in THF (1 mL). The reaction mixture was stirred overnight before it was quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3×15 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 9:1) afforded **15f** as a light brown solid (57 mg, 0.24 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 – 7.35 (m, 3H), 7.34 – 7.32 (m, 1H), 7.18 – 7.16 (m, 1H), 7.02 – 6.99 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.7, 157.1, 134.6, 131.4, 128.8, 126.4, 125.2, 118.6, 115.4, 114.0, 113.8, 56.1, 55.3.

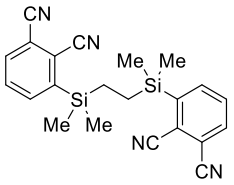
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2937, 2838, 2226, 1609, 1579, 1516, 1464, 1456, 1437, 1412, 1298, 1262, 1245, 1178, 1110, 1067, 1035, 1018, 1000, 907, 831, 792, 745.

MS (EI, 70 eV): *m/z* (%) = 240 (15), 239 (100), 224 (17), 209 (9), 193 (7), 153 (7).

HRMS (EI): *m/z* calcd. for [$C_{15}H_{13}NO_2$]: 239.0946; found: 239.0942 (M^+).

M.p. (°C): 99.5 – 100.3.

3,3'-(Ethane-1,2-diylbis(dimethylsilanediyl))diphthalonitrile (17)



The flow system (FlowSyn, Uniqsis) was dried by flushing it with dry THF (flow rate of all pumps: 1.00 mL min^{-1}, run-time: 30 min). Injection loop A (4.0 mL) was loaded with *i*-PrMgCl·LiCl (0.45 M in dry THF, 0.9 equiv.) and injection loop B (4.0 mL) was loaded with 3-iodophthalonitrile (**14a**, 0.5 M in dry THF, 1.0 equiv.). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 0.75 mL min^{-1}) and mixed in a coiled reactor (1 mL, residence time: 30 s, 25 °C). The combined streams were collected in a flame-dried, argon flushed 25 mL flask equipped with a magnetic stirrer and a septum containing 1,2-bis(chlorodimethylsilyl)ethane (**16k**, 1.935 g, 9 mmol, 0.6 equiv.) in THF (20 mL) at room temperature. After 8 min, the injection loops were reloaded with the reactant solution and *i*-PrMgCl·LiCl, injected into the separate THF streams again and collected in the same flask as well. This reload was repeated 5 times to reach a total volume of 30 mL reactant solution (15 mmol). After collection in the flask containing the electrophile the mixture was stirred for another hour at room temperature before it was quenched with sat. aq. NH_4Cl (200 mL). The aq. layer was extracted with EtOAc (3×300 mL), the combined organic fractions were dried over anhydrous Mg_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, *i*-hex:EtOAc = 10:1) afforded **17** as a white solid (1.605 g, 4.03 mmol, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 – 7.82 (dd, *J* = 8.0 Hz, *J* = 1.4 Hz, 1H), 7.80 – 7.78 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.71 – 7.68 (t, *J* = 8.0 Hz, 1H), 0.84 (s, 2H), 0.45 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 146.3, 139.0, 133.7, 131.9, 120.4, 117.2, 116.5, 116.0, 6.8, −3.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 2965, 2922, 2891, 2234, 2226, 1568, 1560, 1407, 1274, 1252, 1209, 1147, 1137, 1066, 942, 853, 842, 808, 782, 759, 716, 702.

MS (EI, 70 eV): *m/z* (%) = 399 (19), 398 (54), 397 (38), 385 (11), 384 (29), 383 (83), 371 (18), 370 (45), 369 (35), 362 (15), 361 (42), 348 (11), 186 (18), 185 (100), 170 (10), 144 (22), 130 (14), 117 (12), 116 (11), 43 (16).

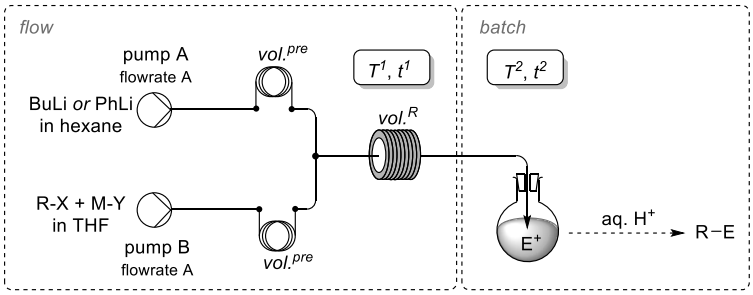
HRMS (EI): *m/z* calcd. for [$C_{22}H_{22}N_4Si_2$]: 398.1383; found: 398.1376 (M^+).

M.p. (°C): 142.4 – 143.4.

4 Preparation of Polyfunctional Diorgano-Magnesium and –Zinc Reagents Using In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuos Flow

4.1 Typical Procedure (TP 8)

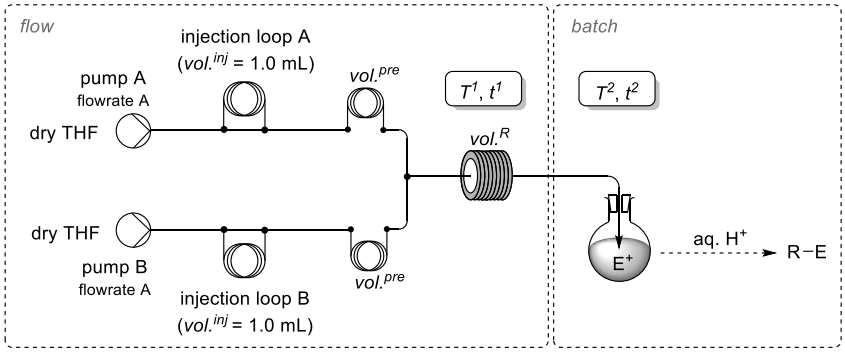
Typical procedure using a Vapourtec E-series flow setup



Scheme 47: General flow setup for the in situ trapping halogen-lithium exchange using a Vapourtec E-series flow setup.

A *n*-BuLi or PhLi solution in hexane (0.3 M, 1.5 equiv.) and a solution of the aryl halide substrate (R – X, 0.20 M, 1.0 equiv.) and metallic salt (M – Y, 0.1 M, 0.5 equiv.) in THF were prepared. The solutions were pumped from their flasks through a suction needle at flow rate A = 3.0 – 10.0 mL min^{-1} and flow rate B = flow rate A. After passing a PTFE tubing (vol^{pre} = 1.0 – 2.0 mL, T^1 = −78 – 0°C, residence time: 6 – 20 s) for precooling, the solutions were mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (vol^R = 0.02 – 5.3 mL, residence time: t^1 = 0.06 – 53.0 s, T^1 = −78 – 25 °C) and was subsequently injected in a flask containing a stirred, cooled (T^1 = −40 – 25°C) solution of an electrophile E^+ (1.2 – 2.5 equiv.) and catalyst, if applicable, in 1 mL THF per mmol of substrate. The reaction mixture was stirred further for the indicated times and temperatures (T^2, reaction time: t^2) and quenched with sat. aq. NH_4Cl solution. The aq. phase was extracted with EtOAc and the organic phases were dried and filtrated. After removal of the solvent *in vacuo*, flash column chromatographical purification with suited *i*-hex:EtOAc mixtures afforded the pure products R – E.

Typical procedure using a Uniqsis flow setup

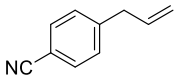


Scheme 48: General flow setup for the in situ trapping halogen-lithium exchange using a Uniqsis flow setup.

A *n*-BuLi or PhLi solution in hexane (0.3 M, 1.5 equiv.) and a solution of the aryl halide substrate (R – X, 0.20 M, 1.0 equiv.) and metallic salt (M – Y, 0.1 M, 0.5 equiv.) in THF were prepared. Injection loop A (vol^{inj} = 1.0 – 2.0 mL) was loaded with the exchange reagent (*n*-BuLi or PhLi) and injection loop B (vol^{inj} = 1.0 – 2.0 mL) was loaded with the solution of the substrate (R – X) and the metallic salt M – Y The solutions were simultaneously injected into separate streams of hexane and THF, respectively (pump A: THF, pump B: THF, flow rates: 3.0 – 10.0 mL min^{-1}), which each passed a pre-cooling loop (vol^{pre} = 1.0 – 2.0 mL, T^1 = −78 – 0°C, residence time: 6 – 20 s), before they were mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (vol^R = 0.02 – 5.3 mL, residence time: t^1 = 0.06 – 53.0 s, T^1 = −78 – 25 °C) and was subsequently injected in a flask containing a stirred, cooled (T^1 = −40 – 25°C) solution of an electrophile E^+ (1.1 – 2.5 equiv.) and catalyst, if applicable, in 1 mL THF per mmol of substrate. The reaction mixture was stirred further further for the indicated times and temperatures (T^2, reaction time: t^2) and quenched with sat. aq. NH_4Cl solution. The aq. phase was extracted with EtOAc and the organic phases were dried and filtrated. After removal of the solvent *in vacuo*, flash column chromatographical purification with suited *i*-hex:EtOAc mixtures afforded the pure products R – E.

4.2 Preparation of the products

4-Allylbenzonitrile (20a)

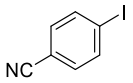


According to **TP 8**, a solution of 4-bromobenzonitrile (**18a**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (**21a**, 121 mg, 1.0 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in

THF. Stirring was continued for 10 min at 25 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, purification *via* HPLC afforded the title compound **20a** as a pale yellow oil (40 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.58 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 5.92 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 0H), 5.17 – 5.04 (m, 1H), 3.44 (d, *J* = 6.7 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 145.8, 135.8, 132.4 (2C), 129.5 (2C), 119.2, 117.4, 110.2, 40.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2922, 2854, 2228, 1608, 1458, 1374, 1260, 1176, 1096, 994, 918, 814, 702.
MS (EI, 70 eV): *m/z* (%) = 144 (11), 143 (98), 142 (100), 140 (20), 116 (37), 115 (75), 89 (15).
HRMS (EI): *m/z* calcd. for $[C_{10}H_8N]$: 142.0657, found 142.0650 ($M^+ - H$).

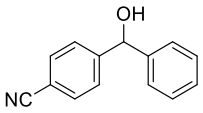
4-Iodobenzonitrile (20b)



According to **TP 8**, a solution of 4-bromobenzonitrile (**18a**, 0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred solution of iodine (**21b**, 254 mg, 1.00 mmol, 2.5 equiv.) in THF. Stirring was continued for 10 min at 25 °C before sat. aq. $Na_2S_2O_3$ solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 49:1) afforded the title compound **20b** as a pale yellow powder (75 mg, 0.33 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 – 7.73 (m, 2H), 7.46 – 7.30 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 138.7 (2C), 133.3 (2C), 118.3, 111.9, 100.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2958, 2926, 2870, 2226, 1910, 1684, 1644, 1588, 1578, 1474, 1390, 1370, 1342, 1302, 1274, 1244, 1222, 1204, 1112, 1056, 1010, 962, 816, 766, 732, 700.
MS (EI, 70 eV): *m/z* (%) = 229 (100), 130 (12).
HRMS (EI): *m/z* calcd. for $[C_7H_4IN]$: 228.9388; found 228.9382 (M^+).
M.p. (°C): 170.2 – 170.8.

4-(Hydroxy(phenyl)methyl)benzonitrile (20c)



According to **TP 8**, a solution of 4-bromobenzonitrile (**18a**, 0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of benzaldehyde (**21c**, 64 mg, 0.60 mmol, 1.5 equiv.) in THF. Stirring was continued for 1 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **20c** as colorless crystals (58 mg, 0.28 mmol, 70% yield).

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

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.0, 142.9, 132.3 (2C), 129.0 (2C), 128.4, 127.1 (2C), 126.8 (2C), 118.9, 111.2, 75.7.

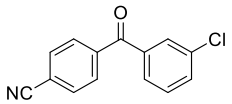
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3462, 3418, 2926, 2882, 2870, 2232, 2226, 1663, 1608, 1599, 1513, 1503, 1491, 1450, 1404, 1339, 1320, 1276, 1230, 1187, 1172, 1114, 1079, 1044, 1027, 1018, 862, 846, 802, 770, 732, 723, 702, 675.

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

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

M.p. (°C): 80.7 – 81.0.

4-(3-Chlorobenzoyl)benzonitrile (20d)

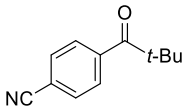


According to **TP 8**, a solution of 4-bromobenzonitrile (**18a**, 0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-chlorobenzoyl chloride (**21d**, 105 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 1 h at 0 °C before sat. aq. NH_4Cl solution was added to

quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 49:1) afforded the title compound **20d** as a white solid (81 mg, 0.34 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 – 7.84 (m, 2H), 7.84 – 7.78 (m, 2H), 7.76 (t, *J* = 1.8 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.46 (t, *J* = 7.9 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.7, 140.6, 138.1, 135.1, 133.4, 132.4 (2C), 130.3 (2C), 130.1, 130.0, 128.2, 118.0, 116.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3091, 3076, 3064, 2923, 2854, 2228, 1728, 1646, 1606, 1588, 1567, 1463, 1416, 1403, 1312, 1292, 1279, 1268, 1247, 1180, 1149, 1120, 1074, 1019, 999, 969, 961, 929, 900, 853, 817, 789, 753, 730, 707, 672, 663.
MS (EI, 70 eV): *m/z* (%) = 241 (35), 226 (11), 225 (14), 191 (10), 190 (45), 140 (22), 139 (100), 130 (45), 111 (37), 102 (36), 75 (13), 50 (10), 44 (30), 43 (17).
HRMS (EI): *m/z* calcd. for [$C_{14}H_8ClNO$]: 241.0294; found 241.0286 (M^+).
M.p. (°C): 95.4 – 95.8.

4-Pivaloylbenzonitrile (20e)

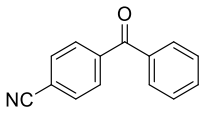


According to **TP 8**, a solution of 4-bromobenzonitrile (**18a**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of pivaloyl chloride (**21e**, 72 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 1 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 49:1) afforded the title compound **20e** as a colorless oil (58 mg, 0.31 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.69 (s, 4H), 1.31 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 208.5, 142.9, 132.1 (2C), 128.1 (2C), 118.2, 114.3, 44.5, 27.7 (3C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2933, 2896, 2872, 2231, 2168, 1678m 1478, 1465, 1400, 1367, 1275, 1220, 1192, 1170, 1118, 1034, 1018, 965, 953, 844, 766, 697.

MS (EI, 70 eV): *m/z* (%) = 131 (17), 130 (21), 103 (15), 102 (18), 57 (100), 41 (27).
HRMS (EI): *m/z* calcd. for [$C_{12}H_{13}NO$]: 187.0997; found 187.0999 (M^+).

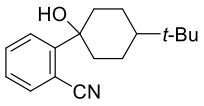
4-Benzoylbenzonitrile (20f)



According to **TP 8**, a solution of 4-bromobenzonitrile (**18a**, 0.20 M, 0.40 mmol) and CuCN·2LiCl (0.22 M, 0.22 mmol, 1.1 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of benzoyl chloride (**21f**, 84 mg, 0.60 mmol, 1.5 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 19:1) afforded the title compound **20f** as a white solid (66 mg, 0.32 mmol, 80% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 – 7.85 (m, 2H), 7.82 – 7.76 (m, 4H), 7.67 – 7.61 (m, 1H), 7.55 – 7.48 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.1, 141.4, 136.5, 133.5, 132.3 (2C), 130.4 (2C), 130.2 (2C), 128.8 (2C), 118.1, 115.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 2924, 2226, 1648, 1594, 1578, 1556, 1544, 1446, 1404, 1308, 1276, 1210, 1174, 1144, 1114, 1072, 1018, 1000, 966, 940, 928, 856, 794, 734, 692, 676.
MS (EI, 70 eV): *m/z* (%) = 207 (48), 206 (10), 130 (26), 105 (100), 77 (25).
HRMS (EI): *m/z* calcd. for [$C_{14}H_9NO$]: 207.0684; found 207.0679 (M^+).
M.p. (°C): 113.8 – 114.1.

2-(4-(*tert*-Butyl)-1-hydroxycyclohexyl)benzonitrile (20g)

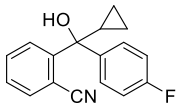


According to **TP 8**, a solution of 2-bromobenzonitrile (**18b**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-(*tert*-butyl)cyclohexan-1-one (**21g**, 85 mg, 0.55 mmol, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three

times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 7:3) afforded the title compound **20g** as a white solid (99 mg, 0.36 mmol, 73% yield, d.r. 84:16).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.81 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.52 (td, *J* = 7.5, 1.1 Hz, 1H), 7.43 (td, *J* = 7.5, 1.0 Hz, 1H), 7.24 (dt, *J* = 7.6, 0.9 Hz, 1H), 1.86 – 1.73 (m, 5H), 1.65 – 1.50 (m, 2H), 1.24 – 1.11 (m, 1H), 0.92 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 152.2, 132.1 (2C), 128.7 (2C), 124.1, 120.7, 88.2, 47.2, 37.4 (2), 32.7, 27.7 (3C), 23.6 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3286, 2942, 2868, 2224, 1744, 1676, 1660, 1466, 1438, 1364, 1310, 1240, 1148, 1062, 1008, 924, 904, 854, 840, 756, 694, 656.
MS (EI, 70 eV): *m/z* (%) = 201 (10), 200 (12), 160 (14), 160 (14), 159 (100), 158 (52), 146 (10), 145 (13), 130 (17).
HRMS (EI): *m/z* calcd. for [$C_{17}H_{23}NO$]: 257.1780; found 257.1773 (M^+).
M.p. (°C): 73.4 – 74.6.

2-(Cyclopropyl(4-fluorophenyl)(hydroxy)methyl)benzonitrile (20h)



According to **TP 8**, a solution of 2-bromobenzonitrile (**18b**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl(4-fluorophenyl)methanone (**21h**, 90 mg, 0.55 mmol, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 7:3) afforded the title compound **20h** as a colorless crystals (93 mg, 0.35 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.85 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.41 (m, 4H), 7.27 – 7.21 (m, 1H), 7.05 – 6.95 (m, 2H), 1.71 (tt, *J* = 8.3, 5.4 Hz, 1H), 0.72 – 0.63 (m, 1H), 0.58 – 0.50 (m, 1H), 0.50 – 0.38 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.5 (d, *J* = 247.4 Hz), 149.8, 137.7, 137.7, 132.3 (2C), 129.0, 128.1 (d, *J* = 8.2 Hz, 2C), 124.0, 122.3, 115.4 (d, *J* = 21.5 Hz, 2C), 89.8, 19.8, 2.3, 1.7.

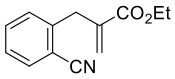
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3296, 3012, 1764, 1676, 1604, 1508, 1466, 1368, 1336, 1304, 1226, 1160, 1046, 1004, 966, 950, 898, 830, 752, 714, 662.

MS (EI, 70 eV): *m/z* (%) = 239 (21), 227 (14), 226 (100), 130 (31).

HRMS (EI): *m/z* calcd. for [$C_{17}H_{14}FNO$]: 267.1059; found 268.1136 (M^+).

M.p. (°C): 112.7 – 114.0.

Ethyl 2-(2-cyanobenzyl)acrylate (20i)



According to **TP 8**, a solution of 2-bromobenzonitrile (**18b**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of ethyl 2-(bromomethyl)acrylate (**21i**, 138 µL, 1.0 mmol, 2.0 equiv.) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 30 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **20i** as a colorless oil (73 mg, 0.34 mmol, 68% yield).

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

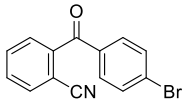
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.3, 142.7, 138.2, 133.0, 132.8, 130.3, 127.6, 127.1, 118.0, 113.1, 61.1, 36.6, 14.2.

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

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

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

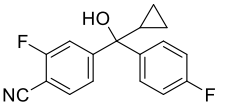
2-(4-Bromobenzoyl)benzonitrile (20j)



According to **TP 8**, a solution of 2-bromobenzonitrile (**18b**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-bromobenzoyl chloride (**21j**, 165 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **20j** as colorless crystals (111 mg, 0.39 mmol, 78% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.88 – 7.83 (m, 1H), 7.75 – 7.60 (m, 7H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 192.9, 141.1, 134.9, 134.4, 132.4, 132.2 (2C), 131.8 (2C), 131.7, 130.0, 129.5, 117.0, 112.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2854, 2226, 1732, 1662, 1580, 1476, 1428, 1306, 1292, 1272, 1192, 1180, 1068, 1010, 926, 840, 766, 754, 730, 716, 678.
MS (EI, 70 eV): *m/z* (%) = 207 (15), 206 (100), 185 (10), 185 (50), 183 (11), 183 (51), 130 (13).
HRMS (EI): *m/z* calcd. for [$C_{14}H_8BrNO$]: 284.9789; found 284.9785 (M^+).
M.p. (°C): 148.1 – 150.2.

4-(Cyclopropyl(4-fluorophenyl)(hydroxy)methyl)-2-fluorobenzonitrile (20k)

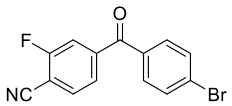


According to **TP 8**, a solution of 4-bromo-2-fluorobenzonitrile (**18c**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl(4-fluorophenyl)methanone (**21h**, 90 mg, 0.55 mmol, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical

purification (silica gel, *i*-hex:EtOAc = 92:8) afforded the title compound **20k** as colorless crystals (105 mg, 0.37 mmol, 74% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.53 (dd, *J* = 8.1, 6.5 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.34 (dd, *J* = 10.4, 1.6 Hz, 1H), 7.24 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.07 – 6.97 (m, 2H), 2.08 (s, 1H), 1.63 – 1.50 (m, 1H), 0.82 – 0.68 (m, 1H), 0.60 – 0.40 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.0 (d, *J* = 78.8 Hz), 161.5 (d, *J* = 67.7 Hz), 156.2 (d, *J* = 6.9 Hz), 141.4 (d, *J* = 3.3 Hz), 133.0, 128.9 (d, *J* = 8.2 Hz, 2C), 123.2, 123.1, 115.4 (d, *J* = 21.4 Hz, 2C), 114.7 (d, *J* = 20.8 Hz), 114.1, 99.7 (d, *J* = 15.6 Hz), 21.5, 2.7, 1.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3418, 2244, 1618, 1602, 1568, 1504, 1496, 1422, 1342, 1220, 1158, 1106, 1044, 996, 874, 824, 800, 736.
MS (EI, 70 eV): *m/z* (%) = 258 (16), 259 (100), 244 (12), 161 (11), 148 (18), 148 (59), 123 (25), 109 (26).
HRMS (EI): *m/z* calcd. for [$C_{17}H_{13}F_2NO$]: 285.0965; found 285.0961 (M^+).
M.p. (°C): 78.4 – 78.9.

4-(4-Bromobenzoyl)-2-fluorobenzonitrile (20l)



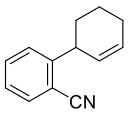
According to **TP 8**, a solution of 4-bromo-2-fluorobenzonitrile (**18c**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-bromobenzoyl chloride (**21j**, 165 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 97:3) afforded the title compound **20l** as a colorless crystals (112 mg, 0.37 mmol, 74% yield).

scale-up:
In addition, a sufficient scale-up of the reaction was demonstrated according to **TP 8**. A solution of 4-bromo-2-fluorobenzonitrile (**18c**, 0.20 M, 10 mmol) and $MgCl_2$·LiCl (0.1 M, 5 mmol, 0.5 equiv.) in THF (total volume: 50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 15 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The flow rates were constant over a total runtime of 660 sec. The combined stream passed a 0.25 mL reactor

tube (1.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-bromobenzoyl chloride (**21j**, 3.30 g, 11 mmol, 1.1 equiv.) in THF. Stirring was continued for 3 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×100 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 92:8) afforded the title compound **20l** as colorless crystals (2.31 g, 7.6 mmol, 76%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.78 (dd, *J* = 7.8, 6.4 Hz, 1H), 7.71 – 7.56 (m, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 192.6 (d, *J* = 1.7 Hz), 163.0 (d, *J* = 261.9 Hz), 143.4 (d, *J* = 6.5 Hz), 134.6, 133.9, 132.3 (2C), 131.5 (2C), 129.2, 125.8 (d, *J* = 3.9 Hz), 117.5 (d, *J* = 20.9 Hz), 113.2, 105.2 (d, *J* = 15.8 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2236, 1660, 1584, 1564, 1494, 1418, 1396, 1298, 1274, 1216, 1104, 1068, 1010, 896, 872, 858, 840, 826, 754, 686.
MS (EI, 70 eV): *m/z* (%) = 185 (13), 185 (97, 183 (13), 183 (100), 157 (19), 155 (19), 148 (15), 148 (10), 100 (11), 76 (10), 75 (10).
HRMS (EI): *m/z* calcd. for [$C_{14}H_7BrFNO$]: 302.9695; found 302.9687 (M^+).
M.p. (°C): 114.0 – 115.4.

1',2',3',4'-Tetrahydro-[1,1'-biphenyl]-2-carbonitrile (20m)



According to **TP 8**, a solution of 2-iodobenzonitrile (**18d**, 0.20 M, 0.40 mmol) and $ZnCl_2$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-bromocyclohexene (**21k**, 161 mg, 1.00 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 10 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 99:1) afforded the title compound **20m** as pale yellow oil (59 mg, 0.32 mmol, 80% yield).

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

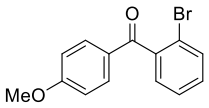
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 150.4, 133.0, 132.9, 130.1, 128.4, 128.1, 126.7, 118.2, 112.1, 40.2, 31.7, 25.0, 21.0.

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

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

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

(2-Bromophenyl)(4-methoxyphenyl)methanone (20n)



According to **TP 8**, a solution of 1-bromo-4-methoxybenzene (**18e**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 5 mL reactor tube (12 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 2-bromobenzoyl chloride (**21l**, 165 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **20n** as colorless crystals (98 mg, 0.34 mmol, 68% yield).

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

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 194.6, 164.3, 141.2, 133.2, 132.8 (2C), 131.0, 129.2, 128.9, 127.3, 119.5, 114.0 (2C), 55.7.

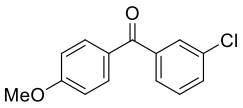
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2972, 2840, 1654, 1596, 1572, 1510, 1486, 1428, 1308, 1292, 1246, 1178, 1150, 1112, 1020, 926, 860, 822, 760, 734, 692, 654.

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

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

M.p. (°C): 92.2 – 93.5.

(3-Chlorophenyl)(4-methoxyphenyl)methanone (20o)



According to **TP 8**, a solution of 1-bromo-4-methoxybenzene (**18e**, 0.20 M, 0.50 mmol) and $MgCl_2 \cdot LiCl$ (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 5 mL reactor tube (12 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-chlorobenzoyl chloride (**21d**, 131 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **20o** as colorless crystals (71 mg, 0.28 mmol, 56% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.82 – 7.78 (m, 2H), 7.72 (dd, *J* = 2.1, 1.5 Hz, 1H), 7.61 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.52 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 6.98 – 6.95 (m, 2H), 3.88 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 194.1, 163.6, 140.1, 134.5, 132.7 (2C), 131.9, 129.7, 129.6, 129.6, 127.9, 113.8 (2C), 55.6.

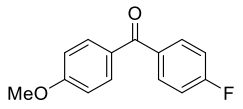
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 2844, 1644, 1602, 1566, 1506, 1456, 1418, 1302, 1282, 1252, 1170, 1152, 1114, 1028, 962, 896, 838, 756, 706, 668.

MS (EI, 70 eV): *m/z* (%) = 246 (22), 135 (100).

HRMS (EI): *m/z* calcd. for $[C_{14}H_{11}ClO_2]$: 246.0448; found 246.0441 (M^+).

M.p. (°C): 71.4 – 72.3.

(4-Fluorophenyl)(4-methoxyphenyl)methanone (20p)

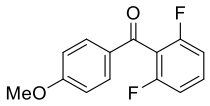


According to **TP 8**, a solution of 1-bromo-4-methoxybenzene (**18e**, 0.20 M, 0.50 mmol) and $MgCl_2 \cdot LiCl$ (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 5 mL reactor tube (12 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-fluorobenzoyl chloride (**21m**, 119 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and

the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **20p** as a white solid (87 mg, 0.34 mmol, 67% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.79 (dt, *J* = 8.8, 2.7 Hz, 4H), 7.14 (t, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 194.2, 165.2 (d, *J* = 253.2 Hz), 163.4, 134.6, 132.5 (2C), 132.4 (d, *J* = 8.9 Hz, 2C), 130.1, 115.4 (d, *J* = 21.8 Hz, 2C), 113.8 (2C), 55.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 1644, 1592, 1570, 1500, 1460, 1418, 1406, 1304, 1286, 1258, 1224, 1146, 1110, 1098, 1020, 960, 928, 852, 840, 764, 676.
MS (EI, 70 eV): *m/z* (%) = 230 (46), 199 (14), 135 (100), 123 (15).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{11}FO_2$]: 230.0743; found 230.0738 (M^+).
M.p. (°C): 86.8 – 88.0.

(2,6-Difluorophenyl)(4-methoxyphenyl)methanone (20q)

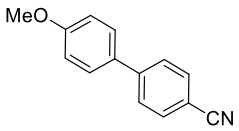


According to **TP 8**, a solution of 1-bromo-4-methoxybenzene (**18e**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 5.0 mL reactor tube (12 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 2,5-difluorobenzoyl chloride (**21n**, 132 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **20q** as colorless crystals (90 mg, 0.31 mmol, 61% yield).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 7.87 – 7.81 (m, 2H), 7.41 (tt, *J* = 8.4, 6.3 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.96 – 6.93 (m, 2H), 3.86 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 187.4, 164.6, 159.8 (dd, *J* = 250.9, 7.7 Hz, 2C), 132.2 (2C), 131.7 (t, *J* = 9.9 Hz), 130.1 , 117.4 (t, *J* = 22.3 Hz), 114.1 (2C) , 111.9 (d, *J* = 22.3 Hz, 2C), 55.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3090, 2940, 2844, 1736, 1650, 1622, 1598, 1574, 1464, 1456, 1424, 1284, 1264, 1236, 1188, 1142, 1120, 1024, 1000, 928, 844, 790, 766, 724, 688, 654.
MS (EI, 70 eV): *m/z* (%) = 248 (42), 141 (11), 135 (100), 77 (10).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{10}F_2O_2$]: 248.0649; found 248.0643 (M^+).

M.p. (°C): 89.9 – 91.1.

4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile (20r)



According to **TP 8**, a solution of 4-bromoanisole (**18e**, 0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 5.0 mL reactor tube (25 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of $ZnCl_2$ (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. The mixture was stirred for 15 min and then PEPPSI-*i*-Pr (5.4 mg, 0.008 mmol, 2 mol%) and 4-iodobenzonitrile (**20b**, 137 mg, 0.6 mmol, 1.5 equiv.) were added. Stirring was continued overnight at 25 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 19:1) afforded the title compound **20r** as colorless crystals (73 mg, 0.35 mmol, 88% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.69 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 3.87 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3, 145.3, 132.7 (2C), 131.6, 128.5 (2C), 127.2 (2C), 119.2, 114.6 (2C), 110.2, 55.5.

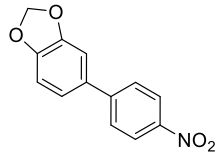
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2222, 1604, 1576, 1514, 1492, 1470, 1446, 1420, 1396, 1312, 1306, 1294, 1266, 1240, 1188, 1176, 1110, 1036, 1020, 1000 970, 936, 854, 822, 812, 768, 738, 718, 698, 666.

MS (EI, 70 eV): *m/z* (%) = 210 (15), 209 (100), 194 (50), 166 (61), 140 (35), 139 (13).

HRMS (EI): *m/z* calcd. for [$C_{14}H_{11}NO$]: 209.0841; found 209.0834 (M^+).

M.p. (°C): 96.9 – 101.2.

5-(4-Nitrophenyl)benzo[d][1,3]dioxole (20s)

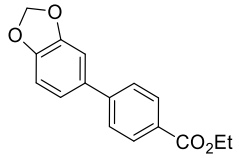


According to **TP 8**, a solution of 5-bromobenzo[*d*][1,3]dioxole (**18f**, 0.20 M, 0.40 mmol) and $MgCl_2 \cdot LiCl$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 18 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 5.0 mL reactor tube (16.7 s,

0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of $ZnCl_2$ (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. The mixture was stirred for 15 min and then PEPPSI-*i*-Pr (5.4 mg, 0.008 mmol, 2 mol%) and 1-iodo-4-nitrobenzene (**21o**, 149 mg, 0.6 mmol, 1.5 equiv.) were added. Stirring was continued overnight at 25 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 99:1) afforded the title compound **20s** as a yellow solid (82 mg, 0.34 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 (dt, *J* = 9.0, 2.6, 2.0 Hz, 2H), 7.65 (dt, *J* = 9.0, 2.5, 2.0 Hz, 2H), 7.15 – 7.06 (m, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.04 (s, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.7, 148.6, 147.4, 146.9, 133.1, 127.5 (2C), 124.3 (2C), 121.6, 109.0, 107.7, 101.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2854, 1594, 1506, 1494, 1478, 1440, 1410, 1334, 1294, 1280, 1258, 1232, 1202, 1186, 1154, 1110, 1032, 1012, 974, 962, 926, 876, 846, 810, 752, 740, 720, 692, 658.
MS (EI, 70 eV): *m/z* (%) = 243 (100), 242 (11), 213 (24), 185 (15), 167 (11), 139 (76).
HRMS (EI): *m/z* calcd. for [$C_{13}H_9NO_4$]: 243.0532; found 243.0527 (M^+).
M.p. (°C): 124.0 – 124.9.

Ethyl 4-(benzo[*d*][1,3]dioxol-5-yl)benzoate (20t)



According to **TP 8**, a solution of 5-bromobenzo[*d*][1,3]dioxole (**18f**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 18 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 5.0 mL reactor tube (16.7 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of $ZnCl_2$ (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. The mixture was stirred for 15 min and then PEPPSI-*i*-Pr (5.4 mg, 0.008 mmol, 2 mol%) and ethyl 4-iodobenzoate (**21p**, 166 mg, 0.6 mmol, 1.5 equiv.) were added. Stirring was continued overnight at 25 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 24:1) afforded the title compound **20t** as colorless crystals (75 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (dt, *J* = 8.6, 2.2 Hz, 2H), 7.57 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.13 – 7.05 (m, 2H), 6.95 – 6.81 (m, 1H), 6.01 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.6, 148.4, 147.9, 145.3, 134.4, 130.2 (2C), 129.0, 126.7 (2C), 121.1, 108.8, 107.8, 101.4, 61.1, 14.5.

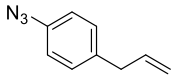
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2986, 2942, 2902, 2788, 1704, 1604, 1522, 1502, 1484, 1440, 1410, 1368, 1314, 1288, 1270, 1254, 1234, 1180, 1148, 1102, 1034, 1020, 1010, 932, 890, 856, 848, 812, 768, 738, 700, 656.

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

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

M.p. (°C): 92.9 – 93.2.

1-Allyl-4-azidobenzene (24a)



According to **TP 8**, a solution of 1-azido-4-iodobenzene (**22a**, 0.20 M, 1.00 mmol) and $ZnCl_2$ (0.1 M, 0.50 mmol, 0.5 equiv.) in THF (total volume: 5.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 1.50 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of allyl bromide (**21a**, 0.22 mL, 2.5 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 1.5 h at −40 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×60 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **24a** as a pale yellow oil (114 mg, 0.72 mmol, 72% yield).

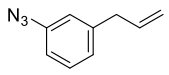
scale-up:

Scale-up of the reaction was achieved according to **TP 8**. A solution of azido-4-iodobenzene (**22a**, 0.20 M, 4.90 mmol) and $ZnCl_2$ (0.1 M, 2.45 mmol, 0.5 equiv.) in THF (total volume: 24.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 7.35 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer over a total runtime of 250 sec. The combined stream passed a 0.25 mL reactor tube (1.25 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of allyl bromide (**21a**, 1.06 mL, 12.25 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.49 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 1 h at −40 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq.

phase was extracted three times with EtOAc (3×150 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded **24a** as a pale yellow oil (464 mg, 2.91 mmol, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.17 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.3 Hz, 2H), 6.02 – 5.87 (m, 1H), 5.12 – 5.06 (m, 1H), 5.10 – 5.02 (m, 1H), 3.40 – 3.33 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 138.0, 137.3, 137.0, 130.1 (2C), 119.2 (2C), 116.2, 39.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2108, 1611, 1510, 1505, 1434, 1357, 1284, 1184, 1120, 1082, 994, 805, 735.
MS (EI, 70 eV): *m/z* (%) = 159(20), 132(15), 131(100), 130(82), 128(17), 127(12), 116(18), 104(23), 103(28), 97(13), 95(14), 91(15), 85(13), 83(14), 81(14), 78(23), 77(20), 71(17), 69(21), 63(11), 57(21), 55(13), 41(28), 40(15).
HRMS (EI): *m/z* calcd. for [$C_9H_9N_3$]: 159.0796; found 159.0788 (M^+).

3-Allyl-4-azidobenzene (24b)

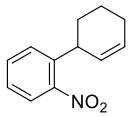


According to **TP 8**, a solution of 1-azido-3-iodobenzene (**22b**, 0.20 M, 1.00 mmol) and $ZnCl_2$ (0.1 M, 0.50 mmol, 0.5 equiv.) in THF (total volume: 5.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 1.50 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of allyl bromide (**21a**, 0.22 mL, 2.5 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 1.5 h at −40 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×60 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **24b** as a pale yellow oil (132 mg, 0.83 mmol, 83%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 7.28 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.86 (s, 1H), 5.95 (ddt, *J* = 18.8, 9.5, 6.7 Hz, 1H), 5.12 (s, 1H), 5.14 – 5.06 (m, 1H), 3.38 (d, *J* = 6.7 Hz, 2H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 142.2, 140.2, 136.8, 129.9, 125.4, 119.3, 116.9, 116.6, 40.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3047, 2924, 2108, 1603, 1558, 1483, 1444, 1356, 1288, 1203, 1168, 1101, 1073, 1021, 994, 941, 914, 885, 775, 695.
MS (EI, 70 eV): *m/z* (%) = 133(17), 132(27), 131(100), 116(24), 115(17), 111(17), 106(19), 104(26), 103(23), 97(23), 91(30), 85(23), 83(28), 78(23), 77(50), 71(27), 69(32), 65(16), 57(43), 55(26), 51(16), 44(59), 43(27), 41(36).

HRMS (EI): *m/z* calcd. for [$C_9H_9N_3$]: 159.0796; found 159.0791 (M^+).

2'-Nitro-1,2,3,4-tetrahydro-1,1'-biphenyl (24c)



According to **TP 8**, a solution of 1-bromo-2-nitrobenzene (**22c**, 0.20 M, 0.40 mmol) and $ZnCl_2$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-bromocyclohexene (**21k**, 161 mg, 1.0 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 10 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **24c** as pale yellow oil (76 mg, 0.37 mmol, 93% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.52 (td, *J* = 7.6, 1.3 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.36 – 7.29 (m, 1H), 6.02 – 5.93 (m, 1H), 5.63 – 5.55 (m, 1H), 4.00 – 3.89 (m, 1H), 2.26 – 2.15 (m, 1H), 2.16 – 2.05 (m, 2H), 1.81 – 1.61 (m, 2H), 1.61 – 1.49 (m, 1H).

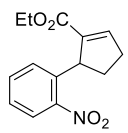
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.9, 140.7, 132.6, 130.4, 129.8, 129.0, 127.0, 124.2, 36.9, 31.8, 25.0, 21.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3022, 2928, 2860, 2838, 1650, 1606, 1576, 1520, 1478, 1444, 1348, 1294, 1252, 1222, 1190, 1164, 1144, 1134, 1078, 1060, 1036, 984, 956, 932, 902, 884, 854, 840, 784, 744, 726, 698, 660.

MS (EI, 70 eV): *m/z* (%) = 186 (54), 169 (11), 168 (80), 167 (48), 158 (33), 156 (21), 153 (15), 152 (15), 147 (14), 146 (61), 143 (37), 141 (18), 132 (17), 131 (10), 130 (100), 129 (13), 128 (40), 127 (11), 118 (11), 117 (21), 115 (57), 105 (13), 103 (10) 102 (10), 92 (11), 91 (20), 89 (11), 77 (23).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{12}NO_2$]: 202.0868; found 202.0861 ($M^+ - H$).

Ethyl 5-(2-nitrophenyl)cyclopent-1-ene-1-carboxylate (24d)

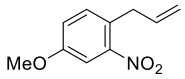


According to **TP 8**, a solution of 1-bromo-2-nitrobenzene (**22c**, 0.20 M, 0.40 mmol) and $ZnCl_2$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in

hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of ethyl 5-bromocyclopent-1-ene-1-carboxylate (**21q**, 131 mg, 0.6 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 1 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 19:1) afforded the title compound **24d** as a brown-red oil (81 mg, 0.31 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.12 – 7.06 (m, 1H), 4.72 – 4.54 (m, 1H), 4.07 – 3.91 (m, 2H), 2.82 – 2.53 (m, 2H), 1.98 – 1.88 (m, 1H), 1.33 – 1.17 (m, 1H), 1.03 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.3, 149.5, 146.6, 140.1, 138.3, 133.0, 128.2, 127.0, 124.3, 60.3, 45.4, 33.8, 32.1, 14.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2936, 2906, 2872, 1758, 1710, 1634, 1608, 1578, 1522, 1478, 1446, 1352, 1292, 1266, 1204, 1188, 1140, 1098, 1032, 1018, 956, 930, 902, 852, 824, 784, 746, 708, 684, 662.
MS (EI, 70 eV): *m/z* (%) = 216 (79), 205 (15), 198 (20), 188 (26), 187 (24), 185 (30), 172 (80), 171 (49), 170 (100), 169 (15), 168 (21), 161 (16), 160 (37), 159 (16), 157 (21), 155 (18), 154 (53), 146 (16), 145 (89), 144 (22), 143 (38), 142 (40), 141 (59), 140 (18), 139 (34), 130 (30), 129 (37), 128 (52), 127 (32), 117 (21), 116 (22), 115 (98), 77 (17), 55 (32).
HRMS (EI): *m/z* calcd. for [$C_{12}H_{10}NO_3$]: 216.0661; found 216.0669 ($M^+ - C_2H_5O$).

1-Allyl-4-methoxy-2-nitrobenzene (24e)



According to **TP 8**, a solution of 1-bromo-4-methoxy-2-nitrobenzene (**22d**, 0.20 M, 0.40 mmol) and $ZnCl_2$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.10 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (**21a**, 121 mg, 1.0 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 10 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After

removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 49:1) afforded the title compound **24e** as a red-brown oil (56 mg, 0.29 mmol, 73% yield).

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

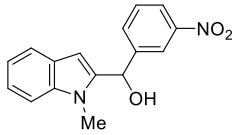
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.5, 149.7, 135.6, 132.9, 126.9, 119.9, 116.8, 109.4, 55.9, 36.5.

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

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

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

(1-Methyl-1*H*-indol-2-yl)(3-nitrophenyl)methanol (24f)



According to **TP 8**, a solution of 1-iodo-3-nitrobenzene (**22e**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 20 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 1-methyl-1*H*-indole-3-carbaldehyde (**21r**, 96 mg, 0.60 mmol, 1.5 equiv.) in THF. Stirring was continued for 1.5 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **24f** as a red gel (67 mg, 0.24 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.44 – 8.28 (m, 1H), 8.14 – 7.99 (m, 1H), 7.92 – 7.73 (m, 1H), 7.59 – 7.43 (m, 2H), 7.40 – 7.20 (m, 2H), 7.17 – 7.04 (m, 1H), 6.85 (s, 1H), 6.19 (s, 1H), 3.74 (s, 3H), 2.62 – 2.49 (m, 1H).

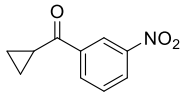
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.4, 146.1, 137.6, 132.5, 129.2, 127.7, 125.9, 122.5, 122.3, 121.4, 119.9, 119.5, 117.2, 109.7, 69.2, 32.9.

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

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

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

Cyclopropyl(3-nitrophenyl)methanone (24g)



According to **TP 8**, a solution of 1-iodo-3-nitrobenzene (**22e**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 20 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropanecarbonyl chloride (**21h**, 63 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 1.5 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, purification *via* HPLC afforded the title compound **24g** as a white solid (48 mg, 0.25 mmol, 63% yield).

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

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

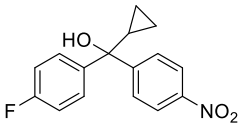
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3094, 1662, 1614, 1580, 1526, 1476, 1440, 1418, 1384, 1350, 1316, 1282, 1222, 1172, 1110, 1080, 1046, 1016, 1000, 922, 894, 878, 850, 822, 802, 752, 716, 686, 664.

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

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

M.p. (°C): 73.9 – 75.0.

Cyclopropyl(4-fluorophenyl)(4-nitrophenyl)methanol (24h)

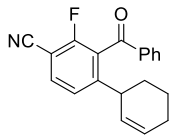


According to **TP 8**, a solution of 1-iodo-4-nitrobenzene (**22f**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed

with an overall 16 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.08 s, −60 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl(4-fluorophenyl)methanone (**21h**, 99 mg, 0.60 mmol, 1.5 equiv.) in THF. Stirring was continued for 1.5 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **24h** as an orange oil (82 mg, 0.29 mmol, 73% yield).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.15 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.57 (dt, *J* = 9.0, 2.1 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.05 – 6.98 (m, 2H), 1.98 (s, 1H), 1.63 – 1.57 (m, 1H), 0.77 – 0.69 (m, 1H), 0.59 – 0.50 (m, 2H), 0.50 – 0.45 (m, 1H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 162.3 (d, *J* = 247.3 Hz), 154.5, 147.0, 141.2, 129.0 (d, *J* = 8.1 Hz, 2C), 127.6 (2C), 123.3 (2C), 115.3 (d, *J* = 21.3 Hz, 2C), 76.6, 21.7, 2.6, 1.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3538, 3082, 3010, 1602, 1506, 1424, 1408, 1346, 1316, 1224, 1160, 1108, 1098, 1026, 1014, 988, 964, 930, 906, 878, 852, 830, 804, 750, 708, 696.
MS (EI, 70 eV): *m/z* (%) = 260 (15), 259 (100), 246 (14), 183 (11), 165 (11), 150 (37), 123 (37), 109 (13).
HRMS (EI): *m/z* calcd. for [$C_{16}H_{13}FNO_3$]: 286.0879; found 286.0868 ($M^+ - H$).

2-Benzoyl-3-fluoro-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-4-carbonitrile (24i)



According to **TP 8**, a solution of 3-benzoyl-4-bromo-2-fluorobenzonitrile (**22g**, 0.20 M, 0.40 mmol) and $ZnCl_2$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 20 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-bromocyclohexene (**21k**, 161 mg, 1.00 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 30 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 19:1) afforded the title compound **24i** as a colorless oil (94 mg, 0.31 mmol, 78% yield).

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

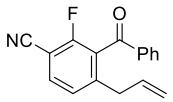
^{13}C-NMR (201 MHz, $CDCl_3$): δ / ppm = 192.4, 160.2, 158.9, 153.3, 136.7, 134.8, 133.9, 130.6, 129.6 (2C), 129.2 (2C), 127.8, 125.0, 113.7, 99.4, 39.2, 32.0, 24.7, 21.1.

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

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

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

4-Allyl-3-benzoyl-2-fluorobenzonitrile (24j)



According to **TP 8**, a solution of 3-benzoyl-4-bromo-2-fluorobenzonitrile (**22g**, 0.20 M, 0.40 mmol) and $ZnCl_2$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 20 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (**21a**, 122 mg, 1.00 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 10 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 19:1) afforded the title compound **24j** as a colorless oil (68 mg, 0.26 mmol, 65% yield).

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 7.79 (d, *J* = 7.3 Hz, 2H), 7.69 – 7.63 (m, 2H), 7.52 – 7.48 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 5.80 – 5.71 (m, 1H), 5.04 (dq, *J* = 10.3, 1.3 Hz, 1H), 4.98 (dq, *J* = 17.0, 1.5 Hz, 1H), 3.34 (d, *J* = 6.8 Hz, 2H).

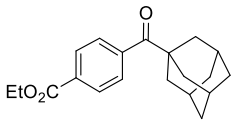
^{13}C-NMR (201 MHz, $CDCl_3$): δ / ppm = 192.1, 160.4, 159.1, 146.7, 136.5, 134.8, 134.1, 134.0, 129.6 (2C), 129.1 (2C), 126.4, 118.6, 113.5, 99.9, 37.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3084, 3066, 2236, 1670ß, 1640, 1613, 1596, 1564, 1480, 1450, 1428, 1316, 1278, 1252, 1202, 1174, 1160, 1100, 1028, 1012, 992, 918, 832, 770, 742, 706, 686, 674.

MS (EI, 70 eV): *m/z* (%) = 265 (14), 264 (19), 251 (17), 250 (100), 247 (11), 246 (20), 244 (11), 221 (14), 208 (13), 188 (44), 187 (31), 159 (10), 158 (24), 105 (17), 91 (18), 77 (25).

HRMS (EI): *m/z* calcd. for [$C_{17}H_{12}FNO$]: 265.0903; found 265.0903 (M^+).

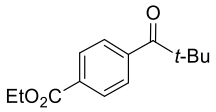
Ethyl 4-((1*s*,3*s*)-adamantane-1-carbonyl)benzoate (24k)



According to **TP 8**, a solution of ethyl 4-iodobenzoate (**22h**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 16 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of 1-adamantanecarbonyl chloride (**21t**, 119 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at −40 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 99:1) afforded the title compound **24k** as a colorless oil (86 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.09 – 2.04 (m, 3H), 2.00 – 1.92 (m, 6H), 1.79 – 1.66 (m, 6H), 1.40 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 210.3, 166.1, 144.0, 131.7, 129.3 (2C), 126.8 (2C), 61.4, 47.1, 39.0 (3C), 36.6 (3C), 28.1 (3C), 14.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2904, 2850, 2167, 1717, 1674, 1608, 1569, 1503, 1475, 1452, 1400, 1367, 1345, 1269, 1231, 1198, 1179, 1161, 1021, 988, 951, 931, 860, 829, 776, 767, 716, 696, 662.
MS (EI, 70 eV): *m/z* (%) = 312 (13), 136 (25), 135 (100), 93 (18), 79 (21).
HRMS (EI): *m/z* calcd. for [$C_{20}H_{24}O_3$]: 312.1725; found 312.1721 (M^+).

Ethyl 4-pivaloylbenzoate (24l)



According to **TP 8**, a solution of ethyl 4-iodobenzoate (**22h**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 16 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of pivaloyl chloride (**21e**, 72 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at −40 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc

(3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 99:1) afforded the title compound **24l** as a colorless oil (72 mg, 0.31 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.32 (s, 9H).

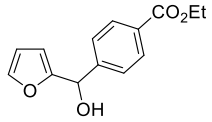
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 209.6, 166.0, 143.0, 132.2, 129.4 (2C), 127.4 (2C), 61.4, 44.5, 27.8 (3C), 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2971, 2933, 2872, 2168, 1718, 1680, 1569, 1502, 1477, 1463, 1448, 1402, 1367, 1310, 1271, 1187, 1104, 1020, 956, 862, 853, 816, 789, 734, 717, 703.

MS (EI, 70 eV): *m/z* (%) = 178 (21), 177 (100), 149 (12), 57 (16), 43 (32).

HRMS (EI): *m/z* calcd. for [$C_{14}H_{18}O_3$]: 234.1256; found 234.1254 (M^+).

Ethyl 4-(furan-2-yl(hydroxy)methyl)benzoate (24m)



According to **TP 8**, a solution of ethyl 4-iodobenzoate (**22h**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 16 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (−40 °C) solution of furfural (**21u**, 58 mg, 0.60 mmol, 1.5 equiv.) in THF. Stirring was continued for 3 h at −40 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 8:2) afforded the title compound **24m** as a light orange oil (73 mg, 0.30 mmol, 75% yield).

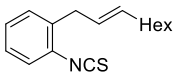
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.30 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.10 (d, *J* = 3.3 Hz, 1H), 5.86 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.88 (s, 1H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.6, 155.4, 145.8, 142.9, 130.1, 129.8 (2C), 126.5 (2C), 110.4, 107.8, 69.7, 61.1, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 2982, 2938, 2906, 1712, 1696, 1652, 1612, 1578, 1504, 1464, 1414, 1392, 1368, 1310, 1272, 1174, 1142, 1102, 1074, 1010, 940, 928, 884, 866, 828, 812, 792, 736, 706, 678.

MS (EI, 70 eV): *m/z* (%) = 246 (21) 229 (27), 219 (14), 218 (100), 217 (11), 201 (68), 189 (12), 178 (10), 177 (89), 175 (15), 173 (24), 155 (14), 151 (45), 149 (44), 145 (48), 129 (21), 128 (25), 127 (17), 123 (37), 117 (29), 115 (32), 105 (20), 97 (15), 95 (65), 79 (13), 77 (14).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{14}O_4$]: 246.0892; found 246.0886 (M^+).

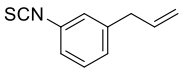
1-Isothiocyanato-2-(non-1-en-3-yl)benzene (24n)



According to **TP 8**, a solution of 1-bromo-2-isothiocyanatobenzene (**22i**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 16 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of (*E*)-1-bromonon-2-ene (**21v**, 123 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 1 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **24n** as a pale yellow oil (70 mg, 0.27 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.18 (m, 4H), 5.60 – 5.45 (m, 2H), 3.40 (d, *J* = 5.6 Hz, 2H), 2.03 (q, *J* = 6.4 Hz, 2H), 1.38 – 1.21 (m, 8H), 0.91 – 0.83 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 137.7, 133.6, 130.1, 127.6, 127.6, 127.3, 126.5, 126.4, 35.6, 32.7, 31.9, 29.5, 29.0, 22.8, 22.8, 14.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2924, 2870, 2854, 2176, 2076, 1598, 1578, 1484, 1450, 1378, 966, 934, 904, 752, 724, 672.
MS (EI, 70 eV): *m/z* (%) = 258 (61), 226 (92), 216 (23), 202 (32), 188 (30), 174 (33), 170 (17), 168 (22), 163 (48), 162 (100), 161 (45), 156 (42), 155 (30), 154 (34), 149 (64), 148 (60), 130 (54), 129 (26), 128 (33), 121 (15), 118 (20), 117 (31), 116 (26), 115 (32).
HRMS (EI): *m/z* calcd. for [$C_{16}H_{20}NS$]: 258.1316; found 258.1312 (M^+ − H).

1-Allyl-3-isothiocyanatobenzene (24o)

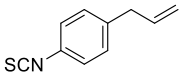


According to **TP 8**, a solution of 1-bromo-3-isothiocyanatobenzene (**22j**, 0.20 M, 0.50 mmol) and $ZnCl_2$ (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 18 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.022 mL reactor tube (0.07 s,

−60 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (**21a**, 151 mg, 1.25 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 30 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **24o** as a colorless oil (57 mg, 0.33 mmol, 65% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.27 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.11 (dddd, *J* = 7.7, 1.5, 1.0, 0.4 Hz, 1H), 7.09 – 7.04 (m, 2H), 5.93 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.15 – 5.06 (m, 2H), 3.37 (dtd, *J* = 6.8, 1.4, 0.7 Hz, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.1, 136.4, 136.4, 131.4, 129.6, 127.8, 126.0, 123.5, 116.9, 39.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2978, 2906, 2246, 2050, 2042, 1640, 1600, 1580, 1482, 1438, 1410, 1292, 1164, 1080, 992, 916, 898, 822, 780, 702, 680, 654.
MS (EI, 70 eV): *m/z* (%) = 175 (74), 174 (12), 118 (10), 117 (100), 116 (22), 115 (70).
HRMS (EI): *m/z* calcd. for [$C_{10}H_9NS$]: 175.0456; found 175.0448 (M^+).

1-Allyl-4-isothiocyanatobenzene (24p)

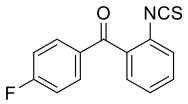


According to **TP 8**, a solution of 1-bromo-4-isothiocyanatobenzene (**22k**, 0.20 M, 0.50 mmol) and $ZnCl_2$ (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.022 mL reactor tube (0.15 s, −60 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (**21a**, 151 mg, 1.25 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.05 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 30 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **24p** as a colorless oil (59 mg, 0.34 mmol, 67% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.16 (d, *J* = 0.7 Hz, 4H), 5.93 (ddt, *J* = 16.8, 10.2, 6.7 Hz, 1H), 5.13 – 5.04 (m, 2H), 3.38 (dt, *J* = 6.7, 1.5 Hz, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 139.7, 136.6 (2C), 129.9 (3C), 125.9 (2C), 116.7, 39.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 2978, 2902, 2180, 2050, 2042, 1638, 1604, 1502, 1432, 1418, 1294, 1248, 1196, 1106, 992, 916, 838, 800, 722, 676.

MS (EI, 70 eV): *m/z* (%) = 176 (11), 175 (100), 148 (22), 117 (93), 116 (24), 115 (59).
HRMS (EI): *m/z* calcd. for [$C_{10}H_9NS$]: 175.0456; found 175.0449 (M^+).

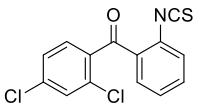
(4-Fluorophenyl)(2-isothiocyanatophenyl)methanone (24q)



According to **TP 8**, a solution of 1-bromo-2-isothiocyanatobenzene (**22i**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 16 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 4-fluorobenzoyl chloride (**21m**, 95 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 1.5 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 24:1) afforded the title compound **24q** as a light yellow oil (64 mg, 0.25 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.89 – 7.81 (m, 2H), 7.56 – 7.45 (m, 2H), 7.41 – 7.33 (m, 2H), 7.21 – 7.13 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.0, 166.3 (d, *J* = 256.2 Hz), 135.0, 133.2 (d, *J* = 3.0 Hz, 2C), 132.8, 132.9, 132.1, 130.1, 129.8, 127.5, 127.1, 116.1 (d, *J* = 22.1 Hz, 2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 2926, 2166, 2062, 1662, 1594, 1572, 1532, 1504, 1478, 1444, 1410, 1378, 1304, 1288, 1262, 1230, 1200, 1148, 1102, 1094, 1042, 1012, 938, 926, 890, 848, 816, 778, 752, 734, 706, 678, 660.
MS (EI, 70 eV): *m/z* (%) = 257 (56), 256 (33), 197 (53), 162 (90), 134 (36), 123 (19), 123 (100), 95 (17), 75 (12).
HRMS (EI): *m/z* calcd. for [$C_{14}H_8FNOS$]: 257.0311; found 257.0304 (M^+).

(2,4-Dichlorophenyl)(2-isothiocyanatophenyl)methanone (24r)

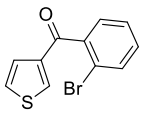


According to **TP 8**, a solution of 1-bromo-2-isothiocyanatobenzene (**22i**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 16 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.94 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of

2,4-dichlorobenzoyl chloride (**21w**, 126 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 4 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 97:3) afforded the title compound **24r** as a light yellow solid (73 mg, 0.24 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 (ddd, *J* = 7.8, 1.6, 0.5 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.48 (dd, *J* = 1.9, 0.3 Hz, 1H), 7.45 (dd, *J* = 8.2, 0.3 Hz, 1H), 7.39 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.37 – 7.31 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.3, 138.1, 136.9, 136.7, 133.8, 133.4, 133.0, 131.3, 131.3, 130.5, 130.5, 128.4, 127.8, 127.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3086, 2924, 2854, 2190. 2172, 2116, 1908, 1740, 1674, 1580, 1566, 1554, 1478, 1442, 1378, 1302, 1278, 1270, 1242, 1160, 1138, 1104, 1054, 940, 916, 872, 828, 800, 788, 758, 704, 666.
MS (EI, 70 eV): *m/z* (%) = 307 (11) 274 (36), 273 (15), 272 (100), 175 (27), 173 (41), 162 (74), 134 (32), 109 (10).
HRMS (EI): *m/z* calcd. for [$C_{14}H_7Cl_2NOS$]: 306.9625; found 306.9618 (M^+).
M.p. (°C): 80.0 – 81.8.

(2-Bromophenyl)(thiophen-3-yl)methanone (27a)



According to **TP 8**, a solution of 3-bromothiophene (**25a**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 1 mL reactor tube (10 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 2-bromobenzoyl chloride (**21l**, 165 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **27a** as colorless crystals (96 mg, 0.34 mmol, 72% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.79 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.64 (ddd, *J* = 7.9, 1.1, 0.6 Hz, 1H), 7.56 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.44 – 7.30 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 189.3, 141.6, 141.3, 136.1, 133.5, 131.3, 128.8, 127.8, 127.2, 126.8, 119.4.

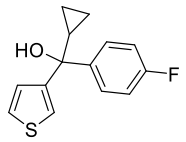
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974, 2858, 1622, 1562, 1476, 1446, 1432, 1404, 1302, 1274, 1252, 1156, 1110, 1066, 1012, 996, 914, 842, 804, 738, 668.

MS (EI, 70 eV): *m/z* (%) = 188 (11), 187 (100), 185 (11), 183 (11), 111 (56).

HRMS (EI): *m/z* calcd. for [$C_{11}H_7BrOS$]: 265.9401; found 265.9396 (M^+).

M.p. (°C): 81.3 – 81.9.

Cyclopropyl(4-fluorophenyl)(thiophen-3-yl)methanol (27b)



According to **TP 8**, a solution of 3-bromothiophene (**25a**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 1 mL reactor tube (10 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl(4-fluorophenyl)methanone (**21h**, 90 mg, 0.55 mmol, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **27b** as a yellow oil (95 mg, 0.39 mmol, 77% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.38 (m, 2H), 7.32 (ddd, *J* = 3.0, 1.4, 0.4 Hz, 1H), 7.25 (ddd, *J* = 5.0, 3.0, 0.4 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.94 (ddd, *J* = 5.0, 1.4, 0.4 Hz, 1H), 2.01 (s, 1H), 1.65 – 1.55 (m, 1H), 0.70 – 0.59 (m, 1H), 0.58 – 0.42 (m, 3H).

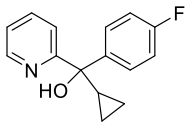
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 168.3, 140.7, 139.7, 135.6, 131.3, 128.8, 128.6 (d, *J* = 11.2 Hz, 2C), 128.7 (d, *J* = 179.5 Hz, 2C), 126.2, 61.0, 33.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3496, 3104, 3006, 1658, 1588, 1506, 1430, 1410, 1394, 1282, 1222, 1158, 1144, 1046, 1024, 968, 860, 850, 832814, 764, 740, 684.

MS (EI, 70 eV): *m/z* (%) = 220 (67), 207 (22), 136 (12), 123 (100), 111 (16).

HRMS (EI): *m/z* calcd. for [$C_{14}H_{13}FOS$]: 248.0671; found 248.0666 (M^+).

Cyclopropyl(4-fluorophenyl)(pyridin-4-yl)methanol (27c)



According to **TP 8**, a solution of 4-iodopyridine (**25b**, 0.20 M, 0.50 mmol) and $MgCl_2 \cdot LiCl$ (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 18 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.83 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of cyclopropyl(4-fluorophenyl)methanone (**21h**, 90 mg, 0.55 mmol, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 3:7) afforded the title compound **27c** as colorless crystals (76 mg, 0.31 mmol, 62% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.47 (s, 2H), 7.47 – 7.39 (m, 2H), 7.33 – 7.28 (m, 2H), 7.05 – 6.97 (m, 2H), 2.55 (s, 1H), 1.56 (tt, *J* = 8.0, 5.5 Hz, 1H), 0.72 – 0.64 (m, 1H), 0.58 – 0.44 (m, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.1 (d, *J* = 247.1 Hz), 155.9, 149.4 (2C), 141.7 (d, *J* = 3.3 Hz), 128.8 (d, *J* = 8.1 Hz, 2C), 121.6 (2C), 115.1 (d, *J* = 21.3 Hz, 2C), 75.9, 21.2, 2.2, 1.3.

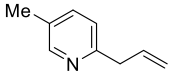
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3186, 3004, 1602, 1506, 1422, 1408, 1358, 1300, 1222, 1194, 1158, 1148, 1068, 1028, 1016, 994, 968, 878, 840, 816, 802, 730, 686.

MS (EI, 70 eV): *m/z* (%) = 216 (15), 215 (100), 202 (14), 123 (32), 109 (13), 106 (17), 95 (15), 78 (13).

HRMS (EI): *m/z* calcd. for $[C_{15}H_{14}FNO]$: 243.1049; found 243.1062 (M^+).

M.p. (°C): 1514.3 – 156.8.

2-Allyl-5-methylpyridine (27d)

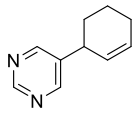


According to **TP 8**, a solution of 2-bromo-5-methylpyridine (**25c**, 0.20 M, 1.00 mmol) and $ZnCl_2$ (0.1 M, 0.50 mmol, 0.5 equiv.) in THF (total volume: 5.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 6 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 5.0 mL reactor tube (53 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (**21a**, 302 mg, 2.50 mmol, 2.5 equiv.) in THF. Stirring was continued for 1 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After

removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 8:2) afforded the title compound **27d** as pale yellow oil (84 mg, 0.63 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.34 (d, *J* = 2.2 Hz, 1H), 7.38 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.10 – 5.92 (m, 1H), 5.18 – 5.03 (m, 2H), 3.57 – 3.46 (m, 2H), 2.27 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.2, 149.8, 137.1, 136.1, 130.5, 122.3, 116.6, 42.5, 18.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2927, 2861, 1665, 1602, 1568, 1484, 1448, 1380, 1254, 1186, 1132, 1029, 886, 830, 745, 723.
MS (EI, 70 eV): *m/z* (%) = 134(0.5), 133(10), 132(100), 117(36).
HRMS (EI): *m/z* calcd. for [$C_9H_{11}N$]: 133.0891; found 132.0808 ($M^+ - H$).

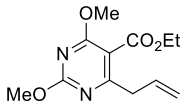
5-(Cyclohex-2-en-1-yl)pyrimidine (27e)



According to **TP 8**, a solution of 5-bromopyrimidine (**25d**, 0.20 M, 0.40 mmol) and $ZnCl_2$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 12 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.25 s, 0 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3-bromocyclohexene (**21k**, 161 mg, 1.00 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 10 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **27e** as a light brown oil (43 mg, 0.27 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.08 (s, 1H), 8.59 (s, 2H), 6.04 – 5.97 (m, 1H), 5.69 – 5.61 (m, 1H), 3.48 – 3.38 (m, 1H), 2.17 – 2.00 (m, 3H), 1.79 – 1.50 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.0, 156.5 (2C), 139.2, 130.6, 127.3, 37.3, 32.1, 24.9, 20.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3022, 2928, 2858, 2838, 1716, 1672, 1610, 1560, 1432, 1408, 1370, 1346, 1326, 1302, 1256, 1230, 1184, 1164, 1136, 1110, 1078, 1046, 1036, 984, 958, 910, 890, 880, 848, 824, 794, 758, 722, 704, 668.
MS (EI, 70 eV): *m/z* (%) = 160 (81), 159 (27), 146 (10), 145 (100), 132 (16), 131 (53), 118 (15), 105 (13), 104 (15), 78 (12).
HRMS (EI): *m/z* calcd. for [$C_{10}H_{12}N_2$]: 160.1000; found 160.0994 (M^+).

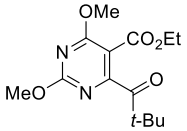
Ethyl 4-allyl-2,6-dimethoxypyrimidine-5-carboxylate (27f)



According to **TP 8**, a solution of ethyl 4-iodo-2,6-dimethoxypyrimidine-5-carboxylate (**25e**, 0.20 M, 0.40 mmol) and $ZnCl_2$ (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 16 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.08 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of allyl bromide (**21a**, 122 mg, 1.00 mmol, 2.5 equiv.) and CuCN·2LiCl solution (0.04 mL, 1.0 M in THF, 0.1 equiv.) in THF. Stirring was continued for 10 min at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 19:1) afforded the title compound **27f** as a colorless oil (71 mg, 0.28 mmol, 70% yield).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 6.03 – 5.95 (m, 1H), 5.16 – 5.08 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 3.52 (dt, *J* = 6.7, 1.5 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 169.6, 169.3, 165.9, 164.8, 133.9, 117.6, 108.1, 61.6, 55.1, 54.7, 40.3, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 2960, 1726, 1638, 1560, 1482, 1458, 1374, 1360, 1298, 1256, 1208, 1194, 1120, 1106, 1078, 1058, 1018, 996, 972, 946, 916, 868, 848, 814, 780, 746, 728, 686.
MS (EI, 70 eV): *m/z* (%) = 251 (30), 224 (10), 223 (100), 207 (19), 205 (73), 19 0(12), 179 (20).
HRMS (EI): *m/z* calcd. for [$C_{12}H_{15}N_2O_4$]: 252.1110; found 251.1032 (M^+ − H).

Ethyl 2,4-dimethoxy-6-pivaloylpyrimidine-5-carboxylate (27g)

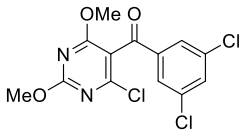


According to **TP 8**, a solution of ethyl 4-iodo-2,6-dimethoxypyrimidine-5-carboxylate (**25e**, 0.20 M, 0.40 mmol) and $MgCl_2$·LiCl (0.1 M, 0.20 mmol, 0.5 equiv.) in THF (total volume: 2.00 mL) and a solution of phenyllithium (0.30 M in hexane/dibutyl ether, 0.60 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 20 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.06 s, −40 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of pivaloyl chloride (**21e**, 72 mg, 0.60 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.44 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three

times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 19:1) afforded the title compound **27g** as a pale yellow oil (79 mg, 0.27 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.29 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 1.34 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 208.2, 170.0, 169.2, 164.8, 163.9, 105.7, 61.8, 55.7, 55.1, 43.7, 27.2 (3C), 14.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 2962, 2936, 2874, 1740, 1704, 1568, 1552, 1484, 1460, 1374, 1360, 1274, 1236, 1200, 1120, 1060, 1032, 986, 946, 872, 860, 824, 786, 768, 726, 680.
MS (EI, 70 eV): *m/z* (%) = 251 (16), 239 (67), 211 (89), 185 (14), 167 (100), 140 (25), 139 (40), 109 (24).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{20}N_2O_5$]: 296.1372; found 296.1367 (M^+).

(4-Chloro-2,6-dimethoxypyrimidin-5-yl)(3,5-dichlorophenyl)methanone (27h)

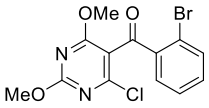


According to **TP 8**, a solution of 4-chloro-5-iodo-2,6-dimethoxypyrimidine (**25f**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.08 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 3,5-dichlorobenzoyl chloride (**21x**, 157 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **27h** as a white solid (125 mg, 0.36 mmol, 72% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.66 (d, *J* = 1.9 Hz, 2H), 7.60 (t, *J* = 1.9 Hz, 1H), 4.09 (s, 3H), 3.96 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 188.5, 169.6, 164.7, 158.6, 138.9, 136.1 (2C), 133.9, 127.7 (2C), 111.7, 56.0, 55.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1676, 1564, 1536, 1464, 1390, 1328, 1244, 1202, 1160, 1084, 1034, 968, 942, 874, 796, 770, 744, 664.
MS (EI, 70 eV): *m/z* (%) = 348 (11), 346 (12), 203 (33), 201 (100), 173 (10), 76 (15).

HRMS (EI): *m/z* calcd. for [$C_{13}H_9Cl_3N_2O_3$]: 345.9679; found 345.9671 ($M^+ - H$).
M.p. (°C): 83.1 – 84.0.

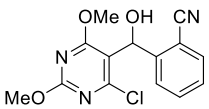
(2-Bromophenyl)(4-chloro-2,6-dimethoxypyrimidin-5-yl)methanone (27i)



According to **TP 8**, a solution of 4-chloro-5-iodo-2,6-dimethoxypyrimidine (**25f**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.08 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of 2-bromobenzoyl chloride (**21l**, 165 mg, 0.75 mmol, 1.5 equiv.) and CuCN·2LiCl solution (0.55 mL, 1.0 M in THF, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **27i** as white crystals (110 mg, 0.32 mmol, 63% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.64 (d, 1H), 7.62 (dd, *J* = 2.3, 1.6 Hz, 1H), 7.43 – 7.33 (m, 2H), 4.06 (s, 3H), 3.92 (s, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 190.4, 169.9, 164.4, 159.4, 138.9, 134.5, 133.3, 131.8, 127.7, 121.2, 113.9, 55.9, 55.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1682, 1582, 1536, 1460, 1386, 1364, 1286, 1236, 1198, 1154, 1078, 1020, 938, 918, 866, 792, 752, 724, 654.
MS (EI, 70 eV): *m/z* (%) = 358 (13), 356 (10), 277 (11), 203 (33), 201 (100), 185 (17), 183 (18), 76 (16).
HRMS (EI): *m/z* calcd. for [$C_{13}H_{10}BrClN_2O_3$]: 355.9563; found 355.9558 ($M^+ - H$).
M.p. (°C): 111.3 – 113.6.

2-((4-Chloro-2,6-dimethoxypyrimidin-5-yl)(hydroxy)methyl)benzonitrile (27j)



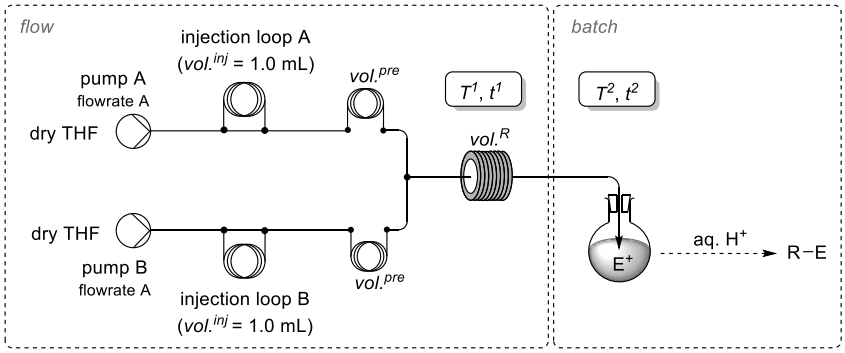
According to **TP 8**, a solution of 4-chloro-5-iodo-2,6-dimethoxypyrimidine (**25f**, 0.20 M, 0.50 mmol) and $MgCl_2$·LiCl (0.1 M, 0.25 mmol, 0.5 equiv.) in THF (total volume: 2.50 mL) and a solution of *n*-BuLi (0.30 M in hexane, 0.75 mmol, 1.5 equiv.) were prepared. The precooled solutions were mixed with an overall 9 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (0.08 s, −20 °C) and was subsequently injected in a flask containing a stirred, cooled (0 °C) solution of

2-formylbenzonitrile (**21y**, 72 mg, 0.55 mmol, 1.1 equiv.) in THF. Stirring was continued for 2 h at 0 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 6:4) afforded the title compound **27j** as colorless crystals (90 mg, 0.30 mmol, 59% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.88 (dd, 1H), 7.55 – 7.42 (m, 2H), 7.17 (dd, *J* = 7.1, 1.3 Hz, 1H), 6.85 (d, *J* = 1.0 Hz, 1H), 3.99 (s, 3H), 3.77 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 170.4 (2C), 164.1, 161.1 (2C) , 145.3, 132.2, 129.0, 123.7, 121.3, 108.4, 77.7, 55.7, 55.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3292, 1770, 1686, 1584, 1544, 1492, 1452, 1398, 1378, 1300, 1220, 1202, 1176, 1064, 1020, 1008, 964, 956, 886, 858, 852, 782, 748, 708, 658.
MS (EI, 70 eV): *m/z* (%) = 271 (15), 270 (100), 242 (31), 200 (20), 185 (24), 132 (12).
HRMS (EI): *m/z* calcd. for $[C_{14}H_{12}ClN_3O_3]$: 304.0489; found 304.0482 ($M^+ - H$).
M.p. (°C): 143.5 – 145.2.

5 Sodiation of Arenes and Heteroarenes in Continuous Flow

5.1 Typical Procedure (TP 9)



Typical procedure using a Uniqsis flow setup

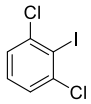
A NaDa solution (0.175 – 0.221 M, 0.90 or 1.05 equiv) in DMEA and a solution of the (hetero)aryl substrate (0.156 – 0.230 M, 1.0 equiv) in THF were prepared. Injection loop A ($vol.^{inj}$ = 1.0 mL) was loaded with the NaDA solution and injection loop B ($vol.^{inj}$ = 1.0 mL) was loaded with the solution of the substrate. The solutions were simultaneously injected into separate streams of THF (flow rates: 5 mL min^{-1}), which each passed a pre-cooling loop ($vol.^{pre}$ = 1.0 mL, T^1 = −20 to −78 °C, residence time: 12 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube and stainless steel needle ($vol.^{R}$ = 0.08 mL, residence time: t^1 = 0.5 s, T^1 = −78 to −20 °C) changing diameter from 0.25 mm to 0.8 mm and thus achieving better mixing and was subsequently injected into a flask containing a stirred, cooled (T^2 = 0 °C) solution of an electrophile E^+ (1.5 – 10.0 equiv) in THF. The reaction mixture was stirred further for the indicated time and temperature (T^2, reaction time: t^2) and quenched with an indicated (sat. aq.) solution. The aq. phase was extracted with EtOAc or hexane and the organic phases were dried and filtrated. After removal of the solvent *in vacuo*, flash column chromatographical purification with suited *i*-hex:EtOAc mixtures afforded the pure products R – E.

5.2 Attempted Batch Sodiation

Batch sodiation of 2-chloropyrazine (**28g**) was attempted according to the reported procedure by *Collum*.[145] A solution of 2-chloropyrazine (**28g**, 22 mg, 0.195 mmol, 1.00 equiv) in THF (1 mL) was treated with NaDA (0.205 M, 1 M, 1.05 equiv) at −78 °C. After 10 s a solution of iodine in THF (1 M, 0.975 mL, 5 equiv) was added dropwise at −78 °C under vigorous stirring. The reaction mixture was quenched by addition of sat. aq. $Na_2S_2O_3$. GC-analysis revealed complete decomposition of the starting material and no product formation.

5.3 Preparation of the Products

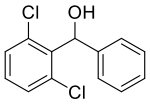
1,3-Dichloro-2-iodobenzene (31a)



According to **TP 9**, a solution of 1,3-dichlorobenzene (**28a**, 0.175 M, 0.175 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.184 M in DMEA, 0.184 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of iodine (**30a**, 222 mg, 0.875 mmol, 5.00 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. $Na_2S_2O_3$. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **31a** as white crystals (40 mg, 0.147 mmol, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 140.8, 129.8 (2C), 127.4 (2C), 103.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2921, 2850, 1556, 1421, 1392, 1252, 1184, 1147, 1130, 1080, 1012, 967, 893, 769, 697, 684.
MS (EI, 70 eV): *m/z* (%) = 276 (10), 274 (64), 272 (100), 175 (19), 173 (30), 127 (23), 109 (17).
HRMS (EI): *m/z* calcd. for [$C_6H_3Cl_2I$]: 271.8656; found 271.8651 (M^+).
M.p. (°C): 54.7 – 58.7.

(2,6-Dichlorophenyl)(phenyl)methanol (31b)



According to **TP 9**, a solution of 1,3-dichlorobenzene (**28a**, 0.167 M, 0.167 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.175 M in DMEA, 0.175 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred benzaldehyde solution (**30b**, 26 µL, 0.250 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **31b** as a colorless liquid (40 mg, 0.16 mmol, 95%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.32 (m, 4H), 7.32 – 7.27 (m, 3H), 7.22 (dd, *J* = 8.6, 7.4 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 3.43 (d, *J* = 10.3 Hz, 1H).

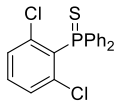
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 141.6, 137.9, 135.3 (2C), 129.6, 129.5 (2C), 128.4 (2C), 127.4 (2C), 125.5, 72.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3563, 3435, 3060, 3028, 1601, 1579, 1562, 1494, 1449, 1435, 1400, 1250, 1176, 1148, 1089, 1020, 916, 865, 826, 778, 766, 734, 695, 660.

MS (EI, 70 eV): *m/z* (%) = 254 (39), 252 (59), 251 (14), 199 (26), 177 (10), 175 (63), 173 (100), 165 (10), 152 (14), 79 (21), 78 (27), 77(14).

HRMS (EI): *m/z* calcd. for [$C_{13}H_{10}Cl_2O$]: 252.0109; found 252.0105 (M^+).

(2,6-Dichlorophenyl)diphenylphosphine sulphide (31c)



According to **TP 9**, a solution of 1,3-dichlorobenzene (**28a**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of chlorodiphenylphosphane (**30c**, 90 µL, 0.500 mmol, 2.50 equiv) in THF. Stirring was continued for 30 min at 0 °C before sulfur (513 mg, 2.00 mmol, 10.0 equiv) was added portionwise. After stirring the solution for 16 h at 25 °C, 2 M NaOCl was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **31c** as a highly viscose yellow liquid (53 mg, 0.148 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 – 7.91 (m, 4H), 7.49 – 7.37 (m, 6H), 7.34 – 7.31 (m, 3H).

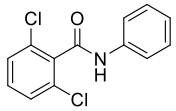
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 139.5, 139.4, 135.2, 134.4, 132.5, 132.4, 131.3 (4C), 131.2 (2C), 131.1 (2C), 128.8 (2C), 128.6 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 2977, 1732, 1568, 1552, 1480, 1437, 1416, 1372, 1395, 1240, 1185, 1146, 1093, 1044, 998, 900, 773, 722, 694, 688.

MS (EI, 70 eV): *m/z* (%) = 329 (33), 328 (19), 327 (100), 219 (15), 217 (47), 183 (28), 181 (14).

HRMS (EI): *m/z* calcd. for [$C_{18}H_{13}Cl_2PS$]: 361.9850; found 361.9846 (M^+).

2,6-Dichloro-*N*-phenylbenzamide (31d)



According to **TP 9**, a solution of 1,3-dichlorobenzene (**28a**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of isocyanatobenzene (**30d**, 55 µL, 0.500 mmol, 2.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **31d** as a white solid (34 mg, 0.128 mmol, 64%).

^{1}H-NMR (400 MHz, CD_3CN): δ / ppm = 8.87 (s, 1H), 7.67 – 7.60 (m, 2H), 7.48 – 7.44 (m, 2H), 7.43 – 7.36 (m, 3H), 7.21 – 7.15 (m, 1H).

^{13}C-NMR (101 MHz, CD_3CN): δ / ppm = 163.5, 139.3, 137.0, 132.6, 132.2 (2C), 130.0 (2C), 129.1 (2C), 125.6, 120.7 (2C).

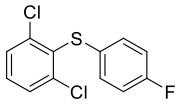
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3240, 2193, 3131, 3064, 3042, 1653, 1620, 1598, 1579, 1552, 1534, 1491, 1448, 1430, 1376, 1324, 1268, 1235, 1194, 1177, 1145, 1087, 1026, 915, 887, 798, 778, 759, 744, 701, 685.

MS (EI, 70 eV): *m/z* (%) = 177 (10), 175 (64), 109 (11).

HRMS (EI): *m/z* calcd. for [$C_{10}H_8N$]: 265.0061; found 265.0056 (M^+).

M.p. (°C): 175.5 – 177.5.

(2,6-Dichlorophenyl)(4-fluorophenyl)sulfane (31e)



According to **TP 9**, a solution of 1,3-dichlorobenzene (**28a**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of (4-fluorophenyl) benzenesulfonothioate (**30e**, 134 mg, 0.500 mmol, 2.50 equiv) in THF. The reaction was instantly quenched by the addition of 2 M NaOCl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **31e** as a colorless liquid (41 mg, 0.150 mmol, 75%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.48 – 7.44 (m, 2H), 7.31 – 7.28 (m, 1H), 7.25 – 7.19 (m, 2H), 7.01 – 6.95 (m, 2H).

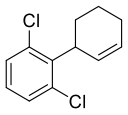
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.9 (d, *J* = 246.5 Hz), 141.8, 132.3 (2C), 130.9 (d, *J* = 2.1 Hz), 130.8 (2C), 130.6 (d, *J* = 3.3 Hz, 2C), 129.1, 116.3 (d, *J* = 22.1 Hz, 2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1589, 1565, 1553, 1487, 1423, 1400, 1292, 1226, 1187, 1155, 1140, 1106, 1088, 1042, 1012, 821, 773, 734, 711, 698, 676, 667, 659.

MS (EI, 70 eV): *m/z* (%) = 274 (21), 272 (30), 203 (12), 202 (100), 157 (12).

HRMS (EI): *m/z* calcd. for [$C_{12}H_7Cl_2FS$]: 271.9630; found 271.9623 (M^+).

2',6'-Dichloro-1,2,3,4-tetrahydro-1,1'-biphenyl (31f)



According to **TP 9**, a solution of 1,3-dichlorobenzene (**28a**, 0.167 M, 0.167 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.175 M in DMEA, 0.175 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohex-1-ene (**30f**, 49 µL, 0.418 mmol, 2.5 equiv) and CuCN·2LiCl (0.02 mL, 1.0 M in THF, 0.02 mmol, 0.10 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **31f** as a colorless oil (28 mg, 0.125 mmol, 75%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 – 7.26 (m, 2H), 7.08 (t, *J* = 8.0 Hz, 1H), 5.80 (dddd, *J* = 7.8, 5.0, 2.9, 1.0 Hz, 1H), 5.64 (ddd, *J* = 10.1, 2.9, 1.5 Hz, 1H), 4.34 (dddd, *J* = 12.0, 7.0, 4.0, 2.5 Hz, 1H), 2.20 – 1.67 (m, 6H).

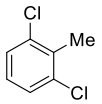
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 140.4, 129.1 (2C), 127.7 (3C), 126.8 (2C), 40.0, 26.5, 24.6, 23.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2931, 2859, 1580, 1559, 1430, 1246, 1182, 1149, 1080, 1045, 983, 933, 900, 846, 797, 775, 761, 729, 718, 690.

MS (EI, 70 eV): *m/z* (%) = 226 (100), 213 (28), 211 (45), 191 (18), 187 (15), 185 (23), 176 (17), 174 (47), 172 (75), 165 (27), 163 (88), 161 (13), 159 (22), 156 (12), 155 (29), 150 (20), 149 (26), 137 (19), 128 (65), 127 (19), 115 (25), 76 (14), 67 (13).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{12}Cl_2$]: 226.0316; found 226.0311 (M^+).

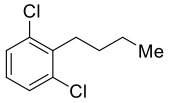
1,3-Dichloro-2-methylbenzene (31g)



According to **TP 9**, a solution of 1,3-dichlorobenzene (**28a**, 0.190 M, 0.380 mmol) in THF (total volume: 2 mL) and a solution of NaDA (0.200 M in DMEA, 0.400 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of iodomethane (**30g**, 60 µL, 1.900 mmol, 5.00 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with hexane (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, pentane) afforded the title compound **31g** as a colorless liquid (33 mg, 0.205 mmol, 54%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.27 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 1H), 2.47 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 135.6 (2C), 134.6, 127.9 (2C), 127.3, 17.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2854, 1561, 1434, 1378, 1269, 1202, 1153, 1086, 1054, 1000, 804, 769, 759, 692.
MS (EI, 70 eV): *m/z* (%) = 162 (31), 160 (49), 127 (33), 125 (100), 89 (28).
HRMS (EI): *m/z* calcd. for [$C_7H_6Cl_2$]: 159.9847; found 159.9840 (M^+).

2-Butyl-1,3-dichlorobenzene (31h)

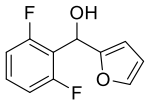


According to **TP 9**, a solution of 1,3-dichlorobenzene (**28a**, 0.190 M, 0.190 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.200 M in DMEA, 0.200 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of *n*butyl bromide (**30h**, 0.20 mL, 1.90 mmol, 10.0 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with hexane (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, pentane) afforded the title compound **31h** as a colorless liquid (20 mg, 0.101 mmol, 53%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26 (d, *J* = 8.0 Hz, 2H), 7.06 – 7.01 (m, 1H), 3.08 – 2.79 (m, 2H), 1.62 – 1.51 (m, 2H), 1.50 – 1.40 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 138.9 (2C), 135.4, 128.2 (2C), 127.4, 31.2, 30.5, 22.9, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2928, 2871, 2860, 1582, 1561, 1466, 1456, 1434, 1379, 1265, 1192, 1182, 1152, 1104, 1086, 1078, 962, 927, 822, 799, 790, 771, 758, 721.
MS (EI, 70 eV): *m/z* (%) = 204 (20), 202 (31), 163 (11), 162 (23), 161 (65), 160 (35), 159 (100), 127 (12), 125 (34), 123 (19), 89 (20).
HRMS (EI): *m/z* calcd. for [$C_{10}H_{12}Cl_2$]: 202.0316; found 202.0308 (M^+).

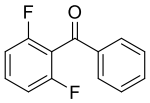
(2,6-Difluorophenyl)(furan-2-yl)methanol (31i)



According to **TP 9**, a solution of 1,3-difluorobenzene (**28b**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of furan-2-carbaldehyde (**30i**, 25 µL, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 10:1) afforded the title compound **31i** as a highly viscose brown liquid (37 mg, 0.176 mmol, 88%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 (d, *J* = 1.0 Hz, 1H), 7.34 – 7.24 (m, 1H), 6.93 (t, *J* = 8.4 Hz, 2H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.21 (d, *J* = 3.3 Hz, 1H), 6.17 (s, 1H), 2.92 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.0 (dd, *J* = 248.9, 7.9 Hz, 2C), 153.8, 142.8, 130.1 (t, *J* = 10.7 Hz), 116.9 (t, *J* = 16.5 Hz), 112.0 (d, *J* = 25.5 Hz, 2C), 110.6, 107.3, 62.3 (t, *J* = 4.3 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3410, 3115, 2926, 2855, 1758, 1703, 1624, 1593, 1468, 1396, 1336, 1270, 1233, 1192, 1144, 1086, 994, 940, 898, 886, 783, 740, 722.
MS (EI, 70 eV): *m/z* (%) = 210 (20), 193 (26), 183 (10), 182 (100), 173 (11), 164 (21), 153 (15), 141 (88), 138 (10), 133 (14), 127 (12).
HRMS (EI): *m/z* calcd. for [$C_{11}H_8F_2O_2$]: 210.0492; found 210.0487 (M^+).

(2,6-Difluorophenyl)(phenyl)methanone (31j)

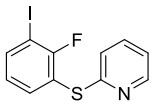


According to **TP 9**, a solution of 1,3-difluorobenzene (**28b**, 0.195 M, 0.195 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.205 M in DMEA, 0.205 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −40 °C) and was subsequently injected in a flask containing

a stirred solution of benzoyl chloride (**30j**, 57 µL, 0.488 mmol, 2.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **31j** as a colorless liquid (30 mg, 0.138 mmol, 71%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 – 7.85 (m, 2H), 7.66 – 7.59 (m, 1H), 7.53 – 7.40 (m, 3H), 7.06 – 6.96 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 189.1, 160.0 (dd, *J* = 251.7, 7.6 Hz, 2C), 137.0, 134.4, 132.0 (t, *J* = 9.9 Hz), 129.8 (2C), 128.9 (2C), 117.2 (t, *J* = 21.8 Hz), 112.2 – 111.8 (m, 2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1672, 1621, 1588, 1583, 1462, 1449, 1316, 1294, 1275, 1266, 1233, 1180, 1145, 1072, 1026, 1004, 926, 847, 800, 762, 732, 696, 686.
MS (EI, 70 eV): *m/z* (%) = 218 (57), 198 (34), 141 (97), 114 (15), 105 (100), 77 (53), 74 (10), 63 (27).
HRMS (EI): *m/z* calcd. for [$C_{13}H_8F_2O$]: 218.0543; found 218.0538 (M^+).

(2-(2-Fluoro-3-iodophenyl)thio)pyridine (31k)

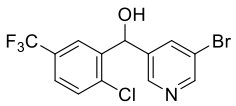


According to **TP 9**, a solution of 1-fluoro-2-iodobenzene (**28c**, 0.190 M, 0.190 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.200 M in DMEA, 0.200 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of aldrithiol (**30k**, 105 mg, 0.475 mmol, 2.50 equiv) in THF. The reaction was instantly quenched by the addition of 2 M NaOCl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **31k** as a white solid (39 mg, 0.118 mmol, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.41 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.82 (ddd, *J* = 7.9, 5.7, 1.6 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.09 – 7.01 (m, 2H), 6.95 (td, *J* = 7.8, 0.7 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5 (d, *J* = 247.0 Hz), 158.4 (d, *J* = 1.3 Hz), 149.9, 141.0 (d, *J* = 1.8 Hz), 137.2, 136.9, 126.5 (d, *J* = 4.6 Hz), 121.9, 120.7, 119.3 (d, *J* = 21.1 Hz), 82.3 (d, *J* = 27.5 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1574, 1559, 1556, 1447, 1428, 1418, 1277, 1223, 1152, 1129, 1087, 1082, 1055, 1046, 990, 882, 819, 776, 770, 760, 741, 724, 711.
MS (EI, 70 eV): *m/z* (%) = 312 (19), 205 (12), 204 (100), 203 (11), 185 (16), 127 (47).
HRMS (EI): *m/z* calcd. for [$C_{11}H_7FINS$]: 330.9328; found 330.9325 (M^+).

M.p. (°C): 72.3 – 74.1.

(5-Bromopyridin-3-yl)(2-chloro-5-(trifluoromethyl)phenyl)methanol (31l)



According to **TP 9**, a solution of 1-chloro-4-(trifluoromethyl)benzene (**28d**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of 5-bromonicotinaldehyde (**30l**, 93 mg, 0.500 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **31l** as a colorless viscous liquid (62 mg, 0.169 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.48 (d, *J* = 17.6 Hz, 2H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.83 (t, *J* = 2.0 Hz, 1H), 7.54 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 6.21 (s, 1H), 3.86 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.3, 146.7, 140.9, 139.2, 137.5, 135.9, 135.9, 130.5, 130.3 (q, *J* = 33.2 Hz), 126.4 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 3.8 Hz), 122.4 (q, *J* = 272.4 Hz), 69.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3165, 2848, 1611, 1583, 1562, 1478, 1421, 1323, 1275, 1248, 1202, 1167, 1122, 1099, 1079, 1036, 1021, 916, 886, 873, 826, 768, 737, 708, 695, 661, 654.
MS (EI, 70 eV): *m/z* (%) = 209 (26), 207 (24), 184 (11), 179 (28), 163 (25), 161 (82), 160 (32), 159 (12), 158 (99), 157 (13), 156 (100), 145 (58), 144 (15), 143 (17), 131 (27), 129 (26), 125 (41), 78 (23), 76 (34), 75 (13), 74 (12), 39 (36), 50 (18).
HRMS (EI): *m/z* calcd. for [$C_{13}H_8BrClF_3NO$]: 364.9430; found 364.9415 (M^+).

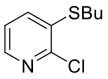
3-(Butylthio)-2-chloropyridine (31m)

According to **TP 9**, a solution of 2-chloropyridine (**28e**, 0.167 M, 0.167 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.175 M in DMEA, 0.175 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of iodine (**30a**, 216 mg, 0.835 mmol, 5.00 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. $Na_2S_2O_3$. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After

removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **31m** as white crystals (24 mg, 0.09 mmol, 53%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.37 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.15 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.8, 4.7 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.6, 148.9, 148.8, 123.2, 94.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920, 2851, 1554, 1546, 1385, 1252, 1208, 1135, 1057, 1011, 1004, 982, 794, 742, 720.
MS (EI, 70 eV): *m/z* (%) = C_5H_3ClIN]: 241 (32), 239 (100), 127 (20), 114 (11), 112 (31), 76 (15).
HRMS (EI): *m/z* calcd. for [C_5H_3ClIN]: 238.8999; found 238.8993 (M^+).
M.p. (°C): 92.7 – 93.7.

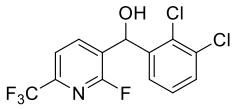
3-(Butylthio)-2-chloropyridine (31n)



According to **TP 9**, a solution of 2-chloropyridine (**28e**, 0.167 M, 0.167 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.175 M in DMEA, 0.175 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of dibutyl disulfid (**30m**, 94 µL, 0.418 mmol, 2.50 equiv) in THF. The reaction was instantly quenched by the addition of 2 M NaOCl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **31n** as an orange oil (26 mg, 0.129 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.19 (dd, *J* = 7.8, 4.7 Hz, 1H), 2.93 (t, *J* = 7.3, 2H), 1.75 – 1.64 (m, 2H), 1.56 – 1.45 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.1, 145.1, 135.2, 135.1, 122.7, 31.8, 30.5, 22.2, 13.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2929, 2872, 1547, 1464, 1433, 1379, 1346, 1212, 1143, 1128, 1064, 1042, 1035, 787, 757, 728, 655.
MS (EI, 70 eV): *m/z* (%) = 201 (25), 147 (36), 145 (100), 108 (21).
HRMS (EI): *m/z* calcd. for [$C_9H_{12}ClNS$]: 201.0379; found 201.0374 (M^+).

(2,3-Dichlorophenyl)(2-fluoro-6-(trifluoromethyl)pyridin-3-yl)methanol (31o)



According to **TP 9**, a solution of 2-fluoro-6-(trifluoromethyl)pyridine (**28f**, 0.190 M, 0.190 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.200 M in DMEA, 0.200 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of 2,3-dichlorobenzaldehyde (**30n**, 84 mg, 0.285 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **31o** as a colorless highly viscous liquid (46 mg, 0.129 mmol, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 – 7.89 (m, 1H), 7.58 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 1H), 6.44 (s, 1H), 2.82 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3 (d, *J* = 246.3 Hz), 145.6 (dd, *J* = 36.3, 13.8 Hz), 140.7 (d, *J* = 4.9 Hz), 140.1, 133.8, 131.0, 130.6, 127.9 (q, *J* = 120.7 Hz), 127.8, 126.2, 121.4 (q, *J* = 272.8 Hz), 118.5 (dq, *J* = 6.0, 3.0 Hz), 67.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1611, 1587, 1568, 1476, 1451, 1410, 1350, 1279, 1193, 1173, 1141, 1117, 1103, 1051, 1035, 974, 924, 878, 858, 821, 784, 773, 747, 742, 721, 699, 678.
MS (EI, 70 eV): *m/z* (%) = 341 (12), 339 (18), 304 (26), 194 (23), 192 (100), 177 (20), 175 (44), 174 (27), 173 (68), 166 (44), 165 (66), 164 (19), 149 (31), 148 (14), 147 (47), 146 (54), 145 (11), 139 (18), 138 (11), 126 (10), 114 (10), 111 (19), 109 (12), 75 (15).
HRMS (EI): *m/z* calcd. for [$C_{13}H_7Cl_2F_4NO$]: 338.9841; found 338.9833 (M^+).

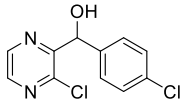
2-Chloro-3-iodopyrazine (31p)

According to **TP 9**, a solution of 2-chloropyrazine (**28g**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of iodine (**30a**, 127 mg, 0.500 mmol, 2.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. $Na_2S_2O_3$. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After

removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **31p** as light yellow crystals (31 mg, 0.129 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.30 (d, *J* = 2.4 Hz, 1H), 8.28 (d, *J* = 2.4 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.8, 142.7, 142.1, 119.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2920, 2849, 1820, 1721, 1531, 1494, 1463, 1424, 1409, 1377, 1336, 1311, 1253, 1228, 1181, 1170, 1139, 1056, 1024, 858, 778.
MS (EI, 70 eV): *m/z* (%) = 242 (32), 240 (100), 127 (36), 115 (25), 113 (73), 88 (10), 86 (30).
HRMS (EI): *m/z* calcd. for [$C_4H_2ClIN_2$]: 239.8951; found 239.8945.
M.p. (°C): 77.0 – 78.8.

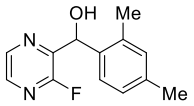
(4-Chlorophenyl)(3-chloropyrazin-2-yl)methanol (31q)



According to **TP 9**, a solution of 2-chloropyrazine (**28g**, 0.190 M, 0.190 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.200 M in DMEA, 0.200 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 4-chlorobenzaldehyde (**30o**, 40 mg, 0.285 mmol, 1.5 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **31q** as a yellow liquid (38 mg, 0.154 mmol, 79%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.56 (d, *J* = 2.5 Hz, 1H), 8.38 (d, *J* = 2.5 Hz, 1H), 7.32 – 7.27 (m, 4H), 6.00 (d, *J* = 7.3 Hz, 1H), 4.66 (d, *J* = 7.8 Hz, 1H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 154.4, 147.7, 143.4, 141.4, 139.0, 134.4, 129.0 (2C), 129.0 (2C), 71.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3397, 1489, 1401, 1368, 1291, 1243, 1187, 1152, 1105, 1087, 1037, 1013, 946, 875, 836, 821, 805, 779, 764, 749, 732, 722, 690, 674, 661, 658, 652.
MS (EI, 70 eV): *m/z* (%) = 256 (17), 254 (26), 143 (16), 141 (48), 141 (34), 140 (20), 139 (100), 125 (12), 116 (14), 115 (22), 114 (45), 113 (24), 111 (11), 79 (15), 77 (40), 75 (12).
HRMS (EI): *m/z* calcd. for [$C_{11}H_8Cl_2N_2O$]: 254.0014; found 254.0007 (M^+).

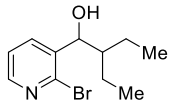
(2,4-Dimethylphenyl)(3-fluoropyrazin-2-yl)methanol (31r)



According to **TP 9**, a solution of 2-fluoropyrazine (**28h**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −60 °C) and was subsequently injected in a flask containing a stirred solution of 2,4-dimethylbenzaldehyde (**30p**, 40 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 8:2) afforded the title compound **31r** as a pale yellow oil (45 mg, 0.194 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.57 – 8.45 (m, 1H), 8.30 – 8.06 (m, 1H), 7.02 (s, 1H), 6.96 – 6.85 (m, 2H), 6.19 (s, 1H), 2.46 (s, 3H), 2.28 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.5 (d, *J* = 255.0 Hz), 146.0 (d, *J* = 29.2 Hz), 140.6 (d, *J* = 8.4 Hz), 140.3 (d, *J* = 4.9 Hz), 138.3, 136.5, 135.6, 131.9, 127.3, 127.1, 67.8 (d, *J* = 5.9 Hz), 21.2, 19.21 (d, *J* = 1.6 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3391, 3014, 2922, 1710, 1614, 1537, 1502, 1453, 1407, 1379, 1265, 1198, 1171, 1110, 1037, 932, 893, 859, 838, 810, 762, 718.
MS (EI, 70 eV): *m/z* (%) = 216 (11), 214 (13), 213 (100), 201 (23), 199 (13), 135 (16), 134 (99), 133 (61), 107 (25), 105 (26), 99 (10), 91 (23), 79 (10).
HRMS (EI): *m/z* calcd. for [$C_{13}H_{13}FN_2O$]: 232.1012; found 232.1006 (M^+).

1-(2-Bromopyridin-3-yl)-2-ethylbutan-1-ol (31s)



According to **TP 9**, a solution of 2-bromopyridine (**28i**, 0.190 M, 0.190 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.200 M in DMEA, 0.200 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-ethylbutanal (**30q**, 29 mg, 0.285 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **31s** as a yellow oil (32 mg, 0.124 mmol, 65%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.25 (dd, *J* = 4.7, 2.0 Hz, 1H), 7.86 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.29 (dd, *J* = 7.7, 4.6 Hz, 1H), 5.07 (t, *J* = 4.0 Hz, 1H), 2.15 (s, 1H), 1.70 – 1.63 (m, 1H), 1.57 – 1.49 (m, 1H), 1.40 – 1.29 (m, 3H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H).

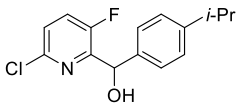
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 148.7, 141.9, 140.6, 137.4, 122.9, 72.9, 45.6, 22.7, 19.9, 11.7, 11.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2931, 2873, 1575, 1559, 1458, 1401, 1379, 1181, 1130, 1103, 1065, 1052, 1040, 1016, 837, 805, 773, 754, 744, 735, 705.

MS (EI, 70 eV): *m/z* (%) = 189 (55), 188 (98), 187 (56), 186 (100), 185 (17), 183 (12), 158 (10), 156 (11), 130 (23), 122 (29), 108 (14), 107 (38), 106 (25), 105 (24), 81 (17), 79 (58), 78 (46).

HRMS (EI): *m/z* calcd. for [$C_{11}H_{16}BrNO$]: 257.0415; found 257.0407 (M^+).

(6-Chloro-3-fluoropyridin-2-yl)(4-isopropylphenyl)methanol (31t)



According to **TP 9**, a solution of 2-chloro-5-fluoropyridine (**28j**, 0.190 M, 0.190 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.200 M in DMEA, 0.200 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 4-isopropylbenzaldehyde (**30r**, 42 mg, 0.285 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **31t** as white crystals (41 mg, 0.147 mmol, 77%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.04 (s, 1H), 7.69 (d, *J* = 5.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.01 (d, *J* = 3.0 Hz, 1H), 2.89 (h, *J* = 13.9, 7.0 Hz, 1H), 2.70 (s, 1H), 1.23 (d, *J* = 6.9 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 155.9 (d, *J* = 255.2 Hz), 149.8, 146.8 (d, *J* = 2.9 Hz), 143.3 (d, *J* = 12.9 Hz), 138.2, 137.2 (d, *J* = 26.5 Hz), 127.2 (2C), 126.7 (d, *J* = 1.1 Hz, 2C), 122.1 (d, *J* = 1.9 Hz), 69.5 (d, *J* = 1.8 Hz), 34.0, 24.0 (2C).

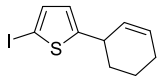
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3262, 3246, 3241, 3227, 2956, 1605, 1462, 1427, 1422, 1353, 1297, 1285, 1256, 1244, 1194, 1180, 1164, 1090, 1052, 1018, 921, 895, 849, 837, 831, 814, 755, 717, 663.

MS (EI, 70 eV): *m/z* (%) = 264 (22), 262 (13), 261 (11), 248 (11), 238 (18), 236 (56), 160 (31), 159 (16), 158 (100), 147 (13), 130 (17), 119 (22), 115 (11), 105 (12), 91 (24), 59 (10).

HRMS (EI): *m/z* calcd. for [$C_{15}H_{15}ClFNO$]: 279.0826; found 279.0822 (M^+).

M.p. (°C): 105.8 – 107.2.

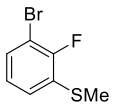
2-(Cyclohex-2-en-1-yl)-5-iodothiophene (31u)



According to **TP 9**, a solution of 2-iodothiophene (**28k**, 0.195 M, 0.195 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.205 M in DMEA, 0.205 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 3-bromocyclohexene (**30f**, 79 mg, 0.488 mmol, 2.50 equiv) and CuCN·2LiCl (0.01 mL, 1.0 M in THF, 5 mol%) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **31u** as a pale brown oil (43 mg, 0.148 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.06 (d, *J* = 3.6 Hz, 1H), 6.52 (dd, *J* = 3.7, 0.9 Hz, 1H), 5.92 – 5.82 (m, 1H), 5.74 (dd, *J* = 9.9, 3.2 Hz, 1H), 3.73 – 3.61 (m, 1H), 2.13 – 1.95 (m, 3H), 1.79 – 1.58 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.8, 136.6, 129.1, 129.0, 125.4, 70.1, 37.1, 32.4, 25.0, 20.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3018, 2919, 2849, 1720, 1646, 1587, 1455, 1444, 1428, 1402, 1377, 1347, 1309, 1295, 1253, 1133, 1050, 973, 940, 894, 869, 790, 753, 721, 684.
MS (EI, 70 eV): *m/z* (%) = 163 (4), 135 (5), 127 (100).
HRMS (EI): *m/z* calcd. for [$C_{10}H_{11}IS$]: 289.9626; found 289.9618 (M^+).

(3-Bromo-2-fluorophenyl)(methyl)sulfane (31v)



According to **TP 9**, a solution of 1-bromo-2-fluorobenzene (**28l**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −60 °C) and was subsequently injected in a flask containing a stirred solution of dimethyldisulfide (**30s**, 57 mg, 0.600 mmol, 3.00 equiv) in THF. The reaction was instantly quenched by the addition of 2 M NaOCl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **31v** as a light orange oil (31 mg, 0.140 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.39 – 7.33 (m, 1H), 7.21 – 7.16 (m, 1H), 7.01 – 6.95 (m, 1H), 2.48 (s, 3H).

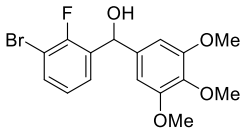
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.5 (d, *J* = 244.6 Hz), 130.5, 127.8 (d, *J* = 18.3 Hz), 127.6 (d, *J* = 2.1 Hz), 125.3 (d, *J* = 4.5 Hz), 109.4 (d, *J* = 21.5 Hz), 15.8 (d, *J* = 2.8 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3069, 2923, 2853, 1710, 1583, 1559, 1442, 1434, 1319, 1286, 1234, 1203, 1158, 1093, 1080, 1058, 970, 957, 880, 820, 758, 704.

MS (EI, 70 eV): *m/z* (%) = 222 (99), 220 (100), 189 (41), 187 (41), 176 (15), 174 (16), 140 (14), 126 (55).

HRMS (EI): *m/z* calcd. for [C_7H_6BrFS]: 219.9358; found 219.9351 (M^+).

(3-Bromo-2-fluorophenyl)(3,4,5-trimethoxyphenyl)methanol (31w)



According to **TP 9**, a solution of 1-bromo-2-fluorobenzene (**28l**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −60 °C) and was subsequently injected in a flask containing a stirred solution of 3,4,5-trimethoxybenzaldehyde (**30t**, 59 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1 → 4:1 → 2:1) afforded the title compound **31w** as a colorless liquid (59 mg, 0.159 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.49 – 7.43 (m, 2H), 7.03 (td, *J* = 7.9, 0.8 Hz, 1H), 6.60 (s, 2H), 6.05 (s, 1H), 3.82 (s, 6H), 3.81 (s, 3H).

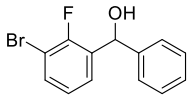
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.2 (d, *J* = 247.1 Hz), 153.4 (2C), 138.1, 137.6, 132.7 (d, *J* = 14.0 Hz), 132.7, 126.7 (d, *J* = 3.5 Hz), 125.4 (d, *J* = 4.4 Hz), 109.2 (d, *J* = 21.2 Hz), 103.4 (d, *J* = 0.8 Hz, 2C), 70.1 (d, *J* = 2.9 Hz), 60.9, 56.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3480, 3393, 2966, 2936, 2836, 2827, 1592, 1505, 1450, 1415, 1400, 1331, 1310, 1273, 1227, 1183, 1177, 1122, 1083, 1070, 1059, 996, 970, 921, 883, 861, 838, 829, 796, 785, 766, 753, 734, 714, 677.

MS (EI, 70 eV): *m/z* (%) = 372 (49), 370 (54), 203 (60), 201 (65), 169 (100), 154 (13), 138 (21).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{16}BrFO_4$]: 370.0216; found 370.0208 (M^+).

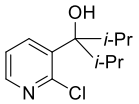
(3-Bromo-2-fluorophenyl)(phenyl)methanol (31x)



According to **TP 9**, a solution of 1-bromo-2-fluorobenzene (**28l**, 0.210 M, 0.210 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.221 M in DMEA, 0.221 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −60 °C) and was subsequently injected in a flask containing a stirred solution of benzaldehyde (**30b**, 33 mg, 0.315 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 19:1) afforded the title compound **31x** as a pale yellow oil (48 mg, 0.171 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.54 – 7.43 (m, 2H), 7.41 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 7.08 – 7.01 (m, 1H), 6.13 (s, 1H), 2.39 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.2 (d, *J* = 247.3 Hz), 142.3, 132.9, 132.7 (2C), 128.8 (2C), 128.2, 126.8 (d, *J* = 3.6 Hz), 126.5 (d, *J* = 0.8 Hz), 125.4 (d, *J* = 4.4 Hz), 109.3 (d, *J* = 21.2 Hz), 70.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3320, 3064, 3031, 2915, 1950, 1881, 1809, 1683, 1602, 1573, 1493, 1450, 1314, 1226, 1190, 1168, 1127, 1081, 1036, 1023, 918, 870, 818, 773, 725, 696.
MS (EI, 70 eV): *m/z* (%) = 283 (13), 282 (86), 281 (13), 280 (88), 279 (14), 205 (10), 203 (100), 201 (100), 185 (11), 184 (11), 183 (52), 172 (11), 165 (11), 152 (11), 123 (11), 107 (17), 105 (91), 96 (20), 94 (18), 79 (56), 78 (70), 77 (33).
HRMS (EI): *m/z* calcd. for [$C_{13}H_{10}BrFO$]: 279.9899; found 279.9893 (M^+).

3-(2-Chloropyridin-3-yl)-2,4-dimethylpentan-3-ol (33a)



According to **TP 9**, a solution of 2-chloropyridine (**28e**, 0.195 M, 0.195 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.205 M in DMEA, 0.205 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −20 °C) and was subsequently injected in a flask containing a stirred solution of 2,4-dimethylpentan-3-one (**32a**, 33 mg, 0.293 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1 → 1:1) afforded the title compound **33a** as colorless crystals (30 mg, 0.132 mmol, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.28 (dd, *J* = 4.6, 1.9 Hz, 1H), 8.09 (s, 1H), 7.24 (dd, *J* = 7.9, 4.5 Hz, 1H), 2.77 (s, 2H), 0.95 (d, *J* = 6.7 Hz, 6H), 0.81 (d, *J* = 6.9 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.6, 147.5, 140.1, 121.7, 81.6, 34.3 (2C), 18.6 (2C), 17.2 (2C).

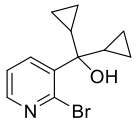
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3374, 2993, 2962, 2935, 2877, 2848, 1591, 1573, 1554, 1463, 1454, 1384, 1371, 1330, 1321, 1296, 1235, 1224, 1177, 1167, 1151, 1119, 1097, 1059, 1013, 996, 987, 956, 912, 869, 834, 809, 752, 747, 658.

MS (EI, 70 eV): *m/z* (%) = 186 (30), 184 (91), 182 (10), 148 (100), 142 (24), 140 (77), 133 (14), 130 (34), 120 (20), 117 (11), 112 (17), 106 (15), 92 (10), 78 (23), 77 (11).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{16}ClN$]: 209.0971; found 209.0965 ($M^+ - H_2O$).

M.p. (°C): 113.8 – 115.4.

(2-Bromopyridin-3-yl)dicyclopropylmethanol (33b)



According to **TP 9**, a solution of 2-bromopyridine (**28i**, 0.180 M, 0.180 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.189 M in DMEA, 0.189 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of dicyclopropylmethanone (**32b**, 31 µL, 0.27 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **33b** as colorless crystals (26 mg, 0.100 mmol, 54%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.25 (dd, *J* = 4.6, 1.9 Hz, 1H), 8.07 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.25 (dd, *J* = 7.8, 4.6 Hz, 1H), 1.95 (s, 1H), 1.65 (tt, *J* = 8.2, 5.7 Hz, 2H), 0.81 – 0.72 (m, 2H), 0.62 (tdd, *J* = 8.3, 7.0, 4.6 Hz, 2H), 0.42 – 0.32 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.9, 144.0, 140.5, 137.2, 122.5, 73.0, 19.3 (2C), 4.2 (2C), 1.1 (2C).

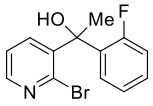
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3377. 3083, 3007, 1571, 1555, 1434, 1427, 1389, 1314, 1261, 1234, 1212, 1184, 1169, 1120, 1110, 1049, 1040, 1006, 973, 958, 920, 909, 853, 824, 795, 780, 735, 731, 662.

MS (EI, 70 eV): *m/z* (%) = 241 (21), 239 (23), 228 (53), 226 (53), 199 (12), 197 (11), 186 (95), 184 (100), 160 (74), 158 (15), 156 (15), 154 (12), 132 (10), 130 (43), 118 (16), 117 (42), 115 (10), 91 (14), 89 (13), 81 (13), 79 (13), 78 (17), 69 (19).

HRMS (EI): *m/z* calcd. for [$C_{10}H_{10}BrNO$]: 238.9946; found 238.9939 ($M^+ - C_2H_4$).

M.p. (°C): 137.9 – 139.7.

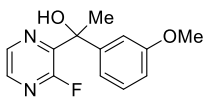
1-(2-Bromopyridin-3-yl)-1-(2-fluorophenyl)ethan-1-ol (33c)



According to **TP 9**, a solution of 2-bromopyridine (**28i**, 0.180 M, 0.180 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.189 M in DMEA, 0.189 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 1-(2-fluorophenyl)ethan-1-one (**32c**, 33 µL, 0.27 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **33c** as a grey solid (30 mg, 0.101 mmol, 56%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.28 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.20 – 8.15 (m, 1H), 7.70 (td, *J* = 8.1, 1.8 Hz, 1H), 7.35 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.19 (td, *J* = 7.6, 1.3 Hz, 1H), 6.92 (ddd, *J* = 11.8, 8.1, 1.3 Hz, 1H), 2.02 (d, *J* = 0.8 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.6 (d, *J* = 246.3 Hz), 148.8, 142.7 (d, *J* = 1.3 Hz), 140.5, 136.5 (d, *J* = 2.9 Hz), 132.6 (d, *J* = 10.7 Hz), 129.8 (d, *J* = 8.6 Hz), 128.8 (d, *J* = 3.6 Hz), 124.0 (d, *J* = 3.4 Hz), 122.9, 116.3 (d, *J* = 22.4 Hz), 74.2, 28.1 (d, *J* = 1.3 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3262, 3076, 2982, 2923, 2867, 1770, 1728, 1609, 1574, 1556, 1485, 1451, 1440, 1404, 1389, 1367, 1277, 1248, 1231, 1225, 1200, 1185, 1160, 1134, 1101, 1087, 1052, 1039, 1031, 991, 922, 863, 845, 816, 803, 757, 748, 726, 661.
MS (EI, 70 eV): *m/z* (%) = 283 (13), 282 (98), 281 (12), 280 (100), 200 (21), 198 (39), 186 (20), 184 (22), 178 (14), 173 (10), 172 (40), 170 (16), 159 (25), 157 (23), 139 (25), 123 (20).
HRMS (EI): *m/z* calcd. for [$C_{13}H_{11}BrFNO$]: 295.0008; found 294.9996 (M^+).
M.p. (°C): 101.8 – 102.0.

1-(3-Fluoropyrazin-2-yl)-1-(3-methoxyphenyl)ethan-1-ol (33d)

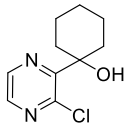


According to **TP 9**, a solution of 2-fluoropyrazine (**28h**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −60 °C) and was subsequently injected in a flask containing a stirred solution of 1-(3-methoxyphenyl)ethan-1-one (**32d**, 45 mg, 0.300 mmol, 1.50 equiv) in THF.

The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **33d** as a light yellow oil (38 mg, 0.153 mmol, 77%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.53 – 8.46 (m, 1H), 8.22 (t, *J* = 2.2 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.06 – 7.00 (m, 2H), 6.87 – 6.82 (m, 1H), 5.35 (s, 1H), 3.82 (s, 3H), 2.06 (d, *J* = 1.8 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.0, 157.5 (d, *J* = 255.4 Hz), 148.9 (d, *J* = 27.1 Hz), 146.3, 141.1 (d, *J* = 8.6 Hz), 139.6 (d, *J* = 5.0 Hz), 129.5, 118.2 (d, *J* = 1.8 Hz), 112.9, 112.0 (d, *J* = 1.5 Hz), 74.1 (d, *J* = 6.8 Hz), 55.4, 26.6 (d, *J* = 4.0 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3428, 3071, 2983, 2938, 2836, 1600, 1584, 1538, 1486, 1452, 1433, 1399, 1366, 1317, 1289, 1249, 1195, 1164, 1115, 1088, 1040, 996, 935, 857, 787, 769, 700, 684.
MS (EI, 70 eV): *m/z* (%) = 249 (11), 248 (81), 233 (30), 229 (17), 205 (20), 151 (100), 150 (21), 135 (37), 125 (33), 99 (10), 97 (28), 77 (11), 43 (23).
HRMS (EI): *m/z* calcd. for [$C_{13}H_{13}FN_2O_2$]: 248.0961; found 248.0955 (M^+).

1-(3-Chloropyrazin-2-yl)cyclohexan-1-ol (33e)



According to **TP 9**, a solution of 2-chloropyrazine (**28g**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of cyclohexanone (**32e**, 29 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **33e** as colorless crystals (30 mg, 0.141 mmol, 71%).

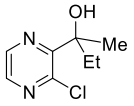
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (d, *J* = 2.4 Hz, 1H), 8.34 (d, *J* = 2.4 Hz, 1H), 4.90 (s, 1H), 2.48 (td, *J* = 13.1, 4.5 Hz, 2H), 1.95 – 1.76 (m, 3H), 1.74 – 1.66 (m, 2H), 1.62 – 1.52 (m, 2H), 1.45 – 1.33 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.4, 147.1, 142.4, 140.1, 73.8, 34.3 (2C), 25.3, 22.0 (2C).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3413, 2953, 2922, 2890, 2852, 1446, 1440, 1388, 1365, 1341, 1327, 1272, 1236, 1183, 1130, 1087, 1063, 1035, 1014, 982, 913, 867, 835, 789, 771.

MS (EI, 70 eV): *m/z* (%) = 212 (20), 194 (10), 186 (17), 184 (47), 171 (11), 149 (80), 141 (45), 130 (12), 128 (35), 116 (11), 115 (19), 114 (25), 99 (11), 98 (25), 79 (13), 57 (18), 56 (12), 55 (15), 44 (100), 43 (47), 42 (15), 41 (28).

HRMS (EI): *m/z* calcd. for [$C_{10}H_{13}ClN_2O$]: 212.0716; found 212.0707 (M^+).

M.p. (°C): 71.6 – 73.1.

2-(3-Chloropyrazin-2-yl)butan-2-ol (33f)



According to **TP 9**, a solution of 2-chloropyrazine (**28g**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of butan-2-one (**32f**, 22 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **33f** as a pale yellow oil (24 mg, 0.129 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (d, *J* = 2.4 Hz, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 5.34 (s, 1H), 2.33 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.97 (dq, *J* = 14.2, 7.5 Hz, 1H), 1.68 (s, 3H), 0.69 (t, *J* = 7.4 Hz, 3H).

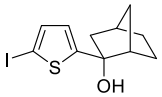
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.8, 147.0, 142.6, 139.9, 74.6, 32.5, 26.5, 8.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 2971, 2932, 2877, 1726, 1551, 1457, 1436, 1371, 1351, 1286, 1236, 1197, 1130, 1061, 1035, 996, 927, 858, 796, 776.

MS (EI, 70 eV): *m/z* (%) = 159 (29), 115 (17), 43 (37).

HRMS (EI): *m/z* calcd. for [$C_8H_{11}ClN_2O$]: 186.0560; found 186.0545 (M^+).

2-(5-Iodothiophen-2-yl)bicyclo[2.2.1]heptan-2-ol (33g)

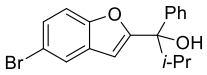


According to **TP 9**, a solution of 2-iodothiophene (**28k**, 0.195 M, 0.195 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.205 M in DMEA, 0.205 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of bicyclo[2.2.1]heptan-2-one (**32g**, 32 mg, 0.293 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and

filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **33g** as a colorless liquid (38 mg, 0.119 mmol, 61%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.07 (d, *J* = 3.8 Hz, 1H), 6.65 (d, *J* = 3.8 Hz, 1H), 2.43 (d, *J* = 2.7 Hz, 1H), 2.34 – 2.29 (m, 1H), 2.24 (ddd, *J* = 13.1, 4.8, 2.8 Hz, 1H), 2.15 – 2.05 (m, 1H), 2.02 (s, 1H), 1.68 – 1.57 (m, 2H), 1.53 – 1.37 (m, 3H), 1.37 – 1.31 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.2, 136.5, 124.6, 79.6, 72.5, 50.0, 48.1, 38.9, 37.3, 28.8, 22.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3409, 2948, 2867, 1731, 1474, 1452, 1445, 1423, 1373, 1308, 1291, 1252, 1228, 1212, 1188, 1163, 1130, 1121, 1069, 1041, 1002, 964, 952, 929, 918, 821, 790, 753.
MS (EI, 70 eV): *m/z* (%) = 302 (19), 274 (100), 252 (13), 237 (12), 193 (12), 175 (37), 147 (36), 127 (55).
HRMS (EI): *m/z* calcd. for [$C_{11}H_{13}IOS$]: 319.9732; found 319.9726 (M^+).

1-(5-Bromobenzofuran-2-yl)-2-methyl-1-phenylpropan-1-ol (33h)



According to **TP 9**, a solution of 5-bromobenzofuran (**28m**, 0.195 M, 0.195 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.205 M in DMEA, 0.205 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 2-methyl-1-phenylpropan-1-one (**32h**, 43 mg, 0.293 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 95:5) afforded the title compound **33h** as a colorless viscous liquid (61 mg, 0.177 mmol, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64 (d, *J* = 1.8 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.39 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 6.68 (s, 1H), 2.80 (hept, *J* = 6.8 Hz, 1H), 2.44 (s, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.2, 153.6, 143.1, 130.4, 128.3 (2C), 127.4, 126.8, 125.7 (2C), 123.7, 116.0, 112.8, 102.4, 78.8, 36.3, 17.4, 16.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3572, 3475, 3058, 3025, 2966 2931, 2874, 1609, 1599, 1585, 1490, 1442, 1386, 1366, 1343, 1317, 1258, 1242, 1163, 1147, 1117, 1077, 1049, 1013, 981, 938, 901, 865, 793, 749, 699, 673.
MS (EI, 70 eV): *m/z* (%) = 328 (27), 326 (27), 324 (12), 303 (16), 302 (17), 300 (19), 231 (18), 225 (23), 223 (27), 215 (13), 207 (24), 202 (20), 198 (11), 196 (12), 169 (10), 167 (10), 129 (15), 128 (13),

117 (14), 115 (33), 105 (79), 103 (10), 98 (18), 96 (19), 91 (12), 89 (10), 82 (31), 81 (100), 79 (91), 78 (18), 77 (26).

HRMS (EI): *m/z* calcd. for [$C_{18}H_{15}BrO$]: 326.0306; found 326.0300 ($M^+ - H_2O$).

4-(2,6-Difluorophenyl)tetrahydro-2*H*-pyran-4-ol (33i)

According to **TP 9**, a solution of 1,3-difluorobenzene (**28b**, 0.195 M, 0.195 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.205 M in DMEA, 0.205 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of tetrahydro-4*H*-pyran-4-one (**32i**, 57 mg, 0.293 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **33i** as a white solid (23 mg, 0.107 mmol, 55%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.17 (m, 1H), 6.88 (dd, *J* = 10.9, 8.4 Hz, 2H), 4.00 (t, *J* = 11.0 Hz, 2H), 3.81 (dd, *J* = 10.3, 5.0 Hz, 2H), 2.77 – 2.72 (m, 1H), 2.44 (td, *J* = 13.5, 4.8 Hz, 2H), 2.01 (d, *J* = 13.8 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.0 (dd, *J* = 247.8, 9.0 Hz, 2C), 129.1 (t, *J* = 12.1 Hz, 2C), 122.3 (t, *J* = 13.2 Hz), 114.3 – 111.5 (m), 71.9 (t, *J* = 2.3 Hz), 63.6 (2C), 38.0 (t, *J* = 4.6 Hz, 2C).

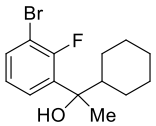
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3357, 2975, 2962, 2935, 2923, 2881, 2853, 1618, 1578, 1571, 1464, 1454, 1429, 1391, 1362, 1329, 1305, 1290, 1260, 1230, 1208, 1141, 1122, 1093, 1076, 1029, 1019, 988, 966, 915, 836, 796, 730, 706.

MS (EI, 70 eV): *m/z* (%) = 214 (17), 196 (47), 185 (15), 170 (100), 169 (18), 168 (76), 158 (14), 156 (56), 142 (23), 141 (74), 140 (36), 139 (10), 127 (49), 114 (28), 113 (19), 100 (31), 73 (10), 72 (13), 57 (10), 43 (74), 42 (53).

HRMS (EI): *m/z* calcd. for [$C_{11}H_{12}F_2O_2$]: 214.0805; found 214.0804 (M^+).

M.p. (°C): 76.9 – 78.8.

1-(3-Bromo-2-fluorophenyl)-1-cyclohexylethan-1-ol (33j)

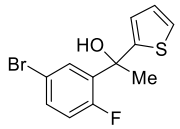


According to **TP 9**, a solution of 1-bromo-2-fluorobenzene (**28l**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared.

The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −60 °C) and was subsequently injected in a flask containing a stirred solution of 1-cyclohexylethan-2-one (**32j**, 38 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex) afforded the title compound **33j** as a highly viscose colorless liquid (33 mg, 0.110 mmol, 55%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.49 (td, *J* = 7.6, 1.7 Hz, 1H), 7.44 (ddd, *J* = 8.0, 6.4, 1.7 Hz, 1H), 6.99 (td, *J* = 7.9, 0.8 Hz, 1H), 1.90 – 1.76 (m, 4H), 1.72 – 1.61 (m, 2H), 1.59 (d, *J* = 1.8 Hz, 3H), 1.36 – 0.96 (m, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.6 (d, *J* = 246.2 Hz), 136.7 (d, *J* = 13.4 Hz), 132.1, 127.4 (d, *J* = 4.5 Hz), 124.7 (d, *J* = 4.2 Hz), 110.0 (d, *J* = 23.5 Hz), 76.6 (d, *J* = 4.8 Hz), 46.5 (d, *J* = 3.2 Hz), 27.5, 27.0, 26.7 (d, *J* = 0.5 Hz), 26.5, 26.0, 26.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3603, 3473, 2929, 2852, 1600, 1565, 1437, 1374, 1334, 1293, 1245, 1225, 1197, 1175, 1159, 1127, 1086, 1059, 1030, 1004, 971, 939, 906, 892, 868, 847, 822, 800, 778, 762, 731, 673, 656.
MS (EI, 70 eV): *m/z* (%) = 219 (96), 217 (100), 216 (10).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{18}BrFO$]: 300.0525; found 300.0510 (M^+).

1-(5-Bromo-2-fluorophenyl)-1-(thiophen-2-yl)ethan-1-ol (33k)



According to **TP 9**, a solution of 1-bromo-4-fluorobenzene (**28n**, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −40 °C) and was subsequently injected in a flask containing a stirred solution of 1-(furan-2-yl)ethan-1-one (**32k**, 38 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **33k** as a pale orange oil (42 mg, 0.140 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (dd, *J* = 7.2, 2.6 Hz, 1H), 7.40 (ddd, *J* = 8.6, 4.3, 2.6 Hz, 1H), 7.25 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.96 – 6.86 (m, 3H), 2.66 (d, *J* = 3.1 Hz, 1H), 2.05 (d, *J* = 1.1 Hz, 3H).

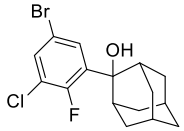
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.1 (d, *J* = 247.6 Hz), 151.3 (d, *J* = 1.0 Hz), 136.3 (d, *J* = 12.4 Hz), 132.4 (d, *J* = 8.7 Hz), 130.2 (d, *J* = 3.6 Hz), 126.8, 125.3, 124.3 (d, *J* = 1.7 Hz), 118.1 (d, *J* = 24.7 Hz), 116.9 (d, *J* = 3.3 Hz), 72.8 (d, *J* = 2.0 Hz), 30.1 (d, *J* = 3.7 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3422, 3104, 3072, 2976, 2934, 1572, 1475, 1447, 1434, 1391, 1374, 1351, 1322, 1254, 1234, 1219, 1195, 1163, 1127, 1087, 1078, 1053, 1015, 917, 893, 859, 843, 813, 785, 749, 698, 669.

MS (EI, 70 eV): *m/z* (%) = 287 (10), 285 (11), 284 (61), 281 (15), 203 (26), 202 (100), 201 (14), 184 (15), 183 (15), 170 (31), 159 (13), 157 (15), 101 (18).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{10}BrFOS$]: 299.9620; found 299.9612 (M^+).

2-(5-Bromo-3-chloro-2-fluorophenyl)adamantan-2-ol (33l)



According to **TP 9**, a solution of 4-bromo-2-chloro-1-fluorobenzene (**28o**, 0.190 M, 0.190 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.200 M in DMEA, 0.200 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of adamantan-2-one (**32l**, 45 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **33l** as a white solid (40 mg, 0.114 mmol, 57%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.48 (s, 1H), 7.46 (s, 1H), 2.60 (s, 2H), 2.39 (dd, *J* = 12.8, 3.0 Hz, 2H), 1.91 – 1.78 (m, 4H), 1.76 – 1.65 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.6 (d, *J* = 252.0 Hz), 136.0 (d, *J* = 11.3 Hz), 132.1, 130.3 (d, *J* = 4.6 Hz), 123.8 (d, *J* = 21.8 Hz), 116.4 (d, *J* = 4.2 Hz), 77.1 (d, *J* = 2.3 Hz), 37.5, 35.8, 35.8, 35.2 (2C) , 33.0 (2C), 27.1, 26.6 (d, *J* = 1.0 Hz).

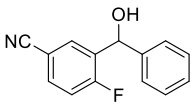
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3358, 3335, 2935, 2899, 2847, 1562, 1451, 1388, 1384, 1355, 1331, 1244, 1220, 1195, 1173, 1166, 1161, 1102, 1082, 1052, 1009, 997, 985, 942, 921, 877, 854, 838, 754, 735, 688, 668.

MS (EI, 70 eV): *m/z* (%) = 342 (31), 340 (25), 237 (31), 235 (24), 225 (20), 223 (12), 210 (14), 208 (11), 207 (31), 206 (19), 184 (12), 183 (28), 171 (11), 170 (26), 165 (11), 151 (24), 149 (18), 133 (15), 128 (16), 121 (13), 93 (39), 92 (11), 91 (52), 81 (75), 80 (23), 79 (100), 78 (31), 77 (19), 67 (25), 45 (17), 44 (66), 42 (27).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{17}BrClFO$]: 358.0135; found 358.0131 (M^+).

M.p. (°C): 98.2 – 101.0.

4-Fluoro-3-(hydroxy(phenyl)methyl)benzonitrile (36a)



According to **TP 9**, a solution of 4-fluorobenzonitrile (**34**, 0.220 M, 0.220 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.199 M in DMEA, 0.199 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of benzaldehyde (**30b**, 35 mg, 0.330 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **36a** as a colorless crystals (34 mg, 0.150 mmol, 75%).

scale-up:

In addition, a convenient scale-up of the reaction according to **TP 9** was demonstrated. A solution of 4-fluorobenzonitrile (**34**, 0.228 M) in THF (total volume: 30 mL, 6.84 mmol) and a solution of NaDA (0.205 M in DMEA, 30 mL, 6.15 mmol, 0.9 equiv) were prepared. The solutions were injected into 6 mL loading coils and subsequently precooled and mixed with an overall 10 mL·min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of benzaldehyde (**30b**, 1.05 g, 9.90 mmol, 1.50 equiv) in THF. This procedure was repeated 5 times, leading to a total amount of 30 mL collected in the same flask. Stirring was continued for 5 min at 0 °C before sat. aq. NH_4Cl was added to quench the reaction. The aq. phase was extracted three times with EtOAc (3×100 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **36a** as colorless crystals (1.06 g, 4.67 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 – 7.93 (m, 1H), 7.56 (ddd, *J* = 8.5, 4.8, 2.2 Hz, 1H), 7.43 – 7.29 (m, 5H), 7.10 (dd, *J* = 9.6, 8.5 Hz, 1H), 6.10 (s, 1H), 2.51 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.1 (d, *J* = 256.6 Hz), 141.7, 133.5 (d, *J* = 9.6 Hz), 133.2 (d, *J* = 14.6 Hz), 132.2 (d, *J* = 5.6 Hz), 129.0 (2C), 128.5 (2C), 126.5 (d, *J* = 1.2 Hz), 118.3, 116.9 (d, *J* = 23.3 Hz), 108.8 (d, *J* = 3.8 Hz), 69.6 (d, *J* = 2.8 Hz).

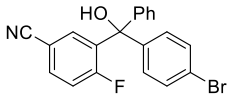
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3496, 2922, 2904, 2232, 1606, 1586, 1486, 1453, 1412, 1393, 1346, 1300, 1280, 1244, 1219, 1190, 1133, 1112, 1076, 1044, 1026, 927, 911, 837, 808, 760, 695, 685, 656.

MS (EI, 70 eV): *m/z* (%) = 227 (58), 225 (19), 208 (24), 205 (11), 149 (12), 148 (100), 122 (17), 121 (37), 105 (66), 100 (10), 79 (43), 78 (17), 77 (33).

HRMS (EI): *m/z* calcd. for [$C_{14}H_{10}FNO$]: 227.0746; found 227.0741 (M^+).

M.p. (°C): 103.7 – 105.6.

3-((4-Bromophenyl)(hydroxy)(phenyl)methyl)-4-fluorobenzonitrile (36b)



According to **TP 9**, a solution of 4-fluorobenzonitrile (**34**, 0.230 M, 0.230 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.207 M in DMEA, 0.207 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of (4-bromophenyl)(phenyl)methanone (**32m**, 90 mg, 0.345 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **36b** as white crystals (71 mg, 0.186 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.66 (ddd, *J* = 8.4, 4.6, 2.2 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.40 – 7.35 (m, 3H), 7.33 (dd, *J* = 7.4, 2.2 Hz, 1H), 7.25 – 7.13 (m, 5H), 3.28 (d, *J* = 6.8 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.0 (d, *J* = 256.7 Hz), 143.8, 143.4, 135.9 (d, *J* = 11.7 Hz), 134.4 (d, *J* = 10.3 Hz), 134.2 (d, *J* = 4.7 Hz), 131.6 (2C), 129.3 (d, *J* = 1.1 Hz), 128.7, 128.6 (3C), 127.3, 122.5, 118.1, 118.1, 117.8, 108.7 (d, *J* = 3.7 Hz), 80.3.

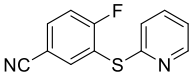
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3453, 2237, 1585, 1484, 1446, 1403, 1398, 1338, 1262, 1236, 1195, 1189, 1171, 1134, 1108, 1073, 1033, 1021, 1008, 970, 917, 892, 835, 829, 816, 768, 734, 727, 707, 702, 691, 675, 667, 659, 654.

MS (EI, 70 eV): *m/z* (%) = 304 (10), 281 (12), 263 (22), 261 (22), 226 (10), 207 (45), 185 (37), 183 (36), 154 (13), 148 (100), 105 (30), 77 (12).

HRMS (EI): *m/z* calcd. for [$C_{20}H_{13}BrFNO$]: 381.0165; found 381.0160 (M^+).

M.p. (°C): 168.1 – 170.3.

4-Fluoro-3-(pyridin-2-ylthio)benzonitrile (36c)

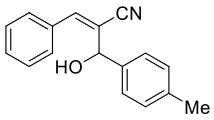


According to **TP 9**, a solution of 4-fluorobenzonitrile (**34**, 0.228 M, 0.228 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.205 M in DMEA, 0.205 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing

a stirred solution of aldrithiol (**30k**, 126 mg, 0.570 mmol, 2.50 equiv) in THF. The reaction was instantly quenched by the addition of 2 M NaOCl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 4:1) afforded the title compound **36c** as white crystals (38 mg, 0.165 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.41 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.89 (dd, *J* = 6.4, 2.1 Hz, 1H), 7.70 (ddd, *J* = 8.6, 4.6, 2.1 Hz, 1H), 7.59 (ddd, *J* = 8.0, 7.5, 1.9 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 7.20 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.8 (d, *J* = 258.2 Hz), 156.3 (d, *J* = 1.3 Hz), 150.2, 140.0 (d, *J* = 2.4 Hz), 137.3, 135.0 (d, *J* = 9.4 Hz), 122.9, 121.7 (d, *J* = 19.7 Hz), 121.5, 117.6 (d, *J* = 24.4 Hz), 117.5, 109.5 (d, *J* = 4.3 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2228, 1576, 1559, 1483, 1456, 1415, 1389, 1267, 1245, 1115, 1070, 1044, 985, 906, 830, 759, 735, 731, 721, 713, 676.
MS (EI, 70 eV): *m/z* (%) = 230 (20), 212 (10), 211 (100), 78 (19).
HRMS (EI): *m/z* calcd. for [$C_{12}H_6FN_2S$]: 229.0236; found 229.0231 ($M^+ - H$).
M.p. (°C): 106.7 – 108.3.

(*Z*)-2-(Hydroxy(*p*-tolyl)methyl)-3-phenylacrylonitrile (39a)



According to **TP 9**, a solution of cinnamonitrile (**37a**, 0.200 M, 0.200 mmol; *E/Z* >99:1) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of 4-methylbenzaldehyde (**30u**, 36 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 9:1) afforded the title compound **39a** as a light yellow solid (46 mg, 0.185 mmol, 93%; *E/Z* = 5:95).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.37 (m, 6H), 7.35 – 7.31 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.73 (d, *J* = 5.2 Hz, 1H), 2.38 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 145.5, 138.9, 137.1, 133.3, 130.1, 129.9 (2C), 129.4 (2C), 129.0 (2C), 126.3 (2C), 118.8, 118.5, 69.6, 21.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3498, 3026, 2918, 2855, 2214, 1613, 1574, 1513, 1491, 1446, 1390, 1358, 1320, 1304, 1246, 1213, 1192, 1181, 1159, 1134, 1122, 1078, 1040, 1021, 1000, 950, 931, 896, 866, 843, 826, 796, 755, 739, 697, 666.

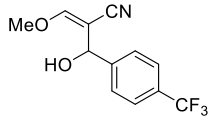
MS (EI, 70 eV): *m/z* (%) = 283 (10), 282 (14), 281 (73), 267 (13), 265 (24), 249 (15), 248 (75), 234 (29), 232 (14), 231 (100), 230 (79), 227 (10), 225 (37), 221 (10), 220 (33), 217 (11), 216 (75).

HRMS (EI): *m/z* calcd. for [$C_{17}H_{14}NO$]: 248.1075; found 248.1071 ($M^+ - H$).

M.p. (°C): 115.9 – 117.9.

Configuration of the double bond of the major stereoisomer was determined by X-ray crystallography. See crystallographic data section for details.

(*Z*)-2-(Hydroxy(4-(trifluoromethyl)phenyl)methyl)-3-methoxyacrylonitrile (39b)



According to **TP 9**, a solution of 3-methoxyacrylonitrile (**37b**, *E*/*Z* = 83:17, 0.200 M, 0.200 mmol) in THF (total volume: 1 mL) and a solution of NaDA (0.210 M in DMEA, 0.210 mmol, 1.05 equiv) were prepared. The precooled solutions were mixed with an overall 10 mL min^{-1} flow rate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.5 s, −78 °C) and was subsequently injected in a flask containing a stirred solution of (4-trifluoromethyl)benzaldehyde (**30v**, 52 mg, 0.300 mmol, 1.50 equiv) in THF. The reaction was instantly quenched by the addition of sat. aq. NH_4Cl. The aq. phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *i*-hex:EtOAc = 3:1) afforded the title compound **39b** as a pale orange solid (36 mg, 0.140 mmol, 70%; *E*/*Z* < 1:99).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.63 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 0.8 Hz, 1H), 5.80 (s, 1H), 3.92 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3, 144.7 (d, *J* = 1.4 Hz), 130.5 (q, *J* = 32.4 Hz, 2C), 126.2, 125.8 (q, *J* = 3.8 Hz, 2C), 124.2 (q, *J* = 272.2 Hz), 116.9, 97.5, 66.5, 62.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3391, 2952, 2922, 2852, 2224, 1712, 1632, 1457, 1446, 1411, 1319, 1259, 1206, 1161, 1148, 1118, 1110, 1064, 1052, 1015, 973, 961, 917, 869, 853, 788, 771, 724, 700.

MS (EI, 70 eV): *m/z* (%) = 257 (12), 256 (65), 240 (13), 238 (22), 236 (16), 228 (26), 227 (13), 226 (25), 225 (34), 224 (94), 223 (17), 223 (20), 222 (42), 214 (73), 210 (11), 208 (68), 207 (34), 206 (88), 203 (12), 200 (17), 198 (30), 197 (100), 196 (99), 195 (66), 194 (25), 188 (52), 187 (10), 186 (15), 185 (11).

HRMS (EI): *m/z* calcd. for [$C_{12}H_9F_3NO_2$]: 256.0585; found 256.0579 ($M^+ - H$).

M.p. (°C): 99.9 – 101.8.

Configuration of the double bond of the major stereoisomer was determined by X-ray crystallography. See crystallographic data section for details.

6 Crystallographic Data

Single Crystal X-Ray Diffraction Studies

Single crystals of compound **5g**, **8d**, **10**, **39a**, and **39b** suitable for X-ray diffraction, were obtained by slow evaporation of a DCM solutions. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection was performed with the CrysAlis CCD software; [146] CrysAlis RED software[147] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[148] was applied. The structures were solved with SHELXS-97, [149] refined with SHELXL-97[150] and finally checked using PLATON. [151]

[146] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[147] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[148] SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.
[149] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen,Germany.
[150] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[151] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

(*E*)-Ethyl 2'-methoxy-5'-(phenyldiazene)-[1,1'-biphenyl]-4-carboxylate (5g)

CCDC 1532299 containes the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

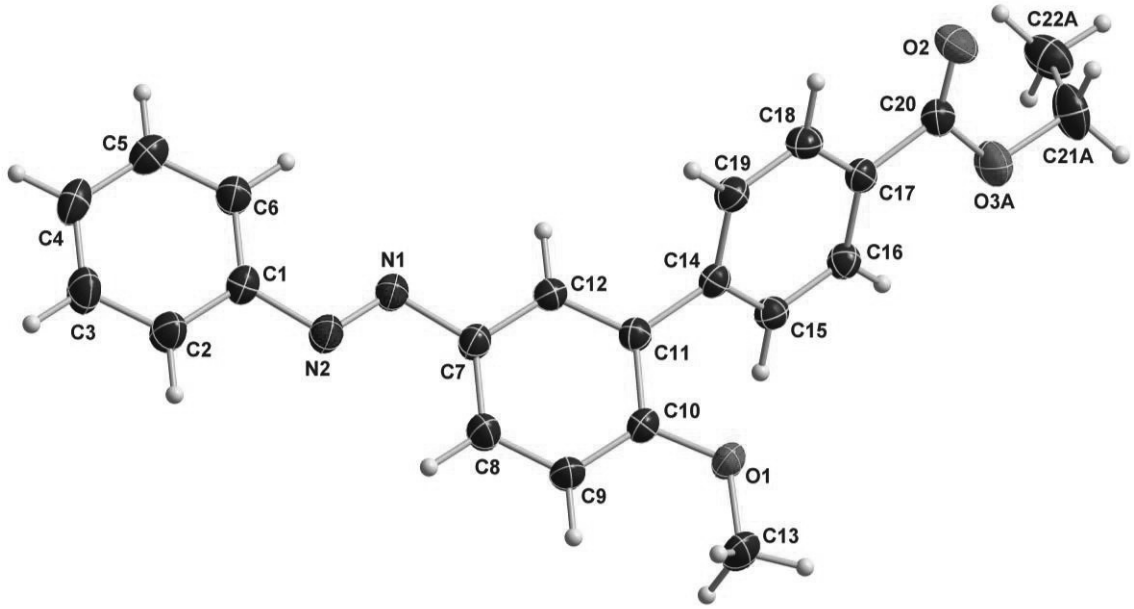


Figure 1: Molecular structure of compound **5g** in the crystal, DIAMOND[152] representation; thermal ellipsoids are drawn at 50% probability level. The ethoxy group is disordered over two positions; only one position has been shown for clarity.

[152] DIAMOND, Crystal Impact GbR., Version 3.2i.

Table 14: Details for X-ray data collection and structure refinement for compound **5g**.

Chemical formula	$C_{22}H_{20}N_2O_3$
Formula mass	360.4
Crystal system, space group	monoclinic, P21/*n*
Temperature (K)	173(2)
a, *b*, *c* [Å]	14.0620(4), 7.4549(3), 18.2784(6)
α, β, γ [°]	90.0, 104.220(4), 90.0
V [Å^3]	1857.43(11)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.289
Radiation type	Mo *Ko*
μ [mm^{-1}]	0.087
Crystal size [mm]	0.20 × 0.10 × 0.10
Crystal description	orange yellow block
Absorption correction	Multi-scan
F(000)	760
Θ range [°]	4.22 – 25.24
Index ranges	$-18 \leq h \leq 19$; $-9 \leq k \leq 10$; $-25 \leq l \leq 25$
No. of collected, unique and observed reflections	18815, 5202. 3678
R_{int}	0.0316
R_1, wR_2 (2σ data)	0.0450, 0.1007
R_1, wR_2 (all data)	0.0702, 0.1152
GOOF on F^2	1.021
Peak/hole [e Å^{-3}]	0.230 / −0.179

Table 15: Selected bond lengths [Å] of compound **5g**.

O1 – C10	1.363(1)	C4 – C3	1.376(2)
O1 – C13	1.428(2)	C4 – C5	1.384(2)
C11 – C12	1.388(2)	C2 – C3	1.387(2)
C11 – C10	1.407(2)	C20 – O3A	1.325(11)
C11 – C14	1.485(2)	C20 – O3B	1.369(9)
C16 – C15	1.382(2)	C22A – C21A	1.497(9)
C16 – C17	1.395(2)	C21A – O3A	1.463(16)
C10 – C9	1.396(2)	C22B – C21B	1.498(9)
C15 – C14	1.395(2)	C21B – O3B	1.464(14)
C19 – C18	1.386(2)	C1 – C6	1.389(2)
C19 – C14	1.399(2)	C12 – C7	1.388(2)
N2 – N1	1.252(1)	C17 – C20	1.486(2)
N2 – C1	1.428(2)	O2 – C20	1.199(2)
C18 – C17	1.392(2)	C9 – C8	1.384(2)
N1 – C7	1.425(2)	C7 – C8	1.393(2)
C1 – C2	1.386(2)	C6 – C5	1.386(2)

Table 16: Selected bond angles [°] of compound **5g**.

C10 – O1 – C13	118.0(1)	C1 – C2 – C3	120.1(1)
C12 – C11 – C10	118.1(1)	O2 – C20 – O3A	123.1(5)
C12 – C11 – C14	119.9(1)	O2 – C20 – O3B	122.5(4)
C10 – C11 – C14	122.0(1)	O2 – C20 – C17	124.6(1)
C15 – C16 – C17	120.4(1)	O3A – C20 – C17	111.4(5)
O1 – C10 – C9	123.5(1)	O3B – C20 – C17	112.0(4)
O1 – C10 – C11	116.0(1)	C4 – C5 – C6	120.7(1)
C9 – C10 – C11	120.5(1)	C4 – C3 – C2	120.2(1)
C16 – C15 – C14	120.6(1)	O3A – C21A – C22A	111.9(7)
C18 – C19 – C14	120.8(1)	C20 – O3A – C21A	115.3(9)
N1 – N2 – C1	114.5(1)	O3B – C21B – C22B	107.5(6)
C15 – C14 – C19	118.8(1)	C20 – O3B – C21B	118.8(7)
C15 – C14 – C11	121.2(1)	C18 – C17 – C20	118.5(1)
C19 – C14 – C11	120.0(1)	C16 – C17 – C20	122.0(1)
C19 – C18 – C17	120.0(1)	C8 – C9 – C10	120.2(1)
N2 – N1 – C7	114.3(1)	C12 – C7 – C8	119.6(1)
C2 – C1 – C6	119.9(1)	C12 – C7 – N1	115.6(1)
C2 – C1 – N2	115.4(1)	C8 – C7 – N1	124.9(1)
C6 – C1 – N2	124.7(1)	C5 – C6 – C1	119.4(1)
C7 – C12 – C11	121.7(1)	C3 – C4 – C5	119.8(1)
C18 – C17 – C16	119.5(1)	C9 – C8 – C7	120.0(1)

Table 17: Selected torsion angles [°] of compound **5g**.

C13 – O1 – C10 – C9	−2.0(2)	C11 – C12 – C7 – N1	−180.0(1)
C13 – O1 – C10 – C11	176.8(1)	N2 – N1 – C7 – C12	−174.8(1)
C12 – C11 – C10 – O1	−178.2(1)	N2 – N1 – C7 – C8	6.3(2)
C14 – C11 – C10 – O1	0.4(2)	C2 – C1 – C6 – C5	0.5(2)
C12 – C11 – C10 – C9	0.6(2)	N2 – C1 – C6 – C5	−179.6(1)
C14 – C11 – C10 – C9	179.2(1)	C10 – C9 – C8 – C7	0.4(2)
C17 – C16 – C15 – C14	0.2(2)	C12 – C7 – C8 – C9	0.5(2)
C16 – C15 – C14 – C19	0.3(2)	N1 – C7 – C8 – C9	179.4(1)
C16 – C15 – C14 – C11	178.4(1)	C6 – C1 – C2 – C3	−0.1(2)
C18 – C19 – C14 – C15	−0.5(2)	N2 – C1 – C2 – C3	180.0(1)
C18 – C19 – C14 – C11	−178.6(1)	C18 – C17 – C20 – O2	1.1(2)
C12 – C11 – C14 – C15	−126.3(1)	C16 – C17 – C20 – O2	−179.4(1)
C10 – C11 – C14 – C15	55.0(2)	C18 – C17 – C20 – O3A	170.6(3)
C12 – C11 – C14 – C19	51.7(2)	C16 – C17 – C20 – O3A	−10.0(3)
C10 – C11 – C14 – C19	−127.0(1)	C18 – C17 – C20 – O3B	−168.5(3)
C14 – C19 – C18 – C17	0.2(2)	C16 – C17 – C20 – O3B	10.9(4)
C1 – N2 – N1 – C7	−179.7(1)	C3 – C4 – C5 – C6	0.0(2)
N1 – N2 – C1 – C2	175.4(1)	C1 – C6 – C5 – C4	−0.5(2)
N1 – N2 – C1 – C6	−4.5(2)	C5 – C4 – C3 – C2	0.4(2)
C10 – C11 – C12 – C7	0.4(2)	C1 – C2 – C3 – C4	−0.3(2)
C14 – C11 – C12 – C7	−178.3(1)	O2 – C20 – O3A – C21A	−10.7(7)
C19 – C18 – C17 – C16	0.4(2)	O3B – C20 – O3A – C21A	84.(2)
C19 – C18 – C17 – C20	179.8(1)	C17 – C20 – O3A – C21A	179.7(5)
C15 – C16 – C17 – C18	−0.5(2)	C22A – C21A – O3A – C20	−85.0(9)
C15 – C16 – C17 – C20	−180.0(1)	O2 – C20 – O3B – C21B	12.1(8)
O1 – C10 – C9 – C8	177.7(1)	O3A – C20 – O3B – C21B	−86.(3)
C11 – C10 – C9 – C8	−1.0(2)	C17 – C20 – O3B – C21B	−177.9(5)
C11 – C12 – C7 – C8	−1.0(2)	C22B – C21B – O3B – C20	100.4(7)

(*E*)-2-Iodo-4-(phenyldiazenyl)benzonitrile (8d)

CCDC 1532300 containes the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

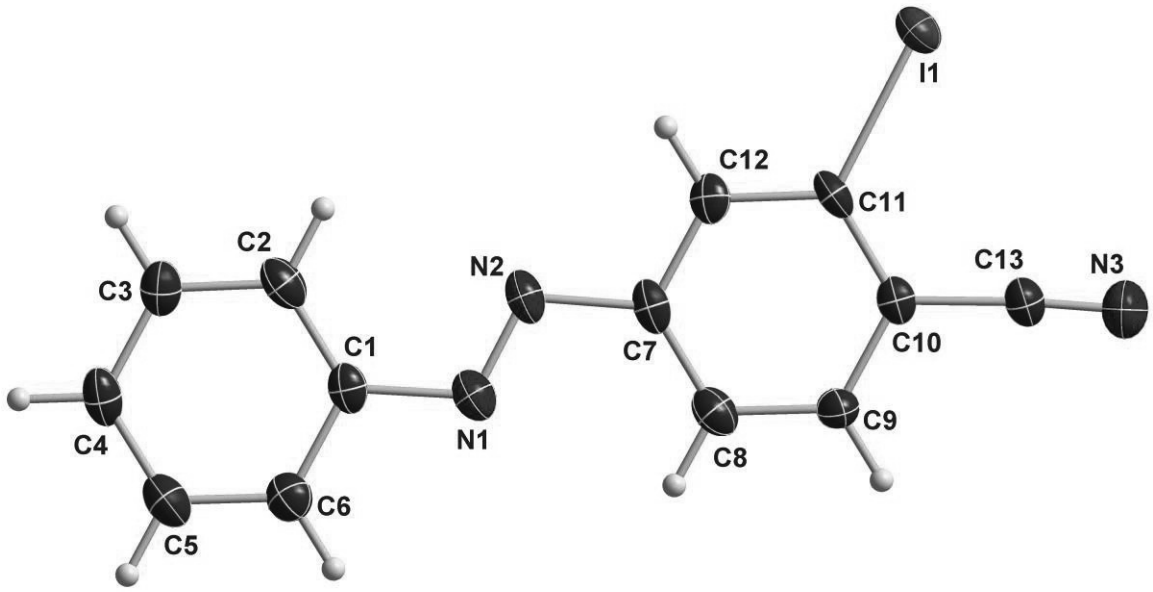


Figure 2: Molecular structure of compound **8d** in the crystal, DIAMOND[152] representation; thermal ellipsoids are drawn at 50% probability level.

Table 18: Details for X-ray data collection and structure refinement for compound **8d**.

Chemical formula	$C_{13}H_8IN_3$
Formula mass	333.12
Crystal system, space group	orthorhombic, $P2_12_12_1$
Temperature (K)	173(2)
a, b, c [Å]	4.5407(2), 11.7732(5), 22.2216(9)
α, β, γ [°]	90.0, 90.0, 90.0
V [Å^3]	1187.94(9)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.863
Radiation type	Mo *Ko*
μ [mm^{-1}]	2.675
Crystal size [mm]	0.22 × 0.07 × 0.02
Crystal description	orange yellow rod
Absorption correction	Multi-scan
F(000)	640
Θ range [°]	4.42 – 25.24
Index ranges	$-5 \leq h \leq 6$; $-15 \leq k \leq 15$; $-29 \leq l \leq 29$
No. of collected, unique and observed reflections	11029, 2918, 2517
R_{int}	0.0693
R_1, wR_2 (2σ data)	0.0412, 0.0848
R_1, wR_2 (all data)	0.0518, 0.0890
GOOF on F^2	1.024
Peak/hole [e Å^{-3}]	1.442 / −0.583

Table 19: Selected bond lengths [Å] of compound **8d**.

I1 – C11	2.086(7)	C4 – C5	1.380(12)
C7 – C12	1.384(11)	C4 – C3	1.389(12)
C7 – C8	1.384(11)	C6 – C5	1.381(11)
C7 – N2	1.434(10)	C6 – C1	1.394(11)
C13 – N3	1.135(10)	C10 – C9	1.388(10)
C13 – C10	1.452(11)	C10 – C11	1.392(11)
N2 – N1	1.250(9)	C12 – C11	1.398(10)
C8 – C9	1.389(11)	C2 – C3	1.383(11)
N1 – C1	1.434(10)	C2 – C1	1.387(11)

Table 20: Selected bond angles [°] of compound **8d**.

C12 – C7 – C8	120.7(8)	C11 – C10 – C13	121.3(7)
C12 – C7 – N2	113.9(7)	C7 – C12 – C11	120.3(7)
C8 – C7 – N2	125.4(8)	C2 – C1 – C6	120.2(8)
N3 – C13 – C10	176.2(9)	C2 – C1 – N1	124.9(7)
N1 – N2 – C7	113.0(7)	C6 – C1 – N1	115.0(7)
C7 – C8 – C9	119.5(8)	C10 – C9 – C8	120.0(7)
N2 – N1 – C1	114.1(7)	C2 – C3 – C4	120.6(8)
C3 – C2 – C1	119.3(8)	C4 – C5 – C6	120.1(8)
C5 – C4 – C3	119.9(8)	C10 – C11 – C12	118.7(7)
C5 – C6 – C1	119.9(8)	C10 – C11 – I1	122.1(6)
C9 – C10 – C11	120.8(7)	C12 – C11 – I1	119.2(6)
C9 – C10 – C13	117.9(7)		

Table 21: Selected torsion angles [°] of compound **8d**.

C12 – C7 – N2 – N1	−177.6(7)	C11 – C10 – C9 – C8	0.4(12)
C8 – C7 – N2 – N1	1.1(11)	C13 – C10 – C9 – C8	179.7(7)
C12 – C7 – C8 – C9	−0.5(12)	C7 – C8 – C9 – C10	−0.1(12)
N2 – C7 – C8 – C9	−179.1(8)	C1 – C2 – C3 – C4	−0.9(13)
C7 – N2 – N1 – C1	−179.6(6)	C5 – C4 – C3 – C2	0.6(13)
C8 – C7 – C12 – C11	0.8(12)	C3 – C4 – C5 – C6	0.0(13)
N2 – C7 – C12 – C11	179.5(7)	C1 – C6 – C5 – C4	−0.3(13)
C3 – C2 – C1 – C6	0.6(13)	C9 – C10 – C11 – C12	−0.2(11)
C3 – C2 – C1 – N1	179.4(8)	C13 – C10 – C11 – C12	−179.4(7)
C5 – C6 – C1 – C2	0.0(13)	C9 – C10 – C11 – I1	−179.4(6)
C5 – C6 – C1 – N1	−178.9(7)	C13 – C10 – C11 – I1	1.3(10)
N2 – N1 – C1 – C2	0.6(11)	C7 – C12 – C11 – C10	−0.4(11)
N2 – N1 – C1 – C6	179.5(8)	C7 – C12 – C11 – I1	178.8(6)

(*E*)-1-(4-Butyl-2,6-dichlorophenyl)-2-(2,6-dichloro-3-iodophenyl)diazene (10)

CCDC 1532301 containes the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

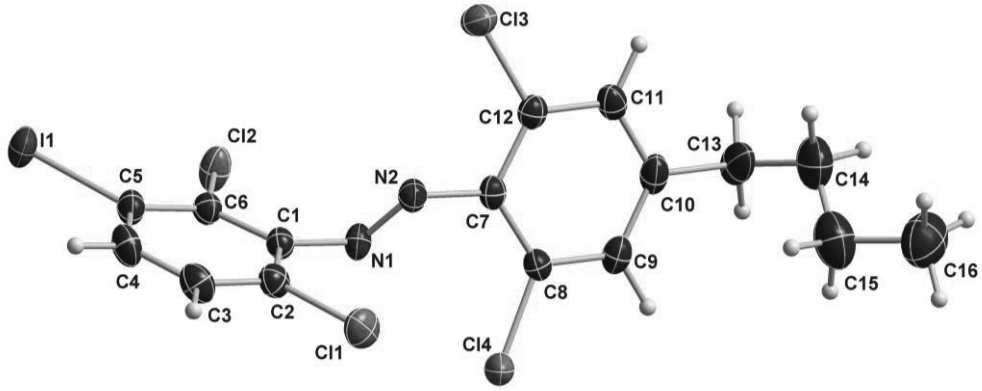


Figure 3: Molecular structure of compound **10** in the crystal, DIAMOND[152] representation; thermal ellipsoids are drawn at 50% probability level.

Table 22: Details for X-ray data collection and structure refinement for compound **10**.

Chemical formula	$C_{16}H_{13}Cl_4IN_2$
Formula mass	501.98
Crystal system, space group	triclinic, *P*-1
Temperature (K)	173(2)
a, *b*, *c* [Å]	8.1132(2), 10.9951(3), 11.5650(3)
α, β, γ [°]	63.992(2), 87.106(2), 77.999(2)
V [Å^3]	905.95(4)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.840
Radiation type	Mo *Ko*
μ [mm^{-1}]	2.356
Crystal size [mm]	0.42 × 0.24 × 0.07
Crystal description	orange red block
Absorption correction	Multi-scan
F(000)	488
Θ range [°]	4.22 – 25.24
Index ranges	$-11 \leq h \leq 11$; $-15 \leq k \leq 15$; $-16 \leq l \leq 16$
No. of collected, unique and observed reflections	18484, 5511, 4670
R_{int}	0.0234
R_1, wR_2 (2σ data)	0.0315, 0.0761
R_1, wR_2 (all data)	0.0402, 0.0818
GOOF on F^2	1.033
Peak/hole [e Å^{-3}]	1.252 / −0.708

Table 23: Selected bond lengths [Å] of compound **10**.

I1 – C5	2.087(2)	C2 – C3	1.388(3)
Cl3 – C12	1.737(2)	C3 – C4	1.377(4)
Cl1 – C2	1.729(2)	C11 – C10	1.397(4)
Cl4 – C8	1.735(2)	C14 – C15	1.451(6)
Cl2 – C6	1.728(2)	C10 – C9	1.379(4)
N2 – N1	1.247(3)	C9 – C8	1.388(3)
N2 – C7	1.426(3)	C15 – C16	1.564(5)
C1 – C2	1.386(3)	C12 – C11	1.380(3)
C1 – C6	1.399(3)	C13 – C14	1.464(5)
C1 – N1	1.439(3)	C13 – C10	1.515(3)
C7 – C12	1.395(3)	C6 – C5	1.391(3)
C7 – C8	1.399(3)	C5 – C4	1.393(4)

Table 24: Selected bond angles [°] of compound **10**.

N1 – N2 – C7	114.7(2)	C15 – C14 – C13	117.3(3)
C2 – C1 – C6	119.2(2)	C9 – C10 – C11	118.6(2)
C2 – C1 – N1	122.7(2)	C9 – C10 – C13	120.4(2)
C6 – C1 – N1	118.1(2)	C11 – C10 – C13	120.9(2)
C12 – C7 – C8	117.1(2)	C3 – C4 – C5	120.7(2)
C12 – C7 – N2	117.1(2)	C10 – C9 – C8	121.1(2)
C8 – C7 – N2	125.6(2)	C9 – C8 – C7	121.0(2)
N2 – N1 – C1	111.1(2)	C9 – C8 – Cl4	117.6(2)
C11 – C12 – C7	122.1(2)	C7 – C8 – Cl4	121.3(2)
C11 – C12 – Cl3	118.8(2)	C14 – C15 – C16	114.2(4)
C7 – C12 – Cl3	119.1(2)	C4 – C5 – I1	118.5(2)
C14 – C13 – C10	116.4(3)	C1 – C2 – C3	120.7(2)
C5 – C6 – C1	120.3(2)	C1 – C2 – Cl1	120.9(2)
C5 – C6 – Cl2	121.5(2)	C3 – C2 – Cl1	118.3(2)
C1 – C6 – Cl2	118.3(2)	C4 – C3 – C2	119.7(2)
C6 – C5 – C4	119.3(2)	C12 – C11 – C10	120.0(2)
C6 – C5 – I1	122.1(2)		

Table 25: Selected torsion angles [°] of compound **10**.

N1 – N2 – C7 – C12	138.0(2)	C1 – C2 – C3 – C4	−2.1(4)
N1 – N2 – C7 – C8	−47.2(3)	Cl1 – C2 – C3 – C4	179.6(2)
C7 – N2 – N1 – C1	178.2(2)	C7 – C12 – C11 – C10	1.6(3)
C2 – C1 – N1 – N2	−66.6(3)	Cl3 – C12 – C11 – C10	−176.0(2)
C6 – C1 – N1 – N2	116.4(2)	C10 – C13 – C14 – C15	63.1(5)
C8 – C7 – C12 – C11	1.4(3)	C12 – C11 – C10 – C9	−3.5(3)
N2 – C7 – C12 – C11	176.6(2)	C12 – C11 – C10 – C13	173.8(3)
C8 – C7 – C12 – Cl3	179.0(2)	C14 – C13 – C10 – C9	−96.9(4)
N2 – C7 – C12 – Cl3	−5.9(3)	C14 – C13 – C10 – C11	85.9(4)
C2 – C1 – C6 – C5	3.7(3)	C2 – C3 – C4 – C5	2.0(4)
N1 – C1 – C6 – C5	−179.1(2)	C6 – C5 – C4 – C3	1.0(4)
C2 – C1 – C6 – Cl2	−175.7(2)	I1 – C5 – C4 – C3	−177.5(2)
N1 – C1 – C6 – Cl2	1.5(3)	C11 – C10 – C9 – C8	2.4(4)
C1 – C6 – C5 – C4	−3.9(3)	C13 – C10 – C9 – C8	−174.9(3)
Cl2 – C6 – C5 – C4	175.5(2)	C10 – C9 – C8 – C7	0.6(4)
C1 – C6 – C5 – I1	174.5(2)	C10 – C9 – C8 – Cl4	−175.5(2)
Cl2 – C6 – C5 – I1	−6.1(3)	C12 – C7 – C8 – C9	−2.5(3)
C6 – C1 – C2 – C3	−0.7(3)	N2 – C7 – C8 – C9	−177.2(2)
N1 – C1 – C2 – C3	−177.7(2)	C12 – C7 – C8 – Cl4	173.5(2)
C6 – C1 – C2 – Cl1	177.5(2)	N2 – C7 – C8 – Cl4	−1.3(3)
N1 – C1 – C2 – Cl1	0.5(3)	C13 – C14 – C15 – C16	170.4(3)

(*Z*)-2-(Hydroxy(*p*-tolyl)methyl)-3-phenylacrylonitrile (39a)

CCDC 1831884 containes the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

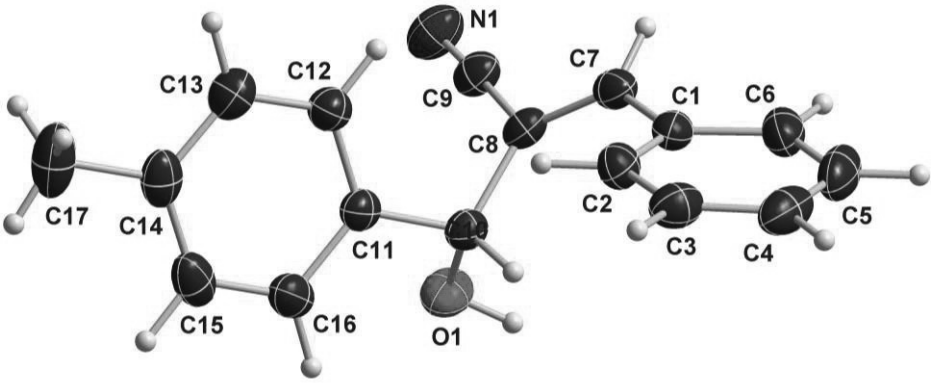


Figure 4: Molecular structure of compound **39a** in the crystal, DIAMOND[152] representation; thermal ellipsoids are drawn at 50% probability level. The ethoxy group is disordered over two positions; only one position has been shown for clarity.

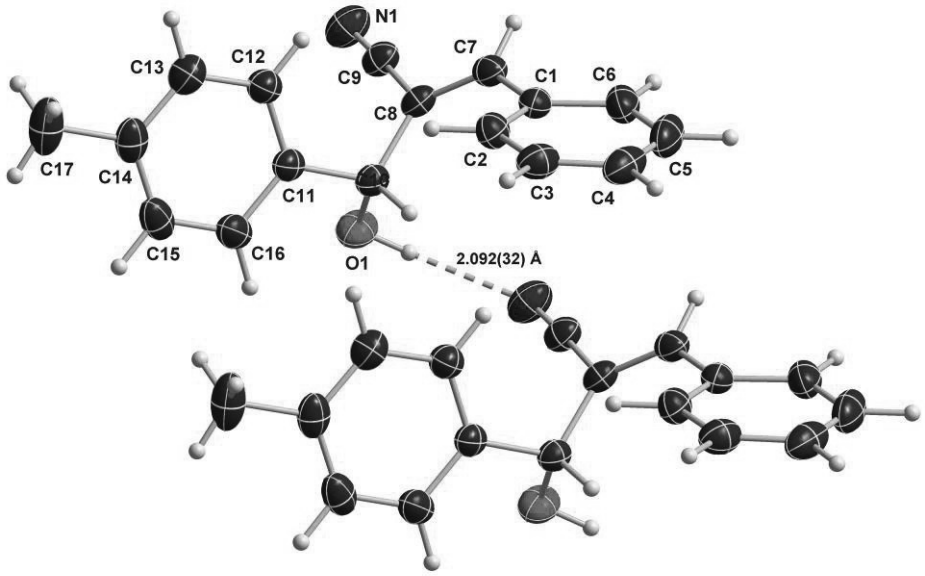


Figure 5: Hydrogen bonding in the crystal of compound **39a**, DIAMOND[152] representation; thermal ellipsoids are drawn at 50% probability level. Symmetry code for the second (not labeled) molecule: 1+x, y, z.

Table 26: Details for X-ray data collection and structure refinement for compound **39a**.

Chemical formula	$C_{17}H_{15}NO$
Formula mass	249.30
Crystal system, space group	monoclinic, P21/*c*
Temperature (K)	143(2)
a, *b*, *c* [Å]	5.43338(5), 15.5658(15), 15.8523(12)
α, β, γ [°]	90.0, 90.515(7), 90.0
V [Å^3]	1340.8(2)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.235
Radiation type	Mo *Ko*
μ [mm^{-1}]	0.077
Crystal size [mm]	0.49 × 0.12 × 0.07
Crystal description	colorless rod
Absorption correction	Multi-scan
F(000)	528
Θ range [°]	4.17 – 25.24
Index ranges	$-6 \leq h \leq 6$; $-19 \leq k \leq 19$; $-19 \leq l \leq 18$
No. of collected, unique and observed reflections	9448, 2726, 1501
R_{int}	0.0744
R_1, wR_2 (2σ data)	0.0570, 0.1081
R_1, wR_2 (all data)	0.1207, 0.1329
GOOF on F^2	0.994
Peak/hole [e Å^{-3}]	0.197 / −0.204

Table 27: Selected bond lengths [Å] of compound **39a**.

O1 – C10	1.434(3)	C14 – C13	1.384(3)
C8 – C7	1.342(3)	C14 – C15	1.386(3)
C8 – C9	1.443(3)	C14 – C17	1.509(3)
C8 – C10	1.521(3)	C12 – C13	1.387(3)
C11 – C12	1.387(3)	C6 – C5	1.382(4)
C11 – C16	1.392(3)	C3 – C4	1.377(4)
C11 – C10	1.512(3)	C5 – C4	1.384(4)
C1 – C6	1.391(3)	N1 – C9	1.148(3)
C1 – C2	1.395(3)	C16 – C15	1.387(3)
C1 – C7	1.466(3)	C2 – C3	1.388(3)

Table 28: Selected bond angles [°] of compound **39a**.

C7 – C8 – C9	119.5(2)	C15 – C14 – C17	121.4(2)
C7 – C8 – C10	126.9(2)	C13 – C12 – C11	120.7(2)
C9 – C8 – C10	113.6(2)	C5 – C6 – C1	120.5(3)
C12 – C11 – C16	118.3(2)	C14 – C15 – C16	121.6(2)
C12 – C11 – C10	122.3(2)	C4 – C3 – C2	120.5(3)
C16 – C11 – C10	119.4(2)	C6 – C5 – C4	120.3(3)
O1 – C10 – C11	107.7(2)	C14 – C13 – C12	121.4(2)
O1 – C10 – C8	108.3(2)	C3 – C4 – C5	119.6(3)
C11 – C10 – C8	114.2(2)	N1 – C9 – C8	177.5(3)
C6 – C1 – C2	118.9(2)	C8 – C7 – C1	127.1(2)
C6 – C1 – C7	119.4(2)	C3 – C2 – C1	120.1(2)
C2 – C1 – C7	121.7(2)	C13 – C14 – C15	117.6(2)
C15 – C16 – C11	120.3(2)	C13 – C14 – C17	120.9(2)

Table 29: Selected torsion angles [°] of compound **39a**.

C12 – C11 – C10 – O1	−132.8(2)	C7 – C1 – C2 – C3	179.5(2)
C16 – C11 – C10 – O1	48.3(3)	C16 – C11 – C12 – C13	−1.0(3)
C12 – C11 – C10 – C8	−12.5(3)	C10 – C11 – C12 – C13	−179.9(2)
C16 – C11 – C10 – C8	168.7(2)	C2 – C1 – C6 – C5	2.8(3)
C7 – C8 – C10 – O1	−129.0(2)	C7 – C1 – C6 – C5	−178.6(2)
C9 – C8 – C10 – O1	48.0(2)	C13 – C14 – C15 – C16	−1.7(4)
C7 – C8 – C10 – C11	111.0(3)	C17 – C14 – C15 – C16	177.6(2)
C9 – C8 – C10 – C11	−71.9(2)	C11 – C16 – C15 – C14	0.5(4)
C12 – C11 – C16 – C15	0.9(3)	C1 – C2 – C3 – C4	−0.6(3)
C10 – C11 – C16 – C15	179.8(2)	C1 – C6 – C5 – C4	−1.3(3)
C9 – C8 – C7 – C1	177.4(2)	C15 – C14 – C13 – C12	1.6(4)
C10 – C8 – C7 – C1	−5.7(4)	C17 – C14 – C13 – C12	−177.7(2)
C6 – C1 – C7 – C8	141.0(2)	C11 – C12 – C13 – C14	−0.3(4)
C2 – C1 – C7 – C8	−40.5(3)	C2 – C3 – C4 – C5	2.2(4)
C6 – C1 – C2 – C3	−1.9(3)	C6 – C5 – C4 – C3	−1.3(4)

(*Z*)-2-(Hydroxy(4-(trifluoromethyl)phenyl)methyl)-3-methoxyacrylonitrile (39b)

CCDC 1831885 containes the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

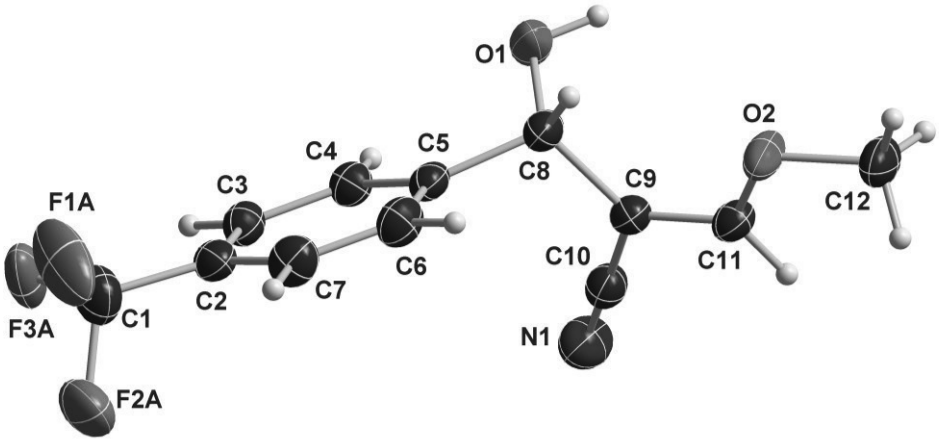


Figure 6: Molecular structure of compound **39b** in the crystal, DIAMOND[152] representation; thermal ellipsoids are drawn at 50% probability level. The CF_3 group is disordered over two positions.

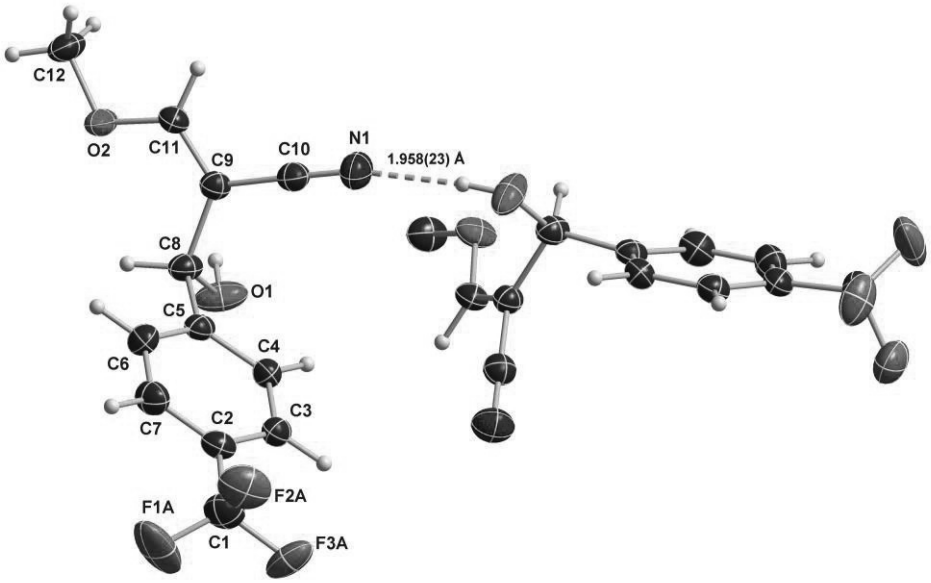


Figure 7: Hydrogen bonding in the crystal of compound **39b**, DIAMOND[152] representation; thermal ellipsoids are drawn at 50% probability level. Symmetry code for the second (not labeled) molecule: −x, −0.5+y, 0.5−z.

Table 30: Details for X-ray data collection and structure refinement for compound **39b**.

Chemical formula	$C_{12}H_{10}F_3NO_2$
Formula mass	257.21
Crystal system, space group	monoclinic, P21/*c*
Temperature (K)	143(2)
a, *b*, *c* [Å]	12.3101(13), 8.1799(6), 12.7623(11)
α, β, γ [°]	90.0, 112.598(12), 90.0
V [Å^3]	1186.4(2)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.440
Radiation type	Mo *Ko*
μ [mm^{-1}]	0.129
Crystal size [mm]	0.44 × 0.12 × 0.06
Crystal description	colorless rod
Absorption correction	Multi-scan
F(000)	528
Θ range [°]	4.16 – 25.24
Index ranges	$-16 \leq h \leq 16$; $-10 \leq k \leq 10$; $-16 \leq l \leq 17$
No. of collected, unique and observed reflections	10879, 2943, 2130
R_{int}	0.0425
R_1, wR_2 (2σ data)	0.0491, 0.1053
R_1, wR_2 (all data)	0.0719, 0.1204
GOOF on F^2	1.044
Peak/hole [e Å^{-3}]	0.275 / −0.284

Table 31: Selected bond lengths [Å] of compound **39b**.

C9 – C11	1.340(2)	C6 – C7	1.381(2)
C9 – C10	1.426(2)	C1 – F1A	1.312(4)
C9 – C8	1.519(2)	C1 – F2A	1.356(4)
C8 – O1	1.418(2)	C1 – F3A	1.408(5)
C8 – C5	1.512(2)	C10 – N1	1.146(2)
O2 – C11	1.333(2)	C2 – C3	1.383(2)
O2 – C12	1.440(2)	C2 – C7	1.384(2)
C5 – C6	1.386(2)	C2 – C1	1.494(2)
C5 – C4	1.391(2)	C4 – C3	1.386(2)

Table 32: Selected bond angles [°] of compound **39b**.

C11 – C9 – C10	117.2(1)	C7 – C6 – C5	120.8(2)
C11 – C9 – C8	123.6(1)	C6 – C7 – C2	119.8(2)
C10 – C9 – C8	119.0(1)	F1A – C1 – F2A	102.4(4)
O1 – C8 – C5	107.3(1)	F1A – C1 – F3A	116.8(4)
O1 – C8 – C9	111.3(1)	F2A – C1 – F3A	98.3(3)
C5 – C8 – C9	113.6(1)	F1A – C1 – C2	113.5(2)
C11 – O2 – C12	115.2(1)	F2A – C1 – C2	112.5(2)
C6 – C5 – C4	118.9(2)	F3A – C1 – C2	111.9(2)
C6 – C5 – C8	119.8(1)	C7 – C2 – C1	118.7(2)
C4 – C5 – C8	121.2(2)	C3 – C4 – C5	120.5(2)
N1 – C10 – C9	179.1(2)	O2 – C11 – C9	121.1(1)
C3 – C2 – C7	120.1(2)	C2 – C3 – C4	119.8(2)
C3 – C2 – C1	121.1(2)		

Table 33: Selected torsion angles [°] of compound **39b**.

C11 – C9 – C8 – O1	104.5(2)	C3 – C2 – C1 – F1A	−140.1(4)
C10 – C9 – C8 – O1	−71.0(2)	C7 – C2 – C1 – F1A	37.1(5)
C11 – C9 – C8 – C5	−134.3(2)	C3 – C2 – C1 – F2A	104.1(3)
C10 – C9 – C8 – C5	50.1(2)	C7 – C2 – C1 – F2A	−78.6(3)
O1 – C8 – C5 – C6	−145.4(2)	C3 – C2 – C1 – F3A	−5.3(3)
C9 – C8 – C5 – C6	91.2(2)	C7 – C2 – C1 – F3A	172.0(2)
O1 – C8 – C5 – C4	31.6(2)	C1 – C2 – C7 – C6	−175.5(2)
C9 – C8 – C5 – C4	−91.8(2)	C1 – C2 – C3 – C4	175.2(2)
C6 – C5 – C4 – C3	1.7(2)	C5 – C4 – C3 – C2	0.2(2)
C8 – C5 – C4 – C3	−175.3(1)	C4 – C5 – C6 – C7	−2.0(2)
C12 – O2 – C11 – C9	−173.1(2)	C8 – C5 – C6 – C7	175.1(2)
C10 – C9 – C11 – O2	178.9(2)	C5 – C6 – C7 – C2	0.3(3)
C8 – C9 – C11 – O2	3.3(2)	C3 – C2 – C7 – C6	1.8(3)
C7 – C2 – C3 – C4	−2.0(2)		