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Metalation and Halogen-Lithium Exchange of Sensitive Substrates and Mild Ester Homologation in Continuous Flow

von

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aus

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ERKLÄRUNG

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(Maximilian Ganiek)

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Parts of this Ph.D. thesis have been published

A) Communications

1) "Continuous Flow Magnesiation or Zincation of Acrylonitriles, Acrylates and Nitroolefins. Application to the Synthesis of Butenolides"
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2) "Synthesis and Reactivity of Triazaphenanthrenes"
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3) "Barbier Continuous Flow Preparation and Reactions of Carbamoyllithiums for Nucleophilic Amidation"
M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*,10280.

4) "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.

5) "Mild Homologation of Esters *via* Continuous Flow Chloroacetate Claisen Reactions"
M. A. Ganiek, M. V. Ivanova, B. Martin, P. Knochel, *manuscript submitted*.

B) Posters

1) "Continuous Flow Metalations of Acyclic Acrylate Substrates. Applications in the Synthesis of Butenolides and Pyridazines"
M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *9th CaRLa Winter School* **2016**, *56*, Heidelberg, Germany.

2) "Continuous Flow Metalations of Acrylates and Formamides"
M. A. Ganiek, G. Berionni, M. Ketels, M. R. Becker, H. Zipse, P. Knochel, *OMCOS 19* **2017**, Jeju Island, Republic of Korea.

To my family, to the memory of my grandmother,

to Elena and our future.

Abbreviations and Conventions

References citing scientific journals will refer to the first page of an article, while references citing books will be given with the range of relevant pages if applicable. Ibidem (*ibid.*) indicates another citation in the same journal or book, which only differs from the previous one by the authors and/or page number.

Physical constants are used according to the recommendations of the International System of Units (SI)[1]; chemical structures are named according to the IUPAC conventions.[2] The following conventions regarding prefixes are used: If the name of a compound is fully written, the prefix will be fully written as well (*tert*-butyllithium); if the compound name is abbreviated, the prefix will be abbreviated and written in superscript (^{t}BuLi). Abbreviations, which are specific to a topic, will be introduced in the respective chapters. The following abbreviations will be used throughout this thesis:

aq.	aequous
(Het)Ar	(hetero-)aryl substituent
ATR	attenuated total reflection
Bn	benzyl
BPR	back pressure regulator
Bu	butyl
cat.	catalyst
calc.	calculated
conc.	concentrated
Cy	cylohexyl
dba	*trans*,*trans*-dibenzylideneacetone
DCM	dichloromethane
d.r.	diastereomeric ratio
E$^{'}$	electrophile
e.g.	for example
et. al.	and others
EtOAc	ethyl acetate
EI	electron ionization (MS)
eq.	equation
equiv.	mole equivalents
ESI	electrospray ionization (MS)
Et	ethyl

[1] *THE INTERNATIONAL SYSTEM OF UNITS (SI) NIST SPECIAL PUBLICATION 330, 2008 EDITION* (Eds.: B. N. Taylor, A. Thompson), 2008, https://www.nist.gov/pml/special-publication-330, 25.08.2018.
[2] *Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names* (Eds.: H. A. Favre, W. H. Powell), RCS, London, 2013.

FG	functional group
GC	gas chromatography
Het	heteroaryl substituent
HR-MS	high resolution mass spectroscopy
i	*iso*-
ibid.	in the same cited reference
i.d.	inner diameter
i.e.	that is
IR	infrared spectroscopy
M	mol L^{-1}
m	*meta*-
Met	metal
Me	methyl
M.p.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	*ortho*-
p	*para*-
PFA	perfluoroalkoxy alkane
Ph	phenyl
Pr	propyl
PTFE	polytetrafluoroethylene
R	organic substituent
rpm	revolutions per minute (stirring speed)
sat.	saturated
s	*sec*-
t	*tert*-
THF	tetrahydrofuran
TFP	tri-2-furylphosphine
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidyl
TP	typical procedure
Vol	volume

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PART A: GENERAL INTRODUCTION

A. General Introduction

1 Overview

The progress of synthetic organic chemistry as a scientific discipline was enormous since its beginnings in the 19th century.[3] Even more impressive is the impact on human life it has gained through ever new and complex organic molecules applied in the fields of pharmaceutical chemistry, materials chemistry and agrochemisty.[4] It is projected throughout various disciplines that organic chemistry will contribute to solving global challenges concerning the improved usage of renewable energies or the development of novel pharmaceuticals.[4,5,6] However, it is also recognized that the synthesis of functional molecules on industrial scales by itself can pose challenges due to its high energetic demand[5a] and the release of waste by-products.[7] To confine these antagonistic effects already at the molecular level, it is the task of organic chemists to devise efficient and sustainable chemical transformations and arrange these to concise and scalable synthesis routes.[8] The use of organometallic chemistry has greatly facilitated this task by providing unparalleled, efficient ways for the formation of new carbon-carbon and carbon-heteroatom linkages.[9] Further significant advances were achieved in organometallic chemistry with the recent establishment of continuous (micro)flow technologies throughout academic-, development-, and production chemistry,[10,11] The merger of synthetic chemistry and chemical engineering realized in the field of flow chemistry has the potential to bring up new synthetic methods and processes with a more resource-saving profile.[12] Additionally, chemical transformations are made amenable to industrial production, which were previously too difficult to control, thus opening new possibilities in synthetic planning on large scales.[12]

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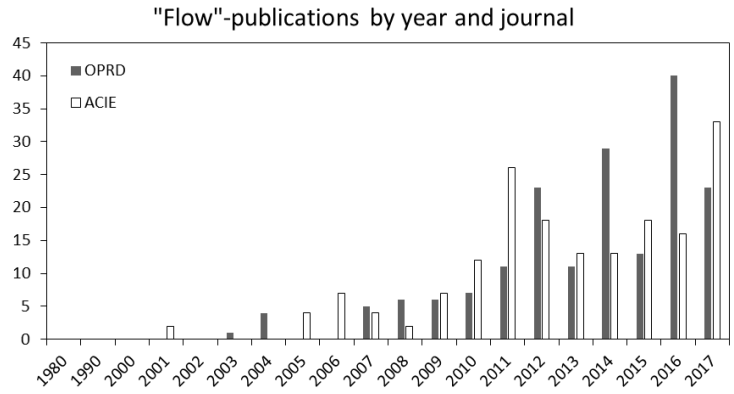
[3] a) K. C. Nicolaou, *Angew. Chem. Int. Ed.* **2013**, *52*, 131; c) S. E. Denmark, *Isr. J. Chem.* **2018**, *58*, 61.
[4] a) P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197; b) N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Ed.* **2010**, 87, 1348; c) D. P. Rotella, *ACS Chem. Neurosci*. **2016**, *7*, 1315; d) M. Yan, P. S. Baran, *Org. Process Res. Dev.* **2017**, *21*, 1091.
[5] a) A. Kreimeyer, P. Eckes, C. Fischer, H. Lauke, P. Schuhmacher, *Angew. Chem.* **2015**, *127*, 3220; b) M. Pischetsrieder, *Angew. Chem. Int. Ed.* **2018**, 57, ahead article.
[6] a) J. Q. Bond, D. M. Alonso, D. Wang, R. M West, J. A. Dumesic, *Science* **2010**, *327*, 1110; b) A. Corma, O. de la Torre, M. Renz, N. Villandier, *Angew. Chem. Int. Ed.* **2011**, *50*, 2375; c) F. He, W. Wang, W. Chen, T. Xu, S. B. Darling, J. Strzalka, Y. Liu, L. Yu, *J. Am. Chem. Soc.*, **2011**, *133*, 3284; d) Y. Yuan, T. J. Reece, P. Sharma, S. Poddar, S. Ducharme, A. Gruverman, Y. Yang, J. Huang, *Nature Mater*. **2011**, *10*, 296.
[7] a) R. A. Sheldon, *Pure Appl. Chem.* **2000**, *72*, 1233; b) D. G. J. Larsson, *Phil. Trans. R. Soc. B* **2014**, *369*, 20130571; c) *Toxics Release Inventory (TRI) 2016 National Analysis, Executive Summary,* United States Environmental Protection Agency, https://www.epa.gov/trinationalanalysis/report-sections-2016-tri-national-analysis, 25.08.2018.
[8] 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, *P. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13197; d) P. J. Dunn, In: *Pharmaceutical Process Development: Current Chemical and Engineering Challenges* (Eds.: J. Blacker, M. T Williams), RSC Publishing, London, **2011**, 117-137; d) C. A. Kuttruff, M. D. Eastgate, P. S. Baran, *Nat. Prod. Rep.* **2014**, *31*, 419; e) D. Stubba, G. Lahm, M. Geffe. J. W. Runyon, A. J. Arduengo III, T. Opatz, *Angew. Chem. Int. Ed*., **2015**, *54*, 14187.
[9] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; b) K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44; c) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[10] a) L. Malet-Sanz, F. Susanne, *J. Med. Chem.* **2012**, *55*, 4062; b) K. F. Jensen, *AIChE J.*, **2017**, *63*, 858.
[11] *Organometallic Flow Chemistry. Topics in Organometallic Chemistry*, (Ed.: T. Noël), Springer, Cham, **2015**.
[12] a) V. Hessel, *Chem. Eng. Technol.* **2009**, *32*, 1655; b) P. Watts, in: *Sustainable Flow Chemistry: Methods and Applications* (Ed.: L. Vaccaro), Wiley-VCH, Weinheim, **2017**, 193-217.

2 Flow chemistry

2.1 Introduction

During the past decade the use of microreactors in continuous operation mode, termed *flow chemistry*,[13] has been established as an alternative operation mode for various types of chemical reactions and operations.[14] Scheme 1 illustrates this trend on the basis of publications in the academic and industrial field since 1980.



Scheme 1: Number of publications from 1980−2017 using the term "flow" in their title. Organic Process and Research Development (OPRD) and Angewandte Chemie Int. Ed. (ACIE) are shown. The SciFinder© search was used and obvious false results are not included in the counting.

Currently, a broad range of flow equipment is commercially available, making a further increase in the application of flow chemistry likely.[15] A number of advantages can result from performing a reaction in a continuous flow system rather than in typical batch reactors such as a round bottom flask.[14] It is advisable to understand and differentiate these effects:[14a,d,e] At the outset, advantages resulting from flow reaction mode are best divided in *reaction performance improvements* and *practical improvements*. The latter comprise aspects such as enhanced safety due to minimized use of reactants at any point in time, benefits from automation, as well as more efficient use of working space and resources.[14b,c] In contrast, reaction performance improvements include enhancement of the chemical yield, selectivity or feasibility of a reaction under given conditions as well as enhanced overall process productivity. The effects in the latter category are discussed in the following.

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[13] Distinct from macro-flow reactions, which are used for over a century in the industrial production of commodity chemicals *via* heterogeneous processes. Compare: a) J. M. Thomas, W. J. Thomas, *Principles and Practice of Heterogeneous Catalysis*, VCH, Weinheim, **1997.**

[14] a) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 7502; b) K. S. Elvira, X. Casadevall i Solvas, R. C. R. Wootton, A. J. deMello, *Nat. Chem.* **2013**, *5*, 905; c) S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chem. Int. Ed.* **2015**, *54*, 10122; d) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796; e) K. F. Jensen, *AIChE J.*, **2017**, *63*, 858.

[15] a) S. Ceylan, L. Coutable, J. Wegner, A. Kirschning, *Chem. Eur. J.* **2011**, *17*, 1884; b) L. Malet-Sanz, F. Susanne, *J. Med. Chem.* **2012**, *55*, 4062.

2.2 Typical Continuous Micro-Flow Setup

Typical elements of a basic flow chemistry setup are shown below (Figure 1). The elements are ordered from left to right according to a proceeding reaction, *i.e.* from reagent delivery to outlet/quench. The reagent solutions are continuously delivered to the reaction by pumps at a defined flowrate. Suitable systems for the delivery of gases or slurries exist as well.[14b] The reagent streams are unified and mixed in various available mixing devices ranging from simple T-pieces (typical inner diameter: i.d. ~0.25−1.0 mm) to sophisticated mixing devices such as slit interdigital micromixers (channel widths down to ~25 µm).[15b,16]

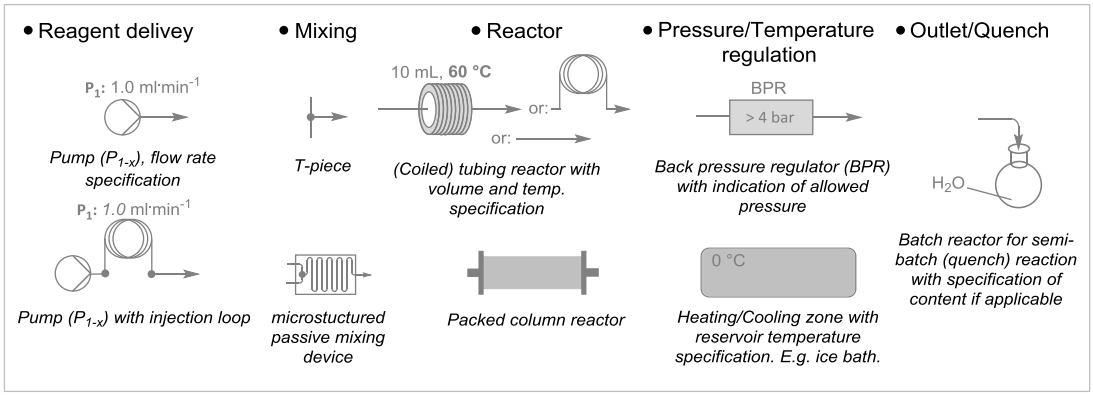

Figure 1: Symbols for the basic modules of a flow chemistry setup from reagent delivery to reaction quench.

Subsequently, the reagents pass a reactor which defines the residence time of the reaction mixture *via* the flow rate and its volume.[17] Furthermore, the reactor allows setting the reaction temperature by means of cooling or heating.[12a] Typical reactors are made from PTFE or stainless steel coiled tubing with inner diameters of i.d. = 0.25−2.00 mm.[14b,15b] The flow system will experience a pressure drop originating from the action of the pumps, however additional pressure can be applied with back pressuring devices.[14d,18b] Finally, the reaction mixture is pumped into a batch vessel, in which the output is collected or reacted in *semi-batch* mode with another reagent, such as a quenching solution. The time of collection defines the scale of a flow reaction; however attention must be paid in the case of non-steady-state operation.[14d]

For illustration, the synthesis of benzoic acid from phenyl bromide *via* a Br/Li exchange followed by addition to CO_2 and acidic quench is shown in Scheme 2 as a prototypical three-stage reaction in either batch or flow mode:[19]

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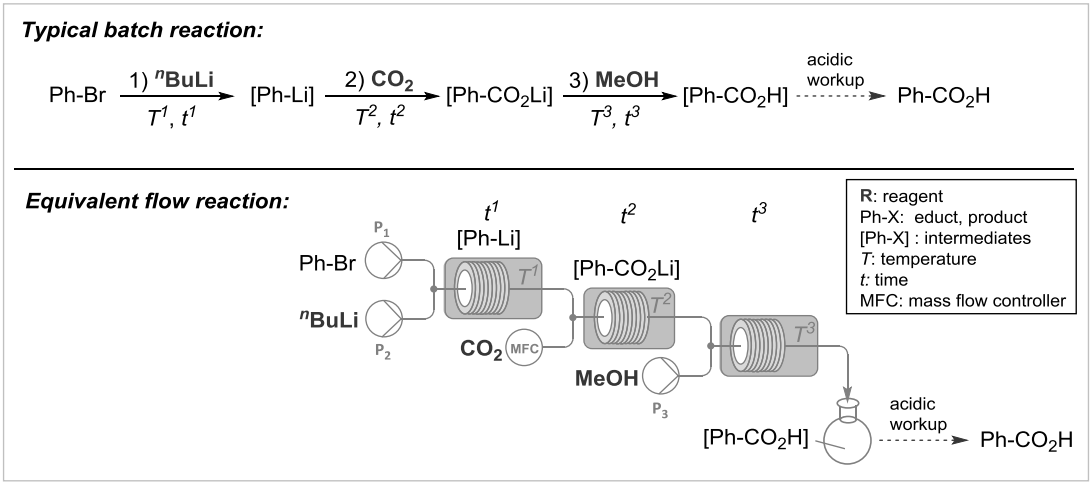
[16] a) L. Falk, J. M. Commenge, *Chem. Eng. Sci.* **2010**, *65*, 405; b) L. Capretto, W. Cheng, M. Hill, X. Zhang, *Top. Curr. Chem.* **2011**, *304*, 27; c) S. Schwolow, J. Hollmann, B. Schenkel, T. Röder, *Org. Process Res. Dev.* **2012**, *16*, 1513; d) K. D. Nagy, B. Shen, T. F. Jamison, K. F. Jensen, *Org. Proc. Res. Dev.* **2012**, *16*, 976.

[17] According to: residence time = reactor volume/combined flow rates; t^r [min]= mL/mL·min^{-1}.

[18] a) F. Ullah, T. Samarakoon, A. Rolfe, R. D. Kurtz, P. R. Hanson, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10959; b) J. M. Sauks, D. Mallik, Y. Lawryshyn, T. Bender, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 1310.

[19] For the realization of such a reaction sequence in flow, see: A. Nagaki, Y. Takahashi, J. Yoshida, *Chem. Eur. J.* **2014**, *20*, 7931.



Scheme 2: Graphical representation of a three stage reaction from Ph-Br→Ph-CO2H in a batch process (upper half) and an equivalent continuous flow reaction (lower half).

Several extensions beyond such a basic flow setup have been introduced, including mainly devices for in-line-analytics and -purification. Hence, in-line IR- or NMR-analytics have been utilized to monitor reaction progress and intermediates as well as for the feedback of automatized reaction optimization.[20] Reaction work-up operations are routinely included into flow systems, *e.g.* using scavenger resins[21] or membranes for extraction of products.[22] Such extensions allow setting up entire reaction sequences, which then operate highly or fully automated.[23] A potential application of such systems is the small-scale on-demand synthesis of active pharmaceutical ingredients or ready-made pharmaceutical preparations.[24]

2.3 Influence of Micro-Flow Setups on the Performance of Chemical Reactions

First of all, it has to be noted that the thermodynamics and kinetics of a given reaction are not changed in a flow setup.[14d] The observed effects in flow chemistry are therefore due to the different macroscopic realization of the reaction.[12a,14] Ultimately, improvements in flow setups can be traced back to the miniaturization of the reaction vessel (Scheme 3).[12,14] The small size of the reactor

[20] a) J. P. McMullen, M. T. Stone, S. L. Buchwald, K. F. Jensen, *Angew. Chem. Int. Ed.* **2010**, *49*, 7076; b) J. Reizmann, K. F. Jensen, *Acc. Chem. Res.* **2016**, *49*, 1786; c) V. Sans, L. Cronin, *Chem. Soc. Rev.* **2016**, *45*, 2032.
[21] a) T. P. Petersen, A. Ritzén, T. Ulven, *Org. Lett.*, **2009**, *11*, 5134; b) F. Venturoni, N. Nikbin, S. V. Ley, I. R. Baxendale, *Org. Biomol. Chem*. **2010**, *8*, 1798.
[22] a) T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 5943; b) A. G. O'Brien, Z. Horváth, F. Lévesque, J. W. Lee, A. Seidel-Morgenstern, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 7028 c) D. X. Hu, M. O'Brien, S. V. Ley, *Org. Lett.* **2012**, *14*, 4246; d) N. Weeranoppanant, A. Adamo, G. Saparbaiuly, E. Rose, C. Fleury, B. Schenkel, K. F. Jensen, *Ind. Eng. Chem. Res.* **2017**, *56*, 4095.
[23] a) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Chem. Commun.* **2010**, *46*, 2450; b) F. Lévesque, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 1706; c) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849; d) P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1192.
[24] a) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11*, 1194; b) 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.

volumes in flow chemistry setups are more efficiently penetrated by heat,[12,15a,25] light[26] and microwave irradiation[27] due to their small reactor diameter and increased surface-to-volume ratio relative to batch reactors used for equal scales (Scheme 3A–B). The efficient heat transfer allows controlling exothermic reactions and establishing a narrow temperature profile in flow reactors.[14d,28] The latter effect can improves the selectivity of reactions, in which temperature overshoots have deletorial effects on the selectivity.[29] Multiphasic reactions, such as solid-liquid reaction systems (packed bed column reactors, resins[30] or solid metal reactors[31]) as well as immiscible liquid-liquid[32] and gas-liquid reaction systems[33] profit from improved interfacial surfaces and smaller diffusion paths in flow setups. Thus, typically conversion, but also selectivity is enhanced in phase-transport limited multiphasic systems.[14,32,33] Furthermore, the small characteristic structures at the mixing point of a flow system allow for scale-independent[12a] fast mixing, if appropriate flowrates and mixing geometries are chosen.[16,34] For instance, using a simple T-piece for mixing, diffusion in a vortex flow can be utilized as highly efficient mixing principle, which leads to a homogenisation of reaction mixtures within the sub-second timescale. More sophisticated static mixers allow homogenisation in the sub-millisecond regime (Scheme 3C).[19c,35] Additionally, the small inner diameter of flow reactor tubing allows precise resolution and control of residence times in a technically simple fashion. The translation of the temporal dimension to a highly resolved spatial dimension in flow can be used under fast-mixing conditions to handle very short-lived intermediates down to a millisecond time regime (Scheme 3D).[35e]

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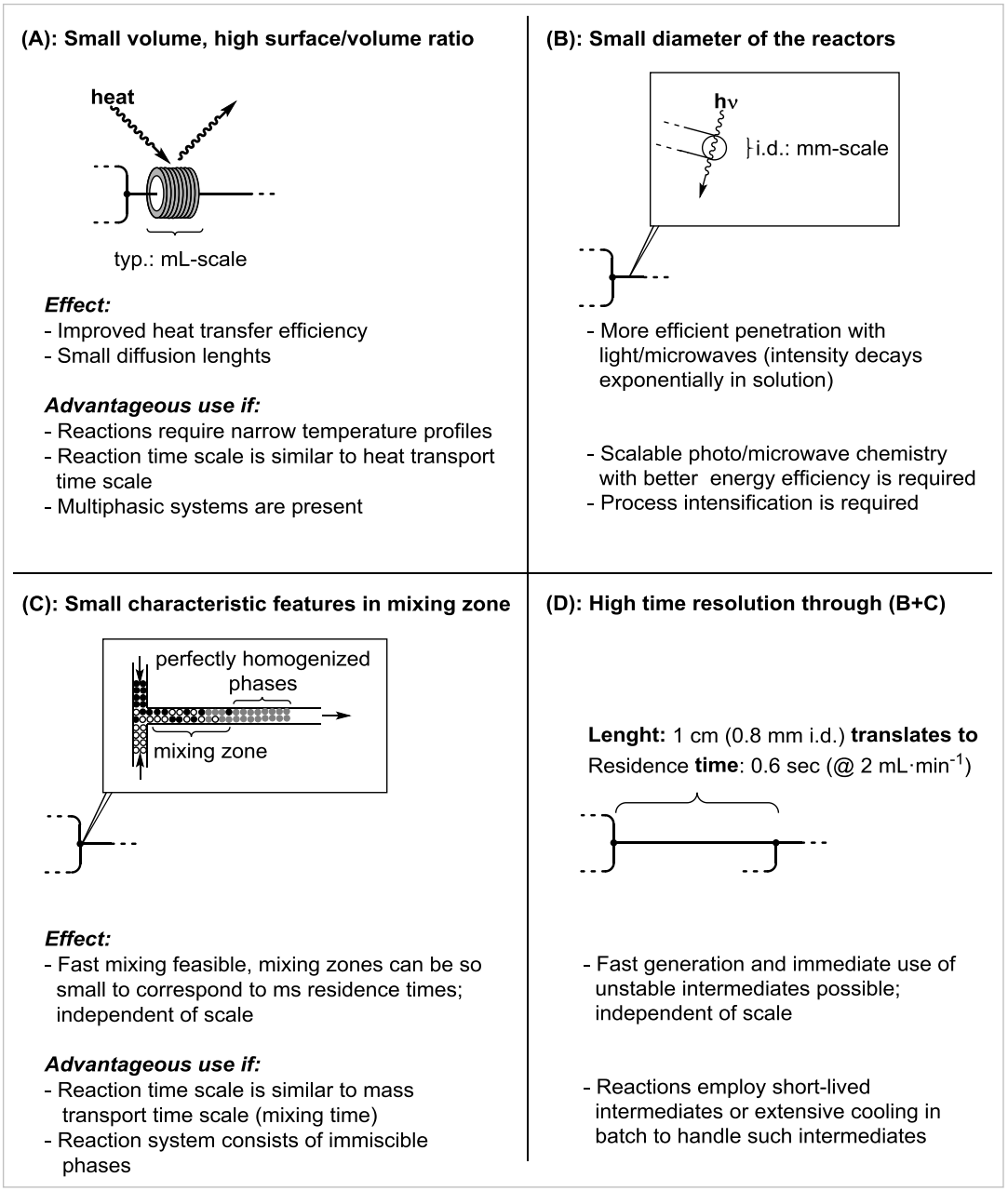
[25] T. Razzaq, T. N. Glasnov, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, *9*, 1321.
[26] a) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025; b) C. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276.
[27] a) E. Comer, M. G. Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8160; b) J. D. Moseley, C. O. Kappe, *Green Chem.* **2011**, *13*, 794; c) J. M. Sauks, D. Mallik, Y. Lawryshyn, T. Bender, M. Organ, *Org. Process Res. Dev.* **2014**, *18*, 1310.
[28] J. Pelleter, F. Renaud, *Org. Proc. Res. Dev.* **2009**, *13*, 698.
[29] a) H. Wakami, J.-i. Yoshida, *Org. Process Res. Dev.* **2005**, *9*, 787; b) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S.V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892.
[30] a) P. H. Seeberger, *Chem Soc. Rev.* **2008**, *37*, 19; b) R. M. Myers, K. A. Roper, I. R. Baxendale, S. V. Ley, in: *Modern Tools for the Synthesis of Complex Bioactive Molecules*, (Eds. J. Cossy, S. Arseniyadis), J. Wiley, New York, **2012**, 359.
[31] a) G. Shore, S. Morin, M. G. Organ, *Angew. Chem. Int. Ed.* **2006**, *45*, 2761; b) Y. Zhang, T. F. Jamison, S. Patel, N. Mainolfi, *Org. Lett.* **2011**, *13*, 280; c) M. A. Kabeshov, B. Musio, S. V. Ley, *React. Chem. Eng.*, **2017**, *2*, 822.
[32] F. Mandrelli, A. Buco, L. Piccioni, F. Renner, B. Guelat, B. Martin, B. Schenkel, F. Venturoni, *Green Chem.* **2017**, *19*, 1425.
[33] a) P. Löb, H. Löwe, V. Hessel, *J. Fluorine Chem*. **2004**, *125*, 1677; b) M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.*, **2015**, *48*, 349.
[34] 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**.
[35] 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) H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J.-i. Yoshida, *Science* **2016**, *352*, 691; f) 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.



Scheme 3: Summary of the effects of miniaturization in flow chemistry setups and their principal applications.

3 Organometallic Chemistry

Since the initial syntheses of compounds containing carbon-metal bonds (C-Met) over 150 years ago,[36] organometallic compounds have become indispensable in organic synthesis – as catalysts, bases and carbon-nucleophile equivalents, allowing for atom- and step-economic synthetic planning.[9] Notably, organometallic compounds exhibit a widely tuneable reactivity, which is given on the one hand by the nature of the metal and on the other hand by the ligands (L_n) of the metal center (C-Met-L_n; Figure 2).[9] These two variables are routinely adjusted in the use of stoichiometric reagents and transition metal catalysts in order to obtain the desired reactivity for the synthetic task at hand. Some examples of of C-Met-L_n compounds are given in Figure 2 with a short explanation of their characteristic reactivity.[37]

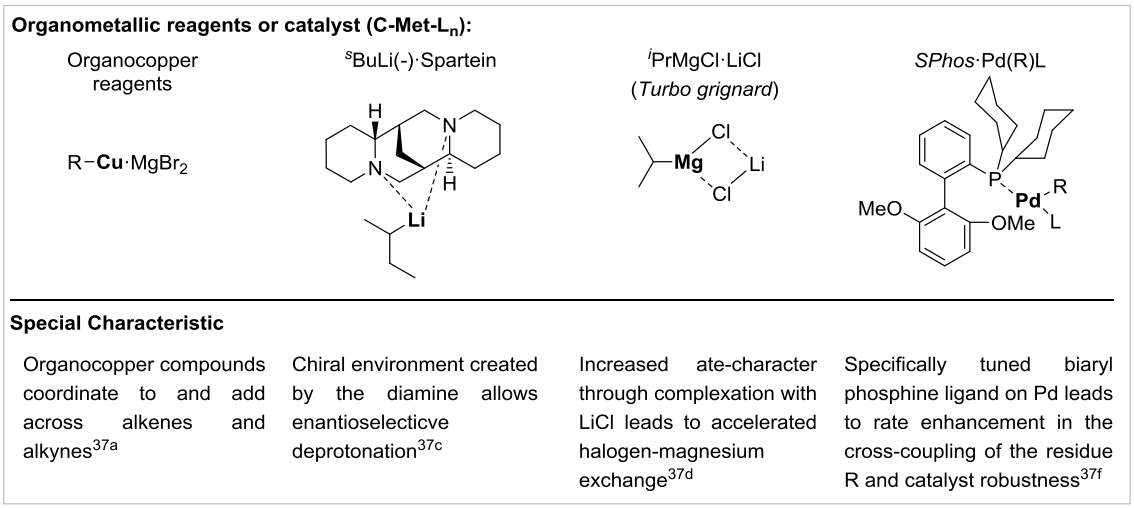


Figure 2: Examples of organometallic compounds (C-Met-Ln) specifically adapted to synthetic tasks via choice of metal and ligand modification.

Organometallic reagents are prepared by various routes, either *via* oxidative insertion or halogen-metal exchange of organic halides or by deprotonative metalation of suited substrates (Scheme 4).[38] Transmetalation gives additionally the possibility to exchange the metal atom of a C-M bond.[39] These

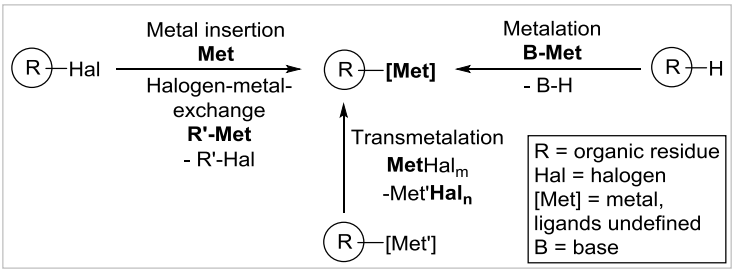
[36] a) E. Frankland, *Liebigs Ann. Chem.* **1848**, *71*, 171; b) W. Hallwachs, A. Schaferik, *Ann. Chem.* **1859**, *109*, 206; c) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322; c) D. Seyferth, *Organometallics* **2001**, *20*, 1488.

[37] For the reactivity of the depicted and further important **R-Met-L_n** containing compounds, see: a) M. S. Kharasch, P. O. Tawney, *J. Am. Chem. Soc.*, **1941**, *63*, 2308; b) A. Alexakis, J. F. Normant, *Synthesis* **1981**, 841; c) D. S. Matteson, *Chem. Rev.* **1989**, *89*, 1535; d) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2282; e) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 333; f) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758; g) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *42*, 1461; h) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289.

[38] Carbo- and hydro-metalations represent alternative syntheses of organometallic compounds, but are omitted due their low relevance for this thesis. For reviews, see: a) H. C. Brown, *Tetrahedron.* **1961**, *12*, 117; b) A. Alexakis, J. F. Normant, *Synthesis* **1981**, 841; c) A. Gómez-SanJuan, N. Sotomayor, E. Lete, *Beilstein J. Org. Chem.* **2013**, *9*, 313.

[39] M. Gardette, A. Alexakis, J. Normant, *Tetrahedron Lett.* **1982**, *23*, 5155; b) A. Alexakis, D. Jachiet, J. F. Normant, *Tetrahedron* **1986**, 42, 560; c) F. Zeng, E.-i. Negishi, *Org. Lett.* **2001**, *3*, 719; d) K. Moriya, M. Simon, R. Mose, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10963.

pathways will be discussed in the following with regard of their scope, limitations and applications in flow chemistry.



Scheme 4: Schematic representation of major preparative routes for organometallic reagents R-[Met]. Brackets indicate an undefined number and type of ligands.

3.1 Preparation of Organometallic Reagents in Batch and Continuous Flow

In choosing an organometallic reagent and preparation method,[40] functional group tolerance must be a central consideration in order to avoid protection group strategies.[8a-b,9] The various preparation methods differ in the employed conditions, reagents and starting materials and thus exhibit different functional group tolerances. Furthermore, the targeted organometallic molecule itself may be subject to decomposition, which depends strongly on the nature of the constituent metal as well as structural features of the organic residue.[41] Likewise, the reactivity of an organometallic reagent depends strongly on the constituent metal.[8a-b] These decisive properties (functional group tolerance, stability and reactivity) can be correlated to the extent bond polarization in the C-Met bond for a given organyl rest.[42] The polarization is easily deducted from the electronegativity difference ΔEN(C-Met) (Figure 3).[9a,43]

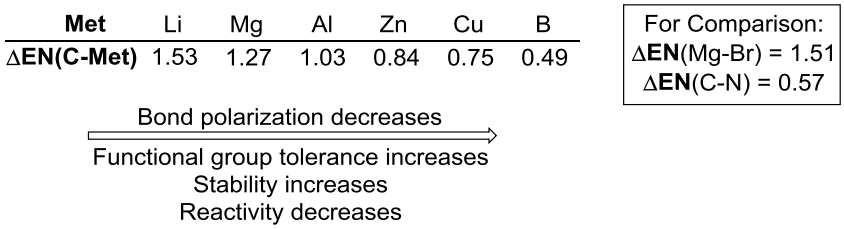


Figure 3: Electronegativity difference (ΔEN) of common C-Met bonds and its correlation to functional group tolerance, stability and reactivity of the corresponding metal organyl species.

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[40] a) *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; b) *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**; c) *The Chemistry of Organozinc Compounds* (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons Ltd, Chichester, **2007**.

[41] s) P. Knochel, in: *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005,** 1-5; For examples of structural influences on organomagnesium stability, see: P. Knochel, A. Krasovsky, I. Sapountzois, *ibid*., 109-172; For examples of structural influences on organolithium stability, see: c) M. Yus, F. Foubelo, *ibid*., 7-37.

[42] The Allred-Rochow scale was used: A. L. Allred, E. G. Rochow, *J. lnorg. Nucl. Chem.* **1958**, *5*, 264; The electronegativity of the carbon atom plays a role too, since it depends on substituents and hybridization, see ref. 43.

[43] C. Elschenbroich, *Organometallchemie 6. Auflage*, Teubner, Wiesbaden **2008**, 19-23.

The pronounced bond polarization of C-Li and C-Mg bonds renders organolithium and *Grignard* reagents so reactive and sensitive, that external cooling is generally applied for their preparation and use to suppress destructive pathways.[41] However, their reactions with electrophiles proceed typically without further activation. Compounds containing predominantly covalent C-Met bonds like boron or zinc organyls are typically not prone to decompose and exhibit high functional group tolerance. The reactivity of these covalent organometallics may however require activation *via* transition metal catalysis and external energy input.[9a] Despite advances in transition metal catalysis and the synthesis of functionalized unpolar organometallics, resorting to reactive polar organometallics is often more cost-economic and has a lower environmental impact if the high reactivity of these reagents is exploited expediently.[14a,29b] Additionally it has to be taken into account, that less reactive organometallics such as organoboronic acids are routinely obtained from polar organometallic precursors,[44] which requires dealing with issues of functional group tolerance and stability nontheless. Therefore, method development with highly reactive organometallic species is a worthwhile field of research, which is currently being changed by the upcoming use of flow setups for their preparation and use.[45]

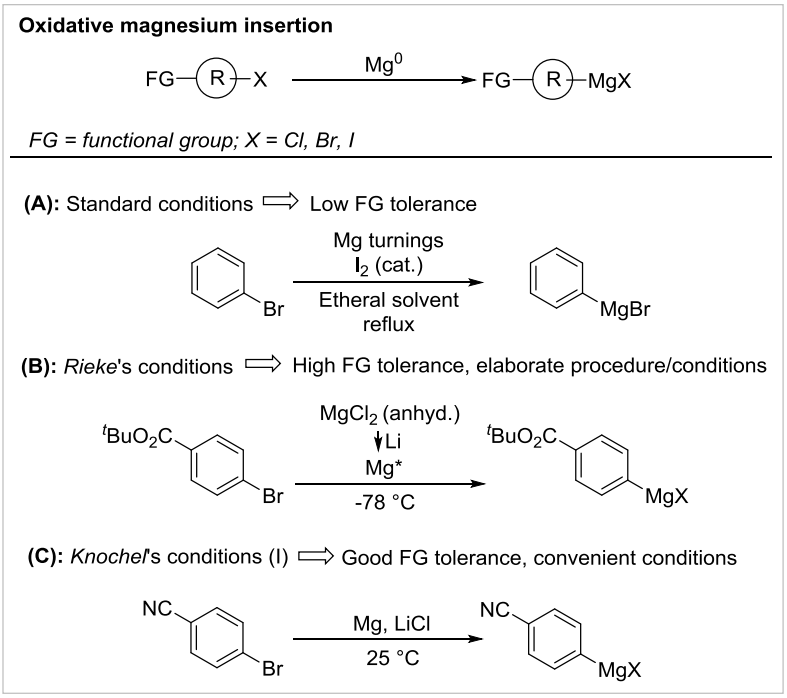
3.1.1 Oxidative Insertions

Pioneered by *Frankland* and *Grignard* in the second half of the 18th century,[36] the oxidative insertion of metals into a carbon-halogen bond became the first general route to organometallic species. This reaction was studied extensively, which led to various modifications.[46] A general advantage of oxidative insertion is its high atom- and cost-efficiency compared to other methods. Lithium insertion is mainly relevant to industrial production, where it is used to produce butyllithium reagents from the corresponding chlorides.[47] Despite the generality of the broadly used magnesium insertion, several limitations are inherent to the method. Firstly, the oxidative Mg insertion is known to proceed through a single electron transfer mechanism, which limits its application in the synthesis of stereochemically defined organometals.[48] Moreover, Mg as well as other metals act as reducing agents towards several

[44] E. Demory, V. Blandin, J. Einhorn, P. Y. Chavant, *Org. Process Res. Dev.* **2011**, *15*, 710; b) A. Hafner, P. Filipponi, L. Piccioni, M. Meisenbach, B. Schenkel, F. Venturoni, J. Sedelmeier, *Org. Process Res. Dev*. **2016**, *20*, 1833.
[45] 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.
[46] a) *Handbook of Grignard Reagents* (Eds.: G. S. Silvermann, P. E. Rakita), New York, **1996**; b) *Grignard Reagents, New Developments* (Ed.: H. G. Richey jr.), Wiley & Sons, New York, **2000**.
[47] a) L. Brandsma, H. Verkruijsse, *Preparative Polar OrganometallicChemistry 1*, Springer-Verlag, London; **1987**; b) U. Wietelmann, R. J. Bauer, in: *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2002**.
[48] a) H. M. Walborsky, *J. Am. Chem. Soc.* **1989**, *11*, 1896; b) H. M. Walborsky, *Acc. Chem. Res.*, **1990**, *23*, 286; c) J. F. Garst, F. Ungváry, in: *Grignard Reagents, New Developments*; (Ed.: H. G. Richey Jr.), Wiley: Chichester, **2000**; 185.

functional groups such as the nitro and azide groups which are therefore not tolerated.[49] A major preparative challenge in oxidative metal insertion is the passivating oxidation layer formed upon exposure to air,[50] which needs to be removed by means of activating agents to enable the insertion reaction.[51] This activation entails an unpredictable reaction onset, which combined with the exothermic insertion reaction, can lead to hazardous thermal runaways.[46] The typically relatively slow Mg insertion indicates reaction temperatures of 25−60 °C (Scheme 5A).[46] However, long reaction times and ambient to high temperatures lead to a lowered functional group tolerance, as organomagnesium reagents react readily with common electrophilic moieties in the absence of cooling.[52] To overcome this limitation, *Rieke* and coworkers described the use of *in situ* formed, unpassivated magnesium (Mg*), resulting from the reduction of $MgCl_2$ by an alkali metal, which undergoes insertion without activation even at cryogenic temperatures (Scheme 5B).[53] Yet, this procedure is limited to small-scale laboratory applications due to the hazardous nature of elemental alkali metals and the experimental effort.[52] Another important improvement was introduced by *Knochel* and coworkers, who demonstrated that stoichiometric amounts of LiCl facilitate the formation of *Grignard* reagents with commercially available Mg even at moderate temperatures between −20 °C and 25 °C (Scheme 5C).[54] This allows maintaining a good group tolerance while still providing an operationally convenient and cost-efficient method. Furthermore, methods for oxidative insertion of zinc in presence of LiCl, *Rieke*-Zn,[53b] or Mg triggered insertion in presence of a zinc salt,[55] were developed, as well as manganese,[56] aluminum,[57] indium[58] or copper[53b,59] insertions, which provide a range of synthetically useful organometallic species.

[49] a) O. Kamm, *Org. Synth.* **1941**, *1*, 445; b) K. F. Keirstead, *Can. J. Chem.*, **1953**, *31*, 1064; c) B. A. Fox, T. L. Threlfall, *Org. Synth.* **1973**, *5*, 346; d) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983; e) W. Lin, X. Zhang, Z. He, Y. Jin, L. Gong, A. Mi, *Synth. Commun.* **2002**, *32*, 3279.
[50] J. F. Garst, M. P. Soriaga, *Coord. Chem. Rev.* **2004**, *248*, 623.
[51] For the prepartation *Grignard*-reagents, typically iodine, 1,2-dibromoethane, diisobutylaluminium hydride, or ideally solutions of the same *Grignard* reagent are used for activation: a) U. Tilstam, H. Weinmann, *Org.Proc. Res. Dev.* **2002**, *6*,906; b) G. S. Silvermann, in: *Handbook of Grignard Reagents* (Eds.: G. S. Silvermann, P. E. Rakita), Marcel Dekker, New York, **1996**, 2-80.
[52] P. Knochel, A. Krasovsky, I. Sapountzis, in: *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005,** 113.
[53] a) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674; b) R. D. Rieke, *Science* **1989**, *246*, 1260.
[54] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed*. **2008**, *47*, 6802.
[55] a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445. b) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; c) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; d) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; e) C. Sämann, V. Dhayalan, P. R. Schreiner, P. Knochel, *Org. Lett.* **2014**, *16*, 2418 and sources therein.
[56] Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198.
[57] a) T. D. Blümke, Y. 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.
[58] a) Y. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; b) Y. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236.
[59] G. W. Ebert, W. L. Juda, R. H. Kosakowski, B. Ma, L. Dong, K. E. Cummings, M. V. B. Phelps, A. E. Mostafa, J. Luo, *J. Org. Chem.* **2005**, *70*, 4314.

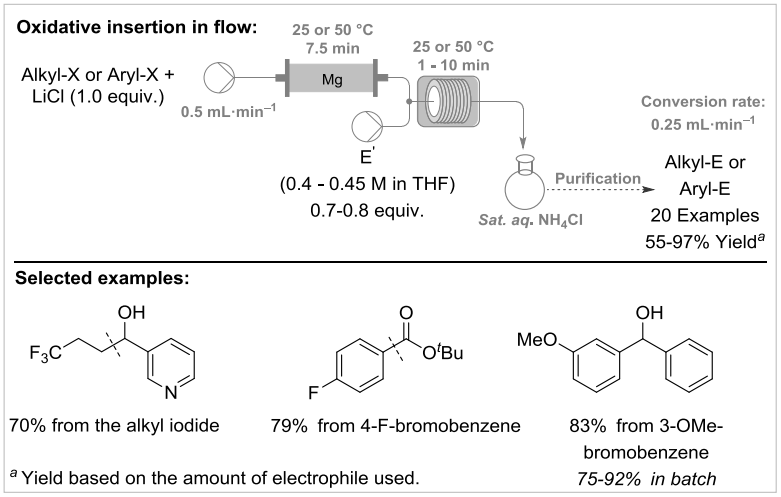


Scheme 5: Oxidative insertion: Important experimental procedures for Mg insertion into aryl bromides and the consequences for functional group tolerance and practicality.

Considering the challenging activation and exothermy of oxidative insertions, flow methods should offer advantages for oxidative insertion reaction from a safety and reproducibility standpoint. Additionally, the fast removal of freshly formed potentially instable organometallics from the hot reaction zones of insertion could be realized using flow equipment. In practice, the organic halide must be brought in contact with the metal by means of a packed column reactor.[60] For instance, *Alcázar* and coworkers reported the oxidative insertion of Mg into aryl and alkyl halides.[60b] A packed Mg column was used and activation was achieved by passing solutions of diisobutylaluminium hydride, trimethylsilyl chloride and 1-bromo-2-chloroethane over the column. Subsequent *Grignard* formation was achieved by passing a 1:1 molar mixture of LiCl and organic halide (0.5 M in THF:toluene = 1:1) over the activated column for 7.5 min at 25 °C (Scheme 6). This procedure led to full conversion of the halides and delivered stable concentrations of Grignard solutions which were quenched in-line with various electrophiles. The researchers noted that a biphenylmethanol product (bottom, right, Scheme 6) was previously synthesized in a batch reactor *via* Mg insertion in lower yield.[60b] However, even higher yields (92%) are reported for the same reaction under batch

[60] a) M. Goldbach, E. Danieli, J. Perlo, B. Kaptein, V. M. Litvinov, B. Blümich, F. Casanova, A. L. L. Duchateau, *Tetrahedron Lett.* **2016**, *57*, 122; b) L. Huck, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar, *Org. Lett.* **2017**, *19*, 3747.

conditions.[61] Analogous protocols for oxidative Zn insertion are also available for the generation of *Reformaski* reagents and benzyl zinc halides.[62]



Scheme 6: Oxidative magnesium insertion into alkyl and aryl halides and in-line quench in continuous flow. Dotted lines indicate the newly formed bond.

Thus far however, improvements of the reaction outcome for oxidative insertion reactions in flow or a direct comparative study including batch experiments were not reported. Hence, practical improvements were the major concern of the cited studies.

3.1.2 Halogen-Metal Exchange

Since the first reports of a bromide-magnesium exchange reaction by *Prévost* in 1931 and halogen-lithium exchanges by *Wittig* and *Gilman*,[63] halogen-metal exchange has become a major route for converting organic halides into organometallic compounds.[64,65] Under appropriate conditions, an organic halide is transformed into its organometallic derivative by treatment with an exchange reagent.[66] The advantages of the reaction are its generality, the possibility to obtain stereodefined

[61] S. Kobayashi, K. Shibukawa, Y. Miyaguchi, A. Masuyama, *Asian J. Org. Chem.* **2016**, *5*, 636.
[62] 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.
[63] a) C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, 1372; b) G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903; c) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106.
[64] For halogen-lithium exchange, see: 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.
[65] For halogen-magnesium exchange, see: 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) R. L.-Y. Bao, R. Zhao, L. Shi, *Chem. Commun.*, **2015**, *51*, 6884.
[66] L. Degennaro, A. Giovine, L. Carroccia, R. Luisi, in: *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications, First Edition.* (Eds.: R. Luisi, V. Capriati), Wiley-VCH, Weinheim, **2014**, 515-526.

intermediates,[67] the lack of activation procedures and often fast reaction rates at ambient to cryogenic temperatures.[65,68] Exchange reactions are equilibrium processes, which lie on the side of the most stabilized carbanion ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec} > sp^3_{tert}$).[65a,69] Electron withdrawing groups can contribute additional stabilization and thus significantly influence the equilibrium.[70] The organic halide sideproduct resulting from an exchange reaction can disturb subsequent reactions such as transition metal catalyzed cross-couplings.[71]

Seminal work by *Parham* and *Köbrich* established the possibility to perform halogen-lithium exchange reactions in the presence of reactive functional groups despite the high reactivity of exchange reagents like ^{n}BuLi and PhLi.[72] Thus, if cryogenic temperatures (−110 to −78 °C) were applied, Br/Li exchange reactions were found to kinetically outcompete the attack of butyl lithium reagents on a *tert*-butyl ester or the decomposition of an *o*-nitro group. The aryllithiums obtained in this way could quenched with electrophiles in high yields (Scheme 7A−B). Similarly, cryogenic conditions were applied in an optimized synthesis of *α*-chloromethyllithium by *Villieras* and coworkers (Scheme 7C).[73] The procedure avoided carbene formation and furnished halohydrin intermediates upon addition to carbonyl compounds, which epoxidized under the reaction conditions. *Knochel* and others demonstrated the advantages of a quick transmetalation of unstable organolithium compounds to form *e.g.* organocopper compounds which are stable at convenient conditions and exhibit an altered reactivity.[66,74] For instance, an aliphatic azide was tolerated in a ^{n}BuLi triggered exchange protocol with quick consecutive transmetalation leading to the corresponding cuprate, which subsequently added smoothly to ethyl propriolate (Scheme 7D). Notably, generation of the alkenyllithium, -zinc or -copper intermediates by other methods would be excluded due to the presence of the azide. Parallel to this approach, a number of protecting groups were developed, such as *Yamamoto*'s supersilyl group, which extend the scope of halogen-lithium exchange by sacrificing

[67] A) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1; b) For stereospecific C(sp2)-hbromine-lithium exchange, see: H. Neumann, D. Seebach, *Tet. Lett.* **1976**, *52*, 4839; For recent examples of a stereoselective C(sp3)-halogen-lithium exchange, see: c) K. Moriya, M. Simon, R. Mose, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10963; and references therein.

[68] a) R. G. Jones, H. Gilman, *Org. Reactions* **1951**, *6*, 331; b) W. F. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861; c) 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.

[69] a) D. E. Applequist, D. F. O'Brien, *J. Am. Chem. Soc.* **1962**, *85*, 74. b) D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.

[70] a) H. J. S. Winkler, H. Winkler, *J. Am. Chem. Soc.* **1966**, *88*, 964; *ibid.* 969. b) J. Villeras, *Bull. Soc. Chim. Fr.* **1967**, 1520.

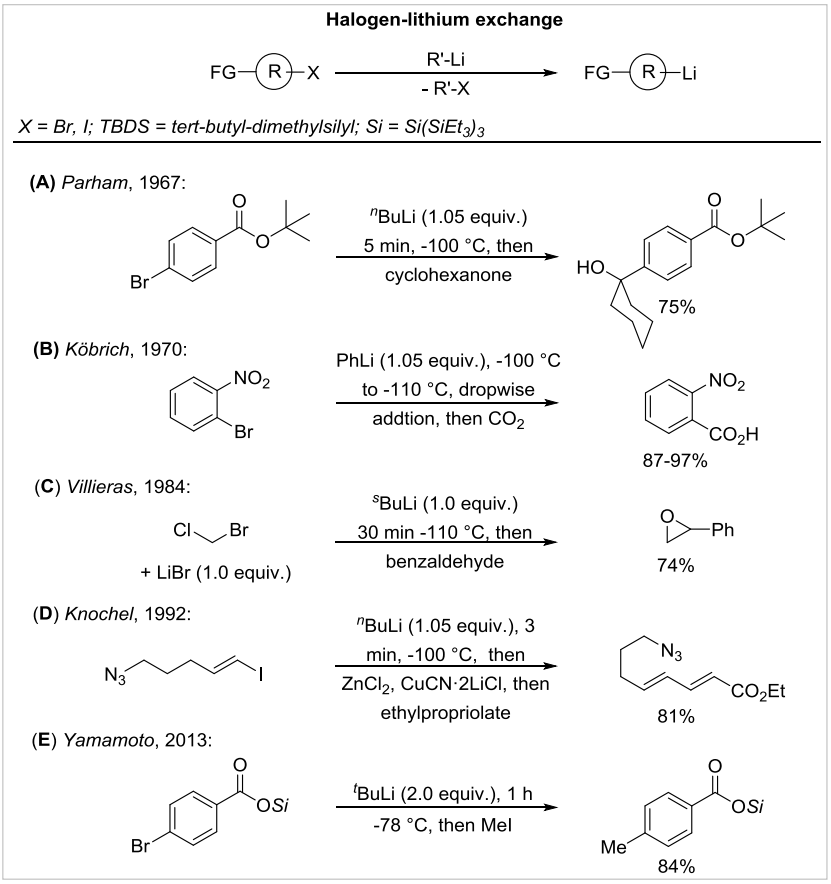
[71] In order to avoid this problem, some procedures include another step, which consumes the exchange byproduct using another equivalent of the exchange reagent: a) H. Neumann, D. Seebach, *Tet. Lett.* **1976**, 52, 4839; b) C. B. Rauhut, V. A. Vu, F. F. Fleming, P. Knochel, Org. Lett. **2008**, *10*, 1187; c) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2010**, *49*, 7543.

[72] a) G. Köbrich, P. Buck, *Chem. Ber.* **1970**, *103*, 1412; b) W. E. Parham, L. D. Jones, Y. Sayed, *J. Org. Chem.* **1975**, *40*, 2394; c) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704; d) W. E. Parham, C. K. Bradscher, *Acc. Chem. Res.* **1982**, *15*, 300.

[73] R. Tarhouni, B. Kirschleger, M. Rambaud, J. Villieras, *Tet. Lett.*, **1984**, *25*, 835.

[74] 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.

step- and atom-economy (Scheme 7E).[75] These two approaches define the limits of batch halogen-lithium exchange. On the one side, even if a transmetalation follows, the generation of lithium intermediates with sensitive functional groups has to proceed at cryogenic conditions. In many cases, decomposition will be faster than addition of a transmetalating reagent or an electrophile can be accomplished. On the other side, protection groups are always an uneconomic solution and not necessarily applicable to every transformation.



Scheme 7: Halogen-metal exchange: Important developments in chemoselective halogen-lithium exchange.

Subsequently, exchange reagents based on Mg and Zn were developed, which exhibited improved functional-group tolerance. Seminal work by *Knochel* and *Cahiez* demonstrated the use of ^{i}PrMgBr or the more nucleophilic (^{i}Pr)$_2$Mg in I/Mg exchange with (hetero)aryl iodides,[76] which was followed by extensions to iodoalkenes, activated cyclopropyl iodides and carbenoid precursors.[65a] Iodonitroarenes on the other hand could be treated with phenyl- or mesityl-*Grignard* reagents, which led to an exchange within minutes even below −40 °C, which allows to prevent the nitro-group from engaging in sidereactions.[77] Less sensitive aryl bromides and alkenyl iodides underwent a smooth exchange at −78 °C with trialkyl lithium magnesiates like ^{n}Bu$_3$MgLi.[78] The introduction of the "*Turbo-Grignard"*

[75] S. Oda, H. Yamamoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 8165.
[76] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.
[77] a) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *9*, 41; b) I. Sapountzis, H. Dube, R. Lewis, N. Gommermann, P. Knochel, *J. Org. Chem.* **2005**, *70*, 2445.
[78] A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333; and references therein.

reagent ^{i}PrMgCl·LiCl turned Br/Mg exchange into a general reaction, which was previously prohibitively slow with ^{i}PrMgCl or dependent on chelating group assistance.[65b,79] Further developments in halogen-metal exchange included the development of several I/Zn exchange protocols and a Cu/I exchange protocol using hindered cuprates in THF at cryogenic conditions.[80] More recently, magnesium zincate $^{t}Bu_3ZnMgCl$ was shown to enable atom efficient Zn-I exchange in THF[81] and toluene-soluble alkylmagnesium alkoxides of type ^{s}BuMgOR·LiOR (R = 2-ethylhexyl) were shown to trigger Br/Mg and Cl/Mg exchange of electron rich haloarenes in toluene within 1 h at most.[82] Despite these highly advanced methods, the limitations of batch exchange chemistry are set by the impractical conditions of halogen-lithium exchange on the one side and the structural dependency of halogen-magnesium, -zinc, and -copper exchanges on the other side. In both cases, the generation of an organometallic species can temporally overlap with its incipient decomposition.

The use of flow setups in halogen-lithium exchange was pioneered by *Yoshida* and marked a fundamentally new approach.[83] By performing *flash chemistry*, *i.e.* by generating reactive and unstable organolithium compounds and reacting them within seconds to microseconds ($10^{0}-10^{-4}$ s), it was demonstrated that the shortcomings of halogen-lithium exchange in batch could be avoided, while the reactive potential of these species is fully utilized. Relying on the fast rate of Br/Li or I/Li exchange[67,68] and the enhanced mixing in flow setups,[84] aryllithiums could be generated, which bear (prohibitively) sensitive functionalities. The costly and energy-intensive cryogenic conditions, which are typically required in batch chemistry, were often greatly moderated, because the quenching reaction of the organolithium intermediate can be set to take place faster than its decomposition.[83] An instructive example of flash chemistry was given by the synthesis of *o*-, *m*-, and *p*-(nitrophenyl)lithium compounds at (−28)−0 °C using PhLi as an exchange reagent in a microflow setup (Scheme 8).[85] Hence, the conditions realized in the flow protocol are considerably more convenient than previously reported for I/Li and I/Mg exchanges and allowed an access to the elusive *m*- and *p*-(nitrophenyl)lithium species and corresponding quenching products with various electrophiles.

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[79] 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.

[80] a) P. Knochel, H. Leuser, L.-Z. Gong, S, Perrone, F. F. Kneisel, in: *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, 2005, 270-282; b) P. Knochel, X. Yang, N. Gommermann, *ibid.*, 382-386.

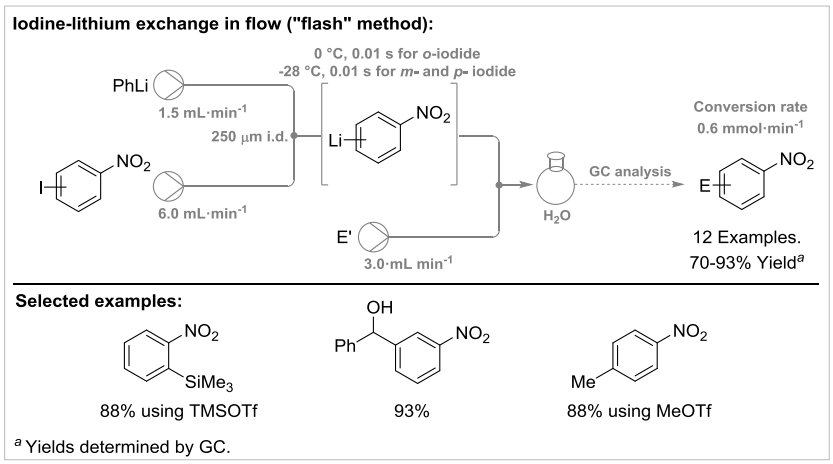
[81] T. D. Bluemke, W. Clegg, P. García-Alvarez, A. R. Kennedy, K. Koszinowski, M. D. McCall, L. Russo, E. Hevia, *Chem. Sci.* **2014**, *5*, 3552.

[82] D. S. Ziegler, K. Karaghiossof, P. Knochel, *Angew.Chem. Int. Ed.* **2018**, *57*, 6701.

[83] J.-i. Yoshida, *Flash Chemistry: Fast Organic Synthesis in Microsystems*, John Wiley & Sons, Ltd, Hoboken, **2008**.

[84] See chapter 2.3.

[85] A. Nagaki, H. Kim, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2009**, *48*, 8063.



Scheme 8: Iodine-lithium exchange with iodoarenes bearing *o*-, *m*-, and *p*-nitro groups in continuous flow with subsequent electrophilic quench.

Applying the principle of flash chemistry to lithium-halogen exchange, a number of aryllithium reagents were made accessible for the first time or at unprecedentedly convenient conditions.[83]

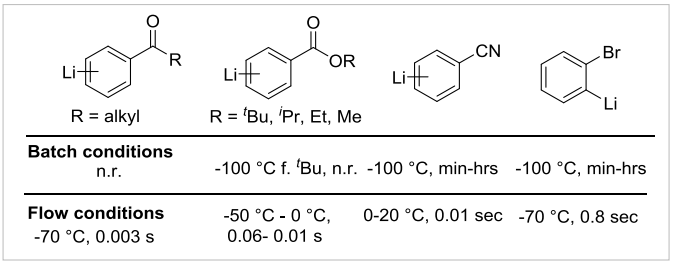


Figure 4: Lithium arenes with sensitive functionalities obtained under batch or flow conditions. N.r. = not reported, indicating that practical realization was not possible.

The advantages of this approach to halogen-lithium exchange were also recognized by industrial chemists and applied for large scale (700 kg) reactions.[86] Furthermore, several flow procedures for halogen-magnesium exchange using EtMgBr or ^{i}PrMgCl·LiCl have been reported, allowing the preparation of aryl and heteroaryl *Grignard* reagents in high yields and productivity at room temperature due to effective reaction heat control.[87] Furthermore, the possibility of automated reactions, in-line reaction monitoring and runs over 24 h (15 kg scale) were demonstrated in these studies.[87]

3.1.3 Directed Metalation

Directed metalation is complementary to the previous approaches in the sense that it does not require organic halide starting materials. Instead, organometallic bases are used to deprotonate the substrate,

[86] N. Kockmann, M. Gottsponer, B. Zimmermann, D. M. Roberge, *Chem. Eur. J.* **2008**, *14*, 7470.
[87] a) H. Wakami, J.-i. Yoshida, *Org. Proc.Res. Dev.* **2005**, *9*,787; b) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2011**, *16*, 1102; c) P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1192; d) A. Nagaki, J.-i. Yoshida, in: *Organometallic Flow Chemistry. Topics in Organometallic Chemistry*, (Eds.: T. Noël), Springer, Cham, **2015** 137-175.

which is turned concomitantly into the corresponding organometal compound.[66] The method can be applied to a vast number of differently hybridized and substituted organyls,[88] under the conditions that its acidity is sufficiently high[66] and kinetic requirements allow for practicable reaction rates.[89] Thus, heteroatom moieties play a crucial role in kinetically facilitating metalations in their proximity and concomitantly providing regioselectivity.[88-90] Alkyl lithium reagents show the highest reactivity in metalation reactions,[66,90] however the high nucleophilicity and the fast rates of competitive halogen-lithium exchanges limit the substrate scope of this method.[63b] Lithium amides in contrast (LiNRR') are less nucleophilic and do generally not engage in halogen-lithium exchange, but their reactivity is sufficient for a broad range of even weakly activated C-H bonds.[89,91] The broadest application field of lithium amides is in metal enolate chemistry, which accounts for large proportions of all performed C-C bond forming reactions in academic laboratories and pharmaceutical production.[92] Furthermore, lithiation using amide bases is a major functionalization route of arenes and heteroarenes.[90,91] The most commonly used lithium amides are LiHMDS (lithium hexamethyldisilazide), LDA (LDA = lithium diisopropyl amide) and the sterically hindered TMPLi (lithium 2,2,6,6-tetramethylpiperidide).[93] Several decades of mechanistic studies and synthetic efforts have led to a good understanding and predictability of the effects governing lithiation reactions with alkyl lithium or lithium amide bases.[91-93] However, the high reactivity of these reagents warrants in most cases the application of impractical cryogenic temperatures and precludes the presence of a range of electrophilic functionalities in the substrates.[94]

Similar to halogen-metal exchanges, this method saw great enhancement in scope and practicality by the introduction of reagents with less electropositive metal counter ions, leading thereby to more stable organometallic products. The development of sterically hindered, LiCl complexed, soluble Mg- and Zn- amide bases (TMPMetCl·LiCl, Met = Mg,[95] Zn[96]) as well as zincate bases[97] has allowed to

[88] a) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356; b) R. D. Clark, A. Jahangir, *Org. React.* **1995**, *47*, 1; c) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161; d) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069.
[89] a) H. W. Gschwend, H. R. Rodriguez, *Org. React.* **1979**, *26*, 1; b) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.
[90] a) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.
[91] M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376.
[92] a) D. Seebach, *Angew. Chem. Int. Ed.* **1988**, *27*, 1624; b) L. R. Liou, A. J. McNeil, A. Ramirez, G. E. S. Toombes, J. M. Gruver, D. B. Collum, *J. Am. Chem. Soc.* **2008**, *130*, 4859; c) E. Haimov, Z. Nairoukh, A. Shterenberg, T. Berkovitz, T. F. Jamison, I. Marek, *Angew.Chem. Int. Ed.* **2016**, *55*, 551.
[93] a) R. R. Fraser, T. S. Mansour, *J. Org. Chem.* **1984**, *49*, 3442; b) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470; c) K. A. Mack, D. B. Collum, *J. Am. Chem. Soc.* **2018**, *140*, 4877; d) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544.
[94] For a study about selectivity in lithium amide chemistry, see: a) M. S. Viciu, L. Gupta, D. B. Collum, *J. Am. Chem. Soc.* **2010**, *132*, 6361; For reviews on the use of TMPMgCl·LiCl and TMPMgZnCl·LiCl, see: b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794; c) K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302; d) M. Balkenhohl, P. Knochel, *SynOpen* **2018**, *2*, 78.
[95] 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.

access metalated unsaturated compounds bearing high degrees of functionality. The method was further extended to other metal amide bases (TMPZnOPiv·LiCl, Piv = $C(O)C(CH_3)_3$, $(TMP)_2Zn·2MgCl_2·2LiCl$, $(TMP)_2Mg·2LiCl$, $(TMP)_2Fe·2MgCl_2·4LiCl$, $(TMP)_2Mn·2MgCl_2·4LiCl$, $(TMP)_4Zr·4MgCl_2·6LiCl$, $(TMP)_3La·3MgCl_2·5LiCl$),[98] all of which have specific properties in metalation reactions.

Recent research by *Knochel*[99] and others[100] has described the advantageous use of flow setups in metalation chemistry. For instance, electron poor *N*-heterocycles, such as pyridines have been extensively used as metalation substrates using TMPMgCl·LiCl in batch chemistry.[94d] While these substrates are suited for metalation due to the coordinating *N*-heteroatoms and the acidity of the ring protons,[101] nucleophilic addition to the ring is an incipient sidereaction in using magnesium amide bases. Therefore, usage of low temperatures is mandatory in batch experiments.[94a,95g, 102] However, a transfer of this reaction type to a microflow setup has allowed to magnesiate heterocycles at convenient 0 °C to 25 °C, likely due to short reaction times and uniform heat distribution. *Knochel* and coworkers demonstrated in this work, that a considerably improved yield was obtained in flow for

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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.

[96] 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.

[97] a) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802; b) V. L. Blair, D. C. Blakemore, D. Hay, D. C. Pryde, E. Hevia, *Tetrahedron Lett.* **2011**, *52*, 4590.

[98] In the order of mentioning: a) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302; b) Y. Chen, M. Ellwart, G. Toupalas, Y. Ebe, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 4612; c) Y. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 9236; d) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; e) S. H. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, *47*, 6387; f) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; g) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; h) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237; i) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; j) C. J. Rohbogner, S. Wirth, P. Knochel, *Org. Lett.* **2010**, *12*, 1984; k) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717; l) S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256; m) M. Jeganmohan, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8520; n) S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3304.

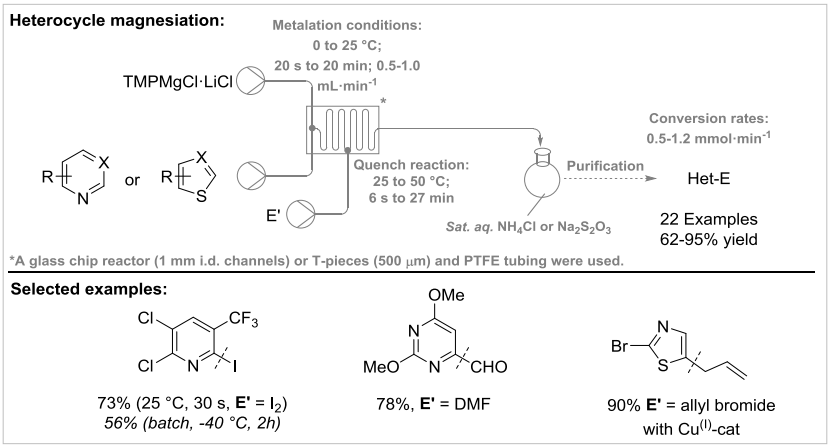
[99] a) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; b) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; c) M. Ketels, D. B. Konrad, K. Karaghiosoff, D. Trauner, P. Knochel, *Org. Lett.* **2017**, *19*, 1666.

[100] a) A. Nagaki, E. Takizawa, J.-i.Yoshida, *J. Am. Chem. Soc.* **2009**, *131*, 1654; *Chem. Eur. J.* **2010**, *16*, 14149; *Chem. Lett.* **2009**, *38*, 486; 1060; b) W. Shu, L. Pellegatti, M. A. Oberli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 10665; c) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2012**, *51*, 3245; d) J. A. Newby, D. W. Blaylock, P. M. Witt, R. M. Turner, P. L. Heider, B. H. Harji, D. L. Browne, S. V. Ley, *Org. Process Res. Dev.* **2014**, *18*, 1221; e) C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4945; f) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463; g) H. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2017**, *139*, 11590; h) T. von Keutz, F. J. Strauss, D. Cantillo, C. O. Kappe, *Tetrahedron* **2018**, *74*, 3113.

[101] a) K. Shen, Y. Fu, J.-N. Li, L. Liu Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568; b) K. Snégaroff, T. T. Nguyen, N. Marquise, Y. S. Halauko, P. J. Harford, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Chevallier, A. E. H. Wheatley, P. C. Gros, F. Mongin, *Chem. Eur. J.* **2011**, *17*, 13284.

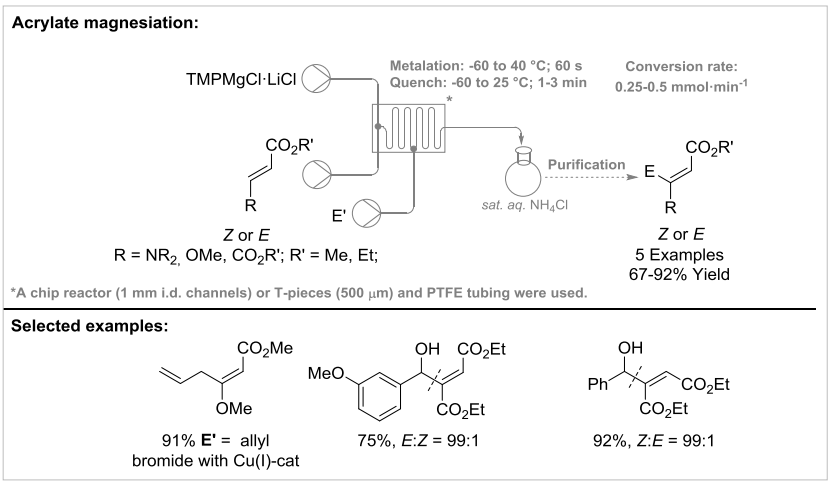
[102] T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933.

the magnesiation of a sensitive CF_3-substituted pyridine, followed by an iodine quench (Scheme 9, first example). Thus, performing the reaction in flow at 25 °C within 30 s furnished 73% of the desired product, whereas conversion in batch at necessary −40 °C was slow and finally gave only 56% of iodinated pyridine (Scheme 9). Applying similarly convenient conditions and using a glass chip flow reactor, a range of sensitive pyridines, pyrimidines, thiazoles and thiophenes could be metalated under scalable conditions and reacted with a broad range of electrophiles in high yields.



Scheme 9: Metalation of sensitive heterocycles using TMPMgCl·LiCl and in-line electrophile quench. Dotted lines indicate the newly formed bonds.

It was further demonstrated, that acrylates, which are prone to polymerization upon metalation, could be magnesiated in high yields (Scheme 10). For instance, *E*- and *Z*-fumarates were magnesiated in a glass chip reactor with enhanced heat control within 1 min at −60 °C and gave addition products with aldehydes without isomerization of the double bonds.

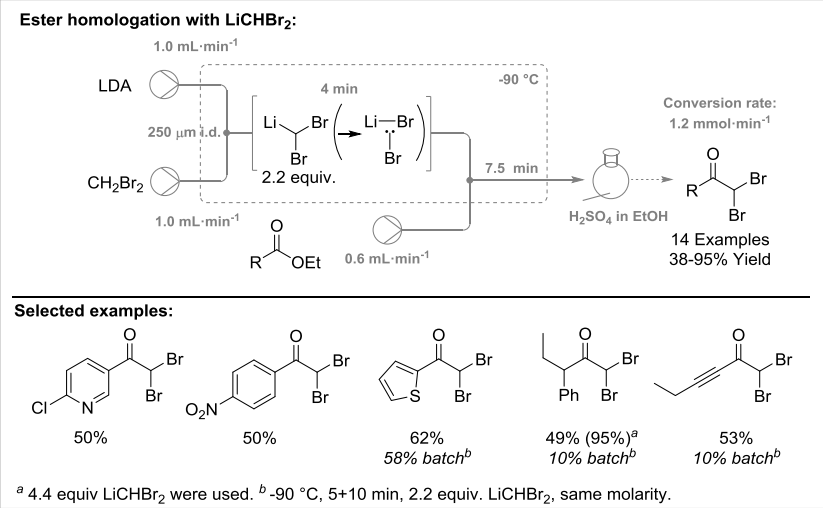


Scheme 10: Metalation of acrylates using TMPMgCl·LiCl and subsequent in-line electrophile quench. Dotted lines indicate the newly formed bonds.

Flow setups were further used to prevent deleterious side-reactions in lithium carbenoid chemistry by *Ley* and coworkers (Scheme 11).[103] Utilizing the improved cooling efficiency and mixing resulted in a

[103] J. Hartwig, J. B. Metternich, N. Nikbin, A. Kirschning, S. V. Ley, *Org. Biomol. Chem.*, **2014**, *12*, 3611.

clean lithiation of dibromomethane with LDA at −90 °C. Subsequent in-line reaction with various esters furnished the expected homologated products. The avoidance of LiBr elimination and carbene formation is achieved in this case by thermal control, although in an improved fashion compared to batch experiments. This advantage led to slightly improved yields with most substrates, compared to small-scale batch experiments under similar conditions. Such effects should be increasingly notable on larger scales.



Scheme 11: Ester dibromomethylation with LiCHBr2 in continuous flow at −90 °C and comparison with results obtained using a conventional flask.

A significant reaction improvement under flow conditions was observed if acidic protons in *α*-position to the ester were present. This observation was attributed to suppression of a net $LiCHBr_2$ retro-addition under flow conditions, which in the batch reactions appeared to be due to a reaction of the addition intermediate with excess $LiCHBr_2$.

3.1.4 Transmetalation

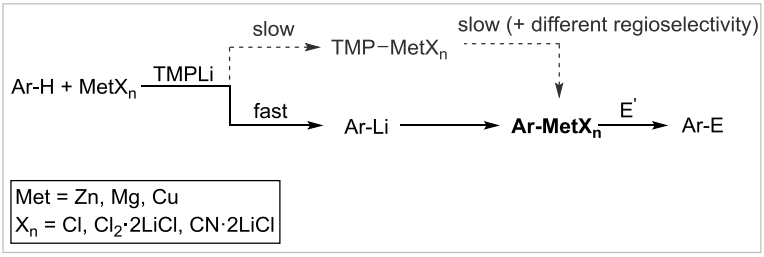
Transmetalation is a common method used for transforming unstable organometallics not only into more stable intermediates, but also into species with a new, desirable reactivity.[104] This approach can tentatively be traced back to *Gilman*'s first investigations of organocopper compounds in 1936.[105] Additionally, transmetalation is an elementary step in catalytic cycles in cross-coupling chemistry.[106]

[104] a) B. H. Lipshutz, in: *Synthetic Procedures Involving Organocopper Reagents in Organometallics in Synthesis* (Ed.: M. Schlosser), John Wiley & Sons, Ltd, Chichester, **1994**, pp. 283-382; b) M. T. Reetz, in: *Titanium in Organic Synthesis in Organometallics in* Synthesis (Ed.: M. Schlosser), John Wiley & Sons, Ltd, Chichester. **1994**, pp. 195-282; c) *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**; d) *The Chemistry of Organozinc Compounds* (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons Ltd, Chichester, **2007**; e) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470.

[105] C. Elschenbroich, *Organometallchemie 6. Auflage*, Teubner, Wiesbaden **2008**, 235.

[106] a) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley, Weinheim, **2004**.

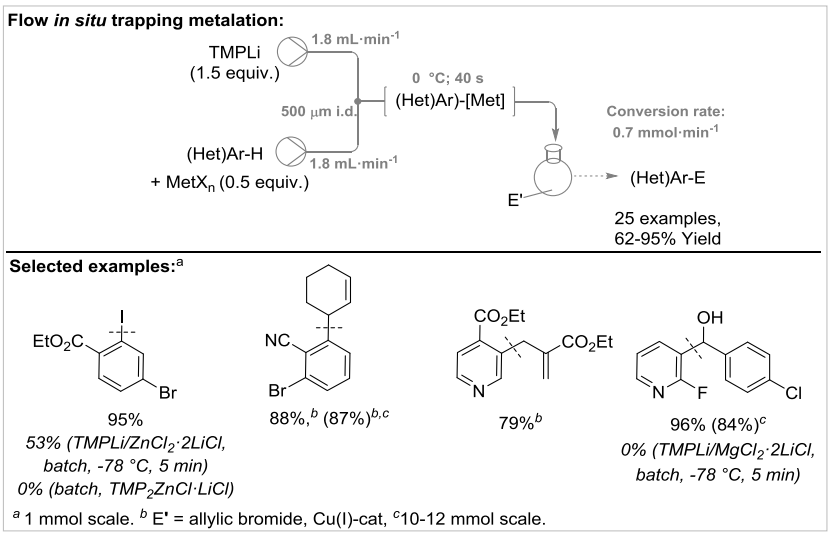
Typical transmetalations with metal halides are driven by the formation of the more ionic salt and the more covalent carbon metal bond.[107] As discussed above, transmetalation requires the preceding unstable organometallic to be at least stable until the addition of the transmetalation agent is finished. The problem of performing fast transmetalations of very unstable organometallic precursors was partially alleviated by the use of flow reactors, which allow for very short residence times before transmetalation occurs.[108] Another batch-compatible approach was proposed by *Knochel* and coworkers with an *in situ* trapping metalation (Scheme 12).[109]



Scheme 12: *In situ* trapping metalation of aromatic substrates leading to zincated and magnesiated aryls. TMPLi was proven to be the metalating agent under the reaction conditions.[109]

Thus, treating premixed solutions of aryls and LiCl complexed $MgCl_2$, $ZnCl_2$ or CuCN salts allowed for an immediate (*in situ*) transmetalation of the initially formed aryllithium compound. Based on mechanistic studies, the reaction of TMPLi with the aryl was estimated to proceed at least six times faster than the reaction with the metal salt under the reaction conditions.[109] This allowed to prepare arylmagnesium, -copper, and -zinc compounds at −78 °C on a 0.5 mmol scale and in some cases with a novel regioselectivity. Importantly, the method gave access to organometal species, which are not accessible with a consecutive transmetalation or with the classical zinc and magnesium TMP-bases ($TMPMetX_n$) in a batch reactor. However, the procedure required cryogenic temperatures and reactions on larger scales than 0.5 mmol represented significant challenges. However, transferring the reaction to a microflow setup, it was shown, that these shortcomings were efficiently avoided, likely due to the more uniform reactant concentration distribution within the reaction vessel.[110] Thus, the exchange could be performed at 0 °C within 40 s with a broader substrate scope and on larger scales (Scheme 13).[111]

[107] C. Elschenbroich, *Organometallchemie 6. Auflage,* Teubner, Wiesbaden **2008**, 32; *ibid.* 62; *ibid.* 605-607.
[108] a) A. Nagaki, Y. Moriwaki, J. Yoshida, *Chem. Commun*. **2012**, *48*, 11211; c) A. Nagaki, K. Hirose, O. Tonomura, T. Taga, S. Taniguchi, S. Hasebe, N. Ishizuka, J.-i. Yoshida, *Org. Process Res. Dev.* **2016**, *20*, 687.
[109] 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.
[110] This indicates that the already similar rates for the desired and undesired reaction pathway in the *in situ* metalation procedure are becoming more even at higher temperatures and/or that inhomogeneities of the reactant concentration and heat distribution might influence the reaction outcome at larger scales. Typically, mixing in small scale batch reactors is appreciably good, yet deteriorates with increasing scale, see 14d.
[111] M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501.



Scheme 13: *In situ* trapping metalation in continuous flow using TMPLi in the presence of $ZnCl_2 \cdot 2LiCl$ or $MgCl_2 \cdot 2LiCl$ using a flow setup. Dotted lines indicate the newly formed bonds.

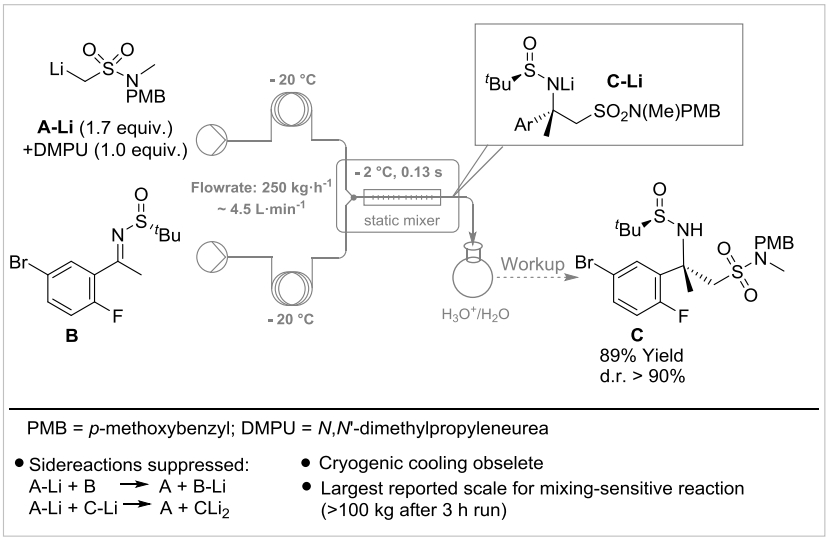
The flow *in situ* transmetalation method was subsequently extended to the use of lithium dicyclohexylamide (Cy_2NLi) as base, which is a significantly more economic reagent than TMPLi but also less sterically hindered and thus less selective. This potential drawback was compensated for under flow conditions, thus allowing an *in situ* trapping flow metalation of a broad range of functionalized arenes, heteroarenes and acrylate derivatives under economically more attractive conditions.[112]

3.1.5 Reactions of Organometallic Species in Continuous Flow Systems

Not only the generation of reactive organometallic species has benefited from the use of flow micro-reactors but also their subsequent reactions. These reactions are often exothermic and fast, which gives rise to side-product formation as well as mixing-dependent yields and selectivity.[113] A recent example was reported by process chemists involved in the synthesis of an intermediate *en route* to *verubecestat*, a promising drug candidate for the treatment of Alzheimer's disease (**C,** Scheme 14).[114] The yield of the key addition reaction of lithiated methyl sulfonamide **A-Li** to the chiral ketimine **B** electrophile was found to be strongly dependent on the quality of mixing. Studies showed that competing proton transfer reactions between **A-Li** and the electrophile **B** or the intermediate **C-Li** took place competitively in inhomogeneous (batch) reaction mixtures, thereby consuming the active reagent **A-Li** and diminishing the yield. Working under high-flowrate/fast mixing conditions with static mixing devices allowed the kinetically favored pathway to proceed without sidereactions and leading to **C**. The application of cryogenic temperatures was obsolete with 0.13 s residence time under

[112] M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649.
[113] a) H. O. House, D. D.Traficante, R. A. Evans, *J. Org. Chem.* **1963**, *28*, 349; b) H. O. House, D. D.Traficante, *J. Org. Chem.* **1963**, *28*, 356.
[114] D. A. Thaisrivongs, J. R. Naber, N. J. Rogus, G. Spencer, *Org. Process Res. Dev.* **2018**, *22*, 403.

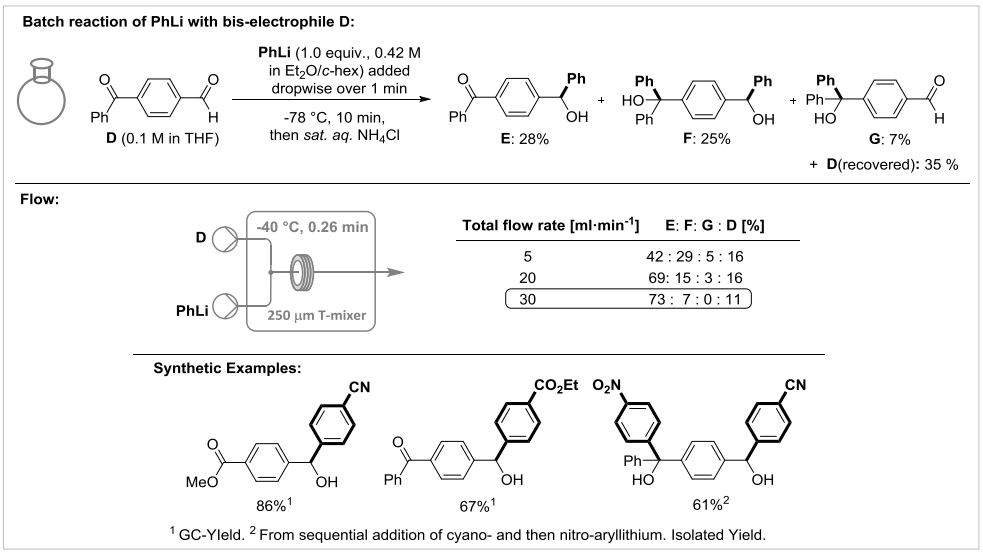
flow conditions, and cooling was only applied to guarantee stability of **A-Li** during the operation and to remove the reaction heat sufficiently. Notably, the reaction was performed on a pilot-plant scale with stable runs over several hours and delivering batches of > 100 kg product. The authors concluded, that their report likely describes the largest scale experiments involving a controlled mixing-sensitive reaction.



Scheme 14: Synthesis of intermediate **C** en route to *Verubecestat* in a flow setup on pilot-plant scale.

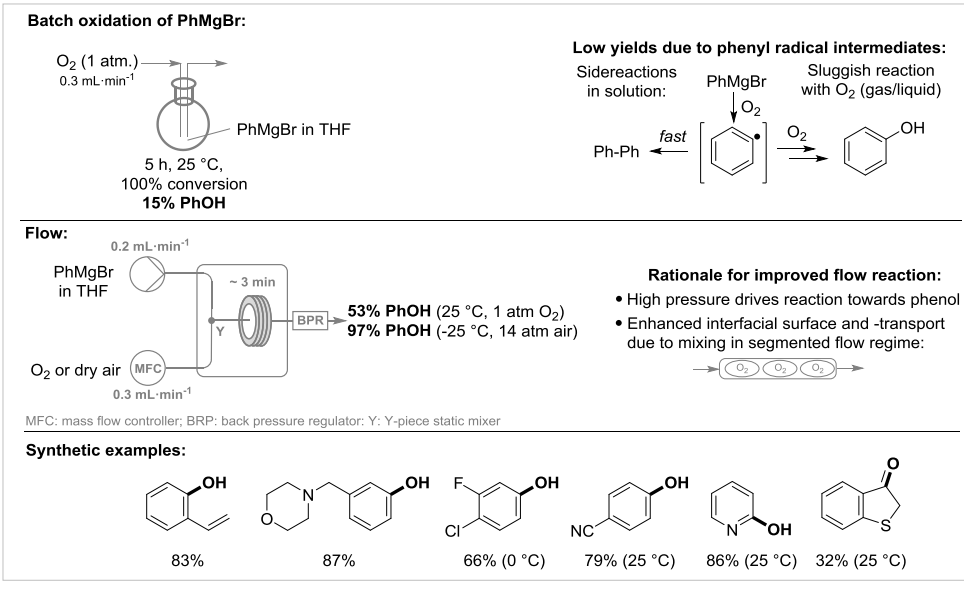
Furthermore, *Yoshida*'s group reported an interesting study regarding the chemoselective addition of aryl lithium reagents to carbonyl groups (Scheme 15).[115] Thus, aryl organolithium reagents were reacted with bis-electrophiles bearing two different carbonyl functions, such as an aldehyde and a ketone. Interestingly, the selectivity for addition of PhLi to an aldehyde over a ketone (in bis-electrophile **D**) was shown to be impractically low in a batch flask, furnishing equimolar amounts of the desired product **E** and double addition product **F** (25−28%) in batch, along with ketone addition product **G** (7%) and remaining starting material **D**. Conducting the reaction under flow conditions at various flowrates demonstrated that the product distribution is favorably shifted towards the desired product of exclusive addition to the aldehyde, **E**, (70%) as mixing was improved *via* higher flowrates. The principle was subsequently applied to chemoselectively obtain addition products in high yields with various bis-electrophiles as well with as flash-chemistry derived[83] functionalized organolithium nucleophiles. Finally, a sequential twofold addition of different nucleophiles was realized, providing the expected diol in 61% over three steps, which confirmed the high chemoselectivity under the optimized flow conditions.

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



Scheme 15: Chemoselective addition of aryllithium reagents (bold marking) to bis-electrophiles and its dependency on the mixing quality.

A last example from the *Jamison* group highlights the advantageous use of a flow micro-reactor setup for gas/liquid interphasic reactions.[116] The oxidation of alkyl *Grignard* reagents by molecular oxygen or dry air are well-known and provide a route to alcohols without using toxic reagents. However, this reaction gave only low yields in batch for the conversion of PhMgBr to phenol (17%), likely caused by inefficient interphasic mixing of the reactive species with oxygen and competitive reactions of the involved aryl radicals in the liquid phase (Scheme 16).



Scheme 16: Oxidation of aryl *Grignard* compounds with O_2 enabled by enhanced interfacial mass transfer in a flow reactor.

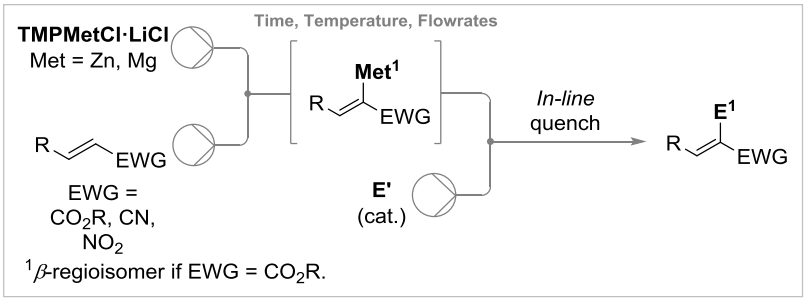
The interfacial surface and reactions between gaseous O_2 and the liquid THF phase was greatly enhanced,[33] leading to an improved 53% yield of phenol within 3 min under otherwise similar

[116] Z. He, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *53*, 3353.

conditions. Further pressurizing the system with dry air and applying −15 °C reaction temperature gave a quantitative yield of phenol. Subsequently, a broad range of aryl and heteroaryl *Grignard* reagents was converted to the corresponding phenols, including examples with challenging functionalization.

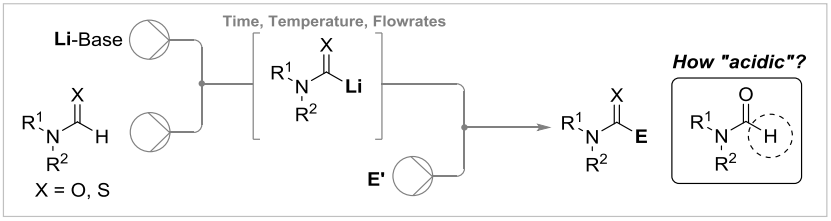
4 Objectives

Based on previous results in the batch metalation and flow magnesiation of acrylate derivatives, the scope of continuous flow acrylate metalations should be investigated to demonstrate possible extensions of this acrylate functionalization under convenient reaction conditions. Especially the use of TMPZnCl·LiCl for zincations in continuous flow systems was not yet investigated and it was envisioned that a process intensification could be achieved with scalable high temperature zincation reactions (Scheme 17).[117]



Scheme 17: Continuous flow magnesiation and zincation and subsequent in-line electrophile quench of substituted acrylonitriles, acrylates and nitroolefins.

Furthermore, the application of flow methods for the improved handling of highly unstable (thio)carbamoyllithium species should be investigated. The aim was to develop a convenient, near-ambient temperature process, which starts from easily available (thio)formamides. *In situ* trapping methods should be applied if necessary. An extension of the functional group tolerance of this chemistry was proposed as a desirable goal. Mechanistical insights regarding the structure and energetics of lithiated formamides should be gained to allow further extension of this chemistry (Scheme 18).[118]



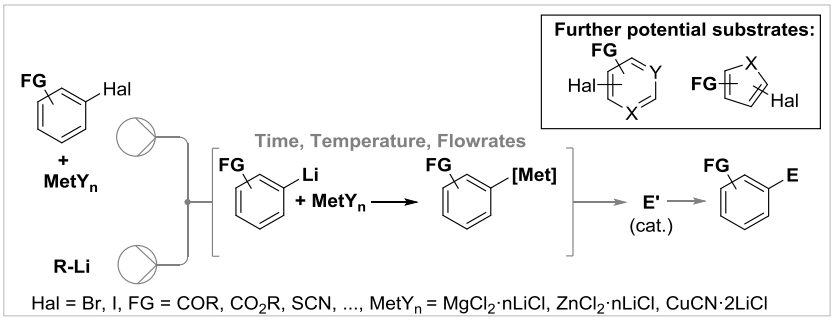
Scheme 18: Continuous flow preparation and reactions of carbamoyllithiums for nucleophilic amidation.

Moreover, a flow *in situ* trapping halogen-lithium exchange was planned in analogy to prior batch and flow *in situ* trapping metalations. The fact that halogen-lithium exchanges are extremely fast reactions should facilitate an exchange even in presence of a metal salt additive and thereby enable an *in situ*

[117] This project was developed in cooperation with Dr. Matthias R. Becker and Dr. Marthe Ketels. The project was commenced by Maximilian A. Ganiek during the work on Master's thesis and finalized during the PhD studies, see: M. A. Ganiek, *Metalation and Reactions of Functionalized Acrylate Derivatives using TMP-Bases in a Continuous Flow System*, Master Thesis, **2015**, LMU München.

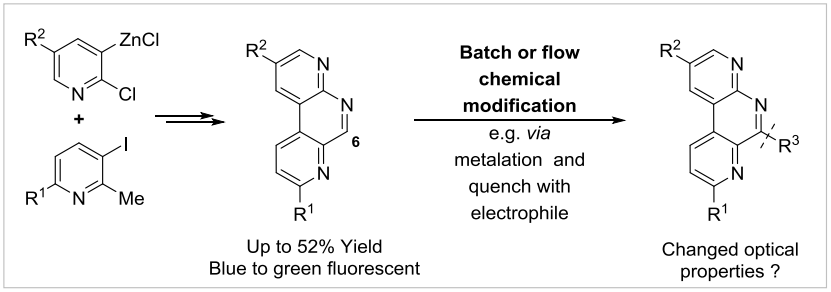
[118] This project was developed in cooperation with Dr. Matthias R. Becker in synthetic aspects and with Dr. Guillaume Berionni and Prof. Dr. Hendrik Zipse in theoretical aspects.

transmetalation of the newly generated aryllithium compound, thus minimizing the possibility for decomposition. This would effectively combine the generality of the halogen-lithium exchange reaction with the functional group tolerance of, for example, zinc organometallic reagents. The use of flow conditions was estimated to play a critical role to achieve mild conditions. The aim was therefore to develop a suitable continuous flow reaction protocol and to demonstrate that aromatic organometallics bearing highly sensitive groups can be accessed and reacted under mild conditions. Furthermore, the scope of the reaction should be extended to other unsaturated substrates such as halopyridines (Scheme 19).[119]



Scheme 19: *In situ* trapping halogen-metal exchange of (hetero)arenes in the presence of metal salt additives.

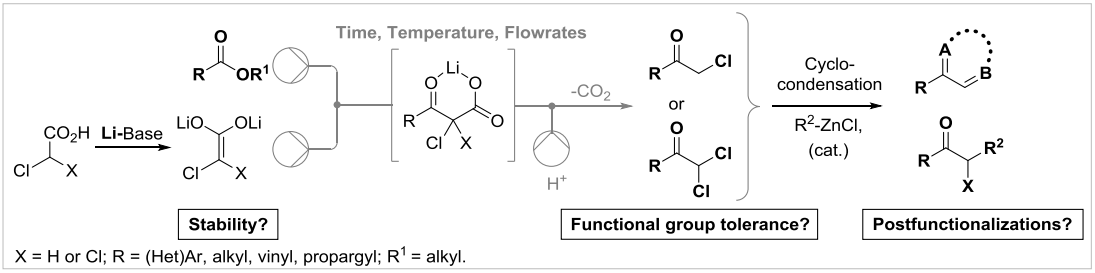
Another project entailed the functionalization of a novel triazaphenantrene scaffold, which was sythesized from two pyridine units and showed potentially interesting optical properties. The developed synthesis route allowed for modification of two positions in the ring by the judicious choice of starting materials, however the C6-position was unlikely to be easily functionalized in an analogous fashion. The vicinity of two coordinating nitrogen atoms to the C6 position indicated instead the use of organometallic reagents to achieve a functionalization of the azaphenantrene scaffold. The functionalization could apply batch or flow methods, and should allow installing various organic residues (R^3, Scheme 20).[120]



Scheme 20: Functionalization of a novel triazaphenantrene by means of chemical modification of the C6-position. Dotted lines indicate the newly formed bond.

[119] This project was developed in cooperation with Dr. M. Ketels and Niels Weidmann, see: M. Ketels, Dissertation, LMU München, **2018** and N. Weidmann, Dissertation, LMU München.
[120] This project was developed in cooperation with Dr. Sarah Fernandez and Mariia Karpacheva in synthetic aspects, optical measurements were performed and interpreted by Fabian C. Hanusch, Stephan Reuter, Prof. Dr. Thomas Bein and Dr. Florian Auras.

The last project comprises the development of a convenient ester chloro-homologation method[121] from economically attractive and easily available chloroactetic acid dianions (Scheme 21).[122]



Scheme 21: Ester chloromethylation and bis-chloromethylation with chloroacetic acid lithium enolates. Right side: potential postfunctionalizations of the mono- and bis-chloro ketone products leading to heterocycles and substitution products.

Resorting to enolate-derived nucleophiles instead of the typically employed lithium carbonoids would avoid halomethane precursors, which have an increasingly restricted accessibility due to environmental legislation. Moreover, practical and mild conditions and an increased functional group tolerance could be possibly obtained by using enolate type reagents. Potential advantages over the halogenation of ketones, which is an alternative entry to chloroketones, should additionally be demonstrated by accessing products, which are difficult to obtain under halogenation conditions. The instable lithium dianions suggest a flow procedure to ensure convenient reaction conditions, since scattered previous reports of batch use of chloroacetic acid dianion often suggest excess reagent use and cryogenic conditions in all cases. An extension of the method for the synthesis of dichloroketones was not yet described in the literature; however a realization would give access to another useful class of chloroketones. Postfunctionalization of the obtained chloroketones should underline the utlity of the obtained bis-electrophilic chloroketone compounds. For this purpose, development and demonstration of cyclocondensation reactions leading to functionalized heterocycles and cross-couplings with zinc organometallics were proposed.

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[121] The term homologation is referring to a conversion of one member of a homologous series into the other by changing the number of a repetitive unit, which can be a methylene bridge -(CH_2)- group, see: T. E. Brown, H. E. LeMay, B. E. Bursten, C. Murphy, P. Woodward, M. E. Stoltzfus, *Chemistry: The Central Science, 13 ed*, Pearson Education, London, .**2014**. The term homologation is also used less strictly throughout acknowledged resources (compare the different definition bandwith: F. A. Carey, R. J. Sundberg, *Advanced OrganicChemistry Fifth Edition Part B: Reactions and Synthesis*, Springer, New York, **2007**, 784–786; R. Brückner, *Advanced Organic Chemistry*, Elsevier, Amsterdam, **2002**, 453–457) Typically also reactions are included in the definition of homologation reactions, which enable a reaction *sequence* leading to *overall homologation* through introduction of a carbon unit and a simple functional group interconversion. Example: The Seyferth-Gilbert reaction converts an aldehyde (R-CHO) into an alkyne (R-C≡CH), which is not a homologation by strict definition. However, if a consecutive hydrolysis is performed, the product of an overall homologation is obtained (R-CH_2CHO). Likewise the herein presented "chloro-homologation" can be conceived as being part of a *homologation sequence*, R-C(O)Cl→R-C(O)OMe→R-C(O)CH_2Cl, and it was shown that even the direct R-C(O)Cl→R-C(O)CH_2Cl conversion is viable. In the case of the reaction R-C(O)OMe→R-C(O)$CHCl_2$ however, "*ester→dichloroketone elongation*" or "*dichloromethylation*" is a more suitable description in accordance with the above cited textbook by R. Brückner.

[122] This project was developed in cooperation with Dr. Maria V. Ivanova and is based on preliminary attempted chloro-homologations by S. Sevinc and Dr. Martin Benjamin (Novartis Pharma AG).

B. RESULTS AND DISCUSSION

1 Continuous Flow Magnesiation or Zincation of Acrylonitriles, Acrylates and Nitroolefins

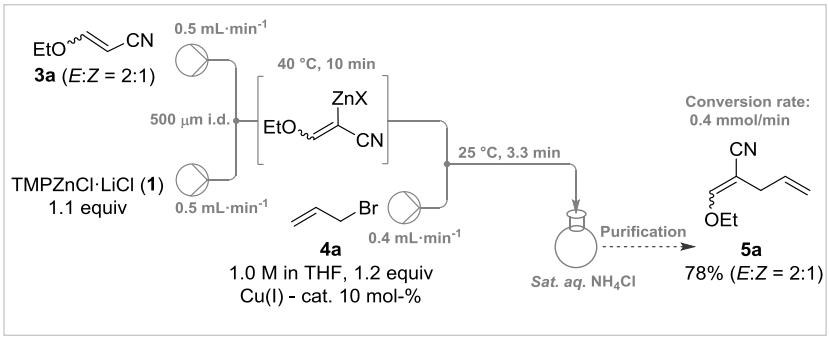
1.1 Introduction[123]

The directed metalation of *α,ß*-unsaturated carbonyl derivatives is an important reaction since, after quenching with various electrophiles, highly functionalized unsaturated products are obtained.[124] These compounds are useful building blocks for the synthesis of natural products and heterocycles,[125] many of which are biologically relevant, such as *tetronic acids*.[126] The lithiation of acrylate derivatives and nitroolefins is often difficult to control due to their sensitivity to nucleophilic reagents leading to polymerization and side reactions.[127] Hence, such lithiations are usually carried out at cryogenic reaction temperatures (−78 °C or −110 °C).[124,125a,128] The use of kinetically highly active bases such as TMPZnCl·LiCl[96] (**1**), $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$,[98d] or zincate bases[97] improves the stability of the organometallic intermediates but still requires low metalation temperatures.[124b] Previously, it was shown that continuous flow technology also considerably improves metalation reactions.[129] Hence, the use of TMPZnCl·LiCl (**1**) and TMPMgCl·LiCl[95] (**2**) for the flow metalation and functionalization of acrylates, acrylonitriles and nitroolefins was investigated as well as in-line quenches with various electrophiles leading to polyfunctional unsaturated products.

[123] The compounds **5h**, **7a**−**b**, **e** and **8k** were synthesized by Dr. M. Ketels under guidance of M. A. Ganiek and will be shown for the sake of completeness. Analytical data is found in the corresponding publication.
[124] a) R. R. Schmidt, R. Betz, *Synthesis* **1982**, 748; b) T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914; For alternative preparations of alkenyl organometals, see also: c) S. Sengupta, V. Snieckus, *J. Org. Chem.* **1990**, *55*, 5680; d) M. A. Reed, M. T. Chang, V. Snieckus, *Org. Lett.* **2004**, *6*, 2297.
[125] a) R. R. Schmidt in *Natural Product Chemistry* (Ed: A. Rahman), Springer, Berlin, **1986**; b) D. Smirnow, P. B. Hopkins, *Synth. Commun.* **1986**, *16*, 1187; c) *Name Reactions in Heterocyclic Chemistry* (Eds.: J. J. Li, E. J. Corey), Wiley, Hoboken, **2005**; c) D. R. Rogue, J. L. Neill, J. W. Antoon, E. P. Stevens, *Synthesis* **2005**, 2497; d) T. Kao, T. S. Syu, Y. Jhang, W. Lin, *Org. Lett*. **2010**, *12*, 3066; e) J. Bonnamour, C. Bolm, *Org. Lett.* **2011**, *13*, 2012; f) B. H. Patel, A. M. Mason, A. G. M. Barrett, *Org. Lett.* **2011**, *13*, 5156; f) S. Seo, M. C. Willis, *Org. Lett.* **2017**, *19*, 455.
[126] a) A. L. Zografos, D. Georgiadis, *Synthesis* **2006**, *19*, 3157; b) L. Vieweg, S. Reichau, R. Schobert, P. F. Leadlay, R. D. Süssmuth, *Nat. Prod. Rep*. **2014**, *31*, 1554.
[127] a) J. Buddrus, *Grundlagen der Organischen Chemie, 4. Auflage*, de Gruyter, Berlin, **2011**, 445; *ibid.* 891; b) R. Quirk, in: *Handbook of Polymer Synthesis, Characterization, and Processing*, (Eds.: E. Saldívar-Guerra, E. Vivaldo-Lima), John Wiley & Sons Ltd, Chichester, **2013**, 127; c) A. Nagaki, Y. Takahashi, K. Akahori, J.-i. Yoshida, *Macromol. React. Eng.* **2012**, *6*, 467.
[128] a) R. R. Schmidt, J. Talbiersky, P. Russegger, *Tetrahedron Lett.* **1979**, *44*, 4273; b) B. A. Feit, U. Melamed, R. R. Schmidt, H. Speer, *Tetrahedron* **1981**, *37*, 2143; c) D. C. Harrowven, H. S. Peon, *Tetrahedron Lett*. **1994**, *35*, 9101; d) D. C. Harrowven, H. S. Peon, *Tetrahedron Lett*. **1996**, *52*, 1389.
[129] a) T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933; b) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; c) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501.

1.2 Zincation of Acrylonitriles and Nitroolefins and Subsequent In-line Reactions

Initial studies focused on the flow metalation of acrylonitriles and nitroolefins (**3**), which are sensitive to basic conditions.[127] It was found that 3-ethoxyacrylonitrile (**3a**, *E*:*Z* = 2:1) was smoothly zincated at the *α*-position with TMPZnCl·LiCl (**1**) at 40 °C within 10 min in a flow apparatus (Scheme 22). After an in-line quench with allyl bromide (**4a**) in the presence of a copper catalyst (10 mol-% CuCN·2LiCl)[130] the expected product **5a** (*E*:*Z* = 2:1) is obtained in 78% isolated yield. In contrast, a reported batch synthesis of **5a** using lithium diisopropylamide for the metalation requires maintaining −110 °C temperature for the lithiation and −110 °C to −50 °C for the subsequent allylation over several hours for each step.[131]



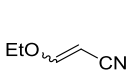
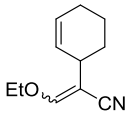
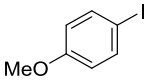
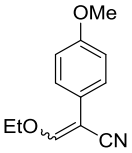
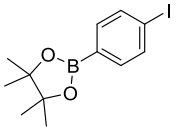
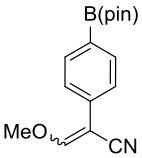
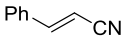
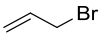
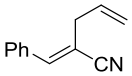
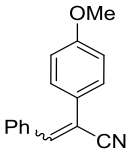
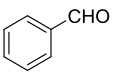
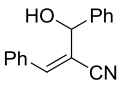
Scheme 22: Zincation and allylation of 3-ethoxyacrylonitrile (**3a**) in continuous flow.

This zincation procedure has a broad scope (Table 1). Thus allylation of zincated **3a** with 3-bromo-1-cyclohexene (**4b**) or Pd-catalyzed *Negishi* cross-coupling[132,133,134] with 4-iodoanisole (**4c**) gave the expected products **5b** and **5c** in 92−96% yield (entries 1−2).[135] An analog procedure using acrylonitrile **3b (***E*:*Z* = 1:1**)** as starting material led to cross-coupling product **5d** bearing a boronic ester in 70% yield (entry 3). Furthermore, *trans*-cinnamonitrile (**3c**) reacted smoothly with TMPZnCl·LiCl (**1**) at 90 °C within 10 min, and after allylation **5d** is obtained in 75% yield (entry 4). A mechanical back pressure regulator (BPR) was used to retain the reaction solution in the liquid phase. This procedure poses in principle no limit to scalability, which constitutes an advantage over

[130] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[131] D. Smirnow, P. B. Hopkins, *Synth. Commun.* **1986**, *16*, 1187.
[132] a) E.-i. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[133] In-line *Negishi* cross-coupling have since attracted considerable interest: a) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463; b) G. A. Price, A. Hassan, N. Chandrasoma, A. R. Bogdan, S. W. Djuric, M. G. Organ, *Angew. Chem. Int. Ed.* **2017**, *56*, 13347; c) I. Abdiaj, A. Fontana, M. V. Gomez, A. de la Hoz, J. Alcázar, *Angew.Chem. Int. Ed.* **2018**, *57*, 8473.
[134] For P(2-furyl)$_3$ (TFP), see: V. Farina, B. Krisnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585.
[135] Elevated temperatures are likely not causing isomerisation of the alkenyl zinc reagents (compare Table 1; entries 1-4), The presence of Pd-catalyst might facilitate the observed isomerization. For a possible mechanistic explanation, see: B. X. Li, D. N. Le, K. A. Mack, A. McClory, N.-K. Lim, T. Cravillion, S. Savage, C. Han, D. B. Collum, H. Zhang, F. Gosselin, *J. Am. Chem. Soc.* **2017**, *139*, 10777.

pressurized sealed tube batch reactors.[136] Thus, repeating this allylation reaction on a 10 mmol scale did not require any reaction condition changes[137] and furnished **5e** in an improved yield of 83% after 35 min reaction time and purification.

Table 1: Flow zincation of acrylonitriles and nitroolefins (3) with TMPZnCl·LiCl (1) and in-line quenching with electrophiles (4) leading to α-functionalized products (5).

Entry	Substrate (metalation conditions)	Electrophile	Product/Yield[a]
1	 **3a** (40 °C; 10 min)	 **4b**	 **5b**: 92%, *E*:*Z* = 2:1[b,g]
2	**3a**	 **4c**	 **5c**: 96%, *E*:*Z* = 6:1[c,g]
3	 **3b** *E*:*Z* = 1:1; (40 °C; 10 min)	 **4d**	 **5d**: 70%, *E*:*Z* = 2.5:1[c,g]
4	 **3c** (90 °C; 10 min)	 **4a**	 **5e**: 75%,[b] 83%[b,f]
5	**3c**	**4c**	 **5f**: 99%, *E*:*Z* = 8:1[c,g]
6	**3c**	 **4e**	 **5g**: 63%[d]

[136] For similar setups using this possibility in order to heat reactions above the boiling point of the solvent compare: a) T. Razzaq, T. N. Glasnov, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, 132; b) T. Noël, T. J. Maimone, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 8900; c) M. R. Becker, P. Knochel, *Org. Lett.*, **2016**, *18*, 1462; For a pressurized flow reactor without mechanical constrictions to the flow path: b) J. M. Sauks, D. Mallik, Y. Lawryshyn, T. Bender, M. Organ, *Org. Process Res. Dev.* **2014**, *18*, 1310.

[137] For further examples of 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) A. Hafner, P. Filipponi, L. Piccioni, M. Meisenbach, B. Schenkel, F. Venturoni, J. Sedelmeier; *Org. Process Res. Dev.* **2016**, *20*, 1833.

Table 1 continued.

7	**3d** (0 °C; 5 min)	**4f**	**5h**: 64%[e]
8	**3d**	**4a**	**5i**: 73%[b]
9	**3e** (25 °C; 3.3 min)	**4a**	**5j**: 78%[b]

[a] Yield of isolated product after column chromatographical purification on a 1.0 or 2.0 mmol scale. pin = 2,3-dimethylbutane-2,3-diol. [b] Obtained by a Cu-catalyzed allylation.[130] [c] Obtained using 2 mol-% $Pd(dba)_2$ and 4 mol-% TFP.[132,134] [d] Obtained by adding 10 mol- % TMSCl to PhCHO. [e] Obtained by a Cu-catalyzed acylation.[130] [f] Yield on a 10 mmol scale. [g] Yield based on the amount of electrophile used.

Negishi cross-coupling[132] of *α*-zincated **3c** with 4-iodoanisole (**4c**) proceeded in flow within 25 min at 60 °C leading to the cinnamonitrile **5f** (99%, *E*:*Z* = 8:1, entry 5). Furthermore, quenching of zincated **3c** with benzaldehyde (**4e**, 10 min, 70 °C) produced the allylic alcohol **5g** in 63% as the single *E*-stereoisomer (entry 6). Usually, Csp^2-Zn halogenide species are unreactive towards carbonyls,[138] however the high temperatures allowed the reaction to proceed in this case to furnish **5g** in the presence of a catalytic amount of TMSCl. Additionally, the zincation of nitroolefins **3d-e** proceeded at 0 – 25 °C within 3-5 min under continuous flow conditions and led to new *α*-functionalized nitroolefins (**5g** – **i**) after in-line allylation or acylation (entries 7 – 9).

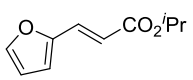
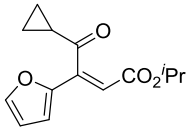
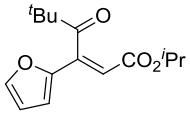
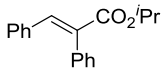
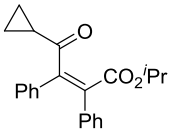
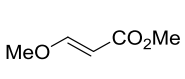
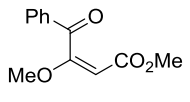
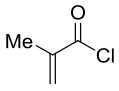
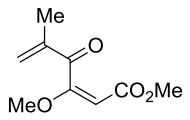
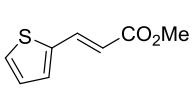
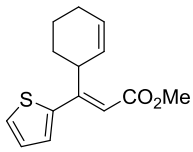
1.3 Magnesiation of Acrylic Esters and Subsequent In-line Reactions

Acrylic esters required stronger bases like TMPMgCl·LiCl (**2**) in order to undergo efficient metalation.[124b] To broaden the scope of the flow metalation/quenching sequence, acylations of magnesiated acrylates with acid chlorides were performed (Table 2, entries 1 – 5). Hence, after optimization of the flow reaction conditions (temperature, flowrate, residence time and catalyst loading) the preparation of highly electrophilic Michael-acceptors[139] such as **7a** – **e** could be performed without substantial losses in yield due to side-reactions. While the metalation of *ß*-heteroatom substituted acrylates such as **6c** is well investigated,[124] *ß*-aryl or -heteroaryl acrylates have thus far not been reported to undergo metalation. Under appropriate conditions, *ß*-magnesiation of aryl and

[138] P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel, in: *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**, 251.
[139] For the effect of various and even multiple electron-withdrawing groups on the electrophilicity of Michael acceptors, compare: D. S. Allgäuer, H. Jangra, H. Asahara, Z. Li, Q. Chen, H. Zipse, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2017**, *139*, 13318.

heteroaryl acrylates (**6a**–**b,** and **6d**) occurred readily. For instance, ß-(2-furyl) acrylate (**6a**) was smoothly magnesiated at 10 °C within 5 min despite the presence of acidic protons on the furan ring, furnishing the expected enones after acylation in 68–69% yield (entries 1–2). Furthermore, the quantitative benzoylation of **6c** allowed the synthesis of 1 mmol of enone **7d** per minute at the chosen flowrate (entry 4). Thus, running the reaction for 15 min gave 15 mmol **7d** in 99% yield after isolation, confirming the good scalability[137] of this method.

Table 2: Flow ß-magnesiation of acrylate substrates (**6**) with TMPMgCl·LiCl (**2**) followed by in-line allylation and acylation leading to functionalized products (**7**).

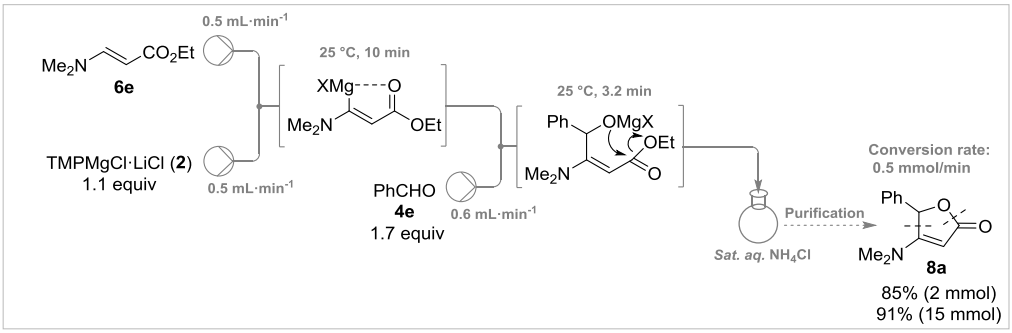
Entry	Substrate (metalation conditions)	Electrophile	Product/Yield[a,b]
			
1	**6a** (10 °C; 5 min)	**4f**	**7a**: 69%
			
2	**6a**	**4g**	**7b**: 68%
			
3	**6b** (50 °C; 5 min)	**4f**	**7c**: 61%
			
4	**6c** (40 °C; 2.5 min)	**4h**	**7d**: 99%; 99%[c]
			
5	**6c**	**4i**	**7e**: 63%[c]
			
6	**6d** (−25 °C; 1 min)	**4b**	**7f**: 72%

[a] Yield of isolated product after column chromatographical purification on a 1.0 or 2.0 mmol scale.[b] Obtained by a CuCN·2LiCl catalyzed or mediated reaction, see ref. 130. The catalyst was present in the electrophile solution.[c] Reaction performed on a 15 mmol scale.

Interestingly, the acylation of magnesiated **6c** with methacryloyl chloride (**4i**) allowed the synthesis of the methyl ester of *penicillic acid*[140] (**7e**) in 63% yield on a 15 mmol scale (entry 5). In this case, applying fast flowrates (5 mL·min^{-1}) during the acylation was necessary to avoid side reactions to an acceptable extent. In contrast to **6a**, thiophene acrylate derivative **6d** required low temperatures (−25 °C) to suppress metalation of the heteroaromatic moiety. The resulting low conversion of **6d** at −25 °C could not be increased with longer residence times (5 min or 15 min). However, increased flowrates (5 mL·min^{-1} during the metalation step) triggered high conversion of **6d** and the desired allylated product **7f** was obtained in 72% yield in presence of 5 mol-% CuCN·2LiCl.

1.4 Magnesiation of Acrylic Esters for the Synthesis of Furan-2-(5*H*)-ones

Many butenolides are biologically active[126] and their synthesis by the addition of *ß*-metalated acrylates to aldehydes is well-known.[124b,125a,128] Whereas *ß*-lithiated acrylates often give low yields upon addition to an aldehyde,[128b,c] their *ß*-magnesiated analogs react smoothly to the desired products.[124b] For example, *E*-ethyl 2-dimethylamino acrylate (**6e**) was quantitatively magnesiated with TMPMgCl·LiCl (**2**) at room temperature within 10 min in continuous flow (Scheme 23). In-line quenching with benzaldehyde (**4e**) led to furan-2(*5H*)-one **8a** (85−91%) after spontaneous lactonization.



Scheme 23: Flow synthesis of furan-2(5*H*)-one **8a** from acrylate **6e** *via* spontaneous lactonization of the intermediate magnesium alkoxide.

This butenolide synthesis has a broad scope and various furan-2(*5H*)-ones (**8**) were prepared in an analogous manner in 61−98% yield (Table 3). Electron-poor and -rich aromatic aldehydes (**4j**−**k**, entries 1−2; **4m**−**n**, entries 4−5), as well as *α,ß*-unsaturated (**4p**, entry 8), benzylic (**4q**, entry 9) or aliphatic aldehydes (**4l**, **r**−**s** entries 3, 10, 12) were used as electrophiles furnishing the expected product in all cases. Scaling up of the reactions leading to **8h** and **8l** to 10 mmol (entries 7 and 11) furnished the desired products in unchanged yield after reaction times of 4 min and 40 min, respectively.

[140] I. E. Yates, J. K. Porter, *Appl. Environ. Microb.* **1982**, *44*, 1072.

Table 3: Synthesis of furan-2(5*H*)-ones (**8**) by magnesiation of acrylates (**6**) and quenching with aldehydes.

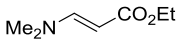
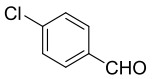
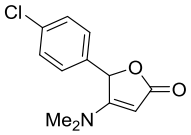
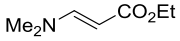
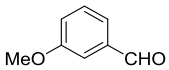
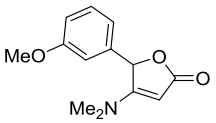
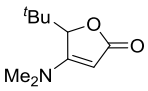
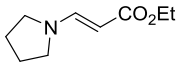
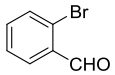
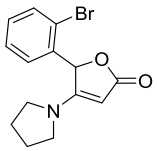
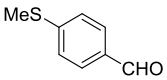
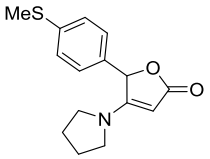
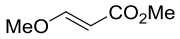
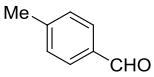
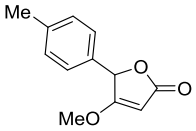
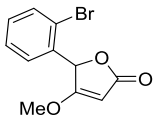
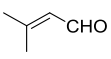
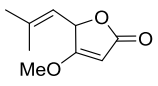
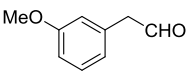
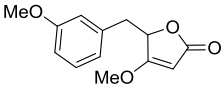
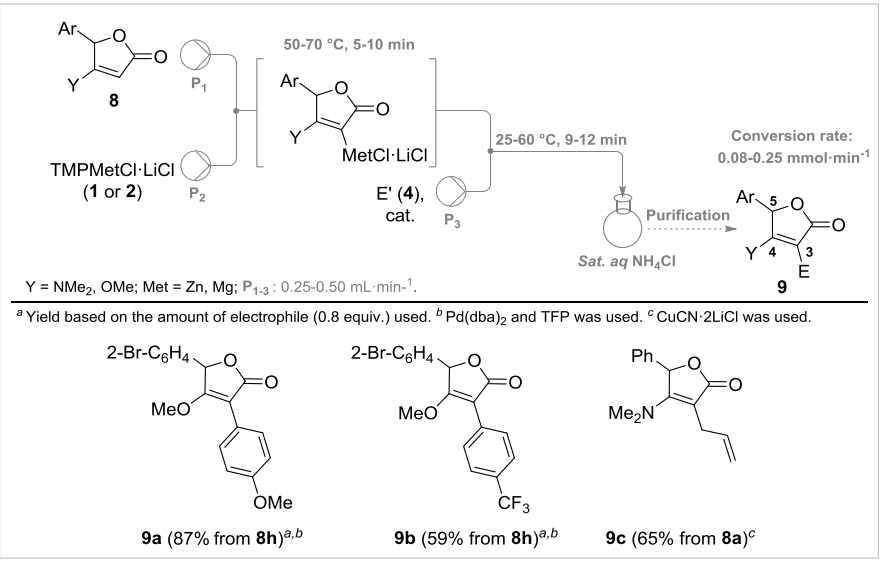
Entry	Substrate (metalation conditions)	Electrophile	Product/Yield[a,b]
1	 **6e** (25 °C; 10 min)	 **4j**	 **8b**: 64%
2	 **6e**	 **4k**	 **8c**: 79%
3	**6e**	 **4l**	 **8d**: 81%
4	 **6f** (25 °C; 10 min)	 **4m**	 **8e**: 70%
5		 **4n**	 **8f**: 67%
6	 **6c** (40 °C; 2.5 min)	 **4o**	 **8g**: 67%
7	**6c**	**4m**	 **8h**: 61%, 67%[b]
8	**6c**	 **4p**	 **8i**: 63%
9	**6c**	 **4q**	 **8j**: 65%

Table 3 continued.

10	**6a** (10 °C; 5 min)	**4r**	**8k**: 83%[c]
11	**6e** (50 °C; 5 min)	**4e**	**8l**: 73%, 73%[b]
12	**6e**	**4s**	**8m**: 98%

[a] Yield of isolated product after column chromatographical purification on a 1.0 or 2.0 mmol scale. Quenching with the electrophile (0.8–2.1 equiv.) was performed at 25 °C for 1.3–13 min. [b] Isolated yield on a 10 mmol scale. [c] Yield based on the amount of electrophile (0.8 equiv.) used.

Since furan-2(5*H*)-ones with substituents in the 3-position are occurring in bioactive molecules,[126] representative flow metalations of **8a** and **8h** in the 3-position were demonstrated (Scheme 24).



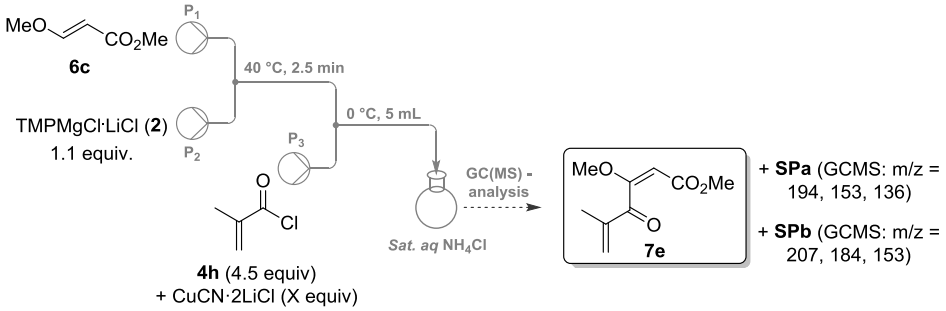
Scheme 24: Synthesis of 3,4,5-substituted butenolides **9** by continuous flow metalation and in-line quench with organic halide electrophiles (**4**) in the presence of Cu(I)- or Pd(0)-catalysts.

Thus, the high temperature zincation (70 °C, 5 min) of butenolide **8h** and in-line cross-coupling[132-134] with the corresponding aryl iodides led to bisarylic tetronates **9a** and **9b** in 59–87% yield. Furthermore, magnesiation (50 °C, 10 min) of **8a** led to the corresponding 3,4,5-substituted butenolide (**9c**) after Cu(I)-catalyzed allylation[130] in 65% yield. This method offers thus a modular access to fully substituted butenolides.

1.5 Optimization Studies for Two Selected Examples

As mentioned in chapter 1.3, increased flowrates were found to improve the reactions leading to **7e** and **7f**. Initial attempts to acylate magnesiated **6c** with an excess of the sensitive electrophile methacryloyl chloride **4i**[139] under typical conditions led to only 29% yield of the desired product **7e**, while two sideproducts (**SPa**–**b**) accounted for the majority of losses (Table 4, entry 1). Increasing the overall flowrate from 3 mL·min^{-1} to 5 mL·min^{-1} shifts the selectivity notably in favor of **7e** and promotes product formation, thus revealing a strong mixing sensitivity in the acylation step (entry 2). Further improvement was achieved by optimization of the amount of copper catalyst[141] furnishing **7e** in appreciable 63% yield (entry 3). In this case, sidereactions were successfully reduced by improving the mixing (by means of higher flowrates).[35] This can be tentatively attributed to a competition of several reactions, which are only in slight favor of product formation. Imperfect mixing may in this case "disguise" the true kinetics in favor of product formation due to the presence of concentration gradients across the reactant solution.[142] The application of flow chemistry with its superior mixing capabilities provides an efficient solution to synthetic problems of this kind, which is only recently reported as a strong argument for the use of flow chemistry.[143]

Table 4: Optimization of the synthesis of compound **7e**.



Entry	Total flowrate (P_{1+2+3}) [mL·min^{-1}]	X (equiv. Cu-cat.)	Absolute yield **7e** [%][a]	Rel. amount **7e** [%][b]	Rel. amount [%][b] **SPa**	Rel. amount [%][b] **SPb**
1	3.0	0.5	29	40	45	15
2	5.0	0.5	49	53	40	7
3	**5.0**	0.8	**63% (isol.)**	**62**	**28**	**10**

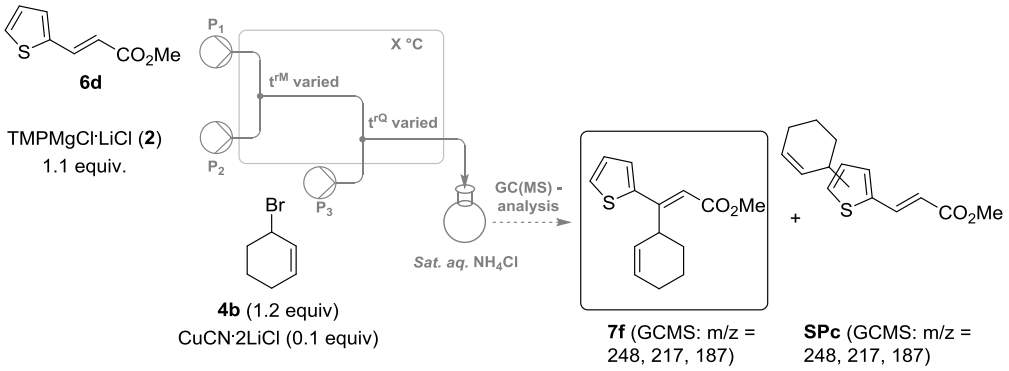
[a] Yield calculated based on calibrated GC using undecane as an internal standard and entry 3 as a reference for isolated yield. [b] Intensities of the product peaks of **7e**, **SPa** and **SPb** relative to the undecane standard peak, normalized to 100%.

Another interesting example provided the metalation of thiophene derivative **6d**. By choosing conditions, which are similar to known batch reactions[124b] (Table 5, entry 1: 5 min, −40 °C,

[141] 0.8 equiv. CuCN·2LiCl gave the best result in terms of yield and selectivity; a further increase in copper mediator led to decreased yield (not shown).
[142] a) P. Rys, *Acc. Chem. Res.* **1975**, *9*, 345; b) P. Rys, *Angew. Chem. Int. Ed.* **1977**, *16*, 807.
[143] a) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; b) D. A. Thaisrivongs, J. R. Naber, N. J. Rogus, G. Spencer, *Org. Process Res. Dev.* **2018**, *22*, 403.

0.6 mL·min^{-1}) only low conversion was observed. Thus only small amounts of the desired product **7f** were obtained together with side-product **SPc** resulting from metalation and allylation of the thiophene ring. Upon extending the residence time for metalation and allylation, inferior results in terms of selectivity were observed and conversion was not improved (entry 2). On the other hand, increased temperatures and flowrates (0 °C, 7.5 mL·min^{-1}) strongly promoted conversion of the substrate **6d**,[144] but the high temperature gave increasingly rise to thiophene metalation product **SPc** (entry 3). Pleasingly, the 7.5 mL·min^{-1} flowrate could ensure a good conversion even at lower temperatures, which allowed to effectively suppress byproduct formation (entries 4–5), furnishing the desired product **7f** in 72% isolated yield at −25 °C reaction temperature.

Table 5: Optimization of the synthesis of compund **7f**.



Entry	Total flowrate (P_{1+2+3}) [mL·min^{-1}]	t^{rM} [min]	t^{rQ} [min]	Temp. X [°C]	Recovered starting material **6d** (relative)[a]	Selectivity [a] **SPc/7f**
1	0.6	5.0	8.3	−40	7.02	0.06
2	0.3	10.0	16.7	−30	8.07	0.14
3	7.5	1.0	1.3	0	0.00	0.43
4	7.5	1.0	1.3	−20	1.23	0.19
5	**7.5**	**1.0**	**1.3**	**−25**	1.00	**0.12**[b]

[a] SPc was identified by GCMS and ^{1}H-NMR: vinylic H signals were still present in the reaction crude of an analogous reaction with allyl bromide. Selectivity was determined by GC analysis using undecane as an internal standard. [b] 72% isolated yield of **7f**.

[144] For another example, in which higher flowrates enhance conversion despite shorter residence times, see: D. Webb, T. F. Jamison, *Org. Lett.* **2012**, *14*, 568.

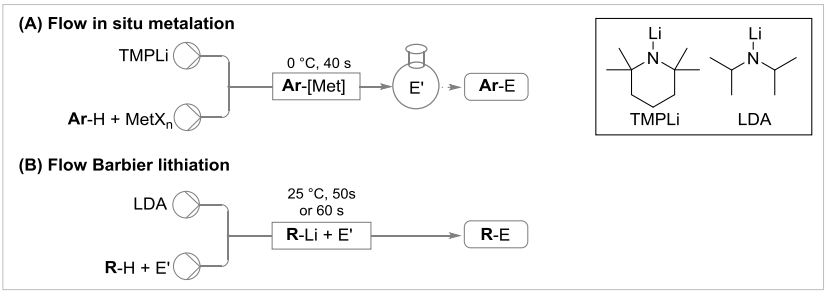
2 Barbier Continuous Flow Preparation and Reactions of Carbamoyllithiums for Nucleophilic Amidation

2.1 Introduction[145]

The amide group is a ubiquitous functionality, present in 25% of commercially available drugs.[146] Also, analogous thioamide derivatives have gained attention as antibiotics as well as bio-isosteric optical labels in proteins and versatile synthons for heterocyclic synthesis or C-H activation.[147] Numerous protocols for amidations and, to a lesser extent, for thioamidations have been developed.[148] The major challenges in modern amidation chemistry are the development of atom economical methods and the valorization of new potential starting materials.[146,148] In this context, amidations and thioamidations involving the lithiation of formamide precursors are of special interest due to their atom-economical generation and the high reactivity of the intermediates. Furthermore, their acyl anion type reactivity allows accessing valuable product structures.[149,150,151] For instance, *Reeves et. al.* have utilized carbamoyllithiums for the synthesis of α-amino amides with high stereoselectivity.[152] More recently, *Yoshida* and coworkers have demonstrated a reductive lithiation of carbamoyl chlorides protocol with lithium naphthalenide at −78 °C in continuous flow for the synthesis of

[145] The compounds **12b**−**c**, **g**, **k**, **16a**−**b**, **d** were synthesized by Dr. M. Becker under guidance of M. A. Ganiek and will be shown for the sake of completeness. Analytical data is found in the corresponding publication.
[146] a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem*. **2007**, *9*, 411; b) H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson, *Chem. Soc. Rev.* **2014**, *43*, 2714.
[147] a) T. Sifferlen, M. Rueping, K. Gademann, B. Jaun, D. Seebach, *Helv. Chim. Act.* **1999**, *82*, 2067; b) T. S. Jagodszinski, *Chem. Rev.* **2003**, *103*, 197; c) M. C. Bagley, J. W. Dale, E. A. Merritt, X. Xiong, *Chem. Rev.* **2005**, *105*, 685; d) R. F. Wissner, S. Batjargal, C. M. Fadzen, E. J. Petersson, *J. Am. Chem. Soc.* **2013**, *135*, 6529; e) R. W. Newberry, B. VanVeller, R. T. Raines, *Chem. Commun.* **2015**, *51*, 9624; f) P. Jain, P. Verma, G. Xia, J. Yu, *Nat. Chem.* **2017**, *9*, 140.
[148] a) S. Fukuoka, M. Ryang, S. Tsutsu, *J. Org. Chem.* **1971**, *36*, 2721; b) A. Tillack, I. Rudloff, M. Beller, *Eur. J. Org. Chem.* **2001**, 523; c) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471. d) S. Fuse, Y. Mifune, T. Takahashi, *Angew. Chem. Int. Ed.* **2014**, *53*, 851; e) H. Saeidian, S. Vahdati-Khajehi, H. Bazghosha, Z. Mirjafary, *J. Sulfur Chem.* **2014**, *35*, 700; f) T. Krause, S. Baader, B. Erb, L. J. Gooßen, *Nat. Commun.* **2016**, *7*, 11732; g) R. M. de Figueiredo, J. S. Suppo, J. M. Campagne, *Chem. Rev.* **2016**, *116*, 12029.
[149] D. Seebach, *Angew. Chem. Int. Ed.* **1969**, *8*, 639.
[150] a) U. Schöllkopf, F. Gerhart, *Angew. Chem. Int. Ed.* **1967**, *6*, 805; b) B. Banhidai, U. Schöllkopf, *Angew. Chem. Int. Ed.* **1973**, *12*, 836; c) D. Enders, D. Seebach, *Angew. Chem. Int. Ed.* **1973**, *12*, 1014; f) R. R. Fraser, P. R. Hubert, *Can. J. Chem.* **1974**, *52*, 185; d) W. Lubosch, D. Enders; D. Seebach, *Chem. Ber.* **1976**, *109*, 1309; e) V. Rautenstrauch, M. Joyeux, *Angew. Chem., Int. Ed.* **1979**, *18*, 83; f) T. Hiiro, T. Mogami, N. Kambe, S. Fujiwara, N. Sonoda, *Synth. Commun.* **1990**, *20*, 703; g) D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1993**, *34*, 7115; h) C. Zhu, X. Creary, *J. Am. Chem. Soc.* **1995**, *117*, 5859; i) N. Kambe, T. Inoue, T. Takeda, S. Fujiwara, N. Sonoda, *J. Am. Chem. Soc*. **2006**, *128*, 12650.
[151] For naturally occuring and pharmaceutically important α-ketoamides, see: a) Y. Kumar, M. Shaw, R. Thakur, A. Kumar, *J. Org. Chem.*, **2016**, *81*, 6617; b) M. Yan, P. S. Baran, *Org. Process Res. Dev.*, **2017**, *21*, 1091.
[152] a) Z. Tan, M. A. Herbage, Z. S. Han, M. A. Marsini, Z. Li, G. Li, Y. Xu, K. R. Fandrick, N. C. Gonnella, S. Campbell, S. Ma, N. Grinberg, H. Lee, B. Z. Lu, C. H. Senanayake, J. T. Reeves, *J. Am. Chem. Soc.* **2013**, *135*, 5565; b) C. Lorenc, K. Camara, Z. Li, H. Lee, C. A. Busacca, C. H. Senanayake, J. T. Reeves *J. Org. Chem.* **2014**, *79*, 5895.

functionalitized α-ketoamides.[153] A more classical approach is to generate a transient organometallic species in the presence of trapping agents (*Barbier* conditions)[154] like aldehydes, ketones, Me_3SiCl or $B(O^iPr)_3$.[155] Recently, it was shown that *in situ* trapping of highly reactive polyfunctional aryllithiums can be realized using a metallic salt ($MetX_n$) as trapping reagent ($MetX_n$ = $ZnCl_2 \cdot 2LiCl$, $MgCl_2 \cdot 2LiCl$, $CuCN \cdot 2LiCl$, $LaCl_3 \cdot 2LiCl$; Scheme 25).[156] In this project, *in situ* metalation of a substrate (R-H = R^1R^2NCHO) was performed not in the presence of a metallic salt but directly in the presence of an organic electrophile (E', such as a ketone, an aldehyde, a *Weinreb* amide, an allylic bromide or a disulfide) in continuous flow for the trapping of unstable carbamoyl- and thiocarbamoyl-lithium intermediates (R-E). The resulting flow *Barbier* method is characterized by exceptionally convenient conditions (Scheme 25).



Scheme 25: Continuous flow methods using either an *in situ* metalation (**A**) or a *Barbier* procedure (**B**).

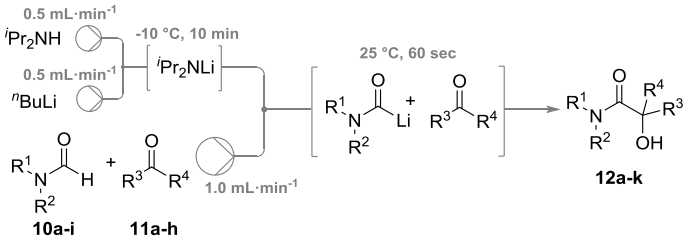
2.2 Continuous Flow Generation and *In Situ* Reactions of Carbamoyllithiums

Thus, a mixture of *N*,*N*-diethyl formamide (**10a**) and cyclohexanone (**11a**, 0.7 equiv.) in THF was mixed in a simple T-mixer (0.5 mm i.d.) with a lithium diispropylamide solution (LDA, 1.2 equiv.) and after a residence time of 1 min at 25 °C the α-hydroxy amide **12a** was obtained in 95% yield (Table 6, entry 1). In contrast, all attempts to generate carbamoyllithiums in the absence of an electrophile at non-cryogenic temperatures led to extensive decomposition. Since LDA solutions are known to be unstable upon storage,[66] a protocol for its in-line preparation was devised using a ^{n}BuLi solution in hexanes and a diisopropyl amine solution in THF. In this manner, only bench-stable reagents were used and the scalabilty was extended. The efficient cooling in flow allows applying

[153] The following communication was published during the course of the here presented work: A. Nagaki, Y. Takahashi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2016**, *55*, 5327.
[154] P. Barbier, *C. R. Hebd. Acad. Sci.* **1899**, *128*, 110.
[155] a) T. D. Krizan, J. C. Martin, *J. Am. Chem. Soc.* **1983**, *105*, 6155; b) P. E. Eaton, R. M. Martin, *J. Org. Chem.* **1988**, *53*, 2728; c) C. Blomberg, *The Barbier Reaction and Related One-Step Processes*, Springer, Berlin, **1993**; d) J. Kristensen, M. Lysén, P. Vedsø, M. Bergtrup, *Org. Lett.* **2001**, *3*, 1435; e) H. M. Hansen, M. Bergtrup, J. Kristensen, *J. Org. Chem.* **2006**, *71*, 2518; f) D. Tilly, J. Fu, B. Zhao, M. Alessi, A. S. Castanet, V. Snieckus, J. Mortier, *Org. Lett.* **2010**, *12*, 68; g) E. Demory, V. Blandin, J. Einhorn, P. Y. Chavant, *Org. Process Res. Dev.* **2011**, *15*, 710.
[156] a) A. Frischmuth, M. Fernández, N. M. Barl, F. Achreiner, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928; b) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed*. **2015**, *54*, 12501.

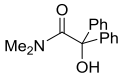
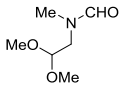
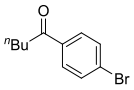
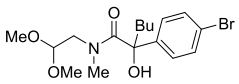
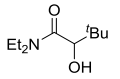
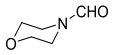
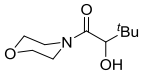
moderate −10 °C during the LDA formation step. The fully optimized *Barbier* flow procedure provided a range of *α*-hydroxy amides (**12b**−**i**) in 58−91% yield by the addition of lithiated *N*,*N*-dialkyl formamides to various ketones (**11a**−**g**; Table 6, entries 1−9). Pivaldehyde (**11h**) was additionally found to be a good electrophile, furnishing the *α*-hydroxy-amides **12j**−**k** in 61−91% yield (entries 10−11). Additional functional groups like an epoxide, an ester or a cyano group were not tolerated.[149,153] However, a ketal, an acetal or an aryl halide proved to be compatible with the flow reaction conditions, thus providing functionalities for further derivatization (entries 5, 7, 9).

Table 6: Continuous flow generation of carbamoyllithiums in the presence of a carbonyl electrophile (**11**) leading to *α*-hydroxy amides of type **12**.



Entry	Formamide	Electrophile	Product/Yield[a]
1	**10a**	**11a**	**12a**: 95%
2	**10b**	**11a**	**12b**: 72%
3	**10c**	**11a**	**12c**: 63%
4	**10d**	**11b**	**12d**: 69%
5	**10e**	**11c**	**12e**: 72%
6	**10f**	**11d**	**12f**: 58%
7	**10g**	**11e**	**12g**: 79%

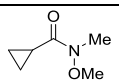
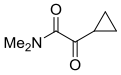
Table 6 continued.

			
8	**10a**	**11f**	**12h**: 79%
			
9	**10h**	**11g**	**12i**: 63%
			
10	**10a**	**11g**	**12j**: 91%
			
11	**10i**	**11g**	**12k**: 61%

[a] Yield of isolated product. The reactions were performed on a 1 or 2 mmol scale.

The procedure was also readily extended to *Weinreb* amide electrophiles[157] and to the related *N*-morpholino amides[158] of type **13**, providing a range of *α*-keto amides of type **14** in 61–85% yield (Table 7). These acylations were usually performed on a 1.0 mmol scale (collection during 2 min), but a scale-up was possible without further changes to the reaction conditions. Thus, the preparation of *α*-keto amide **14b** was performed on a 35 mmol scale (collection during 70 min) in comparable yield to the 1.0 mmol scale reaction leading to related product **14a** (entries 1–2). Further examples demonstrated, that acetals and ketals (entries 3, 6, 10), aryl halides (entries 7–8) and a silyl ether (entry 11) are tolerated under the reaction conditions. This *Barbier* flow method could further be performed with an isocyanate electrophile (**15a**), leading to the unsymmetrical 1,2-diamide (**16a**) in 54% yield (entry 12). Allylations using 3-bromocyclohexene (**15b**) furnished the allylic amides (**16b**–**c**) in 58–60% yield (entries 13–14). Finally, using dibutyl disulfide (**15c**) as quenching electrophile led to *S*-butyl dibutylcarbamothioate (**16d**) in 88% yield (entry 15).

Table 7: Continuous flow generation of carbamoyllithiums in the presence of amides (**13**) and various other electrophiles (**15**) leading to products of type **14** and **16** at 25 °C.

Entry	Formamide	Electrophile	Product/Yield[a]
			
1	**10g**	**13a**	**14a**: 63%

[157] S. Nahm, S. M. Weinreb, *Tetrahedron Lett*. **1981**, *22*, 3815.
[158] a) Y. Chen, M. Ellwart, G. Toupalas, Y. Ebe, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 4612; b) R. Peters, P. Waldmeier, A. Joncour, *Org. Proc. Res. Dev.* **2005**, *9*, 508.

Table 7 continued.

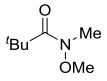
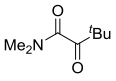
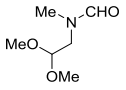
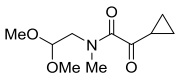
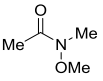
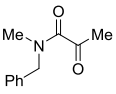
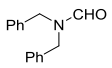
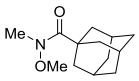
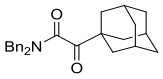
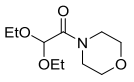
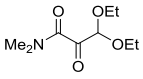
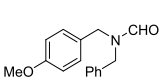
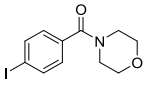
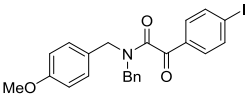
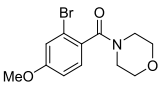
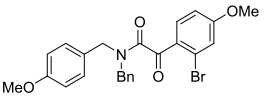
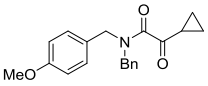
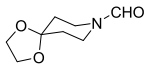
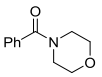
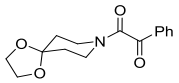
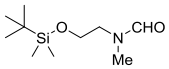
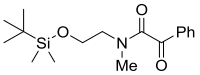
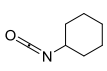
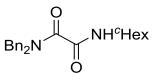
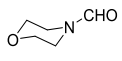
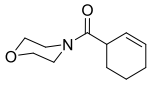
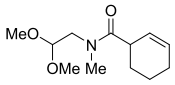
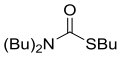
			
2	**10g**	**13b**	**14b**: 65%[b]
			
3	**10h**	**13a**	**14c**: 76%
			
4	**10c**	**13c**	**14d**: 72%
			
5	**10j**	**13d**	**14e**: 76%
			
6	**10g**	**13e**	**14f**: 75%
			
7	**10k**	**13f**	**14g**: 82%
			
8	**10k**	**13g**	**14h**: 82%
			
9	**10k**	**13a**	**14i**: 85%
			
10	**10e**	**13h**	**14j**: 61%
			
11	**10l**	**13h**	**14k**: 63%
			
12	**10j**	**15a**	**16a**: 54%
			
13	**10i**	**15b**	**16b**: 60%[c]

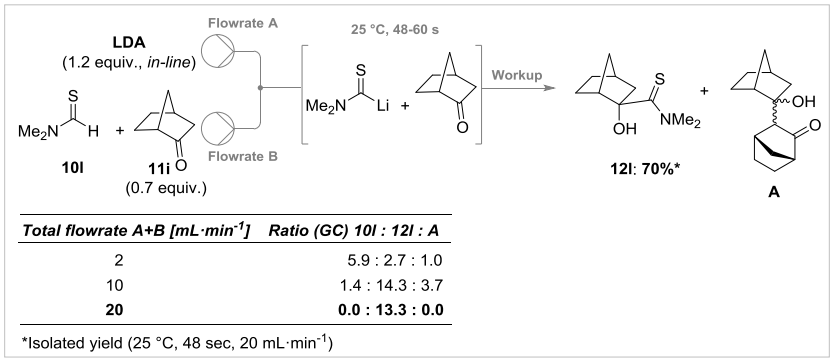
Table 7 continued.

			
14	**10h**	**15b**	**16c**: 58%[c]
		$(SBu)_2$	
15	**10d**	**15c**	**16d**: 88%

[a] Yield of isolated product. The reactions were performed on a 1 or 2 mmol scale. [b] Yield on a 35 mmol scale. [c] The reaction was performed in the presence of 10 mol-% CuCN·2LiCl.

2.3 Continuous Flow Generation and *In Situ* Reactions of Thiocarbamoyllithiums

A further extension to the generation of nucleophilic thioamides such as *N*,*N*-dimethyl thioformamide **10l** using the flow lithiation was envisioned. However, dimethylthioformamide **10l** was not efficiently metalated under the previous conditions (total flowrate 2 mL·min^{-1}, Scheme 26) and only a minor proportion of starting material was transformed to the desired tertiary alcohol **12l**. Furthermore, aldol by-products (**A**) resulting from enolization of the ketone **11i**, were found in considerable amounts. This unfavourable product distribution could be improved by adjusting the overall flowrate (compare flowrates 2, 10 and 20 mL·min^{-1}, Scheme 26).



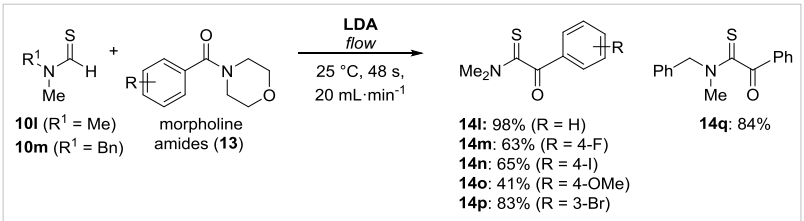
Total flowrate A+B [mL·min^{-1}]	*Ratio (GC) 10l : 12l : A*
2	5.9 : 2.7 : 1.0
10	1.4 : 14.3 : 3.7
20	**0.0 : 13.3 : 0.0**

*Isolated yield (25 °C, 48 sec, 20 mL·min^{-1})

Scheme 26: Optimization of the flowrate for the reaction of lithiated thioformamide **10l** with norcamphor **11i**. Uncalibrated gas chromatography (GC) peaks were used to compare the relative product distributions.

Hence, a favourable selectivity was observed by merely adjusting the flowrate.[159] Under the refined conditions (20 mL·min^{-1}, 25 °C, 48 sec), the desired product **12l** was obtained in 70% isolated yield without aldol type sideproducts. Furthermore, conducting this flow *Barbier* lithiation of thioformamides (**10l**–**m**) in the presence of *N*-morpholine benzamides (**13**) gave a reliable access to valuable[150h] α-keto thioamides **14** in 41–98% yield (Scheme 27).

[159] This effect may be a result of similar deprotonation kintetics of **10l** and **11i** in favour of **10l**, which becomes only fully apparent at high flow rates. The productive reaction pathway was likely concealed at low flowrates due to mass transfer limitations (imperfect mixing), see refs. 14d,142.



Scheme 27: Flow *Barbier* acylations of thioformamides **10l**–**m** with various aryl morpholine amides (**13**) leading to *α*-keto thioamides **14l**–**q**.

2.4 Mechanistic studies with a Carbamoyllithium Species[160]

Interestingly, under the optimized flow conditions shown in chapters 2.2–2.3 and in related reported batch reactions,[150b] side-products derived from a lithiation of the electrophiles (*e.g.* ketones or benzamide derivatives)[161] were usually not found.[162] To explain the preferential formamide lithiation, the relative free energies of lithiation of formamide **10a** in comparison with other well-known C-H acids[163] such as 2-phenyl-1,3-dithiane (**B**), 3,5-difluoroanisole (**C**) and 3,5-difluorobenzene (**D**) were determined by performing competition experiments using pivaldehyde (**11h**) as electrophile (Figure 5). The competition experiments were performed under reaction conditions (25 °C, 1 min) according to a previously reported experimental framework.[164] The obtained relative free energies ΔΔG° of lithiation (with **10a** taken as reference) show that formamide **10a** is located between the dithiane **B** and 1,3-fluorobenzenes (**C**–**D**) with respect to its lithiation preference. The free energy difference for lithiation of 0.4 kcal·mol^{-1} between 1,3-difluorobenzenes **C** and **D** is similar to the reported value of 0.48 kcal·mol^{-1} in the case of the lithiation with TMPLi in THF at −75 °C.[163c] According to this ordering of ΔΔG values in Figure 5 (**C** < **10a** < **D**), the thermodynamic acidity of formamide **10a** could be approximated to be pK_a = 31, according to 33 < pK_a (**10a**) < 28.[163] This ranking was further confirmed by *ab initio* calculations.

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[160] The competition experiments were performed by M. A. Ganiek under guidance of Dr. G. Berionni, who also performed the corresponding calculations leading to the results of Figure 5. *Ab initio* calculations were performed and interpreted by Prof. Dr. H. Zipse. The results are shown here for the sake of completeness according to the corresponding publication.

[161] For instance, ketones (11) are easily metalated with LDA, but even morpholino arylmethanones, *Weinreb* amides (13) and halobenzene moieties can be metalated or decomposed by lithium amide bases: a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) S. L. Graham, T. H. Scholz, *Tetrahedron Lett.* **1990**, *31*, 6269; c) L. Gupta, A. C. Hoepker, K. J. Singh, D. B. Collum, *J. Org. Chem.* **2009**, *74*, 2231; d) A. Cederbalk, M. Lysén, J. Kehler, J. L. Kristensen, *Tetrahedron* **2017**, *73*, 1576; e) M. J. Houghton, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11057.

[162] A single exception was **11d**, which partially engaged in aldol reactions leading to minor amounts of aldol self-condensation products, which were detected by GC-MS.

[163] For the experimental pK_a value of 2-phenyl-1,3-dithiane in DMSO (30.7), and for the calculated pK_a value in THF (32.8), see: a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456; b) S. Sakthivel, R. B. Kothapallia, R. Balamurugan, *Org. Biomol. Chem.* **2016**, *14*, 1670. For the calculated pK_a value of 1,3-difluoro-benzene in THF (28.0), see: c) F. Mongin, C. Curty, E. Marzi, F. R. Leroux, M. Schlosser, *ARKIVOC* **2015**, *4*, 48.

[164] For related competition experiments and their theoretical foundation, see: a) L. Shi, Y. Chu, P. Knochel, H. Mayr, *Angew. Chem. Int. Ed.* **2008**, *47*, 202; b) H. Mayr, J.-P. Dau-Schmidt, *Chem. Ber.* **1994**, *127*, 213; c) J.-P. Dau-Schmidt, H. Mayr, *Chem. Ber.* **1994**, *127*, 205.

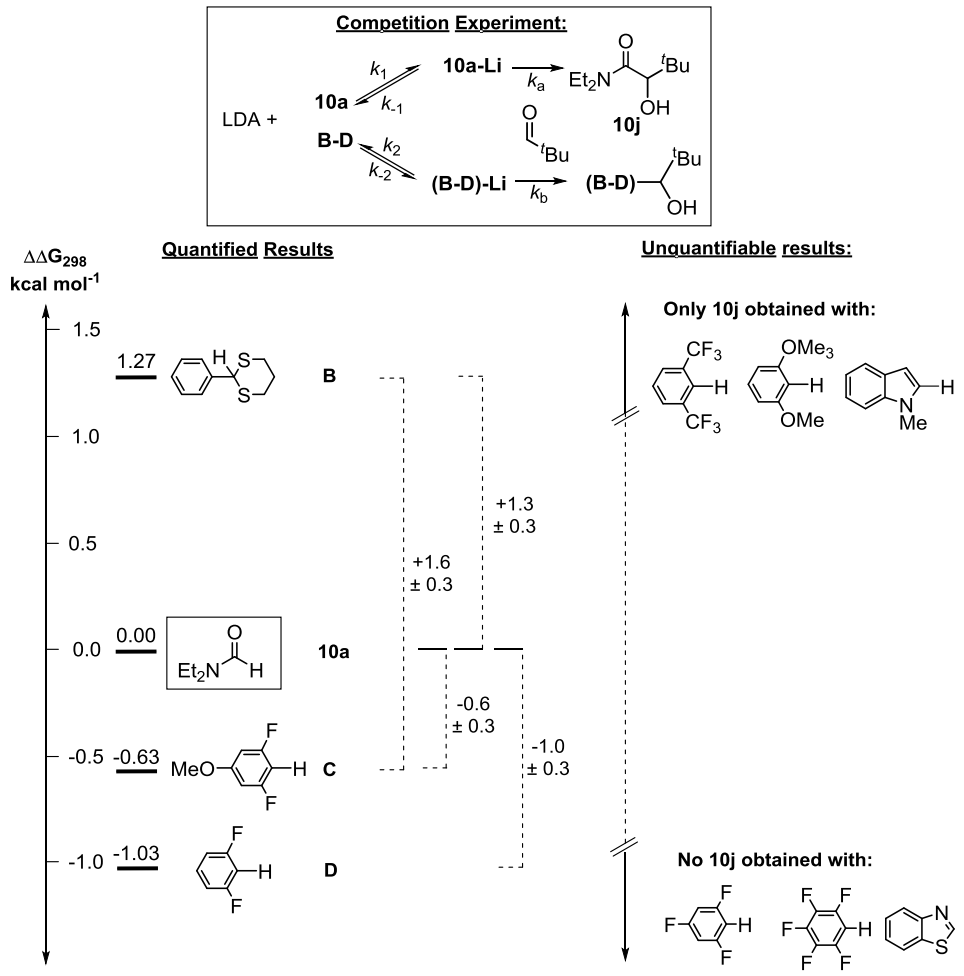


Figure 5: Relative free energy of LDA-mediated lithiation of **10a** taken as reference compared to other C-H acids (**B**–**D**) in THF at 25 °C. $\Delta\Delta G° = 1.364 \log K_{rel}$. Reference acids, which gave only one detectable product (right side) were not amenable to quantification: Control experiments demonstrated that the results of the competition experiments were independent of the concentration and the time before quenching (t = 1 or 10 min).

In line with earlier theoretical studies,[152a] the structure of monomeric carbamoyllithiums such as the one derived from DMF is that of a side-on complex (Figure 6). Reaction free energies for generation of lithiated DMF from monomeric LDA are positive (that is, unfavorable) by 7.2 kcal·mol^{-1},[165] which is in obvious disagreement with the synthetic and equilibration experiments. However, much more favorable lithiation energies are obtained starting from the dimeric LDA structure, whose relevance in THF solution has been demonstrated repeatedly.[166] The lithiation of DMF is exergonic by 2.5 kcal·mol^{-1} under these conditions due to favorable Lewis acid/Lewis base interactions between the amide lone pair electrons and the second lithium cation. Applying this dimer model to the lithiation of 1,3-difluorobenzene (**D**) and benzothiazole (Figure 6) predicts reaction free energies in the same order as observed in the lithiation experiments, which further supports the relevance of these aggregates in THF solution (Figure 6). Furthermore, the experimental (Figure 5) and theoretical (Figure 6, right

[165] Calculated at the gas phase MP2(FC)/6-311++G(2df,2p)//B3LYP-D3/6-31+G(d) level in combination with solvation free energies in THF calculated with the SMD continuum solvation model at B3LYP-D3/6-31+G(d) level. See experimental part for further details.
[166] D. B. Collum, A. J. McNeil, A. Ramirez, *Angew. Chem. Int. Ed.* **2007**, *46*, 3002.

scale) ΔΔG of metalation are following similar trends as the reported pK_a values of the selected C-H reference acids.[163] It remains striking that the lithiation of formamides **10** can be performed in the presence of enolizable ketones like **11a**−**d** and **11g** which are much stronger C-H acids (pK_a ~20). This demonstrates that the lithiation of **10a** by LDA is kinetically strongly favored, presumably due to an exceptionally strong complex induced proximity effect.[167] The coordination of the formamide moiety to LDA is thus a kinetically determining factor which surpasses C-H acidity and thermodynamic considerations. Similar coordination effects were recently described for rationalizing the regioselectivities of the lithiation of a series of aromatic dithianes, which was mainly controlled by coordination effects and kinetics, rather by than the thermodynamics of lithiation.[163b,168]

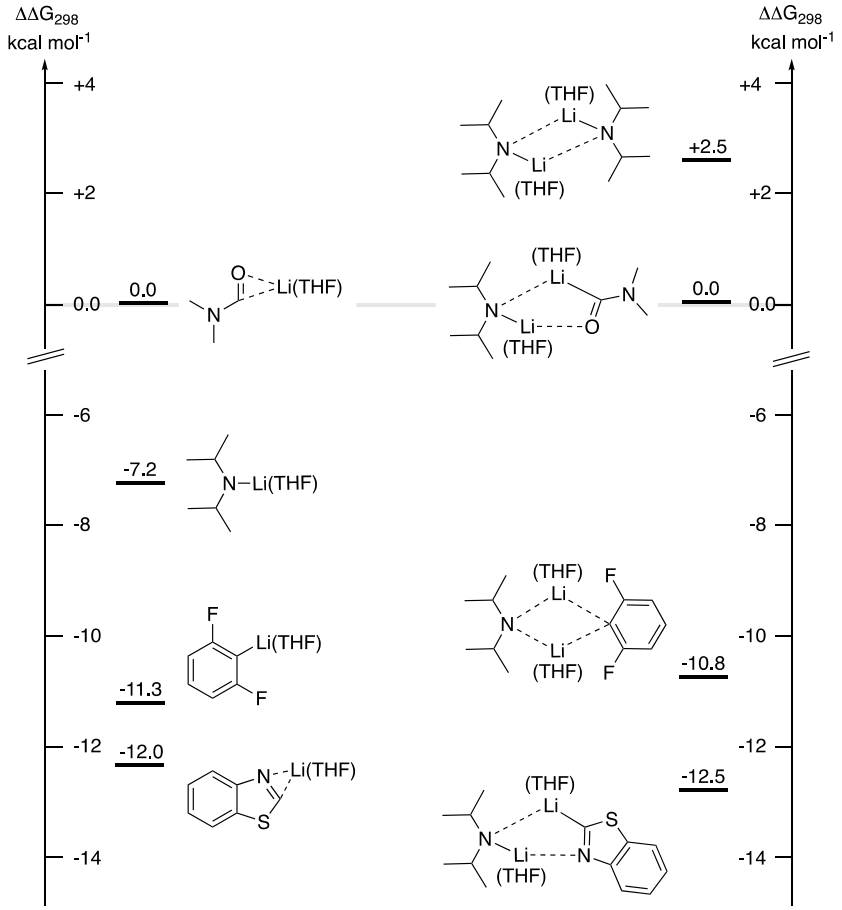


Figure 6: Theoretically calculated relative free energies of LDA-mediated lithiation taking LDA as the reference in THF at 25 °C, ref.165. Left scale: Assuming monomeric structures; Right scale: dimeric structures.

Overall, this Barbier continuous flow procedure constitutes an extension of the previously reported *in situ* trapping metalations[156] and it opens the way to design other Barbier type reactions involving unstable intermediates.

[167] a) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986,** *19*, 356; b) D. R. Hay, Z. Song, S. G. Smith, P. Beak, *J. Am. Chem. Soc.* **1988**, *110*, 8145; c) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.
[168] J. Chandrasekhar, J. G. Andrade, P. von Ragué Schleyer, *J. Am. Chem. Soc.*, **1981**, *103*, 5612.

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[169]

Organolithiums are key organometallic intermediates in organic synthesis.[64] The halogen-lithium exchange reaction is a standard preparation of organolithium compounds[67,170] and provides additionally access to a broad variety of other useful organometallic species after transmetalation.[104,171] The scope of halogen-lithium exchange reactions is limited by the presence of sensitive functional groups in these unsaturated substrates,[170c] precluding the presence of an ester, a nitro, an azide or an isothiocyanato group.[172] These limitations were avoided to some extent by the use of cryogenic temperatures,[170c] special protecting groups[173] or by fast consecutive transmetalations to less reactive organometallics.[74] Continuous flow setups have emerged as a powerful tool for solving synthetic problems,[174] including some aforementioned functional group incompatibilites of aryllithium compounds. For instance, *Yoshida* and coworkers have utilized fast mixing in custom-made flow setups and the thus enabled reaction times in the second to sub-millisecond regime in order to achieve the generation and subsequent reaction of lithiated arenes bearing aldehyde, ketone, ester, isothiocyanate, cyano or nitro groups.[175] Recently, *Knochel* and coworkers have shown that the scope of metalations of arenes (Ar-H) with a strong base like TMPLi is increased by performing these metalations in the presence of metallic salts ($MetY_n$).[176] The resulting organometallics (Ar-Met) are more stable than the initially generated lithium reagents and can be broadly functionalized with a

[169] The compounds **20b, e, f , 21b, c, 20w,ae** and **24h**–**j** were synthesized by Dr. M. Ketels after a common establishment of the general reaction conditions. The compounds **20c**–**d**, **g**–**l, n**–**q**, **t**–**v**, **x**–**ac**, **af**–**ai**, **21a**, –**d**, **24a**–**c** and **24e**–**g** were synthesized by N. Weidmann under guidance of Dr. M. Ketels. All compounds will be shown for the sake of completeness, analytical data is found in the corresponding publication.

[170] See chapter 3.1.2.

[171] a) A. Boudier, L. A. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; c) D. R. Armstrong, E. Crosbie, E. Hevia, R. E. Mulvey, D. L. Ramsay, S. D. Robertson, *Chem. Sci.* **2014**, *5*, 3031; d) M. Uzelac, A. R. Kennedy, E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2016**, *55*, 13147.

[172] 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.

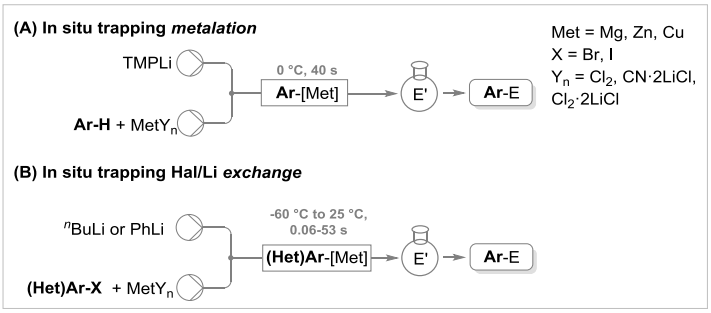
[173] S. Oda, H. Yamamoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 8165.

[174] See chapter 2 for references.

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

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

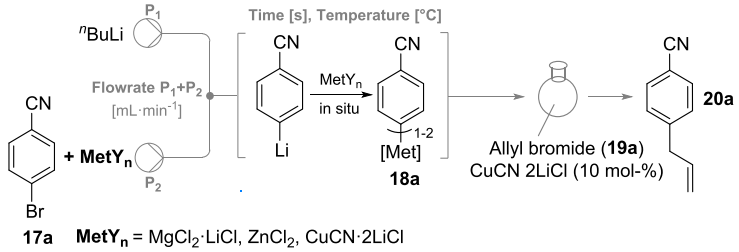
variety of electrophiles (E'). The scope and reaction conditions of this *in situ* trapping procedure are further improved by switching from a batch to a continuous flow setup (Scheme 28A).[176b-c] Aware of the fast rate of the halogen-lithium exchange,[68] an analogous *in situ trapping exchange* procedure was envisioned (Scheme 28B) and is described in the following.



Scheme 28: *In situ* trapping metalation (**A**) and exchange (**B**) in commercially available continuous flow setups.

First, the reaction conditions of the bromine-lithium exchange for 4-bromobenzonitrile (**17a**) with ^{n}BuLi as exchange reagent were optimized for a convenient reaction temperature of 0 °C (Table 8). Optimized flow conditions using 1.5 equiv. ^{n}BuLi in absence of a metal salt led to the allylated arene **20a** in 17% GC-yield after quenching with allyl bromide (**19a**, 2.5 equiv.) and CuCN·2LiCl[130] (10 mol-%; entry 1). This low yield may be due to the competitive addition of ^{n}BuLi or the newly generated aryllithium to the cyano group and polymerization.[172a,177] In contrast, addition of the well-soluble $MgCl_2$·LiCl (1.1 equiv.) to **17a** under otherwise identical conditions led to the magnesiated species **18a** and the allylated product **20a** in 57% (entry 2).

Table 8: Optimization of the *in situ* trapping bromine-lithium exchange for 4-bromobenzonitrile (**17a**) with ^{n}BuLi using a batch allylation to determine the amount of formed organometal species **18a** leading to allylated product **20a.**



Entry	MetY$_n$ (equiv.)	^{n}BuLi equiv.	Temperature [°C]	Flowrate [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

[177] Only traces of starting material were recovered. The reactions obtained by treating benzonitriles with ^{n}BuLi are known to lead to complex mixtures with a difficult to characterize composition: ref. 172a.

Table 8 continued.

5	$MgCl_2$·LiCl (0.5)	1.5	0	16.0	0.94	78
6	$MgCl_2$·LiCl (0.5)	1.5	0	6.0	2.50	85
7	$MgCl_2$·LiCl (0.5)	1.5	25	6.0	2.50	38
8	$ZnCl_2$ (0.5)	1.5	0	6.0	2.50	82
9	$ZnCl_2$ (0.5), *batch*	1.5	0−(−78)	stirred[b]	5.0−90	0−20
10	CuCN·2LiCl (1.1)	1.5	0	6.0	2.50	71
11	$ZnCl_2$ (0.5) + ^{n}BuLi (1.5)[b]		0	6.0	2.50	0
12	$MgCl_2$·LiCl (0.5) + ^{n}BuLi (1.5)[b]		0	6.0	2.50	26

[a] GC-yield determined using dodecane as an internal standard. [b] 200-1200 rpm stirrer rate, 0.5 mmol scale. [c] Metallic salt $MetY_n$ mixed with ^{n}BuLi in batch at −78 °C and then injected in flow.

Notably, in presence of $MgCl_2$·LiCl, the majority of unreacted starting material was recovered, which was not the case in absence of the metal salt. It was further found, that conversion and concomitantly the yield of **20a** were improved by lowering the equivalents of $MgCl_2$·LiCl (0.5 equiv., entry 3) and increasing the equivalents of ^{n}BuLi (1.5 equiv., entries 5−7). Comparison of different flowrates and residence times showed a pronounced sensitivity of the reaction to changes in the flowrate and thus mixing efficiency with an optimum of yield (85%) was achieved at 6 mL·min^{-1} total flowrate and 2.5 sec residence time (entries 4−6). Conducting the reaction at 25 °C instead of 0 °C under otherwise optimal conditions caused a decrease of the yield (entry 7). However the optimum temperature of 0 °C for the flow *in situ* trapping exchange is remarkable, if compared with analogous batch reaction protocols, which resort to cooling to −78 °C and lower without exceptions.[170b,175a] Instead of $MgCl_2$·LiCl, also $ZnCl_2$ or CuCN·2LiCl could be used as *in situ* transmetalating agents leading to **20a** in 71−82% GC-yield (entries 8, 10−11). Notbaly, the attempted batch variant of the *in situ* trapping with $ZnCl_2$ under a variety of conditions gave a maximum yield of 20% **20a** at -78 °C (entry 9). To confirm the order of exchange and transmetalation, the metal salts ($MetY_n$) were premixed with ^{n}BuLi in batch at −78 °C for 20 min in the same stoichiometry present during the *in situ* trapping. The resulting solutions of zinc- or magnesiate species[178] were reacted with aryl bromide **17a** in flow using the optimized *in situ* trapping conditions. In the case of the zincate species no reaction occurred (entry 10)[178b,d] and in the case of the magnesiate species only 26% GC-yield of the allylated arene **20a** were obtained (entry 11).[178a] This indicates that zincate and magnesiate species are unlikely to account for the observed high-yielding exchange reaction and hence the order of reaction steps is assumed to be a halogen-lithium exchange followed by transmetalation.

[178] For exchange reactions between aryl halides and metalate species, compare: a) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333 and references therein; b) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017; c) E. Gioria, J. M. Martínez-Ilarduya, P. Espinet, *Organometallics* **2014**, *33*, 4394; d) T. D. Blümke, W. Clegg, P. García-Alvarez, A. R. Kennedy, K. Koszinowski, M. D. McCall, L. Russo, E. Hevia, *Chem. Sci.* **2014**, *5*, 3552.

3.2 *In Situ* Trapping Halogen-Lithium Exchange on Electron-Poor Benzonitriles and Electron-Rich Anisole Derivatives

The intermediate magnesium species **18a** was used in various quenching reactions with electrophiles. Thus, an iodolysis led to aryl iodide **20b** in 83% isolated yield (Table 9, entry 1). The addition of diarylmagnesium **18a** to benzaldehyde (**19c**) provided benzylic alcohol **20c** in 70% yield (entry 2). Batch acylation of the magnesium reagent **18a** in the presence of CuCN·2LiCl with acyl chlorides such as 3-chlorobenzoyl chloride (**19d**) and pivaloyl chloride (**19e**) led to the expected ketones **20d** and **20e** 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 **18b**, which reacted similarly with benzoyl chloride (**19f**) providing benzophenone **20f** in 80% yield (entry 5). The range of benzonitrile substrates was extended to the 2-bromo- and 4-bromo-2-fluoro-derivatives (**17b–c**) which were converted to the corresponding diarylmagnesium species (**18c** and **18d**) under modified 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 9: *In situ* exchange transmetalation for sensitive aryl iodides and bromides of type **17** leading *via* intermediate diorganozincs or -magnesiums of type **18** to polyfunctional arenes of type **20** and biaryls **21**.

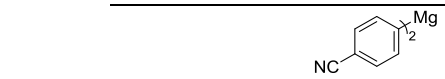
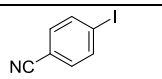
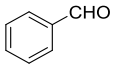
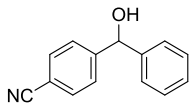
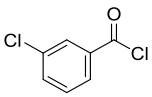
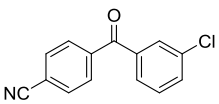
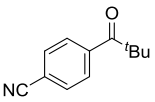
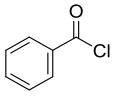
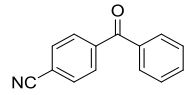
Entry	Metal species (T, Flowrate, t)	Electrophile	Product/Yield[a]
			
1	**18a** (0 °C, 6 mL·min^{-1}, 2.5 s)	**19b**	**20b**: 83%
			
2	**18a**	**19c**[d]	**20c**: 70%
			
3	**18a**	**19d**[e,f]	**20d**: 85%
			
4	**18a**	**19e**[e,f]	20e: 78%
			
5	**18b** (0 °C, 6 mL·min^{-1}, 2.5 s)	**19f**[f]	**20f**: 80%

Table 9 continued.

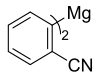
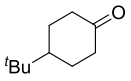
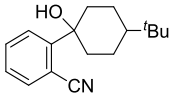
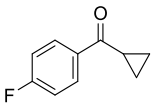
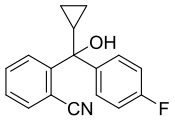
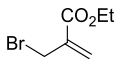
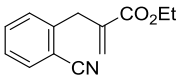
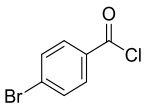
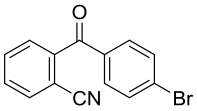
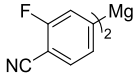
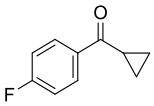
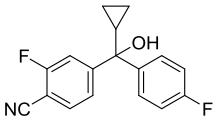
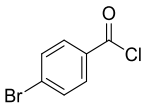
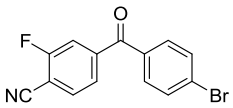
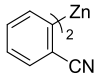
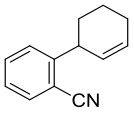
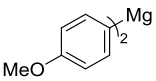
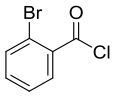
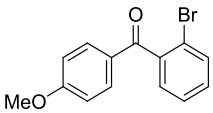
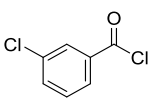
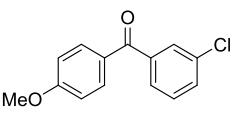
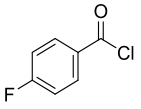
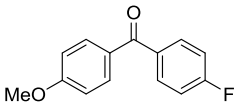
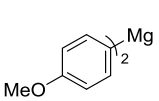
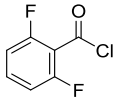
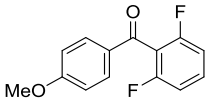
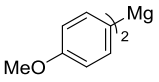
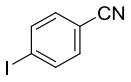
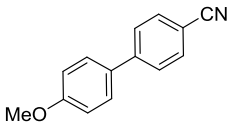
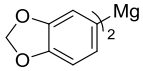
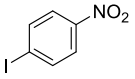
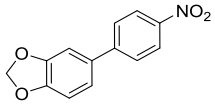
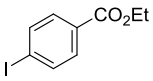
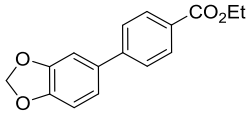
			
6	**18c** (0 °C, 9 mL·min^{-1}, 1.7 s)	**19g**[d]	**20g**: 73% (*d.r.* = 84:16)
			
7	**18c**	**19h**[d]	**20h**: 70%
			
8	**18c**	**19i**[g]	**20i**: 68%
			
9	**18c**	**19j**[e,f]	**20j**: 78%
			
10	**18d** (0 °C, 9 mL·min^{-1}, 1.7 s)	**19h**[d]	**20k**: 74%
			
11	**18d**	**19j**[d]	**20l**: 74% (76%)[h]
			
12	**18e** (0 °C, 9 mL·min^{-1}, 1.7 s) [b]	**19k**[g]	**20m**: 80%
			
13	**18f** (0 °C, 12 mL·min^{-1}, 25 s)	**19l**[e,f]	**20n**: 68%[c]
			
14	**18f**	**19d**[e,f]	**20o**: 56%
			
15	**18f**	**19m**[e,f]	**20p**: 67%

Table 9 continued.

16	 **18f**	 **19n**[e,f]	 **20q**: 61%
17	 **18f**	 **19o**[i]	 **21a**: 88%
18	 **18g** (0 °C, 18 mL·min^{-1}, 17 s)	 **19p**[i]	 **21b**: 85%
19	**18g**	 **19q**[i]	 **21c**: 70%

[a] Yield of analytically pure isolated product. Metal species prepared from the corresponding aryl bromide. [b] Metal species prepared from the corresponding aryl iodide.[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] Cross-coupling conditions: 1.5 equiv. Ar-I, 2 mol-% PEPPSI-IPr, 25 °C, 10 h after transmetalation with 1.1 equiv. $ZnCl_2$.

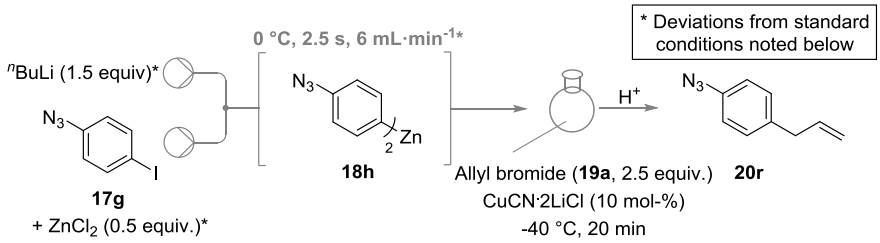
While most reactions were performed on a 0.5 mmol scale, the *in situ* trapping exchange reaction protocol can be conveniently scaled up by simply extending the runtime. Thus, benzophenone **20l** was prepared on a 10 mmol scale in 76% yield (entry 11) without further optimization.[137] It was also possible to perform an iodine-lithium exchange on 2-iodobenzonitrile (**17d**) using similar conditions (0.5 equiv. $ZnCl_2$, 0 °C, 6 mL min^{-1}, 2.5 s), providing the diarylzinc species **18e**. Allylation with 3-bromocyclohexene (**19k**) afforded 1,2-disubstituted benzonitrile **20m** in 80% yield (entry 12). Also electron-rich aryl bromides like 4-bromoanisole (**17e**) were transmetalated *in situ* in the presence of $MgCl_2$·LiCl and quenched with various acyl chlorides **19l**–**n** in batch leading to ketones **20n**–**q** in 56–68% yield (entries 13–16). Furthermore, electron-rich 4-bromoanisole **17e** and 5-bromobenzo[*d*][1,3]dioxole **17f** furnished diarylmagnesiums **18f**–**g** under the established conditions, which after batch-transmetalation with $ZnCl_2$ underwent *Negishi* cross-coupling[132] with a range of aryl iodides **19o**–**q** in the presence of *Organ's* catalyst PEPPSI-IPr[179] leading to polyfunctional biphenyls **21a**–**c** in 70–88% yield (entries 17–19).

[179] N. Hadei, E. A. B. Kantchev, C. J. O'Brie, J. Christopher, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805.

3.3 *In Situ* Trapping Halogen-Lithium Exchange on Substrates Bearing Highly Sensitive Functionalities

Considering halogen-lithium exchanges with more sensitive groups than a nitrile, only halogen-lithium exchanges of *o*-nitroarenes, *tert*-butyl- and triethylsilyl-trisilanol benzoic esters and an alkenyl iodide containing an aliphatic azide at −100 °C under batch conditions are known.[170,173] Furthermore, several flow protocols for ester-, ketone- and nitro-containing arenes applying fast micromixing and residence times down to 0.0015 s are reported.[175] However, the fast kinetics of halogen-lithium exchange could alternatively allow an *in situ* transmetallation exchange with aryl halides bearing the aforementioned and even more challenging functional groups. Testing this hypothesis, it was found that 4-iodophenyl azide[180] (**17g**) decomposes completely in the absence of a metal salt upon performing an exchange with 1.0 or 1.5 equiv. ^{n}BuLi in flow at 0 °C for 2.5 or 15 s (Table 10, entries 1−3).[181]

Table 10: Product distribution for the iodine-lithium exchange with **17g** using ^{n}BuLi as exchange reagent in presence or absence of $ZnCl_2$ under various conditions, detected by an allylation quench.



Entry	Deviation from standard conditions	Recovered **17**g [%][a]	Yield **20**r [%][b]
1	No salt additive	traces	0
2	No salt additive, 1.0 equiv. ^{n}BuLi	traces	0
3	No salt additive, 1.0 equiv. ^{n}BuLi, 15 s	traces	0
4	0.5 equiv. $ZnCl_2$ *consecutive*	43	8
5	none	23	53
6	0.5 equiv. $ZnCl_2$ *in situ*, 1.25 s, −40 °C, 12 mL·min^{-1}	11	72

[a] Determined using dodecane as an internal standard. [b] Entry 6 refers to isolated yield (1.0 mmol), entries 1−5 were determined by GC using dodecane as an internal standard.

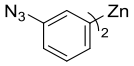
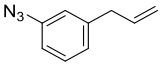
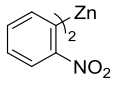
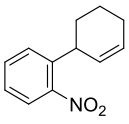
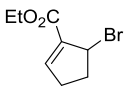
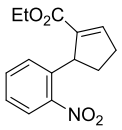
In contrast, if the initially formed lithium species was transmetalated with $ZnCl_2$ in batch after 2.5 s at 0 °C (fast consecutive quenching, entry 4), the product **20r** is obtained in only 8% yield and substantial decomposition of the starting material was observed. If standard *in situ* quenching (0 °C, 2.5 s, 0.5 equiv. $ZnCl_2$, entry 5) was applied 53% of allylated product **20r** as well as 23% starting

[180] 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.

[181] In these reactions, neither the expected allylation product **20r** was found nor distinct identifiable products.

material were recovered. Finally, adapting various parameters of the situ trapping (such as flowrate and temperature) led to the desired allylated phenyl azide **20r** in 72% isolated yield after the batch allylation (entry 6).[182]Analogously to the prior example, *m*-allyl azidobenzene (**20s**) was obtained in 83% yield from the iodide **17h** (Table 11, entry 1). Furthermore, nitro-, ketone- and ester-group containing aryl halides were tested due to the pivotal role of these functionalities in organic synthesis. The challenges posed by these functional groups due to competitive electron transfer and nucleophilic addition reactions with organometallic reagents are well-known.[170,172] 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[70] than a competitive transmetalation of PhLi, which allows an efficient generation of diarylzincs and -magnesiums (**18j**–**s**). Thus, bis-(nitroaryl)zincs and -magnesiums **18j**–**m** were generated from the corresponding aryl halides **17i**–**l** bearing *o*-, *m*- and *p*-nitro groups . Allylation, acylation and addition to indole aldehyde **19s** or ketone **19h** in batch furnished the desired functionalized nitro arenes **20s**–**x** in 60–93% yield (entries 2–7). Similarly, aryl bromide **17m**, containing a ketone gave biszinc species **18n** by *in situ* trapping exchange reactions at −40 °C in the presence of $ZnCl_2$. Typical quenching conditions led to the allylated products **20y**–**z** in 65–78% yield (entries 8–9). Furthermore, ethyl 4-iodobenzoate (**17n**) led to ketones **20aa**–**ab** and to the secondary alcohol **20ac** *via* the diarylmagnesium **18o** in 70–78% (entries 10–12). It was further possible to perform a bromine-lithium exchange on aryl bromides bearing a *p*-, *m*-, and *o*-isothiocyanate moiety without subsequent nucleophilic additions to the isothiocyanate.[172d,175d] After various copper mediated allylations or acylations, the desired products **20ad**–**ah** were obtained in 60–68% yield (entries 13–17).

Table 11: *In situ* exchange transmetalation for highly sensitive aryl iodides and bromides **17** leading *via* intermediate diorganozincs or -magnesiums of type **18** to polyfunctional arenes of type **20**.

Entry	Metal species (T, Flowrate, t)	Electrophile	Product/Yield[a]
			
1	**18i** (−40 °C, 12 mL·min^{-1}, 1.25 s)[b]	**19a**[c]	**20s**: 83%
			
2	**18j** (−20 °C, 12 mL·min^{-1}, 1.25 s)[d]	**19k**[c]	**20t**: 93%
			
3	**18j**	**19r**[c]	**20u**: 78%

[182] Scale-up of this reaction from 1 to 5 mmol provided aryl azide **20r** in 60% yield.The losses are likely due the use of another, newly prepared batch of azide starting material.

Table 11 continued.

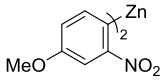
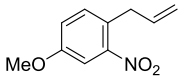
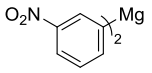
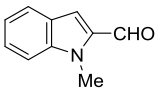
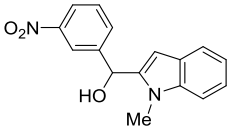
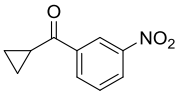
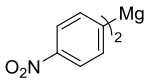
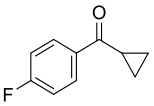
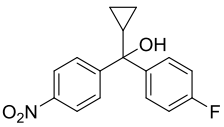
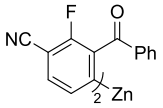
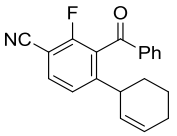
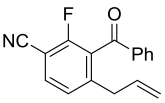
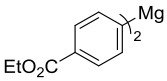
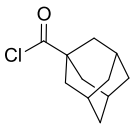
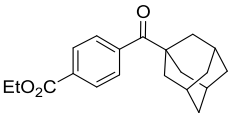
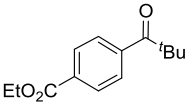
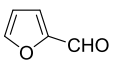
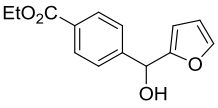
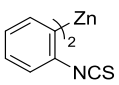
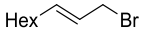
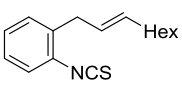
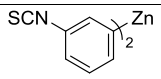
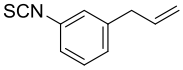
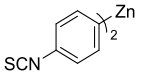
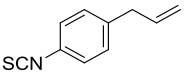
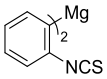
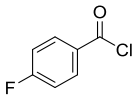
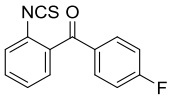
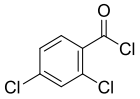
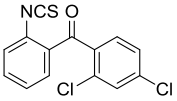
			
4	**18k** (−20 °C, 12 mL·min^{-1}, 0.10 s)[d]	**19a**[c]	**20v**: 73%
			
5	**18l** (−20 °C, 20 mL·min^{-1}, 0.06 s)[b]	**19s**[e]	**20w**: 60%
			
6	**18l**	**19t**[f]	**20x**: 63%
			
7	**18m** (−60 °C, 16 mL·min^{-1}, 0.08 s)[b]	**19h**[e]	**20y**: 73%
			
8	**18n** (−40 °C, 20 mL·min^{-1}, 0.06 s)[d]	**19k**[c]	**20z**: 78%
			
9	**18n**	**19a**[c]	**20aa**: 65%
			
11	**18o** (−40 °C, 16 mL·min^{-1}, 0.94 s)[b]	**19u**[f]	**20ab**: 70%
			
12	**18o**	**19e**[f]	**20ac**: 78%
			
13	**18o**	**19v**[e]	**20ad**: 75%
			
14	**18p** (−20 °C, 12 mL·min^{-1}, 1.25 s)[d]	**19w**[c]	**20ae**: 68%

Table 11 continued.

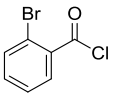
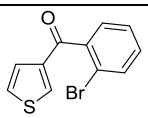
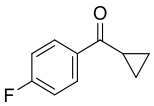
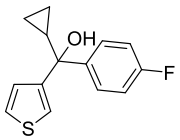
			
15	**18q** (−60 °C, 18 mL·min^{-1}, 0.07 s)[d]	**19a**[c]	**20af**: 65%
			
16	**18r** (−60 °C, 9 mL·min^{-1}, 0.15 s)[d]	**19a**[c]	**20ag**: 67%
			
17	**18s** (−20 °C, 16 mL·min^{-1}, 0.94 s)[d]	**19m**[f]	**20ah**: 63%
			
18	**18s**	**19x**[f]	**20ai**: 60%

[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.

3.4 *In Situ* Trapping Halogen-Lithium Exchange on Heterocycles

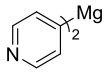
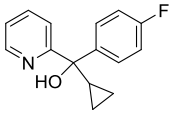
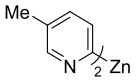
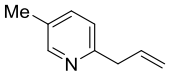
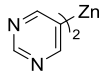
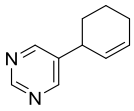
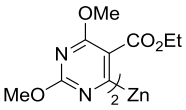
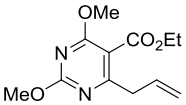
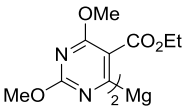
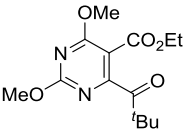
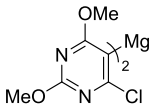
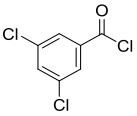
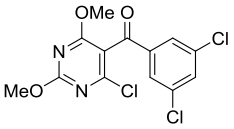
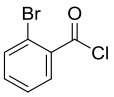
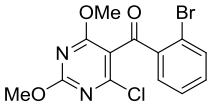
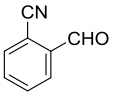
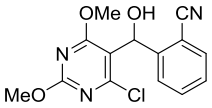
The preparation of polyfunctional heterocyclic organometallics is of key importance for the pharmaceutical and agrochemical industry.[183] Bearing this in mind, sulfur- and nitrogen-containing heterocyclic halides were subjected to *in situ* trapping exchange reactions (Table 12).

Table 12: *In situ* trapping exchange transmetalation for heteroaryl 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, Flowrate, t)	Electrophile	Product/Yield[a]
			
1	**23a** (0 °C, 6 mL·min^{-1}, 10 s) [b]	**19l**[c]	**24a**: 72%
			
2	**23a**	**19h**[d]	**24b**: 77%

[183] For a comprehensive introduction, see: 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, Second Edition*, Wiley, Weinheim, **2003**; For recent advances in heterocycle functionalizeation, see: c) R. E. Miller, T. Rantanen, K. A. Ogilvie, U. Groth, V. Snieckus, *Org. Lett.* **2010**, *12*, 2198; d) C. Schneider, E. David, A. A. Toutov, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 2722; e) J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2012**, *14*, 5400; f) F. Sandfort, M. J. O'Neill, J. Cornella, L. Wimmer, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3319.

Table 12 continued.

			
3	**23b** (0 °C, 18 mL·min^{-1}, 0.83 s)[e]	**19h**[d]	**24c**: 62%
			
4	**23c** (0 °C, 6 mL·min^{-1}, 53 s)[b]	**19a**[f]	**24d**: 63%
			
5	**23d** (0 °C, 12 mL·min^{-1}, 1.25 s)[b]	**19k**[f]	**24e**: 68%
			
6	**23e** (−40 °C, 16 mL·min^{-1}, 0.08 s)[e]	**19a**[f]	**24f**: 70%
			
7	**23f** (−40 °C, 20 mL·min^{-1}, 0.06 s)[e]	**19e**[c]	**24g**: 68%
			
8	**23g** (−20 °C, 9 mL·min^{-1}, 1.7 s)[e]	**19x**[c]	**24h**: 72%
			
9	**23g**	**19l**[c]	**24i**: 63%
			
10	**23g**	**19y**[d]	**24j**: 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.

For instance, 3-bromothiophene (**22a**) was converted readily to the reactive diheteroarylmagnesium species **23a** at 0 °C within 10 s without isomerization to the 2-magnesium species (entry 1).[184]

[184] The mentioned isomerizations are known to occur with 5-membered heterocyclic 3-lithio-derivatives above −40 °C: a) I. Bock, H. Bornowski, A. Ranft, H. Theis, *Tetrahedron* **1990**, *46*, 1199; b) Y. Hayashi, K. Okano, A. Mori, *Org. Lett.* **2018**, *20*, 958.

Subsequent copper-mediated batch acylation with 2-bromobenzoyl chloride (**19l**) led to the heterocyclic ketone **24a** in 72% yield and batch addition to ketone **19h** led to tertiary alcohol **24b** in 77% yield (entry 2). To expand the range of substrates, different pyridines and pyrimidines were subjected successfully to the bromine-lithium exchange. Thus, pyridine derivatives **22b** and **22c** underwent the *in situ* trapping exchange (entries 3–4). Quenching of the bispyridyl-zinc and -magnesium reagents **23b** and **23c** in batch led to the tertiary alcohol **24c** and allylated picoline **24d** in 62–63% yield (entries 3–4). Furthermore, 5-bromopyrimidine (**22d**) and the fully substituted iodopyrimidines **22e** and **22f** 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 or acylated pyrimidines **24f** and **24g** in 68–70% yield (entries 6–7). Interestingly, uracil derived, electron-rich iodopyrimidine **22g** underwent an efficient exchange using the same method and the reactive metal species **23g** was quenched with different benzoyl chlorides **19x** and **19l** and aldehyde **19y** in subsequent batch reactions leading to ketones **24h** and **24j** and alcohol **24j** in 59–72% yield (entries 8–10). Despite extensive experimentation, the *in-situ* trapping halogen lithium exchange could not be extended to alkenyl halide substrates, which might be due to by the different kinetics of halogen-lithium exchange with alkenyl substrates.

4 Synthesis and Reactivity of Triazaphenanthrenes

4.1 Introduction[185]

Six-membered *N*-heterocyclic molecules have found numerous applications due to their biological or physical properties.[186] Especially a number of privileged ring systems have been extensively studied (*e.g.* pyridines,[187] quinolines,[188] isoquinolines,[189] acridines[190] or diazines[191]).

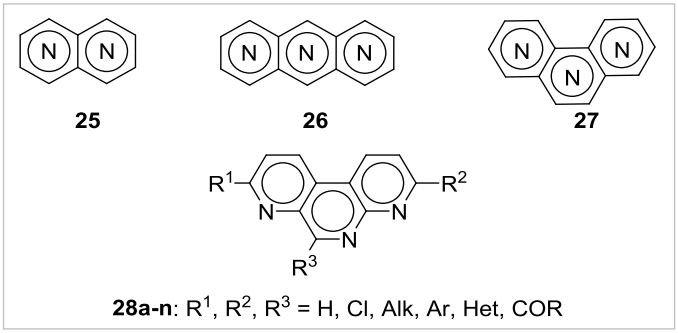


Figure 7: Fused six-membered *N*-heteroaromatics. Triazaphenanthrenes of type **28** were target structures.

Annelated six-membered *N*-heteroaromatics bearing one nitrogen atom per ring (Figure 7), such as naphthyridines (**25**)[192] are much less studied, and the corresponding triazaanthracenes (**26**)[193] and triazaphenanthrenes (**27**)[194] are almost unknown.

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[185] The synthesis leading to **28a** was developed and performed by Dr. S. Fernandez, and repeated by M. Karpacheva. Analytic data is found in the corresponding publication. The synthesis of functionalized derviatives **28d**–**m** was optimized and performed by M. A. Ganiek.

[186] a) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667; b) *Modern Heterocyclic Chemistry*; (Eds.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga), Wiley, Weinheim, **2011**. (c) C.-V. T. Vo, J. W. Bode, *J. Org. Chem.* **2014**, *79*, 2809.

[187] a) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043; b) M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052; c) T. L. S. Kishbaugh, *Prog. Heterocycl. Chem.* **2012**, *24*, 343 ; d) C. Allais, J.-M. Grassot, J. Rodriguez, T. Constantieux, *Chem. Rev.* **2014**, *114*, 10829.

[188] a) N. M. Ahmad, J. J. Li, *Adv. Heterocycl. Chem.* **2003**, *84*, 1; b) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627; c) S. A. Yamashkin, E. A. Oreshkina, *Chem. Heterocycl. Compd.* **2006**, *42*, 701; d) R. I. Khusnutdinov, A. R. Bayguzina, U. M. Dzhemilev, *J. Organomet. Chem.* **2014**, *768*, 75; e) Y. Mao, C. Zhu, Z. Kong, J. Wang, G. Zhu, X. Ren, *Synthesis*, **2015**, *47*, 3133; f) Y.-R. Liu, H.-Y. Tu, X.-G. Zhang, *Synthesis*, **2015**, *47*, 3460.

[189] a) D. Badia, L. Carrillo, E. Dominguez, I. Tellitu, *Recent Res. Dev. Org. Chem.* **1998**, *2*, 359; b) R. He, Z.-T. Huang, Q.-T. Zheng, C. Wang, *Tetrahedron Lett.* **2014**, *55*, 5705.

[190] a) P. Belmont, J. Bosson, T. Godet, M. Tiano, *Anti-Cancer Agents Med. Chem.* **2007**, *7*, 139; b) R. Kumar, M. Kaur, M. Kumari, *Acta Pol. Pharm.* **2012**, *69*, 3.

[191] a) L. Yet, *Prog. Heterocycl. Chem.* **2012**, *24*, 393; b) F. Lassagne, F. Chevallier, T. Roisnel, V. Dorcet, F. Mongin, L. R. Domingo, *Synthesis* **2015**, *47*, 2680; c) A. V. Biitseva, I. V. Rudenko, O. V. Hordiyenko, I. V. Omelchenko, A. Arrault, *Synthesis* **2015**, *47*, 3733.

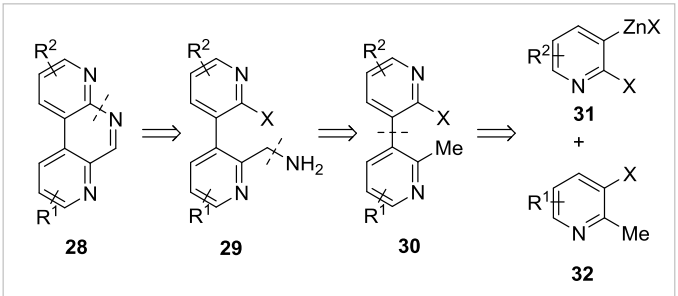
[192] a) C. F. H. Allen, *Chem. Rev.* **1950,** *47*, 275; b) W. W. Paudler, T. J. Kress, *J. Org. Chem.* **1967,** *32*, 832; c) V. P. Litvinov, *Russ. Chem. Rev.* **2004**, *73*, 637; d) J. Egea, C. de los Rios, *Curr. Top. Med. Chem.* **2011**, *11*, 2807; e) R. Greiner, R. Blanc, C. Petermayer, K. Karaghiosoff, P. Knochel, *Synlett* **2016**, *27*, 231.

[193] a) S. Carboni, A. Da Settimo, I. Tonetti, *J. Heterocycl. Chem.* **1970**, *7*, 875; b) M. Winkler, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 1805.

[194] a) F. H. Case, J. A. Brennan, *J. Am. Chem. Soc.* **1959,** *81*, 6297; b) W. Czuba, *Rocz. Chem.* **1967,** *41*, 289; c) Y. Hamada, M. Sato, I. Takeuchi, *J. Pharm. Soc. Jpn.* **1975,** *95*, 1492; d) C. F. Nutaitis, M. Brennan, *Org. Prep. Proced. Int.* **2004,** *36*, 367; e) T. Cailly, F. Fabis, R. Legay, H. Oulyadi, S. Rault, *Tetrahedron* **2007,** *63*, 71.

4.2 Synthesis of Triazaphenanthrenes Starting from Two Pyridine Units

Due to the potential applications of triazaphenanthrenes derived from **27**, a general synthesis of such heterocycles using a *Negishi* cross-coupling[195] with polyfunctional zinc intermediates was investigated.[196] A retrosynthesis of pyridonaphthyridines **28** involving an intramolecular *N*-arylation of the bis-pyridine as final ring closure was envisioned, possibly catalyzed by transition metals.[197] The aminopyridine (**29**) would be readily prepared from the bis-pyridine (**30**) by selective halogenation and amination of the methyl substituent. This polyfunctional bis-pyridine (**30**) would be available by a *Negishi* cross-coupling of the 3-zincated 2-chloropyridine (**31**) with the 3-halogenated 2-picoline (**32**; Scheme 29).



Scheme 29: Retrosynthetic analysis for the synthesis of pyridonaphthyridines **28** from two pyridine units.

With this synthetic route in mind, the polyfunctional zinc reagents of type **31** were prepared from the corresponding 3-bromo-2-chloropyridines by a bromine-magnesium exchange using ^{i}PrMgCl·LiCl[198] and transmetalation with $ZnCl_2$. The obtained pyridyl zinc reagents underwent a *Negishi* cross-coupling with the iodopicolines (**32a**–**b**) within 1–5 h in THF at 50 °C in the presence of 2 mol-% $Pd(PPh_3)_4$ (Scheme 30).[199] As expected, the presence of electron-withdrawing substituents on the pyridylzinc reagents (**31**) significantly lowered the cross-coupling efficiency.

---

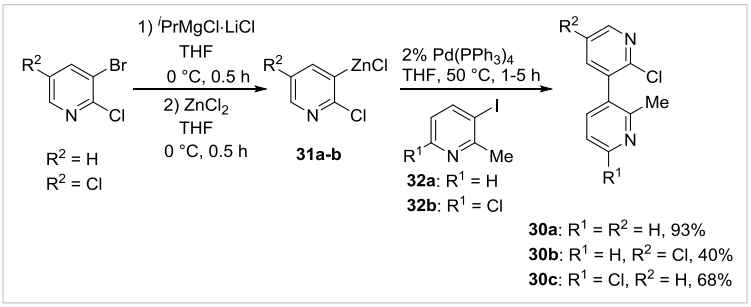
[195] a) *Cross-Coupling reactions. A Practical Guide* (Ed.: N. Miyaura), Springer, Berlin, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley, Weinheim, **2004**; c) E.-i. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738.

[196] The syntheses of compounds **28** was planned, optimized and performed by Dr. S. Fernandez. See: S. Fernandez, Dissertation **2016**, LMU München. M. Karpacheva repeated and extended these syntheses to obtain material for further functionalization. The functionalization of the obtained compounds as well as further starting material syntheses were performed during the course of this thesis. The overall results are shown here for the sake of completeness.

[197] a) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125; b) M. Taillefer, N. Xia, A. Ouali, *Angew. Chem. Int. Ed.* **2007**, *46*, 934; c) A. Correa, O. Garcia Mancheno, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; d) D. Guo, H. Huang, J. Xu, H. Jiang, H. Liu, *Org. Lett.* **2008**, *10*, 4513; e) D. S. Surry, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2008**, *47*, 6338; f) F. Monnier, M. Taillefer, *Angew. Chem., Int. Ed.* **2009**, *48*, 6954; g) D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57; h) D. S.Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27; i) M. Corpet, C. Gosmini, *Synthesis* **2014**, *46*, 2258; j) A. K. Steib, S. Fernandez, O. M. Kuzmina, M. Corpet, C. Gosmini, P. Knochel, *Synlett* **2015**, *26*, 1049.

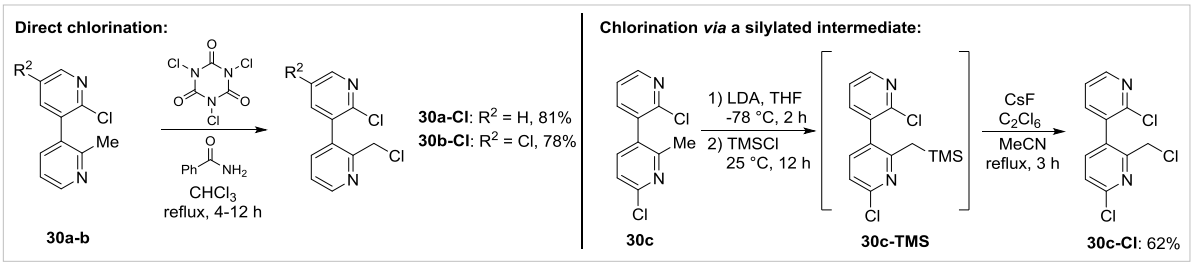
[198] For similar applications, see: a) N. M. Barl, V. Werner, C. Saemann, P. Knochel, *Heterocycles* **2014**, *88*, 827; b) R. Li-Yuan Bao, R. Zhao, L. Shi, *Chem. Commun.* **2015**, *51*, 6884.

[199] Various catalyst systems were screened and $Pd(PPh_3)_4$ gave the best results in most cases. However, for the cross-coupling of **31a** with **32b**, better yields were obtained using 2 mol-% $Pd(OAc)_2$/4 mol-% SPhos, see: N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916; b) Y. Yang, N. J. Oldenhius, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013,** *52*, 615.



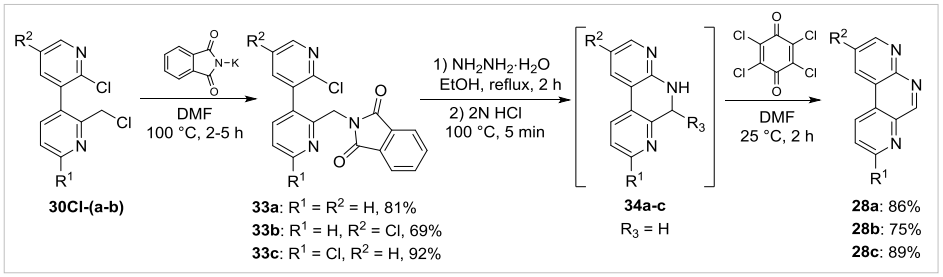
Scheme 30: *Negishi* cross-coupling employed in the synthesis of the bis-pyridines **30a**–**c**.

For the introduction of an amino function, the 2-methyl substituent was first converted into a chloromethyl group (Scheme 31). Isocyanuric acid promoted chlorination did not proceed in the case of electron-poorer bispyridine **30c** and hence lithiation with LDA, followed by trapping with TMSCl was performed to generate intermediate **30c-TMS**, which was chlorinated by *Fraser*'s method.[200]



Scheme 31: Chlorination of the picolyl derivatives **30a**–**c** leading to picolyl chlorides **30(a–c)-Cl**.

Gabriel reaction[201] using potassium phthalimide (DMF, 100 °C, 2–5 h) provided the phthalimides (**33a–c**) in 69–92% yield. Deprotection of the phthalimides (**33a–c**) using hydrazine hydrate in ethanol gave aminomethyl intermediates of type **29**, which underwent a spontaneous ring closure under the reaction conditions, providing the dihydrotriazaphenanthrenes (**34a–c**).



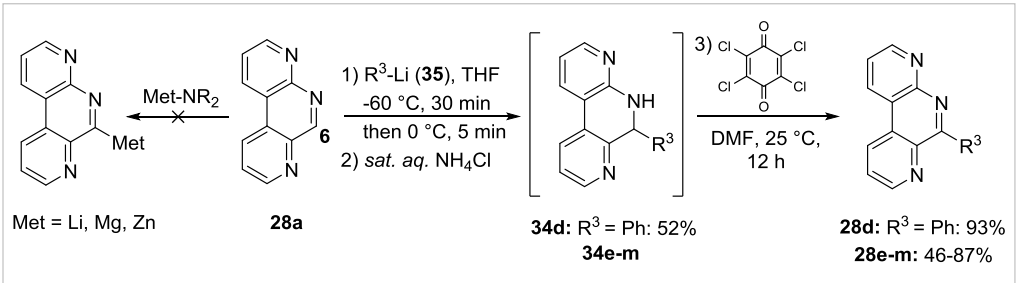
Scheme 32: *Gabriel* synthesis, cyclisation and oxidation leading to the azaphenanthrenes **28a**–**c**.

Treatment with chloranil in DMF (25 °C, 2 h) led to the aromatized target molecules (**28a–c**) in 75–89% yield (Scheme 32).

[200] For the chlorination using trichloroisocyanuric acid: a) G. E. Jeromin, W. Orth, B. Rapp, W. Weiß, *Chem. Ber.* **1987**, *120*, 649; b) U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 384; For the sequence of lithiation-silylation-chlorination, see: c) C. L. Fraser, N. R. Anastasi, J. J. S. Lamba, *J. Org. Chem.* **1997**, *62*, 9314; d) S. A. Savage, A. P. Smith, C. L. Fraser, *J. Org. Chem.* **1998**, *63*, 10048.
[201] U. Ragnarsson, L. Grehn, *Acc. Chem. Res.* **1991**, *24*, 285.

4.3 Functionalization of Triazaphenanthrenes with Organolithium Reagents at the 6 Position

With the synthesis of these new *N*-heterocycles established, their functionalization was studied. The appendages of the peripheral rings are in principle set by the choice of starting materials as realized with the products **28b**–**c**. However, using this approach for the introduction of a substituent at the C6 position could be challenging considering the additional sterical crowding in the *Negishi* coupling and *Gabriel* synthesis (compare Scheme 30 and Scheme 32). Instead, a metalation of the C6 position seemed to offer a plausible method to further functionalize triazaphenanthrenes **28**. However, various attempts of metalations of **28a** with TMP-bases (TMPLi, $TMP_2Mg{\cdot}2LiCl$, TMPMgCl·LiCl, $TMP_2Zn{\cdot}2LiCl$, TMPZnCl·LiCl[98]), even in the presence of $BF_3{\cdot}OEt_2$,[202] and under continuous flow conditions led either to complex mixtures or recovery of starting material. Attempted direct additions of organomagnesium compounds gave similar results. However, the treatment of **28a** with the more nucleophilic organolithium reagents **35**[203] at −60 °C for 0.5 h led to addition at the C6 position. The product **34d** resulting from addition of PhLi (**35a**) could be isolated in modest yield (Scheme 33). If the crude addition product was directly subjected to rearomatization with chloranil (DMF, 25 °C), the C6-functionalized triazaphenanthrene **28d** was obtained in 93% yield after chromatographical purification. The scope of this addition-oxidation sequence was subsequently investigated (Table 13).



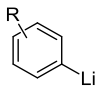
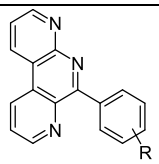
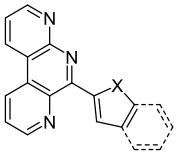
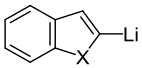
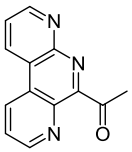
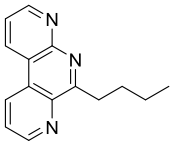
Scheme 33: Functionalization of azaphenanthrene **28a** by addition of organolithium reagents (**35**) and oxidation leading to C6-functionalized azaphenanthrenes **28d**–**m**.

Thus, a range of aryllithium reagents bearing electron-donating (**35b**) and withdrawing groups (**35c**–**d**) reacted well with **28a**, leading to the azaphenanthrenes **28e**–**g** in 62–87% yields after rearomatization (Table 13, entries 1–3). Also, heterocyclic lithium derivatives smoothly added to the pyridonaphthyridine **28a**. Thus, 2-lithiofuran (**35e**), 2-lithiothiophene (**35f**), as well as 2-lithiobenzofuran (**35g**) and 2-lithiobenzothiophene (**35h**), led to azaphenanthrenes **28h**–**k** in 46–80% yield (entries 4–7). Interestingly, 1-lithio-1-ethoxyethene[204] (**35i**) reacted well with **28a** under these reaction conditions, and the keto-azaphenanthrene derivative **28l** was obtained in 90% yield after mild acidic workup and purification (entry 8). Surprisingly, also the alkyllithium reagent

[202] a) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451; b) Q. Chen, X. Mollat d. Jourdin, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 4958.
[203] See chapter 3.
[204] J. E. Baldwin, G. A. Hoefle, O. W. Jr. Lever, *J. Am. Chem. Soc.* **1974**, *96*, 7126.

^{n}BuLi (**35j**) underwent selective C6 addition to the azaphenanthrene core without concurrent metalation, affording the butyl-substituted azaphenanthrene **28m** in 76% yield (entry 9).

Table 13: Functionalization of azaphenanthrene (**28a**) with organolithium reagents of type **35** leading to substituted pyridonaphthyridines (**28e**–**m**).

Entry	Organolithium reagent	Product/Yield[a]
		
1	**35b**: R = 4-OMe	**28e**: R = 4-OMe, 87%
2	**35c**: R = 4-CF_3	**28f**: R = 4-CF_3, 68%
3	**35d**: R = 3-F	**28g**: R = 3-F, 62%
		
4	**35e**: X = O	**28h**: X = O, 80%
5	**35f**: X = S	**28i**: X = S, 46%
		
6	**35g**: X = O	**28j**: X = O, 70%
7	**35h**: X = S	**28k**: X = S, 68%
		
8	**35i**	**28l**: 90%
	^{n}BuLi	
9	**35j**	**28m**: 76%

[a] Isolated yields on a 0.1 mmol scale after purification by flash column chromatography.

Alkinyllithium however reagents did not give the desired products, and starting material was recovered. The high selectivity for C6 addition can tentatively be ascribed to a precoordination of the organolithiums by the N6 nitrogen. Overall it is noteworthy that the described method allows a functionalization of the azaphenantrene heterocycle by forming new C-C bonds without transition-metal catalysis. Such procedures are of general interest, because even small transition metal contaminations can pose serious challenges to synthetic applications (*e.g.* < 10–0.1 ppm Pd in pharmaceuticals),[209d,e] especially when well-coordinating aza-heterocyclic moieties are present in the products.[209]

4.4 Spectroscopic Characterization of the New Triazaphenanthrenes[205]

It was noted that depending on the substituent the color of the new pyridonaphthyridines ranges from almost colorless (**28a**, **28d**) to intense yellow (**28k**). As the observable optical transitions allow for insights into the electronic structure and are of key importance for a potential application of the newly synthesized materials as dyes or molecular semiconductors, we analyzed the optical properties using steady-state and time-resolved spectroscopic methods. The UV-Vis spectra of **28a**, **28d** and **28h**–**k** exhibit a distinct vibrational fine structure with a double-peak close to the absorption edge (Figure 8 and Experimental part). These spectral features are sharpest for the particularly rigid molecules **28a**, **28h** and **28j** and appear more broadened for the thiophene-containing compounds **28i** and **28k**. The overall shape of the spectra close to the absorption edge, however, is very similar among all six compounds, indicating a similar electronic structure close to the frontier molecular orbitals. While the bare azaphenanthrene **28a** absorbs light only at wavelengths below 350 nm, the absorption onset of the substituted pyridonaphthyridines is red-shifted as the conjugated π-system is extended.

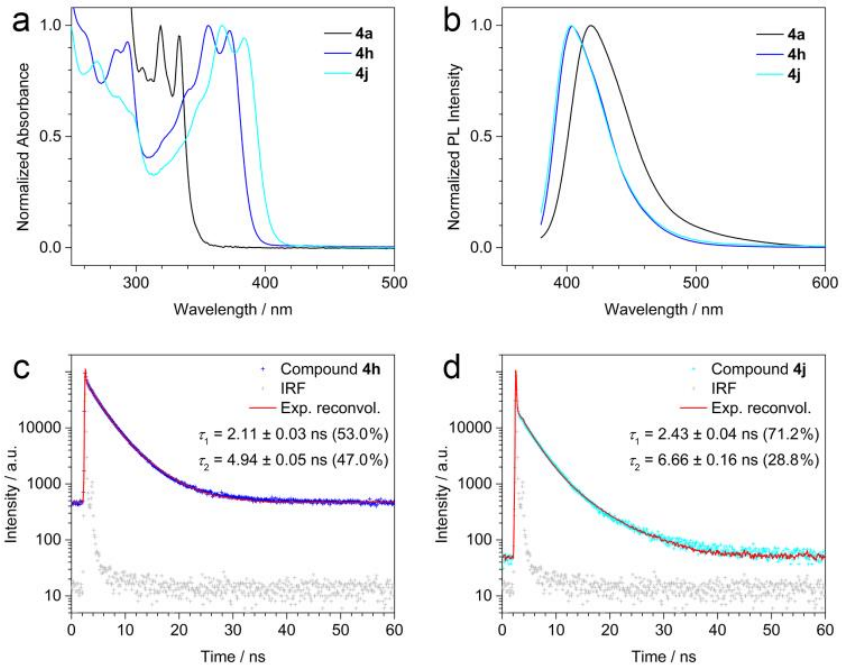


Figure 8: **a**) Optical absorption spectra of the parent azaphenanthrene **28a** and the furan- and benzofuran-substituted compounds **28h** and **28j** (termed **4a**, **4h** and **4j** in the figure). For clarity, the spectra were normalized to the low-energy double peak absorption feature. (**b**) The corresponding photoluminescence (PL) spectra measured with 300 nm (**28a**) and 365 nm excitation (**28h, j**). (**c**), (**d**) Time-correlated single photon counting (TCSPC) traces of **28h** and **28j**, respectively. The instrument response function is displayed in grey.

Upon photoexcitation with UV light the compounds emit strongly in the 400–450 nm range (**Figure 8** and Supporting Information of the respective publication). While the emission maximum seems almost not affected by the selection of the substituent, the photoluminescence quantum yield (PLQY)

[205] The spectroscopic measurements, characterization and interpretation of these compounds was performed by F.C. Hanusch, S. Reuter, T. Bein, and F. Auras. The results are reproduced here for the sake of completeness. Further details of the characterizations and spectra are found in the Supporting Information of the corresponding publication.

reveals differences between the differently substituted compounds. The highest PLQY of 23% was observed for **28d**. Also, the furan-containing **28h** and **28j** exhibit decent quantum yields of above 10%, whereas the thiophene-based analogues **28i** and **28k** show only moderate PLQYs. Systematically lower quantum yields for sulfur-containing heterocycles compared to their oxygen analogues have also been observed for quinoxaline derivatives.[206] These differences might result from a competing non-radiative deactivation mechanism that is more pronounced for the sulfur-containing heterocycles. In order to analyze these differences in more detail, we studied the PL decay of the furan- and thiophene-containing compounds via time-correlated single photon counting (TCSPC) experiments. All four materials exhibit bi-exponential decay curves with the lifetimes being significantly longer for the furan compounds. In particular, the shorter-lived decay component τ_1 was found to be about doubled compared to the thiophene analogues. This observation further supports the existence of a competing decay mechanism that is more dominant for the thiophene compounds.

[206] J. Nafe, S. Herbert, F. Auras, K. Karaghiosoff, T. Bein, P. Knochel, *Chem. Eur. J.* **2015**, *21*, 1102.

5 Mild Chlorohomologation and Bischloromethylation of Esters *via* Continuous Flow Chloroacetate Claisen Reactions

5.1 Introduction[207]

Mono- and bis- α-chloro ketones are characterized by their two distinct, mutually enhanced electrophilic sites (C-Cl and C=O; compare **36**, X = Cl and **37**, X = H, Scheme 34), which accounts for their widespread use, particularly in cyclocondensations leading to heterocycles.[208] Such cyclizations of functionalized precursors are cost-economic and avoid challenging cross-coupling steps and transition metal purging,[209] thus making novel approaches to pre-functionalized α-chloro ketones **36** and **37** an attractive goal. A common access to α-halo ketones is the halogenation of ketones,[210] which especially on scale requires dealing with challenging waste streams, toxic reagents and corrosivity (Route A, Scheme 34).[211] Furthermore, such halogenations are known to suffer from low regioselectivity of chlorination, potential multiple chlorination, and incompatibilities with several common functionalities.[210,212] In contrast, the acylation of lithium carbenoids allows avoiding the issue of site-selectivity *a priori* and enables performing mono- or bis-chlorination *at will* (Route B). Based on the pioneering work of *Köbrich* and *Villieras*, recent research in lithium carbenoid

[207] The compounds **36e**–**f**, **37h**, **n**–**m** and **40a**, **c**, **g**, **k** were synthesized by Dr. M. V. Ivanova under guidance of M. A. Ganiek according to the optimized conditions. The compounds are shown here for the sake of completeness. Analytical data is found in the Supporting Information of the corresponding publication.

[208] a) N. D. Kimpe, R. Verhe, in: *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*, (Eds.: S. Patai and Z. Rappoport), Wiley, Chichester, **1988**; b) A. W. Erian, S. M. Sherif, H. M. Gaber, *Molecules* **2003**, *8*, 793; c) *Name Reactions in Heterocyclic Chemistry*; J. J. Li, E. J. Corey, (Eds.); John Wiley & Sons: Hoboken, **2005**.

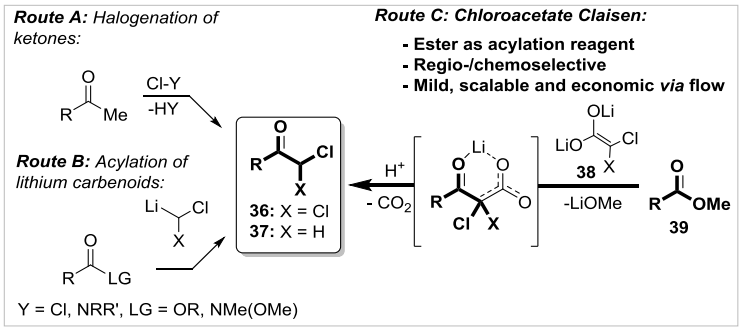
[209] a) C. Valente, S. Calimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314; *Angew. Chem.* **2012**, *124*, 3370; b) M. A. Düfert, K. L. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 12877; c) M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287; For an example of purging metal impurities: d) J. Recho, R. J. G. Black, C. North, J. E. Ward, R. D. Wilkes, *Org. Process Res. Dev.* **2014**, *18*, 626; e) K. K. Hii, K. Hellgardt: *Catalysis in Flow: Why Leaching Matters*. In: *Organometallic Flow Chemistry. Topics in Organometallic Chemistry*, (Ed.: T. Noël), Springer, Cham, **2015,** 249-262.

[210] Typical halogenation conditions: a) R. R. Fraser, F. Kong, *Synth. Commun.* **1988**, *18*, 1071; b) Z. Chen, B. Zhou, H. Cai, W. Zhu, X. Zou, *Green Chem.* **2009**, *11*, 275; c) Z. S. Zhoua, L. Li, X. H. He, *Chin. Chem. Lett.* **2012** *23*, 1213; d) R. Prebil, S. Stavber, *Adv. Synth. Catal.* **2014**, *356*, 1266 and sources therein; For other approaches, see: d) Y. Wang, G. L. V. Damu, J. Lv, R. Geng, D. Yang, C. Zhou *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 5363; e) M. A. Romero-Reyes, I. Zaragoza-Galicia, H. F. Olivo, M. Romero-Ortega, *J. Org. Chem.* **2016**, *81*, 9515; f) R. D. C. Gallo, A. Ahmad, G. Metzker, A. C. B. Burtoloso, *Chem. Eur. J.* **2017**, *23*, 16980.

[211] For a thorough discussion of E-factors in related aromatic halogenation, see: a) K. Smith, G, A. El-Hiti, *Green Chem.*, **2011**, *13*, 1579; The hazardous and unselective nature of halogenation reactions has prompted the development of suitable flow-protocols: b) R. Becker, S. A. M. W. van den Broek, P. J. Nieuwland, K. Koch, F. P. J. T. Rutje, *J. Flow Chem.* **2012**, *2*, 87; c) V. D. Pinho, B. Gutmann, L. S. M. Miranda, R. O. M. A. de Souza, C. O. Kappe, *J. Org. Chem.* **2014**, *79*, 155; d) 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; e) D. Cantillo, and C. O.Kappe, *React. Chem. Eng.*, **2017**, *2*, 7.

[212] For the instability of N-,O-,S- benzylic, dithiane, allylic and other groups under various halogenating conditions, see: a) Peter G. M. Wuts, Theodora W. Greene, *Greene's Protective Groups in Organic Synthesis*, Fourth Edition, John Wiley & Sons: Hoboken, NJ, **2006**; For alkene and alkyne halogenation, see: b) A. Palisse, S. F. Kirsch, *Org. Biomol. Chem.*, **2012**, *10*, 804; c) A. J. Cresswell, S. T.-C. Eey, S. E. Denmark, *Angew.Chem. Int. Ed.* **2015**, *54*, 15642.

chemistry has further demonstrated the possibilities of such an approach.[213] Due to the thermal instability of the involved lithium carbenoid species,[213a] several flow protocols were devised to enhance the scalability and practicality of halomethyl lithium chemistry.[214]



Scheme 34: Different routes towards bis-*α*,*α*'-chloroketones (**36**, X = Cl) and *α*-chloroketones (**37**, X = H).

However, several drawbacks of Route B will remain: (i) halomethyl lithium reagents are incompatible with a number of electrophilic functionalities; (ii) the availability of pro-nucleophiles like CH_2ClBr is increasingly restricted due to environmental legislation;[215] (iii) monohalo-homologation leading to chloroketones **37** usually requires the use of special acylating agents such as *Weinreb* amides to avoid overaddition.[213b,e,g] From a standpoint of maximizing functional group-tolerance, minimizing environmental impact and using broadly available starting materials, a chloroacetate *Claisen* ester homologation (**CAC**, Route C) would provide an attractive alternative.[216] In this *Claisen*-type chloromethylation, chloroacid lithium dianions **38** undergo acylation with esters **39**. The resulting primary addition product liberates CO_2 after the workup and thereby excludes over-addition to, or enolisation of, ketones **36** and **37**, which are well-known challenges in Route B.[213b, 214b] However, an inspection of the scarce literature on **CAC** reactions suggests the use of excess amounts of nucleophilic reagent (up to 4 equiv.) at cryogenic conditions (−78 °C for several hours), likely due to the limited thermal stability of the lithium acetate dianions and due to the high exothermy of the

[213] a) G. Köbrich, *Angew. Chem. Int. Ed.* **1972**, *11*, 473 and references therein; b) P. Entmayr, G. Köbrich, *Chem. Ber.* **1976**, *109*, 2175; c) J. Villieras, M. Rambaud, R. Tarhouni, B. Kirschleger, *Synthesis* **1981**, 68; *Tetrahedron Lett.* **1984**, *25*, 835; d) C. J. Kowalski, M. S. Haque, *J. Org. Chem.* **1985**, *50*, 5140; e) V. Pace, L. Castoldi, S. Monticelli, M. Rui, S. Collin *Synlett* **2017**, *28*, 879 and references therein; f) G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace, R. Luisi, *J. Am. Chem. Soc.* **2017**, *139*, 13648; g) L. Castoldi, W. Holzer, T. Langer, V. Pace, *Chem. Commun.* **2017**, *53*, 9498; h) V. Pace, L. Castoldi, E. Mazzeo, M. Rui, T. Langer, W. Holzer, *Angew.Chem. Int. Ed*. **2017**, *56*, 12677.

[214] a) A. Nagaki, S. Tokuoka, S. Yamada, Y. Tomida, K. Oshiro, H. Amii, J. Yoshida, *Org. Biomol. Chem.* **2011**, *9*, 7559; b) J. Hartwig, J. B. Metternich, N. Nikbin, A. Kirschning, S. V. Ley, *Org. Biomol. Chem.* **2014**, *12*, 3611; c) L. Degennaro, F. Fanelli, A. Giovine, R. Luisi, *Adv. Synth. Catal.* **2015**, *357*, 21; d) A. Hafner, V. Mancino, M. Meisenbach, B. Schenkel, J. Sedelmeier, *Org. Lett.* **2017**, *19*, 786.

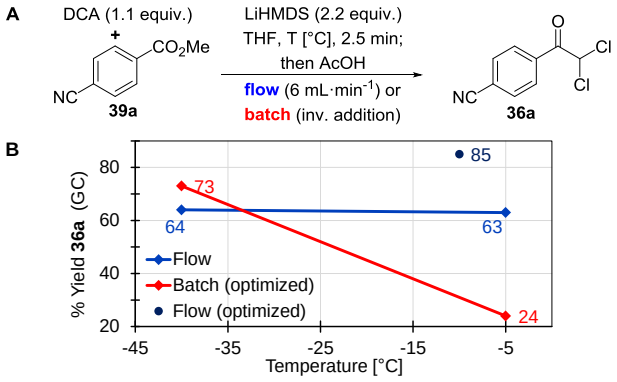
[215] G. J. M. Velders, A. R. Ravishankara, M. K. Miller, M. J. Molina, J. Alcamo, J. S. Daniel, D. W. Fahey, S. A. Montzka, S. Reimann, *Science* **2012**, *335*, 922.

[216] The chloroacid pro-nucleophiles are accessible on large scale without restrictions and esters are regarded as ubiquitous feedstock starting materials: L. Guo, A. Chatupheeraphat, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 11810. The non-carbenoid nature of the employed nucleophile provides enhanced thermal stability and a moderate nucleophilicity, see: a) J. Villieras, *J. Organomet. Chem.*, **1972**, *34*, 209.

involved *Brønsted* acid-base reactions.[217] Furthermore, despite the above mentioned potential, compatibility with sensitive functional groups or an extension beyond mono-chloro ketones **37** was not yet demonstrated. Aware of previous reports on enolate chemistry in continuous flow[218] and the special challenges presented by chloroacetate dianion enolates, a continuous flow **CAC** chloromethylation was envisioned. By improved handling of exothermic reactions and unstable intermediates at short and reproducible residence times, convenient conditions should be obtained.

5.2 Chloromethylation of Functionalized Aromatic Esters

Preliminary batch experiments showed that methyl 4-cyano benzoate (**39a**) readily undergoes a **CAC** reaction with dichloroacetic acid (DCA) and LiHMDS, leading to chloroketone **36a** after quenching with AcOH (Scheme 35A). This not only confirmed the potential of Route C in tolerating a cyano moiety but also gave access to dichloroketones for the first time *via* this route. Careful optimization of this model reaction identified temperature, reagent stoichiometry, quenching and the mode of addition as decisive reaction parameters, providing **36a** in a maximum GC-yield of 73% in batch (Scheme 35B, red data points).[219]



Scheme 35: Performance comparison of flow and batch reactors in the dichloromethylation of methyl 4-cyano benzoate (**39a**).

Interestingly, the yield in this batch reaction dropped significantly, if temperatures above −40 °C were applied, which is likely due to the limited heat removal capacity of the batch reactor.[220]In contrast, by

[217] a) C. R. Johnson, T. R. Bad, *J. Org. Chem*. **1982**, *47*, 1205; b) P. Coutrot, A. El Gadi, *Synthesis*, **1982**, 115; c) X. Wang, J. K. Thottathil, R.P. Polniaszek, *Synlett* **2000**, *6*, 90; d) K. C. Fortner, M. D. Shair, *J. Am. Chem. Soc.* **2007**, *129*, 1032; e) I. N. Houpis, R. Liu, L. Liu, Y. Wang, N. Z Dong, X. Zhao, Y. Zhang, T. Xiao, Y. Wang, D. Depre, U. Nettekoven, M. Vogel, R. Wilson, S. Collier, *Adv. Synth. Catal.* **2013**, *355*, 1829. For related lithium enolates of α-heterosubstituted acid derviatives, see: a) S. Oda, H. Yamamoto, *Org. Lett.* **2013**, *15*, 6030; b) K. Yu, P. Lu, J. J. Jackson, T.-A. D. Nguyen, J. Alvarado, C. E. Stivala, Y. Ma, K. A. Mack, T. W. Hayton, D. B. Collum, A. Zakarian, *J. Am. Chem. Soc.* **2017**, *139*, 527.

[218] a) D. Leonardo, C. Claudia, D. A. Sonia, L. Renzo, *J. Flow Chem*. **2016**, *6*, 136; b) T. von Keutz, F. J. Strauss, D. Cantillo, C. O. Kappe, Tetrahedron **2018**, *74*, 3113.

[219] See the Experimental part for screening details.

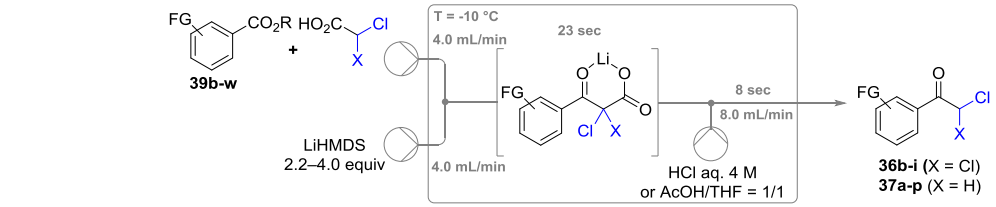
[220] T. Noël, Y. Su, V. Hessel, *Beyond Organometallic Flow Chemistry: The Principles Behind the Use of Continuous-Flow Reactors for Synthesis*, in: *Organometallic Flow Chemistry. Topics in Organometallic Chemistry*, (Ed.: T. Noël) Springer, Cham, **2015**, 14-19.

transferring the reaction to a 3-pump flow setup with in-line acidic quench the yield of **36a** did not change at either −40 °C or −5 °C (2.5 min residence time), underlining the superior handling under flow conditions.[221] Shortening of the residence time to 23 sec and increasing the total flowrate to 16 $mL \cdot min^{-1}$ improved the performance further, likely accounted for by a minimal thermal decomposition of the *in situ* generated dianion nucleophile of type **38** at −10 °C under flow conditions (85% GC-yield **36a**, 81% isolated; Scheme 38B, blue data points).

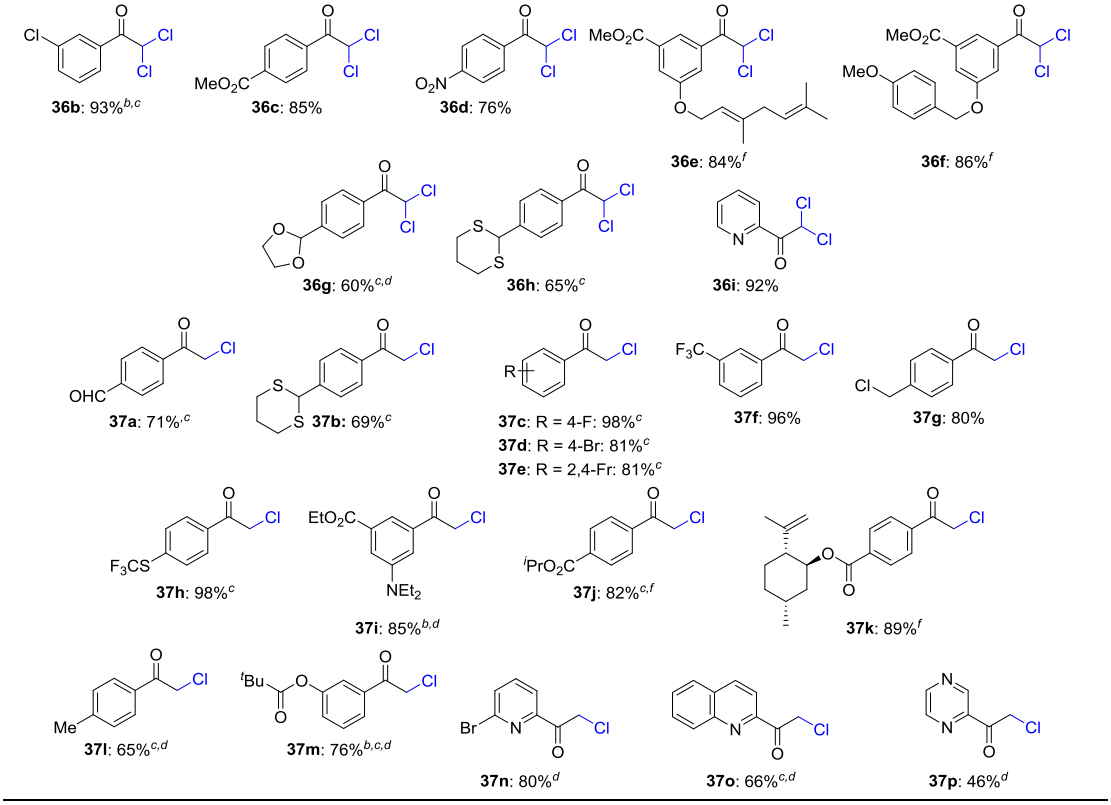
Under these optimized conditions, other benzoic esters with various functional groups were tested to probe the chemoselectivity of the flow **CAC** reaction protocol (Table 14). Ethyl esters can be employed without restrictions, yielding for example the dichloroketone **36b** in excellent 93% yield. Furthermore, various sensitive electrophilic functional groups like an additional ester or a nitro group remained untouched under the optimized reaction conditions and gave dichloroketones **36c**−**d** in good yields after reaction with 1.1 equiv. dianion (76−85%). Pleasingly, also functional groups, which are reactive under halogenation conditions such as allyl ethers, benzyl ethers and ketals[222], are tolerated, giving the expected products **36e**−**g** in 60−86% yield. Furthermore, the dithiane bis-chloroketone **36h** was obtained in 65% yield**.** Notably, a dithiane moiety in **36h** is reactive under both strongly basic and oxidative conditions. Finally, also an isopicolinate posed no challenge for bischloromethylation after switching to an AcOH quench (**36i**, 92%). The same reaction condition could be equally applied to the synthesis of mono-chloroketones **37** using CA instead of DCA: By choosing additionally the HCl_{aq} quench protocol, the aldehyde bearing mono-chloroketone **37k** was obtained in 71% yield. Similarly, dithiane mono-chloroketone **37a** was obtained in almost identical yields to its bis-chloro congener (65%). Additionally a range of *o*-, *m*,- and *p*-halogenated mono-chloroacetophenones and related CF_3-, SCF_3-, and CH_2Cl- bearing chloroketones **37c**−**h** were obtained in excellent yields, confirming the tolerance of useful aryl halogenide moieties and the low acidity of LiHMDS and reagent **4**. Interestingly, the *in situ* formed dianions **38** exhibited an unparalleled ability to undergo selective mono-addition to symmetrical or sterically biased diesters, furnishing the expected mono-homologated products **36c** and **37i**−**k** in 82−89% yield with excellent selectivity. Electron-rich benzoic esters required the use of > 1.0 equiv. of dianion **38** to furnish the desired products **37l**−**m** in satisfying yields of 60−71%. Finally, a bromopyridine-, a quinoline- and a pyrazine-ester successfully underwent chlorohomologation, furnishing the heterocyclic products **37n**−**p** in 46−80% yield. Notably, electron poor azine derivatives were previously not reported in acylations using lithium carbenoids.[213,214]

[221] The controlled quench in the flow setup also eliminated previously observed fluctuations of the yield.
[222] L. C. Anderson, H. W. Pinnick, *J. Org. Chem.*, **1978**, *43*, 3417.

Table 14: Continuous flow chloromethylation of aromatic esters **39b**–**w**, leading to bis-*α*-chloroketones **36b**–**k** or mono-chloroketones **37a**–**n**.



FG = functional group; R = Me, Et; 0.8 mm i.d. tubing and 0.5 mm i.d. T-pieces.



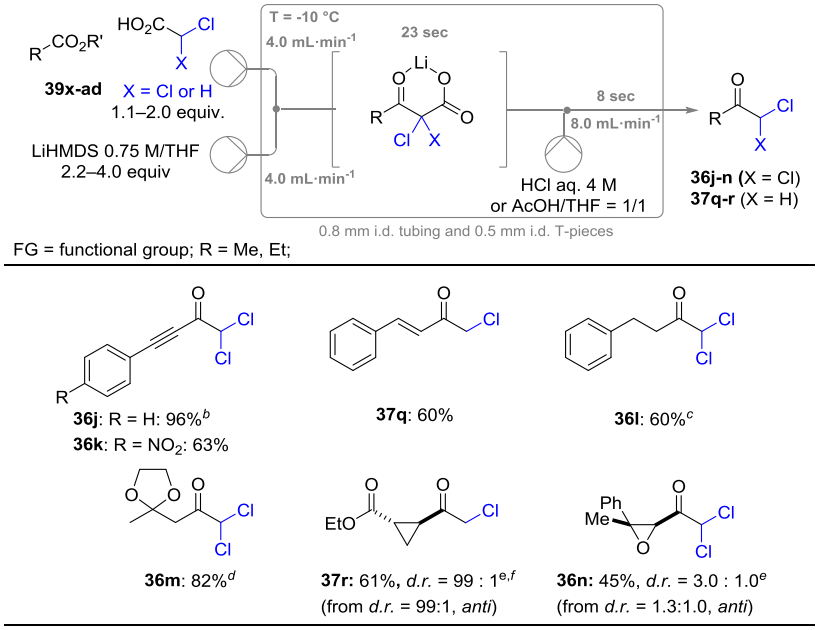
[a] Isolated yield of analytically pure compound. 1.1 equiv. dianion and aqueous HCl were used if not stated otherwise.[b] The ethyl ester was used.[c] 2.0–2.4 equiv. dianion were used for chloromethylation.[d] A solution of AcOH/THF = 1/1 (v/v) was used for quenching.[e] 3% of bis-chlorohomologation product was formed. [f] No bis-chloromethylation detected.

5.3 Chloromethylation of Non-Aromatic Esters

In order to further explore the scope of flow **CAC** reactions, various representative non-aromatic esters were subjected to the established reaction conditions (Table 15). Thus, propriolates were smoothly bis-chloromethylated under standard conditions in 63–96% yield (**36j**–**k**). Likewise, a cinnamic ester and aliphatic benzyl ester underwent mono- or bis-chloromethylation in 60% yield in the presence of excess reagent (**37q**, **36l**), confirming the possibility for unsaturated and aliphatic esters to undergo a **CAC** reaction. Aliphatic ketal product **36m** is of special interest, due to the fact that halogenations of 1,3-dicarbonyls and related compounds exclusively lead to methylene-

halogenated products,[223] while a **CAC** gives rise to the "peripheral" chloroketone **36m** in 82% yield. Due to the prevalence of cyclopropanes in drug molecules,[224] a *trans*-diester was subjected to chlorohomologation, furnishing the desymmetrized, stereoisomerically pure cyclopropanoate **37r** in 61% yield. A related reaction with an ethyl glycidate (*d.r.* = 1.3:1.0, *trans*) gave diastereochemically enriched *trans*-bischloroketone **36n** (*d.r.* = 3.0:1.0) in 45% yield, indicating a concomitant isomerization *e.g. via* ring-metalation. Concludingly, a broad structural and functional variety is tolerated by the flow CAC protocol. Overall, the demonstrated method fills a methodological gap between the oxidative conditions of halogenations and the harsh conditions presented by lithium carbenoid nucleophiles.

Table 15: Continuous flow **CAC** of non-aromatic esters **39x**–**ad**, leading to mono- or bis-*α*-chloroketones **36j**–**n** and **37q**–**r**, respectively.



[a] Isolated yield of analytically pure compound. 1.5–2.4 equiv. dianion and aqueous HCl were used if not stated otherwise. [b] 1.1 equiv. dianion were used. [c] The benzyl ester was used. [d] A solution of AcOH/THF = 1/1 (v/v) was used for quenching. [e] The ethyl ester was used. [f] No bis-homologation detected.

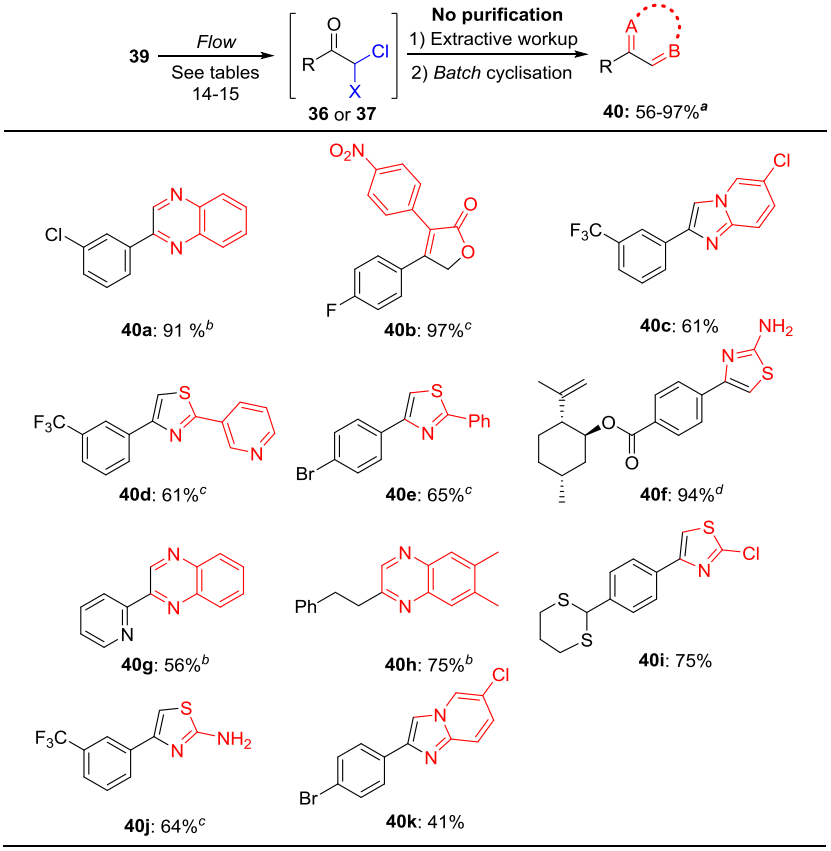
5.4 Post-Functionalizations of Chloroketones with Heteronucleophiles Leading to Heterocycles

It was found, that **CAC** crude reaction products typically display a clean profile in ^{1}H-NMR and gas chromatography, which was utilized in subsequent cyclocondensation reactions with the reaction crudes after only a simple extractive workup (Table 16, yields with respect to the initial ester). Using

[223] Methylene ("internal") halogenation is even observed when one carbonyl of an 1,3dicarbonyl is acetal-protected: C. Daubié, C. Bacquet-Einhorn, D. Lelandais, *Can. J. Chem.* **1984**, *62*, 1548.
[224] S. J. Chawner, M. J. Cases-Thomas, J. A. Bull, *Eur. J. Org. Chem.* **2017**, 5015.

this telescoped protocol, pharmaceutically relevant heterocyclic compounds[225] which are nitrogen- and heteroatom-rich (**40d, f**–**g**, **j**), display advantageous halogenation for further manipulations (**40c**; **e**, **i**, **k**) or contain acidic protons (**40b**, **f**, **j**) were obtained in good to excellent yields (41–94%) over two steps. Notably, none of the bonds constituent of these products was forged by means of transition metal catalysis. Especially the cyclization precursors **37a**, **k** and **36l**, which are challenging to obtain without the **CAC** method, were successfully transformed to **40f**, and **40h**–**i** in 75–94% yield, respectively.

Table 16: Utilization of functionalized chloroketones **36** or **37** obtained as crude products (except **37i**, purified) from flow **CAC** reaction in subsequent cyclisation reactions leading to heterocycles **40**.



[a] Isolated yield with respect to ester starting material. See the Experimental part for full reaction details.[b] The bischloride was used.[c] The monochloride was used.[d] The monochloride was used after column chromatography.

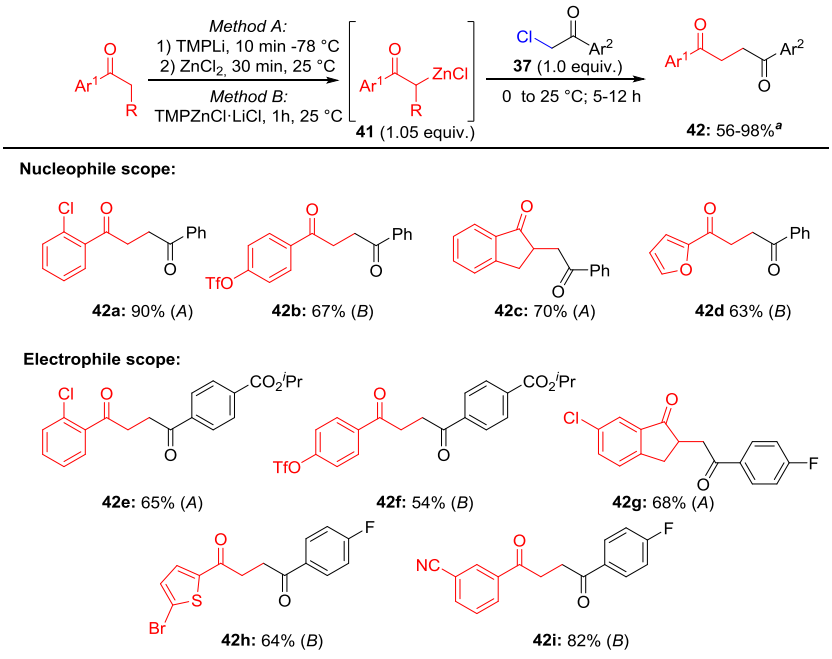
5.5 Post-Functionalizations of Chloroketones with Carbon-Nucleophiles

Attempting to use chloroketones **36** and **37** as cross-coupling electrophiles revealed that these chloroketones are challenging to use in the presence of organometallic species and common catalytically active metals such as Ni, Pd or Cu. Hence, oxidative homocoupling of organozinc

[225] a) A. Ayati, S. Emami, A. Asadipour, A. Shafiee, A. Foroumadi, *Eur. J. Med. Chem*. **2015**, *97*, 699; d) A. C. Pinheiro, T. C. Mendonça Nogueira, M.V.N. de Souza, *Anti-Cancer Agent Me*, **2016**, *16*, 1339; b) M. T. Chhabria, S. Patel, P. Modi, P. S. Brahmkshatriya, *Curr Top Med Chem*. **2016**, *16*, 2841; c) A. Deep, R. K. Bhatia, R. Kaur, S. Kumar, U. K. Jain, H. Singh, S. Batra, D. Kaushik, P. K. Deb, *Curr Top Med Chem*. **2017**, *17*, 238; d) P. A. Jackson, J. C. Widen, D. A. Harki, K. M. Brummond, *J. Med Chem.* **2017**, *60*, 839.

reagents typically accounted for the formation of the major products in presence of chloroketones. This problem has been observed and partly solved in prior reports of related cross-couplings, especially if secondary chloroketones were used.[226] In the course of this work, it was found, that acetophenone-derived zinc enolates of type **41** selectively underwent chloride substitution in the absence of catalysts with primary chloroketones **37**, *i.e.* the products obtained by **CAC** reaction (Table 17).[227] Thus, valuable 1,4-diketones **42** were accessed under mild conditions (25 °C, 5–12 h). An initial screening identified zinc enolates derived from either electron-rich and -poor acetophenones and furanyl actate as suited electrophiles, furnishing asymmetic diketones **42a–d** in 63–90% yield with chloroacetophenone. Zinc enolates with sensitive functionalities were obtained by using TMPZnCl·LiCl as base. Using either of the two methods, a variety of polyfunctional 1,4-diketones (**42e–i**) were further obtained in 54–82% yield using **CAC** reaction products **37c** and **37j**. As expected for zinc enolates, various functionalities like a nitrile, an ester, a triflate, and halogens are tolerated by this protocol. This method constitutes a straightforward and to date unexplored, transition-metal-free synthesis of important precursors to *Paal-Knorr* chemistry.[226d]

Table 17: Substitution reaction of chloroketones **37** with zinc enolates of type **41** leading to functionalized 1,4-diketones **42**.



[a] Isolated yield with respect to chloroketone. Reactions performed on a 0.5 mmol scale. Method indicated in brackets.

[226] a) N. M. Nevar, A. V. Kel'in, O. G. Kulinkovich, *Synthesis* **2000**, 1259; b) M. Yasuda, S. Tsuji, Y. Shigeyoshi, A. Baba, *J. Am. Chem. Soc.* **2002**, *124*, 7441; b) C. F. Malosh, J. M. Ready, *J. Am. Chem. Soc.* **2004**, *126*, 10240; c) L. Plístil, T. Solomek, J. Wirz, D. Heger, P. Klán, *J. Org. Chem.* **2006**, *71*, 8050; d) C. Liu, Y. Deng, J. Wang, Y. Yang, S. Tang, A. Lei, *Angew. Chem. Int. Ed.* **2011**, *50*, 7337; and references therein; e) X. Chen, X. Liu, J. T. Mohr, *J. Am. Chem. Soc.* **2016**, *138*, 6364.

[227] See Experimental part for reaction optimization of the reaction conditions.

6 Summary

Microflow setups offer enhanced residence time control, mixing, and heat transfer compared to batch chemistry. These features make them ideal for reactions employing unstable, highly reactive reagents. This work focused on applying these features of continuous flow setups to metalation, halogen-metal exchange and enolate chemistry. Additionally, the synthesis and derivatization of a novel heterocyclic scaffold by batch methods was described.

First, the metalation of acrylonitriles, acrylates and nitroolefins with TMPZnCl·LiCl and TMPMgCl·LiCl in continuous flow was investigated. For the metalation and subsequent in-line quenches of various substrates, conditions were achieved, which are hardly accessible with batch reactors. These special operation windows include intense mixing regimes as well as scale-independent high-temperature (> 60 °C) reactions above the boiling point of THF. Furthermore, a new subclass of acrylate starting materials was shown to undergo efficient metalation with TMPMgCl·LiCl. Finally, the scope of accessible furanones *via* metalation chemistry was exhaustively explored due to the biological relevance of this compound class.

Second, the lithiation of (thio)formamides by LDA in presence of electrophiles was revisited due to the relevance of nucleophilic amidation, which typically gives access to α-hydroxy and α-keto amides. While cryogenic conditions are usually applied in batch, the newly developed *Barbier* flow procedure proceeds at ambient temperature with economic reagent stoichiometries. The reaction was combined with the prior in-line generation of LDA at −10 °C. The favorization of formamide lithiation even in the presence of well-known C-H acids was systematically investigated with the aid of competition experiments, which allowed a placement of the lithiation enthalpy of diethylformamide among well-known C-H acids. The combination of these results with *ab initio* studies provided further insights regarding these difficult to characterize intermediates.

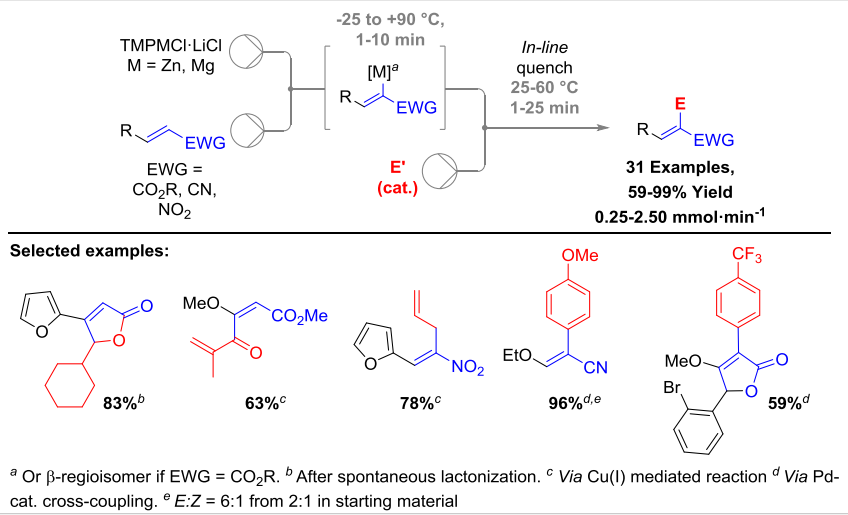
Furthermore, a novel *in situ* trapping halogen-lithium exchange was developed. This method combines the generality of halogen-lithium exchange with the functional group tolerance exhibited by organomagnesium-, zinc- and copper-compounds. Intense mixing flow conditions at temperatures up to 0 °C enabled the performance of this exchange/*in situ* transmetalation sequence, which furnished bis(hetero)aryl organometallics bearing highly sensitive moieties such as esters, ketones, isothiocyanates, azides and nitro groups. Quenching in semi-batch mode gave access to functionalized aryl and heteroaryl alcohols, ketones, biaryls, iodides and allylation products.

Finally, the last two methods describe transition-metal free syntheses for aryl-heteroaryl and heteroaryl-heteroaryl units. First, a simple batch method for regioselective addition of organolithium reagents to a novel fused *N*-heterocycle, followed by reoxidation, was described, which led to an array of modified triazaphenantrenes with varying optical properties. Second, the development of an ester chloromethylation to the corresponding mono- and bis-chloroketone derivatives was described. The reaction can be telescoped into subsequent cyclocondensations, furnishing aryl-heteroaryl products.

Handling the unstable dianions of chloroacids in continuous flow with improved control of exothermy, the mono- and bis-chloromethylations proceeded under practical conditions and thus offers an alternative to hazardous, unsustainable and less selective chloroketones synthesis routes.

6.1 Continuous Flow Magnesiation or Zincation of Acrylonitriles, Acrylates and Nitroolefins

A range of highly functionalized acrylates and related derivatives was obtained *via* metalations using TMPMgCl·LiCl or TMPZnCl·LiCl bases and subsequent in-line quenching reactions (Scheme 36). This method was expediently used for the generation of various 2(5*H*)-furanones by flow magnesiation of acrylates and subsequent reaction with aldehydes. Important principles in flow chemistry were demonstrated, such as (a) minimization of energy-intensive cooling due to fast trapping of reactive intermediates, (b) selectivity enhancement *via* improved mixing, (c) process-intensification due to efficient heat removal or input and (d) scalable heating above the boiling point of the solvent even on large scales.

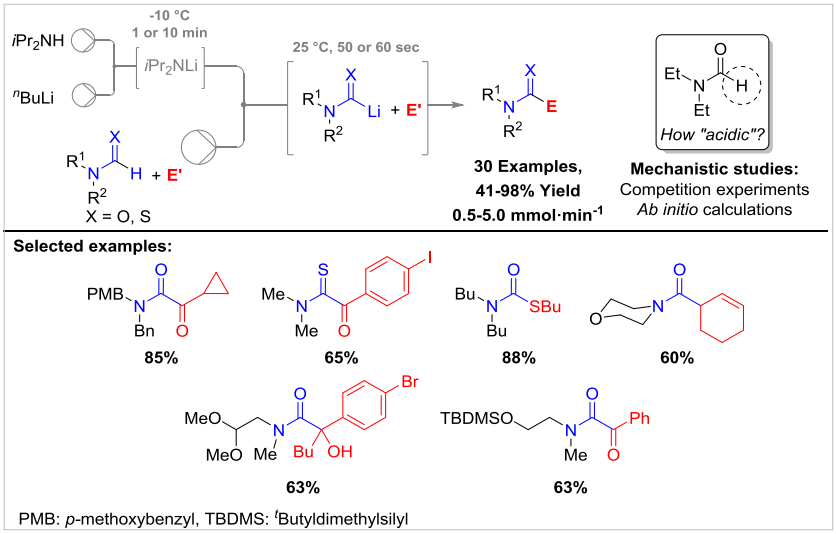


Scheme 36: Summary of continuous flow magnesiation or zincation of acrylonitriles, acrylates and nitroolefins.

6.2 Barbier Continuous Flow Preparation and Reactions of Carbamoyllithiums for Nucleophilic Amidation

A flow protocol for nucleophilic amidation and thioamidation *via* carbamoyllithium intermediates was developed (Scheme 37). Despite the unstable nature of the employed intermediates, practical and scalable reaction conditions could be demonstrated in a continuous flow setup (25 °C, 1 min; bench-stable, inexpensive starting materials). Hence the previously reported necessity of energy-consuming cryogenic temperatures in batch mode (−78 °C or −100 °C) were found to be obsolete. An in-line preparation of LDA was developed, which allows using exclusively bench stable reagent solutions and thus maintaining full scalabilty. Thus, scale-ups up to 35 mmol under unchanged experimental

conditions were demonstrated. Testing the functional group tolerance of this transformation further revealed the possibilities to tolerate protected carbonyls, haloarenes and a silyl ether, which provide appreciable functionalities for further derivatizations.



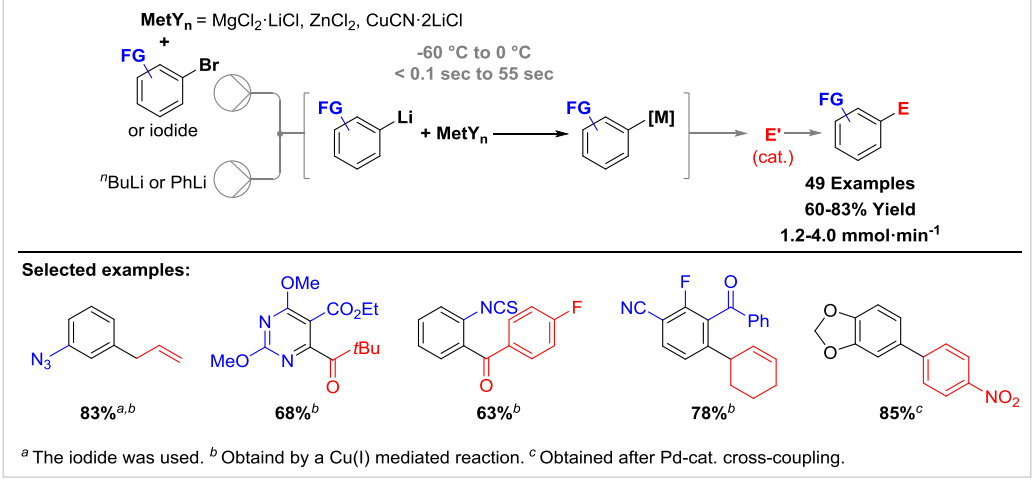
Scheme 37: Summary of *Barbier* continuous flow preparation and reactions of carbamoyllithiums for nucleophilic amidation.

Despite the presence of strong C-H acids during the reaction (*e.g.* aliphatic ketones) the formamides were always preferentially deprotonated leading to the "*carbamoyl-anion*" derived products. Competition experiments with diethylformamide under reaction conditions allowed putting the lithiation enthalpy of this formamide in relation to well-known C-H acids such as fluorobenzenes. The trend of the experimental results was confirmed by *ab initio* calculations, which gave further insight in the structures of the title compounds in solution. The reason for the preferential formamide deprotonation is thus kinetic in its nature, which can be attributed to the Lewis basicity of these compounds. The extension of the *Barbier* flow method to analog thioformamides was only possible after intensifying the mixing through high flowrates, which likely helped to eliminate mass-transfer limitations.

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

This project aimed at extending the functional group tolerance of lithium-halogen exchange, which is one of the most general entries to (hetero)aryl organometal compounds. Therefore the salt of a less electropositive metal (Mg, Zn, Cu) was premixed with aryl halide starting materials to allow an instant transmetalation after the fast halogen-lithium exchange. This leads to organometallic species that tolerate sensitive functionalities even at moderate temperatures. A flow setup was used to enable

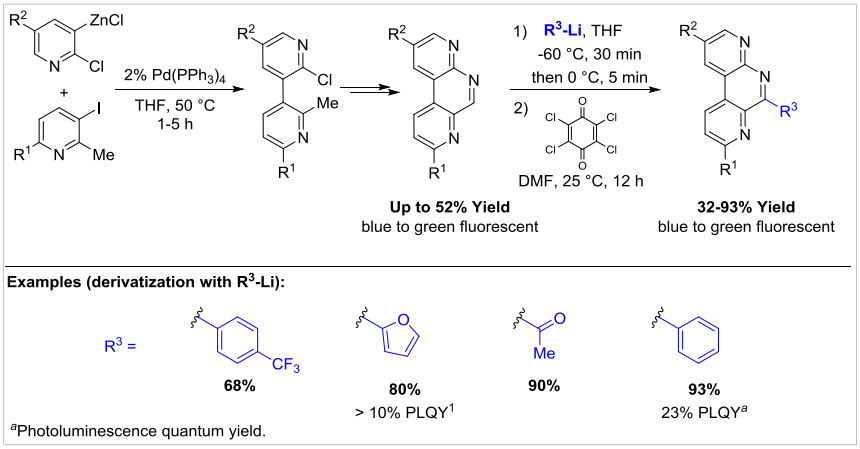
efficient mixing between exchange reagent and the substrate mixture thus allowing the described chemistry to proceed in a high-yielding fashion. The resulting diarylmagnesium or diarylzinc species were trapped with various electrophiles, furnishing the desired polyfunctional (hetero)arenes in high yields. It was demonstrated on scales up to 10 mmol, that this method enables the functionalization of aryl- and heteroaryl bromides and iodides containing highly sensitive groups such as isothiocyanate, nitro, azide, or ester groups using commercially available flow equipment. Notably, an iodine-lithium exchange in presence of an aryl azide had not been reported previously.



Scheme 38: Summary of preparation of polyfunctional diorgano-magnesium and -zinc reagents using *in situ* trapping halogen-lithium exchange of highly functionalized (hetero)aryl halides in continuous flow.

6.4 Synthesis and Reactivity of Triazaphenanthrenes

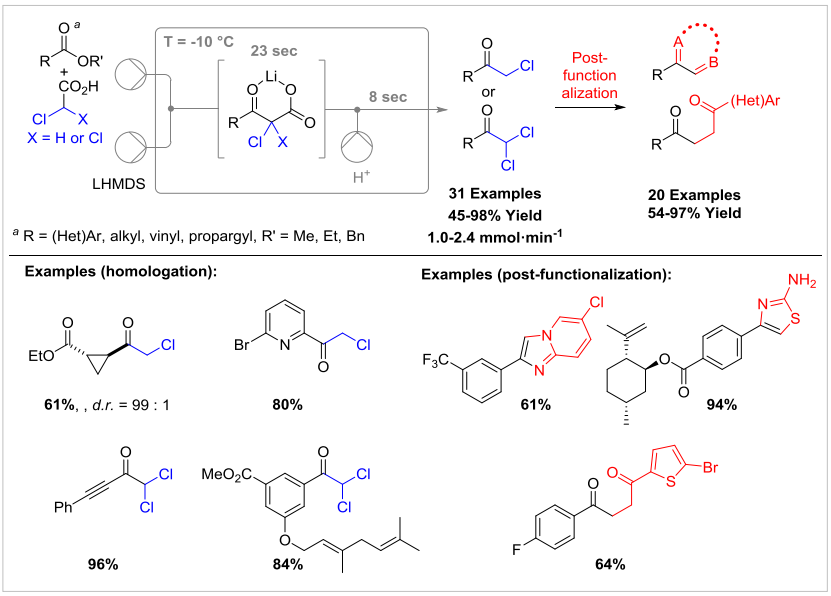
Pyridonaphthyridines (triazaphenanthrenes) were prepared in 4 steps and in 13–52% overall yield using *Negishi* cross-couplings between iodopicolines and 2-chloro-pyridylzinc derivatives (Scheme 39). After chlorination, *Gabriel* amination and spontaneous ring-closure, the final aromatization leading to the triazaphenanthrenes was achieved with chloraniline. This heterocyclic scaffold underwent a nucleophilic addition of lithium organyls at position C6 leading to further functionalized pyridonaphthyridines after re-oxidation. Thus, by utilizing the inherent reactivity of the triazaphenanthrene scaffold, this method furnished formal hetoaryl-(het)aryl, heteroaryl-vinyl, and heteroaryl-alkyl coupling products without transition metal catalysis (Scheme 39). The influence of these chemical modifications on the optical properties was studied by steady-state and time-resolved optical spectroscopy.



Scheme 39: Summary of synthesis and reactivity of triazaphenanthrenes New functionalizations of the C6-position of the triazaphenantrene core indicated in blue.

6.5 Mild Chloromethylation of Esters *via* Continuous Flow Chloroacetate Claisen Reactions

The selective chloromethylation of highly functionalized esters using chloroacetic acid and LiHMDS (HMDS = hexamethyldisilazide) in a continuous flow setup was developed. This chloroacetate *Claisen* (**CAC**) reaction is for the first time extended to bischloromethylation using dichloro-acetic acid, thus giving access to the under-explored *α,α'*-bis-chloroketones. The use of flow conditions enables an efficient reaction of the unstable chloroacetate dianion intermediates, leading to unprecedented scalability, mild reaction conditions and reagent stoichiometry (−10 °C, < 1 min, 1.1–2.4 equiv. dianion). The scope of **CAC** reactions was for the first time broadly tested with various starting materials including sp, sp^2 and sp^3 bound esters bearing various functionalities.



Scheme 40: Summary of mild chloromethylation of esters *via* continuous flow chloroacetate *Claisen* reactions.

Of special interest is the tolerance of alkenes, allylic, benzylic, ketal and thioether moieties, because these are usually not compatible with the oxidative halogenation conditions applied in ketone

halogenation. On the other hand, also functionalities were tolerated, which are incompatible with lithium halocarbenoids, which were alternatively applied in haloketone synthesis. In summary, aryl halides, epoxides, electron-poor heterocycles, nitro-, and cyano- groups as well as additional (secondary) esters are tolerated by the **CAC** flow protocol. It was thus demonstrated, that the developed flow **CAC** method fills a methodological gap between harsh halogenation reactions and those of highly instable and nucleophilic lithium carbenoids. The clean profiles of the obtained crude products allowed their subsequent in several cyclisations to heterocycles of broad interest. The high chemoslectivity of **CAC** reactions could be translated to corresponding heterocycles. Furthermore, a novel, catalyst-free substitution of the obtained monochloro ketone products with (hetero)aryl zinc enolates leading was developed, which leads to valuable 1,4-diketones.

C. EXPERIMENTAL PART

1 General Considerations

Batch reactions involving moisture sensitive reagents were carried out in oven dried (60 °C, 1 bar) and subsequently heat-gun dried (650 °C, < 1 mbar) glassware under an argon atmosphere using standard *Schlenck* techniques.[228] Syringes were purged with argon three times before anhydrous solvents or reactant solutions were transferred. Dry solvents were available freshly refluxed over sodium benzophonene ketyl under nitrogen. Tetradecane (*n*-$C_{14}H_{30}$), dodecane (*n*-$C_{12}H_{26}$) or undecane (*n*-$C_{11}H_{24}$) were used as internal standards.

Flow reactions were carried out with solutions of known titer in dry solvents using oven dried and flame-dried glassware under an argon atmosphere as reagent reservoir. Tetradecane ($^{n}C_{14}H_{30}$), dodecane ($^{n}C_{12}H_{26}$) or undecane ($^{n}C_{11}H_{24}$) were used as internal standards. A Vapourtec E-series Integrated Flow Chemistry System[229] with 3rd Pump Kit, Organometallic Kit, Collection Valve Kit and Cryogenic Reaction Kit or a Uniqsis FlowSyn system was used. If the Vapourtec System was used, hexane solutions of ^{n}BuLi or PhLi and THF solutions of the remaining reactants were kept in flasks with rubber septa under an argon atmosphere during the reactions. If the Uniqsis system was used, carrier solvents as well as reactant solutions were stored under argon and injected to carrier solvent streams. Reactions were performed in a glass chip or in coiled tube reactors. The glass chip (borosilicate glass; 1.0 mm i.d. channels; purchased from Uniqsis had a reaction volume of 0.5 mL + 1.0 mL plus 0.5 mL pre-cooling volume for each reagent. Coiled reactors were made from PFA or PTFE Teflon (i. d. = 0.8 mm) and T-pieces (i.d. = 0.5 mm or 1.0 mm; inner volume: negligible; < 20 µL) were used as mixers. Prior to performing reactions, the systems were dried once by flushing with dry THF (flowrate of all pumps: 1.00 mL/min; run-time: 10 min – 30 min), in between reactions 5 – 10 mL were used for flushing out residual reagent contaminations.

After using the flow system, all residual reagents were flushed out with dry THF, then water was flushed through for at least 5 min (flowrate of all pumps: 1.00 mL/min).

1.1 Solvents

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

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

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

***iso*-hexane** and **Et_2O** for column chromatography was distilled prior to use.

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[228] Compare: C. M. Davis, K. A. Curran, *J. Chem. Educ.*, **2007**, 84, 1822.

[229] More detailed information on this flow system is available from Vapourtec (https://www.vapourtec.com/products/e-series-flow-chemistry-system-overview/).

1.2 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Preparation procedures for specific starting materials are given at the beginning of the respective chapters.

^{n}BuLi solution in hexane was purchased from Albemarle and the concentration was determined by titration against 1,10-phenanthroline in THF with dry *i*-PrOH.[230]

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

^{i}PrMgCl·LiCl solution in THF was obtained from Albemarle and the concentration was determined by titration against iodine.[231]

CuCN·2LiCl[232] 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.

$MgCl_2$ solution (0.5 M in THF) was prepared in a *Schlenk*-flask equipped with a magnetic stirrer and a septum. Mg turnings (2.55 g, 105 mmol) and THF (200 mL) were added and an ice bath was held ready. 1,2-Dichloroethane (9.90 g, 100 mmol, 7.92 mL) was added first in a small portion (ca. 1 mL). After clouding and gas evolution started, the remaining 1,2-Dichloroethane was added dropwise at 25 °C. In case of imminent thermal runaway, ice bath cooling was applied. The reaction mixture was further 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

TMPZnCl·LiCl[233] and **TMPMgCl·LiCl**[234] solutions in THF were prepared according to literature procedures and titrated with benzoic acid in THF using 4-(phenylazo)diphenylamine as indicator.

1.3 Chromatography

Flash column chromatography (**CC**) was performed using silica (SiO_2) (0.040−0.063 mm, 230−400 mesh ASTM) from Merck. Thin layer chromatography (**TLC**) was performed using aluminum plates covered with SiO_2 (Merck 60, F-254). Spots were visualized under UV light, with $KMnO_4$ stain

[230] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[231] A. Krasovskiy, P. Knochel, *Synthesis*, **2006**, 890.
[232] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[233] a) S. H. Wunderlich, P. Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685; b) M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1468.
[234] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; *Angew. Chem.* **2006**, *118*, 3024.

($KMnO_4$ (1.5.0 g), K_2CO_3 (10 g), KOH (0.1 g) in water (100 mL), CAM stain (1 g $Ce(SO_4)_2$, 5 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 5 mL conc. H_2SO_4, 100 mL H_2O) or neat iodine absorbed on silica gel. Gas chromatography (**GC**) was performed with instruments of the type Hewlett-Packard 6890 or 5890 Series II, using a column of the type HP 5 (Hewlett-Packard, 5% phenylmethylpolysiloxane; length: 9−10 m, diameter: 0.25 mm, film thickness: 0.25 μm). The detection was accomplished using a flame ionization detector. For the combination of gas chromatography with mass spectroscopic detection (GC-MS), a GC-MS of the type Hewlett-Packard 6890 / MSD 5793 networking was used (column: HP 5-MS, Hewlett-Packard; 5% phenylmethylpolysiloxane; length: 15 m, diameter 0.25 mm; film thickness: 0.25 μm).

1.4 Analytical Data

Nuclear magnetic resonance (**NMR**) spectra were recorded on Bruker ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δH: 7.26; δC: 77.16). For the observation of the observed signal multiplicities, the following abbreviations were used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet) and m (multiplet). ^{13}C-NMR signals, which are unequivocally attributable to X multiple (chemically equivalent) carbon atoms, are reported with declaration of the number of carbon atoms (XC). Mass spectra (**MS**) and high resolution mass spectra (**HRMS**) were recorded on a Finnigan MAT95Q or Finnigan MAT90 instrument for electron impact ionization (**EI**) and electrospray ionization (**ESI**). Melting points (**M.p.**s) are uncorrected and were measured on a Büchi B.540 apparatus. Infrared spectra (**IR**) were recorded from 3000−600 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 or dissolved in $CDCl_3$. The absorption bands are reported in wavenumbers (cm^{-1}) and characterized as weak (w), medium (m), strong (s), or broad (br) if the bands showed significant broadening. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR and capillary GC.

2 Continuous Flow Magnesiation or Zincation of Acrylonitriles, Acrylates and Nitroolefins

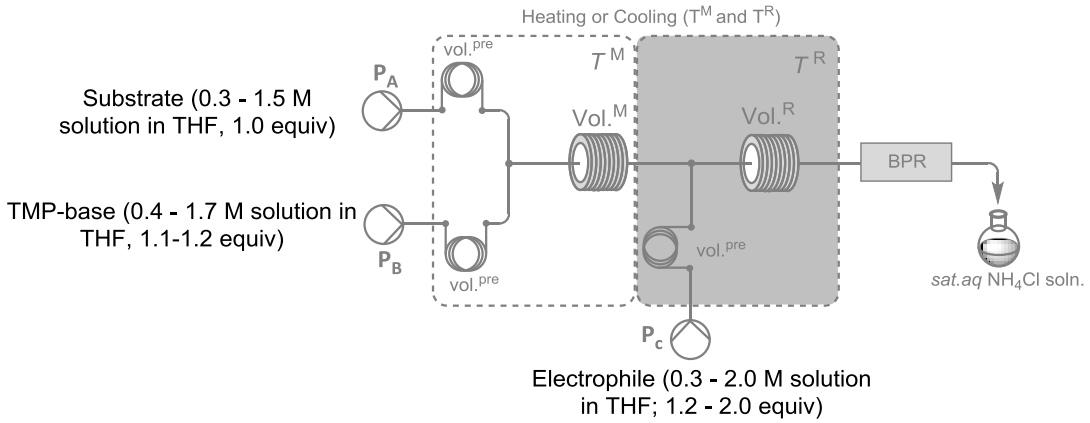
2.1 Preparation of starting materials

If not commercially available, the following procedures were used for the preparation of starting materials:

Alkyl esters were prepared according to *Fischer*'s method from the corresponding acid in the alcohol in presence of catalytic sulfuric acid and anhydrous $MgSO_4$.[235]

***E*-Ethyl-acrylate esters** were prepared by a modified *Horner-Wadsworth-Emmons* protocol: [236] A solution of methyl diethylphosphonoacetate (0.9 equiv.) in dry THF (113.9 mL) was placed in a dry *Schlenk*-flask equipped with a magnetic stirring bar and a septum under Ar. MeMgCl (0.9 equiv., 2.38 M) was added dropwise and the reaction mixture was allowed to stir at room temperature for 15 min. The aldehyde (1.0 equiv.) was added dropwise and the reaction mixture was heated at reflux (75 – 80 °C) for 4 h. The reaction was quenched with *sat. aq.* NH_4Cl solution (4 mL) and extracted with EtOAc. After drying the organic layers over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. Purification by CC furnished the pure products.

2.2 Typical Procedure 1 (TP 1, Electrophiles used in excess)



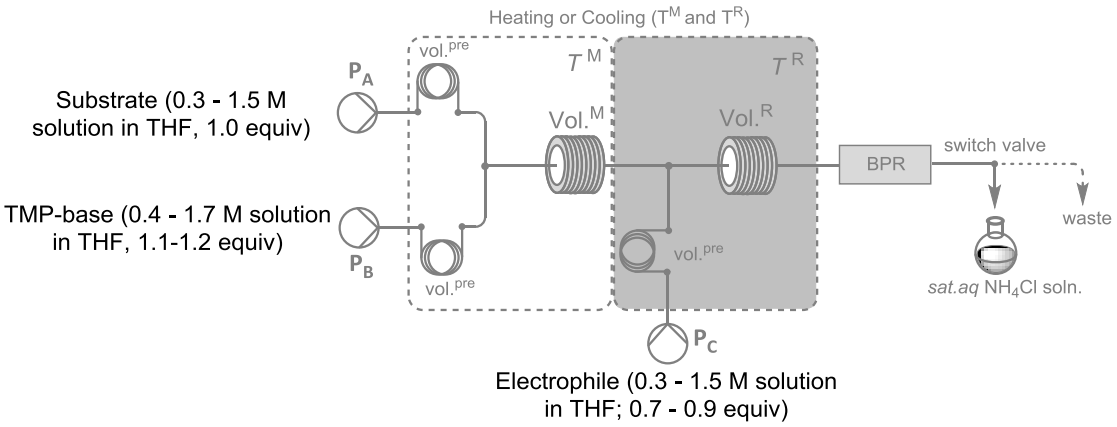
Scheme 41: TP1 flow setup.

A commercially available setup from Vapourtec Ltd. (E-Series) was used (Scheme 41). The reagent solutions were prepared in flasks under argon and suction needles delivered the solutions directly through the pumps (P_A, P_B, P_c) to the reactors ($Vol.^M$, $Vol.^R$). The concentrations of substrate and electrophile were adapted to the titer of the base solution (*i.e.* typ. ca. 1 M) or, if critical, to the solubility of the substrate in THF. The flow system was assembled from PFA or PTFE Teflon tubings and T-pieces (i.d. = 0.5 mm). If heating of any parts of the system above 50 °C was applied, a mechanical back pressure regulator (BPR) was installed as indicated above. The pressure was regulated in a way to keep the solvent (THF in all reactions) in the liquid phase at the given temperature, usually in a range from 1 to 3 bar. If cooling was applied, pre-cooling loops ($vol.^{pre}$ = 0.5 mL or 1 mL) were installed before the reagents were mixed in T-mixers. To compensate large temperature differences (*e.g.* T^R = 50 °C >> T^M = 0 °C), an intermediate loop was used to cool down

[235] See, for example: J. Spekreijse et al., *Green Chem.* **2012**, *14*, 2747.
[236] M.H. Katcher, A. Sha, A. G. Doyle; *J. Am. Chem. Soc.* **2011**, 133, 15902.

or heat the reagent mixtures appropriately before quenching with the electrophile solution occurred. The system was dried by flushing with dry THF (flowrate of all pumps: 1.00 mL/min, minimum run time: 20 min). Substrate and base solutions (pumps A and B) were always pumped with the same flowrates. The electrophile stream (C) enfolded the stream segment of the combined streams from A and B. The entire crude output containing the reacted substrate was collected for a pre-defined time according to the desired scale of the reaction. The product stream was collected in a flask containing *sat. aq.* NH_4Cl solution (15 mL/mmol substrate) in order to ensure, that all organometallic reagents were quenched at this point. The quench solutions were stirred with a magnetically stirrer to quickly dissolve salts in the aqueous phase and prevent clogging at the reaction outlet.

2.3 Typical Procedure 2 (TP 2, Nucleophile used in excess)

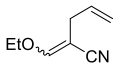


Scheme 42: TP 2 flow setup.

The setup shown for **TP 1** was also applied for **TP 2**. Additionally, a switch valve was installed after the coiled reactiors ($Vol.^M$ and $Vol.^R$) as well as a BPR (if used). The switch valve was programmed to collect the desired volumes of crude reaction mixture by switching between a collection and a waste output. The first minute of crude reaction mixture was discarded *via* the waste vial to ensure collection during the steady-state regime. Then the crude reaction mixture was collected during a defined time corresponding to the desired scale of the reaction. Subsequent product stream was discarded again *via* the waste vial. The collection flask contained *sat. aq.* NH_4Cl (15 mL/mmol substrate) for quenching of all organometallic reagents. The quench solutions were stirred with a magnetically stirrer to quickly dissolve salts in the aqueous phase and prevent clogging.

2.4 Preparation of the Products

2-(ethoxymethylene)pent-4-enenitrile (5a)



Following **TP 1**, solutions of 3-ethoxyacrylonitrile[237] (**3a**; 2.86 mL, 0.70 M) and TMPZnCl·LiCl solution (**1**; 2.86 mL, 0.77 M, 1.1 equiv.) were each pumped at 0.50 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor ($Vol.^M$ = 10 mL; t^M = 10:00 min; T^M = 40 °C).The combined stream was mixed with a third stream (pump C; flowrate: 0.42 mL/min) of allyl bromide solution (**4a**, 1.0 M, 1.2 equiv.) containing a catalytic amount of CuCN·2LiCl (0.08 M, 0.1 equiv.). The combined streams passed a second coiled reactor ($Vol.^R$ = 5 mL; t^R = 3:30 min; T^R = 25 °C) and were then collected. The aqueous layer was extracted with EtOAc (3x25 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, CC purification (*iso*-hexane:EtOAc = 8:2) gave *E*-**5a** (major) and *Z*-**5a** (minor) in a 2:1 ratio as pale brown oils (total amount: 213 mg, 1.55 mmol, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.86 (s, 1H***E***), 6.63 (s, 1H***Z***), 5.76 – 5.71 (m, 1H), 5.19 – 5.04 (m, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 2.91 – 2.86 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

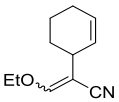
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 159.3, 134.0, 117.7, 117.2, 88.1, 70.4, 32.9, 15.3.

IR (Diamond-ATR, neat): $\tilde{\nu}/cm^{-1}$= 2983(w), 2212(s), 1645(s), 1399(w), 1306(s), 1233(s), 1179(s), 1144(s), 1019(m), 993(m), 917(m), 882(s).

MS (70 eV, EI): *m/z* (%) = 137(19), 81(32), 80(100), 54(18), 53(26), 52(12), 38(14).

HRMS (EI): *m/z* calcd. for [$C_8H_{11}NO$]: 137.0841; found: 137.0839 [M^+].

2-(cyclohex-2-en-1-yl)-3-ethoxyacrylonitrile (5b)



A back pressure regulator was installed and adjusted to maintain 1 bar pressure during the reaction. According to **TP 2**, solutions of 3-ethoxyacrylonitrile[3] (**3a**; 1.61 mL, 1.24 M) and TMPZnCl·LiCl (**1**; 1.61 mL,1.49 M, 1.2 equiv.) were each pumped with 0.500 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor ($Vol.^M$ = 5 mL; t^M = 10:00 min; T^M = 40 °C). The combined stream was mixed in a T-mixer with a third stream (pump C; flowrate: 0.482 mL/min) of 3-bromo-cyclohexene solution (**4b**, 1.0 M, 0.8 equiv.) charged with a catalytic amount of CuCN·2LiCl (0.125 M, 0.1 equiv.). The reagent solutions passed a second coiled reactor ($Vol.^R$ = 5 mL; t^R = 3:22 min; T^R = 25 °C). After discarding 1.0 min prerun, a volume equivalent to 1.0 mmol of starting material was collected. The aqueous layer was extracted with EtOAc (3×25 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in*

[237] Purchased as *E*:*Z* = 1.7:1 mixture from Aldrich, verified by GC and 1H-NMR analysis.

vacuo, CC purification (*iso*-hexane:EtOAc = 8:2) afforded *E*-**5b** (major) and *Z*-**5b** (minor) in a 2:1 ratio as pale yellow oils (total amount: 261 mg, 1.47 mmol, 92%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ppm = 6.80 (s, 1H***Z***), 6.60 (s, 1H***E***), 5.90 – 5.80 (m, 1H), 5.52 – 5.43 (m, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.38 – 3.26 (m, 1H), 2.13 – 1.92 (m, 2H), 1.90 –1.73 (m, 2H), 1.67 – 1.48 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

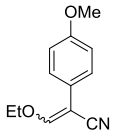
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 157.8, 129.9, 127.5, 119.5, 97.8, 70.6, 31.9, 28.1, 24.6, 21.4, 15.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2934(w), 2207(m), 1631(s), 1446(w), 1302(m), 1215(s), 1197(s),1140(s), 1108(m), 1021(m), 985(m), 887(m), 869(m), 844(m), 807(m), 778(m), 724(m), 597(w).

MS (70 eV, EI): *m/z* (%) = 177(71), 149(51), 148(30), 134(22), 121(59), 120(56), 106(26),97(16), 95(22), 94(14), 93(100), 92(18), 91(24), 81(30), 80(28), 79(47), 78(17), 77(35), 67(33), 66(37), 65(30), 55(15), 53(32), 52(17), 51(22), 41 (54).

HRMS (EI): *m/z* calcd. for [$C_{11}H_{15}NO$]: 177.1154: 177.1150 [M^+].

3-ethoxy-2-(4-methoxyphenyl)acrylonitrile (5c)



A back pressure regulator was installed and adjusted to maintain 2 bar pressure during the reaction. Procedure **TP 2** was used. Solutions of 3-ethoxyacrylonitrile[3] (**3a**; 1.45 mL, 1.38 M) and TMPZnCl·LiCl (**1**; 1.45 mL, 1.52 M, 1.1 equiv.) were each pumped at a 0.250 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor ($Vol.^M$ = 5 mL; t^M = 10:00 min; T^M = 40 °C). The combined stream was mixed with a stream (pump C; flowrate: 0.276 mL/min) of 4-iodoanisole solution (**4c,** 1.0 M, 0.8 equiv.) with catalytic amounts of $Pd(dba)_2$ and TFP (in this order: 0.025 M, 0.02 equiv.; 0.05 M, 0.04 equiv.). The combined streams passed a second coiled reactor ($Vol.^R$ = 10 mL; t^R = 12:49 min; T^R = 60 °C). After discarding 1.0 min prerun, a volume equivalent to 1.0 mmol of starting material was collected. The aqueous layer was extracted with EtOAc (3x25 mL) and CH_2Cl_2 (2x25 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, CC (*iso*-hexane:EtOAc = 9:1→ 7:3) afforded of *E*-**5c** (major) and *Z*-**5c** (minor) in a 6:1 ratio as yellowish oils (total amount: 156 mg, 0.77 mmol, 96%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.70 – 7.63 (m, 2H), 7.15 (s, 1H***Z***) 6.99 (s, 1H***E***), 6.93 – 6.87 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

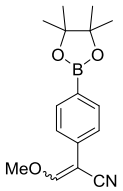
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 159.1, 156.5, 128.9 (2C), 123.4, 119.7, 114.0 (2C), 93.4, 71.9, 55.4, 15.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2936(w), 1725(m), 1670(m), 1596(s), 1511(s), 1460(m), 1254(s), 1166(s), 1088(s), 1024(s), 833(s), 767(m), 753(m), 689(m).

MS (70 eV, EI): *m/z* (%) = 204(10), 203(73), 176(10), 175(100), 174(38), 147(23), 146(48),145(15), 135(15), 132(28), 116(11), 103(10), 91(11), 77(15), 76(16), 57(13), 51(11).

HRMS (EI): *m/z* calcd. for [203.0946]: 203.0944 [M^+].

3-methoxy-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acrylonitrile 5d



A back pressure regulator was installed and adjusted to maintain 2 bar pressure during the reaction. Procedure **TP 2** was used. Solutions of 3-methoxyacrylonitrile[238] (**3b**; 1.0 M) and TMPZnCl·LiCl (**1**; 1.14 M, 1.1 equiv.) were each pumped at a 0.250 mL/min flowrate (pump A and B). The streams were combined in a T-mixer (i.d. = 0.5 mm) followed by a coiled reactor ($Vol.^M$ = 5 mL; t^M = 10:00 min; T^M = 40 °C). The combined stream was mixed with a stream (pump C; flowrate: 0.250 mL/min) of 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane solution (**4d,** 0.8 M, 0.8 equiv.) with catalytic amounts of $Pd(dba)_2$ and TFP (in this order: 0.02 M, 0.02 equiv.; 0.04 M, 0.04 equiv.). The combined streams passed a second coiled reactor ($Vol.^R$ = 10 mL; t^R = 12:49 min; T^R = 60 °C). After discarding 1.0 min prerun, a volume equivalent to 1.0 mmol of starting material was collected. The aqueous layer was extracted with EtOAc (3x25 mL) and CH_2Cl_2 (2x25 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, CC (*iso*-hexane:EtOAc = 7:3) afforded a 2.5:1 mixture of *Z*-**5d** (major) and *E*-**5d** (minor) as colorless solid (160 mg, 0.56 mmol, 70%).

M. p. (°C): 108-112.

^{1}H-NMR (400 MHz, $CDCl_3$, isomeric mixture): δ/ppm = 7.77 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.00 (s, 1H,***E***), 7.22(s, 1H, ***Z***) 3.97 (s, 3H), 1.31 (s, 12H)..

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 159.9, 135.6, 135.0 (2C), 133.3, 126.8 (2C), 119.1, 94.3, 84.0, 63.2 (2C), 25.0(4C).

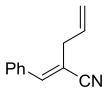
IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2925(w), 2212(w), 1626(m), 1605(m), 1454(w), 1397(m), 1356(s), 1325(s), 1212(m), 1150(s), 1095(s), 1017(m), 963(s), 887(m), 860(m), 843(s), 823(m), 745(m), 671(m), 654(s).

MS (70 eV, EI): *m/z* (%) = 285(31), 270(14), 199(29), 186(27), 185(34), 70(13), 61(18), 45(16), 43(100).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{20}BNO_3$]: 285.1536: 285.1537 [M^+].

[238] Purchased as *E*:*Z* = 1:1 mixture from Aldrich, verified by GC and ^{1}H-NMR analysis.

(*E*)-2-benzylidenepent-4-enenitrile (5e, with scale-up)



A back pressure regulator was installed and adjusted to maintain 2 bar pressure in the flow system system during the reaction. Following **TP 1**, solutions of trans-cinnamonitrile (**3c**; 1.77 mL, 1.13 M) and TMPZnCl·LiCl (**1**; 1.77 mL, 1.24 M, 1.1 equiv.) were each pumped at a 0.25 mL/min flowrate (pump A and B) and the streams were combined in a T-mixer followed by a coiled reactor ($Vol.^{M}$ = 10 mL; t^{M} = 10:00 min; T^{M} = 90 °C). The combined stream containing the zincated intermediate was mixed in a T-piece with a stream (pump C; flowrate: 0.34 mL/min) of allyl bromide solution (**4a**, 1.0 M, 1.2 equiv.), which contained a catalytic amount of CuCN·2LiCl (0.08 M, 0.1 equiv.). The stream of reactants passed a second coiled reactor ($Vol.^{R}$ = 2 mL; t^{R} =2:23 min; T^{R} = 25 °C) and the crude product stream was collected. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. Column chromatographic purification (*iso*-hexane:EtOAc = 95:5 → 9:1) afforded **5e** as a yellow oil (254 mg, 1.50 mmol, 75%).

With the same setup, 10 mmol starting material (**3c**; 8.85 mL, 1.13 M) furnished **5e** in 83% yield (1.40 g, 8.27 mmol) after analogous purification.

Spectroscopic data matched those previously reported for this compound.[239]

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ppm = 7.84 – 7.28 (m, 5H), 6.96 (s, 1H), 6.02 – 5.82 (m, 1H), 5.33 – 5.21 (m, 2H), 3.23-3.13 (m, 2H).

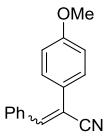
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 144.8, 143.7, 133.4, 132.7, 132.3, 129.8, 129.3, 128.6, 118.5, 117.9, 109.2, 39.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3084(w), 2210(m), 1640(w),1621(w), 1494(w), 1448(m), 1431(w), 1217(w), 992(m), 923(s), 750(s), 690(s).

MS (70 eV, EI): *m/z* (%) = 169 (34), 168(47), 167(10), 154(100), 153(10), 142 (14), 141(34),140(15), 129(13), 128(15), 127(23), 115(24).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{11}N$]: 169.0891; found: 168.0788 [M-H^+].

2-(4-methoxyphenyl)-3-phenylacrylonitrile (5f)



A back pressure regulator was installed and adjusted to maintain 2 bar pressure during the reaction. According to **TP 2**, solutions of *trans*-cinnamonitrile (**3c**; 1.43 mL, 0.70 M) and TMPZnCl·LiCl (**1**; 1.43 mL, 0.77 M, 1.1 equiv.) were pumped at 0.25 mL/min flowrate (pump A and B) and the streams were mixed in a T-piece. The combined stream passed a coiled reactor ($Vol.^{M}$ = 5 mL; t^{M} = 10:00 min;

[239] Tomioka, T. et al., *J. Org. Chem.* **2011**, *76*, 8053.

T^M = 90 °C) and was subsequently mixed with a stream (pump C; flowrate: 0.25 mL/min) of 4-iodoanisole solution (**4c**, 0.49 M, 0.6 equiv.) with catalytic amounts of $Pd(dba)_2$ and TFP (in this order: 0.016 M, 0.02 equiv., 0.032 M, 0.04 equiv.). The reactants passed a second coiled reactor ($Vol.^R$ = 19 mL; t^R = 25:20 min; T^R = 60 °C). After discarding 1:00 minute prerun, a volume equivalent to 1.0 mmol starting material was collected. The aqueous layer was extracted with EtOAc (4×25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatographic purification (*iso*-hexane:EtOAc = 95:5) gave a 8:1 mixture (total amount: 140 mg, 0.59 mmol, 99%) of yellow oil Z-**5f** (minor) and colourless solid *E*-**5f** (major).

M.p. (°C): 86-90.(***E***)

^{1}H−NMR (300 MHz, $CDCl_3$): δ/ppm = 7.90 – 7.82 (m, 2H), 7.66 – 7.57 (m, 2H), 7.45 – 7.39 (m, 3H), 7.26 (s, 1H***E***), 7.10 (s, 1HZ), 7.01 – 6.93 (m, 2H), 3.86 (s, 3H).

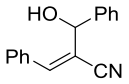
^{13}C−NMR (75 MHz, $CDCl_3$): δ/ppm =160.6, 140.3, 134.1, 130.3, 129.2 (2C), 129.1 (2C), 127.5 (2C), 127.1, 118.3, 114.6 (2C), 111.5, 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3005(w), 2839(w), 2214(m), 1605(s), 1573(m), 1509(s), 1459(m), 1439(m), 1281(m), 1250(s), 1178(s), 1118(m), 1031(s), 931(m), 896(m), 832(s), 820(s),769(s), 746(s), 692(s).

MS (70 eV, EI): *m/z* (%) = 236(16), 235(100), 234(22), 220(12), 204(16), 192(10), 191(13), 190(19), 177(10), 165(24).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{13}NO$]: 235.0997; found: 235.0952 [M^+].

(*Z*)-2-(hydroxy(phenyl)methyl)-3-phenylacrylonitrile (5g)



A back pressure regulator was installed and adjusted to maintain 2.5 bar pressure during the reaction. Following **TP 1**, solutions of trans-cinnamonitrile (**3c**; 1.77 mL, 1.13 M) and TMPZnCl·LiCl (**1**; 1.77 mL,1.24 M, 1.1 equiv.) were each pumped at a 0.25 mL/min flowrate (pump A and B) and the streams were combined in a T-mixer followed by a coiled reactor ($Vol.^M$ = 5 mL; t^M = 10:00 min; T^M = 90 °C). The stream containing the zincated intermediate was mixed in a T-piece with a stream (pump C; flowrate: 0.46 mL/min) of benzaldehyde solution (**4e**, 1.5 M, 2.0 equiv.) charged with a sub-stoichiometric amount of TMSCl[240] (0.08 M, 0.1 equiv.). The combined reactant stream passed a second reactor ($Vol.^R$= 10 mL; t^R = 10:25 min; T^R = 70 °C). After collecting the crude product stream, the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, column chromatography (*iso*-hexane:EtOAc = 8:2) furnished alcohol **5g** as a yellow oil (292 mg, 1.24 mmol, 62%).

[240] Trimethyl silyl chloride (TMSCl) was necessary to suppress the formation of various byproducts, the product formation also occurs in absence of TMSCl.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ppm = 7.86 – 7.68 (m, 2H), 7.52 – 7.30 (m, 9H), 5.47 (s, 1H), 2.54(br s, 1H).

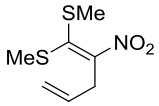
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 142.8, 140.0, 133.1, 130.8, 129.2, 129.1 (2C), 129.0 (2C), 129.0 (2C), 126.6 (2C), 117.3, 114.4, 75.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3430 (OH, m), 3061(w), 3029(w), 2214(m), 1622(m), 1493(m), 1449(m), 1392(m), 1212(m), 1191(m), 1076(m), 1040(m), 1024(m), 932(m), 902(m), 724(s), 688(s).

MS (70 eV, EI) *m/z* (%) = 235 (27), 140(20), 130(68), 129(23), 107(53), 106(11), 105(100), 103(11), 102(23), 91(11), 79(57), 78(19), 77(70).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{13}NO$]: 235.0997; found: 235.0995 [M^+].

(2-nitropenta-1,4-diene-1,1-diyl)bis(methylsulfane) (5i)



Following **TP 1**, solutions of (2-nitroethene-1,1-diyl)bis(methylsulfane) (**3d**; 2.27 mL, 0.44 M in 75 vol-% THF and 25 vol-% DMPU[8]) and TMPZnCl·LiCl solution (**1**; 2.27 mL, 0.49 M, 1.1 equiv.) were each pumped at 0.50 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor (Vol.^{M}= 5 mL; t^M= 5:00 min; T^M= 0 °C).The combined stream was mixed with a stream (pump C; flowrate: 0.50 mL/min) of allyl bromide solution (**4a**, 0.88 M, 2.0 equiv.) charged with CuCN·2LiCl (0.044 M, 0.1 equiv.). The combined stream passed a second coiled reactor (Vol.^{R}= 10 mL; t^R= 6:40 min; T^R= 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (3x30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, column chromatography (*iso*-hexane:EtOAc = 9:1) gave **5i** as a yellow oil (150 mg, 0.73 mmol, 73%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.86-5.76 (m, 1H), 5.17 – 5.09 (m, 2H), 3.71-3.68 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H).

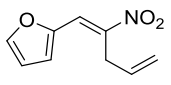
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.74, 145.97, 132.29, 117.89, 36.88, 18.64, 18.10.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2982(w), 2926(w), 2255(w), 1711(w), 1639(w), 1526(s), 1482(m), 1415(s), 1356(m), 1284(s), 1234(m), 1132(w), 1090(w), 990(m), 953(m), 912(s), 895(s), 863(m), 767(w), 730(s), 675(m).

MS (70 eV, EI): *m/z* (%) = 205(12), 126(38), 112(78), 111(60), 102(12), 97(97), 96(13), 90(14), 85(30), 75(29), 70(12), 70(14), 69(27), 69(23), 65(14), 61(19), 61(24), 53(21), 45(16), 45(29), 43(100), 41(42).

HRMS (EI): *m/z* calcd. for [$C_7H_{11}NO_2S_2$]: 205.0231; found: 205.0226 [M^+].

(*E*)-2-(2-nitropenta-1,4-dien-1-yl)furan (5j)



Following **TP 1**, solutions of (E)-2-(2-nitrovinyl)furan (**3e**; 2.00 mL, 0.50 M) and TMPZnCl·LiCl solution (**1**; 2.00 mL, 0.60 M, 1.1 equiv.) were each pumped at 0.75 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor (Vol.^{M}= 5 mL; t^{M}= 3:20 min; T^{M}= 25 °C).The combined stream was mixed with a stream (pump C; flowrate: 0.75 mL/min) of allyl bromide solution (**4a**, 0.75 M, 1.5 equiv.) containing CuCN·2LiCl (0.05 M, 0.1 equiv.). The combined stream passed a second coiled reactor (Vol.^{R}= 10 mL; t^{R}= 4:27 min; T^{R}= 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (3x50 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, column chromatographic purification (*iso*-hexane:EtOAc = 95:5) gave **5j** as a red oil (149 mg, 0.78 mmol, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.89 (s, 1H), 7.64 (d, *J* = 1.5 Hz, 1H), 6.85 (d, *J* = 3.5 Hz, 1H), 6.58 (dd, *J* = 3.5, 1.5 Hz, 1H), 5.95-5.85 (m, 1H), 5.23 – 5.08 (m, 2H), 3.81-3.79 (m, 2H).

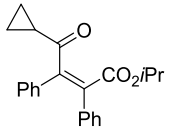
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.7, 146.7, 146.1, 132.4, 121.3, 119.9, 117.3, 113.1, 31.5.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$/ cm^{-1} = 2361(w), 1651(m), 1512(s), 1475(w), 1424(w), 1316(s), 1023(m), 912(w), 904(s), 884(m), 860(w), 755(w), 712(m) 667(w).

MS (70 eV, EI): *m/z* (%) = 179(35), 132(15), 104(15), 103(47), 97(11), 91(19), 85(11), 83(84), 79(20), 78(26), 77(51), 71(15), 70(12), 69(15), 65(11), 65(11), 61(20), 57(17), 55(15), 55(19), 53(11), 51(20), 45(17), 44(25), 43(16), 43(100), 41(21).

HRMS (EI): *m/z* calcd. for [$C_9H_9NO_3$]: 179.0582; 179.0580 [M^+].

Isopropyl (*Z*)-4-cyclopropyl-4-oxo-2,3-diphenylbut-2-enoate (7c)



According to **TP 2**, solutions of isopropyl (*E*)-2,3-diphenylacrylate (**6b**; 4.00 mL, 0.50 M) and TMPMgCl·LiCl (**2**; 4.00 mL, 0.58 M, 1.1 equiv.) were each pumped at 0.50 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor (Vol.^{M} = 5 mL; t^{M} = 5:00 min; T^{M} = 50 °C) and was subsequently mixed with a third stream (pump C; flowrate: 0.25 mL/min) of cyclopropanecarbonyl chloride solution (**4f**, 0.80 M, 0.8 equiv.) charged with a sub-stoichiometric amount of CuCN·2LiCl (0.5 M, 0.5 equiv.). The combined stream passed a second coiled reactor (Vol.^{R} = 10 mL; t^{R} = 8:00 min, T^{R} = 0 °C). After discarding 10 vol-% prerun of the reactant solution, a volume equivalent to 1 mmol starting material was collected. The aqueous layer was extracted with EtOAc (3x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 8:2) afforded enone **7c** as a colourless solid (325 mg, 0.97 mmol, 61%).

M.p. (°C): 84-87.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 6.99 (m, 10H), 5.16 (hept, *J* = 6.3 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.26 (d, *J* = 6.3 Hz, 6H), 1.20 – 1.15 (m, 2H), 0.90-0.85 (m, 2H).

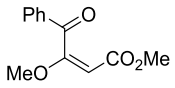
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 204.5, 168.2, 147.0, 136.3, 135.3, 135.0, 130.0 (2C), 129.9 (2C), 128.5 (2C), 128.3, 128.1, 128.0 (2C), 69.2, 21.6 (2C), 21.2, 12.8 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2988(w), 2934(w), 1700(s), 1674(s), 1609(w), 1489(w), 1443(m), 1373(m), 1346(m), 1298(m), 1236(s), 1204(s), 1178(m), 1125(s), 1103(s), 1092(s), 1027(m), 1007(m), 936(m), 923(m), 896(m), 845(w), 814(w), 801(w), 765(m), 739(s), 729(m), 698(s).

MS (70 eV, EI): *m/z* (%) = 335(15), 334(59), 292(15), 291(56), 275(23), 251(43), 247(33), 224(10), 223(45), 207(10), 179(42), 178(100), 177(11), 176(17), 152(12), 43(30) 41(50).

HRMS (EI): *m/z* calcd. for [$C_{22}H_{22}O_3$]: 334.1569; found: 334.1565 [M^+].

Methyl (*E*)-3-methoxy-4-oxo-4-phenylbut-2-enoate (7d, with scale-up)



According to **TP 1**, solutions of methyl (*E*)-3-methoxyacrylate (**6c**; 1.0 mL, 1.0 M) and TMPMgCl·LiCl (**2**;1.0 mL, 1.20 M, 1.2 equiv.) were each pumped with a 1.00 mL/min flowrate (pump A and B) and the streams were combined in a T-mixer. The combined stream passed a coiled reactor (Vol.^{M}= 5 mL; t^M= 2.5 min; T^M= 40 °C) and was mixed in a T-mixer with a third stream (pump C; flowrate: 1.00 mL/min) of benzoyl chloride solution (**4h**, 2.0 M, 2.0 equiv.), charged with a sub-stoichiometric amount of CuCN·2LiCl (0.5 M, 0.5 equiv.).The combined streams passed a coiled reactor immersed in an ice bath (Vol.^{R}= 14 mL; t^R= 4:40 min; T^R= 0 °C) and were then collected. The aqueous layer was extracted three times with 40 mL of EtOAc each. The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatographic purification (*iso*-hexane:EtOAc = 8:2) afforded **7d** quantitatively as pale blueish crystals (219 mg, 0.996 mmol, 99%).

With the same setup 15 mmol starting material (**5c**; 15.0 mL, 1.00 M) furnished **7d** in 99% yield (3.26 g, 14.83 mmol) after analogous purification.

M.p. (°C): 81.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 – 7.88 (m, 2H), 7.62 – 7.55 (m, 1H), 7.51 – 7.43 (m, 2H), 5.40 (s, 1H), 3.84 (s, 3H), 3.55 (s, 3H)

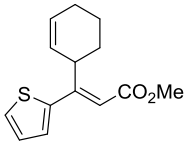
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 190.6, 168.1, 166.6, 134.5, 134.0, 129.2 (2C), 128.9 (2C), 93.4, 57.1, 51.5.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$/ cm^{-1} = 3002(w), 2956(w), 1737(m), 1710(s), 1620(m), 1436(m), 1359(s), 1279(m), 1220(s), 1195(m), 1143(s), 1091(m), 1075(m), 1051(m), 927(w), 824(w), 763(w), 594(w), 571(w).

MS (70 eV, EI): *m/z* (%) = 220(2), 190(22), 105(100), 78(58).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{12}O_4$]: 220.0736; 220.0733 [M^+].

Methyl (*E*)-3-(cyclohex-2-en-1-yl)-3-(thiophen-2-yl)acrylate (7f)



TP 1 was used. Solutions of methyl (*E*)-3-(thiophen-2-yl)acrylate (**6d**; 1.00 mL, 1.0 M) and TMPMgCl·LiCl solution (**2**; 1.00 mL, 1.12 M, 1.1 equiv.) were each pumped at 2.50 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor ($Vol.^M$ = 5 mL; t^M = 1:00 min; T^M= −25 °C).The combined stream was mixed with a third stream (pump C; flowrate: 2.50 mL/min) of allyl bromide (**4a**, 1.20 M, 1.2 equiv) with CuCN·2LiCl (0.1 M, 0.1 equiv.). The combined stream passed a second coiled reactor ($Vol.^R$= 10 mL; t^R= 1:20 min; T^R= -25 °C) and was then collected. The aqueous layer was extracted with EtOAc (3x50 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, column chromatographic purification (*iso*-hexane:EtOAc = 97:3) gave **7f** as a colourless solid (179 mg, 0.72 mmol, 72%). The product decomposes within ca. one hour under air at room temperature to a complex mixture of unidentified compounds.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74-7.63 (m, 1H), 7.19 (s, 1H), 7.10 – 6.89 (m, 1H), 6.70 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.19-6.03 (m, 1H), 5.89 – 5.58 (m, 1H), 3.70 (s, 3H), 3.60 (s, 1H), 2.15 – 1.91 (m, 2H), 1.78 – 1.47 (m, 3H), 1.32 – 0.68 (m, 1H).

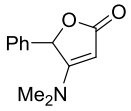
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.7, 154.9, 138.0, 137.4, 131.5, 129.3, 128.8, 124.8, 115.2, 51.7, 37.3, 32.3, 25.0, 20.6.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$/ cm^{-1} = 2952(w), 1713(s), 1656(w), 1630(m), 1600(m) 1575(w), 1474(w), 1461(w), 1426(w), 1402(w), 1362(m), 1319(w), 1273(w), 1244(w), 1211(s), 1190(s), 1130(w), 1053(w), 1035(w), 1014(m), 952(w), 903(s), 851(w), 797(w), 725(s).

MS (70 eV, EI): *m/z* (%) = 249(17), 248 (100), 233 (42), 220(17), 217(19), 216(15), 205(10), 189(14), 188(14), 187(13), 161(10), 160(10), 128(11), 115(11), 115 (12).

HRMS (EI): *m/z* calcd. for [$C_{14}H_{16}O_3NS_2$]: 248.0871; found: 248.0863 [M^+].

4-(dimethylamino)-5-phenylfuran-2(5*H*)-one (8a, with scale-up)



According to **TP 1**, solutions of ethyl (*E*)-3-(dimethylamino)acrylate (**6e**; 1.98 mL, 1.01 M) and TMPMgCl·LiCl (**2**; 1.0 mL, 1.11 M, 1.1 equiv.) were each pumped at 0.50 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor ($Vol.^M$ = 10 mL; t^M = 10:00 min; T^M = 25 °C) and was subsequently mixed with a third stream (pump C; flowrate: 0.57 mL/min) of benzaldehyde solution (**4e**; 1.51 M, 1.7 equiv.). The combined stream passed a second coiled reactor ($Vol.^R$ = 5 mL; t^R = 3:11 min, T^R = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (4x25 mL) and CH_2Cl_2 (2x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatographic purification (*iso*-hexane:EtOAc = 10:1 → EtOAc) afforded lactone **8a** as a colourless liquid (344 mg, 1.69 mmol, 85%).

With the same setup 15 mmol starting material (**6e**; 15.0 mL, 1.00 M) furnished **8a** in 91% yield (2.79 g, 13.74 mmol) after analogous purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ppm = 7.45 – 7.17 (m, 5H), 5.70 (s, 1H), 4.75 (s, 1H), 2.76 (m, 6H).

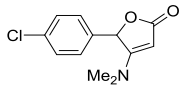
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 174.1, 170.3, 135.2, 129.6, 129.2 (2C), 127.9 (2C), 83.0, 80.2, 40.3 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3109(w), 2925(w), 1709(s),1597(s), 1437(m), 1401(m), 1316(s), 1263(m), 1170(s), 1005(s), 973(m), 905(s), 873(m), 841(m), 788(s),774(s), 720(s), 704(s), 671(m) .

MS (70 eV, EI): m/z (%) = 203(33), 69(100), 68(10), 41(11).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{13}NO_2$]: 203.0946; found: 203.0945 [M^+].

5-(4-chlorophenyl)-4-(dimethylamino)furan-2(5*H*)-one (8b)



According to **TP 1**, solutions of ethyl (*E*)-3-(dimethylamino)acrylate (**6e**; 1.98 mL, 1.01 M) and TMPMgCl·LiCl (**2**; 1.0 mL, 1.11 M, 1.1 equiv.) were each pumped at 0.50 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor ($Vol.^M$ = 10 mL; t^M = 10:00 min; T^M = 25 °C) and was subsequently mixed with a third stream (pump C; flowrate: 0.53 mL/min) of 4-chloro benzaldehyde solution (**4j**; 2.00 M, 2.1 equiv.). The combined stream passed a second coiled reactor ($Vol.^R$ = 5 mL; t^R = 3:11 min, T^R = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (3x25 mL) and CH_2Cl_2 (2x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 10:1 → EtOAc) afforded lactone **8b** as a colourless solid (304 mg, 1.28 mmol, 64%).

M.p. (°C): 121-126.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ppm = 7.38 – 7.25 (m, 4H), 5.70 (s, 1H), 4.77 (s, 1H), 2.79 (m, 6H).

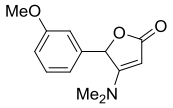
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 173.8, 170.0, 135.7, 133.8, 129.6 (2C), 129.4 (2C), 83.3, 79.4, 40.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3114(w), 2924(w), 1711(s),1612(s), 1490(m), 1435(m), 1413(m), 1307(m), 1174(s), 1092(m), 1009(s), 974(m), 905(s), 871(s), 845(s), 825(s), 795(s), 734(m).

MS (70 eV, EI): m/z (%) = 237(14), 97(15), 69(100).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{12}ClNO_2$]: 237.0557; found: 237.0555 [M^+].

4-(dimethylamino)-5-(3-methoxyphenyl)furan-2(5*H*)-one (8c)



According to **TP 1**, solutions of ethyl (*E*)-3-(dimethylamino)acrylate (**6e**; 1.98 mL, 1.01 M) and TMPMgCl·LiCl (**2**; 1.0 mL, 1.11 M, 1.1 equiv.) were each pumped at 0.50 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor ($Vol.^M$ = 10 mL; t^M = 10:00 min; T^M = 25 °C) and was subsequently mixed with a third stream (pump C; flowrate: 0.43 mL/min) of 3-methoxy benzaldehyde solution (**4k**; 2.00 M, 1.7 equiv.). The combined stream passed a second coiled reactor ($Vol.^R$ = 5 mL; t^R = 3:11 min, T^R = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (3x25 mL) and CH_2Cl_2 (2x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 9:1 → EtOAc) afforded lactone **8c** as a colourless solid (370 mg, 1.59 mmol, 79%).

M.p. (°C): 167-168.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.41 – 7.18 (m, 1H), 6.99 – 6.73 (m, 3H), 5.67 (s, 1H), 4.76 (s,1H), 3.79 (s, 3H), 2.80 (m, 6H).

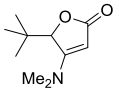
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 173.8, 170.0, 135.7, 133.8, 129.6 (2C), 129.4 (2C), 128.0, 83.3, 79.4, 40.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2922(m), 2851(w), 1714(s), 1620(s), 1607(s), 1489(m), 1437(m), 1408(m), 1306(m), 1284(s), 1228(m), 1162(m), 1089(w),1048(m), 1003(s), 973(m), 904(m), 871(m), 866(m), 788(s), 763(s), 725(s), 702(m).

MS (70 eV, EI): m/z (%) = 233(25), 189(12), 69(100).

HRMS (EI): *m/z* calcd. for [$C_{13}H_{15}NO_3$]: 233.1052; 233.1052 [M^+].

5-(tert-butyl)-4-(dimethylamino)furan-2(5*H*)-one (8d)

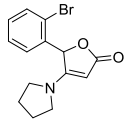


According to **TP 1**, solutions of ethyl (*E*)-3-(dimethylamino)acrylate (**6e**; 1.89 mL, 1.06 M) and TMPMgCl·LiCl (**2**; 1.89 mL, 1.17 M, 1.1 equiv.) were each pumped at 0.250 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor ($Vol.^M$ =

5 mL; t^M = 10:00 min; T^M = 25 °C) and was subsequently mixed with a third stream (pump C; flowrate: 0.265 mL/min) of pivaldehyde solution (**4l**;1.50 M, 1.5 equiv.). The combined stream passed a second coiled reactor (Vol.^{R} = 10 mL; t^R = 13:20 min, T^R = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (3x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc:NEt_3 = 2:1:0.03 → 1:1:0.03) afforded lactone **8d** as a pale yellow oil (298 mg, 1.63 mmol, 81%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ/ppm = 4.67 (s, 1H), 4.57 (s, 1H), 2.77 (s, 6H), 0.92 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 174.2, 172.7, 87.7, 84.7, 41.7 (2C), 37.1, 25.8 (3C).
IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2958(w), 1712(s), 1601(s), 1471(w), 1442(m), 1402(m), 1393(m), 1363(m), 1337(s), 1318(m), 1303(m), 1172(s), 1157(m), 1134(s), 1043(m), 1009(s), 975(m), 939(w), 915(s), 866(m), 786(s), 773(s), 725(s).
MS (70 eV, EI): m/z (%) = 183(15), 127(91), 126(100), 99(16), 98(60), 42(19), 41(22).
HRMS (EI): *m/z* calcd. for [$C_{10}H_{17}NO_2$]: 183.1259; 183.1244 [M^+].

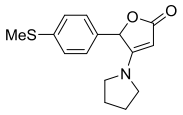
5-(2-bromophenyl)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (8e)



According to **TP 1**, solutions of ethyl (*E*)-3-(pyrrolidin-1-yl)acrylate (**6f**; 1.98 mL, 1.01 M) and TMPMgCl·LiCl (**2**; 1.0 mL, 1.11 M, 1.1 equiv.) were pumped at 0.50 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor (Vol.^{M} = 10 mL; t^M = 10:00 min; T^M = 25 °C) and then mixed with a third stream (pump C; flowrate: 0.57 mL/min) of 2-bromobenzaldehyde solution (**4m**; 1.50 M, 1.7 equiv.) in a T-mixer. The combined streams passed a second coiled reactor (Vol.^{R} = 14 mL; t^R = 8:55 min; T^R = 25 °C) and the crude product stream was subsequently collected. The aqueous layer was extracted with EtOAc (3x25 mL) and CH_2Cl_2 (2x25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatographic purification (*iso*-hexane: EtOAc:NEt_3 = 5:5:0.1 → 4:6:0.1) afforded lactone **8e** as a colorless solid (429 mg, 1.39 mmol, 70%).
M.p. (°C): 151.
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.67 – 7.53 (m, 1H), 7.40 – 7.17 (m, 3H), 6.29 (s, 1H), 4.72 (s, 1H), 3.27 (m, 3H), 2.64 (m, 1H), 2.16 – 1.64 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 174.3, 167.5, 134.2, 133.3, 131.1, 128.6, 128.6, 125.2, 82.4, 78.6, 50.0, 48.0, 26.0, 24.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3114(w), 2980(w), 2865(w), 1725(s), 1608(s), 1469(m), 1425(m), 1356(m), 1292(s), 1154(s), 1016(s), 988(m), 889(s), 864(s), 837(m), 772(s), 739(s), 724(m).

MS (EI, 70 eV): m/z (rel. Intensity) = 309(16), 307(15), 151(11), 95(100), 55(12), 41(15).
HRMS (EI): *m/z* calcd. for [$C_{14}H_{14}{}^{81}BrNO_2$]: 309.0187); found: 309.0171 [M^+].

5-(4-(methylthio)phenyl)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (8f)



According to **TP 1**, solutions of ethyl (*E*)-3-(pyrrolidin-1-yl)acrylate (**6f**; 1.98 mL, 1.01 M) and TMPMgCl·LiCl (**2**; 1.0 mL, 1.11 M, 1.1 equiv.) were pumped at 0.50 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor (Vol.^{M} = 10 mL; t^M = 10:00 min; T^M = 25 °C) and then mixed with a third stream (pump C; flowrate: 0.86 mL/min) of 4-(methylthio)benzaldehyde solution (**4n**; 1.00 M, 1.7 equiv.) in a T-mixer. The combined streams passed a second coiled reactor (Vol.^{R} = 14 mL; t^R = 7:32 min; T^R = 25 °C) and the crude product stream was subsequently collected. The aqueous layer was extracted with EtOAc (4x25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatographic purification (*iso*-hexane: EtOAc:NEt_3 = 1:1:0.02) afforded lactone **8f** as a colorless solid (368 mg, 1.34 mmol, 67%).

M.p. (°C): 155-156.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.34 – 7.17 (m, 4H), 5.69 (s, 1H), 4.69 (s, 1H), 3.43 – 2.63 (m, 4H), 2.50 (s, 3H), 2.31 – 1.62 (m, 4H).

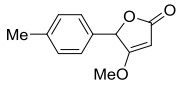
^{13}C-NMR (75 MHz, $CDCl_3$): *δ*/ppm = 174.5, 167.5, 140.6, 131.4, 128.5 (2C), 126.5 (2C), 81.9, 79.9, 49.9, 48.1, 25.9, 24.6, 15.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2873(w), 1795(w), 1718(s), 1595(s), 1492(m), 1459(m), 1425(m), 1348(m), 1302(s), 1286(m), 1160(s), 1088(m), 1006(s), 982(s), 896(s), 872(s), 818(s), 783(s).

MS (70 eV, EI): *m/z* (%) = 276(11), 275(58), 151(33), 95(100), 55(11).

HRMS (EI): *m/z* calcd. for [$C_{15}H_{17}NO_2S$]: 275.0980; found: 275.0972 [M^+].

4-methoxy-5-(p-tolyl)furan-2(5*H*)-one (8g)



According to **TP 1**, solutions of methyl (*E*)-3-methoxyacrylate (**6c**; 2.22 mL, 0.90 M) and TMPMgCl·LiCl (**2**; 2.22 mL, 0.99 M, 1.1 equiv.) were each pumped at 2.50 mL/min flowrates (pump A and B) and the streams were mixed in a T-piece. The stream passed a coiled reactor (Vol.^{M} = 5 mL; t^M = 1:00 min; T^M = 40 °C) and was subsequently mixed with a third stream (pump C; flowrate: 2.25 mL/min) of 4-methylbenzaldehyde solution (**4o**; 2.00 M, 2.0 equiv.). The combined stream passed a second coiled reactor (Vol.^{R} = 10 mL; t^R = 1:20 min, T^R = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (2x25 mL). The organic layers were combined and dried

over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 5:1 → 1:1) afforded lactone **8g** as a colourless solid (271 mg, 1.33 mmol, 67%).

M.p. (°C): 95-98.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ppm = 7.43 – 7.21 (m, 4H), 5.69 (s, 1H), 5.21 – 5.17 (s, 1H), 3.87 (s,3H), 2.40 (s, 3H).

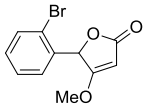
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 181.8, 172.7, 139.5, 131.1, 129.6 (2C), 126.7 (2C), 88.3, 80.4, 59.7, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3432 (w), 3299 (w), 2945(w), 2922(w), 1739(s), 1721(s), 1628(s), 1513(m), 1453(m), 1354(m), 1290(m), 1247(m), 1158(s), 1035(s), 986(s), 898(s), 810(s), 732(s).

MS (70 eV, EI): *m/z* (%) = 205 (11), 204 (70), 189 (22), 120 (13), 119 (100), 115 (14), 91 (44), 85 24), 84 (31), 77 (11), 65 (16).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{12}O_3$]: 204.0786; found: 204.0777 [M^+].

5-(2-bromophenyl)-4-methoxyfuran-2(5*H*)-one (8h)



According to **TP 1**, solutions of methyl (*E*)-3-methoxyacrylate (**6c**; 2.22 mL, 0.90 M) and TMPMgCl·LiCl (**2**; 2.22 mL, 0.99 M, 1.1 equiv.) were each pumped at 2.50 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor (Vol.^{M} = 5 mL; t^M = 1:00 min; T^M = 40 °C) and was subsequently mixed with a third stream (pump C; flowrate: 2.25 mL/min) of 2-bromobenzaldehyde solution (**4m**; 1.50 M, 1.5 equiv.). The combined stream passed a second coiled reactor (Vol.^{R} = 10 mL; t^R = 1:20 min, T^R = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (4x25 mL) and DCM (2x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 2:1) afforded lactone **8h** as a colourless solid (327 mg, 1.22 mmol, 61%).

With the same setup 10 mmol starting material (**6c**; 10.0 mL, 1.00 M) furnished **8h** in 67% yield (1.81 g, 6.72 mmol) after analogous purification.

M.p. (°C): 136-138.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ppm = 7.63-7.59 (m, 1H), 7.39 – 7.14 (m, 3H), 6.27 (s, 1H), 5.21 (s, 1H), 3.86 (s, 3H).

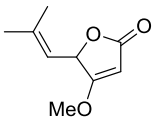
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 181.8, 172.5, 133.5, 133.4, 131.0, 128.1, 127.8, 124.1, 88.9, 79.2, 59.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3121(w), 1790(w), 1746(s), 1622(s), 1436(w), 1349(m), 1288(m), 1250(m), 1157(m), 1026(m), 987(m), 936(m), 892(m), 834(s), 754(s), 740(m), 726(m).

MS (70 eV, EI): *m/z* (%) = 270(33), 268(38), 234(15), 189(40), 183(41), 161(11), 157(14), 155(11),113(11), 105(11), 102(17), 101(10), 89(16), 85(100), 84(21), 77(34), 76(15), 75(21), 51(11), 50(12).

HRMS (EI): *m/z* calcd. for [$C_{11}H_9BrO_3$]: 267.9735; found: 267.9735 [M^+].

4-methoxy-5-(2-methylprop-1-en-1-yl)furan-2(5*H*)-one (8i)



According to **TP 1**, solutions of methyl (*E*)-3-methoxyacrylate (**6c**; 1.89 mL, 1.06 M) and TMPMgCl·LiCl (**2**; 1.89 mL, 1.17 M, 1.1 equiv.) were each pumped at 1.00 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor ($Vol.^M$ = 2 mL; t^M = 1:00 min; T^M = 40 °C) and was subsequently mixed with a third stream (pump C; flowrate: 1.00 mL/min) of 3-methylbut-2-enal solution (**4p**; 1.59 M, 1.5 equiv.). The combined stream passed a second coiled reactor ($Vol.^R$ = 10 mL; t^R = 3:20 min, T^R = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (4x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 7:3 → 2:1) afforded lactone **8i** as a colourless solid (211 mg, 1.25 mmol, 63%).

M.p. (°C): 99-109.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ppm = 5.40 (d, *J* = 8.8 Hz, 1H), 5.03 (s, 1H), 4.98 (d, *J* = 8.8 Hz, 1H), 3.83 (s, 3H), 1.77 (s, 3H), 1.76 (s, 3H).

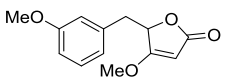
^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 182.1, 172.8, 142.8, 117.9, 88.4, 76.2, 59.6, 25.9, 18.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3121(w), 2947(w), 1738(s), 1627(s), 1453(m), 1439(m), 1378(m), 1350(s), 1292(m), 1278(m), 1242(s), 1162(s), 1013(s), 975(s), 956(m), 935(m), 901(s), 830(s), 817(s), 723(s), 674(m).

MS (70 eV, EI): *m/z* (%) = 168(40), 167(15), 153(17), 126(15), 125(11), 123(10), 85(18), 84(31), 83(20), 79(10), 57(10), 55(21), 53(15), 43(10), 43(10), 41(31).

HRMS (EI): *m/z* calcd. for [$C_9H_{12}O_3$]: 168.0786; found: 168.0779 [M^+].

4-methoxy-5-(3-methoxybenzyl)furan-2(5*H*)-one (8j)



According to **TP 1**, solutions of methyl (*E*)-3-methoxyacrylate (**6c**; 1.89 mL, 1.06 M) and TMPMgCl·LiCl (**2**; 1.89 mL, 1.17 M, 1.1 equiv.) were each pumped at 1.0 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor ($Vol.^M$ = 2 mL; t^M = 1:00 min; T^M = 40 °C) and was subsequently mixed with a third stream (pump C; flowrate: 0.75 mL/min) of 2-(3-methoxyphenyl)acetaldehyde solution (**4q**; 2.00 M, 1.5 equiv.). The

combined stream passed a second coiled reactor (Vol.^{R} = 10 mL; t^{R} = 3:38 min, T^{R} = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (4x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 7:3 → 2:1) afforded lactone **8j** as a colourless oil (153 mg, 0.65 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.20-7.16 (m, 1H), 6.83 – 6.71 (m, 3H), 4.97 (dd, *J* = 6.4, 3.7 Hz, 1H), 4.93 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.21 (dd, *J* = 14.5, 3.7 Hz, 1H), 2.89 (dd, *J* = 14.5, 6.4 Hz, 1H).

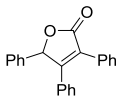
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 181.3, 172.3, 159.6, 136.2, 129.4, 122.0, 115.2, 112.8, 89.7, 78.8, 59.4, 55.3, 37.8.

IR (Diamond-ATR, Acetone): $\tilde{\nu}$/ cm^{-1} = 2946(w), 1759(s), 1700(s), 1635(s), 1490(m), 1457(w), 1382(w), 1309(w), 1263(m), 1244(m), 1153(s), 1051(m),1041(m), 987(w), 966(w), 926(w), 873(w), 805(m), 698(s).

MS (70 eV, EI): *m/z* (%) = 235(10), 234(67), 122(12), 121(100), 91(11), 85(16).

HRMS (EI): *m/z* calcd. for [$C_{13}H_{14}O_4$]: 234.0892; found: 234.0890 [M^{+}].

3,4,5-triphenylfuran-2(5*H*)-one (8l)



According to **TP 1**, solutions of isopropyl (*E*)-2,3-diphenylacrylate (**6b**; 2.00 mL, 0.50 M) and TMPMgCl·LiCl (**2**; 2.00 mL, 0.60 M, 1.1 equiv.) were each pumped at 0.50 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor (Vol.^{M} = 5 mL; t^{M} = 5:00 min; T^{M} = 50 °C) and was subsequently mixed with a third stream (pump C; flowrate: 0.50 mL/min) of benzaldehyde solution (**4e**, 0.75 M, 1.5 equiv.). The combined stream passed a second coiled reactor (Vol.^{R} = 10 mL; t^{R} = 6:40 min, T^{R} = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (5x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 9:1) afforded lactone **8l** as a colourless solid (229 mg, 0.73 mmol, 73%). Spectroscopic data matched those previously reported for this compound.[241]

With the same setup 15 mmol starting material (**6b**; 30.0 mL, 0.50 M) furnished **8l** in 73% yield (3.41 g, 10.9 mmol) after analogous purification.

M.p. (°C): 92.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.53 – 7.43 (m, 2H), 7.40 – 7.06 (m, 13H), 6.27 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 172.62, 159.51, 134.86, 131.21, 129.97, 129.93, 129.51 (2C), 129.44, 129.01 (2C), 128.92, 128.78 (2C), 128.64 (2C), 128.42 (2C), 127.72 (2C), 126.94, 83.81.

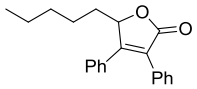
[241] M. Ohashi, H. Saijo, T. Arai,S. Ogoshi, et al. *Organometallics* **2010**, *29*, 6534.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3060(w), 1749(s), 1490(w),1445(m), 1352(m), 1154(m), 1106(w), 1008(m), 742(m), 692(s), 640(s).

MS (70 eV, EI) m/z (%) = 312(11), 207 (18), 179 (28), 178 (16), 136 (10), 105 (64), 85 (25), 83 (23), 77 (31), 71 (11), 70 (22), 69 (25), 59 (12), 58 (19), 57 (100), 56 (26), 55 (41), 51 (11), 43 (80), 43 (72), 41 (56).

HRMS (EI): *m/z* calcd. for [$C_{22}H_{16}O_2$]: 312.1150; found: 312.1144 [M^+].

5-pentyl-3,4-diphenylfuran-2(5*H*)-one (8m)



According to **TP 1**, solutions of isopropyl (*E*)-2,3-diphenylacrylate (**6b**; 2.00 mL, 0.50 M) and TMPMgCl·LiCl (**2**; 2.00 mL, 0.60 M, 1.1 equiv.) were each pumped at 0.50 mL/min flowrates (pump A and B) and the streams were combined in a T-mixer. The stream passed a coiled reactor ($Vol.^M$ = 5 mL; t^M = 5:00 min; T^M = 50 °C) and was subsequently mixed with a third stream (pump C; flowrate: 0.50 mL/min) of *n*-hexanal solution (**4s**; 0.75 M, 1.5 equiv.). The combined stream passed a second coiled reactor ($Vol.^R$ = 10 mL; t^R = 6:40 min, T^R = 25 °C) and was then collected. The aqueous layer was extracted with EtOAc (5x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (*iso*-hexane:EtOAc = 9:1) afforded lactone **8m** as a colourless liquid (300 mg, 0.98 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.53 – 7.08 (m, 10H), 5.59 – 5.30 (m, 1H), 1.96 – 1.72 (m, 1H), 1.62 – 1.39 (m, 3H), 1.33 – 1.17 (m, 4H), 0.95 – 0.69 (m, 3H).

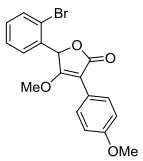
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 172.7, 160.7, 131.6, 130.1, 130.1 129.5 (2C), 129.1 (2C), 128.7, 128.6 (2C), 128.2 (2C), 126.8, 81.8, 32.9, 31.4, 24.2, 22.5, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2954(m), 2927(m), 2859(w), 1749(s), 1445(m), 1333(m), 1164(m), 1084(m), 1002(m), 977(m), 779(m), 756(m), 694(s), 642(m).

MS (70 eV, EI): m/z (%) = 306 (18), 279 (12), 267 (11), 251 (20), 235 (43), 208 (17), 207 (100), 180 (15), 179 (84), 178 (49), 105 (15), 42 (13).

HRMS (EI): *m/z* calcd. for [$C_{21}H_{22}O_2$]: 306.1620; found: 306.1617 [M^+].

5-(2-bromophenyl)-4-methoxy-3-(4-methoxyphenyl)furan-2(5*H*)-one (9a)



A back pressure regulator was installed and adjusted to maintain 2 bar pressure during the reaction. According to **TP 2**, solutions of 5-(2-bromophenyl)-4-methoxyfuran-2(5H)-one (**8h**; 2.0 mL, 0.5 M) and TMPZnCl·LiCl (**1**; 2.0 mL, 0.6 M, 1.2 equiv.) were each pumped with 0.50 mL/min flowrate (pump A and B) and the streams were combined in a T-mixer followed by a coiled reactor

(Vol.^{M} = 5 mL; t^{M} = 5:00 min; T^{M} = 70 °C) The combined stream was mixed in a T-mixer with a third stream (pump C; flowrate: 0.50 mL/min) of 4-iodo-anisole solution (**4e**; 0.4 M, 0.8 equiv.) with catalytic amounts of $Pd(dba)_2$ and TFP (0.01 M, 0.02 equiv. and 0.02 M, 0.04 equiv.). The combined streams passed a second coiled reactor (Vol.^{R} = 14 mL; t^{R} = 9:20 min; T^{R} = 60 °C). After discarding 1:00 minute prerun, a volume equivalent to 1.0 mmol of starting material was collected. The aqueous layer was extracted four times with EtOAc (4x25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatographic purification (*iso*-hexane:EtOAc = 8:2) afforded bisaryl butenolide **9a** as a colorless liquid (262 mg, 0.698 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.83 – 7.77 (m, 2H), 7.68 – 7.63 (m, 1H), 7.40 – 7.32 (m, 1H), 7.31 – 7.25 (m, 2H), 6.99 – 6.92 (m, 2H), 6.40 (s, 1H), 3.83 (s, 3H), 3.72 (s, 3H).

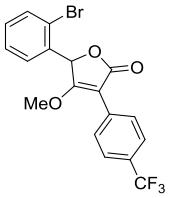
^{13}C-NMR (75 MHz, $CDCl_3$): *δ*/ppm = 172.3, 172.1, 159.3, 133.7, 133.4, 131.4, 129.9 (2C), 128.6, 128.4, 124.9, 121.6, 113.8 (2C), 104.3, 76.8, 59.2, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2923(m), 2853(m), 1740(m), 1640(m), 1605(m), 1511(m), 1458(m), 1359(m), 1296(m), 1244(s), 1161(s), 1033(s), 1017(s), 957(s), 933(m), 835(s), 817(s), 806(m) 772(s), 751(s), 733(m), 692(m), 631(m) .

MS (70 eV, EI): *m/z* (%) = 377 (18), 376 (92), 375 (18), 374 (96), 371 (12), 267 (23), 192 (13), 191 (100), 185 (15), 183 (15), 176 (14), 175 (18), 165 (20), 164 (12), 163 (67), 149 (12), 148 (75),147 (40), 135 (19), 133 (13), 131 (38), 119 (38), 103 (16), 91 (12), 77 (16), 76 (14).

HRMS (EI): *m/z* calcd. for [$C_{18}H_{15}BrO_4$]: 374.0154; 374.0149 [M^{+}].

5-(2-bromophenyl)-4-methoxy-3-(4-(trifluoromethyl)phenyl)furan-2(5*H*)-one (9b)

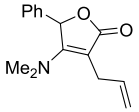


A back pressure regulator was installed and adjusted to maintain 2 bar pressure during the reaction. According to **TP 2**, solutions of 5-(2-bromophenyl)-4-methoxyfuran-2(5H)-one (**8h**;2.0 mL, 0.5 M) and TMPZnCl·LiCl (**1**; 2.0 mL, 0.60 M, 1.2 equiv.) were each pumped with 0.50 mL/min flowrate (pump A and B) and the streams were mixed in a T-piece followed by a coiled reactor (Vol.^{M} = 5 mL; t^{M} = 5:00 min; T^{M} = 70 °C). The combined stream was mixed in a T-mixer with a third stream (pump C; flowrate: 0.50 mL/min) of 1-iodo-4-(trifluoromethyl)benzene solution (**4t,** 0.4 M, 0.8 equiv.) with catalytic amounts of $Pd(dba)_2$ and TFP (0.01 M, 0.02 equiv. and 0.02 M, 0.04 equiv.) .The combined streams passed a second coiled reactor (Vol.^{R} = 14 mL; t^{R} = 9:20 min; T^{R} = 65 °C). After discarding 1:00 minute prerun, a volume equivalent to 1.0 mmol of starting material was collected. The aqueous layer was extracted with EtOAc (4x25 mL). The organic layers were combined and dried over

anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatographic purification (*iso*-hexane:EtOAc = 8:2) afforded **9b** as a colorless liquid (194 mg, 0.47 mmol, 59%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.07 – 8.04 (m, 2H), 7.72 – 7.62 (m, 3H), 7.42 – 7.30 (m, 1H), 7.32 (m, 1H), 7.29 – 7.25 (m, 1H), 6.50 (s, 1H), 3.79 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): *δ*/ppm = 174.7, 171.2, 134.0, 132.9 (2C), 132.8, 131.9, 131.8 ,130.0, 129.7, 128.8, 128.5 (2C), 125.3 (q, *J* = 3.8 Hz), 125.1, 103.5, 76.9, 59.5.
^{19}F-NMR (376 MHz, $CDCl_3$): *δ*/ppm = -62.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2924(w), 1746(s), 1639(s), 1467(m), 1369(m), 1321(s), 1305(s), 1161(s), 1109(s), 1067(s), 1057(s), 1018(s), 959(s), 856(s), 845(m), 835(m), 765(s), 738(m), 729(m), 690(m), 682(m).
MS (EI, 70 eV): m/z (rel. Intensity) = 145 (20), 231 (13), 230 (100), 187 (42), 158 (18).
HRMS (EI): *m/z* calcd. for [$C_{18}H_{12}BrF_3O_3$]: 411.9922; 411.9903 [M^+].

3-allyl-4-(dimethylamino)-5-phenylfuran-2(5*H*)-one (9c)



According to **TP 1**, solutions of 4-(dimethylamino)-5-phenylfuran-2(5*H*)-one (**8a**; 3.33 mL, 0.30 M) and TMPMgCl·LiCl (**2**; 3.33 mL, 0.36 M, 1.2 equiv.) were pumped at 0.25 mL/min flowrate (pump A and B). The streams were combined in a T-mixer followed by a coiled reactor ($Vol.^M$ = 5 mL; t^M = 10:00 min; T^M = 50 °C) and then mixed with a third stream (pump C; flowrate: 0.30 mL/min) of allyl bromide solution (**4a**; 0.50 M, 2.0 equiv.) charged with a catalytic amount of CuCN·2LiCl (0.025 M, 0.1 equiv) in a T-mixer. The combined streams passed a second coiled reactor ($Vol.^R$ = 10 mL; t^R = 12:15 min; T^R = 25 °C) and the crude product stream was subsequently collected. The aqueous layer was extracted with EtOAc (4x25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography (*iso*-hexane: EtOAc = 1:1→EtOAc) furnished lactone **9c** as a colorless liquid (157 mg, 0.65 mmol, 65%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.43 – 7.27 (m, 5H), 6.13 – 5.90 (m, 1H), 5.63 (s, 1H), 5.13-5.12 (m, 1H), 5.10-5.07 (m, 1H), 3.31 – 3.18 (m, 2H), 2.88 (s, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): *δ*/ppm = 175.4, 164.5, 137.8, 135.9, 129.5, 129.3 (2C), 128.0 (2C), 115.1, 92.9, 79.5, 41.0 (2C), 28.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3431(w), 2981(w), 2936(w), 1704(s), 1637(m), 1617(m), 1467(w), 1373(m), 1359(m), 1284(m), 1260(m), 1174(s), 1103(s), 1017(s), 974(s), 912(s), 883(s), 815(m), 747(m,), 703(s), 661(s).
MS (70 eV, EI): *m/z* (%) = 244(14), 243(100), 242(12), 228(16), 200(11), 198(42), 170(12), 162(10), 153(16), 152(91), 128(16), 115(14), 109(22), 108(19), 105(11), 94(67), 91(43), 77(17), 53(10), 44(13), 42(17).

HRMS (EI): *m/z* calcd. for [$C_{15}H_{17}NO_2$]: 243.1259; found: 243.1252 [M^+].

3 Barbier Continuous Flow Preparation and Reactions of Carbamoyllithiums for Nucleophilic Amidation

3.1 Preparation of starting materials

If not commercially available, the following procedures were used for the preparation of starting materials: **Preparation of formamides** from the corresponding amines:[242] *Method A:*[243] Formamides were prepared from formic acid (1.0 equiv), amine (1.0 equiv) and *N,N*-dicyclohexylcarbodiimide (DCC, 1.0 equiv) in dry CH_2Cl_2 (1M). DCC was added portionwise to a solution of the amines and formic acid, and the reaction was allowed to warm to room temperature overnight. After filtration, the combined filtrates were first washed with 10% HCl, then 1% $NaHCO_3$, and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, column chromatographic purification with suitable *iso*-hexane:EtOAc mixtures gave the pure products. *Method B:*[244] Formamides were prepared from the amine (1.0 equiv) and *in situ* generated acetyl formyl anhydride (AFA, 2.6 equiv) in dry THF (1M). Ac_2O (2.6 equiv) and HCO_2H (3.2 equiv) were mixed neat at 25 °C and then stirred 1 h at 40 °C. After cooling to 25 °C, a 1 M solution of the amine in dry THF was added dropwise and the resulting mixture was stirred overnight. *With some amines, the reaction is highly exothermic and cooling with an ice bath is necessary.* After addition of water (same volume as the reaction mixture) and neutralization with K_2CO_3, the mixture was filtered and extracted twice with CH_2Cl_2. After removal of the volatiles *in vacuo*, column chromatographic purification with suitable *iso*-hexane:EtOAc mixtures gave the pure products.

Preparation of thioformamides: Thioformamide **10m** was prepared according to a literature procedure from the corresponding formamide.[245]

Preparation of morpholineamides: In an argon filled flask with a gas outlet was given a 2.5 M solution of the corresponding methyl or ethyl ester (1.0 equiv) in dry THF: morpholine (1:1). Then a mehtylmagnesium chloride solution in THF (ca. 2.5 M, 1.05 equiv) was carefully added *via* syringe. *Attention must be paid to avoid pressure buildups.* The solution is subsequently stirred for 1 h without cooling and quenched with addition of *sat. aq.* NH_4Cl solution. Extraction with EtOAc, drying over anhydrous $MgSO_4$, filtration, removal of the solvent and flash column chromatographic purification with suited *iso*-hexane:EtOAc mixtures furnishes the corresponding morpholine amides.

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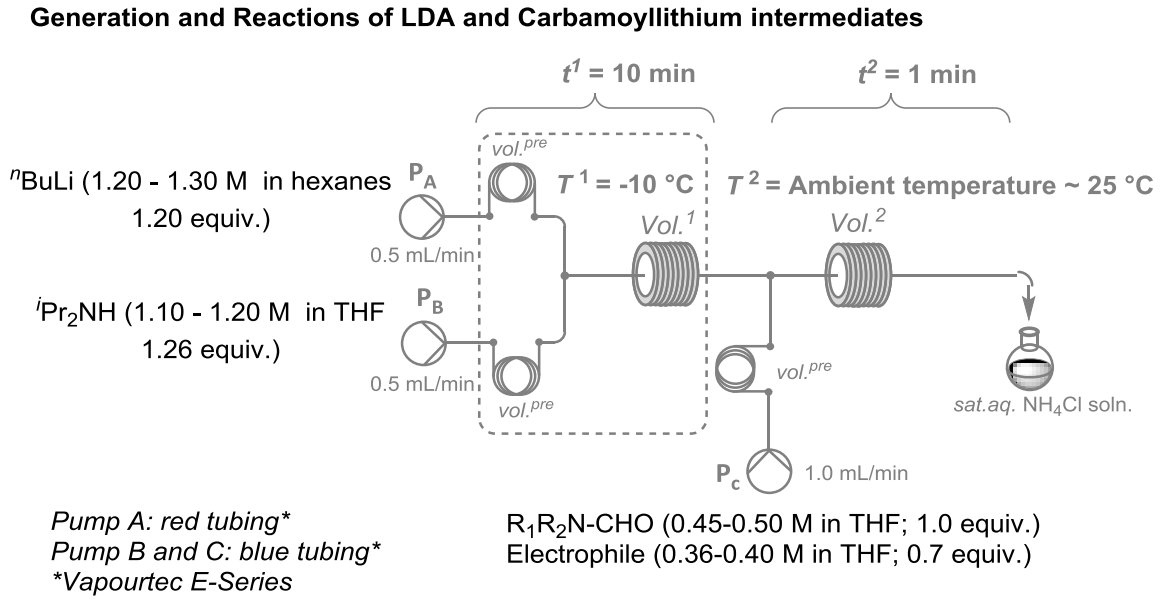
[242] C. J. Gerack, L. McElwee-White, *Molecules* **2014**, *19*, 7689.
[243] See: D. Zeng, Q. Mi, H. Sun, H. Wang, *J. Label Compd. Radiopharm.* **2004**, *47*, 167.
[244] See: J. C. Anderson, M. Harding, *Chem. Commun*., **1998**, 393.
[245] D. Brillon, *Synth. Commun.* **1990**, *20*, 3085.

Preparation of Weinreb amides: Weinreb amides were prepared from the corresponding acid chlorides as described in the literature.[246]

3.2 Analysis of the products

Due to the often pronounced chemical inequivalence of unsymmetrically substituted *N*,*N*-dialkylformamides and to a greater extent that of analogue thioformamides,[247] mixtures of rotamers were often obtained. This effect was further enhanced by the presence of α-keto groups ($R^1R^2NC(O)$-C(O)R) If possible, the corresponding ratio of rotamers is reported in the analytical section.

3.3 Typical Procedure 3 (TP 3, Carbamoyllithium generation and reaction)



Scheme 43: TP 3 flow setup.

A commercially available setup from Vapourtec Ltd. (E-Series) was used for all reactions (Scheme 43). The reagent solutions were prepared in flasks under argon and suction needles delivered the solutions directly through the pumps (A, B, C) to the reactors (Vol.[1], Vol.[2]). Precooling loops (vol.[pre] = 1 mL) were installed before the reagents were mixed in T-mixers.

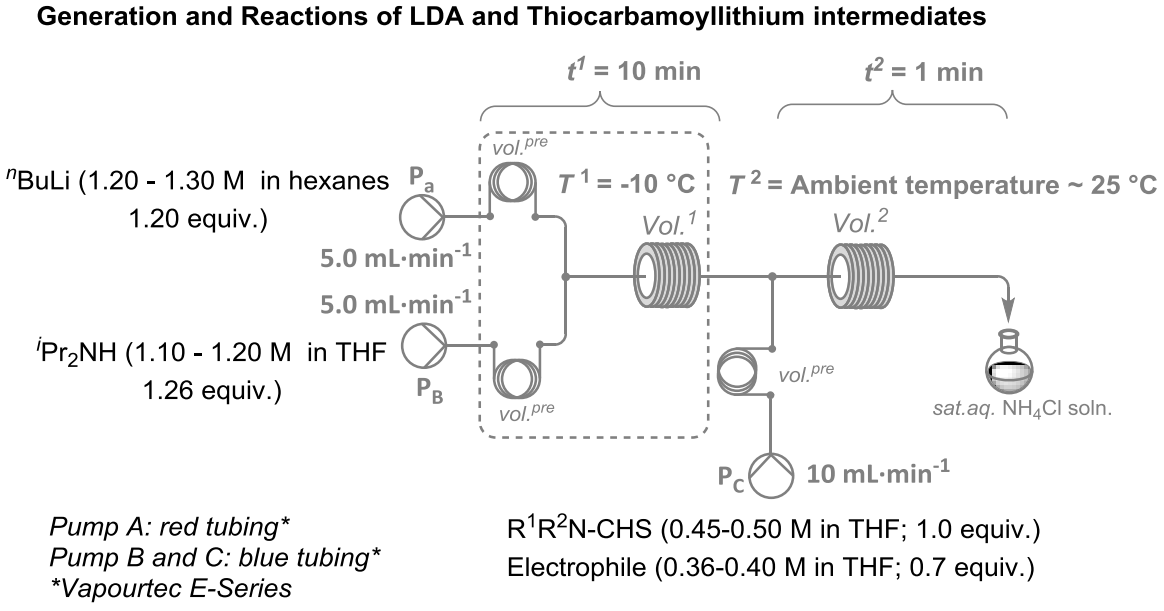
For the continuous flow preparation of LDA, a 1.2−1.3 M solution of ^{n}BuLi (1.20 equiv) in hexane and a 1.1−1.2 M solution of ^{i}Pr$_2$NH (1.26 equiv) in THF were each pumped at 0.50 mL·min^{-1} flowrate

[246] Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem.Soc.* **2010**, *132*, 8862.
[247] a) M. Geffe, L. Andernach, O. Trapp, T. Opatz, *Beilstein J. Org. Chem.* **2014,** *10*, 701–706. b) K. B. Wiberg, P. R. Rablen, *J. Am. Chem.* Soc. **1995,** *117***,** 2201 – 2209. c) T. M. Valega *J. Org. Chem.*, 1966, *31* , 1150 – 1153.

(pump A and B). The streams were combined in a T-mixer (I.D. = 1.0 mm) followed by a 10 mL coiled reactor, immersed in a cooling bath (Vol.^{1} = 10 mL; t^1 = 10:00 min; T^1 = −10 °C).

The lithium diisopropylamine stream[248] was mixed (T-mixer, I.D. = 0.5 mm) with a third stream containing the formamide substrate (0.45−0.50 M; 1.0 equiv) and the electrophile (0.36−0.40 M; 0.7 equiv) (pump C; flowrate: 1.0 mL/min) and the combined streams passed a second coiled reactor (Vol.^{2} = 2 mL; t^2 = 1:00 min; T^2 = 25 °C) and were then passed into a flask with water or a *sat. aq.* NH_4Cl solution (ca. 15 mL/mmol substrate). The quench solutions of larger scale reactions (> 2 mmol) were stirred with a magnetic stirrer to quickly dissolve salts in the aqueous phase and prevent clogging at the reactor output. The aqueous layer was extracted repeatedly with suitable amounts of EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$ or Na_2SO_4. After removal of the solvent *in vacuo*, column chromatographic purification with suitable *iso*-hexane:EtOAc mixtures gave the pure products.

3.4 Typical Procedure 4 (TP 4, Thiocarbamoyllithium generation and reaction)



Scheme 44: TP 4 flow setup.

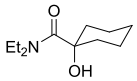
For the continuous flow preparation of LDA, a 1.2-1.3 M solution of ^{n}BuLi (1.20 equiv) in hexane and a 1.1−1.2 M solution of ^{i}Pr$_2$NH (1.26 equiv) in THF were each pumped at 5.00 mL/min flowrate (pump A and B, Scheme 44). The streams were combined in a T-mixer (I.D. = 1.0 mm) followed by a 10 mL coiled reactor, immersed in a cooling bath (Vol.^{1} = 10 mL; t^1 = 1:00 min; T^1 = −10 °C).

[248] Titration of defined amounts of the LDA solution output according to a literature known procedure (A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.*, **1997**, *542*, 28.) indicated reproducible, quantitative LDA formation (for instance, LDA made from 1.28 M BuLi gave 0.63±0.1 M LDA; 98%).

The lithium diisopropylamine stream[248] was mixed (T-mixer, I.D. = 0.5 mm) with a third stream containing the formamide substrate (0.45 – 0.50 M; 1.0 equiv) and the electrophile (0.36 – 0.40 M; 0.7 equiv) (pump C; flowrate: 10.0 mL/min) and the combined streams passed a second coiled reactor ($Vol.^2$ = 16 mL; t^2 = 0:48 min; T^2 = 25 °C) and were then passed into a flask with water or a *sat. aq.* NH_4Cl solution (ca. 15 mL/mmol substrate). The aqueous layer was extracted repeatedly with suitable amounts of EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$ or Na_2SO_4. After removal of the solvent *in vacuo*, column chromatographic purification with suitable *iso*-hexane:EtOAc mixtures gave the pure products.

3.5 Preparation of the Products

N,*N*-Diethyl-1-hydroxycyclohexanecarboxamide (12a)



According to **TP 3**, a mixture of *N*,*N*-diethylformamide (**10a**, 0.50 M, 1.00 mmol) and cyclohexanone (**11a**, 0.35 M, 0.70 mmol) in THF (total volume: 2 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 7:3) afforded the title compound as a colourless crystalline solid (132 mg, 0.66 mmol, 95%).

Mp (°C) : 82-84.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 3.95 (s, OH), 3.84 – 3.11 (m, 4H), 1.87 – 1.78 (m, 2H), 1.78 – 1.59 (m, 7H), 1.28 – 1.22 (m, 1H), 1.22 – 1.05 (m, 6H).

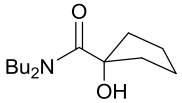
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 175.4, 74.3, 42.4 (2C), 34.9 (2C), 25.5 (2C), 21.9 (3C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3399(w, br), 2961(w), 2929(w), 1605(s), 1461(w), 1426(s), 1378(m), 1289(m), 1272(m), 1217(w), 1166(m), 1056(s), 988(s), 910(w), 818(m), 738(w).

MS (EI, 70 eV): *m/z* (%) = 199(0), 102(29), 101(72), 100(22), 99(100), 86(29), 81(91), 73(22), 72(28), 69(11), 58(49), 57(11), 55(23), 44(12), 43(32), 41(25).

HRMS (EI): *m/z* calc. for [$C_{11}H_{21}NO_2$]: 199.1572; found: 199.1555 [M^+].

N,*N*-Dibutyl-1-hydroxycyclopentanecarboxamide (12d)



According to **TP 3**, a mixture of *N*,*N*-dibutylformamide (**10d**, 0.50 M, 1.00 mmol) and cyclopentanone (**11b**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 equiv) and the combined streams were quenched in

sat. aq. NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 7:3) afforded the title compound as a colourless liquid (116 mg, 0.48 mmol, 69%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.04 (s, OH), 3.35 – 3.22 (m, 4H), 2.14 – 1.98 (m, 2H), 1.92 – 1.65 (m, 6H), 1.60 – 1.46 (m, 3H), 1.29 (q, *J* = 7.5 Hz, 4H), 1.24 – 1.22 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 6H).

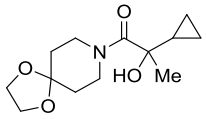
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 175.1, 82.6, 39.9 (2C), 32.0, 29.8, 29.5, 25.2 (2C), 24.0, 22.8, 20.3, 14.0 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3384(w), 2959(m), 2932(w), 2873(w), 1609(s), 1467(w), 1430(w), 1377(w), 1292(w), 1265(m), 1192(w), 1100(w), 1010(w), 908(w), 733(s), 703(s).

MS (EI, 70 eV): *m/z* (%) = 241(0,3), 157(11), 114(100), 86(23), 85(16), 57(12).

HRMS (EI): *m/z* (%) = calc. for [$C_{14}H_{27}NO_2$]: 241.2042; found: 241.2018 [M^+].

2-Cyclopropyl-2-hydroxy-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)propan-1-one (12e)



According to **TP 3**, a mixture of 1,4-dioxa-8-azaspiro[4.5]decane-8-carbaldehyde (**10e**, 0.50 M, 1.00 mmol) and 1-cyclopropylethanone (**11c**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 6:4) afforded the title compound as a colourless liquid (129 mg, 0.51 mmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.68 (s, OH), 3.99 (s, 4H), 3.80 (t, *J* = 5.5 Hz, 2H), 1.74 (t, *J* = 5.8 Hz, 4H), 1.66 – 1.57 (m, 2H), 1.44 (s, 3H), 1.12 – 1.01 (m, 1H), 0.72 – 0.61 (m, 1H), 0.48 – 0.36 (m, 3H).

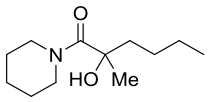
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 175.2, 106.9, 71.6, 64.7 (2C), 43.7, 35.5, 25.6 (2C), 18.5 (2C), 2.0, 1.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3382(br, w), 2962(w), 2884(w), 1616(s), 1440(m), 1359(m), 1338(m), 1265(m), 1243(m), 1188(m), 1143(m), 1092(s), 1033(m), 945(m), 918(m), 902(m), 828(w), 811(w), 735(w), 661(w).

MS (EI, 70 eV): *m/z* (%) = 256(0,4), 171(34), 170(10), 143(69), 142(15), 128(13), 99(31), 98(4), 87(25), 85(96), 43(100), 42(10).

HRMS (EI): *m/z* (%) = calc. for [$C_{13}H_{22}NO_4$]: 255.1471; found: 256.1544 [$M+H^+$].

2-Hydroxy-2-methyl-1-(piperidin-1-yl)hexan-1-one (12f)



According to **TP 3**, a mixture of piperidine-1-carbaldehyde (**10f**, 0.50 M, 1.00 mmol) and hexan-2-one (**11d**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 6:4) afforded the title compound as a colourless liquid (87 mg, 0.40 mmol, 58%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.97 (s, OH), 3.55 (s, 4H), 1.73 – 1.61 (m, 4H), 1.59 – 1.49 (m, 4H), 1.47 – 1.35 (m, 4H), 1.26 (h, J = 7.3 Hz, 2H), 1.12 – 0.99 (m, 1H), 0.85 (t, J = 7.3 Hz, 3H).

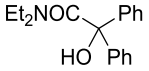
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 174.3, 73.8, 40.3 (2C), 26.6 (2C), 26.2, 26.1, 24.5, 22.9 (2C), 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3382(br; w), 2934(m), 2859(m), 2360(w), 1609(s), 1467(m), 1442(m), 1372(m), 1250(s), 1217(m), 1174(m), 1129(s), 1057(m), 1013(s), 953(m), 922(m), 853(m), 824(w), 752(w), 730(s), 686(m).

MS (EI, 70 eV): *m/z* (%): 214(1), 156(23), 114(45), 113(33), 112(23), 101(100), 98(19), 86(23), 85(38), 84(36), 83(14), 69(15), 57(10), 55(17), 45(25), 43(16), 41(23).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{23}NO_2$] : 213.1729; found: 214.1807 [M+ H^+].

***N*,*N*-Diethyl-2-hydroxy-2,2-diphenylacetamide (12h)**



According to **TP 3**, a mixture of *N*,*N*-diethylformamide (**10a**, 0.50 M, 1.00 mmol) and benzophenone (**11f**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a colourless crystalline solid (150 mg, 0.53 mmol, 76%).

M.p. (°C): 107.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 – 7.21 (m, 10H), 6.18 (s, 1H) 3.40 (q, J = 6.6 Hz, 2H), 2.99 (q, J = 6.4 Hz, 2H), 1.19 (t, J = 6.8 Hz, 3H), 0.10 (t, J = 6.7 Hz, 3H).

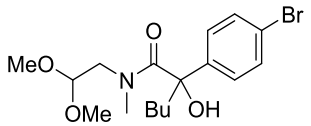
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 172.6, 142.1 (2C), 128.5(4C), 128.4(4C), 127.9 (2C), 80.4, 43.7, 41.9, 12.3, 11.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3310(br,w), 3060(w), 2872(w), 2936(w), 1623(s), 1492(m), 1463(m), 1443(s), 1379(m), 1360(m), 1310(m), 1272(s), 1214(m), 1167(m), 1144(m), 1083(m), 1040(s), 958(m), 940(w), 910(m), 853(w), 763(s), 728(s), 699(s).

MS (EI, 70 eV): m/z (rel. Intensity) = 283(0.17), 184(13), 183(100), 181(12), 165(15), 105(67), 77(29).

HRMS (EI) calc. for [$C_{18}H_{21}NO_2$]: 283.1572; found: 283.1572 [M^+].

2-(4-Bromophenyl)-*N*-(2,2-dimethoxyethyl)-2-hydroxy-*N*-methylpropanamide (12i)



According to **TP 3**, a mixture of *N*-(2,2-dimethoxyethyl)-*N*-methylformamide (**10h**, 0.50 M, 1.00 mmol) and 1-(4-bromophenyl)ethanone (**11g**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 6:4) afforded the title compound as a colourless oil (164 mg, 0.44 mmol, 63%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.49 – 7.40 (m, 2H), 7.29 – 7.18 (m, 2H), 5.34 – 4.43 (m, 2H), 3.68 – 3.50 (m, 1H), 3.34 (m, 7H), 2.69 (m, 2H), 2.99 (s, OH) 2.25 – 2.06 (m, 2H), 1.46 – 0.99 (m, 4H), 0.98 – 0.83 (m, 3H).

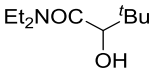
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 174.1, 142.0, 131.9, 127.7, 121.9, 102.7, 77.08, 54.9, 52.4 (2C), 38.1, 36.0, 25.7, 23.1 (2C), 14.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3386(br,w), 2955(w), 2931 (s), 1619(m), 1486(w), 1466(w), 1396(w), 1286(w), 1189(w), 1122(m), 1071(s), 1009(m), 971(m), 826(m), 760(w), 730(w).

MS (EI, 70 eV): *m/z* (%) = 356(2), 240(23), 75(100), 57(43).

HRMS (ESI): *m/z* calcd. for [$C_{17}H_{26}NO_3$]: 387.1045; found: 388.1117 [M+H^+].

***N*,*N*-Diethyl-2-hydroxy-3,3-dimethylbutanamide (12j)**



According to **TP 3**, a mixture of *N*,*N*-diethylformamide (**10a**, 0.50 M, 1.00 mmol) and trimethylacetaldehyde (**11h**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a colourless liquid (120 mg, 0.64 mmol, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.15 – 4.00 (m, 1H), 3.79 (dq, *J* = 14.9, 7.1 Hz, 1H), 3.59 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.29 – 3.21 (m, 1H), 3.13 (dq, *J* = 14.5, 7.2 Hz, 1H), 3.03 (dq, *J* = 14.2, 7.1 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.95 (s, 9H).

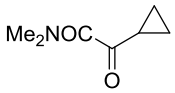
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 173.0, 74.1, 42.3, 40.3, 36.5, 26.1 (3C), 14.3, 13.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436(w; br), 2968(w), 2910(w), 2247(w), 1626(s), 1481(m), 1467(m), 1394(m), 1361(m), 1278(m), 1217(m), 1141(w), 1066(s), 1019(m), 950(w), 909(s), 878(m), 827(m), 728(s), 701(m).

MS (EI, 70 eV): *m/z* (%) = 187(9), 131(96), 130(100), 102(67), 101(42), 87(22), 86(41), 74(14), 73(11), 72(61), 69(12), 58(29), 41(14).

HRMS (EI): *m/z* calc**.** for [$C_{13}H_9N_3O$]: 187.1572; found: 187.1563 [M^+].

2-Cyclopropyl-*N*,*N*-dimethyl-2-oxoacetamide (14a)



According to **TP 3**, a mixture of *N*,*N*-dimethylformamide (**10g**, 0.50 M, 1.00 mmol) and *N*-methoxy-*N*-methylcyclopropanecarboxamide (**13a**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 7:3) afforded the title compound as a colourless liquid (62 mg, 0.44 mmol, 63%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 2.97 (s, 3H), 2.96 (s, 3H), 2.33 – 2.28 (m, 1H), 1.20 – 1.16 (m, 2H), 1.10 – 1.05 (m, 2H).

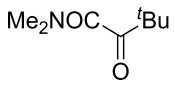
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 201.1, 167.1, 37.2, 34.5, 19.7, 12.8 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3503(w), 1691(m), 1632(s), 1507(w), 1447(w), 1418(m), 1406(m), 1371(m), 1262(w), 1196(w), 1052(s), 1021(s), 995(w), 880(m), 854(w), 746(w).

MS (EI, 70 eV): *m/z* (%): 147(11), 104(11), 103(92), 97(13), 85(25), 83(16), 81(12),75(64), 73(29), 72(36), 71(36), 70(14), 69(23), 58(19), 57(56), 56(11), 55(26), 47(100), 44(26), 43(38), 43(23), 41(20).

HRMS (EI): *m/z* calc. for [$C_7H_{11}NO_2$]: 141.0790; found: 141.0763 [M^+].

***N*,*N*,3,3-Tetramethyl-2-oxobutanamide (14b, scale-up)**



According to **TP 3**, a mixture of *N*,*N*-dimethylformamide (**10g**, 0.50 M, 35.00 mmol) and *N*-methoxy-*N*-methylpivalamide (**13b**, 0.35 M, 24.50 mmol) in THF (total volume: 70.00 mL) reacted with

continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in vigorously stirred *sat. aq.* NH_4Cl solution. The aqueous phase was extracted with EtOAc (3×200 mL) and CH_2Cl_2 (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, *iso*-hexane:EtOAc = 6:4) afforded the title compound as a colourless liquid (2.49 g, 15.85 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 2.95 – 2.88 (m, 3H), 2.86 – 2.80 (m, 3H), 1.23 – 1.16 (m, 9H).

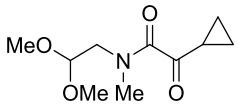
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 208.7, 167.6, 42.9, 36.9, 33.6, 26.5 (3C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2967(w), 2936(w), 1702(m), 1635(s), 1507(w), 1479(m), 1464(m), 1404(m), 1366(w), 1255(w), 1176(w), 1045(s), 1006(s), 896(m), 815(w), 775(w), 750(w), 733(w), 658(m).

MS (EI, 70 eV): *m/z* (%) = 157(27), 85(14), 74(13), 73(10), 72(100), 57(60), 40(16).

HRMS (EI): *m/z* calc. for [$C_8H_{15}NO_2$]: 157.1103; found: 157.1096 [M^+].

2-Cyclopropyl-*N*-(2,2-dimethoxyethyl)-*N*-methyl-2-oxoacetamide (14c)



According to **TP 3**, a mixture of *N*-(2,2-dimethoxyethyl)-*N*-methylformamide (**10h**, 0.50 M, 1.00 mmol) and *N*-methoxy-*N*-methylcyclopropanecarboxamide (**13a**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 97:3) afforded the title compound as a pale yellow oil (115 mg, 0.53 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.55 – 4.37 (m, 1H), 3.50 – 3.44 (m, 1H), 3.42 – 3.39 (m, 1H), 3.39 – 3.37 (m, 3H), 3.37 – 3.34 (m, 3H), 3.06 – 2.99 (m, 3H), 2.41 – 2.23 (m, 1H), 1.22 – 1.02 (m, 4H).

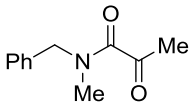
^{13}C-NMR (100 MHz, $CDCl_3$, 2 conformers A : B ~ 1 : 1): δ / ppm = 201.0(A), 200.6(B), 168.0(A), 167.4(B), 103.8(A), 102.6(B), 55.2(A+B), 54.8(A+B), 51.8(A+B), 49.3(A+B), 37.0(A+B), 34.7(A+B), 19.7(A+B), 12.9(A), 12.7(B).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2940(w), 2836(w), 1693(m), 1636(s), 1490(w), 1445(w), 1409(w), 1372(s), 1192(m), 1124(s), 1070(s), 1050(s), 1017(s), 978(m), 924(m), 881(w), 730(s), 687(m).

MS (EI, 70 eV): *m/z* (%): 215 (0), 114(10), 75(100), 69(10).

HRMS (EI): *m/z* calc. for [$C_{10}H_{17}NO_4$]: 215.1158; found: 215.1163 [M^+].

***N*-benzyl-*N*-methyl-2-oxopropanamide (14d)**



According to **TP 3**, a mixture of *N*-benzyl-*N*-methylformamide (**10c**, 0.50 M, 1.00 mmol) and *N*-methoxy-*N*-methylacetamide (**13c**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 6:4) afforded the title compound as a colorless oil (98 mg, 0.51 mmol, 72%).

^{1}H-NMR (600 MHz, $CDCl_3$, 2 conformers A : B = 1 : 1): δ / ppm = 7.38 – 7.17 (m, 10$\mathbf{H_{A+B}}$), 4.57 (s, 2$\mathbf{H_{A+B}}$), 4.47 (s, 2$\mathbf{H_{A+B}}$), 2.89 (s, **3**$\mathbf{H_{A+B}}$), 2.88 (s, 3$\mathbf{H_{A+B}}$), 2.44 (s, 3$\mathbf{H_{A+B}}$), 2.39 (s, 3$\mathbf{H_{A+B}}$).

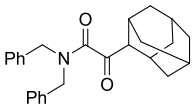
^{13}C-NMR (150 MHz, $CDCl_3$, 2 conformers A:B = 1:1): δ / ppm = 198.7(**A+B**), 167.3(**A**), 166.7(**B**), 135.8(**A**), 135.7(**B**), 129.0(2**A**), 128.9(2**B**), 128.3(2**A**), 128.2(**A**), 127.9(**B**), 127.6(2**B**), 53.4**(A)**, 50.5(**B**), 34.7(**A**), 32.6(**B**), 27.9(**A**), 27.8(**B**).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2509(w), 3032(w), 2930(w), 1712(m), 1634(s), 1496(m), 1454(m), 1414(m), 1354(m), 1264(w), 1219(w), 1168(m), 1090(m), 1018(m), 988(w), 962(m), 820(w), 716(m), 679(s).

MS (EI, 70 eV): *m/z* (%): 191(3), 120(12), 91(100), 43(17).

HRMS (EI): *m/z* calc. for [$C_{11}H_{13}NO_2$]: 191.0946; found: 191.0942 [M^+].

***N*,*N*-Dibenzyl-2-(7-ethylbicyclo[3.3.1]nonan-2-yl)-2-oxoacetamide (14e)**



According to **TP 3**, a mixture of *N*,*N*-dibenzylformamide (**10j**, 0.50 M, 1.00 mmol) and *N*-methoxy-*N*-methyladamantane-2-carboxamide (**13d**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 97:3) afforded the title compound as a colorless oil (207 mg, 0.53 mmol, 76%).

M.p.(°C): 109.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.14 (m, 10H), 4.48 (s, 2H), 4.16 (s, 2H), 2.07 (dt, *J* = 5.7, 3.3 Hz, 3H), 2.00 (d, *J* = 3.2 Hz, 6H), 1.81 – 1.70 (m, 6H).

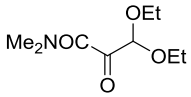
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 207.4, 167.9, 136.1, 135.0, 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.3, 128.3 (2C), 127.8, 50.0, 45.6, 45.1, 38.3 (3C), 36.4 (3C), 27.9 (3C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2907(w), 2886(w), 2360(w), 1697(m), 1622(s), 1586(w), 1495(w), 1450(m), 1404(m), 1365(w), 1344(w), 1191(m), 1158(m), 1148(m), 1079(w), 1039(w), 1028(w), 984(w), 973(w), 953(m), 937(m), 917(w), 819(w), 757(m), 739(s), 727(m), 697(s), 657(s)..

MS (EI, 70 eV): *m/z* (%) 387(3), 224(12), 136(11), 135(85), 92(12), 91(100), 79(12), 44(32)..

HRMS (EI): *m/z* calc. for [$C_{26}H_{29}NO_2$]: 387.2198; found: 387.2190 [M^+].

3,3-Diethoxy-*N*,*N*-dimethyl-2-oxopropanamide (14f)



According to **TP 3**, a mixture of *N*,*N*-dimethylformamide (**10g**, 0.50 M, 1.00 mmol) and 2,2-diethoxy-1-morpholinoethan-1-one (**13e**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 7:3) afforded the title compound as a colourless oil (106 mg, 0.52 mmol, 75%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 5.25 (s, 1H), 3.75 (dq, *J* = 9.2, 7.1 Hz, 2H), 3.64 (dq, *J* = 9.2, 7.2 Hz, 2H), 2.95 (s, 3H), 2.93 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 6H).

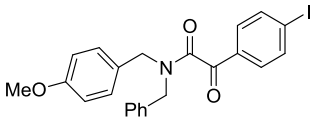
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 194.4, 166.9, 99.5, 64.5 (2C), 36.7, 34.1, 15.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3394(w), 2928(m), 2857(w), 1515(s), 1496(w), 1454(m), 1366(m), 1257(w), 1171(m), 1076(m), 1028(w), 940(w), 909(m), 729(s), 697(s).

MS (EI, 70 eV): *m/z* (%): 147(11), 104(11), 103(92), 97(13), 85(25), 83(16), 81(12),75(64), 73(29), 72(36), 71(36), 70(14), 69(23), 58(19), 57(56), 56(11), 55(26), 47(100), 44(26), 43(38), 43(23), 41(20).

HRMS (EI)*:* *m/z* calc. for [$C_9H_{17}NO_4$]: 203.1158; found: 158.0468 [$M-C_2H_5OH^+$].

***N*-Benzyl-2-(4-iodophenyl)-*N*-(4-methoxybenzyl)-2-oxoacetamide (14g)**



According to **TP 3**, a mixture of *N*-benzyl-*N*-(4-methoxybenzyl)formamide (**10k**, 0.50 M, 1.00 mmol) and (4-iodophenyl)(morpholino)methanone (**13f**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated.

After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a colorless oil (280 mg, 0.57 mmol, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$, mixture of conformers A:B=1:1): δ / ppm = 7.87 (d, J = 8.6 Hz, 4H), 7.67 (d, J = 8.6 Hz, 4H), 7.42 – 7.29 (m, 8H), 7.27 – 7.19 (m, 4H), 7.15 – 7.09 (m, 2H), 6.94 – 6.88 (m, 2H), 6.86 – 6.80 (m, 2H), 4.61 (s, 2$\mathbf{H_A}$), 4.56 (s, 2$\mathbf{H_B}$), 4.26 (s, 2$\mathbf{H_A}$), 4.21 (s, 2$\mathbf{H_B}$), 3.83 (s, 3$\mathbf{H_B}$), 3.79 (s, 3$\mathbf{H_A}$).

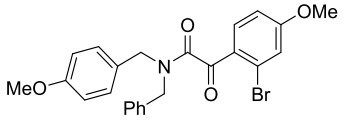
^{13}C-NMR (100 MHz, $CDCl_3$, mixture of conformers): δ / ppm = 190.6, 190.5, 166.9, 166.9, 159.7, 159.5, 138.5, 138.4, 136.0, 134.9, 132.7, 132.7, 131.0, 130.9, 130.2, 129.7, 129.0, 129.0, 128.7, 128.4, 128.2, 128.1, 127.9, 126.7, 114.4, 114.3, 103.4, 103.4, 55.4, 50.0, 49.7, 46.2, 45.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2934(w), 2251(w), 1750(w), 1681(m), 1635(s), 1612(m), 1580(m), 1512(m), 1482(w), 1454(m), 1440(m), 1394(m), 1362(w), 1247s), 1201(m), 1174(s), 1111(w), 1058(m), 1032(m), 1007(m), 954(m), 905(s), 841(m), 753(s), 698(s).

MS (EI, 70 eV): *m/z* (%) =485(3), 231(28), 227(14), 226(90), 121(100), 91(22).

HRMS (EI): *m/z* calc. for [$C_{23}H_{20}INO_3$]: 485.0488; found: 485.0483 [M^+].

***N*-Benzyl-2-(4-iodophenyl)-*N*-(4-methoxybenzyl)-2-oxoacetamide (14h)**



According to **TP 3**, a mixture of *N*-benzyl-*N*-(4-methoxybenzyl)formamide (**10k**, 0.50 M, 1.00 mmol) and (2-bromo-4-methoxyphenyl)(morpholino)methanone (**13g**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a pale yellowish oil (269 mg, 0.57 mmol, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$, mixture of conformers A: B= 1.1:1.0): δ / ppm = 8.18 (dd, J = 3.4, 2.1 Hz, 1H), 7.96 – 7.91 (m, 1H), 7.43 – 7.38 (m, 1H), 7.37 – 7.30 (m, 3H), 7.29 – 7.23 (m, 2H), 7.15 (d, J = 8.7 Hz, 1H), 6.97 (dd, J = 8.7, 1.7 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 4.59 (d, J = 20.9 Hz, 2H), 4.25 (d, J = 18.4 Hz, 2H), 4.01 – 3.95 (m, 1.5$\mathbf{H_B}$), 3.84 (s, 3 $\mathbf{H_{A+B}}$), 3.80 (s, 1.7H $\mathbf{H_A}$).

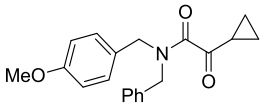
^{13}C-NMR (100 MHz, $CDCl_3$, mixture of conformers): δ / ppm = 190.6, 190.5, 166.9, 166.9, 159.7, 159.5, 138.5, 138.4, 136.0, 134.9, 132.7, 132.7, 131.0, 130.9, 130.2, 129.7, 129.0, 129.0, 128.7, 128.4, 128.2, 128.1, 127.9, 126.7, 114.4, 114.3, 103.4, 103.4, 55.4, 50.0, 49.7, 46.2, 45.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2937(w), 1750(w), 1670(m), 1635(s), 1611(m), 1588(s), 1559(m), 1512(s), 1496(m), 1455(m), 1439(m), 1362(w), 1273(s), 1246(s), 1192(s), 1176(s), 1110(m), 1050(m), 1031(m), 1015(m), 961(m), 906(s), 812(m), 742(s), 700(s).

MS (EI, 70 eV): *m/z* (%) = 467(2), 227(13), 226(100), 215(26), 213(26), 135(18), 121(81), 91(22).

HRMS (EI): *m/z* calc. for [$C_{24}H_{22}BrNO_4$]: 467.0732; found: 467.0731 [M^+].

_N_-Benzyl-2-(4-iodophenyl)-_N_-(4-methoxybenzyl)-2-oxoacetamide (14i)



According to **TP 3**, a mixture of *N*-benzyl-*N*-(4-methoxybenzyl)formamide (**10k**, 0.50 M, 1.00 mmol) and *N*-methoxy-*N*-methylcyclopropanecarboxamide (**13a**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a colorless oil (192 mg, 0.60 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 – 7.28 (m, 3H), 7.27 – 7.22 (m, 2H), 7.21 – 7.14 (m, 2H), 6.92 – 6.84 (m, 2H), 4.52 (s, 1H), 4.48 (s, 1H), 4.36 (s, 1H), 4.30 (s, 1H), 3.83 – 3.78 (m, 3H), 2.45 – 2.35 (m, 1H), 1.29 – 1.18 (m, 2H), 1.16 – 1.05 (m, 2H).

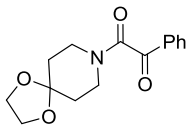
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 201.1, 201.0, 167.9, 167.9, 159.5, 159.3, 136.1, 135.7, 130.0, 129.4, 128.9, 128.8, 128.6, 128.1, 128.0, 127.9, 127.8, 127.4, 114.2, 55.3, 49.8, 49.5, 46.4, 46.1, 20.2, 20.1, 13.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2934(w), 2252(w), 1696(w), 1635(s), 1513(m), 1455(w), 1442(w), 1375(w), 1303(w), 1248(m), 1176(m), 1107(w), 1073(w), 1032(m), 976(m), 905(s), 820(w), 724(s), 699(s).

MS (EI, 70 eV): *m/z* (%) = 324(1), 323(7), 232(12), 226(36), 136(12), 121(100), 91(19), 69(12).

HRMS (EI): *m/z* calc. for [$C_{20}H_{21}NO_3$]: 323.1521; found: 323,1518 [M^+].

1-Phenyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethane-1,2-dione (14j)



According to **TP 3**, a mixture of 1,4-dioxa-8-azaspiro[4.5]decane-8-carbaldehyde (**10e**, 0.50 M, 1.00 mmol) and morpholino(phenyl)methanone (**13h**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three

times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 1:1) afforded the title compound as a colorless solid (118 mg, 0.43 mmol, 61%).

Mp (°C): 106-107.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.62 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 4.02 – 3.89 (m, 4H), 3.83 (t, *J* = 5.8 Hz, 2H), 3.40 (t, *J* = 5.7 Hz, 2H), 1.80 (t, *J* = 5.8 Hz, 2H), 1.67 (t, *J* = 5.7 Hz, 2H).

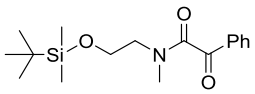
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 191.7, 165.6, 134.9, 133.2, 129.7 (2C), 129.1 (2C), 106.7, 64.7 (2C), 44.1, 39.5, 35.4, 34.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2971(w), 2888(w), 1676(m), 1636(s), 1592(m), 1449(m), 1366(w), 1292(w), 1261(m), 1206(m), 1150(m), 1096(s), 1032(m), 986(m), 944(m), 909(s), 860(m), 807(w), 746(m), 722(s), 694(s), 665(m).

MS (EI, 70 eV): *m/z* (%) = 227(16), 156(16), 155(100), 154(12), 142(16), 137(48), 116(10), 114(19), 112(11), 111(11), 99(11), 95(58), 74(14), 72(40), 69(32), 67(13), 57(13), 55(29), 46(35), 45(26), 44(15), 43(22), 41(26).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}NO_4$]: 275.1158; found: 275.1153 [M^+].

Phenyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethane-1,2-dione (14k)



According to **TP 3**, a mixture of *N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)-N-methylformamide (**10l**, 0.50 M, 1.00 mmol) and morpholino(phenyl)methanone (**13h**, 0.35 M, 0.70 mmol) in THF (total volume: 2.00 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 1:1) afforded the title compound as a colorless oil (142 mg, 0.44 mmol, 63%).

^{1}H-NMR (400 MHz, $CDCl_3$, mixture of conformers A:B = 1.1: 1.0): δ / ppm = 7.98 – 7.92 (m, 2H), 7.66 – 7.58 (m, 1H), 7.53 – 7.44 (m, 2H), 3.91 (t, J = 5.3 Hz, 1H), 3.70 (t, J = 5.7 Hz, 1H), 3.65 (t, J = 5.3 Hz, 1H), 3.35 (t, J = 5.7 Hz, 1H), 3.16 (s, **1.40H_B**), 3.03 (s, **1.54H_A**), 0.93 – 0.87 (m, 5H), 0.85 – 0.81 (m, 4H), 0.10 (s, 3H), -0.03 (s, 3H).

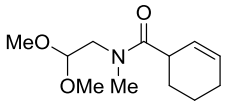
^{13}C-NMR (100 MHz, $CDCl_3$, 1:1.1 mixture of conformers): δ / ppm = 191.9, 191.5, 167.6, 167.3, 134.8, 134.7, 133.4, 133.2, 130.0, 129.8, 129.1, 129.0, 61.6, 61.2, 51.9, 49.5, 37.1, 33.5, 26.0, 18.3, -5.4, -5.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3353(br,w), 2955(w), 2930(w), 1682(w), 1639(m), 1471(w), 1449(w), 1406(w), 1252(w), 1179(w), 1103(m), 1069(w), 1004(w), 907(s), 835(m), 777(m), 725(s).

MS (EI, 70 eV): *m/z* (%) = 323(5), 265(21), 264(100), 216(11), 130(15), 105(71), 77(26), 75(11), 73(34), 44(10), 43(10).

HRMS (EI): *m/z* calc. for [$C_{17}H_{27}NO_3Si$]: 321.1760; found: 323.1909 [$C_{17}H_{27}NO_3{}^{28}Si^+$].

***N*-(2,2-Dimethoxyethyl)-*N*-methylcyclohex-2-ene-1-carboxamide (16c)**



According to **TP 3**, a solution of *N*-(2,2-dimethoxyethyl)-*N*-methylformamide (**10h**; 0.40 M; 2.0 mmol), 3-bromocyclohexene (**15b**; 0.28 M, 1.4 mmol) and CuCN·2LiCl (1.0 M in THF; 10 mol-%) in THF (total volume: 2.5 mL) reacted with continuously generated lithium diisopropylamine (0.48 M, 1.20 equiv) and the combined streams were quenched in water. The *aq.* layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtrated and the solvent was removed *in vacuo*. Purification by flash chromatography (*iso*-hexane:EtOAc = 1:1) afforded **16c** as a colorless oil (93 mg; 0.40 mmol; 58%).

^{1}H-NMR (600 MHz, $CDCl_3$, mixture of conformers A : B = 7:3): δ / ppm = 5.91 – 5.72 (m, 1H), 5.62 – 5.45 (m, 1H), 4.55 – 4.27 (m, 1H; 0.7 (**A**) + 0.3 (**B**)), 3.48 – 3.30 (m, 9H), 3.09 (s, 2H), 2.94 (s, 1H), 2.11 – 1.90 (m, 2H), 1.90 – 1.66 (m, 3H), 1.63 – 1.45 (m, 1H).

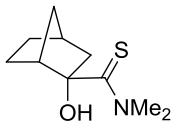
^{13}C-NMR (150 MHz, $CDCl_3$, mixture of conformers): δ / ppm = 175.8, 175.07, 129.7, 129.5, 125.4, 124.8, 103.7, 103.4, 55.4, 55.3, 55.0, 54.9, 52.5, 50.6, 38.9, 38.4, 37.4, 35.1, 26.1, 25.5, 24.7, 21.2, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3481(w), 2935(m), 2836(w), 1631(s), 1449(m), 1403(m), 1293(w), 1186(m), 1119(s), 1070(s), 980(m), 900(m), 832(w), 810(w), 731(m), 720(m), 669(m).

MS (EI, 70 eV): *m/z* (%): 81(16), 75(100), 43(18).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{21}NO_3$]: 227.1521; found: 227.1527 [M^+].

2-Hydroxy-*N*,*N*-dimethylbicyclo[2.2.1]heptane-2-carbothioamide (12l)



According to **TP 4**, a solution of *N*,*N*-dimethylmethanethioamide (**10l**; 0.50 M; 1.0 mmol) and (1*R*,4*S*)-bicyclo[2.2.1]heptan-2-one (**11i**; 0.35 M, 0.7 mmol) in THF (total volume: 2 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 equiv) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The *aq.* layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (*iso*-hexane:EtOAc = 7:3) afforded the title compound as a colorless solid (98 mg; 0.49 mmol; 70%).

Mp (°C): 90-92.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.47 (s, 3H), 3.43 (s, 3H), 3.22 (s, 1H), 2.38 – 2.30 (m, 1H), 2.29 – 2.14 (m, 2H), 1.99 – 1.88 (m, 1H), 1.79 – 1.71 (m, 1H), 1.63 – 1.54 (m, 1H), 1.51 – 1.34 (m, 4H).

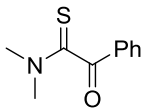
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 206.3, 84.3, 49.0, 47.3, 46.6, 44.0, 40.1, 36.6, 28.9, 22.0.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 3312(w), 2954(w), 2931(w), 1512(m), 1444(w), 1391(m), 1358(w), 1310(w), 1258(m), 1168(w), 1139(w), 1120(w), 1106(w), 1076(s), 1040(s), 1013(s), 975(w), 964(w), 935(w), 896(w), 846(w), 818(w), 808(w), 760(w).

MS (EI, 70 eV): *m/z* (%) = 199(7), 111(12), 89(100), 88(29), 74(12), 67(18), 44(38), 43(48), 42(14).

HRMS (EI): *m/z* calc. for [$C_{10}H_{17}NOS$]: 199.1031: found: 199.1025 [M^+].

***N*,*N*-Dimethyl-2-oxo-2-phenylethanethioamide (14l)**



According to **TP 4**, a solution of *N*,*N*-dimethylmethanethioamide (**10l**; 0.50 M; 1.0 mmol) and morpholino(phenyl)methanone (**13h**; 0.35 M, 0.7 mmol) in THF (total volume: 2 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The *aq.* layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (*iso*-hexane:EtOAc = 8:2) afforded **14l** as a yellowish solid (133 mg; 0.69 mmol; 98%).

Mp (°C): 105.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.97 (d, *J* = 7.9 Hz, 2H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 2H), 3.55 (s, 3H), 3.22 (s, 3H).

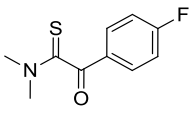
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 197.0, 188.5, 134.3, 133.3, 130.0 (2C), 129.0 (2C), 42.6, 40.6.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2926(w), 1723(w), 1663(s), 1591(m), 1577(m), 1535(s), 1446(m), 1413(s), 1404(s), 1316(m), 1278(s), 1234(s), 1155(s), 1100(s), 1053(m), 1024(m), 998(m), 948(s), 926(m), 846(s), 793(m), 700(s), 682(s), 666(s).

MS (EI, 70 eV): *m/z* (%) = 193(78), 105(100), 90(10), 89(11), 88(41), 77(92), 73(24), 51(37), 50(10), 44(10), 43(13), 42(21).

HRMS (EI): *m/z* calc. for [$C_{10}H_{11}NOS$]: 193.0561; found: 193.0548 [M^+].

2-(4-Fluorophenyl)-*N*,*N*-dimethyl-2-oxoethanethioamide (14m)



According to **TP 4**, a solution of *N*,*N*-dimethylmethanethioamide (**10l**; 0.50 M; 1.0 mmol) and (4-fluorophenyl)(morpholino)methanone (**13i** , 0.35 M, 0.7 mmol) in THF (total volume: 2 mL) reacted

with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The *aq.* layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (*iso*-hexane:EtOAc = 9:1) afforded **14m** as a yellow oil (93 mg; 0.44 mmol; 63%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 – 7.87 (m, 2H), 7.23 – 7.04 (m, 2H), 3.53 (s, 3H), 3.21 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.3 (C=S), 187.0 (C=O), 166.4(d, *J* = 257.3 Hz,1C), 132.8 (d, *J* = 9.5 Hz, 2C), 129.8 (d, *J* = 3.0 Hz, 1C), 116.2 (d, *J* = 22.3 Hz, 2C), 42.5, 40.6.

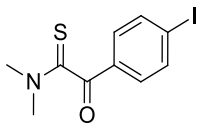
^{19}F-NMR (376 MHz, $CDCl_3$): δ / ppm = -102.68.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2932(w), 1663(s), 1594(m), 1537(s), 1504(m), 1412(m), 1397(s), 1279(m), 1230(s), 1152(s), 1100(m), 1067(m), 1012(w), 998(w), 854(m), 859(m), 844(s), 802(m), 747(m), 724(s), 717(s), 684(m), 666(m).

MS (EI, 70 eV): *m/z* (%) = 211(27), 194(20), 123(45), 95(29), 88(100), 75(12), 73(10), 44(20), 43(12), 42(17).

HRMS (EI): *m/z* calc. for $[C_{10}H_{10}FNOS]^+$: 211.0467; found: 211.046 $[M^+]$.

2-(4-Iodoophenyl)-*N*,*N*-dimethyl-2-oxoethanethioamide (14n)



According to **TP 4**, a solution of *N*,*N*-dimethylmethanethioamide (**10l**; 0.50 M; 1.0 mmol) and (4-iodophenyl)(morpholino)methanone (**13f**; 0.35 M, 0.7 mmol) in THF (total volume: 2 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The *aq.* layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (*iso*-hexane:EtOAc = 9:1) afforded **14n** as a yellowish solid (186 mg; 0.46 mmol; 65%).

Mp (°C): 128-133.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (dt, *J* = 8.6, 2.1 Hz, 2H), 7.66 (dt, *J* = 8.5, 2.1 Hz, 2H), 3.53 (s, 3H), 3.20 (s, 3H).

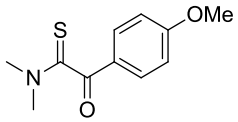
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.0, 187.4, 138.8 (2C), 132.7, 131.2 (2C), 102.7, 42.5, 40.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923(w), 1668(s), 1578(m), 1543(m), 1450(w), 1412(m), 1390(m), 1308(w), 1280(m), 1235(m), 1177(m), 1151(m), 1092(m), 1054(m), 1006(m), 939(m), 848(m), 841(s), 826(m), 735(s), 704(m), 680(m), 664(s).

MS (EI, 70 eV): *m/z* (%) = 318(26), 291(11), 88(100), 76(26), 57(14), 44(49), 43(46).

HRMS (EI): calc. for [$C_{10}H_{10}INOS$]: 318.9528; found: 318.9526 [M^+].

2-(4-Methoxyphenyl)-*N*,*N*-dimethyl-2-oxoethanethioamide (14o)



According to **TP 4**, a solution of *N*,*N*-dimethylmethanethioamide (**10l**; 0.50 M; 1.0 mmol) and (4-methoxyphenyl)(morpholino)methanone (**13j,** 0.35 M, 0.7 mmol) in THF (total volume: 2 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The *aq.* layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (*iso*-hexane:EtOAc = 9:1) afforded **14o** as a yellowish solid (64 mg; 0.29 mmol; 41%).

Mp (°C): 118.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 3.52 (s, 3H), 3.20 (s, 3H).

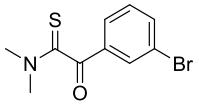
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 197.3, 187.9, 164.6, 132.4 (2C), 126.1, 114.3 (2C), 55.3, 42.5, 40.6.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2927(w), 1652(s), 1597(s), 1540(s), 1506(m), 1448(m), 1397(m), 1316(m), 1304(m), 1285(m), 1245(s), 1263(s), 1155(s), 1100(s), 1053(m), 1016(s), 953(s), 944(m), 787(m), 752(s), 693(m), 662(s).

MS (EI, 70 eV): *m/z* (%) = 223(17), 135(100), 92(10), 88(20), 77(11).

HRMS (EI): *m/z* calc. for [$C_{11}H_{13}NO_2S$]: 223.0667; found: 223.0661 [M^+].

2-(3-Bromophenyl)-*N*,*N*-dimethyl-2-oxoethanethioamide (14p)



According to **TP 4**, a solution of *N*,*N*-dimethylmethanethioamide (**10l**; 0.50 M; 1.0 mmol) and (3-bromophenyl)(morpholino)methanone (**13k ,**0.35 M, 0.7 mmol) in THF (total volume: 2 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The *aq.* layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (*iso*-hexane:EtOAc = 9:1) afforded **14p** as a 6:1 mixture of distinct conformers as a yellow oil (158 mg; 0.58 mmol; 83%).

^{1}H-NMR (400 MHz, $CDCl_3$, 6:1 mix of rotamers, only major): δ / ppm = 8.12 – 8.08 (m, 1H), 7.89 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 1H), 7.71 (ddd, *J* = 7.9, 2.1, 1.0 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 3.54 (s, 3H), 3.23 (s, 3H).

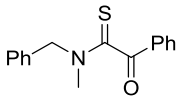
^{13}C-NMR (100 MHz, $CDCl_3$, mix of rotamers, only major): δ / ppm = 195.8, 186.5, 137.1, 135.3, 132.7, 130.5, 128.6, 123.2, 42.6, 40.6.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2932(w), 1663(s), 1594(m), 1533(s), 1504(m), 1463(w), 1411(m), 1397(s), 1279(m), 1239(s), 1151(s), 1100(m), 1066(m), 1011(w), 998(w), 954(m), 859(m), 846(s), 802(m), 749(m), 727(s), 716(s), 668(m).

MS (EI, 70 eV): *m/z* (%) = 273(10), 271(10), 88(100), 76(10), 75(10), 43(21), 42(11).

HRMS (EI): *m/z* calc. for $[C_{10}H_{10}{}^{79}BrNOS]^+$: 270.9666; found: 270.9660 [M^+].

***N*-Benzyl-*N*-methyl-2-oxo-2-phenylethanethioamide (14q)**



According to **TP 4**, a solution of *N*-benzyl-*N*-methylmethanethioamide (**10m**; 0.50 M; 1.0 mmol) and morpholino(phenyl)methanone (**13h**; 0.35 M, 0.7 mmol) in THF (total volume: 2 mL) reacted with continuously generated lithium diisopropylamine (0.60 M, 1.20 mmol) and the combined streams were quenched in *sat. aq.* NH_4Cl solution. The *aq.* layer was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtrated and the solvent was removed *in vacuo*. Purification by flash column chromatography (*iso*-hexane:EtOAc = 9:1) afforded **14q** as a mixture of distinct conformers as colorless solid (158 mg; 0.59 mmol; 84%).

Mp (°C): 85-93.

^{1}H-NMR (400 MHz, $CDCl_3$, 1:1 mixture of conformers): δ / ppm = 8.08 – 7.92 (m, 4H), 7.63 – 7.56 (m, 2H), 7.52 – 7.28 (m, 12H), 7.28 – 7.22 (m, 2H), 5.30 (s, 2H), 4.62 (s, 2H), 3.38 (s, 3H), 3.07 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 1:1 mixture of conformers): δ / ppm = 197.8, 197.3, 188.3, 188.1, 134.5, 134.3 (2C) 133.7, 133.6, 133.3, 130.1, 130.0, 129.2, 129.1, 129.0, 128.9, 128.8, 128.5 (2C) 128.2, 59.2, 55.2, 39.6, 37.9.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2928(w), 1662(s), 1594(w), 1580(w), 1509(s), 1449(m), 1400(m), 1316(w), 1271(m), 1230(m), 1204(m), 1176(m), 1113(m), 1078(m), 1027(w), 1000(w), 943(m), 910(w), 850(m), 731(m), 697(s), 688(s).

MS (EI, 70 eV): m/z (rel. Intensity) = 269(26), 120(21), 91(100), 77(27), 65(10).

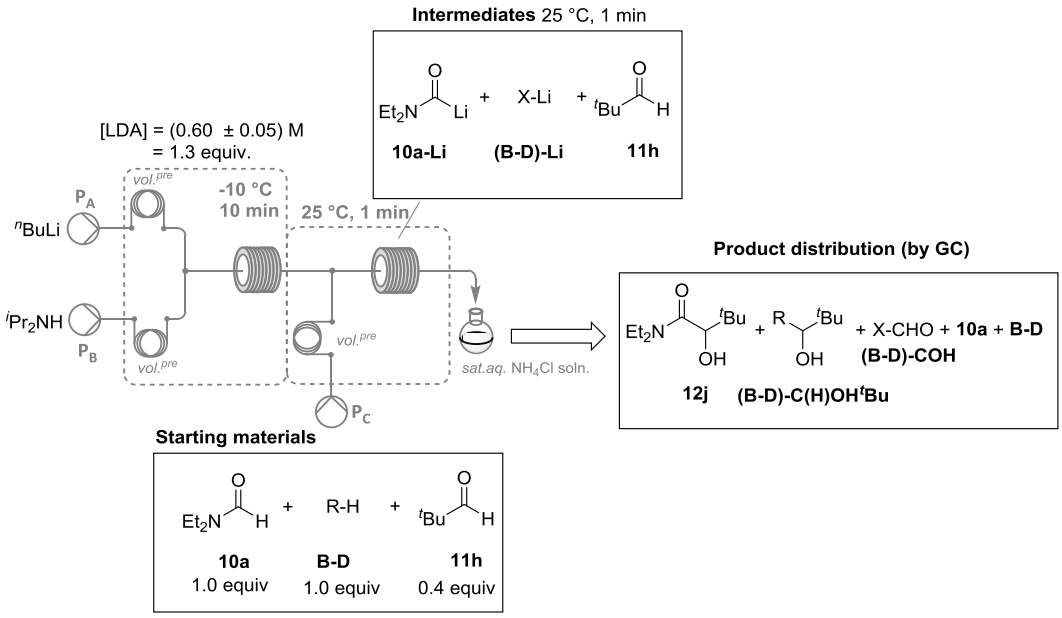
HRMS (EI): *m/z* calc. for $[C_{16}H_{15}NOS]$: 269.0874; found: 269.0876 [M^+].

3.6 Kinetic studies

Under preparative conditions (see **TP 3** for setup, flowrates and reaction conditions), a mixture of *N*,*N*-diethylformamide (**10a**) and a concurrency carbon acid R-H (**B**−**D**) were subjected to metalation

by continuously generated **LDA** in presence of trimethylacetaldehyde [249] (**11h**) for 1.0 min at 25 °C. Two different sets of conditions (**TP 5** and **TP 6**) were tested with respect to the relative amounts of reagents. Gas chromatography (GC) was used to determine the product distribution (see following chapters).

3.6.1 Typical Procedure 5 (TP 5; LDA (2.7 equiv.) Excess, Electrophile Limiting (0.4 equiv))



Scheme 45: Experimental setup TP 5 for competition experiments.

The continuous-flow setup and flowrates described in **TP 3** were used (Scheme 45). A mixture of *N*,*N*-diethylformamide (**10a**, 0.225 M, 0.50 mmol, 1.0 equiv), concurrency carbon acid **R-H** (**B**–**D**, 0.225 M, 0.50 mmol, 1.0 equiv) and electrophile **11h** (0.09 M, 0.20 mmol, 0.4 equiv.) with $^{n}C_{14}H_{30}$ as internal standard (0.010 mL) in dry THF (total volume: 1.11 mL) reacted with continuously generated lithium diisopropylamine (**LDA**, 0.60 M, 1.33 mmol, 1.33 equiv). The combined streams were quenched in *sat. aq.* NH_4Cl solution after a residence time of 1.0 min at 25 °C. Collection was carried out during 0.5 min. EtOAc was added to the thus obtained quenched reaction mixture, and after vigorous stirring and phase separation, aa small aliquot was filtrated over anhydrous $MgSO_4$. GC analysis of this sample was performed as described below in order to determine the absolute yields of

[249] The metalation of **R3** by lithium amide base can lead to the corresponding acyloin-type products via deprotonation and self-addition (C. S. Shiner, A. H. Berks, A. M. Fisher, *J. Am.Chem. Soc*. **1988**, *110*, 957.). This side-reaction was excluded under the experimental conditions of **TP 3** and **TP 4** by comparision of the GC trace of the crude reaction mixtures with that of an authentic sample of acyloin product 4-hydroxy-2,2,5,5-tetramethylhexan-3-one.

the resulting products (**12j**, (**B**−**D**)-**C(H)OH^{t}Bu**) as well as remaining starting materials, if applicable.[250]

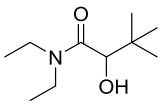
3.6.2 Typical Procedure 6 (TP 6; LDA (1.3 equiv.) Limiting, Stoichiometric Electrophile (0.8 equiv.))

The continuous-flow setup and flowrates described in **TP 3** were used. A mixture of *N*,*N*-diethylformamide (**10a**, 0.45 M, 0.50 mmol, 1.0 equiv), concurrency carbon acid **R**-**H** (**B**−**D**, 0.45 M, 0.50 mmol, 1.0 equiv) and electrophile **11h** (0.36 M, 0.40 mmol, 0.8 equiv) with $^nC_{14}H_{30}$ as internal standard (0.010 mL) in dry THF (total volume: 2.22 mL) reacted with continuously generated lithium diisopropylamine (**LDA**, 0.60 M, 1.33 mmol, 2.67 equiv). The combined streams were quenched in *sat. aq.* NH_4Cl solution after a residence time of 1.0 min at 25 °C. Collection was carried out during 0.5 min. EtOAc was added to the thus obtained quenched reaction mixture, and after vigorous stirring and phase separation, aa small aliquot was filtrated over anhydrous $MgSO_4$. GC analysis of this sample was performed as described below in order to determine the absolute yields of the resulting products (**12j**, (**B**−**D**)-**C(H)OH^{t}Bu**) as well as remaining starting materials, if applicable. [250]

3.6.3 Gas chromatography for determination of the absolute yields of products.

GC analysis was performed on a Agilent 6850 Series gas chromatograph equipped with a standard injector, a FI detector, and an Optima capillary column (15m × 0.25mm (I.D.), Macherey-Nagel). The carrier gas was nitrogen; peak areas were obtained with the integration tool of the GC ChemStation (Rev A09.03 [1417], Agilent) software. For the calibration, isolated independently prepared samples were weighed in, dissolved in EtOAc and 0.0050 mL internal standard (n-$C_{14}H_{30}$) was added. GC analysis of these samples was then performed to determine the corresponding peak areas. At least three data points were used for the resulting calibration curves (Table 18,Figure 9).

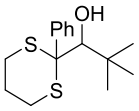
***N*,*N*-diethyl-2-hydroxy-3,3-dimethylbutanamide(12j)**



The compound **12j** was prepared according to the literature using 1 h reaction time in 33% yield.[251] Analytical data of this product was identical to **12j** prepared as described above.

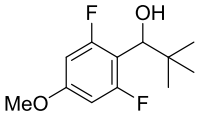
[250] **10a** was not detected. Despite its poor water-solubility it cannot be excluded, that small amounts of **10a** were lost in the aqueous workup. Remaining electrophile **11h** could not be detected reliably due to its low boiling point.
[251] B. Banhidai, U. Schöllkopf, *Angew. Chem. Int. Ed.* **1973**, *12*, 836-837.

2,2-dimethyl-1-(2-phenyl-1,3-dithian-2-yl)propan-1-ol (B-C(H)OH^{t}Bu)



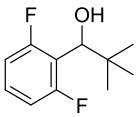
The compound was prepared by lithiation of 2-phenyl-1,3-dithiane (**B**, 0.60 M in THF, 1.5 mmol) with lithium diisopropylamine (0.60 M in hexane:THF = 1:1 , 1.05 equiv) at -78 °C for 10 min (formation of precipitates), followed by addition of neat trimethylacetaldehyde (**11h**, 5.0 equiv), the reaction mixture was allowed to warm to 25 °C over night in the cooling bath. *Sat. aq.* NH_4Cl solution was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and after removal of the solvent *in vacuo*, column chromatographic purification (SiO_2, *iso*-hexane:EtOAc = 9:1, R_f = 0.8) of the crude mixture gave the title compound in 85% yield. chromatographic purification (SiO_2, *iso*-hexane:EtOAc = 9:1, R_f = 0.5) of the crude mixture gave the title compound in 65% yield. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ / ppm = 8.14 – 7.84 (m, 2H), 7.48 – 7.28 (m, 3H), 3.68 (s, 1H), 3.01 (s, 1H), 2.64 (s, 1H), 1.89 (s, 2H), 1.54 (s, 3H), 0.72 (s, 9H). **MS (EI, 70 eV):** *m/z* = 230 (M^+). *This product was not detectable on the GC apparatus used. The product **B-C(H)OH^{t}Bu** was used to qualitatively confirm the formation of **B-C(H)OH^{t}Bu** in reaction crudes using a different GC-apparatus (GCMS). For quantitative analysis, the amount of **B-C(H)OH^{t}Bu** in reaction mixtures was determined using GC by subtraction of the remaining starting material **B** from the amount before the reaction.*

1-(2,6-difluoro-4-methoxyphenyl)-2,2-dimethylpropan-1-ol (C-C(H)OH^{t}Bu)



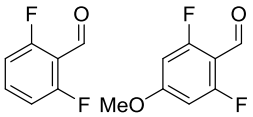
The compound was prepared by lithiation of 1,3-difluoroanisole (**C**, 0.60 M in THF, 1.5 mmol) with lithium diisopropylamine (0.60 M in Hexane:THF = 1:1 , 1.05 equiv) at -78 °C for 10 min, followed by addition of neat trimethylacetaldehyde (**11h**, 5.0 equiv). The mixture was subsequently allowed to warm to 25 °C and *sat. aq.* NH_4Cl solution was added. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, column chromatographic purification (*iso*-hexane:EtOAc = 9:1, R_f = 0.5) of the crude mixture gave the title compound in 81% yield.**^{1}H-NMR (200 MHz, $CDCl_3$):** δ / ppm = 6.40 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 10.1 Hz, 1H), 3.75 (d, *J* = 1.3 Hz, 3H), 2.60 (dt, *J* = 9.9, 3.8 Hz, 1H), 0.94 (t, *J* = 1.5 Hz, 9H).**MS (EI, 70 eV):** *m/z* = 230 (M^+).

1-(2,6-difluorophenyl)-2,2-dimethylpropan-1-ol (D-C(H)OH^{t}Bu)



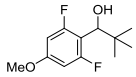
The compound was prepared by lithiation of 1,3-difluorobenzene (**D**) in an analog manner as described for **C-C(H)OH^{t}Bu**. Column chromatographic purification (*iso*-hexane:EtOAc = 8:2, R_f = 0.5) of the crude mixture gave the title compound in 85% yield. **^{1}H-NMR (200 MHz, CDCl$_3$):** δ / ppm = 7.25 – 7.10 (m, 1H), 6.84 (dd, *J* = 10.2, 7.5 Hz, 2H), 4.75 (d, *J* = 10.6 Hz, 1H), 2.55 (d, *J* = 10.9 Hz, 1H), 1.33 – 1.12 (m, 1H), 0.94 (s, 9H). MS (EI, 70 eV): *m/z* = 200 (M^+).

2,6-difluorobenzaldehyde (C-CHO) and 2,6-difluoro-4-methoxybenzaldehyde (D-CHO)



*Lithiation of the fluorobenzols **C** and **D** in the above described manner and subsequent quenching with formamide (**10a,** 5.0 equiv.) led to the formylated products **12b** and **12c** in low yields as confirmed by GCMS analysis of the reaction crudes. Since purification of these benzaldehydes proved problematic, a direct calibration was not possible. Therefore, the calibration parameters of the related alcohols **C-C(H)OH^{t}Bu** and **D-C(H)OH^{t}Bu** were used to approximate the absolute amounts of **C-CHO** and **D-CHO**, respectively*.

Table 18 GC calibration points for all products **12j**, **C-C(H)OH^{t}Bu**; **D-C(H)OH^{t}Bu**;. A linear regression was used. [R2]: coefficient of correlation.

N,N-diethyl-2-hydroxy-3,3-dimethylbutanamide(**12j**)  Molecular Weight: 187,2830	m(**12j**) (mg)	1,9	22,2	13,1	f(x) = 28,041x
	n(**12j**) (mmol)	0,010145	0,118537187	0,069948	
	peak area (**12j**) / peak area (*n*-$C_{14}H_{30}$)	0,194304	3,411132004	1,826654	R^2 = 0.993
1-(2,6-difluorophenyl)-2,2-dimethylpropan-1-ol (**D-C(H)OH^{t}Bu**)  Molecular Weight: 200,2288	m(**D-C(H)OH^{t}Bu**) (mg)	6,8	30,5	2,6	f(x) = 97,370 x
	n(**D-C(H)OH^{t}Bu**) (mmol)	0,033962	0,15232863	0,012985	R^2 = 0.967
	peak area (**D-C(H)OH^{t}Bu**) / peak area (n-$C_{14}H_{30}$)	1,384766	15,32180721	0,547718	
1-(2,6-difluoro-4-methoxyphenyl)-2,2-dimethylpropan-1-ol (**C-C(H)OH^{t}Bu**)  Molecular Weight: 230,2548	m(**C-C(H)OH^{t}Bu**) (mg)	1,8	0,81	0,20	f(x) = 40,704 x
	n(**C-C(H)OH^{t}Bu**) (mmol)	0,0078	0,0035	0,00086	
	peak area (**C-C(H)OH^{t}Bu**) / peak area (*n*-$C_{14}H_{30}$)	0,4	0,17	0,21	
	m(**C-C(H)OH^{t}Bu**) (mg)	9,0	2,5	11,0	R^2 = 0.987
	n(**C-C(H)OH^{t}Bu**) (mmol)	0,039088	0,010858	0,047774	
	peak area (**C-C(H)OH^{t}Bu**) / peak area (*n*-$C_{14}H_{30}$)	1,569	0,43332	1,9459	

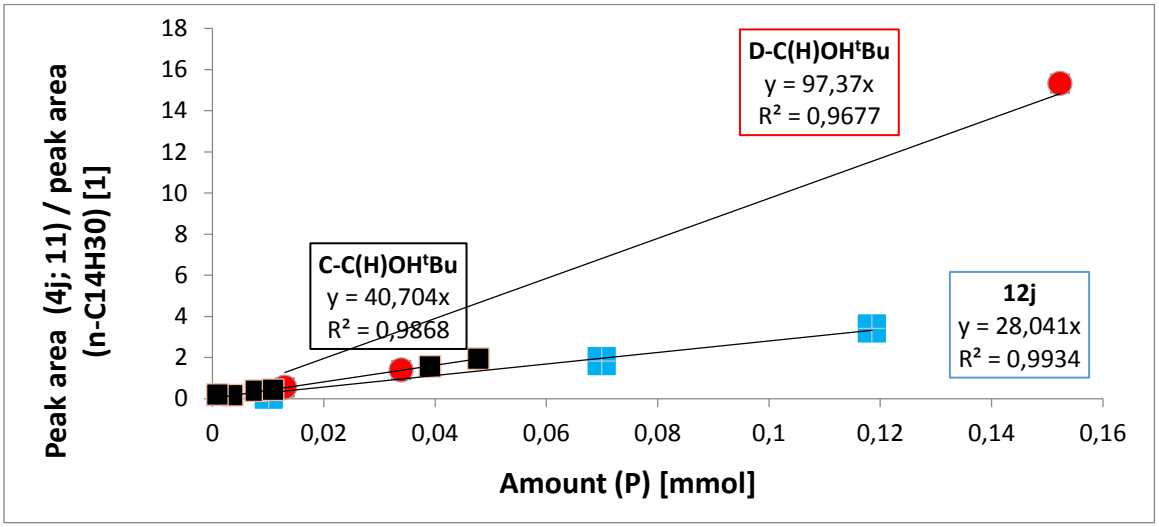


Figure 9 GC calibration for all products. Linear regression parameters for the data points are shown in the graph.

3.6.4 Results of the competition experiments

According to **TP 5** and **TP 6**, **12j** and reference C-H acids were reacted in concurrency experiments and the product distribution was calculated by means of calibrated GC (*vide supra*). All results are listed in Table 19 below.

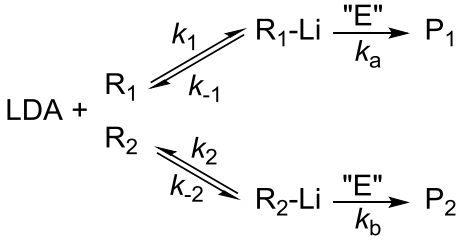
Table 19: Product distributions for all concurrency experiments (TP 5or TP 6) using GC analysis (see **Table 18**). Possible products that were not detected are not listed. Note that side products **C-CHO**, **D-CHO** were determined with the calibration parameters determined for **C-C(H)OH^{t}Bu** and **D-C(H)OH^{t}Bu**, respectively. **B-C(H)OH^{t}Bu** could not be directly detected, but was determined using the remaining starting material: **B-C(H)OH^{t}Bu** / mmol = (0.5 –**B**$_t$). The index *t* refers to amounts of remaining starting materials after the reaction

10a/B-D vs. B-D (0.5 mmol of each reagent)		Conds.	**12j** (mmol)	**D-C(H)OH^{t}Bu** (mmol)	**C-C(H)OH^{t}Bu** (mmol)	**B-C(H)OH^{t}Bu** (mmol)	**E-C(H)OH^{t}Bu**	**C**$_t$ (mmol)	**B**$_t$ (mmol)	**E-CHO** (mmol)	**C-CHO** (mmol)	**D-CHO** (mmol)
		**TP 5**	0.047	0.018	-	-		-	-		0.003	-
10a	**D**	**TP 6**	0.07	0.14	-	-		-	-		0.037	-
10a		**TP 5**	0.040	-	0.018			0.08	-		-	-
10a	**C**	**TP 6**	0.096	-	0.128	-		0.13	-		-	0.025
10a		**TP 5**	0.015	-	-	0.245		-	0.255		-	-
10a	**B**	**TP 6**	0.093	-	-	0.203		-	0.296		-	-
10a	 **E**	**TP 6**	*none*[b]	-	-		*3*[b]			*1*[b]		
D	**B**	**TP 5**	-	0.065	-	0.189			0.311		-	-
D	**B**	**TP 6**	-	0.138	-	0.215			0.285		-	-
C	**B**	**TP 5**	-	-	0.012	0.266		0.121	0.233		-	-
C	**B**	**TP 6**	-	-	0.126	0.235		0.158	0.265		-	-
D	**C**	**TP 5**	-	0.022[a]	0.017[a]	-		0.189[a]	-		-	-
D	**C**	**TP 6**	-	0.059[a]	0.067[a]	-		0.304[a]	-		-	-

[a] The reactions leading to these values contained large amounts of unidentifiable byproducts.[b] No product **12j** was detected. Thioimidazole derived products **E-C(H)OH^{t}Bu** and **E-CHO** were detected in a 3:1 ratio.

3.6.5 Calculation of the relative free energies of lithiation

Competition experiments were performed for determining the relative thermodynamics of lithiation of *N*,*N*-diethyl formamide **10a** (termed $\mathbf{R_1}$ in Scheme 46) with respect to a C-H acid **B-D** (termed $\mathbf{R_2}$) of known pK_a. As the organolithium intermediate R_1-Li is not stable at room temperature, pivaldehyde **11h** (termed **E**) was used as trapping reagent and the absolute yields of products **12j** (P_1) and **B-C(H)OH^{t}Bu**, **C-C(H)OH^{t}Bu** and **D-C(H)OH^{t}Bu** (P_2) were determined.



Scheme 46: Competition reactions used for determining the relative equilibrium constants K_{rel} ($K_{rel} = K_1/K_2$ with $K_1 = k_1/k_{-1}$ and $K_2 = k_2/k_{-2}$) of LDA-mediated deprotonation of 1a (termed "R_1") versus a reference CH acid 10a-d (termed "R_2") in THF at 25 °C.

Determination of a series of relative equilibrium constants K_{rel} ($K_{rel} = K_1/K_2 = \kappa/\kappa'$, see equations 1 and 2 for the definition of the competition constants κ and κ') allowed quantitative comparisons of the free energies of the LDA-mediated lithiation of **10a** versus those of a set of selected substrates **B-D** (*vide supra*). The partial reactions orders for the lithiation step and for the subsequent addition of the organolithium reagent on the aldehyde **11h** have been assumed as simple first-order with respect to every reagent, although these systems could be more complex.[252] Variations of the concentration of LDA and of substrates R by a factor 2 did not affect the relative ratios of products, which shows that the competition experiments are not strongly affected by the initial concentrations. The rate of lithiation was investigated independently by performing the lithiation of 1,3-difluoro-5-methoxybenzene **C** with LDA under analogous experimental conditions (LDA 1.3 equiv, rt). The lithiation was found to be faster than 1 s under these conditions, which should be faster than the rate of attack of the lithium reagent **C-Li** on the pivaldehyde **11h** (**E**).[253]

*Typical procedure **TP 5***: (LDA 2.4 equiv, **E** 0.4 equiv.)

$$\kappa' = \frac{k_a}{k_b} = \frac{\log([R_1]_0/[R_1]_t)}{\log([R_2]_0/[R_2]_t)} \quad \text{Eq(1)}$$

*Typical procedure **TP 6**:* (LDA 1.3 equiv., **E** 0.8 equiv.)

$$\kappa = \frac{k_a K_1}{k_b K_2} = \frac{log([R_1]_0/[R_1]_t)}{log([R_2]_0/[R_2]_t)} \quad \text{Eq(2)}$$

The competition reactions were performed with both reagents R (*N*,*N*-diethyl formamide **10a** and **B-D**) in equimolar quantities (1.0 equiv) and by varying the concentrations of the trapping reagent **E** and the relative concentration of LDA. In the first stage, LDA was used in excess (2.4 equiv., conditions TP3) in order to produce quantitatively both lithiated species **R_1-Li** and **R_2-Li**, with the result that $[\mathbf{R_1}]_0 = [\mathbf{R_1\text{-}Li}]_0$ and $[\mathbf{R_2}]_0 = [\mathbf{R_2\text{-}Li}]_0$.

Only 0.4 equiv. of the electrophile E (*t*BuCHO, **2h**) were used, giving access to the relative rates k_a/k_b of the reaction of both organolithium intermediates with **E**, *via* the competition constant κ', calculated *via* the standard logarithmic formula (Equation 1). The absolute yields of products $[\mathbf{P_1}]_t$ and $[\mathbf{P_2}]_t$ at the end of the reaction were determined by GC, using *n*-$C_{14}H_{30}$ as internal standard. The quantities of unreacted starting materials $[R_i]_t$ at the end of the reaction cannot be experimentally determined by chromatography and were calculated with the equations:

$[R_1]_t = [R_1]_0 - [P_1]_t$ Eq(3)

$[R_2]_t = [R_2]_0 - [P_2]_t$ Eq(4)

Control experiments demonstrated that the relative free deprotonation energies ΔΔG° were independent of the concentration and the time before quenching (t = 1 or 10 min).

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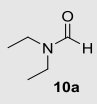
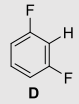
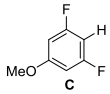
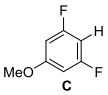
[252] a) J. Liang, A. C. Hoepker, A. C. Bruneau, Y. Ma, L. Gupta, D. B. Collum, *J. Org. Chem.* **2014**, *79*, 11885-11902. b) J. Liang, A. C. Hoepker, R. F. Alegra, Y. Ma, D. Collum, *J. Am. Chem. Soc.* **2015**, *137*, 6292-6303.

[253] a)R. Knorr, C. Behringer, M. Knittl, U. von Roman, E.Lattke, *J. Am. Chem. Soc.* **2017**, *139*, 4690−4703. b) R. Knorr, M. Knittl, C. Behringer, J. Ruhdorfer, P. Böhrer, *J. Org. Chem.* **2017**, *82*, 2843-2854.

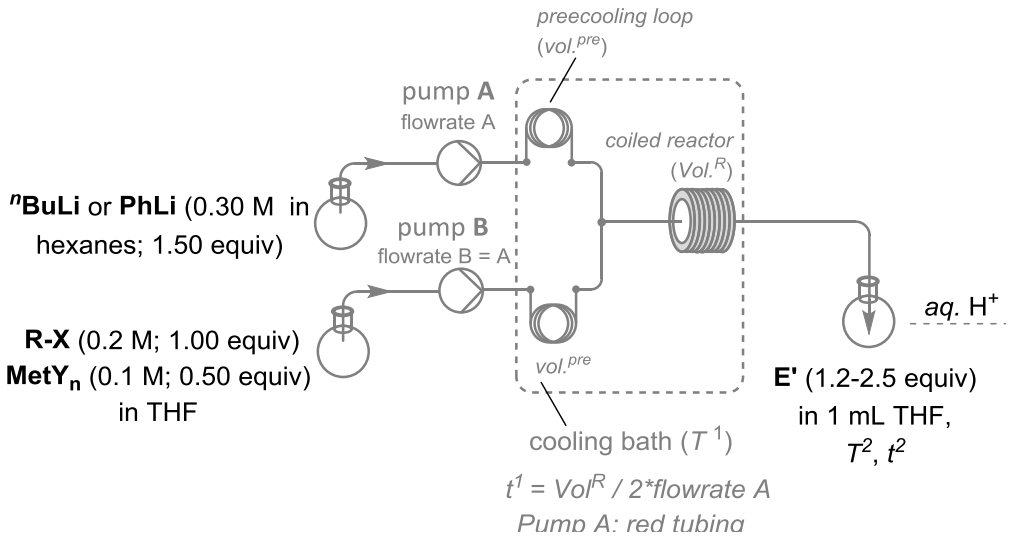
Table 20: Competition constants and relative free energies of lithiation at 25 °C in THF.

R_1/R_2 vs. R_2		Conds.	$\kappa' = \frac{k_a}{k_b}$	$\kappa = \frac{k_a K_1}{k_b K_2}$	$K_{rel} = \frac{K_1}{K_2} = \frac{\kappa}{\kappa'}$	$\Delta\Delta G° = -RT\ln(K_{rel})$
 10a	 D	**TP 5**	2.69		0.17	+1.0 kcal mol^{-1}
		TP 6		0.46		
 10a	 C	**TP 5**	2.27			
		TP 6		0.72	0.32	+0.6 kcal mol^{-1}
 10a	 B	**TP 5**	0.045		8.89	–1.3 kcal mol^{-1}
		TP 6		0.40		
 C	 B	**TP 5**	0.032		14.4	–1.6 kcal mol^{-1}
		TP 6		0.46		

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

4.1 Typical Procedure (TP 7)

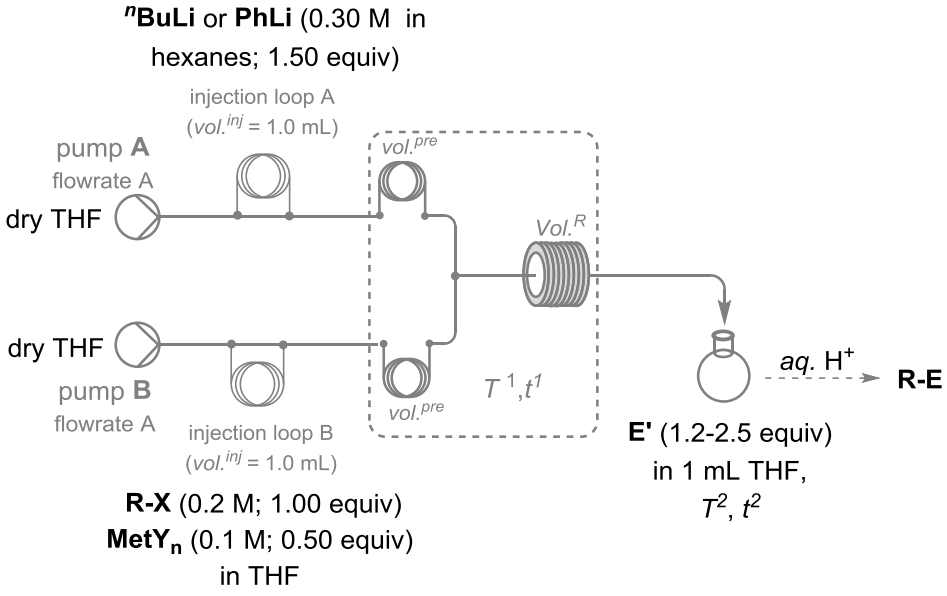
Typical procedure using a Vapourtec E-series flow setup



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 ($MetY_n$, 0.1 M, 0.5 equiv.) in THF were prepared. The solutions were pumped from their flasks through a suction needle at flowrate A = 3.0–10.0 mL min^{-1} and flowrate B = flowrate 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 *iso*-hexane:EtOAc mixtures afforded the pure products R-E.

Typical procedure using a Uniqsis flow setup



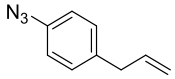
Scheme 48: General flow setup for the *in situ* trapping halogen-lithium exchange using a Uniqusis flow setup.

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 ($MetY_n$, 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 $MetY_n$. The solutions were simultaneously injected into separate streams of hexane and THF, respectively (pump A: THF, pump B: THF, flowrates: 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 *iso*-hexane:EtOAc mixtures afforded the pure products R-E.

4.2 Preparation of the products

1-Allyl-4-azidobenzene (20r, with scale-up)



According to **TP 7**, a solution of 1-azido-4-iodobenzene (**17g**, 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} flowrate 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 (**19a**, 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 (3×30 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, *iso*-hexane) afforded the title compound **20r** as a pale yellow oil (114 mg, 0.72 mmol, 72% yield).

Scale-up:

Scale-up of the reaction was achieved according to **TP 7**. A solution of azido-4-iodobenzene (**17g**, 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} flowrate 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 (**19a**, 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, *iso*-hexane) afforded **20r** 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).

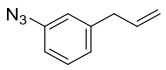
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 138.0, 137.3, 137.0, 130.1 (2C), 119.2 (2C), 116.2, 39.7.

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 (20s)



According to **TP 7**, a solution of 1-azido-3-iodobenzene (**17h**, 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} flowrate 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 (**19a**, 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 (3×30 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, *iso*-hexane) afforded the title compound **20s** 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).

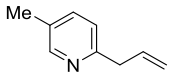
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 142.2, 140.2, 136.8, 129.9, 125.4, 119.3, 116.9, 116.6, 40.1.

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-Allyl-5-methylpyridine (24d)



According to **TP 7**, a solution of 2-bromo-5-methylpyridine (**22c**, 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} flowrate 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 (**19a**, 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 **24d** 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 Synthesis and Reactivity of Triazaphenanthrenes

5.1 Typical procedure for the preparation of organolithium reagents (TP 8):

All solutions of organolithiums were titrated against *i*-PrOH with 1,10-phenantroline as indicator.[254] Except for commercial ^{n}BuLi (**35j**), solutions of lithium reagents were freshly prepared: Phenyllithium **35a** and (4-methoxyphenyl)lithium **35b** were prepared by addition of Li granulas (2.0 equiv) to the corresponding iodides (1.0 equiv) in diethyl ether (0.5 – 1.0 M) at 0 °C and obtained as reddish ca. 0.5-1.0 M solutions after 30 min stirring. (4-(trifluoromethyl)phenyl)lithium **35c** and (3-fluorophenyl)lithium **35d** were obtained as colored solutions (ca. 0.6 – 0.9 M) according to a literature procedure by adding a solution of ^{t}BuLi (2.0 equiv.) to the corresponding iodides (1.0 equiv.) in diethyl ether (1.0 M) at −78 °C and stirring for 30 min.[255] *α*-lithiated heteroaryl reagents **35e** – **h** were prepared by adding ^{n}BuLi solution (1.05 equiv.) to the heteroaryl compounds (1.0 equiv.) in THF

[254] H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[255] Enders, D.; Chelain, E.; Raabe, G. *B. Soc. Chim. Fr.* **1997**, *134*, 299.

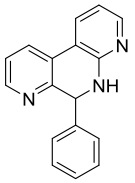
(1.0 M) at −78 °C and stirring for 30 min, followed by 1 h at −10 °C and 5 min at 25 °C. Titration indicated a 0.6−0.9 M concentration of these reagents. (1-ethoxyvinyl)lithium **35i** was prepared according to a literature procedure[256] and obtained as ca. 0.9 M solution in THF/hexanes.

5.2 Typical procedure for the addition of organolithiums and rearomatization (TP 9):

Pyrido[3,2-f][1,7]naphthyridine (**28a**, 18 mg, 0.1 mmol, 1.0 equiv) was dissolved in 1 mL dry THF under an argon atmosphere. Brief heating was applied to ensure that all material was dissolved. The solution was then cooled to −60 °C in a dry ice/acetone bath. The organolithium solution was cooled to -60 °C prior to addition or -40 °C, if precipitation was observed at −60 °C. The precooled solution of organolithium compound (**35**, 0.15 mmol, 1.5 equiv.) was then added dropwise *via* syringe to **28a** and the mixture was stirred for 30 min at −60 °C. The dry ice cooling was subsequently changed to an ice bath (0 °C) and stirring was continued for 5 min. Subsequently, 3 mL of *sat. aq.* NH_4Cl solution was added to quench the reaction. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ and solvents were removed *in vacuo*. The solid residues were dissolved in 2 mL DMF and chloranil (30 mg, 0.12 mmol, 1.2 equiv) was added. The mixture was stirred overnight at room temperature in an open flask before water (10 mL) and ca. 200 mg LiCl were added. The mixture was extracted with EtOAc (5x). After removal of the solvent *in vacuo*, the analytically pure products **28d**−**m** were obtained after flash column chromatography (silica gel, EtOAc + 5% NEt_3).

5.3 Preparation of the products

6-phenylpyrido[3,2-*f*][1,7]naphthyridine (34d)



According to modified **TP 9**, the substituted azaphenanthrene derivative **28d** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35a** (0.52 M in diethyl ether, 1.5 equiv, **TP 8**) and subsequent quenching with *sat. aq.* NH_4Cl solution. Flash column chromatography (EtOAc + 5% NEt_3) furnished **34d** as colorless solid (13 mg, 50%).

M.p. (°C): 220-233.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.44 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.03 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.95 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.87 – 7.77 (m, 1H), 7.44 – 7.34 (m, 2H), 7.32 – 7.14 (m, 4H), 6.71 (dd, *J* = 7.5, 5.0 Hz, 1H), 5.91 (s, 1H), 5.61 (s, 1H).

[256] Baldwin, J. E.; Hoefle, G. A.; Lever, O. W. Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7126.

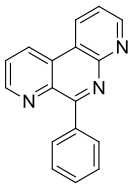
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.9, 153.1, 149.2, 148.9, 143.4, 131.7, 130.7, 130.5, 129.8, 128.7, 127.7, 126.5, 125.1, 122.9, 114.4, 112.4, 61.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3406(w), 3056(w), 2925(w), 1711(s), 1594(w), 1564(m), 1519(w), 1445(m), 1357(m), 1342(m), 1260(w), 1207(w), 1159(s), 793(m), 710(s), 693(m), 686(m).

MS (EI, 70 eV): m/z (rel. Intensity) = 259(24), 258(20), 257(32), 256(24), 183(23), 182(100).

HRMS (EI): *m/z* calcd. for [$C_{17}H_{13}N_3$]: 259.1109; found: 259.1093 [M^+].

6-phenylpyrido[3,2-*f*][1,7]naphthyridine (28d)



According to **TP 9**, the substituted azaphenanthrene derivative **28d** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35a** (0.52 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28d** as colorless solid (24 mg, 93%).

M.p.: 217 - 218 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 9.25 – 9.09 (m, 2H), 8.93 (dd, *J* = 13.8, 8.3 Hz, 2H), 8.39-8.20 (m, 2H), 7.82 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.66 (dd, *J* = 8.0, 4.4 Hz, 1H), 7.62 – 7.49 (m, 3H).

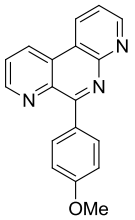
^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 164.0, 153.1, 152.6, 150.9, 141.1, 138.1, 131.8 (2C), 131.4, 130.6, 129.8, 129.2, 127.9 (2C), 125.2, 122.4, 118.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2927, 2360, 2231, 1712, 1556, 1514, 1452, 1434, 1356, 1260, 905, 793, 710, 693, 686.

MS (EI, 70 eV): *m/z* (%) = 258 (25), 257 (100), 129 (10), 84 (12).

HRMS (EI): *m/z* calcd. for [$C_{17}H_{11}N_3$]: 257.0953; found: 257.0950 [M^+].

6-(4-methoxyphenyl)pyrido[3,2-*f*][1,7]naphthyridine (28e)



According to**TP 9**, the substituted azaphenanthrene derivative **28e** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35b** (0.10 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28e** as colorless solid (25 mg, 87%).

M.p.: 156 - 157 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 9.21 – 9.09 (m, 2H), 8.94 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.86 (dd, *J* = 8.2, 1.7 Hz, 1H), 8.42 – 8.37 (m, 2H), 7.81 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.63 (dd, *J* = 8.1, 4.4 Hz, 1H), 7.12 – 7.05 (m, 2H), 3.91 (s, 3H).

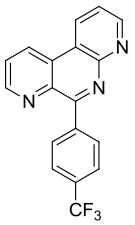
^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 163.2, 161.3, 153.2, 152.5, 150.8, 141.2, 133.6 (2C), 131.3, 130.7, 129.3, 127.9, 125.1, 122.1, 117.9, 113.5 (2C), 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2927, 1605, 1574, 1552, 1449, 1436, 1354, 1299, 1213, 1175, 1030, 968, 833, 789, 712.

MS (EI, 70 eV): *m/z* (%) = 288 (18), 287 (92), 273 (17), 272 (100), 256 (13), 244 (30), 243 (17), 122 (10).

HRMS (EI): *m/z* calcd. for [$C_{18}H_{13}N_3O$]: 287.1059; found: 287.1054 [M^+].

6-(4-(trifluoromethyl)phenyl)pyrido[3,2-*f*][1,7]naphthyridine (28f)



According to**TP 9**, the substituted azaphenanthrene derivative **28f** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35c** (0.65 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28f** as colorless solid (22 mg, 68%).

M.p.: 224 °C

^{1}H NMR (800 MHz, $CDCl_3$): δ/ppm = 9.20 (dd, *J* = 4.3, 1.8 Hz, 1H), 9.17 (dd, *J* = 4.2, 1.6 Hz, 1H), 9.01 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.94 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 2H), 7.87 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.72 (dd, *J* = 8.1, 4.3 Hz, 1H).

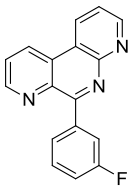
^{13}C NMR (200 MHz, $CDCl_3$): δ/ppm = 173.7, 162.6, 155.5, 152.9, 151.1, 141.4, 140.9, 132.1 (2C), 131.5, 131.5 (q, *J* = 30.5 Hz, 1C), 130.8, 129.4, 125.6, 124.9, 124.4 (q, *J* = 271.4 Hz, 1C), 123.0, 118.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2854, 2360, 2340, 1737, 1714, 1597, 1565, 1453, 1442, 1322, 1259, 1207, 1155, 1119, 1066, 959, 784, 775, 712.

MS (EI, 70 eV): *m/z* (%) = 326 (17), 325 (100), 325 (57).

HRMS (EI): *m/z* calcd. for [$C_{18}H_{10}N_3F_3$]: 325.0827; found: 325.0821 [M^+].

6-(3-fluorophenyl)pyrido[3,2-*f*][1,7]naphthyridine (28g)



According to**TP 9**, the substituted azaphenanthrene derivative **28g** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35d** (0.91 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28g** as colorless solid (17 mg, 62%).

M.p.: 237 - 238 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 9.22 – 9.11 (m, 2H), 8.97 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.90 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.16 – 8.12 (m, 1H), 8.11 – 8.07 (m, 1H), 7.84 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.68 (dd, *J* = 8.2, 4.4 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.25 – 7.19 (m, 1H).

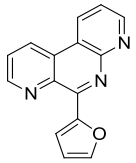
^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 163.7, 162.4, 161.3, 152.8, 151.0, 140.9, 140.0, 131.4, 130.7, 129.4, 129.3, 127.6, 127.6, 124.1 (d, *J* = 265.4 Hz, 1C), 118.9 (d, *J* = 21.5 Hz, 1C), 118.3, 116.7 (d, *J* = 21.5 Hz, 1C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2927, 2857, 1738, 1729, 1596, 1568, 1450, 1442, 1358, 1261, 1059, 791, 712.

MS (EI, 70 eV): *m/z* (%) = 276 (14), 275 (100), 274 (75).

HRMS (EI): *m/z* calcd. for [$C_{17}H_{10}FN_3$]: 275.0859; found: 275.0852 [M^+].

6-(furan-2-yl)pyrido[3,2-*f*][1,7]naphthyridine (28h)



According to**TP 9**, the substituted azaphenanthrene derivative **28h** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35e** (0.90 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28h** as colorless solid (20 mg, 80%).

M.p.: 228 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 9.15 (dd, *J* = 4.2, 1.6 Hz, 1H), 9.12 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.89 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.79 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.33 (dd, *J* = 3.4, 0.7 Hz, 1H), 7.84 – 7.77 (m, 2H), 7.59 (dd, *J* = 8.1, 4.3 Hz, 1H), 6.68 (dd, *J* = 3.4, 1.7 Hz, 1H).

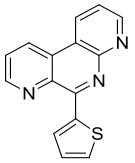
^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 153.2, 152.7, 152.0, 150.8, 150.8, 145.7, 139.9, 131.1, 130.6, 128.9, 125.4, 122.1, 120.5, 117.6, 112.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2943, 2858, 1737, 1729, 1671, 1601, 1569, 1519, 1450, 1442, 1359, 1261, 1058, 792, 712.

MS (EI, 70 eV): *m/z* (%) = 248 (24), 247 (100), 246 (12), 220 (10), 219 (36), 218 (21), 191 (11), 44 (24), 43 (17).

HRMS (EI): *m/z* calcd. for [$C_{15}H_9N_3O$]: 247.0746; found: 247.0745 [M^+].

6-(thiophen-2-yl)pyrido[3,2-*f*][1,7]naphthyridine (28i)



According to **TP 9**, the substituted azaphenanthrene derivative **28i** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35f** (0.64 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28i** as white solid (12 mg, 46%).

M.p.: 221 - 223 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 9.21 – 9.18 (m, 1H), 9.13 (d, *J* = 3.9 Hz, 1H), 8.97 (d, *J* = 3.7 Hz, 1H), 8.93 – 8.90 (m, 1H), 8.84 – 8.80 (m, 1H), 7.84 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.68 (d, *J* = 5.0 Hz, 1H), 7.60 (dd, *J* = 8.0, 4.3 Hz, 1H), 7.28 – 7.26 (m, 1H).

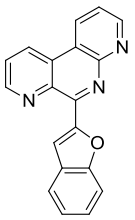
^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 156.5, 153.2, 152.8, 150.3, 140.7, 140.0, 133.7, 133.1, 131.3, 130.7, 128.9, 127.7, 125.5, 121.9, 117.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2853, 1569, 1551, 1506, 1447, 1360, 1223, 1042, 848, 786, 714, 673.

MS (EI, 70 eV): *m/z* (%) = 264 (18), 263 (100), 262 (61).

HRMS (EI): *m/z* calcd. for [$C_{15}H_9N_3S$]: 263.0517; found: 263.0512 [M^+].

6-(benzofuran-2-yl)pyrido[3,2-*f*][1,7]naphthyridine (28j)



According to **TP 9**, the substituted azaphenanthrene derivative **28j** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35g** (0.64 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28j** as colorless solid (10 mg, 34%).

M.p.: 219 - 223 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 9.23 (dd, *J* = 4.2, 1.7 Hz, 1H), 9.19 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.96 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.86 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.81 (s, 1H), 7.88 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.80 – 7.77 (m, 1H), 7.76 – 7.72 (m, 1H), 7.66 (dd, *J* = 8.2, 4.3 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.33 – 7.28 (m, 1H).

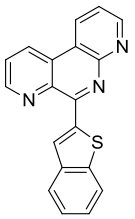
^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 155.7, 153.1, 152.9, 152.3, 151.9, 150.9, 140.5, 131.2, 130.8, 129.2, 129.0, 126.8, 125.5, 123.2, 122.7, 122.6, 118.0, 116.7, 112.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2853, 1595, 1561, 1513, 1462, 1449, 1364, 1343, 1261, 1166, 983, 789, 751, 694.

MS (EI, 70 eV): *m/z* (%) = 298 (21), 297 (100), 296 (28), 269 (10), 268 (11).

HRMS (EI): *m/z* calcd. for [$C_{19}H_{11}N_3O$]: 297.0902; found: 297.0898 [M^+].

6-(benzo[*b*]thiophen-2-yl)pyrido[3,2-*f*][1,7]naphthyridine (28k)



According to **TP 9**, the substituted azaphenanthrene derivative **28k** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35h** (0.78 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28k** as colorless solid (16 mg, 51%).

M.p.: 215 - 216 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 9.32 (s, 1H), 9.20 (dd, *J* = 4.1, 1.4 Hz, 1H), 9.14 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.89 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.80 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.98 – 7.91 (m, 2H), 7.82 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.60 (dd, *J* = 8.2, 4.3 Hz, 1H), 7.44 – 7.36 (m, 2H).

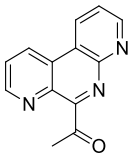
^{13}C NMR (200 MHz, $CDCl_3$): δ/ppm = 156.5, 152.7, 152.7, 150.5, 143.6, 141.5, 140.5, 140.2, 131.6, 131.5, 130.8, 128.9, 126.1, 125.6, 125.4, 124.4, 122.4, 122.3, 118.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2925, 2856, 1711, 1594, 1552, 1564, 1552, 1519, 1456, 1445, 1357, 1342, 1260, 1207, 1172, 1154, 954, 784, 775, 728, 712, 687.

MS (EI, 70 eV): *m/z* (%) = 314 (26), 313 (100), 312 (53), 156 (15).

HRMS (EI): *m/z* calcd. for [$C_{19}H_{11}N_3S$]: 313.0674; found: 313.0666 [M^+].

1-(pyrido[3,2-*f*][1,7]naphthyridin-6-yl)ethanone (28l)



According to **TP 9**, the substituted azaphenanthrene derivative **28l** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35i** (0.91 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. After aqueous workup and extraction with EtOAc, all solvents were removed *in vacuo*. The crude was then re-dissolved in 2 mL of a mixture of methanol and 2 M *aq.* HCl (40:1, 0.05 M) and stirred at room temperature overnight. After aqueous workup, the crude was extracted with EtOAc and flash column chromatography furnished **28l** as colorless solid (20 mg, 90%).

M.p.: 147 °C.

^{1}H NMR (800 MHz, $CDCl_3$): δ/ppm = 9.20 (dd, *J* = 4.1, 1.5 Hz, 1 H), 9.16 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.94 (dd, *J* = 8.4, 1.4 Hz, 1 H), 8.91 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.85 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.75 (dd, *J* = 8.1, 4.3 Hz, 1 H), 2.94 (s, 3 H).

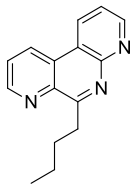
^{13}C NMR (200 MHz, $CDCl_3$): δ/ppm = 201.7, 162.2, 153.0, 152.2, 151.9, 139.3, 131.7, 130.6, 129.3, 126.1, 123.7, 119.2, 30.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2360, 2338, 1714, 1601, 1567, 1455, 1442, 1378, 1346, 1264, 1210, 1152(w), 904, 789, 700.

MS (EI, 70 eV): *m/z* (%) = 224 (15), 223 (100), 195 (30), 181 (26), 180 (80), 154 (14), 153 (18), 126 (18), 43 (16).

HRMS (EI): *m/z* calcd. for [$C_{13}H_9N_3O$]: 223.0746; found: 223.0740 [M^+].

6-butylpyrido[3,2-*f*][1,7]naphthyridine (28m)



According to **TP 9**, the substituted azaphenanthrene derivative **28m** was obtained from **28a** (0.1 mmol) *via* addition of the organolithium reagent **35j** (2.43 M, 1.5 equiv, **TP 8**) and subsequent chloranil-mediated aromatization. Flash column chromatography furnished **28m** as colorless solid (18 mg, 76%).

M.p.: 131 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 9.12 (dd, *J* = 4.3, 1.6 Hz, 1H), 9.10 (dd, *J* = 4.4, 1.8 Hz, 1H), 8.88 (ddd, *J* = 8.3, 1.6, 0.3 Hz, 1H), 8.83 (ddd, *J* = 8.5, 1.7, 0.4 Hz, 1H), 7.79 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.4 Hz, 1H), 3.70 – 3.64 (m, 2H), 2.07 – 2.00 (m, 2H), 1.56 (q, *J* = 7.5 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 169.7, 153.2, 152.1, 150.7, 141.4, 131.4, 130.5, 127.9, 125.4, 122.0, 117.7, 34.6, 30.9, 23.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2943, 2858, 1737, 1729, 1671, 1601, 1569, 1519, 1450(s), 1442, 1359, 1261, 1058, 792, 712.

MS (EI, 70 eV): *m/z* (%) = 237 (45), 211 (15), 210 (23), 209 (20), 208 (100), 207 (42), 206 (17), 196 (53), 195 (20), 194 (25), 182 (27), 181 (26), 180 (25), 155 (12), 71 (13), 57 (21), 43 (13).

HRMS (EI): *m/z* calcd. for [$C_{15}H_{15}N_3$]: 237.1266; found: 237.1274 [M^+].

6 Mild Chlorohomologation and Bischloromethylation of Esters via Continuous Flow Chloroacetate Claisen Reactions

6.1 Reagents

Chloroacetic acid (**CA**) and dichloroacetic acid (**DCA**) are acutely toxic (acute toxicity, oral category 3) and pose severe health hazards, as well as chloroacetophenone (acute toxicity, inhalation, category 3).[257] Working with these substances should therefore only be started after reading the Safety Data Sheets, performing a health risk assessment and taking precautionary measures. The products obtained by the method described herein must be assumed to be equally as toxid as chloroacteophenone, even if no specific information is currently available. *The here presented method provides enhanced safety since the obtained crude products can be subsequently used in their usual fashion (cyclocondesation) without the need for isolation or extensive purification, thus minimizing any exposure to potentially harmful chloroketones.* Reagents were obtained from commercial sources and used without further purification unless otherwise stated. **LiHMDS** (Lithium-bis(trimethylsilyl)amide) was purchased from Sigma-Aldrich as 1.5 M solution in THF and further diluted to 0.75 M with dry THF. Alternatively it was synthesized from commercial ^{n}BuLi and freshly distilled $HN(SiMe_3)_2$. The quality of LiHMDS was crucial for optimal yields, more reliable results were obtained with freshly prepared LiHMDS, which was stored in Schleck flasks under Ar at ≤ 10 °C. **DCA** and **CA** were purchased from Sigma-Aldrich in the highest available purity (99%+) and stored at 10 °C.

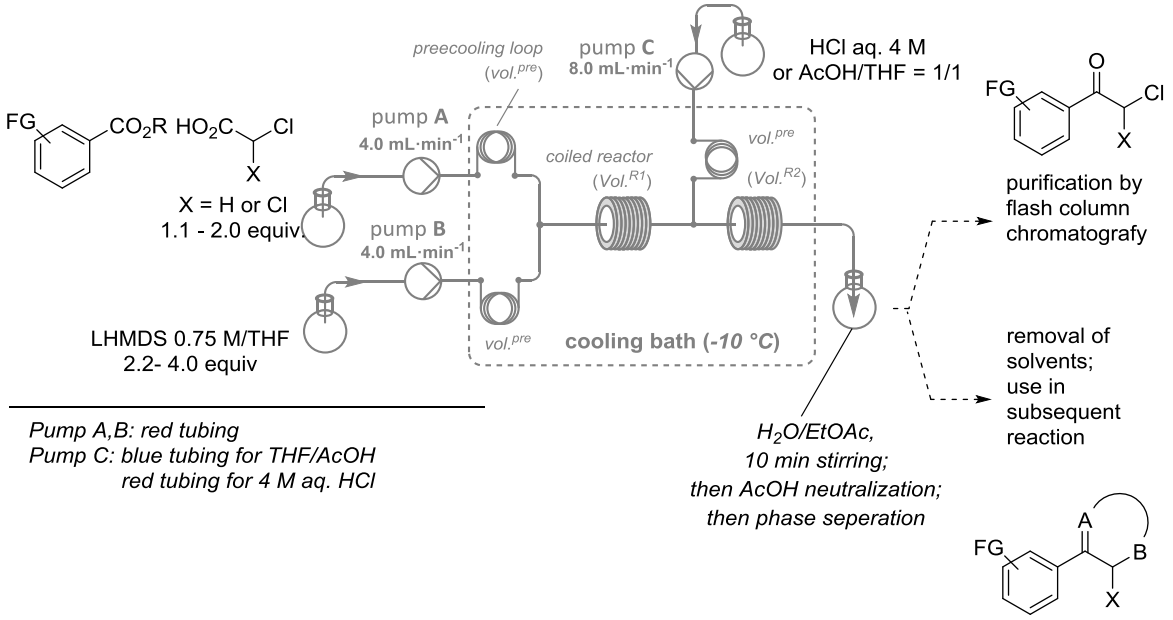
6.2 Analysis of the products

Some chloroketone products were not stable upon normal storage under air at room temperature, a corresponding remark is made.The HRMS of *α,α*'-dichloroketones often showed a molecule peak of ca. +1 or +2 amu (+1 or $2H^+$) or –83 amu ($-CHCl_2^{\cdot}$) compared to the expected mass. The other mass fragments and all other spectroscopic data identified the dichloroketone products unanimously, and the observed mass difference must therefore be a consequence of the HRMS measurement.

[257] Safety data sheets available from Sigma Aldrich (https://www.sigmaaldrich.com/MSDS), CHLOROACETOPHENONE: SAFETY DATA SHEET according to Regulation (EC) No. 1907/2006, Version 5.0 Revision Date 11.10.2012; CHLOROACETIC ACID: SAFETY DATA SHEET, according to Regulation (EC) No. 1907/2006,Version 6.1 Revision Date 02.01.2018; DICHLOROACETIC ACID: SAFETY DATA SHEET, according to Regulation (EC) No. 1907/2006, Version 5.7 Revision Date 15.09.2017

6.3 Typical Procedure (TP 10)

A commercially available setup from Vapourtec Ltd. (E-Series) was used for all reactions (Scheme 43). The reagent solutions were prepared in flasks under argon and suction needles delivered the solutions directly through the pumps (A, B, C) to the reactors ($Vol.^1$, $Vol.^2$). Pre-cooling loops ($vol.^{pre}$ = 1 mL) were installed before the reagents were mixed in T-mixers.



Scheme 49: TP 18 flow setup.

A LiHMDS solution in THF (0.75 M, 2.2−4.0 equiv) and a solution of the benzoic ester substrate (0.18-0.34 M, 1.0 equiv) with the pro-nuclophile (**DCA** or **CA** 0.375 M, 1.1−2.0 equiv) in THF were prepared. The solutions were pumped from their flasks through a suction needle at 4.0 mL·min^{-1} flowrates each (pump A and B). After passing a PTFE precooling loop (vol^{pre} = 1.0 mL; T = −10°C, residence time: 15 s), the solutions were mixed a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (I.D. = 0.8 mm; Vol^{R1} = 3.0 mL; residence time: t^1 = 22.5 s, T^1 = −10 °C) and was combined in a second T-mixer (PFA or PTFE, I.D. = 1.0 mm) with a pre-cooled (vol^{pre} = 1.0 mL; T = −10°C, residence time: 7.5 s) 4 M aequous HCl solution, which was pumped at a 8.0 mL·min^{-1} flowrate. The combined streams passed a second reactor (I.D. = 0.8 mm; Vol^{R2} = 2.0 mL; residence time: t^2 = 8 s, T^2 = −10 °C).[258]

After collecting the reactor output for the desired amount of time in a flask containing a stirring magnetic bar, ca. 5 mL EtOAc and 5 mL H_2O per mmol of substrate were addded. The reaction mixture was stirred further for at least 10 minutes at room temperature or until gas evolution ceased. Subsequently, the phases were split and the aequous phase was extracted with EtOAc three more

[258] If specific reaction mixtures produced excessive back pressure, Vol^{R1} can be modified to a reactor built from 0.25 mL of 0.8 mm i.d. tubing connected to 2.75 mL of 1.6 mm i.d. tubing. Analogously, Vol^{R2} can be built from 0.25 mL of 0.8 mm i.d. tubing connected to 1.75 mL of 1.6 mm

times. The combined organic phases were subsequently dried over $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash column chromatographical purification with suited *iso*-hexane:EtOAc mixtures afforded the pure chloroketones **37** or **36**. Alternatively, the crude reaction mixtures can be subjected to follow-up reactions leading to products **40** after removal of the combined organic phases *in vacuo*.

6.4 Typical Procedure (TP 11)

The same setup as in TP 10 was used. A 1:1 mixture (v:v) of AcOH (99%+) and THF was used for quenching in this procedure. After collection of the reaction output, K_2CO_3 was portionwise added under vigorous stirring to the biphasic mixture until the aequous phase showed a neutral pH. Addition of water may be required to solubilize all K_2CO_3.
The THF used for dilution of the AcOH was dried over KOH and stored over 3 angstrom molsieve in a closed flask prior to mixing with AcOH.

6.5 Typical procedure for the synthesis of 1,4-dicarbonyls using TMPLi (TP 12).

An oven and heat gun-dired (350 °C, ≤ 1 mbar) flask was charged with (hetero-)acetophenone derivative **7** (0.5 mmol, 1.1 equiv.) under Ar and dry THF was added (1 M). Freshly prepared TMPLi[259] in THF (0.55 mmol, 1.2 equiv.) was added dropwise at −78 °C and the reaction mixture was stirred 5 min. Subsequently, dry $ZnCl_2$ solution in THF(1 M, 1.2 1.2 equiv.) was added and the solution was allowed to warm to 25 °C over approx. 30 min. The zinc enolate solution was cooled to 0 C and a 1 M solution of chloroacetophenone **2** in dry THF (1.0 equiv.) was added *via* syringe. The reaction was allowed to warm to 25 °C and reaction progress was monitored by TLC. After typically 2-12 h, the reaction was quenched by addition of *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification over silica gel with suited *iso*-hexane:EtOAc mixtures afforded the title compounds. Due to low polarity differences, some samples had to be purified by preparative reversed-phase HPLC with MeCN:H_2O eluent mixtures to obtain analytically pure compounds.

6.6 Typical procedure for the synthesis of 1,4-dicarbonyls using TMPZnCl LiCl (TP 13)

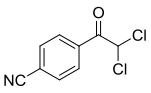
An oven and heat gun-dired (350 °C, ≤ 1 mbar) flask was charged with (hetero-)acetophenone derivative **7** (0.5 mmol, 1.1 equiv.) under Ar and dry THF was added (1.0 M). Freshly titrated

[259] 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.

TMPZnCl·LiCl[260] in THF (0.55 mmol, 1.2 equiv.) was added dropwise at 25 °C and the reaction mixture was stirred 1 h. Subsequently, the zinc enolate solution was cooled to 0 C and a 1.0 M solution of chloroacetophenone **2** in dry THF was added *via* syringe (1.0 equiv.). The reaction was allowed to warm to 25 °C and reaction progress was monitored by TLC. After typically 2-12 h, the reaction was quenched by addition of *sat. aq.* NH_4Cl solution. The aqueous phase was extracted three times with EtOAc (3×10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification over silica gel with suited *iso*-hexane:EtOAc mixtures afforded the title compounds. Due to low polarity differences, some samples had to be purified by preparative reversed-phase HPLC with MeCN:H_2O eluent mixtures to obtain analytically pure compounds.

6.7 Preparation of the chloroketone products according to TP 10 and TP 11

4-(2,2-dichloroacetyl)benzonitrile (36a)



According to **TP 10**, THF solutions of ester **39a** (0.30 M, 2 mmol) with DCA (0.38 M, 1.25 equiv) and LiHMDS, (0.75 M, 2.5 equiv.) were reacted and the reaction output was collected for 1.67 min, corresponding to 2.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 99:1) afforded the title compound as a colorless solid (348 mg, 0.81 mmol, 81% yield).

M.p. (°C): 115.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 – 8.13 (m, 2H), 7.85 – 7.78 (m, 2H), 6.61 (s, 1H).

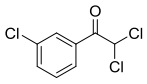
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 184.9, 134.5, 132.7(2C), 130.4(2C), 117.7, 117.6, 67.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2937(w), 2231(w), 1683(s), 1652(m), 1604(w), 1558(m), 1539(m), 1505(m), 1406(w), 1260(m), 1239(m), 1199(m), 1016(m), 861(s), 789(m), 720(s).

MS (EI, 70 eV): *m/z* (%) = 214(0.1), 130(100), 102(32), 70(11), 61(22), 45(22), 43(83).

HRMS (EI): *m/z* calc. for [$C_9H_5Cl_2NO$]: 214.0450; found: 214.9665[M+2H$^+$].

2,2-dichloro-1-(3-chlorophenyl)ethan-1-one (36b)



[260] a) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; b) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837;

According to **TP 10**, THF solutions of ester **39b** (0.15 M) with DCA (0.38 M, 2.5 equiv) and LiHMDS, (0.75 M, 5.0 equiv.) were reacted and the reaction output was collected for 1.67 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a colorless liquid (207 mg, 0.93 mmol, 93% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (t, *J* = 1.9 Hz, 1H), 7.96 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.60 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 6.59 (s, 1H).

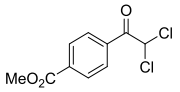
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 184.8, 135.3, 134.4, 132.8, 130.1, 129.7, 127.8, 67.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927(w), 1705(s), 1591(w), 1572(m), 1471(w), 1422(m), 1284(m), 1258(m), 1217(s), 1182(m), 1080(m), 998(m), 900(m), 810(s), 761(m), 713(s), 699(s), 678(s).

MS (EI, 70 eV): *m/z* (%) = 175(10,M+OH), 158(12), 156(37), 111(11), 107(100), 97(16), 95(15), 85(10), 83(15), 80(10), 79(94), 71(15), 70(10), 69(19), 67(10), 61(11), 57(28), 55(23), 53(12), 52(97), 49(13),m 45(12), 43(17), 42(31), 41(15).

HRMS (EI): *m/z* calc. for [$C_8H_5Cl_3O$]: 221.9406; found 221.9390.

Methyl 4-(2,2-dichloroacetyl)benzoate (36c)



According to **TP 10**, the THF solutions of ester **39c** (0.30 M) with DCA (0.36 M, 1.2 equiv) and LiHMDS, (0.75 M, 2.5 equiv.) were reacted and the reaction output was collected for 0.83 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5) afforded the title compound as a colorless solid (210 mg, 0.85 mmol, 85% yield).

M.p. (°C): 82-85.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.27 – 7.99 (m, 4H), 6.66 (s, 1H), 3.96 (s, 3H).

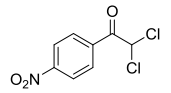
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 185.6, 165.9, 135.2, 134.7, 130.1 (2C), 129.8 (2C), 67.9, 52.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3007(w), 2948(w), 1706(s), 1432(m), 1403(m), 1280(s), 1221(m), 1190(m), 1112(m), 993(m),870(m), 834(w), 800(s), 773(s), 750(s), 693(s), 678(s).

MS (EI, 70 eV): *m/z* (%) = 247(0.01), 217(0.7), 163(6), 135(2), 103(1), 70(1), 61(2), 43(100).

HRMS (EI): *m/z* calc. for [$C_{10}H_8Cl_2O_3$]: 245.9850 found: 246.9930 [$M+H^+$]; 163.0368 [$M-CH_2Cl_2^+$].

2,2-dichloro-1-(4-nitrophenyl)ethan-1-one (36d)



According to **TP 10**, the THF solutions of ester **39d** (0.30 M) with DCA (0.36 M, 1.2 equiv) and LiHMDS, (0.75 M, 2.5 equiv.) were reacted and the reaction output was collected for 0.83 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5) afforded the title compound as a colorless liquid (177 mg, 0.76 mmol, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.36 (dt, *J* = 9.0, 2.1 Hz, 2H), 8.29 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.62 (s, 1H).

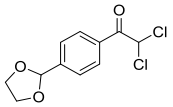
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 184.8, 151.0, 136.0 (2C), 131.2 (2C), 124.1, 67.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3111(w), 1714(m), 1602(w), 1522(s), 1405(w), 1344(s), 1319(m), 1273(m), 11216(m), 1182(m), 1113(w), 1013(w), 994(w), 867(s), 855(s), 806(m), 792(s), 772(s), 729(m), 689(s).

MS (EI, 70 eV): *m/z* (%) = 235(0.07), 150(100), 104(30), 89(10), 85(10), 83(15), 76(26), 75(12), 74(11), 50(20), 46(10).

HRMS (EI): *m/z* calc. for [$C_8H_5Cl_2NO_3$]: 232.9646; found: 235.9864 [M+2H$^+$].

1-(4-(1,3-dioxolan-2-yl)phenyl)-2,2-dichloroethan-1-one (36g)



According to **TP 11**, the THF solutions of ester **39g** (0.17 M) with DCA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was neutralized with solid K_2CO_3 and 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, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a colorless liquid (162 mg, 0.62 mmol, 62% yield), from which small amounts of hydrolysis formed quickly after isolation.

^{1}H-NMR (400 MHz, DMSO-d_6)[261]: δ / ppm = 8.10 (d, *J* = 8.5 Hz, 2H), 7.91 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 5.85 (s, 1H), 4.12 – 3.94 (m, 4H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ / ppm = 186.0, 144.6, 132.1, 129.7, 129.6 (2C), 127.1 (2C), 101.8, 69.1, 65.0.

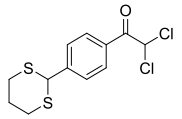
[261] Strong hydrolysis observed in $CDCl_3$ as well as overlaps with CHCl2 signal. 15% hydrolysis in DMSO-d_6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953(w), 2890(w), 1700(s), 1609(w), 1573(w), 1505(w), 1407(m), 1272(s), 1219(s), 1208(s), 1080(s), 1017(m), 992(m), 941(m), 854(m), 840(m), 804(s); 769(s), 692(s).

MS (EI, 70 eV): *m/z* (%) = 263(0.4), 213(10), 211(34), 194(10), 193(100), 181(10), 177(12), 149(54), 133(44), 121(14), 105(25), 104(18), 77(13), 76(16), 65(11)44(13), 43(12)..

HRMS (EI): *m/z* calc. for [$C_{11}H_{10}Cl_2O_3$]: 260.0007; found: 263.0245 [M+3H^+]

1-(4-(1,3-dithian-2-yl)phenyl)-2,2-dichloroethan-1-one (36h)



According to **TP 10**, the THF solutions of ester **39h** (0.17 M) with DCA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5) afforded the title compound as a colorless solid (208 mg, 0.68 mmol, 68% yield).

Mp.(°C): 132.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.63 (dt, *J* = 8.4, 2.0 Hz, 2H), 6.68 (s, 1H), 5.23 (s, 1H), 3.09 (ddd, *J* = 14.6, 12.3, 2.5 Hz, 2H), 3.00 – 2.90 (m, 2H), 2.21 (dtt, *J* = 14.1, 4.7, 2.5 Hz, 1H), 2.04 – 1.90 (m, 1H).

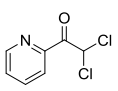
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 185.4, 145.9, 131.2 (2C), 130.4 (2C), 128.6, 67.9, 50.9, 31.9 (2C), 25.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926(w), 2893(w), 1696(s), 1602(m), 1569(m), 1413(m), 1296(m), 1276(m), 1229(m), 1176(m), 1106(w), 994(m), 912(w), 883(m), 863(m), 841(w), 800(m), 778(s), 754(s), 691(m), 676(s).

MS (EI, 70 eV): *m/z* (%) = 307 (39), 306(52), 272(12), 243(10), 241(12), 223(56), 150(13), 149(95), 129(18), 125(20), 121(31), 120(18), 106(22), 105(34), 100(16), 89(17), 77(36), 75(12), 74(100), 73(12), 64(15), 63(17), 57(10), 55(10), 46(24), 44(36), 43(42), 41(33).

HRMS (EI): *m/z* calc. for [$C_{12}H_{12}Cl_2OS_2$]: 305.9707; found: 305.9698.

2,2-dichloro-1-(pyridin-2-yl)ethan-1-one (36i)



According to **TP 11**, the THF solutions of ester **39i** (0.34 M) with DCA (0.38 M, 1.1 equiv) and LiHMDS, (0.75 M, 2.2 equiv.) were reacted and the reaction output was collected for 0.74 min, corresponding to 1 mmol ester. After addition of EtOAc and water and subsequent stirring, the

aqueous phase neutralized with solid K_2CO_3 and 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, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a colorless solid (175 mg, 0.92 mmol, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.70 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.15 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.62 (s, 1H), 7.57 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H).

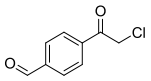
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 186.8, 149.5, 149.4, 137.6, 128.6, 124.3, 66.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020(w), 1721(s), 1582(m), 1437(m), 1308(m), 1285(m), 1253(w), 1197(m), 994(m), 825(s), 778/m), 748(m), 668(s).

MS (EI, 70 eV): *m/z* (%) = 190(7), 189(11), 106(49), 96(17), 78(100).

HRMS (EI): *m/z* calc. for [$C_7H_5Cl_2NO$]: 188.9748; found: 188.9742 [M^+].

4-(2-chloroacetyl)benzaldehyde (37a)



According to **TP 10**, the THF solutions of ester **39g** (0.18 M) with DCA (0.38 M, 2.0 equiv) and LiHMDS, (0.75 M, 4.2 equiv.) were reacted and the reaction output was collected for 2.17 min, corresponding to 1.56 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 7:3) afforded the title compound as a colorless solid (200 mg, 1.10 mmol, 71% yield).

M.p. (°C): 216-220.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.09 (s, 1H), 8.09 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.1 Hz, 2H), 4.70 (s, 2H).

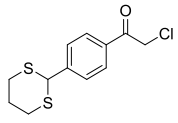
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.2, 190.7, 139.6, 138.3, 129.9 (2C), 129.1 (2C), 45.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2941(w), 1697(s), 1572(w), 1504(w), 1410(w), 1395(m), 1291(m), 1206(s), 1127(w), 998(m), 934(w), 833(m), 818(m), 791(m), 759(s), 690(m).

MS (EI, 70 eV): *m/z* (%) = 181(0.1), 133(100), 105(11), 77(14).

HRMS (EI): *m/z* calc. for [$C_9H_7ClO_2$]: 182.0135; found 181.0050 [M-H^+].

1-(4-(1,3-dithian-2-yl)phenyl)-2-chloroethan-1-one (37b)



According to **TP 10**, the THF solutions of ester **39h** (0.17 M) with CA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 3.50 min, corresponding to 2.38 mmol ester. After addition of EtOAc and water and subsequent stirring, the

aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5) afforded the title compound as a colorless crystals (450 mg, 1.65 mmol, 69% yield).

M.p.(°C): 132.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 5.21 (s, 1H), 4.69 (s, 2H), 3.08 (ddd, *J* = 14.7, 12.3, 2.5 Hz, 2H), 2.94 (dt, *J* = 14.6, 3.3 Hz, 2H), 2.20 (dtt, *J* = 14.1, 4.7, 2.5 Hz, 1H), 1.96 (ddt, *J* = 14.1, 12.2, 3.2 Hz, 1H).

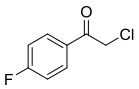
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.6, 145.3, 134.2, 129.2 (2C), 128.6 (2C), 51.1, 46.1, 32.0 (2C), 25.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2910(w), 1702(s), 1601(m), 1411(m), 1276(m), 1231(m), 1169(m), 1085(m), 975(s), 908(m), 883(m), 863(m), 759(s), 713(m), 672(m).

MS (EI, 70 eV): *m/z* (%) = 274(39), 273(13), 272(87), 223(17), 109(11), 207(26), 198(13), 150(11), 149(100), 129(19), 121(34), 120(13), 105(34), 91(23), 77(28), 74(85), 73(15), 46(21), 45(27), 41(14).

HRMS (EI): *m/z* calc. for [$C_{12}H_{13}ClOS_2$]: 272.0096; found: 272.0085 [M^+].

2-chloro-1-(4-fluorophenyl)ethan-1-one (37c)



According to **TP 10**, the THF solutions of ester **39j** (0.15 M) with CA (0.36 M, 2.4 equiv) and LiHMDS, (0.75 M, 5.0 equiv.) were reacted and the reaction output was collected for 1.50 min, corresponding to 0.9 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 995:5) afforded the title compound as a colorless solid (152 mg, 0.88 mmol, 98% yield).

M. p. (°C): 83.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02 – 7.85 (m, 2H), 7.19 – 7.03 (m, 2H), 4.63 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 197.00, 166.53 (d, *J* = 256.6 Hz), 130.57 (d, *J* = 9.4 Hz, 2C), 130.00 (d, *J* = 3.1 Hz), 116.42 (d, *J* = 22.3 Hz, 2C), 65.45.

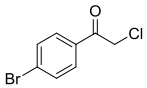
^{19}F NMR (377 MHz, $CDCl_3$) δ / ppm **=** -100.74 – -104.20 (m).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3417(m), 3387(m), 1684(m), 1677(m), 1595(m), 1508(m), 1411(w), 1294(w), 1230(m), 1160(m), 1111(m), 1100(m), 994(w), 979(m), 836(s), 826(m), 769(w).

MS (EI, 70 eV): *m/z* (%) = 172(0.1), 124(7), 123(100),109(5), 95(4), 75(8).

HRMS (EI): *m/z* calc. for [C_8H_6ClFO]: 172.0091; found: 172.0086.

1-(4-bromophenyl)-2-chloroethan-1-one (37d)



According to **TP 10**, the THF solutions of ester **39k** (0.17 M) with CA (0.36 M, 2.4 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.50 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a colorless crystals (190 mg, 0.81 mmol, 81% yield).

Mp.(°C): 127-130.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (dtd, *J* = 8.5, 2.4, 1.8, 0.2 Hz, 2H), 7.65 (dt, *J* = 8.7, 2.4, 1.8 Hz, 2H), 4.65 (s, 2H).

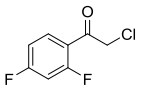
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.4, 133.1, 132.4 (2C), 130.2 (2C), 129.5, 45.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950(w), 1684(s), 1582(s), 1565(m), 184/m), 1394(m), 1311(w), 1296(w), 1210(s), 1182(m), 1074(m), 996(m), 813(s), 776(s), 673(m).

MS (EI, 70 eV): *m/z* (%) = 235(0.07), 150(100), 104(30), 89(10), 85(10), 83(15), 76(26), 75(12), 74(11), 50(20), 46(10).

HRMS (EI): *m/z* calc. for [C_8H_6BrClO]: 231.9292; found: 231.9284 [M^+].

2-chloro-1-(2,4-difluorophenyl)ethan-1-one (37e)



According to **TP 10**, the THF solutions of ester **39l** (0.17 M) with CA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.67 min, corresponding to 1.13 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 99:1) afforded the title compound as a colorless crystals (175 mg, 0.92 mmol, 81% yield).

Mp.(°C): 46.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01 (td, *J* = 8.5, 6.5 Hz, 1H), 7.00 (dddd, *J* = 8.8, 7.6, 2.4, 0.6 Hz, 1H), 6.90 (ddd, *J* = 11.1, 8.5, 2.4 Hz, 1H), 4.67 (d, *J* = 2.9 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 187.8 (d, *J* = 5.1 Hz), 166.5 (dd, *J* = 259.1, 12.5 Hz), 162.7 (dd, *J* = 256.9, 12.7 Hz), 133.3 (dd, *J* = 10.7, 4.3 Hz), 119.5 (dd, *J* = 14.0, 3.7 Hz), 112.9 (dd, *J* = 21.6, 3.3 Hz), 104.8 (dd, *J* = 27.6, 25.6 Hz), 49.7 (s).

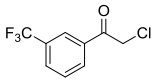
^{19}F-NMR (376 MHz): δ / ppm = -99.27 (q, J = 21.0, 11.6, 8.5 Hz, 1F), -102.88 – -103.30 (m, 1F).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070(w), 1699(s), 1608(s), 1586(m), 1489(m), 1432(m), 1419(m), 1432(m), 1392(m), 1315(m), 1268(m), 1230(s), 1194(s), 1184(m), 1141(m), 1098(s), 1001(m), 968(s), 918(w), 882(s), 821(s),794(m), 756(m), 728(m).

MS (EI, 70 eV): *m/z* (%) = 189(0.02), 141(100), 127(4), 113(4).

HRMS (EI): *m/z* calc. for [$C_8H_5ClF_2O$]: 189.9997; found: 189.9988[M^+].

2-chloro-1-(3-(trifluoromethyl)phenyl)ethan-1-one (37f)



According to **TP 10**, the THF solutions of ester **39m** (0.17 M) with CA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 99:1) afforded the title compound as a colorless liquid (213 mg, 0.96 mmol, 96% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 4.71 (s, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.2, 134.9, 131.9 (d, *J* = 1.4 Hz), 131.8 (q, *J* = 33.1 Hz), 130.6 (q, *J* = 3.6 Hz), 129.8, 125.6 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.6 Hz), 45.7.

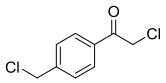
^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -62.92.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921(w), 1709(s), 1612(w), 1437(w), 1332(s), 1265(m), 1166(br,m), 1122(br,s), 1071(s), 790(m), 692(m), 664(m).

MS (EI, 70 eV): *m/z* (%) = 222(0.9),174(10), 173(100), 145(44), 43(22).

HRMS (EI): *m/z* calc. for [$C_9H_6ClF_3O$]: 222.0059; found: 222.0058 [M^+].

2-chloro-1-(4-(chloromethyl)phenyl)ethan-1-one (37g)



According to **TP 10**, the THF solutions of ester **39n** (0.17 M) with CA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a colorless crystals (162 mg, 0.80 mmol, 80% yield).

M.p. (°C): = 89.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm 7.97 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 4.72 (s, 2H), 4.64 (s, 2H).

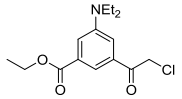
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.6, 143.4, 134.0, 129.04 (2C), 129.00 (2C), 45.9, 45.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2998(w), 1700(s), 1607(m), 1415(m), 1402(m), 1323(w), 1262(m), 1215(s), 1205(s), 1111(m), 998(m), 840(m), 824(s), 787(m), 751(s), 736(s), 671(s).

MS (EI, 70 eV): *m/z* (%) = 202(3), 155(28), 153(100), 125(21), 89(11).

HRMS (EI): *m/z* calc. for [$C_9H_8Cl_2O$]: 201.9952; found: 201.9945[M^+].

Ethyl 3-(2-chloroacetyl)-5-(diethylamino)benzoate (37i)



According to **TP 10**, the THF solutions of ester **39p** (0.30 M) with CA (0.36 M, 1.2 equiv) and LiHMDS, (0.75 M, 2.5 equiv.) were reacted and the reaction output was collected for 0.83 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a colorless crystals (254 mg, 0.85 mmol, 85% yield). Besides, 10 mg (3%) of bis-homologation product were isolated (analysis by GC-MS).

M.p. (°C): 105-107.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.73 (t, *J* = 1.1 Hz, 1H), 7.55 (dd, *J* = 2.7, 1.1 Hz, 1H), 7.40 (t, *J* = 2.6, 1.1 Hz, 1H), 4.76 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 4H), 1.40 (*t*, J = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 6H).

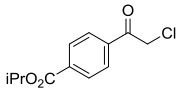
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.4, 166.4, 148.2, 135.4, 132.1, 117.6, 115.9, 114.5, 61.4, 46.6, 44.6 (2C), 14.5, 12.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972(w), 2930(w), 1709(s), 1692(s), 1596(s), 1494(w), 1461(m), 1472(m), 1357(m), 1243(s), 1191(s), 1124(m), 1033(m), 1015(m), 858(m), 782(m), 763(s), 745(m), 667(s).

MS (EI, 70 eV): *m/z* (%) = 297(14), 284(30), 283(15), 282(100), 256(21), 254(67), 248(13), 228(11), 226(34), 208(15), 204(29), 189(13), 176(18), 150(12), 146(11), 132(26), 118(17), 117(20), 104(15), 91(11), 89(10), 75(10).

HRMS (EI): *m/z* calc. for [$C_{15}H_{20}ClNO_3$]: 297.1132; found 297.1123[M^+].

Isopropyl 4-(2-chloroacetyl)benzoate (37j)



According to **TP 10**, the THF solutions of ester **39q** (0.17 M) with CA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a colorless solid (197 mg, 0.82 mmol, 82% yield).

M.p. (°C): 63.

R_f (iHex:EtOAc = 7:3): 0.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (dt, *J* = 8.7, 1.9 Hz, 2H), 7.99 (dt, *J* = 8.7, 1.9 Hz, 2H), 5.27 (hept, *J* = 6.3 Hz, 1H), 4.72 (s, 2H), 1.38 (d, *J* = 6.3 Hz, 6H).

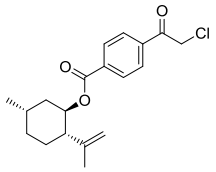
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.9, 165.0, 137.3, 135.6, 130.0 (2C), 128.5 (2C), 69.4, 46.1, 22.0 (2C).

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2938(w), 1702(s), 1472(w), 1495(w), 1395(w), 1283(s), 1208(m), 1182(m), 1127(m), 1097(m), 998(m), 917(m), 848(m), 762(s), 694(m), 673(m).

MS (EI, 70 eV): *m/z* (%) = 240(0.2), 192(12), 191(100), 149(73), 121(13), 104(16), 97(16), 85(14), 83(14), 81(10), 76(17), 71(19), 69(16), 65(12), 57(33), 55(19), 50(10), 43(28), 41(18).

HRMS (EI): *m/z* calc. for [$C_{12}H_{13}ClO_3$]: 240.0553; found: 240.0554 [M^+].

(1*S*,2*R*,5*R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl 4-(2-chloroacetyl)benzoate (37k)



According to **TP 10**, the THF solutions of ester **39r** (0.17 M) with DCA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 2.25 min, corresponding to 1.46 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5) afforded the title compound as a colorless solid (436 mg, 1.31 mmol, 89% yield).

M.p. (°C): = 114.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 5.05 (td, *J* = 10.9, 4.4 Hz, 1H), 4.82 – 4.77 (m, 1H), 4.76 – 4.69 (m, 3H), 2.32 (td, *J* = 11.7, 11.2, 3.5 Hz, 1H), 2.17 (dt, *J* = 11.9, 3.3 Hz, 1H), 1.83 – 1.72 (m, 2H), 1.72 – 1.58 (m, 4H), 1.48 (qd, *J* = 14.3, 13.7, 3.9 Hz, 1H), 1.18 (q, *J* = 11.9 Hz, 1H), 1.05 (td, *J* = 13.5, 13.0, 3.9 Hz, 1H), 0.97 (d, *J* = 6.5 Hz, 3H).

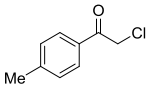
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 190.8, 164.8, 146.0, 137.2, 135.5, 130.0 (2C), 128.4 (2C), 112.2, 75.0, 50.9, 46.0, 40.4, 34.1, 31.4, 30.4, 22.0, 19.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952(w), 1697(s), 1454(w), 1407(w), 1288(m), 1274(s), 1206(m), 1108(s), 998(m), 974(m), 900(m), 891(m), 844(m), 779(m), 762(s), 693(m).

MS (EI, 70 eV): *m/z* (%) =334(1), 285(21), 184(10), 183(100), 182(34), 181(62), 149(41), 137(16),136(94), 132(12), 121(51), 118(20), 108(14), 107(41), 104(60), 94(27), 93(48), 92(12), 90(63), 80(18), 79(19), 77(11), 76(27), 67(11), 65(12), 55(17), 41(30).

HRMS (EI): *m/z* calc. for [$C_{19}H_{23}ClO_3$]: 334.1336; found 334.1326 [M^+].

2-chloro-1-(p-tolyl)ethan-1-one (37l)



According to the **TP 10**, the THF solutions of ester **39s** (0.17 M) with CA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 99:1) afforded the title compound as a colorless liquid (110 mg, 0.65 mmol, 65% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.87 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.70 (s, 2H), 2.44 (s, 3H).

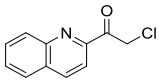
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.7, 145.1, 131.8, 129.6 (2C), 128.7 (2C), 46.0, 21.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983(w), 1732(s), 1701(s), 1685(m), 1606(m), 1445(w), 1372(m), 1238(s), 1204(m), 1184(m), 1044(s), 1002(w), 914(m), 844(w), 809(m), 786(m), 731(s).

MS (EI, 70 eV): *m/z* (%) = 168(0.3), 119(100), 91(27).

HRMS (EI): *m/z* calc. for [C_9H_9ClO]: 168.0342; found: 167.0258 [M-H^+].

2-chloro-1-(quinolin-2-yl)ethan-1-one (37o)



According to **TP 11**, the THF solutions of ester **39v** (0.25 M) with CA (0.36 M, 1.4 equiv) and LiHMDS, (0.75 M, 3.0 equiv.) were reacted and the reaction output was collected for 2.0 min, corresponding to 2.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was neutralized with solid K_2CO_3 and 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, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a colorless oil (272 mg, 1.32 mmol, 66% yield).

^{1}H-NMR (200 MHz, $CDCl_3$): δ / ppm = 9.22 (s, 1H), 8.51 (s, 1H), 8.15 – 7.91 (m, 2H), 7.88 – 7.67 (m, 2H), 5.21 (s, 2H).

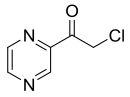
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 192.6, 152.2, 145.8, 135.5, 131.4, 130.6, 130.1, 128.8, 127.8, 121.3, 48.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980(w), 1694(s), 1685(s), 1589(w), 1467(w), 1407(w), 1310(m), 1276(s), 1184(m), 1096(m), 997(m), 910(m), 866(w), 750(s), 727(s), 702(m), 693(m), 674(m).

MS (EI, 70 eV): *m/z* (%) = 205(20), 171(28), 156(41), 129(35), 128(100), 111(10), 101(13), 97(15), 85(16), 83(14), 81(10), 77(15), 71(21), 69(24), 57(40), 56(14), 55(23), 44(19), 43(31), 41(26).

HRMS (EI): *m/z* calc. for [$C_{11}H_8ClNO_3$]: 205.0294; found: 205.0297 [M^+].

2-chloro-1-(pyrazin-2-yl)ethan-1-one (37p)



According to **TP 11**, the THF solutions of ester **39w** (0.18 M) with DCA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.2 equiv.) were reacted and the reaction output was collected for 1.41 min, corresponding to 1 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was neutralized with solid K_2CO_3 and 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, *iso*-hexane:EtOAc = 7:3) afforded the title compound as an off-white solid (72 mg, 0.54 mmol, 46% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.29 (d, J = 1.4 Hz, 1H), 8.84 (d, J = 2.4 Hz, 1H), 8.67 (dd, J = 2.4, 1.5 Hz, 1H), 5.05 (s, 2H).

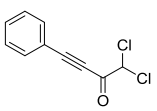
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.8, 148.7, 146.1, 144.0, 143.7, 46.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm-1 = 2942(w), 1718/s), 1571(m), 1465(w), 1401(m), 1389(m), 1316(m), 1225(m), 1169(m), 1051(m), 1018(s), 999(s), 849(s), 787(s), 750(m), 683(s).

MS (EI, 70 eV): m/z (%) = 175(10,M+OH), 158(12), 156(37), 111(11), 107(100), 97(16), 95(15), 85(10), 83(15), 80(10), 79(94), 71(15), 70(10), 69(19), 67(10), 61(11), 57(28), 55(23), 53(12), 52(97), 49(13),m 45(12), 43(17), 42(31), 41(15).

HRMS (EI): m/z calc. for [$C_6H_5ClN_2O$]: 156.0090; found: 156.0087.

2-1,1-dichloro-4-phenylbut-3-yn-2-one (36j)



According to **TP 10**, the THF solutions of ester **39x** (0.18 M) with DCA (0.38 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.2 equiv.) were reacted and the reaction output was collected for 1.39 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the

aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 99:1) afforded the title compound as a pale yellow liquid (205 mg, 0.96 mmol, 96% yield). *Caution: the compound should only be handled in a ventilated fumehood due to lachrymating properties.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 5.99 (s, 1H).

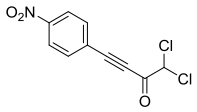
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.9, 133.6 (2C), 131.8, 128.8 (2C), 118.9, 97.9, 83.5, 70.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062(w), 2202(s), 2150(m), 1677(s), 1595(w), 1489(m), 1444(m), 1211(w), 1136(m), 1076(m), 999(m), 922(w), 880(w), 868(w), 793(m), 755(s), 735(m), 685(s).

MS (EI, 70 eV): *m/z* (%) = 212(1), 149(15), 130(10), 129(100), 101(5), 57(9), 43(6).

HRMS (EI): *m/z* calc. for [$C_{10}H_6Cl_2O$]: 211.9796; found 211.9800 [M^+].

1,1-dichloro-4-(4-nitrophenyl)but-3-yn-2-one (36k)



According to **TP 10**, the THF solutions of ester **39y** (0.30 M) with DCA (0.36 M, 1.2 equiv) and LiHMDS, (0.75 M, 2.5 equiv.) were reacted and the reaction output was collected for 0.83 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 99:1) afforded the title compound as a pale yellow liquid (162 mg, 0.63 mmol, 63% yield), which was subject to quick decomposition after isolation.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 8.29 (dt, J = 8.9, 2.1 Hz, 2H), 7.83 (dt, J = 9.0, 2.1 Hz, 2H), 6.01 (s, 1H).

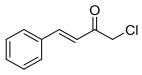
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.5, 149.2, 134.4 (2C), 125.5, 124.0 (2C), 93.6, 85.9, 69.9.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2982(w), 2935(w), 1701(s), 1472(w), 1394(w), 1352(w), 1280(s), 1206(m), 1181(m), 1126(m), 1098(m), 1017(m), 996(m), 915(m), 847(m), 825(m), 788(m), 762(s), 693(s), 672(m).

MS (EI, 70 eV): *m/z* (%) = 256(1), 174(86), 129(10), 128(100), 113(12), 100(24), 87(25).

HRMS (EI): *m/z* calc. for [$C_{10}H_5Cl_2NO_3$]: 259.9646; found 256.9662 [M^+].

(E)-1-chloro-4-phenylbut-3-en-2-one (37q)



According to **TP 11**, the THF solutions of ester **39z** (0.17 M) with CA (0.36 M, 1.1 equiv) and LiHMDS, (0.75 M, 2.2 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was neutralized with solid K_2CO_3 and 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, *iso*-hexane → *iso*-hexane:EtOAc = 95:5) afforded the title compound as a colorless liquid (108 mg, 0.60 mmol, 60% yield), which quickly decomposed.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.72 (d, *J* = 16.1 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.47 – 7.36 (m, 3H), 6.99 (d, *J* = 16.1 Hz, 1H), 4.49 – 3.72 (m, 2H).

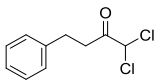
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.4, 145.4, 134.1, 131.3, 129.2 (2C), 128.8 (2C), 121.8, 47.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930(w), 1687(m), 1606(s), 1575(m), 1494(m), 1449(m), 1398(w), 1332(m), 1172(m), 1072(m), 973(m), 915(w), 776(m), 741(s), 687(s).

MS (EI, 70 eV): *m/z* (%) = 180(6), 132(10), 131(100), 103(53), 102(10), 77(18).

HRMS (EI): *m/z* calc. for [$C_{10}H_9ClO$]: 180.0342; found: 180.0333.

1,1-dichloro-4-phenylbutan-2-one (36l)



According to **TP 10**, the THF solutions of ester **39aa** (0.18 M) with DCA (0.38 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.2 equiv.) were reacted and the reaction output was collected for 2.0 min, corresponding to 1.43 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5) afforded the title compound as a colorless oil (187 mg, 0.86 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 5.79 (s, 1H), 3.16 (t, *J* = 7.7 Hz, 2H), 2.99 (t, *J* = 7.5 Hz, 2H).

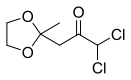
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.5, 140.1, 128.8, 128.5 (2C), 126.6 (2C), 70.0, 36.8, 30.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028(w), 1730(s), 1603(w), 1496(m), 1453(w), 1402(w), 1217(w), 1125(m), 1076(w), 1030(w), 791(m), 733(s), 697(s).

MS (EI, 70 eV): *m/z* (%) = 216(0.5), 138(14), 133(18), 105(100), 103(12), 91(67).

HRMS (EI): *m/z* calc. for [$C_{10}H_{10}Cl_2O$]: 216.0109; found: 216.0100 [M^+].

1,1-dichloro-3-(2-methyl-1,3-dioxolan-2-yl)propan-2-one (36m)



According to the **TP 11**, the THF solutions of ester **39ab** (0.17 M) with DCA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 2.0 min, corresponding to 1.36 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was neutralized with solid K_2CO_3 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, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a pale yellow oil (239 mg, 1.12 mmol, 82% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.03 (s, 1H), 4.03 – 3.86 (m, 4H), 3.16 – 3.01 (m, 2H), 1.41 (s, 3H).

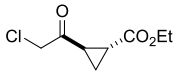
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 192.4, 107.7, 70.4, 64.8 (2C), 45.3, 24.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2985(w), 1739(m), 1597(w), 1378(m), 1209(m), 1109(m), 1044(s), 950(m), 841(m), 770(s).

MS (EI, 70 eV): *m/z* (%) =199(16), 198(2), 197(24), 153(10), 87(100), 83(11), 44(30).

HRMS (EI): *m/z* calc. for [$C_7H_{10}Cl_2O_3$]: 212.0007; found: 197.9766 [M-CH_3^+].

Ethyl (trans)-2-(2-chloroacetyl)cyclopropane-1-carboxylate (37r)



According to the **TP 10**, the THF solutions of ester **39ac** (0.17 M) with DCA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was extracted three times with EtOAc (3×30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a colorless oil (117 mg, 0.61 mmol, 61% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 4.25 (d, *J* = 1.1 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.67 (ddd, *J* = 8.6, 5.7, 3.8 Hz, 1H), 2.26 (ddd, *J* = 8.8, 6.0, 3.8 Hz, 1H), 1.54 (ddd, *J* = 8.6, 6.0, 3.6 Hz, 1H), 1.51 (ddd, *J* = 8.7, 5.7, 3.7 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H).[262]

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 199.5, 171.5, 61.4, 48.8, 26.7, 25.3, 18.0, 14.2.

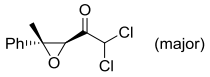
[262] The coupling constants indicate unambiguously, that the hydrogen adjacent to the ketone exhibits one *cis* and *two* trans couplings to the neighbouring on the cyclopropyl hydrogens, which is only realized in the case of the *trans*-product. For reference coupling constants, see: 1) A. F. Bramwell, L. Crombie, P. Hemesley, G. Pattenden, M. Elliott, N. F. Janes, *Tetrahedron* **1969**, *25*, 1727; 2) J. Adams, L. Hoffman, B. M. Trost, *J. Org. Chem.*, **1970**, *35*, 1600.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2984(w), 1715(s), 1407(m), 1366(m), 1329(s), 1267(m), 1204(s), 1182(s), 1083(m), 1051(m), 1023(m), 908(m), 870(m), 774(m), 731(m).

MS (EI, 70 eV): *m/z* (%) = 145(16), 141(100), 113(27), 85(33).

HRMS (EI): *m/z* calc. for [$C_8H_{11}ClO_3$]: 190.0397 ; found: 141.0545 [M-CH_2Cl^+].

2,2-dichloro-1-(3-methyl-3-phenyloxiran-2-yl)ethan-1-one (36n)



(major)

d.r. = 3:1

According to the **TP 11**, the THF solutions of ester **39ad** (0.17 M, d.r. = 1.3 : 1.0, major = *trans* isomer as in the product) [263] with DCA (0.36 M, 2.1 equiv) and LiHMDS, (0.75 M, 4.4 equiv.) were reacted and the reaction output was collected for 1.47 min, corresponding to 1.0 mmol ester. After addition of EtOAc and water and subsequent stirring, the aqueous phase was neutralized with solid K_2CO_3 and 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, *iso*-hexane:EtOAc = 9:1) afforded the title compound as a yellowish liquid (110 mg, 0.45 mmol, 45% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): $\delta_{\mathbf{major}}$ / ppm = 7.55 – 7.23 (m, 5H), 6.01 (s, 1H), 4.07 (s, 1H), 1.68 (s, 3H); $\delta_{\mathbf{minor}}$ / ppm = δ 7.59 – 7.27 (m, 1.7H), 5.56 (s, 0.3H), 4.16 (s, 0.3H), 1.82 (s, 1H).[263]

^{13}C-NMR (101 MHz, $CDCl_3$): $\delta_{\mathbf{major+minor}}$ / ppm = 190.2, 190.1, 139.8, 136.0, 128.8, 128.7, 128.6, 128.6, 126.6, 125.3, 68.5, 67.3, 66.4, 65.3, 63.3, 63.2, 25.0, 17.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2977(w), 1744(m), 1729(m), 1495(w), 1446(w), 1381(m), 1287(w), 1152(w), 1105(w), 1055(w), 1026(w), 990(w), 907(m), 798(m), 729(s), 696(s).

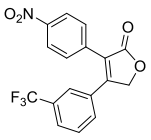
MS (EI, 70 eV): *m/z* (%) = 244(1), 211(11), 209(33), 133(15), 105(54), 104(20), 103(100), 78(16), 77(32), 51(12), 43(29).

HRMS (EI): *m/z* calc. for [$C_{11}H_{10}Cl_2O_2$]: 244.0058; found 244.0036 [M].

Y: 45%

6.8 Preparation of heterocyclic products of type 6

3-(4-nitrophenyl)-4-(3-(trifluoromethyl)phenyl)furan-2(5H)-one (40b)



[263] Determined by NOESY: A Cross-peak between methyl and the epoxide-bound H found is only for the minor product.

2-chloro-1-(3-(trifluoromethyl)phenyl)ethan-1-one (**37f**) was prepared according to **TP 10** on a 0.3 mmol scale. After extraction and drying ($MgSO_4$) of the reaction crude mixture, the solvents were removed *in vacuo*.

According to a modified literature procedure,[264] 176 mg K_2CO_3 (1.27 mmol, 4.3 equiv) were placed in a Schlenck flask and dried under high vacuum (350 °C, ≤ 1 mbar) for 2 min. After cooling, the flask was back-filled with Ar and the crude chloroketone and 56 mg 2-(4-nitrophenyl)acetic acid (0.3 mmol, 1.0 equiv.) were transferred into the flask as solutions in ca. 0.6 mL dry MeCN each. The flask was sealed with a rubber septum and the reaction mixture was heated to 75 °C for 4 h. After cooling to room temperature, water (5 mL) was added, and the aqueous phase was extracted with EtOAc (4×10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2) afforded the title as colorless, crystalline solid (100 mg, 0.29 mmol, 97% yield).

M.p.(°C): 127-129.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.25 (ddd, J = 8.9, 2.3, 2.0 Hz, 2H), 7.73 (d, J = 7.8 Hz, 1H), 7.63 (ddd, J = 8.9, 2.3, 1.9 Hz, 2H), 7.58 – 7.50 (m, 2H), 7.46 (d, J = 7.9 Hz, 1H), 5.26 (s, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.9, 157.2, 148.2, 136.1, 132.3 (q, *J* = 33.1 Hz), 131.1, 131.0, 130.5 (2C), 130.3, 128.0 (q, *J* = 3.6 Hz), 123.8 (q, J = 277.5, 276.8 Hz) 126.1, 124.3 (q, *J* = 3.7 Hz), 124.2 (2C), 70.8.

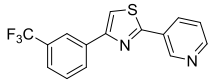
^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = 63.07.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2339(w), 2360(w), 1743(s), 1641(w), 1519(m), 1430(w), 1343(m), 1306(s), 1285(m), 1163(m), 1114(m), 1069(s), 1045(s), 962(w), 916(w), 900(m), 853(s), 813(m), 780(m), 744(w), 710(m), 693(s), 680(m).

MS (EI, 70 eV): *m/z* (%) = 350(22), 349(100), 320(27), 292(97), 291(15), 261(27), 247(17), 246(56), 245(25), 233(17), 227(16), 225(33), 297(25), 196(17), 189(21), 178(31), 177(19), 176(37), 173(64), 165(35), 151(15), 145(29), 75(19), 50(16), 44(61), 43(46).

HRMS (EI): *m/z* calc. for [$C_{17}H_{10}F_3NO_4$]: 349.0562; found: 349.0562.

2-(pyridin-3-yl)-4-(3-(trifluoromethyl)phenyl)thiazole (40d)



2-chloro-1-(3-(trifluoromethyl)phenyl)ethan-1-one (**37f**) was prepared according to **TP 10** on a 1.0 mmol scale. After extraction and drying ($MgSO_4$) of the reaction crude mixture, the solvents were removed *in vacuo*.

The crude chloroketone (1.0 equiv.) was redissolved in 8 mL EtOH (99%) and 1.0 equiv. thionicotinamide was added (138 mg, 1.0 mmol), followed by ca. 30 mg of anhydrous $MgSO_4$. The

[264] H. B. Borate, S. P. Sawargave, S. P. Chavan, M. A. Chandavarkar, R. Iyer, A. Tawte, D. Rao, J. V. Deore, A. S. Kudalea, P. S. Mahajana, G. S.Kangirea, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4873.

mixture was stirred at 25 °C and progress of the reaction was monitored by TLC. After 12 h at 25 °C the mixture was heated to reflux, which led to full conversion after 2 h. After cooling to room temperature, *sat. aq.* $NaHCO_3$ (5 mL) solution was added, and the aqueous phase was extracted with EtOAc (4×10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 6:4) afforded the title compound as colorless, crystalline solid (187 mg, 0.61 mmol, 61% yield).

M.p. (°C): 125.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.24 (s, 1H), 8.69 (d, *J* = 3.9 Hz, 1H), 8.34 (dt, *J* = 8.0, 1.9 Hz, 1H), 8.26 (s, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.67 – 7.53 (m, 3H), 7.42 (dd, *J* = 7.8, 4.7 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.0, 155.3, 151.2, 147.9, 134.9, 133.9, 131.4 (q, *J* = 32.4 Hz), 129.7, 129.6, 129.5, 125.1 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.5 Hz), 123.9, 123.4 (q, *J* = 3.8 Hz), 114.6.

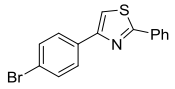
^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -62.66.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079(w), 2923(w), 1570(w), 1449(w), 1419(w), 1333(m), 1317(m), 1270(m), 1153(m), 1112(s), 1094(m), 1070(s), 976(m), 914(m), 910(m), 808(m), 802(m), 767(m), 727(m), 702(m), 688(s).

MS (EI, 70 eV): *m/z* (%) = 307(14), 306(100), 202(72), 201(16), 183(17), 152(22).

HRMS (EI): *m/z* calc. for [$C_{15}H_9F_3N_2S$]: 306.3062; found: 306.0432 [M^+].

4-(4-bromophenyl)-2-phenylthiazole (40e)



1-(4-bromophenyl)-2-chloroethan-1-one (**37d**) was prepared according to **TP 10** on a 1.0 mmol scale. After extraction and drying ($MgSO_4$) of the reaction crude mixture, the solvents were removed *in vacuo*.

The crude chloroketone (1.0 equiv.) was redissolved in 5 mL EtOH (99%) and 1.0 equiv. thiobenzamide in 5 mL EtOH was added (137 mg, 1.0 mmol). The progress of the reaction was monitored by TLC. The mixture was heated to reflux for 2 h and then at 25 °C for 12 h. Subsequently, *sat. aq.* $NaHCO_3$ (5 mL) solution was added, and the aqueous phase was extracted with EtOAc (4×15 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) afforded the title compound as colorless, crystalline solid (201 mg, 0.65 mmol, 65% yield).

M.p. (°C): 129-134.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.09 – 8.00 (m, 2H), 7.92 – 7.83 (m, 2H), 7.61 – 7.53 (m, 2H), 7.51 – 7.43 (m, 4H).

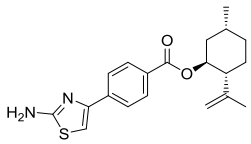
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.3, 155.2, 133.7, 133.6, 132.0 (2C), 130.3, 129.1 (2C), 128.1 (2C), 126.8 (2C), 122.28, 113.13.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3110(w), 2972(w), 2925(w), 1503(w), 1472(m), 1437(m), 1397(w), 1287(w), 1235(m), 1200(w), 1176(w), 1104(w), 1070(m), 1050(m), 1003(m), 1000(m), 975(s), 898(w), 846(m), 829(m), 840(m), 825(s), 763(s), 747(s), 686(s), 671(s).

MS (EI, 70 eV): *m/z* (%) = 318(16), 317(100), 316(16), 315(100), 214(72), 212(76), 207(11), 161(10), 159(11), 133(25), 118(19), 103(13), 89(48).

HRMS (EI): *m/z* calc. for [$C_{15}H_{10}BrNS$]: 314.9717; found: 314.9711 (M^+).

(1*R*,2*R*,5*R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl 4-(2-aminothiazol-4-yl)benzoate (40f)



(1*S*,2*R*,5*R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl 4-(2-chloroacetyl)benzoate (**37k**) was prepared according to **TP 10** on a 0.6 mmol scale and purified as described previously.

The crude chloroketone (0.56 mmol, 1.0 equiv.) was dissolved in 1 mL EtOH (99%) and 1.2 equiv. thiurea was added (52 mg, 0.68 mmol). The progress of the reaction was monitored by TLC. The mixture was stirred 1 h at 25 °C. Subsequently, *sat. aq.* $NaHCO_3$ (5 mL) solution was added, and the aqueous phase was extracted with EtOAc (4×10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a yellow oil (188 mg, 0.53 mmol, 94% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 2H), 6.82 (s, 1H), 5.39 (s, NH_2), 5.02 (td, *J* = 10.9, 4.4 Hz, 1H), 4.79 (s, 1H), 4.74 – 4.68 (m, 1H), 2.30 (td, *J* = 11.5, 10.9, 3.6 Hz, 1H), 2.16 (dt, *J* = 12.1, 3.2 Hz, 1H), 1.75 – 1.67 (m, 4H), 1.62 (dtt, *J* = 11.9, 6.6, 3.4 Hz, 1H), 1.46 (qd, *J* = 14.3, 13.7, 4.0 Hz, 1H), 1.29 – 0.98 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H).

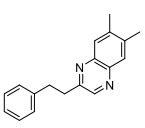
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.8, 166.0, 150.4, 146.3, 138.6, 130.1 (2C), 129.9, 125.8 (2C), 112.1, 104.9, 74.5, 51.0, 40.6, 34.3, 31.5, 30.6, 22.2, 19.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923(w), 1693(s), 1606(m), 1537(m), 1522(m), 1408(m), 1340(m), 1288(s), 1269(s), 1176(m), 1104(s), 1038(m), 1015(m), 962(m), 906(m), 862(m), 843(m), 777(m), 714(s).

MS (EI, 70 eV): *m/z* (%) = 356(6), 220(76), 204(10), 203(100), 175(24).

HRMS (EI): *m/z* calc. for [$C_{20}H_{24}N_2O_2S$]: 356.1558; found: 356.1550 [M].

6,7-dimethyl-2-phenethylquinoxaline (40h)



1,1-dichloro-4-phenylbutan-2-one (**36l**) was prepared according to **TP 10** on a 0.5 mmol scale. After extraction and drying ($MgSO_4$) of the reaction crude mixture, solvents were removed.

According to a modified control-experiment,[Fehler! Textmarke nicht definiert.] 4,5-dimethylbenzene-1,2-diamine (68 mg, 0.5 mmol, 1.0 equiv.), Et_2NH (2 mmol, 146 mg, 4.0 equiv.), and DMF (0.5 M with respect to diamine) were added. The mixture was subsequently stirred at 90°C for 5 h. After cooling to room temperature, water (10 mL) was added, and the aqueous phase was extracted with EtOAc (5×15 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2→9:1) afforded the title compound as a colorless solid (98 mg, 0.37 mmol, 75% yield).

M.p. (°C) = 108-110.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.52 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 7.40 – 7.09 (m, 5H), 3.34 – 3.25 (m, 2H), 3.21 – 3.13 (m, 2H), 2.50 (s, 3H), 2.49 (s, 3H).

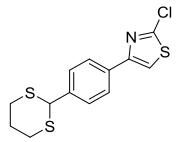
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.6, 145.0, 141.3, 141.1, 140.6, 140.4, 139.6, 128.7 (2C), 128.6 (2C), 128.4, 128.1, 126.4, 38.2, 35.6, 20.5, 20.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924(w), 1555(w), 1484(m), 1450(m), 1364(w), 1303(w), 1208(m), 1133(w), 1028(m), 1002(m), 967(m), 872(m), 748(s), 699(s).

MS (EI, 70 eV): *m/z* (%) = 263(14), 262(67), 261(100), 259(21), 247(29), 246(12), 207(15), 185(54), 171(22), 157(10), 103(16), 91(28), 77(13).

HRMS (EI): *m/z* calc. for [$C_{18}H_{18}N_2$]: 262.1470; found 261.1386 [M-H^+].

4-(4-(1,3-dithian-2-yl)phenyl)-2-chlorothiazole (40i)



1-(4-(1,3-dithian-2-yl)phenyl)-2-chloroethan-1-one (**37b**) was prepared according to **TP 10** on a 2.40 mmol scale. After extraction and drying ($MgSO_4$) of the reaction crude mixture, solvents were removed.

According to a modified procedure,[265] the crude 1-(4-(1,3-dithian-2-yl)phenyl)-2-chloroethan-1-one (1.0 equiv.) was dissolved in MeCN (HPLC grade, 0.2 M). KSCN (466 mg, 4.8 mmol, 2.0 equiv.) was added and the reaction mixture was stirred at 80 °C for 45 min, at which time TLC indicated full consumption of the starting material. After removal of the solvent, the crude was redissolved in dry Et_2O (0.1 M) and HCl gas was bubbled through the solution under stirring. The HCl gas was generated in a separate flask with a septum containing solid NaCl and a magnetic stirred, to which was added dropwise conc. H_2SO_4, (dropping funnel). A teflon tube was used for transfer of the gas. Ca. 20 g NaCl were used to generate HCl over 3 h, and subsequently the HCl saturated ether solution was

[265] R. Yefidoff-Freedman, T. Chen, R. Sahoo, L. Chen, G. Wagner, J. A. Halperin, B. H. Aktas, M. Chorev, *ChemBioChem*, **2014**, *15*, 595.

stirred for 48 h. *Sat. aq.* $NaHCO_3$ solution (10 mL) was slowly added, followed by water (10 mL) and solid K_2CO_3 until neutralization was reached. and the aqueous phase was extracted with EtOAc (5×15 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2→9:1) afforded the title compound as a colorless solid (471 mg, 1.50 mmol, 62% yield).

M.p. (°C) : 94-98.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.38 (s, 1H), 5.22 (s, 1H), 3.10 (ddd, *J* = 14.7, 12.4, 2.5 Hz, 2H), 2.95 (dt, *J* = 14.5, 3.7 Hz, 2H), 2.27 – 2.16 (m, 1H), 2.05 – 1.90 (m, 1H).

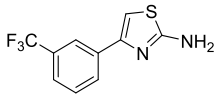
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 153.7, 151.7, 139.5, 133.5, 128.3 (2C), 126.5 (2C), 114.5, 51.1, 32.1 (2C), 25.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2889(w), 1719(w), 1606(w), 1479(m), 1438(m), 1409(m), 1276(m), 1170(m), 1112(w), 1044(s), 1017(w), 913(w), 881(w), 859(m), 844(m), 824(m), 749(s), 728(m), 676(m).

MS (EI, 70 eV): *m/z* (%) = 315(18), 313(39), 250(10), 248(31), 241(38), 240(32), 239(100), 237(81), 195(17), 177(20), 159(12), 145(15).

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}ClNS_3$]: 312.9820; found: 312.9814 [M].

4-(4-(1,3-dithian-2-yl)phenyl)-2-chlorothiazole (40j)



2-chloro-1-(3-(trifluoromethyl)phenyl)ethan-1-one (**37f**) was prepared according to **TP 10** on a 1.0 mmol scale. After extraction and drying ($MgSO_4$) of the reaction crude mixture, the solvents were removed *in vacuo*.

The crude chloroketone (1.0 equiv.) was redissolved in 8 mL EtOH (99%) and 1.0 equiv. thiurea was added (76 mg, 1.0 mmol), followed by ca. 30 mg of anhydrous $MgSO_4$. The mixture was stirred at 25 °C and progress of the reaction was monitored by TLC. After 12 h at 25 °C full conversion was observed and *sat. aq.* $NaHCO_3$ (5 mL) solution was added. The aqueous phase was extracted with EtOAc (4×10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtrated. After removal of the solvent *in vacuo*, flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 6:4) afforded the title compound as colorless, crystalline solid (156 mg, 0.64 mmol, 64% yield).

M.p. (°C): 85-90 (decomposition).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 (s, 1H), 7.99 – 7.87 (m, 1H), 7.60 – 7.43 (m, 2H), 6.81 (s, 1H), 5.21 (s, 2*N*H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.7, 149.9, 135.4, 131.2 (q, *J* = 32.3 Hz), 129.2, 129.2, 124.4 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 273.2 Hz), 123.0 (q, *J* = 3.9 Hz), 104.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = δ -62.66.

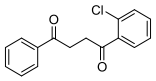
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923(w), 1449(w), 1419(w), 1334(m), 1318(s), 1271(m), 1154(s), 1113(s), 1971(s), 977(m), 914(m), 808(m), 802(m), 768(m), 727(m), 703(m), 689(s).

MS (EI, 70 eV): *m/z* (%) = 245(10), 244(100), 202(28), 152(11).

HRMS (EI): *m/z* calc. for $[C_{10}H_7F_3N_2S]$:244.0282; found: 244.0276 $[M^+]$.

6.9 Preparation of diketones according to TP 12 and TP 13

1-(2-chlorophenyl)-4-phenylbutane-1,4-dione (42a)



According to the **TP 12**, 1-(2-chlorophenyl)ethan-1-one and 2-chloro-1-phenylethan-1-one (**37s**) were reacted and worked up. The substitution was carried out at 0 °C for 3 h. The scale was changed to 1 mmol of chloroacetophenone **2i**. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5→8:2) followed by preparative HPLC afforded the title compound as a colorless solid (127 mg, 0.46 mmol, 90% yield).

M.p. (°C) = 56.

^{1}H-NMR (400 MHz, $CDCl_3$): 8.07 – 7.96 (m, 2H), 7.67 – 7.63 (m, 1H), 7.61 – 7.55 (m, 1H), 7.52 – 7.33 (m, 5H), 3.52 – 3.46 (m, 2H), 3.42 – 3.35 (m, 2H).

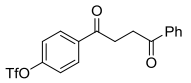
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 202.0, 198.4, 139.4, 136.7, 133.4, 131.9, 131.0, 130.6, 129.5, 128.8 (2C), 128.3 (2C), 127.1, 37.0, 33.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2914(w), 1678(s), 1588(m), 1469(w), 1447(m), 1431(m), 1395(w), 1220(s), 1179(m), 1071(m), 989(s), 742(s), 687(s).

MS (EI, 70 eV): *m/z* (%) = 274(3), 272(10), 254(27), 237(20), 167(12), 141(33), 139(100), 133(13), 105(67), 78(22).

HRMS (EI): *m/z* calc. for $[C_{16}H_{13}ClO_2]$: 272.0604; found: 272.0599 $[M^+]$.

4-(4-oxo-4-phenylbutanoyl)phenyl trifluoromethanesulfonate (42b)



According to the **TP 12**, 4-acetylphenyl trifluoromethanesulfonate and 2-chloro-1-phenylethan-1-one (**37s**) were reacted and worked up. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1→8:2) afforded the title compound as a colorless solid (130 mg, 0.335 mmol, 67% yield).

M.p. (°C) = 85.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.34 – 8.30 (m, 1H), 8.30 – 8.24 (m, 1H), 8.08 – 7.98 (m, 2H), 7.91 – 7.80 (m, 1H), 7.66 – 7.56 (m, 2H), 7.53 – 7.45 (m, 2H), 3.51 (ddd, *J* = 6.7, 5.3, 1.1 Hz, 2H), 3.42 (ddd, *J* = 6.5, 5.3, 1.1 Hz, 2H).

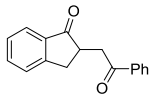
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 198.3, 196.9, 137.7, 136.6, 136.1, 133.5, 132.2, 132.0, 129.8, 128.8, 128.3, 118.1, 113.3, 32.7.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 3069(w), 2910(w), 1696(s), 1681(s), 1595(m), 1580(w), 1480(w), 1446(m), 1430(m), 1394(m), 1358(m), 1235(s), 1210(m), 1149(s), 1022(m), 1002(m), 944(m), 812(s), 762(s), 749(s), 723(m), 686(s).

MS (EI, 70 eV): *m/z* (%) = 386(1.6), 253(34), 236(11), 235(65), 207(13), 178(16), 105(100), 77(29).

HRMS (EI): *m/z* calc. for [$C_{17}H_{13}F_3O_5S$]: 386.0436; found: 386.0427 [M^+].

2-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-inden-1-one (42c)



According to **TP 12**, 2,3-dihydro-1*H*-inden-1-one and 2-chloro-1-phenylethan-1-one (**37s**) were reacted and worked up. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a colorless solid (87 mg, 0.35 mmol, 70% yield).

M.p. (°C) = 101.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02 – 7.95 (m, 2H), 7.83 – 7.78 (m, 1H), 7.63 – 7.55 (m, 2H), 7.50 – 7.44 (m, 3H), 7.43 – 7.36 (m, 1H), 3.77 (dd, *J* = 17.3, 2.3 Hz, 1H), 3.56 (dd, *J* = 17.2, 7.5 Hz, 1H), 3.30 – 3.16 (m, 2H), 2.85 (dd, *J* = 17.4, 4.5 Hz, 1H).

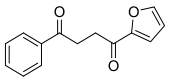
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 208.0, 198.1, 153.7, 136.7, 136.6, 135.0, 133.5, 128.8 (2C), 128.2 (2C), 127.6, 126.7, 124.0, 43.3, 40.1, 33.7.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2902(w), 1705(s), 1681(s), 1608(w), 1596(w), 1447(m), 1359(w), 1293(m), 1278(m), 1232(m), 1203(m), 1180(w), 1009(w), 989(m), 772(m), 753(m), 739(s), 723/s), 688(s).

MS (EI, 70 eV): *m/z* (%) = 250(3), 146(11), 145(100), 117(16), 115(25), 105(42), 77(24).

HRMS (EI): *m/z* calc. for [$C_{17}H_{14}O_2$]: 250.0994; found: 250.0985 [M^+].

1-(furan-2-yl)-4-phenylbutane-1,4-dione (42d)



According to the **TP 12**, 4-acetylphenyl trifluoromethanesulfonate and 2-chloro-1-phenylethan-1-one (**37s**) were reacted and worked up. The scale was changed to 1 mmol of chloroacetophenone **2r**. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1→8:2) afforded the title compound as a colorless wax (146 mg, 0.64 mmol, 64% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 – 7.98 (m, 2H), 7.60 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.50 – 7.44 (m, 2H), 7.26 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.55 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.45 (td, *J* = 6.5, 0.8 Hz, 2H), 3.31 (td, *J* = 6.5, 0.8 Hz, 2H).

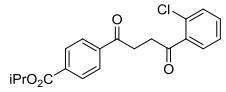
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 198.5, 188.0, 152.7, 146.5, 136.8, 133.3, 128.8 (2C), 128.3 (2C), 117.3, 112.4, 32.4, 32.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920(w), 1666(s), 1594(w), 1566(m), 1464(m), 1447(m), 1394(m), 1369(m), 1352(m), 1236(m), 1152(m), 1083(w), 1021(m), 1001(m), 993(m), 953(m), 889(s), 881(s), 843(w), 763(s), 712(m), 689(s).

MS (EI, 70 eV): *m/z* (%) = 229(2), 228(15), 210(23), 153(10), 123(13), 105(100), 95(26), 77(43).

HRMS (EI): *m/z* calc. for [$C_{14}H_{12}O_3$]: 228.0786; found: 228.0774 [M^+].

Isopropyl 4-(4-(2-chlorophenyl)-4-oxobutanoyl)benzoate (42e)



According to **TP 12**, 1-(2-chlorophenyl)ethan-1-one and isopropyl 4-(2-chloroacetyl)benzoate (**37j**) were reacted and worked up. The substitution was carried out at 0 °C for 3 h. The scale was changed to 1 mmol of chloroacetophenone **2i**. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5→8:2) furnished the title compound as a colorless solid (232 mg, 0.65 mmol, 65% yield).

M.p. (°C) = 65.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 – 8.11 (m, 2H), 8.08 – 8.03 (m, 2H), 7.67 – 7.62 (m, 1H), 7.49 – 7.31 (m, 3H), 5.28 (p, *J* = 6.3 Hz, 1H), 3.50 (td, *J* = 6.3, 1.6 Hz, 2H), 3.40 (td, *J* = 6.3, 1.6 Hz, 2H), 1.39 (d, *J* = 6.3 Hz, 6H).

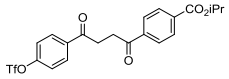
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 201.8, 198.1, 165.4, 139.8, 139.2, 135.0, 132.0, 131.1, 130.7, 129.9 (2C), 129.5, 128.1 (2C), 127.2, 69.2, 36.9, 33.5, 22.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923(w), 1712(s), 1687(s), 1589(w), 1278(s), 1210(m), 1101(s), 991(m), 751(m).

MS (EI, 70 eV): *m/z* (%) = 358(0.1), 191(43), 149(66), 141(32), 139(100), 104(10).

HRMS (EI): *m/z* calc. for [$C_{20}H_{19}ClO_4$]: 358.0972; found: 358.0952 [M^+].

Isopropyl 4-(4-oxo-4-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)butanoyl)benzoate (42f)



According to **TP 13**, 4-acetylphenyl trifluoromethanesulfonate and isopropyl 4-(2-chloroacetyl)benzoate (**37j**) were reacted and worked up. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 95:5→8:2) as a yellow solid (128 mg, 0.27 mmol, 54% yield).

M.p. (°C): 117-124 (decomp.).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.18 – 8.11 (m, 4H), 8.09 – 8.04 (m, 2H), 7.44 – 7.38 (m, 2H), 5.28 (hept, *J* = 6.3 Hz, 1H), 3.59 – 3.38 (m, 4H), 1.39 (d, *J* = 6.3 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 198.1, 196.9, 165.3, 152.7, 139.7, 136.7, 135.0, 130.6 (2C), 130.0 (2C), 128.1 (2C), 121.8 (2C), 120.44 (q, *J* = 320.8 Hz), 69.2, 33.0, 32.7, 22.03 (2C).

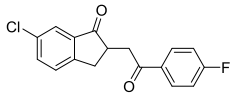
^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -72.71.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2987(w), 1714(m), 1680(s), 1592(w), 1496(w), 1427(m), 1407(m), 1278(m), 1251(m), 1211(s), 1187(m), 1135(s), 1098(s), 1004(m), 872(s), 848(m), 730(s).

MS (EI, 70 eV): *m/z* (%) = 472(1.5), 413(11), 253(50), 205(13), 192(15), 191(100), 149(60), 121(19), 104(17), 65(10), 43(13).

HRMS (EI): *m/z* calc. for [$C_{21}H_{19}F_3O_7S$]: 472.0804; found: 472.0804 [M^+].

6-chloro-2-(2-(4-fluorophenyl)-2-oxoethyl)-2,3-dihydro-1H-inden-1-one (42g)



According to **TP 12**, 6-chloro-2,3-dihydro-1H-inden-1-one and 2-chloro-1-(4-fluorophenyl)ethan-1-one (**37c**) were reacted and worked up. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1) followed by preparative HPLC afforded the title compound as a off-white solid (100 mg, 0.33 mmol, 66% yield).

M.p. (°C) = 143.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.02 – 7.98 (m, 2H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.56 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.17 – 7.12 (m, 2H), 3.71 (dd, *J* = 18.1, 3.2 Hz, 1H), 3.50 (dd, *J* = 17.2, 8.1 Hz, 1H), 3.30 (dd, *J* = 18.1, 8.5 Hz, 1H), 3.19 (tdd, *J* = 8.2, 4.7, 3.2 Hz, 1H), 2.82 (dd, *J* = 17.3, 4.6 Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 206.5, 196.2, 166.1 (d, *J* = 255.4 Hz), 151.6, 138.2, 134.9, 134.0, 132.9 (d, *J* = 3.0 Hz), 130.9 (d, *J* = 9.4 Hz, 2C), 127.9, 123.9, 116.0 (d, *J* = 21.9 Hz, 2C), 43.8, 39.8, 33.2.

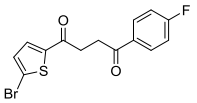
^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -104.42.

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2927(w), 1709(m), 1680(s), 1594(s), 1505(m), 1468(w), 1434(w), 1408(m), 1359(w), 1297(w), 1256(m), 1228(s), 1191(s), 1155(s), 1115(w), 994(m), 831(s), 731(m), 664(m).

MS (EI, 70 eV): *m/z* (%) = 302(2), 181(26), 179(79), 138(12), 123(16), 123(100), 115(24), 95(11).

HRMS (EI): *m/z* calc. for [$C_{17}H_{12}ClFO_2$]: 302.0510; found: 302.0500 [M^+].

1-(5-bromothiophen-2-yl)-4-(4-fluorophenyl)butane-1,4-dione (42h)



According to **TP 13**, 1-(5-bromothiophen-2-yl)ethan-1-one and 2-chloro-1-(4-fluorophenyl)ethan-1-one (**37c**) were reacted and worked up. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 9:1→8:2) furnished the tilte compound as a colorless solid (109 mg, 0.32 mmol, 64% yield).

M.p. (°C): 137.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 – 8.01 (m, 2H), 7.60 – 7.52 (m, 1H), 7.18 – 7.11 (m, 3H), 3.41 (ddd, *J* = 6.8, 5.9, 1.0 Hz, 2H), 3.31 (ddd, *J* = 6.9, 6.0, 1.0 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.8, 190.7, 166.0 (d, *J* = 254.9 Hz), 145.4, 133.1 (d, *J* = 3.0 Hz), 132.3, 131.4, 130.9 (d, *J* = 9.3 Hz, 2C), 122.9, 115.9 (d, *J* = 21.8 Hz, 2C), 32.6, 32.5.

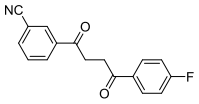
^{19}F NMR (377 MHz, $CDCl_3$) δ / ppm = -104.84 – -104.95 (m).

IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} =2912(w), 1676(w), 1656(s), 1594(m), 1504(w), 1407(s), 1320(m), 1229(m), 1186(m), 1160(m), 1057(w), 992(m), 980(w), 926(w), 848(m), 784(s), 710(w).

MS (EI, 70 eV): *m/z* (%) = 339(0.8), 219(11), 217(12), 191(34), 189(35), 123(13), 122(100).

HRMS (EI): *m/z* calc. for [$C_{14}H_{10}BrFO_2S$]: 339.9569; found: 339.9557 [M^+].

3-(4-(4-fluorophenyl)-4-oxobutanoyl)benzonitrile (42i)



According to **TP 13**, 3-acetylbenzonitrile and 2-chloro-1-(4-fluorophenyl)ethan-1-one (**37c**) were reacted and worked up. Flash chromatographical purification (silica gel, *iso*-hexane:EtOAc = 8:2) afforded the title compound as a colorless solid (115 mg, 0.41 mmol, 82% yield).

M.p. (°C): 65.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.32 (t, *J* = 1.4 Hz, 1H), 8.26 (dt, *J* = 7.9, 1.5 Hz, 1H), 8.10 – 8.02 (m, 2H), 7.86 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.21 – 7.12 (m, 2H), 3.50 – 3.40 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.9, 196.7, 166.08 (d, *J* = 255.0 Hz), 137.7, 136.2, 133.1 (d, *J* = 3.0 Hz), 132.1 (d, *J* = 19.9 Hz), 131.0, 130.9, 129.9, 118.1, 116.0 (d, *J* = 22.0 Hz), 113.4, 32.6.

^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -103.41 – -105.93 (m).

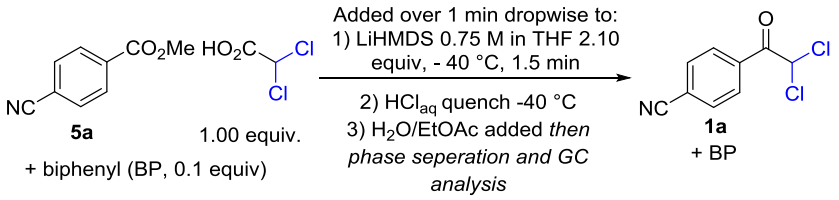
IR (Diamond-ATR, $CDCl_3$): $\tilde{\nu}$ / cm^{-1} = 2912(w), 2235(w), 1674(s), 1594(s), 1425(m), 1315(m), 1220(m), 1202(m), 1159(m), 846(m), 783(s), 679(m).

MS (EI, 70 eV): *m/z* (%) = 281(2), 130(14), 123(100), 102(10), 95(18).

HRMS (EI): *m/z* calc. for [$C_{17}H_{12}FNO_2$]:281.0852; found: 281.0845 [M^+].

6.10 Reaction optimization and mechanistical insights

- A number of batch control experiments were undertaken to demonstrate effects of salt additives and solvents. An increase in lithium salt concentration by LiBr addition caused a decreased yield. An attempt to achieve the twofold deprotonation of dichloroacetic acid with 1 equiv. ^{i}PrMgBr followed by 1 equiv LiHMDS gave lower yields. Switching solvents to toluene gave no conversion, switching to 2Me-THF gave considerably lower yields under flow conditions (not shown).



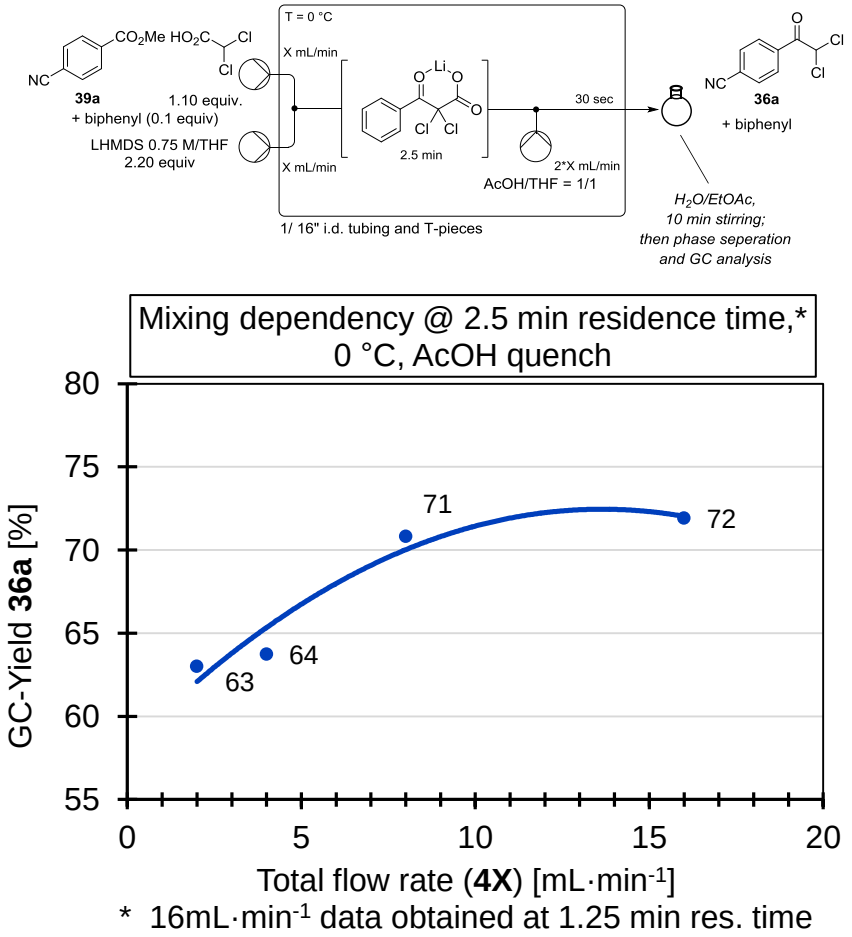
Deviation from condtitions	Result (**1a**/BP)
none	9.7, no **5a** recovered
1 equiv of dry LiBr present	7.3
1 equiv of dry $ZnCl_2$ added	0.3, mainly **5a** recovered
1 equiv iPrMgBr, then 1 equiv LiHMDS	4.9, mainly **5a** recovered
all solvents changed to toluene	0.0

Scheme 50: Effects of additives (tested in batch reactions).

- Furthermore, it was observed that with simple substrates lithium diisopropylamine (LDA) usually gave similar or better yields in comparsion with LiHMDS. Considering previous studies about LiHMDS mediated enolization, the base strength of LiHMDS might be just sufficient for the enolisation of α-chloro lithium acetate and its bis-chloro congener.[266]
- Sideproducts from addition of LDA to esters were detected, yet it was experimentally confirmed that LiHMDS does not react with aromatic esters over at least 45 min at 25 °C.
- LDA containing reaction mixtures showed a tendency for precipitation below ca. -15 °C, which was not observed with LiHMDS.
- KHMDS or NaHMDS gave unchanged to inferior results under otherwise equal conditions.
- To obtain the best possible yield, chemoselectivity and a stable continuous flow process, LiHMDS was used in all experiments.
- Weinreb amides or acid chlorides instead of esters gave also rise to chloromethylation products in unchanged to slightly decreased yields.
- Increasing the concentration from 0.3 M w.r.t CA to 0.6 M w.r.t. CA in batch led to drastically decreased yields at -40 °C. A weaker effect was observed in the flow reactions.
- Prolonged reaction times (*e.g.* > 60 min in batch at -40 °C) did not increase the yield, only the use of more equivalents of dianion led typically to a strong increase in yield.
- Performing semibatch quenches into precooled solutions (≤ −40 °C) of HCl_{aq} or AcOH instead of *in-line* quenches led to significantly lowered yields using the flow reaction protocol (10%). This could only be avoided, if the reaction output was collected in a cooled (≤ −40 °C), Ar-flushed vial followed by addition of precooled acid solution. This procedure was found impractical, especially on larger scales. Hence the in-line quench was the method of choice.
- To determine, wheter the reaction is sensitive to the mixing quality, a number of experiments were performed varying the overall flowrate (**4X**) and reactor volume: The reaction outcome in the synthesis of chloroketone **36a** was analyzed for various flowrates at 0 °C and at fixed 2.5 min

[266] O. Tai, R. Hopson, P. G. Williard, *J. Org. Chem.* **2017**, *82*, 6223.

residence time. Biphenyl was used as an internal standard (Scheme 51). The yield of **1a** was thus at an optimimum beginning from **4X** = 8 mL·min^{-1}. The 16 mL·min^{-1} used in the Typical Procedures were chosen to obtain a good balance between maximium back pressure and productivity. It was also anticipated that more demanding substrates than **39a** might require an increased mixing efficiency provided at 16 mL·min^{-1}.



Scheme 51: Mixing dependency for the flow chloroacetate Claisen reaction.

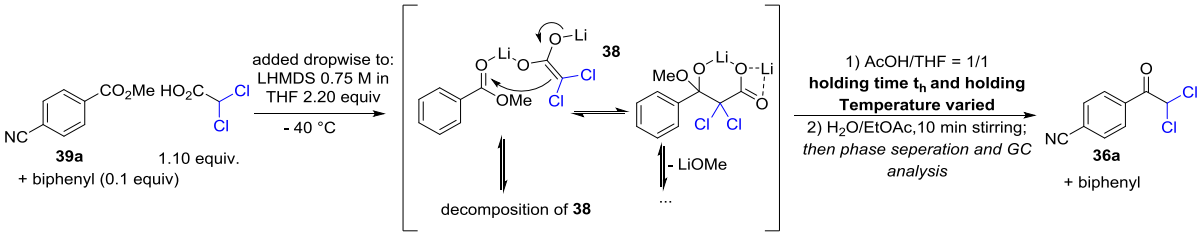
- The use of *Barbier*-type conditions had led to consistently increased yields in preliminary batch experiments. However, the presence of the ester electrophile did not completely prevent obvious decomposition of the dianion intermediate **38**, despite the Barbier procedure: If the time before the acid quench is prolonged at −40 °C or 0 °C, constantly lower yields of chloroketone **36a** are obtained and more ester starting material **39a** is recovered (Scheme 52). The effect is more drastic at 0 °C, which indicates that an addition-retroaddition equilibrium might exist, which leads partially to free dianion **4,** which is subject to thermal decomposition.[267] The equilibrium scenario outlined below is

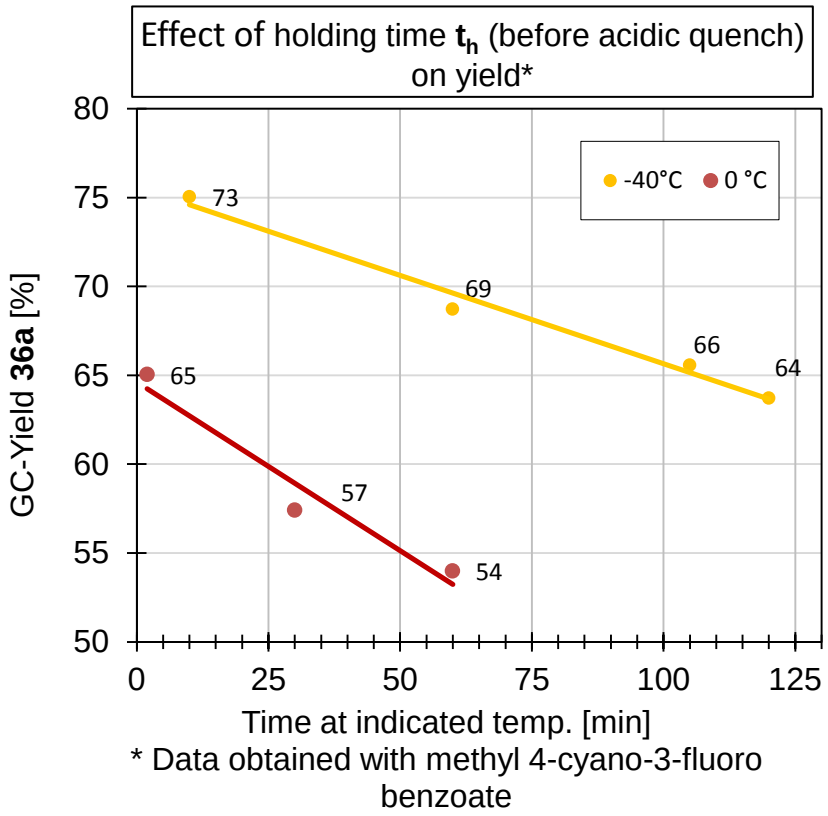
[267] Decomposition products of the dianion **38** could not be unanimously determined, likely due to their water solubility and high polarity. However previous studies proposed the substitution of an acid α-chloride with another molecule of dianion of leading to chlorosuccinic acid, which was isolated from reaction mixtures in

further plausible, because yields are improved with more equiv. of **38** when electron-rich (poor) ester electrophiles are used.

- Furthermore, if the quenching is done wrongly (e.g. dropwise addition of acetic acid for quench) the ester starting material can be recovered almost quantitatively.

- Notably, the yields obtained at practicable time ranges (0.5-10 min in small scale laboratory experiments, ca. 30 min on kg scale experiments) would indicate the necessity of cooling to −40 °C or below to obtain acceptable yields in a batch process.



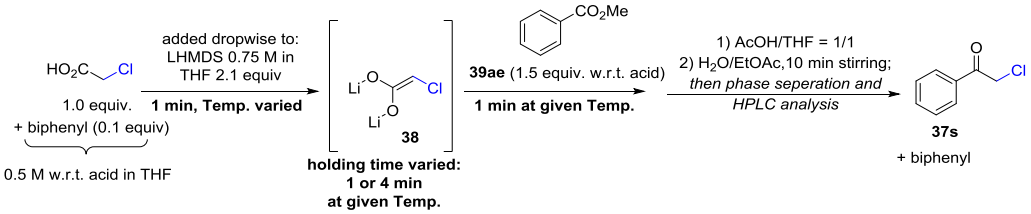


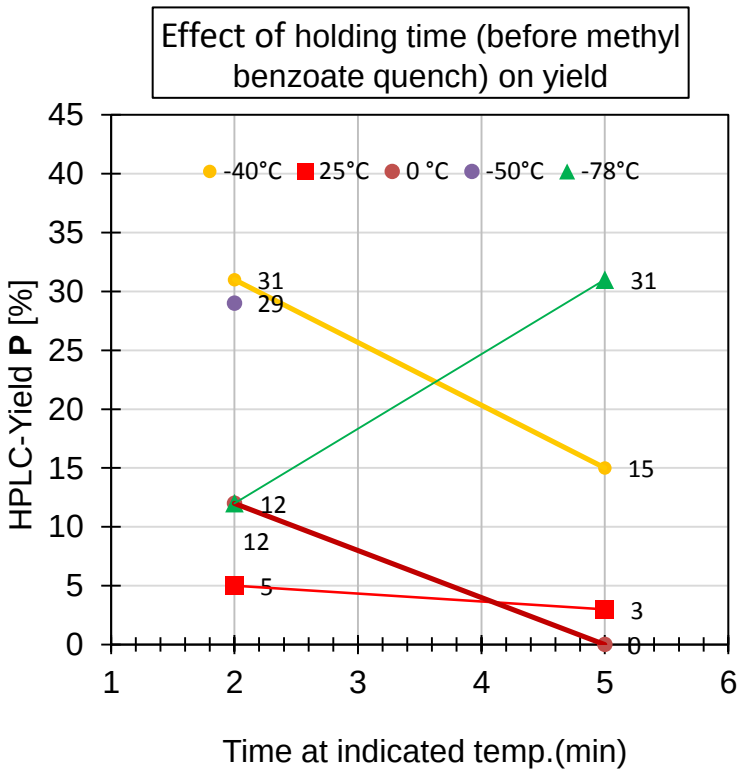
Scheme 52: Instability of the intermediate species *in presence of an ester* monitored by holding experiments. Data points were obtained from individual experiments to exclude decomposition due to contamination during sampling.

- Another stability test of the monochloro acid dianion *in absence of an ester* was performed, using the Chloroacetate *Claisen* reaction as a reliable assay method for the remaining lithium dianion

form of the chlorosuccinic acid dimethyl ester after treatment with diazomethane: C. R. Johnson, T. R. Bad, *J. Org. Chem.* **1982**, *47*, 1205.

species **38** (Scheme 53, excess methyl benzoate was used). The stability of the dianion was surveyed at various temperatures and after 2 min and 5 min with individual experiments. Shorter reaction times were favourable at all temperatures except -78 °C, which is likely due to slowed reaction rates at this low temperature. The effect of the cooling bath temperature was more pronounced: Thus significant changes of the maximium yield obtained were found at the various temperatures, clearly favouring thorough cooling (Scheme 53).

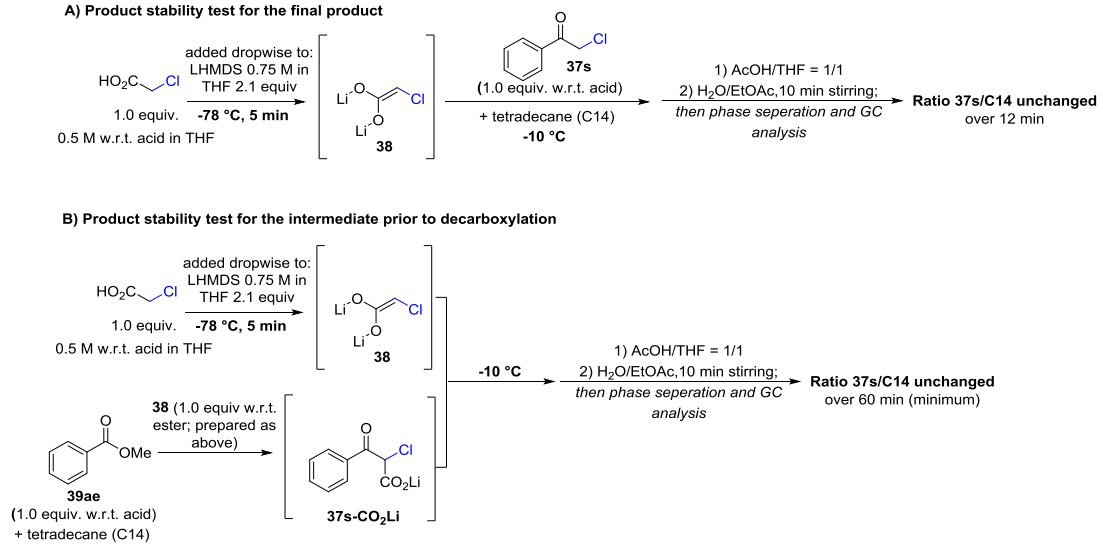




Scheme 53: Stability oft he dianion **38** *in absence of an ester* as monitored by the CAC reaction with an excess of methyl benzoate. The increased yield at -78 °C can be attributed to a slower reaction rate at the low temperature.

- A stability test was performed with the reaction products obtained from the **CAC** reaction, which indicates that the typical reaction product **37s** is stable under the reaction conditions over at least 12 min, thus longer than the reaction timescale under optimized conditions according to GC analysis (Scheme 54, A). To get a more realistic picture, the intermediate **37s-CO_2Li** was generated *in situ*, i.e. before acidic quench and decarboxylation occurred. Treatment of **37s-CO_2Li** with another equivalent of the anion **38** under the reaction conditions gave consistent yields of **37s** over at least 1 h at -10 °C

according to GC analysis (Scheme 54, B). This indicates that the plausible reaction intermediate **37s-CO_2Li,** exisiting prior to the acidic quench, is not subject to decomposition.



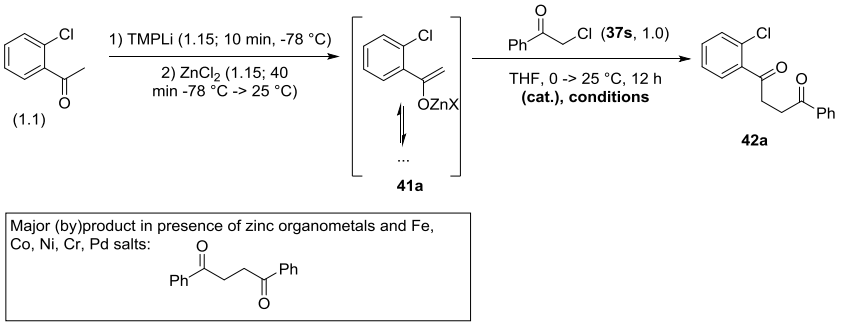
Scheme 54: Stability test for (A) the CAC reaction product **37s** and (B) the reaction intermediate P-CO_2Li prior to decarboxylation.

- Having eliminated product instability, the yield increase of the flow process at high flowrates and short residence times can be related to a limited decomposition of the dianion **38**, which very likely exists in the reaction mixture in equilibrium at any time. A potential degradation product, chlorosuccinic acid, was identified coming from undesired dimerization of the dianion in a precedent study.[267] Hence at both fast and slow flowrates a yield decrease with extended reaction time can be observed. Since the optimal conditions are under *Barbier* conditions, a multi-step process is required to take place after mixing: double deprotonation of the chloro acetic acid, followed by C-C bond formation with the ester and potentially alkoxide expulsion. At slow flow rates the mixing time has to be added to this reaction time, and yields decrease due to parallel dianion decomposition. At fast flow rates mixing time is minimized and therefore the overall time needed for conversion is shortened, and yields are raised by limiting dianion decomposition. Alternatively, the avoidance of an inhomogenous heat distribution due to improved mixing at high flowrates can help avoiding yield losses. This seems plausible, since excess heat was shown to be the major deletorial effect on the yields in Scheme 52 and Scheme 53. At present a deeper mechanistic probing would be required to substantiate these proposals.

The following table shows results from the optimization of the chloride substitution reaction with zinc enolates using an internal standard (tetradecane). Only results are shown that led to product formation (Table 21). The usage of lithium enolate let to quick decomposition (entry 2), using the polar DMPU additive gave no significant improvement (entry 3). A dimer derived from two chloroketones was obtained as major product in presence several catalytically active transition metals. CuCN·2LiCl and

Fe(II)-salts had only a very minor influence on the reaction (Entries 4-6). No reaction was observed with the analog dichloroketone. Aliphatic enolate precursors led also to product formation, albeit with concomitant formation of difficult to remove byproducts.

Table 21: Optimization of 1,4-diketone synthesis



Entry	Conditions	**42a** GC-int. (1h)*	…(3h)*****	…(12h)*
1	no cat	4.99	n.a.	12.29 (**90% isol**)
2	No $ZnCl_2$	Reaction complete early (30min), minor amounts of product		
3	+ 10%vol DMPU	7.49	10.66	12.02 (+more byproducts)
4	1% or 20% CuCN·2LiCl	5.13	11.06	12.20 (similar to entry 1)
5	5% $Fe(acac)_2$	4.86	8.49	9.82 (+dimer byproducts)
6	5% $Fe(Cl)_2$	8.86	6.58	10.92 (+dimer byproducts)
7	2,2-dichloro-1-phenylethan-1-one used	No reaction		

* (Product/Standard ratio)