Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
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FUNCTIONALIZATION OF ARENES AND HETEROARENES BY METALATION WITH TMP-BASES OR METAL INSERTION AND SYNTHESIS OF TETRASUBSTITUTED ALKENYL SULFIDES VIA A CU(I)-MEDIATED CARBOMETALATION

von

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aus

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe erarbeitet.

München, den 29.07.2011

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Cora Dunst

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1. Gutachter: Prof. Dr. Paul Knochel
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TO MY PARENTS & GRANDPARENTS

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Parts of this Ph.D. thesis have been published:

1. Cora Dunst, Albrecht Metzger, Elena Zaburdaeva, Paul Knochel, „Stereoselective Synthesis of Polyfunctional Tetrasubstituted Alkenyl Thioethers *via* a Carbocupration of Alkynyl Sulfides with Aryl and Benzylic Diorganozincs“, *Synthesis, accepted.*

2. Cora Dunst, Paul Knochel, „Regioselective Functionalization of the Thiazole Scaffold using TMPMgCl·LiCl and $TMP_2Zn·2MgCl_2·2LiCl$”, *J. Org. Chem.* **2011**, *76*, 6972.

3. Cora Dunst, Paul Knochel, „Selective Mg Insertion into Substituted Mono- and Di-Chloro Arenes in the Presence of LiCl. A new Preparation of Boscalid”, *Synlett* **2011,** *14*, 2064.

4. Marcel Kienle, Andreas J. Wagner, Cora Dunst, Paul Knochel, „Preparation of Heterocyclic Amines by an Oxidative Amination of Zinc Organometallics Mediated by CuI: A New Oxidative Cycloamination for the Preparation of Annulated Indole Derivatives” *Chem. Asian J.* **2011**, *6*, 517.

5. Stefan Wunderlich, Tomke Bresser, Cora Dunst, Gabriel Monzon, Paul Knochel, „Efficient Preparation of Polyfunctional Organometallics via Directed *ortho*-Metalation”, *Synthesis* **2010**, *15*, 2670.

6. Cora Dunst, Marcel Kienle, Paul Knochel, „Preparation of Heterocyclic Amines via a Copper(I)-Mediated Oxidative Cross-Coupling of Organozinc Reagents with Lithium Amides”, *Synthesis* **2010**, *13*, 2313.

7. Marcel Kienle, Cora Dunst, Paul Knochel, „Oxidative Amination of Heteroaromatic Zinc Reagents Mediated by $PhI(OAc)_2$”, *Org. Lett.* **2009**, *11*, 5158, selected for *Synfacts* **2010**, *2*, 213, selected in „Highlights, C-H Functionalization”, *Angew. Chem. Int. Ed.* **2010**, *49*, 2

Abbreviations

Ac	acetyl	*i*Pr	isopropyl
acac	acetylacetonate	IR	infra-red
aq.	aqueous	*J*	coupling constant (NMR)
Ar	aryl	M	molar
Bn	benzyl	m	multiplet
*n*Bu	butyl	Me	methyl
*s*Bu	*sec*-butyl	min	minute
*t*Bu	*tert*-butyl	mmol	millimole
calcd	calculated	mp	melting point
cat.	catalytic	MS	mass spectroscopy
conc.	concentrated	mw	microwave irradiation
d	doublet	NMR	nuclear magnetic resonance
dba	*trans,trans*-dibenzylideneacetone	Ph	phenyl
DPE	bis(2-diphenylphosphinophenyl)ether	R.	organic substituent
equiv	equivalent	s	singulett
E	electrophile	sat.	saturated
EI	electron-impact ionization	Sphos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
Et	ethyl	t	triplet
FCC	flash column chomatography	THF	tetrahydrofuran
FG	functional group	TIPS	triisopropylsilyl
GC	gas chromatography	TLC	thinlayer chromatography
h	hour	TMP	2,2,6,6-tetramethylpiperidyl
Hex	hexyl	TMS	trimethylsilyl
HRMS	high resolution mass spectroscopy		

A. INTRODUCTION

1. Overview

"*Organic synthesis is considered, to a large extent, to be responsible for some of the most exciting and important discoveries of the twentieth century in chemistry, biology, and medicine, and continues to fuel the drug discovery and development process with myriad processes and compounds for new biomedical breakthroughs and applications*." These words of *K. C. Nicolaou* point out the importance of synthesis in organic chemistry.[1] The discovery of urea in 1828 by *Wöhler*[2] displays the start of organic chemistry. Furthermore, new methodologies especially for the selective carbon-carbon or carbon-heteroatom bond formation became of great importance. Since *Frankland*'s discovery of Et_2Zn[3] in 1848, organometallic chemistry has constantly been developed and found a wide range of applications. In general, organometallic reagents have to be highly reactive and highly selective as well as environmental friendly and economical.[4] Nearly every metal in the periodic table can be used in organic reactions. For instance, Pd, Ni, Ru or Fe found application as catalysts for cross-coupling or metathesis reactions[5], while reagents containing metals such as Li, Mg, Zn or B are mostly used as nucleophiles.[6] In general, the reactivity of such organometallic compounds relies on the ionic character of the carbon-metal bond originating from the difference of electronegativity of the metal center and the carbon atom.[7] For example, organolithium reagents show a high reactivity towards various electrophiles. However, due to the ionic character of the lithium-carbon bond, they show a low tolerance towards functional groups and reactions are only possible at very low temperatures. The selectivity of organometallic reagents increases with the covalent character of the carbon-metal bond. For instance, organozinc reagents[8] have an almost covalent carbon-metal bond and therefore show a higher chemo- and regioselectivity. They are less reactive than organolithium reagents but tolerate a variety of sensitive functions. Organomagnesium reagents play a very special role, due to their high reactivity even at low temperatures and towards many different

[1] Nicolaou, K. C.; Vourloumis, D.; Winsigger, N.; Baran, P.S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44.

[2] Wöhler, F. *Ann. Phys. Chem.* **1828**, *12*, 253.

[3] Frankland, E. *Liebigs Ann, Chem.* **1848,** *71*, 171; *J. Chem. Soc.* **1848**, *2*, 263.

[4] Trost, B. M. *Science* **1991**, *254*, 1471; *Angew. Chem. Int. Ed.* **1995**, *34*, 259.

[5] Tsuji, J. *Transition Metal Reagents and Catalyst: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**.

[6] For an overview, see: *Handbook of Functionalized Organometallics Vol.1* and *2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, Germany, **2005**.

[7] Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000,** *39*, 4415.

[8] Singer, R. D.; Knochel, P. *Chem. Rev.* **1993**, *93*, 2117.

electrophiles while various functional groups can be tolerated. They can be easily prepared and are widely used in organic synthesis due to their low toxicity. Furthermore, their reactivity can be improved by the addition of catalysts like Ni, Pd or Cu or by transmetalation.[9,10] In summary, the importance of new organic compounds and the progress in this field is documented by several Nobel prizes which have been awarded.

2. General Preparation of Organomagnesium or Organozinc Reagents

2.1. Metal Insertion

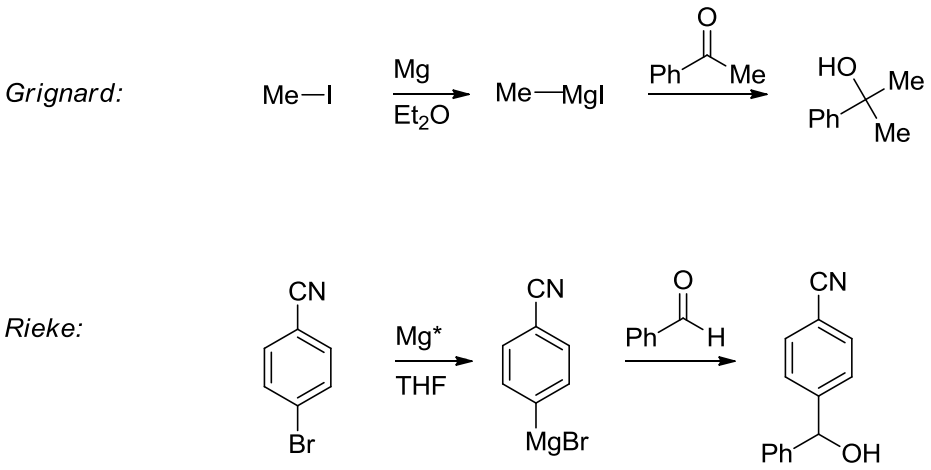
The direct insertion of metals in carbon-halide bonds is of high interest as this provides a cheap and environmental friendly access to organometallics due to the low toxicity of the metal.[4]
The investigation of organomagnesium reagents became an important field of organic chemistry, since *Victor Grignard* made the observation, that methyl iodide reacts with magnesium turnings in the presence of diethyl ether.[11] The use of high temperatures limited the range of functional groups that could be used. In pioneering work, *Rieke* and co-workers developed a highly reactive magnesium powder (Mg*), which is prepared from $MgCl_2$ and lithium naphthalenide (20 mol%).[12] This activated magnesium metal allowed the preparation of Grignard reagents at -78 °C bearing functional groups such as nitriles or esters (Scheme 1).

[9] Negishi, W.; King, A. O.; Okukado, N.J. *J. Org. Chem.* **1977**, *42*, 1821.

[10] (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390; (b) Dübner, F.; Knochel, P. *Angew. Chem*. **1999**, *111*, 391; *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

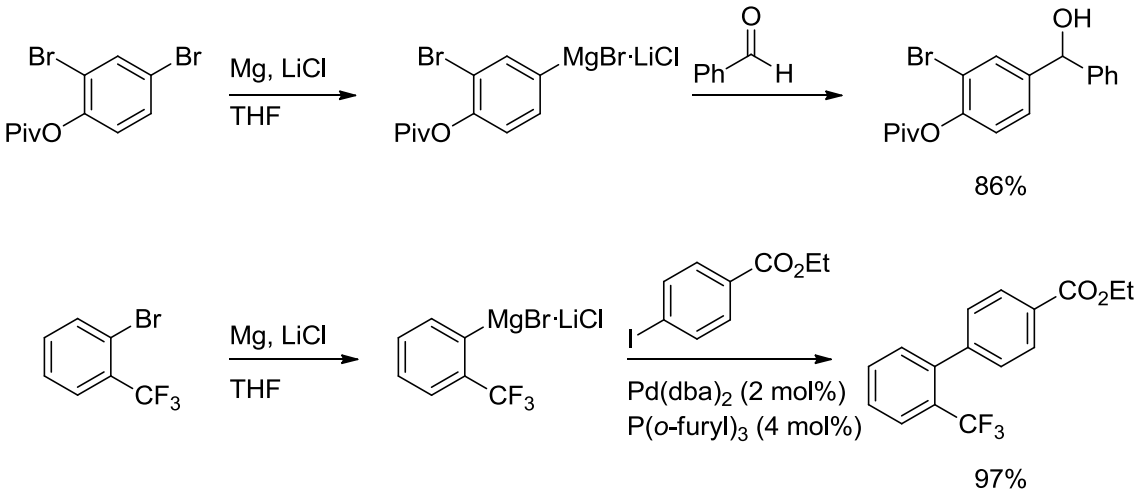
[11] Grignard, V. *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322.

[12] (a) Rieke, R. D. *Science*, **1972**, *94*, 1260. (b) Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178. (c) Rieke, R. D.; Hanson, M. V. *Tetrahedron*, **1997**, *53*, 1925. (d) Rieke, R. D. *Top. Curr. Chem.* **1975**, *59*, 1. (e) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301. (f) Rieke, R. D. *Aldrichimica Acta*, **2000**, *33*, 52.



Scheme 1: Preparation of magnesium reagents.

Since the presence of LiCl enhances the solubility and accelerates the insertion of metals into carbon-halogen bonds, investigated by *Knochel* and co-workers, the magnesium insertion gave access to various sensitive aromatic and heteroaromatic magnesium reagents.[13] The activation with DIBAL (1 mol%) ensures a smooth insertion even in the presence of sensitive substituents like the pivalate- or trifluoromethyl-group (Scheme 2).[14]

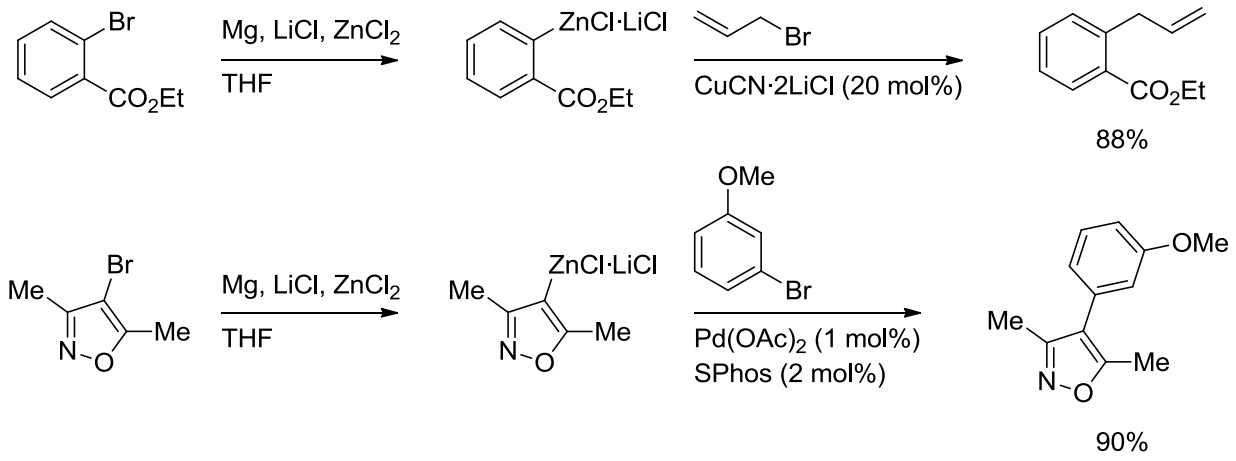


Scheme 2: Preparation of organomagnesium reagents in the presence of LiCl.

[13] (a) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. (b) Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 15.

[14] (a) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem.* **2008**, *120*, 6907; *Angew. Chem. Int. Ed.* **2008**, *47*, 6802. (b) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 7192.

By *in situ* transmetalation of the generated arylmagnesium species it is possible to afford stable organozinc reagents of bromo-substituted aromatic esters or very sensitive heterocycles like isoxazoles (Scheme 3).



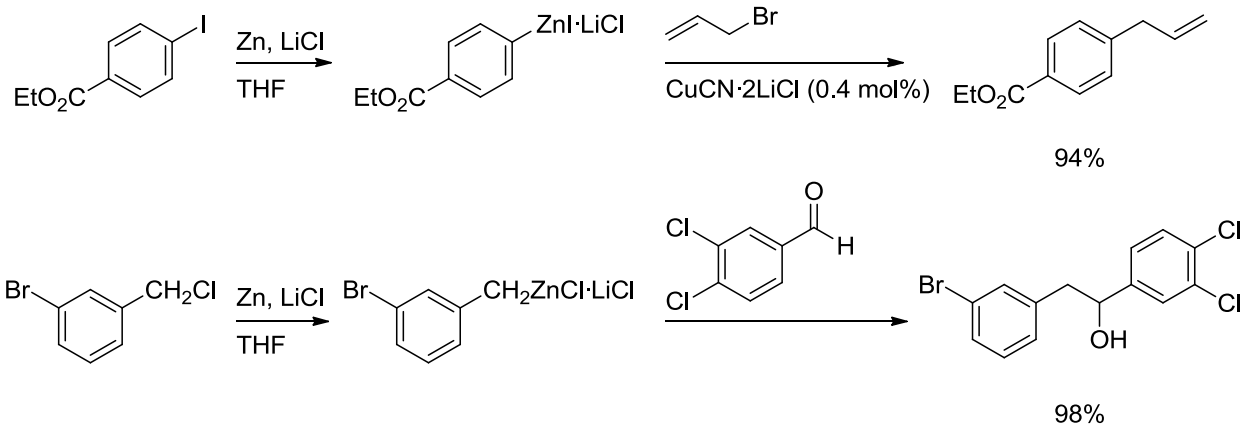
Scheme 3: Preparation of organozinc reagents in the presence of LiCl.

Furthermore, organozinc reagents can also be obtained by direct zinc insertion. Inspired by the work of *Frankland* who synthesized diethylzinc by the reaction of granulated zinc with ethyl iodide[3] and *Rieke* who activated Zn* with two equivalents of lithium naphtalenide[15], *Knochel* and co-workers improved the solubility, stability and reactivity of zinc reagents by the addition of LiCl.[16] Even functionalized benzylic zinc halides became accessible (Scheme 4).[17]

[15] (a) Rieke, R. D. *Science*, **1989**, *246*, 1260. (b) Rieke, R. D.; Li, T.; Burns, T.; Uhm, S. *J. Org. Chem.* **1981**, *46*, 4323. (c) Hanson, M. V.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (d) Hanson, M. V.; Rieke, R. D. *J. Am. Chem. Soc*. **1995**, *117*, 1445. (e) Rieke, R. D.; Hanson, M. V. *Tetrahedron.* **1997**, *53*, 1925.

[16] (a) Boudet, N.; Sase, S.; Sinha, P.; Liu, C.; Krasovskiy, A.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 12358. (b) Krasovskiy, A.; Malakhov, V.; Gavrryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

[17] (a) Metzger, A.; Schade, M. A.; Manolikakes, G.; Knochel, P. *Chem. Asian J.* **2008**, *3*, 1678. (b) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107. (c) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem. Eur. J*. **2009**, *15*, 7192.

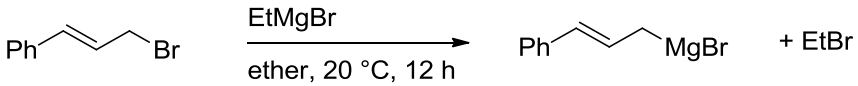


Scheme 4: Zn-insertion in the presence of LiCl.

2.2. Halogen-Metal Exchange Reactions

Organolithium compounds can be prepared by a halogen-lithium exchange, discovered by *Wittig* and *Gilman.*[18] Because of the low functional group tolerance of organolithium reagents, the synthesis of organomagnesium reagents became highly important.

The first halogen-magnesium exchange was reported by *Prévost.*[19] Thus, the reaction of cinnamyl bromide with EtMgBr furnished cinnamylmagnesium bromide in 14% yield (Scheme 5).



Scheme 5: First halogen-bromine exchange reported by *Prévost*.

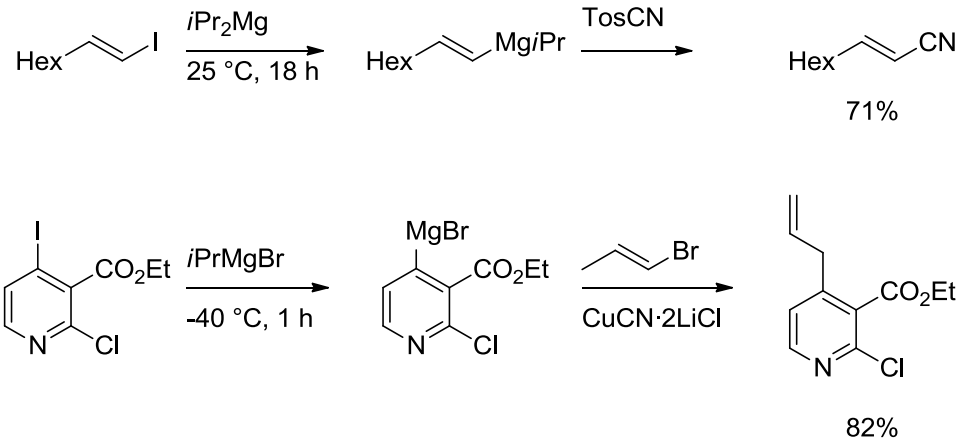
In general, the driving force of this reaction class is the formation of the most stable organometallic reagent ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec}$).[20]

[18] (a) Wittig, G.; Pockels, U.; Dröge, H. *Chem. Ber.* **1938**, *71*, 1903. (b) Jones, R. G.; Gilman, H. *Org. React.* **1951**, *6*, 339. (c) Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106.

[19] Prévost, C. *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.

[20] Hauk, D.; Lang, S.; Murso, A. *Org. Process Res. Dev.* **2006**, *10*, 733.

An iodine-magnesium exchange using *i*Pr_2Mg or *i*PrMgBr was reported by *Knochel* and co-workers.[21] It was found, that aryl iodides bearing electron-withdrawing groups undergo an I/Mg-exchange under mild conditions within a few hours. Furthermore, the tolerance towards various functional groups was described. Thus, this methodology was extended to the synthesis of alkenyl- and heteroaryl-magnesium reagents (Scheme 6).[22]



Scheme 6: Synthesis of alkenyl- and heteroaryl-magnesium reagents by an I/Mg-exchange.

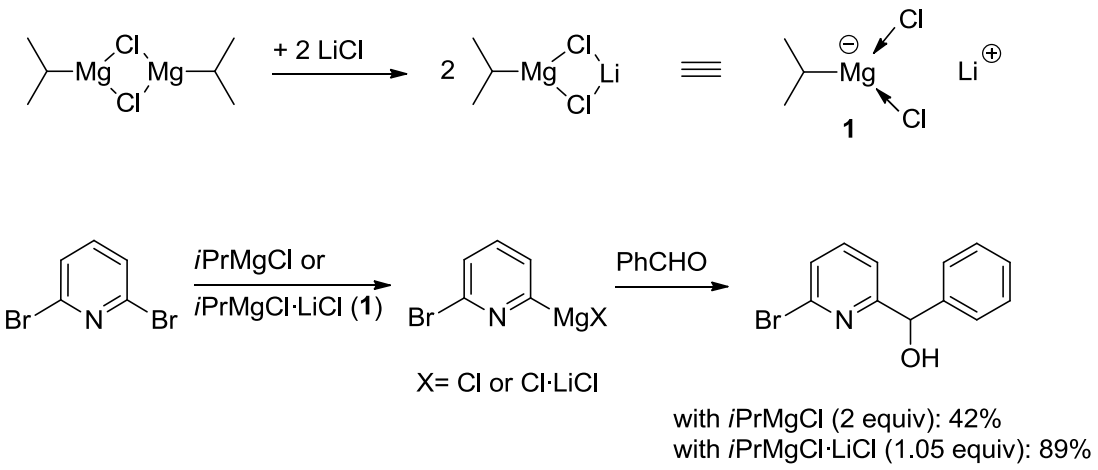
An enormous improvement of this method was achieved by *Knochel* by the addition of LiCl (1 equiv) to *i*PrMgCl.[23] The resulting "ate" like intermediate *i*PrMgCl·LiCl (**1**) showed an increasing reactivity and gave access even to electron-rich organic bromides which are less expensive and more stable in comparison with their corresponding iodinated derivatives.[24] The deaggregation of the organometallic species is proposed to be responsible for the higher solubility and for the enhanced reactivity of the organomagnesium reagents, which are complexed with LiCl (Scheme 7).

[21] (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.

[22] (a) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080. (b) Ababri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618. (c) Vu, V. A.; Sapountzis, I.; Korn, T.; Kopp, F.; Kneisel, F. F.; Gommermann, N.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302. (d) Bérillon, L.; Leprêtre, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359. (e) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583.

[23] (a) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. (b) Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

[24] (a) for selected examples of Br/Mg-exchange, see: (a) Ren, H.; Knochel, P. *Chem. Commun.* **2006**, 726. (b) Liu, C.-Y.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543. (c) Boudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, 3737. (d) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288.



Scheme 7: Acceleration of the Br/Mg-exchange reaction by the addition of LiCl.

2.3. Directed Metalations

The directed metalation of arenes and heteroarenes is one of the most useful methods for the functionalization of these scaffolds. Since the pioneering work of *Hauser* who developed diethyl- and diisopropylaminomagnesium bromides for the self condensation of esters,[25] *Eaton*[26] and *Mulzer*[27] extended this work to the synthesis of sterically hindered TMP-bases, for instance TMPMgBr, TMP_2Mg or TMPMgCl. These bases were useful for the preparation of *ortho*-magnesiated aromatics or for the directed metalation of pyridine derivatives.

However, the limited solubility of such bases in common organic solvents as well as the use of an excess of the magnesium bases (2–7 equiv) and of the electrophiles to achieve high conversions has lowered their general use. Furthermore, the development of the highly reactive TMPMgCl·LiCl (**2**)[28], investigated 2006 by *Knochel* and co-workers, improved the synthesis of metalated aromatics and heteroaromatics. By the reaction of *i*PrMgCl·LiCl (**1**) with TMPH, the amide base can be easily

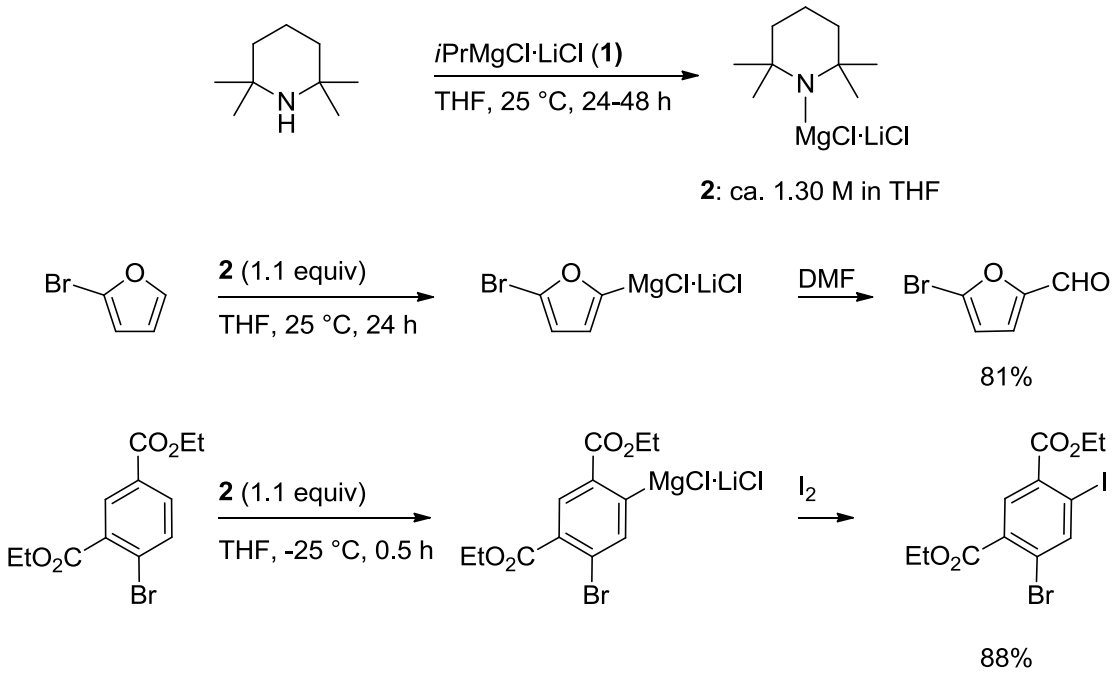
[25] (a) Hauser, C. R.; Walker, H. G. *J. Am. Chem. Soc.* **1947**, *69*, 295. (b) Hauser, C. R.; Frostig, F. C. *J. Am. Chem. Soc.* **1947**, *71*, 1350.

[26] Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016.

[27] Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414.

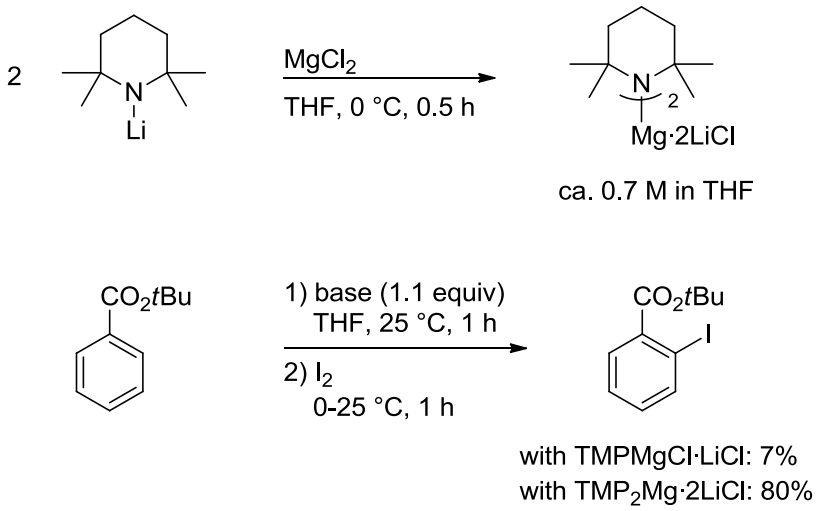
[28] (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed*. **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett*. **2007**, *9*, 5525. (d) Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, *10*, 1715. (e) Stoll, A. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 113. (f) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497. (g) Monzon, G.; Knochel, P. *Synlett* **2010**, 304. (h) García-Alvarez: P. Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.;. O'Hara, C. T.; Weatherstone, S. *Angew. Chem. Int. Ed*. **2008**, *47*, 8079.

prepared and shows long term stability, very good solubility and good compatibility with sensitive functional groups (Scheme 8).



Scheme 8: Preparation of TMPMgCl·LiCl (**2**) and its use in deprotonation reactions.

This work was extended to the synthesis of bis-amide bases, such as $TMP_2Mg{\cdot}2LiCl$[29], which showed an improved reactivity and excellent functional group tolerance, also on large scale.[30] This new mixed Li/Mg base gave access to electron-poor and therefore less activated aromatics (Scheme 9).

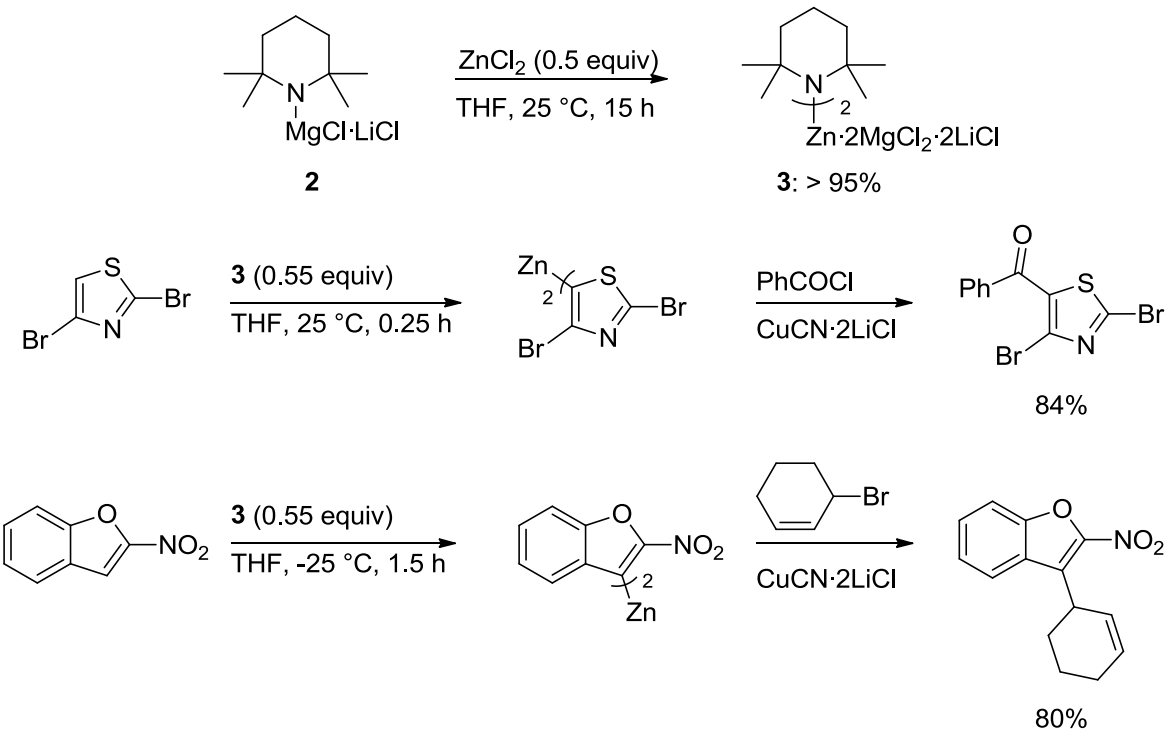


Scheme 9: Preparation and reactivity of $TMP_2Mg{\cdot}2LiCl$.

[29] (a) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. (b) G. C.; Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *46*, 1503.

[30] Wunderlich, S. H.; Rohbogner, C. J.; Unsinn, A.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 339.

Some sensitive functionality groups such as aldehydes and nitro groups and some heterocycles were not tolerated due to fragmentation[31]. Therefore a range of highly active zinc amides, for instance *t*Bu_2Zn(TMP)Li, developed by *Kondo* can be used for the *ortho*-metalation of aromatics and heteroaromatics.[32] Moreover, the chemoselective and chemosensitive zinc base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**3**)[33], investigated by the group of *Knochel*, allows the direct deprotonation of sensitive functionalized aromatics and heteroaromatics under mild conditions (Scheme 10).



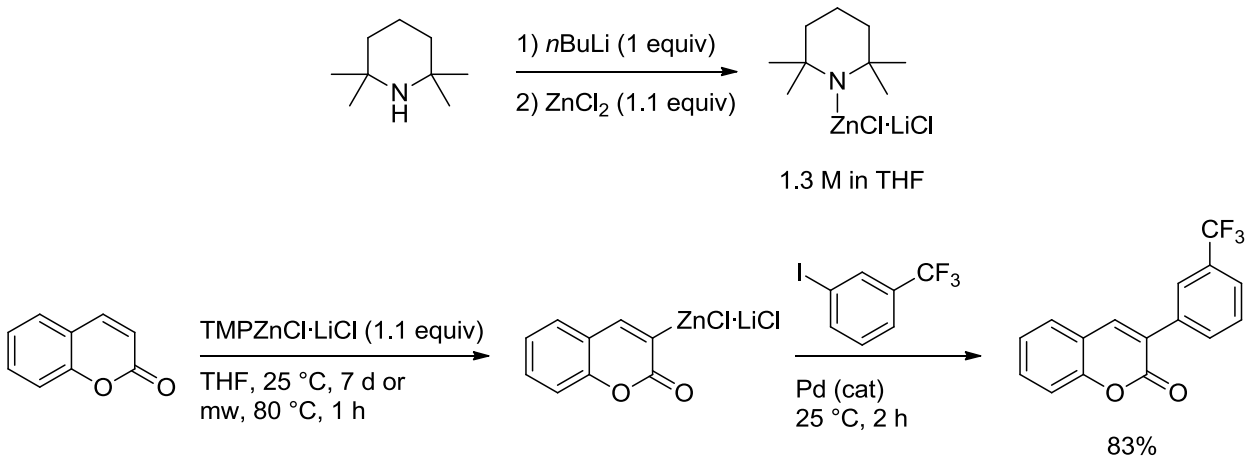
Scheme 10: Preparation of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ and its use in deprotonation reactions.

[31] (a) Micetich, R. G. *Can. J. Chem.* **1970**, *48*, 2006. (b) Meyers, A. I.; Knaus, G. N. *J. Am. Chem. Soc.* **1974**, *95*, 3408. (c) Knaus, G. N.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1189. (d) Miller, R. A.; Smith, M. R.; Marcune, B. *J. Org. Chem.* **2005**, *70*, 9074. (e) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber. Rec.* **1997**, *130*, 1213.

[32] (a) Kondo, Y.; Shilai, H.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539. (b) Imahori, T.; Uchiyama, M.; Kondo, Y. *Chem. Commun.* **2001**, 2450. (c) Schwab, P. F. H.; Fleischer, F.; Michl, J. *J. Org. Chem.* **2002**, *67*, 443. (d) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otami, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514. (e) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. (f) Naka, H.; Morey, J. V.; Haywood, J.; Eisler, D. J.; McPartlin, M.; Garcia, F.; Kudo, H.; Kondo, Y.; Uchiyama, M.; Wheatley, A. E. H. *J. Am. Chem. Soc.* **2008**, *130*, 16193.

[33] (a) Wunderlich S. H.; Knochel P. *Angew. Chem.* **2007**, *119*, 7829; *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. (b) Wunderlich, S. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705. (c) Wunderlich, S. H.; Knochel, P. *Chem. Commun.* **2008**, *47*, 6387. (d) Despotopoulou, C.; Gignoux, C.; McConnell, D.; Knochel, P. *Synthesis* **2009**, 3661.

The lewis acid LiCl is responsible for the excellent solubility of the base as well as the formed diarylzincs. Moreover, the presence of $MgCl_2$ enhances the kinetic basicity. An extension of this work was the investigation of the milder and more selective zinc base TMPZnCl·LiCl[34] which can be used from ambient temperature up to 160 °C under microwave conditions[35] (Scheme 11).



Scheme 11: Preparation of TMPZnCl·LiCl and its use in deprotonation reactions.

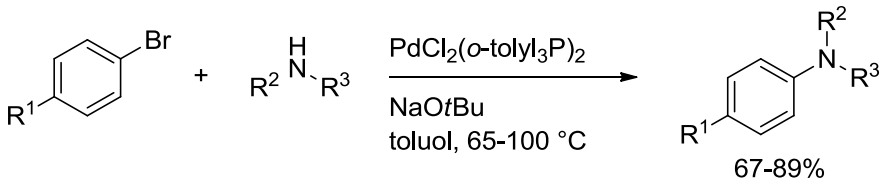
[34] (a) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837. (b) Mosrin, M; Bresser, T.; Knochel, P. *Org. Lett.* **2009**, *11*, 3406. (c) Bresser, T.; Mosrin, M.; Monzon, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686. (d) Bresser, T.; Monzon, G.; Mosrin, M.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 1299.

[35] Mosrin, M; Monzon, G.; Bresser, T.; Knochel, P. *Chem. Commun.* **2009**, 5615.

3. Amination Reactions

3.1. Transition Metal Catalyzed Amination Reactions

Several amination reactions using Pd, Ni or Cu are described in the literature.[36,37] The first Pd-catalyzed C-N bond formation is described in 1983 by *Mital*, where aminotin compounds react with aryl bromides in the presence of palladium.[38] Due to the toxicity and instability of the tin reagents *Buchwald* and *Hartwig* developed in 1995 a new methodology for the conversion of aryl bromides to arylamines (Scheme 12).[39]



Scheme 12: Tin-free synthesis of arylamines.

[36] For selected reviews see: (a) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (e) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (f) Blaser, H.-U.; Indolese, A.; Naud, F.; Nettekoven, U.; Schnyder, A. *Adv. Synth. Catal.* **2004**, *346*, 1583. (g) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (h) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.

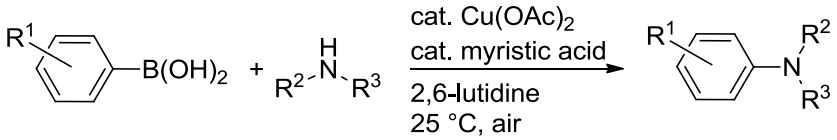
[37] For recent reports: (a) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742. (b) Shekhar, S.; Ryberg, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 3584. (c) Tundel, R. E.; Anderson, K. W; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430. (d) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altmann, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523. (e) Strieter, E. R.; Buchwald, S. L. *Angew. Chem, Int. Ed.* **2006**, *45*, 925. (f) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354. (g) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (h) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5766. (i) Schulz, T.; Torborg, C.; Enthaler, S.; Schäffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Börner, A.; Beller, M. *Chem.Eur. J.* **2009**, *15*, 4528.

[38] Kosugi, M.; Kameyama, M.; Sano, H.; Migita, T. *Chem. Lett.* **1983**, 927,

[39] (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

By the improvement of several ligands, the scope of aminations of aryl chlorides or unactivated aryl halides even under very mild conditions was extended. Chelating ligands like BINAP or DPPF and biaryl ligands like X-Phos have proven to be very efficient.[40]

The Ullmann condensation reaction, where an aryl halide reacts with a nucleopile using copper salts as catalyst displays an alternative to obtain aryl-amines.[41] Due to the harsh reaction conditions such as high temperatures, the presence of strong bases and long reaction times many efforts have been made to improve this reactions. For instance, the copper-catalyzed coupling of arylboronic acids with amines developed by *Buchwald* and co-workers occurs under especially mild conditions (Scheme 13).[42]



Scheme 13: Copper-catalyzed amination reaction at room temperature.

3.2. Oxidative Amination Reactions

Inspired by the work of *Rici*[43], *Yamamoto* and *Maruoka*[44] who focused on the use of oxygen as oxidant, *Knochel* and co-workers developed an oxidative amination using chloranil as a very efficient oxidant.[45] Starting from organomagnesium reagents, prepared by a halogen/Mg-

[40] (a) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584. (b) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6338. (c) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

[41] (a) Ullmann, F. *Ber. Dt. Chem. Ges.* **1903**, *36*, 2382. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

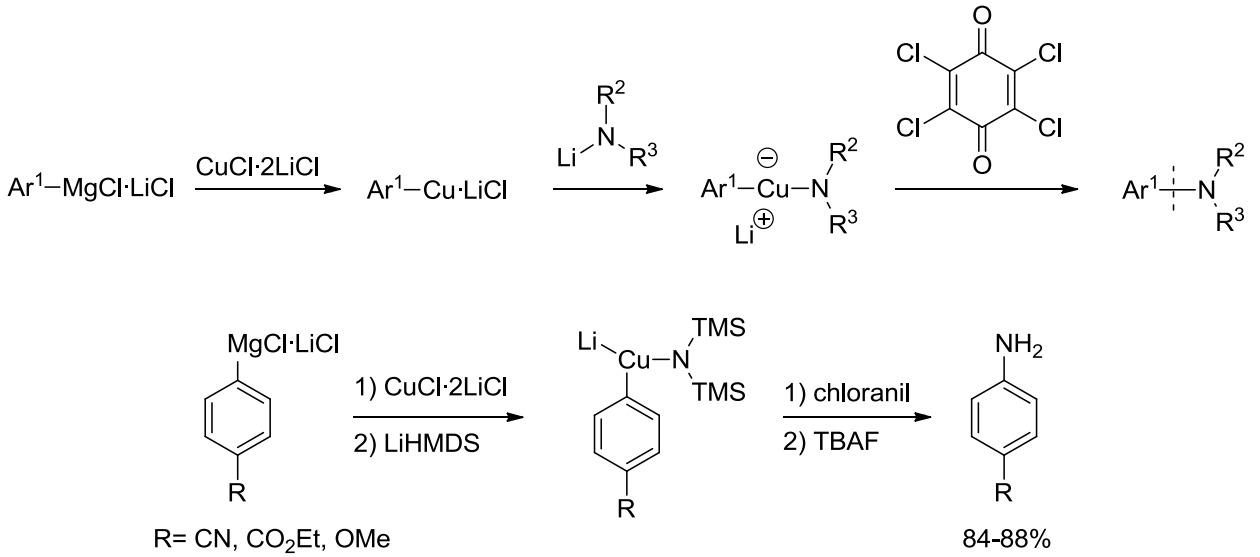
[42] Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.

[43] (a) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620. (b) Alberti, A.; Canè, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677. (c) Canè, F.; Brancaleoni, D.; Dembech, P.; Ricci, A.; Seconi, G. *Synthesis* **1997**, 545. (d) Bernardi, P.; Dembech, P.; Fabbri, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1999**, *64*, 641.

[44] Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739.

[45] (a) del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7838. (b) Kienle, M.; Dubbaka, S. R.; del Amo, V.; Knochel, P. *Synthesis* **2007**, 1272.

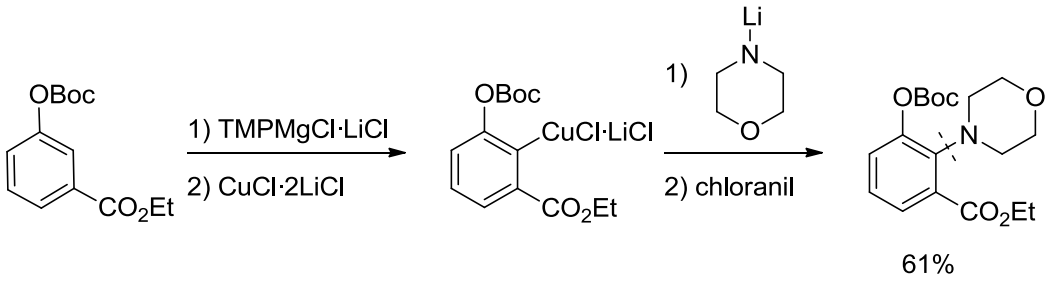
exchange or deprotonation with TMPMgCl·LiCl (**2**), this methodology gave access to polyfunctional primary, secondary and tertiary aryl and heteroaryl amines (Scheme 14).



Scheme 14: General scheme for the oxidative amination reaction and synthesis of primary amines.

First, the organomagnesium reagent is transmetalated with CuCl·2LiCl affording the corresponding copper derivative. After the treatement with a lithium amide and further oxidation with chloranil, the desired amine was obtained. By using this method, a variety of primary amines was obtained in high yield.

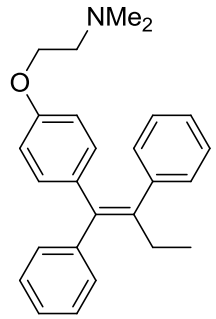
Furthermore, the sensitive functional groups and sterically hindered substrates were tolerated (Scheme 15).



Scheme 15: Synthesis of sterically hindered amines.

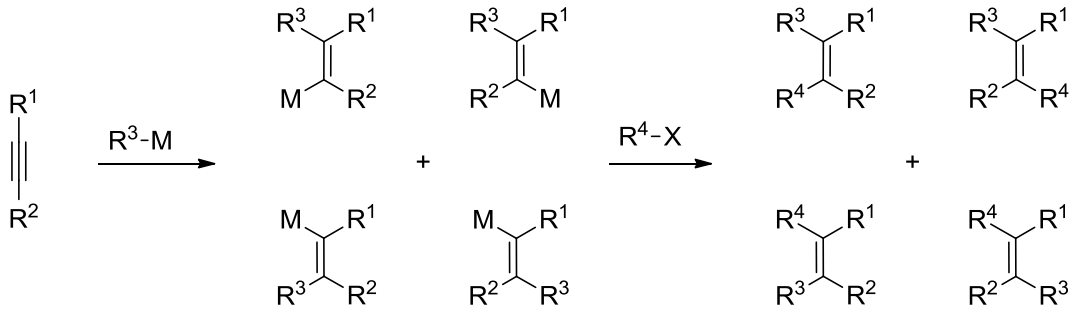
4. Carbometalation Reactions

Multisubstituted olefins are widespread in pharmacologically important molecules, for instance Tamoxifen (Scheme 16).[46]



Scheme 16: Structure of Tamoxifen.

Tamoxifen is a selective estrogen receptor modulator (SERM) with antiestrogenic properties in the breast an estrogenic effects in tissues such as the cardiovascular system or bone. It is the most important anti-breast cancer drug in clinical use, since it is a valuable alternative to hormone replacement therapy.[47] The preparation of polysubstituted stereodefined alkenyl metal derivatives by the addition of a carbon-metal bond of an organometallic species to an alkyne (carbometalation) is one of the major challenges in organic chemistry. The regio- and stereocontrol is an important key in this technology, since many products can be formed (Scheme 17).



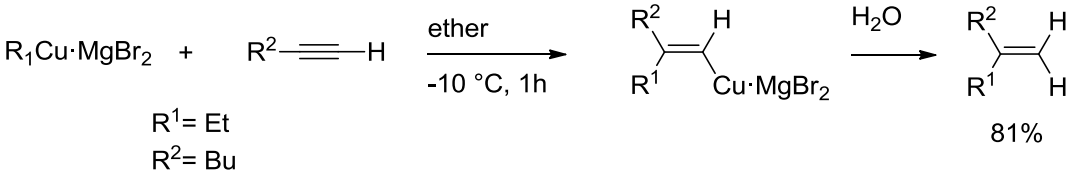
Scheme 17: Isomeric possibilities obtained by carbometalation.

[46] (a) Robertson, D. W.; Katzenellenbogen, J. A.; Hayes, J. R.; Katzenellenbogen, B. S. *J. Med. Chem.* **1982**, *25*, 167. (b) Harper, M. J. K.; Walpole, A. L. *Nature* **1966**, *212*, 87. (c) Al-Hassan, M. I. *Synth. Commun.* **1987**, *17*, 1247. (d) Kamei, T.; Tiami, K.; Yoshida, J. *Adv. Synth. Catal.* **2004**, *346*, 1824. (e) Reiser, O. *Angew. Chem. Ind. Ed.* **2006**, *45*, 2838. (f) Abramovitch, A.; Marek, I. *Eur. J. Org. Chem.* **2008**, 4924. (g) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121. (c) Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1997**, *36*, 93.

[47] While the *Z*-isomer is antiestrogenic, the *E*-isomer is an estrogen agonist: Harper, M. J.; Walpole, A. L. *Nature* **1966**, *212*, 87.

The regioselectivity can be controlled by the use of symmetrical alkynes or the use of directing goups. The stereoselectivity depends on the nature of the metal or the catalysts that is used. These factors influence the addition on the alkyne that can be in a *syn*- (copper, aluminium) or an *anti*- (lithium, magnesium, zinc) fashion.[48] A variety of carbometalation reactions using copper, magnesium, boron and tin reagents is known today.[49] For instance, boron reagents offer good reactivity advantages since they can be used in Pd-catalyzed cross-coupling reactions. The use of tin reagents involves purification and toxicity problems as well as a moderate regioselectivity. The most efficient reagents for the preparation of stereoisomerically pure di-, tri- or tetrasubstituted olefins are copper reagents.

The investigation of carbocupration reactions became a highly important field, since *Normant* made the observation, that copper reagents of type $RCu{\cdot}MgX_2$ reacted with acetylenes in total regio- and stereoselectivity (Scheme 18).[50]



Scheme 18: Carbocupration of acetylenes by *Normant.*

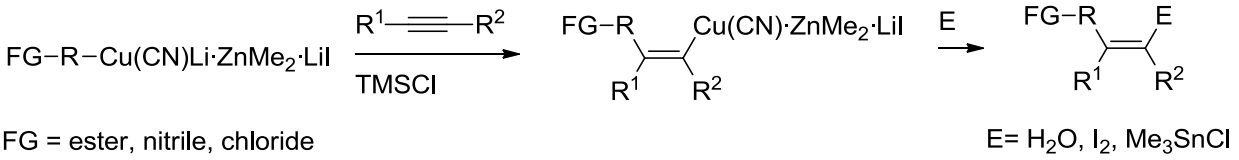
Knochel and coworkers extended this work using organozinc reagents which are transmetalated with $CuCN{\cdot}nLiCl$ (n= 1-2, Scheme 19).[51]

[48] for excellent reviews see: (a) Ogilvie, W. W.; Flynn, A. B. *Chem. Rev.* **2007**, *107*, 4698. (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (c) Basheer, A.; Marek, I. *Beilstein J. Org. Chem.* **2010**, *6*, No. 77.

[49] (a) Itami, K.; Kamei, T.; Yoshida J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (b) Das, J. P.; Chechik, H.; Marek, I. *Nat. Chem.* **2009**, *1*, 128. (c) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Gerard, J.; Hevesi, L. *Tetrahedron* **2004**, *60*, 367. (f) Creton, I.; Marek, I.; Brasseur, D.; Jestin, J.-L.; Normant, J.-F. *Tetrahedron Lett.* **1994**, *35*, 6873.

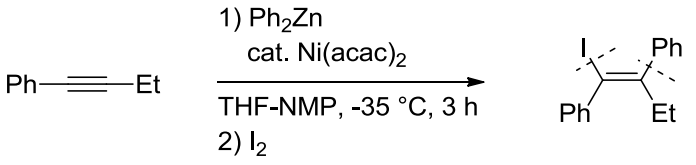
[50] Normant, J. F.; Bourgain, M. *Tetrahedron Lett.* **1971**, *27*, 2583.

[51] (a) Rao, S. A.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735. (b) Rao, S. A.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 7579.



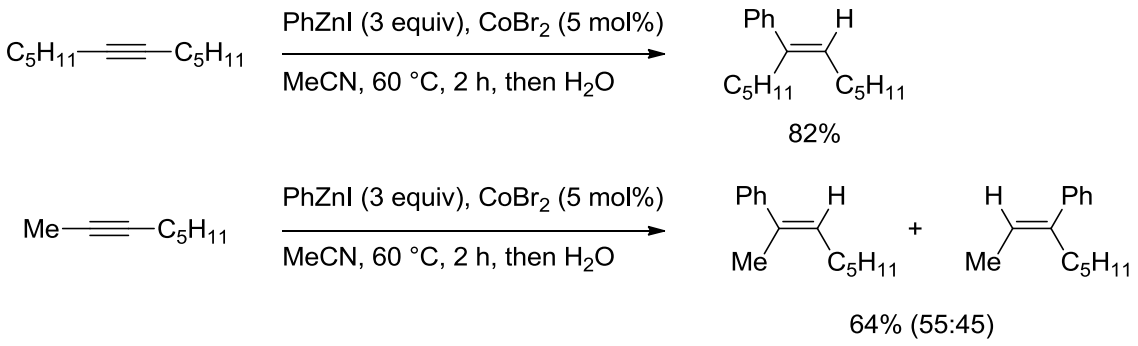
Scheme 19: Carbometalation of alkynes using Cu-reagents of type FG-RCu(CN)ZnMeI.

Furthermore, the addition of dialkylzincs or diphenylzinc in the presence of catalytic amounts of $Ni(acac)_2$ in THF:NMP led to syn-carbozincation products in excellent regio- and stereoselectivity (Scheme 20).



Scheme 20: Addition of diorganozinc reagents to alkynes in the presence of $Ni(acac)_2$.

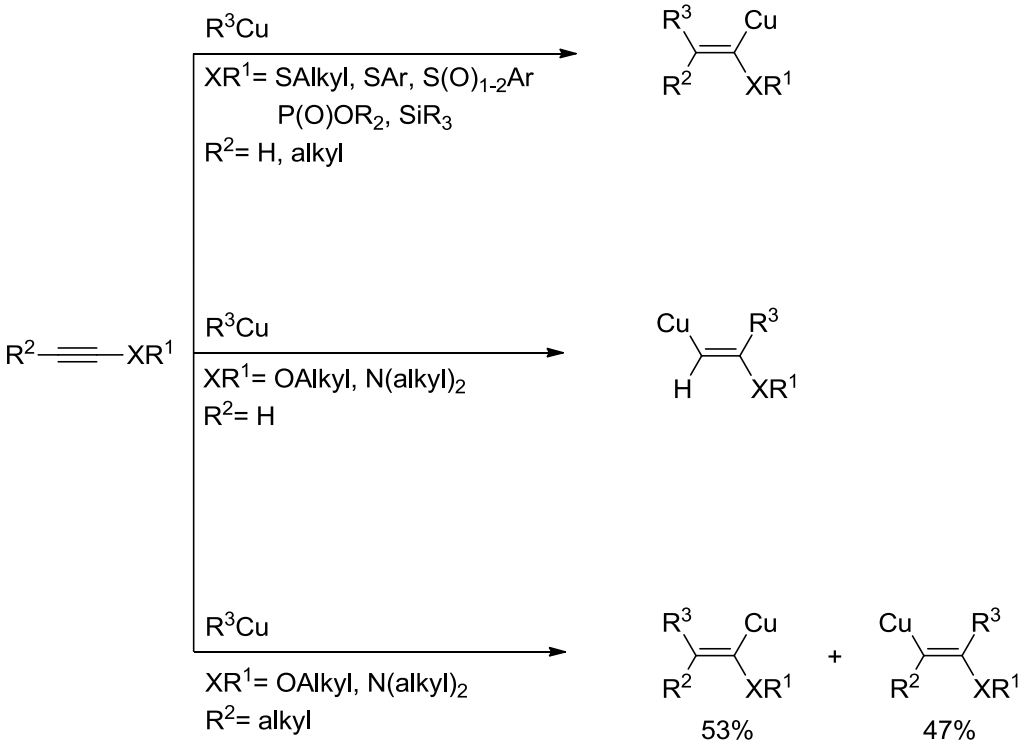
Recently, *Oshima* and co-workers described a carbometalation reaction of alkynes using organozinc reagents in the presence of $CoBr_2$ (Scheme 21).[52] In this work the mainly symmetrical alkynes are described. Futhermore, in the case of unsymmetrically substituted alkynes, the selectivity of the regioisomers is decreased.



Scheme 21: Carbometalation of alkynes with zinc reagents and cobalt catalysis.

[52] (a) Murakami, K.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2010**, *16*, 7688. (b) Murakami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2009**, *11*, 2373.

The regioselectivity of carbocupration reactions can be increased by using α-heterosubstituted alkynes bearing O-, N-, P-, S- or Si-substituents. Interestingly, the directing effect of oxygen and nitrogen is opposite to the one of sulfur-, phosphorus and silicon-substituted alkynes (Scheme 22).[53]

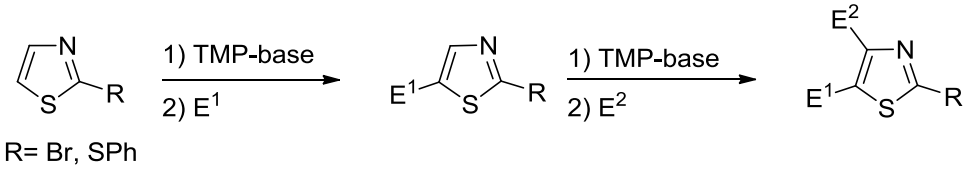


Scheme 22: Influence of α-heterosubstituted alkynes in carbometalation reactions.

[53] Levin, A.; Basheer, A.; Marek, I. *Synlett* **2010**, *2*, 329 and references therein. For a review see: Basheer, A.; Marek, I. *Beilstein J. Org. Chem.* **2010**, *6*, No. 77.

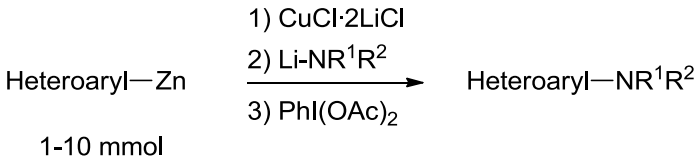
5. Objectives

In a first project, the synthesis of 2,4,5-trisubstituted thiazoles was attempted. The synthetic sequence should be general and the reagents used should be compatible with a broad range of functional groups. Starting from commercially available 2-bromothiazole, successive metalations using TMPMgCl·LiCl (**2**) or TMP_2·2$MgCl_2$·2LiCl (**3**) should lead to the corresponding magnesated or zincated thiazoles. These heterocyclic organometallics can react with various electrophiles providing highly functionalized thiazoles.



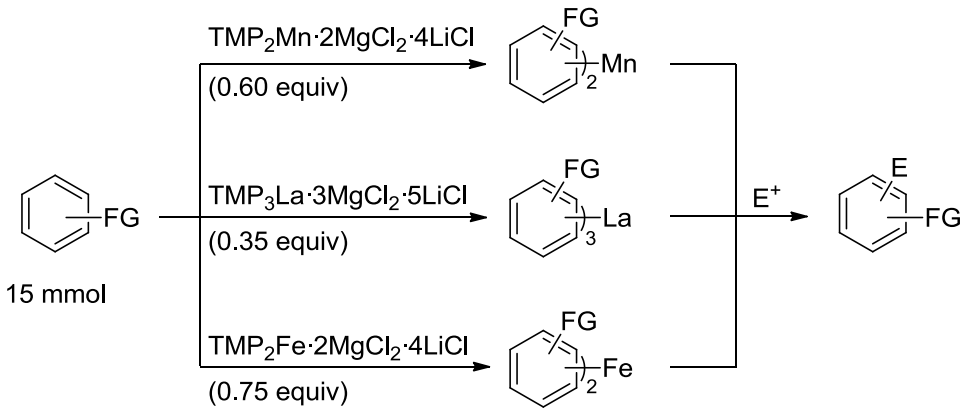
Scheme 23: Full functionalization of the thiazole scaffold using TMPMg·LiCl (**2**) or TMP_2·2$MgCl_2$·2LiCl (**3**).

Furthermore, a Cu(I)-mediated oxidative amination reaction was extended to various zincated heterocycles obtained by metalation with TMP-bases, Br/Mg-exchange and further transmetalation with $ZnCl_2$ or metal insertion in the presence of $ZnCl_2$ and LiCl. As an application, the optimization of this methodology in large-scale reactions was investigated (Scheme 24).



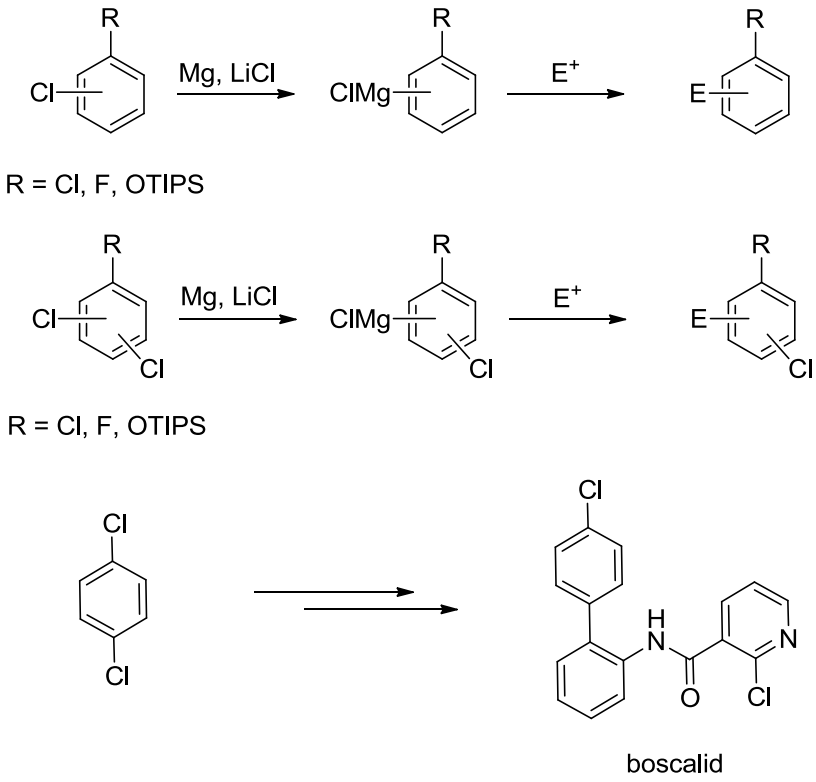
Scheme 24: Oxidative amination of zincated heterocycles.

In a third subject, substituted aromatics were functionalized on a 15 mmol scale using the recently developed TMP-manganese, -lanthanum and –iron-bases (Scheme 25).



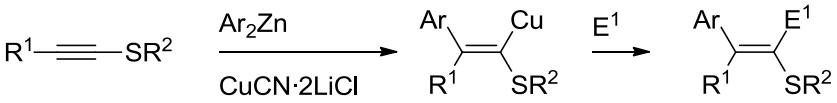
Scheme 25: Efficent preparation of polyfunctional organometallics *via* directed *ortho*-metalation using TMP-bases of Mn, La and Fe.

The fourth topic was addressed to the LiCl-mediated Mg insertion into polysubstituted aryl chlorides bearing up to three chloro substituents in *ortho* or *meta* position since these substrates are inexpensive and usually commercially available. The resulting Grignard reagents react with various electrophiles. As an application, a new formal synthesis of boscalid should be developed, which is of biological interest (Scheme 26).



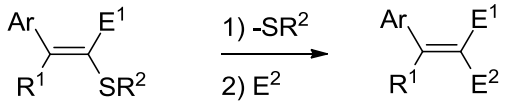
Scheme 26: Selective Mg insertion into substituted mono- and di-chloro arenes in the presence of LiCl. Application to the synthesis of boscalid.

As a further project, a general method for the synthesis of tetrasubstituted thioethers was investigated by the carbocupration of alkynyl sulfides using functionalized aryl and benzylic diorganozinc reagents in the presence of CuCN·2LiCl. The intermediate alkenylcopper reagents should react with various electrophiles furnishing a broad range of highly functionalized alkenes with excellent stereoselectivity (Scheme 27).



Scheme 27: Cu(I)-mediated carbometalation using diarylzinc reagents leading to tetrasubsituted alkenyl sulfides.

The last research goal was to explore the removal of the thioether-substituent yielding tetra-functionalized olefins (Scheme 28).



Scheme 28: Preparation of functionalized olefins.

B. RESULTS AND DISCUSSIONS

1. Regioselective Functionalization of the Thiazole Scaffold using TMPMgCl·LiCl and $TMP_2Zn·2MgCl_2·2LiCl$

1.1. Introduction

Thiazoles are an important class of heterocycles which are present in many natural products[54] possessing antitumor, antifungal, antibiotic or antiviral effects.[55] Some functionalized thiazoles have found applications as liquid crystals,[56] while others are used as cosmetic sunscreens.[57]
The standard syntheses of substituted thiazoles are cyclization reactions such as the Hantzsch reaction where an α-haloketone reacts with a thioamide (Scheme 29).[58]

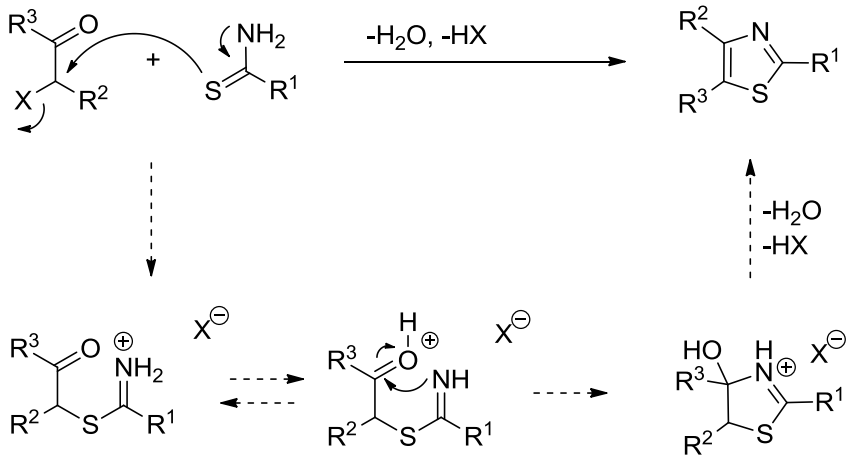
[54] (a) Schneider, T. L.; Walsh, C. T. *Biochemistry* **2004**, *43*, 15946. (b) Chatterjee, A.; Schroeder, F. C.; Jurgenson, C. T.; Ealick, S. E.; Begley, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 11394.

[55] (a) Lewis, J. R. *Nat. Prod. Rep.* **1996**, *13*, 435. (b) Steinmetz, H.; Irschik, H.; Kunze, B.; Reichenbach, H.; Höfle, G.; Jansen, R. *Chem. Eur. J.* **2007**, *13*, 5822. (c) Ung, A. T.; Pyne, S. G. *Tetrahedron:* Asymmetry 9 **1998**, 1395. (d) Müller, H. M.; Delgado, O.; Bach, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4771. (e) Altmann, K.-H.; Pfeiffer, B.; Arseniyadis, S.; Pratt, B. A.; Nicolaou, K. C. *ChemMedChem* **2007**, *2*, 396. (f) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (g) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996,** *61*, 4623. (h) Takayama, H.; Kato, K.; Kimura, M.; Akita, H. *Heterocycles* **2007**, *71*, 75.

[56] (a) Kiryanov, A. A.; Sampson, P.; Seed, A. J. *J. Org. Chem.* **2001**, *66*, 7925. (b) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M; Ikeda, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (c) Dölling, K.; Zaschke, H.; Schubert, H. *J. Prakt. Chem.* **1979**, *321*, 643.

[57] (a) Bach, T.; Heuser, S. *Tetrahedron Lett.* **2000**, *41*, 1707. (b) Jayatilake, G. S.; Baker, B. J. *Org. Lett.* **1999**, *1*, 661.

[58] (a) Hantzsch, A. *Ann. Chem.* **1888**, *249*, 1. (b) Heck, S.; Dömling, A. *Synlett* **2000**, *3*, 424. (c) Stump, B.; Kohler, R. C.; Schweizer, W. B.; Diederich F. *Heterocycles* **2007**, *27*, 293. (d) Obushak, N. D.; Matiichuk, V. S.; Ganushchak, N. I.; Martyak, R. L. *Chem. Heterocycl. Compd.* **1999**, *35*, 93. (e) Obushak, N. D.; Matiichuk, V. S.; Ganushchak, N. I.; Martyak, R. L. *Chem. Heterocycl. Compd.* **1997**, *33*, 1000. (f) Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Ghazanfarpour-Darani, M. *Mol. Divers.* **2009**, *13*, 295.



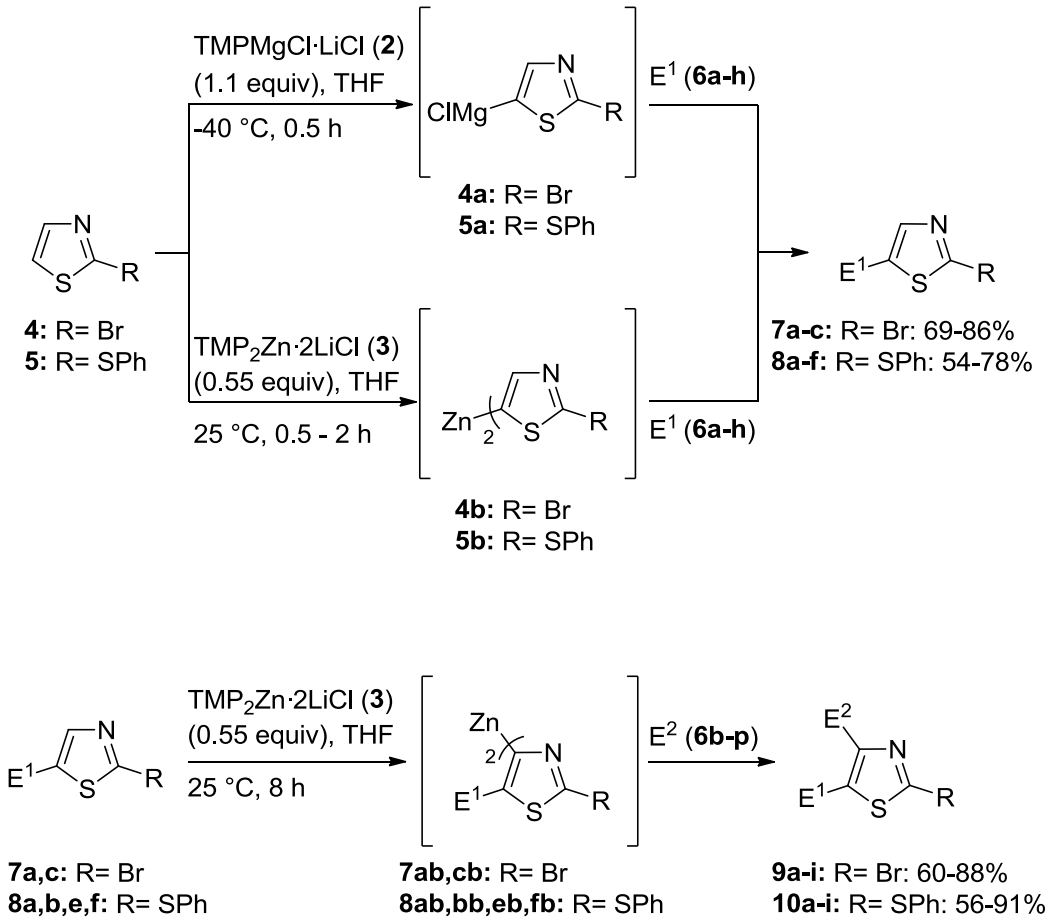
Scheme 29: Hantzsch thiazole synthesis.

Furthermore, electrophilic and nucleophilic substitution sequences or functionalizations *via* halogen dance have been described.[59]

1.2. Results and Discussions

Starting from 2-substituted thiazoles such as 2-bromothiazole (**4**) or 2-(phenylthio)-1,3-thiazole (**5**), directed metalations using TMPMgCl·LiCl[28] (**2**) or $TMP_2Zn·2MgCl_2·2LiCl$[33] (**3**, abbreviated TMP_2Zn for the sake of clarity) occurs exclusively in position 5 and leads respectively to the 5-metalated thiazoles **4a**, **5a** and **4b**, **5b** (Scheme 30). Subsequent reaction with electrophiles (**6a-h**) affords 2,5-disubstituted thiazoles **7a-c** and **8a-f** in 54–86% yield.

[59] (a) Holzweber M.; Schnürch M.; Stanetty P. *Synlett* **2007,** *19*, 3016. (b) Schnürch M.; Khan A. F.; Mihovilovic M. D.; Stanetty P. *Eur. J. Org. Chem.* **2009**, 3228. (c) Boga, C.; Del Vecchio, E.; Forlani, L.; Todesco, P. E. *J. Organomet. Chem.* **2000**, *601*, 233. (d) Roger, J.; Požgan, F.; Doucet, H. *J. Org. Chem.* **2009**, *74*, 1179. (e) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951. (f) Athmani, S.; Bruce, A.; Iddon, B. *J. Chem. Soc. Perkin Trans. 1* **1992**, 215. (g) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7996.



Scheme 30: Functionalization of the thiazole scaffold at the 5- and 4-position.

Thus, starting from readily available 2-bromothiazole **4**, a selective magnesation using TMPMgCl·LiCl (**2**, 1.1 equiv, –40 °C, 0.5 h) leads to the Grignard reagent **4a**. Alternatively, the zincated intermediate **4b** can be prepared using TMP_2Zn (**3**, 0.55 equiv, 25 °C, 0.5 h).

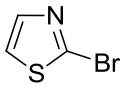
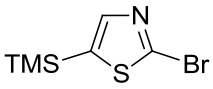
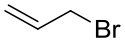
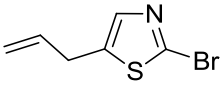
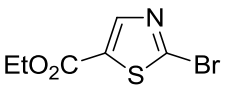
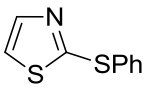
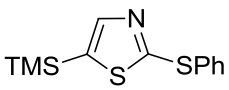
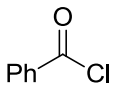
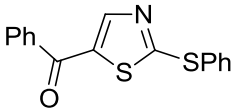
1.2.1. Functionalization of the Thiazole Scaffold at the 5-Position

The magnesated thiazole **4a** reacts with TMSCl, NC-CO_2Et or allyl bromide (20% CuCN·2LiCl[10]) furnishing the 2,5-disubstituted thiazoles **7a**–**c** in 69–86% yield (Table 1, entries 1–3). Similarly, 2-(phenylthio)-1,3-thiazole (**5**) is metalated within 0.5 h using TMPMgCl·LiCl (**2,** 1.1 equiv) at –40 °C or using TMP_2Zn (**3**, 0.55 equiv, 2 h) at 25 °C. The metalated reagent **5a** reacts with TMSCl giving 2-(phenylthio)-5-(trimethylsilyl)thiazole **8a** in 80% yield (entry 4). A Pd-catalyzed acylation[60] of **5b** (2% $Pd(PPh_3)_4$) provides the ketone **8b** in 78% yield (entry 5).

[60] Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.

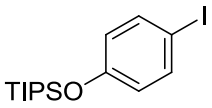
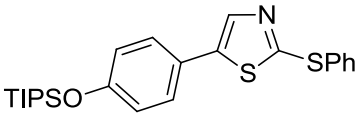
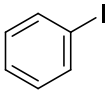
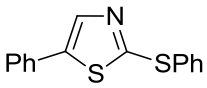
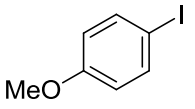
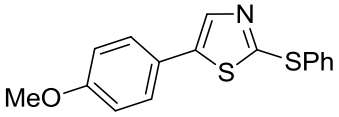
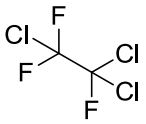
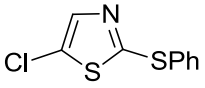
Negishi cross-coupling[61] reactions with various aryl iodides **6e**–**g** using $Pd(dba)_2$ (3%) and P(*o*-furyl)$_3$[62] (6%) afford the arylated thiazoles **8c**–**e** in 83–95% yield (entries 6–8). Chlorination with 1,1,2-trichloro-1,2,2-trifluoroethane leads to the 5-chlorinated thiazole **8f** (–50 °C, 4 h) in 54% yield (entry 9).

Table 1: Products of type **7** and **8** obtained by metalation at the 5-position of thiazoles **4** or **5** and reaction with electrophiles.

entry	substrate (metalation conditions)	electrophile E[1] (conditions)	functionalized product yield (%)[a]
1		TMSCl	
	4 (**2**, –40 °C, 30 min)	**6a** (–50 °C, 30 min)	**7a** (86)
2	**4**		
	(**2**, 25 °C, 30 min)	**6b** (0 to 25 °C, 1 h)[b]	**7b** (69)
3	**4**		
	(**2**, –40 °C, 30 min)	**6c** (25 °C, 5 h)	**7c** (80)
4		TMSCl	
	2 (**2**, –40 °C, 30 min)	**6a** (–50 °C, 30 min)	**8a** (80)
5	**5**		
	(**3,** 25 °C, 2 h)	**6d** (25 °C, 1 h)[c]	**8b** (78)

[61] (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340; (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298; (c) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

[62] (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. (c) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

6	**5**		
	(**3,** 25 °C, 2 h)	**6e** (25 °C, 3 h)[d]	**8c** (87)
7	**5**		
	(**3,** 25 °C, 2 h)	**6f** (25 °C, 1 h)[d]	**8d** (95)
8	**5**		
	(**3,** 25 °C, 2 h)	**6g** (25 °C, 3 h)[d]	**8e** (83)
9	**5**		
	(**2**, –40 °C, 30 min)	**6h** (–50 °C, 4 h)	**8f** (54)

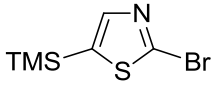
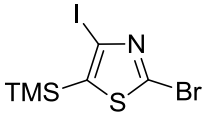
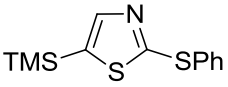
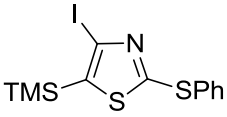
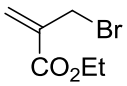
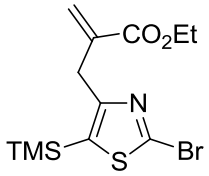
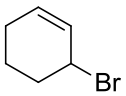
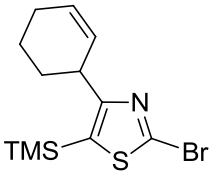
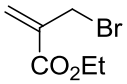
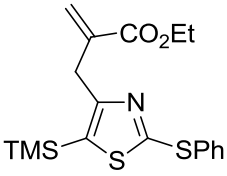
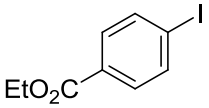
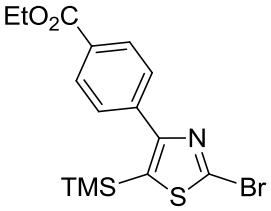
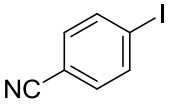
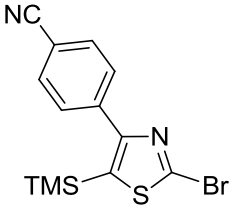
[a] Isolated yield of analytically pure product. [b] After transmetalation with 20%. CuCN·2LiCl [c] 2% $Pd(PPh_3)_4$ catalyzed acylation reaction. [d] 3% $Pd(dba)_2$, 6% P(o-furyl)$_3$ catalyzed cross-coupling reaction.

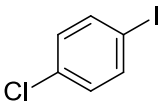
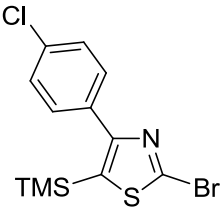
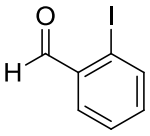
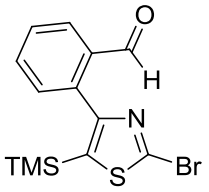
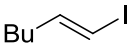
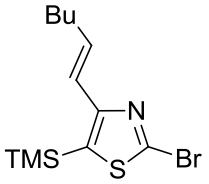
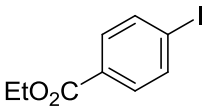
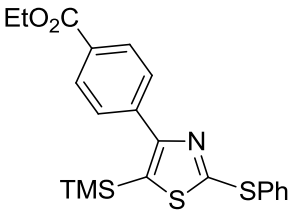
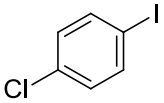
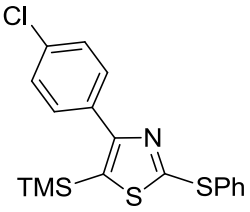
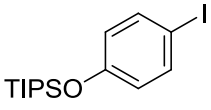
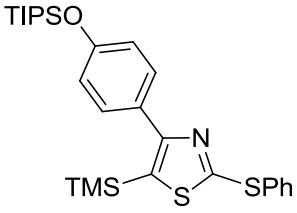
1.2.2. Functionalization of the Thiazole Scaffold at the 4-Position

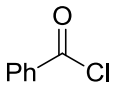
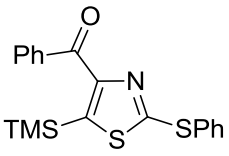
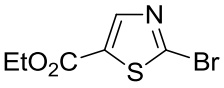
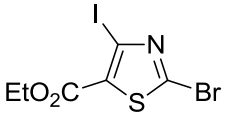
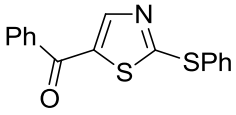
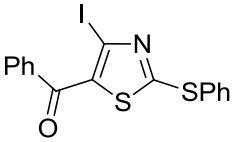
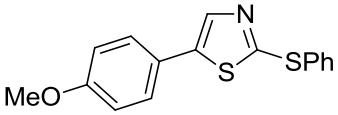
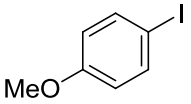
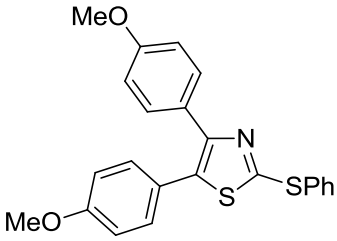
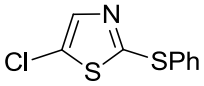
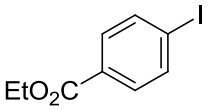
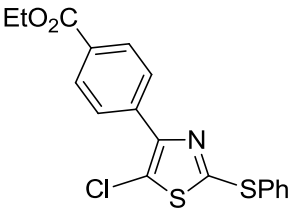
After protecting the 5-position with a TMS-group, a subsequent zincation at position 4 is achieved at 25 °C within 8 h using TMP_2Zn (**3**, 0.55 equiv, Scheme 30). The zincated species **7ab** and **8ab** react with I_2 and yield the iodinated thiazoles **9a** and **10a** in 85–86% yield (Table 2, entries 1–2). Copper(I)-catalyzed allylation (20% CuCN·2LiCl) with various allylic bromides like ethyl 2-(bromomethyl)acrylate[63] (**6j**) or 3-bromocyclohex-1-ene (**6k**) leads to the 4-allylated products **9b**-**c**, **10b** in 72–77% yield (entries 3–5). The 4-arylated and alkenylated thiazoles **9d**–**h**, **10c**–**e** are obtained by Negishi cross-coupling reactions with various aryl or alkenyl iodides (3% $Pd(dba)_2$, 6% P(*o*-furyl)$_3$) in 63–91% yield (entries 6–13). Due to oligomerization side reactions, Pd-catalyzed cross-coupling reactions of the zincated 2-bromothiazoles afford lower yields compared to the same cross-coupling reactions with the zincated 2-(phenylthio)-5-(trimethylsilyl)thiazole derivatives **7ab**. The ketone **10f** is obtained by a Pd-catalyzed acylation reaction (2% $Pd(PPh_3)_4$) with benzoyl chloride in 78% yield (entry 14).

[63] (a) Rambaud, M.; Villiéras, J. *Synthesis* **1984**, 406; (b) Villiéras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

Table 2: Products of type **9** and **10** obtained by zincation of thiazoles (**7a,c, 8a,b,e,f**) at the 4-position using TMP_2Zn (**3**) at 25 °C and reaction with electrophiles.

entry	substrate (metalation time)	electrophile E^2 (time)	functionalized product, yield (%)[a]
1		I_2	
	7a (8 h)	**6i** (10 min)	**9a** (85)
2		I_2	
	8a (8 h)	**6i** (10 min)	**10a** (86)
3	**7a**		
	(8 h)	**6j** (5 h)[b]	**9b** (72)
4	**7a**		
	(8 h)	**6k** (2 h)[b]	**9c** (77)
5	**8a**		
	(8 h)	**6j** (1.5 h)[b,c]	**10b** (77)
6	**7a**		
	(8 h)	**6l** (4.5 h)[d]	**9d** (70)
7	**7a**		
	(8 h)	**6m** (15 h)[d]	**9e** (71)

8	**7a**		
	(8 h)	**6n** (2 h)[d]	**9f** (63)
9	**7a**		
	(8 h)	**6o** (5 h)[d]	**9g** (70)
10	**7a**		
	(8 h)	**6p** (2 h)[d]	**9h** (65)[e]
11	**8a**		
	(8 h)	**6l** (3 h)[d]	**10c** (91)
12	**8a**		
	(8 h)	**6n** (6 h)[d]	**10d** (73)
13	**8a**		
	(8 h)	**6e** (20 h)[d,f]	**10e** (76)

14	**8a**		
	(8 h)	**6d** (3 h)[g]	**10f** (78)
15		I_2	
	7c (2 h)	**6i** (10 min)	**9i** (60)
16		I_2	
	8b (8 h)	**6i** (10 min)	**10g** (70)
17			
	8e (2 h)	**6g** (2 h)[d]	**10h** (80)
18			
	8f (2 h)	**6l** (0.5 h)[d]	**10i** (88)

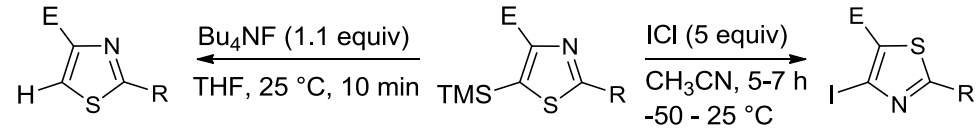
[a] Isolated yield of analytically pure product. [b] After transmetalation with 20%.- 100% CuCN·2LiCl. [c] At 0–25 °C. [d] 3% $Pd(dba)_2$, 6% P(o-furyl)$_3$ catalyzed cross-coupling reaction. [e] Exclusively the *E*-isomer was observed. [f] At 40 °C. [g] 2 % $Pd(PPh_3)_4$ catalyzed acylation reaction.

Interestingly, using TMP_2Zn (**3**), a regioselective zincation at the 4-position of thiazoles bearing an ester, an aryl or a halogen group (**7b**,**8b,e,f**) is achieved leading to the corresponding zincated thiazoles (**7cb** and **8bb,eb,fb**). The reaction with various electrophiles provides the 4,5-disubstituted thiazoles in 60–88% yield (entries 15–18). Thus, iodination affords the 4-iodinated thiazoles **9i** and **10g** in 60–70% yield (entries 15–16). Pd-catalyzed cross-coupling reactions with aryl iodides lead to the trisubstituted thiazoles **10h**–**i** in 80–88% yield (entries 17–18).

1.2.3. Deprotection of the TMS-Group with Bu_4NF or ICl

Deprotection of the TMS-group with TBAF provides the 2,4-difunctionalized thiazoles **11a**–**c** and **12** in 80–90% yield (Table 3, entries 1–4). Alternatively, by the addition of ICl[64] the 5-iodinated thiazoles **13a**–**c** (entries 5–7) are obtained in 77–92% yield. These heterocyclic iodides can be further used as electrophiles in Pd-catalyzed cross-coupling reactions.[59, 65]

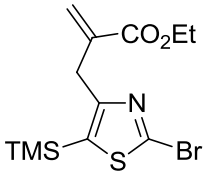
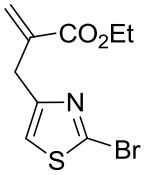
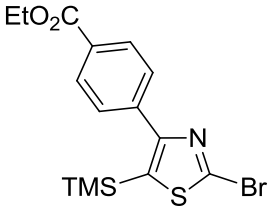
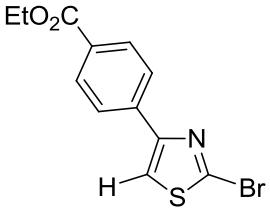
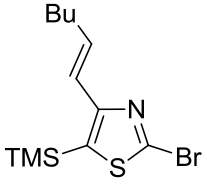
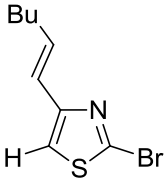
Table 3: Products of type **11**, **12** and **13** obtained by transformations of silylated thiazoles of type **8**, **9** and **10**.



11a-c: R= Br: 85-90%
12: R= SPh: 80%

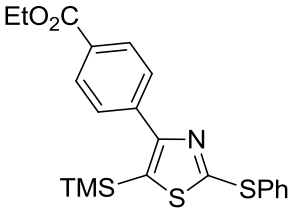
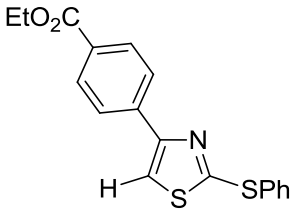
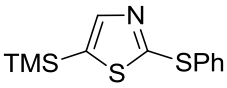
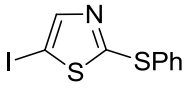
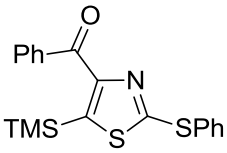
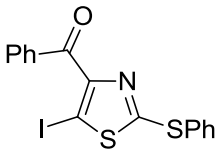
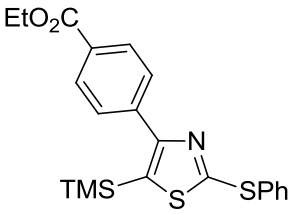
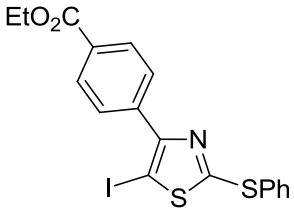
9b,d,h: R= Br
8a,10c,d: R= SPh

13a-b: R= SPh 77-92%

entry	substrate	reagent (conditions)	deprotected product, yield (%)[a]
1		Bu_4NF	
	9b	(25 °C, 10 min)	**11a** (80)
2		Bu_4NF	
	9d	(25 °C, 10 min)	**11b** (90)
3		Bu_4NF	
	9h	(25 °C, 10 min)	**11c** (85)

[64] Felix G.; Dunogues J.; Calas R. *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 402.

[65] (a) Jiang, P.; Morales, G. M.; You, W.; Yu L. *Angew. Chem. Int. Ed.* **2004**, *43*, 4471. (b) Khan, A. F.; Schnürch, M.; Mihovilovic, M. D.; Stanetty, P. *Lett. Org. Chem.* **2009**, *6*, 171.

4		Bu_4NF	
	10d	(25 °C, 10 min)	**12** (80)
5		ICl	
	8a	(25 °C, 3 h)	**13a** (77)
6		ICl	
	10g	(–50 to 25 °C, 5 h)	**13b** (92)
7		ICl	
	10c	(–50 to 25°C, 7 h)	**13c** (92)

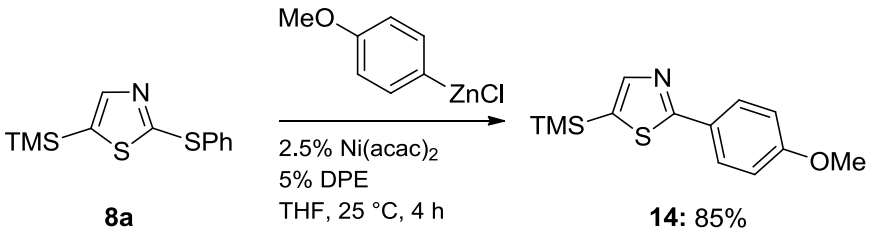
[a] Isolated yield of analytically pure product.

1.2.4. Further Functionalization of the Thiazole Scaffold

The 2-phenylthio thiazoles undergo further cross-coupling reaction at the position 2 with various organometallic reagents.[66] Thus, the Ni-catalyzed cross-coupling reaction of the disubstituted

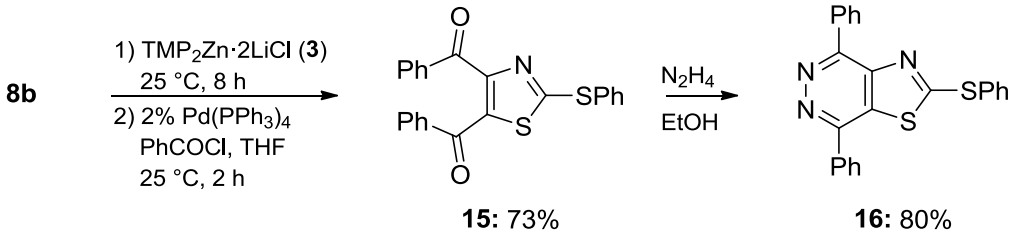
[66] (a) Melzig, L.; Metzger, A.; Knochel, P. *Chem. Eur. J.* **2011**, *17*, 2948. (b) Melzig, L.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 2131. (c) Metzger, A.; Melzig, L.; Knochel, P. *Synthesis*, **2010**, *16*, 2853. (d) Metzger, A.; Melzig, L.; Despotopoulou, C.; Knochel, P. *Org. Lett.* **2009**, *11*, 4228. (e) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. (f) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (g) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803. (h) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Synlett* **2002**, *3*, 447.

thiazole **8a** using 2.5% $Ni(acac)_2$, 5% DPE[67] and (4-methoxyphenyl)zinc chloride affords the thiazole **14** at 25 °C within 4 h in 85% yield (Scheme 31).



Scheme 31: Ni-catalyzed cross-coupling of the 2-phenylthio thiazole (**7a**).

Thiazolopyridazines are known for their useful biological properties.[68] They are readily obtained by cyclization of 4,5-diketothiazoles with hydrazine hydrate. Starting from the 5-keto-thiazole **8b** a direct metalation with TMP_2Zn (**3**) affords the zincated thiazole at 25 °C within 8 h (Scheme 32). The resulting zinc organometallic undergoes a Pd-catalyzed acylation reaction with benzoyl chloride (2% $Pd(PPh_3)_4$) furnishing the trisubstituted thiazole **15** in 73% yield. A smooth cyclization occurs when **15** is treated with hydrazine hydrate (25 °C, 10 min) leading to the functionalized thiazolopyridazine **16** in 80% yield.



Scheme 32: Preparation of a functionalized thiazolopyridazine (**16**) from the thiazole **8b**.

[67] Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; Goubitz, k.; Fraanje, J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

[68] (a) Klein, M.; Sandner, P.; Frey, R.; Riedl, B.; Christensen, O. WO 2007118602, **2007**. (c) Simiti, I.; Coman, M. *Arch. Pharm.* **1983**, *316*, 1013. (c) Makki, M. S. I.; Faidallah, H. M. *J. Chin. Chem. Soc.* **1996**, *43*, 433.

2. Oxidative Amination of Heteroaromatic Zinc Reagents Mediated by $PhI(OAc)_2$

2.1. Introduction

Heteroaromatics belong to one of the most important classes of compounds in medicinal chemistry.[69] Especially amines containing five-membered heteroaryl groups such as furans, thiophenes, thiazoles, and pyrazoles are widely found in both natural products and drugs.[70] Whereas the direct amination of six-membered heterocyclic halides proceeds even uncatalyzed at high temperatures or high pressure,[71] the amination of five-membered heteroaromatics has been hampered for a long time. However, due to the work of *Buchwald* and *Hartwig* and others on Pd-catalyzed aminations,[36,37] many functional five- and six-membered heterocylic amines are nowadays available.[72] Nonetheless, these protocols still have some limitations, such as long reaction times and the use of strong bases. In addition, some functional groups such as iodides and bromides are not compatible with this Pd-catalyzed amination procedure. Thus, the development of other mild and general methods for the amination of heteroaromatics is still an important goal.
Recently, the oxidative amination of arylcopper reagents[43,44] starting from organomagnesium reagents furnishing primary, secondary, and tertiary amines using chloranil as an oxidation reagent was described.[45] For the oxidative amination of heterocyclic copper derivatives obtained by transmetalation from zinc organometallics, the use of chloranil was unsatisfactory. Furthermore, the scale-up of such aminations was difficult with this oxidation reagent. Thus, the use of $PhI(OAc)_2$ as oxidation reagent[73] gave superior results.

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[69] (a) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; John Wiley & Sons: Weinheim, 1997. (b) Wipf, P.; Wang, Z. *Org. Lett.* **2007,** *9*, 1605.

[70] (a) Metzger, J. V. *Thiazole and its Derivatives*; John Wiley & Sons: New York, 1979. and references therein. (b) Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197. (c) Walcynski, K.; Guryn, R.; Zuiderveld, O. P.; Timmermann, H. *Il Farmaco* **1999**, *54*, 684.

[71] Kosuki, H.; Sakai, H.; Shinohara, T. *Synlett* **2000**, *1*, 116.

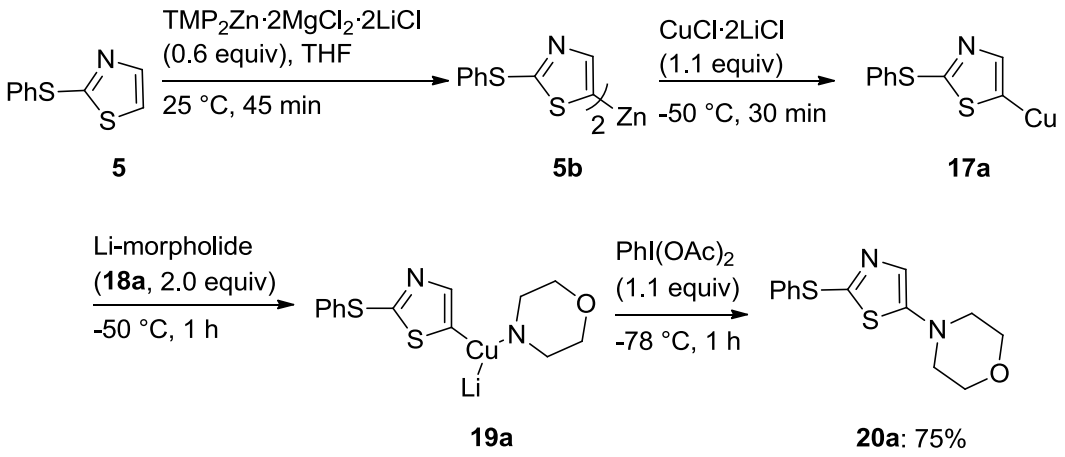
[72] (a) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861. (b) Hooper, M. W.; Hartwig, J. F. *Organometallics* **2003**, *22*, 3394. (c) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965. (d) Reddy, C. V.; Kingston, J. V.; Verkade, J. G. *J. Org. Chem.* **2008**, *73*, 3047. (e) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109. (f) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586.

[73] For an excellent overview of hypervalent iodine compounds, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. For recent reports, see: (b) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulisa, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (c) Kar, A.; Mangu, N.; Kaiser, H. M.; Tse, M. K. *J. Organomet. Chem.*

2.2. Results and Discussions

2.2.1. Oxidative Amination of Zincated Heterocycles Obtained by Metalation with $TMP_2Zn·2MgCl_2·LiCl$

Thiazole derivatives containing an amino function in position 4 or 5 can be obtained either from *R*-thiocyanonitriles[58e,f] or *via* the Cornforth rearrangement.[74] Thus, 2-(phenylthio)thiazole (**5**) is zincated using $(TMP)_2Zn$ (**3**, 0.55 equiv) at 25 °C within 2 h furnishing the diarylzinc compound **5b**. After the addition of CuCl·2LiCl (1.1 equiv) the corresponding copper derivative **17a** is obtained. Further addition of *N*-lithium morpholide (**18a**, 2.0 equiv) affords the amidocuprate **19a**. The subsequent oxidation of **19a** using $PhI(OAc)_2$ (1.1 equiv) provides the thiazole amine derivative **20a** in 82% yield with only traces of the corresponding homocoupling product as byproduct (Scheme 33).



Scheme 33: Zincation of 2-(phenylthio)thiazole (**5**) with TMP_2Zn (**3**) followed by an oxidative amination reaction.

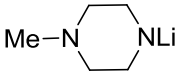
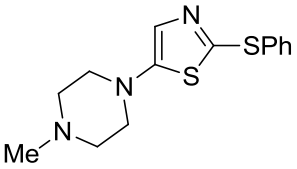
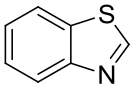
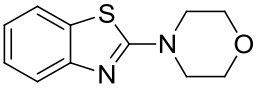
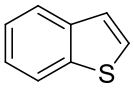
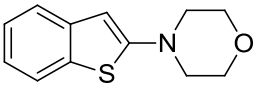
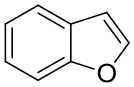
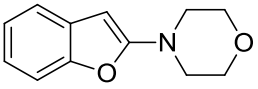
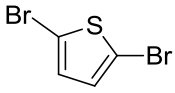
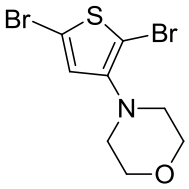
A range of thiazoles and other heterocycles can be aminated following this procedure in 60-75% yield (Table 4). Thus, the copper derivative **17a** also reacts with *N*-lithium *N*′-methylpiperazide (**18b**), leading to the tertiary amine **20b** in 72% yield, respectively (entry 1). These phenylthio thiazoles are useful intermediates since the phenylthio group can serve as a leaving group in

2009, *694*, 524. (d) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558. For the synthesis and application of related hypervalent iodine compounds, see: (e) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610. (f) Bielawski, M.; Olofsson, B. *Org. Synth.* **2009**, *86*, 308.

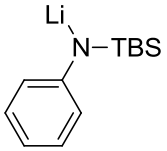
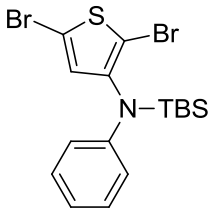
[74] Corrao, S. L.; Macielag, M. J.; Turchi, I. J. *J. Org. Chem.* **1990**, *55*, 4484.

cross-coupling reactions.[66] Benzo[*d*]thiazole (**21a**) and benzo[*b*]thiophene (**21b**) are aminated with *N*-lithium morpholide (**18a**) furnishing the 2-benzo[*d*]thiazole and 2-benzo[*b*]thiophene amines **20c** and **20d** in 73% yield (entries 2-3). Benzofuran (**21c**) as well as 2,5-dibromothiophene (**21d**) are zincated using microwave irradiation (100 °C, 1 h)[75] followed by an oxidative amination, yielding the corresponding amines **20e-g** in 60-70% yield (entries 4-6).

Table 4: Oxidative amination of heterocycles after zincation with TMP_2Zn (**3**).

entry	substrate (metalation conditions)	lithium amide	product, yield (%)[a]
1	**5**		
	(25 °C, 2 h)	**18b**	**20b** (72)
2		**18a**	
	21a (25 °C, 1 h)		**20c** (73)
3		**18a**	
	21b (25 °C, 24 h)		**20d** (73)
4		**18a**	
	21c (100 °C, 1 h, mw)		**20e** (60)
5		**18a**	
	21d (100 °C, 1 h, mw)		**20f** (70)

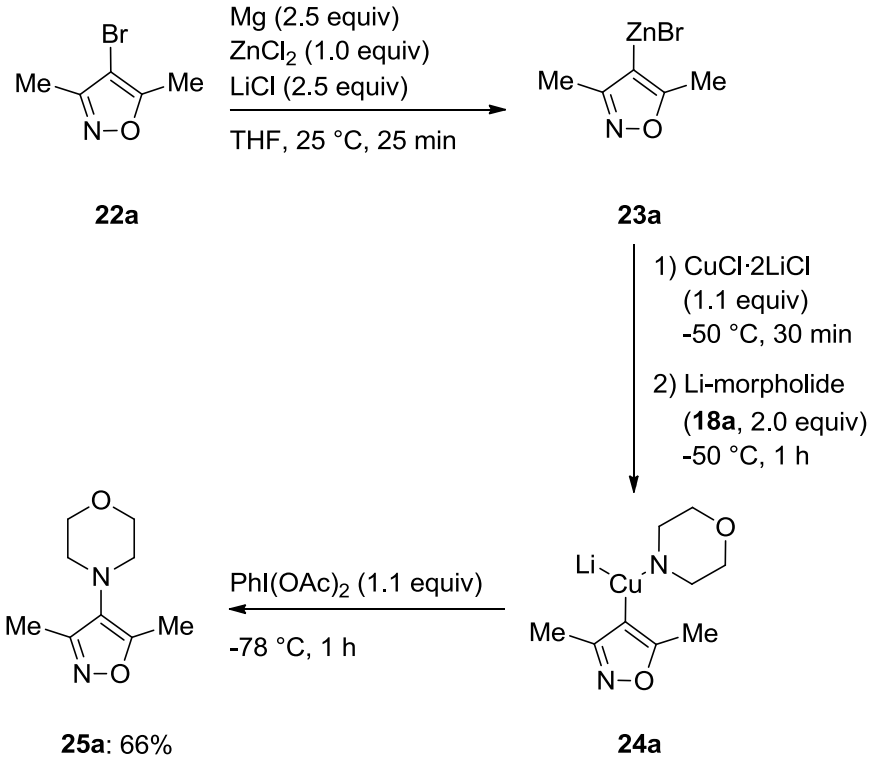
[75] For microwave accelerated zincations, see: Wunderlich, S.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705.

6	**21d**		
	(100 °C, 1 h, mw)	**18c**	**20g** (67)

[a] Isolated yield of analytically pure product.

2.2.2. Oxidative Amination of Zincated Heterocycles Obtained by Mg Insertion in the Presence of LiCl and ZnCl

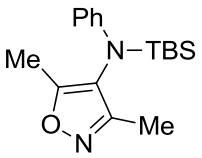
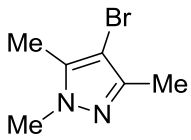
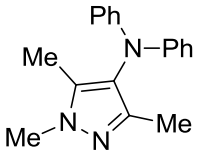
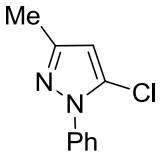
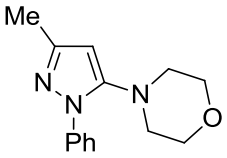
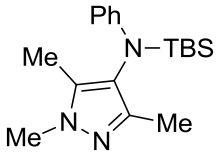
This amination method can be applied to several zincated heterocycles obtained by a Mg insertion in the presence of $ZnCl_2$ and LiCl.[14] Thus, 4-bromo-3,5-dimethylisoxazole (**22a**) is treated with Mg turnings (2.5 equiv) in the presence of LiCl (2.5 equiv) and $ZnCl_2$ (1 equiv), furnishing the zinc species **23a** at 25 °C within 0.25 h. After transmetalation with CuCl·2LiCl (1.1 equiv) and the addition of *N*-lithium morpholide (**18a**, 2.0 equiv), the amidocuprate **24a** is obtained. Oxidation of **24a** using $PhI(OAc)_2$ (1.1 equiv) leads to the desired tertiary amine **25a** in 66% yield (Scheme 34).

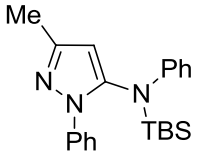


Scheme 34: Mg insertion in the presence of LiCl and $ZnCl_2$ and subsequent oxidative amination.

This zinc derivative **23a** also reacts with the TBDMS-protected amide (**18c**) (after transmetalation with CuCl·2LiCl), leading to the tertiary amine **25b** in 60% yield, respectively (Table 5, entry 1). Other heterocycles such as **22c** and **d** can also be converted to the corresponding zinc compounds by the previous described Mg insertion in the presence of $ZnCl_2$ at 25 °C within 0.25–1 h. These zinc reagents are aminated by the oxidative amination, yielding the tertiary amines **25e-f** in 60-70% yield (entries 2-3). Using this protocol, it is possible to prepare various protected secondary amines. After zincation of the corresponding heteroaromatics **22b** and **c** and subsequent oxidative amination, the TBDMS-protected diarylamines **25g-h** are obtained in 66-70% yield (entries 4-5).

Table 5: Oxidative amination of zinc reagents obtained by Mg insertion in the presence of $ZnCl_2$.

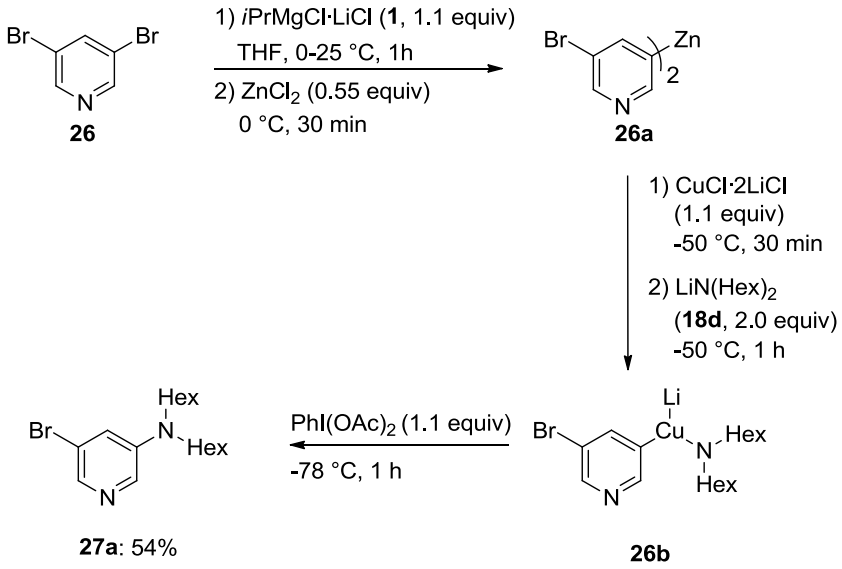
entry	substrate (metalation conditions)[a]	lithium amide	product, yield (%)[a]
1	**22a**	**18c**	
	(25 °C, 0.25 h)		**25b** (60)
2		$LiNPh_2$	
	22b (25 °C, 0.25 h)	**18d**	**25c** (70)
3		**18a**	
	22c (25 °C, 0.25 h)		**25d** (60)
4	**22b**	**18c**	
	(25 °C, 1 h)		**25e** (66)

5	**22c**	**18c**	
	(25 °C, 1 h)		**25f** (70)

[a] Isolated yield of analytically pure product.

2.2.3. Oxidative Amination of Zincated Heterocycles in Large Scale

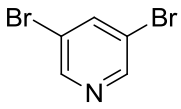
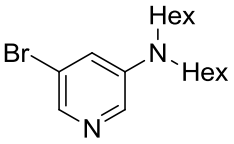
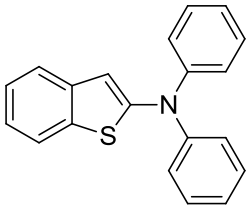
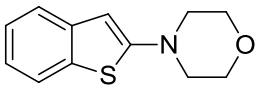
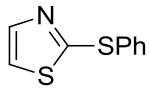
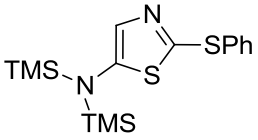
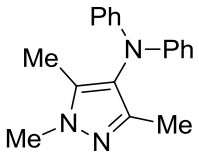
Furthermore, the previously described zinc reagents are suitable for large-scale oxidative amination reactions, regardless if the zinc reagent is formed by metalation using TMP_2Zn (**4**), by Mg insertion in the presence of $ZnCl_2$ or by addition of a $ZnCl_2$ solution to a preformed Grignard reagent. Thus, the treatment of 3,5-dibromopyridine (**26**, 10 mmol) with *i*PrMgCl·LiCl (**1**) and subsequent addition of $ZnCl_2$ (0.55 equiv) provides the corresponding zinc reagent **26a**. Addition of CuCl·2LiCl (1.1 equiv) and reaction with lithium *N*,*N*-dihexylamide (**18d**) furnishes the amidocuprate **26b**. Oxidation of **26b** using $PhI(OAc)_2$ leads to the desired triarylamine **27a** in 54% yield (Scheme 35).



Scheme 35: Oxidative amination of 3,5-dibromopyridine (**26**) mediated by $PhI(OAc)_2$ on a 10 mmol scale.

After zincation of benzo[*b*]thiophene (**21b**) and 2-(phenylthio)-1,3-thiazole (**5**) with TMP_2Zn (**3**) the corresponding zinc species is also smoothly aminated on a 10 mmol scale, furnishing the desired amines **20d** and **27b,c** in 60-75% yield (Table 6, entries 2-4). The best results were obtained when only 0.55 equiv of $ZnCl_2$ was used. Nonetheless, zinc reagents obtained by magnesium insertion in the presence of $ZnCl_2$ and LiCl,[14] therefore containing 1 equiv of $ZnCl_2$, are also well suited for these larger scale reactions. Thus, the previously described amination of **22b** on a 10 mmol scale furnishes the tertiary amine **25c** in 66% yield (entry 5; compared to 70% yield on a 1 mmol scale, Table 5, entry 3).

Table 6: Oxidative amination of zinc reagents on a 10 mmol scale.

entry	substrate	metalation (conditions)	lithium amide	product, yield (%)[a]
1		*i*PrMgCl·LiCl	$LiN(Hex)_2$	
	26	**1**, 25 °C, 1 h	**18e**	**27a** (54)
2	**21b**	TMP_2Zn	**18d**	
		3, 25 °C, 24 h		**27b** (60)
3	**21b**	**3**	**18a**,	
		25 °C, 24 h		**20d** (75)
4		**3**	$LiN(TMS)_2$	
	5	25 °C, 2 h	**18f**	**27c** (63)
5	**22b**	Mg, $ZnCl_2$, LiCl	$LiNPh_2$	
		25 °C, 0.25 h	**18d**	**25c** (66)

[a] Isolated yield of analytically pure product.

3. Efficient Preparation of Polyfunctional Organometallics *Via* Directed *Ortho*-Metalation Using TMP-Bases of La, Mn and Fe

3.1. Introduction

The metalation of functionalized unsaturated substrates provides useful intermediates in organic synthesis. Besides traditional and well investigated Li-reagents,[76] a number of mixed ate-bases have been developed und structurally investigated.[77] Although these efforts seemed to be promising, there is still a need for neutral and easily manageable chemoselective bases for the metalation of organic substrates. Recently, it was reported that the treatment of TMPMgCl·LiCl[28] (**2**) with metallic chlorides such as $ZnCl_2$,[33] $MnCl_2$·2LiCl,[78] $FeCl_2$·2LiCl[79] and $LaCl_3$·2LiCl[80] leads to room temperature stable and kinetically highly active metalation reagents. The metalations occur under mild conditions (usually close to 25 °C) and display a high atom

[76] (a) Snieckus, V. *Chem. Rev*. **1990**, *90*, 879. (b) Whisler, M. C.; MacNeil, S.; Beak, P.; Snieckus, V. *Angew. Chem. Int. Ed*. **2004**, *43*, 2206. (c) Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376. (d) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. (e) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. (f) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev*. **2005**, *105*, 827. (g) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667.

[77] (a) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatley, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc*. **2007**, *129*, 1921. (b) Uchiyama, M.; Kobayashi, Y.; Furuyama, T.; Nakamura, S.; Kajihara, Z.; Miyoshi, T.; Sakamoto, T.; Kondo, Y.; Morokuma, K. *J. Am. Chem. Soc*. **2008**, *130*, 472. (c) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc*. **2007**, *129*, 15102. (d) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595. (e) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602. (f) L'Helgoual'ch, J-M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177. (g) Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E.; O'Hara, C. T.; Russo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 731. (h) Alborés, P.; Carrella, L.; Clegg, W.; García-Álvarez, P.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; Rentschler, E.; Russo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 3317. (i) Mulvey, R. E. *Acc. Chem. Res.* **2009**, *42*, 743. (j) Carrella, L. M.; Clegg, W.; Graham, D. V.; Hogg, L. M.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; Rentschler, E.; Russo, L. *Angew. Chem. Int. Ed.* **2007,** *46*, 4662. (k) Blair, V. L.; Clegg, W.; Conway, B.; Hevia, E.; Kennedy, A.; Klett, J.; Mulvey, R. E.; Russo, L. *Chem. Eur. J*. **2008**, *14*, 65. (l) Blair, V. L.; Carrella, L. M.; Clegg, W.; Conway, B.; Harrington, R. W.; Hogg, L. M.; Klett, J.; Mulvey, R. E.; Rentschler, E.; Russo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6208. (m) Blair, V. L.; Carrella, L. M.; Clegg, W.; Klett, J.; Mulvey, R. E.; Rentschler, E.; Russo, L. *Chem. Eur. J*. **2009**, *15*, 856.

[78] Wunderlich, S. H.; Kienle, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.

[79] Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.

[80] Wunderlich, S. H.; Knochel, P. *Chem. Eur. J*. **2010**, *16*, 3304.

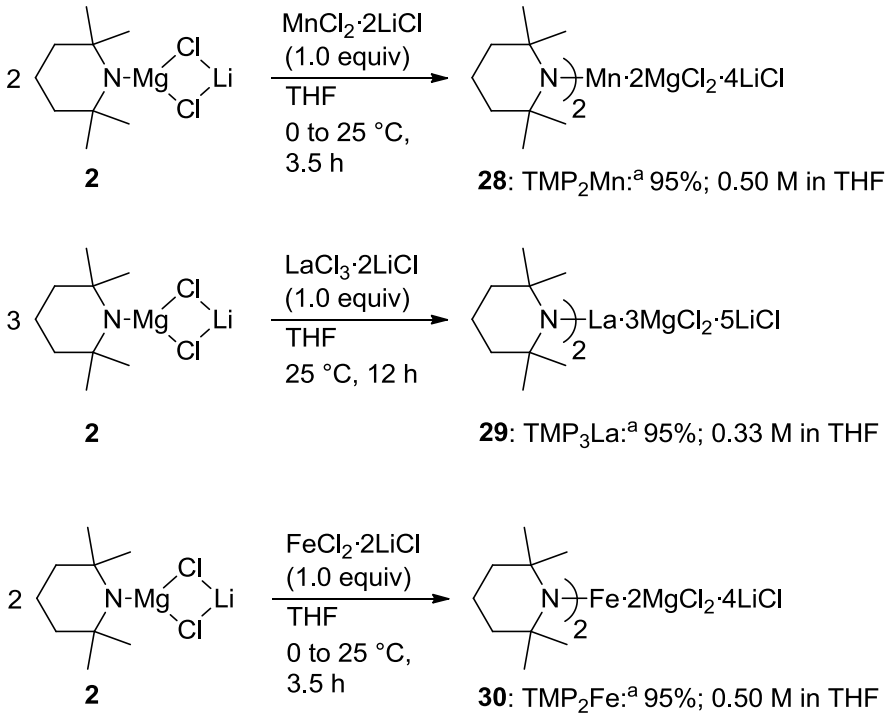
economy since all TMP moieties are used for the directed metalation. The resulting organometallics can contain a variety of functional groups and they react with a number of electrophiles (in the presence of an appropriate catalyst if needed). Furthermore, changing the metal of the amide-bases also changes the behavior of the corresponding organometallic reagent. Usually, the optimization of these metalation procedures was carried out in 1-2 mmol scale. Thus, the preparation of functionalized organometallics using metalation reagents of Mn, Fe, La to experiments in larger scales (approx. 3-4 g scale) was investigated.

3.2. Results and Discussion

The amide bases **28-30** are efficiently prepared by the transmetalation of TMPMgCl·LiCl (**2**; Scheme 36). Thus, the reaction of TMPMgCl·LiCl (**2;** 2.0 equiv) with a solution of $MnCl_2 \cdot 2LiCl$[81] (1 M in THF) provides the reagent $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**28**) in >95% yield by stirring the mixture for 30 min at 0 °C and further for 3 h at 25 °C. Similarly, the new Fe(II)-base $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**29**) is obtained by the similar reaction of TMPMgCl·LiCl (**2**; 2 equiv) with a solution of $FeCl_2 \cdot 2LiCl$ (1 M in THF). Additionally, $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**30**) is prepared by the reaction of TMPMgCl·LiCl (**2**; 3.0 equiv) with the THF soluble complex $LaCl_3 \cdot 2LiCl$[82] in THF for 12 h. All three bases can be stored at 25 °C under inert gas atmosphere for at least 2 months without decomposition.

[81] Solinas, I.; Lutz, H. D. *J. of Solid State Chem.* **1995**, *117*, 34.

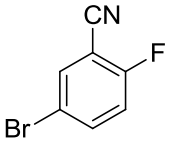
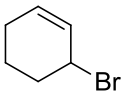
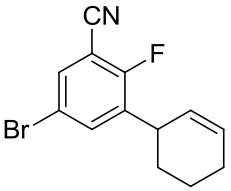
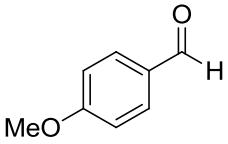
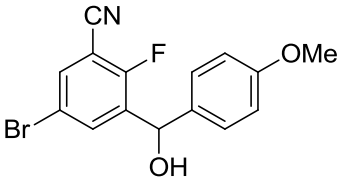
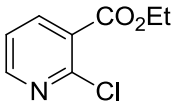
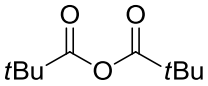
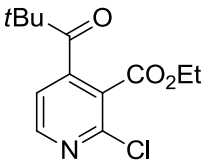
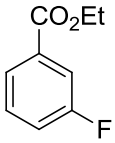
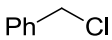
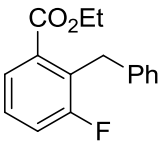
[82] (a) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497. (b) Metzger, A.; Gavryushin, A.; Knochel, P. *Synlett* **2009**, 1433.



Scheme 36: Preparation of the amide bases of Mn, Fe and La. [a]LiCl and $MgCl_2$ have been omitted for the sake of clarity.

Thus, the metalation of 5-bromo-2-fluoro-benzonitrile (**31a**) with TMP_2Mn (**28**, 0.6 equiv) is achieved in position adjacent to the fluorine substituent and is completed within 0.5 h at 0 °C. A CuCN·2LiCl catalyzed allylation with 3-bromo cyclohexene furnishes the 1,2,3,5-tetrasubstituted arene **32a** in 96% yield (Table 7, entry 1). Furthermore, 5-bromo-2-fluorobenzonitrile (**31a**) can also be metalated with TMP_3La (**29**, 0.35 equiv) at -35 °C within 0.5 h. Subsequent reaction with 4-methoxybenzaldehyde furnishes the alcohol **32b** in 80% yield (entry 2). Moreover, the fully metalated ethyl 2-chloronicotinate (**31b**) is obtained after 45 min at –20 °C using TMP_3La (**29**; 0.35 equiv). Subsequent acylation with 2,2-dimethylpropanoic anhydride provides the highly functionalized pyridine **32c** in 80% yield (entry 3). Furthermore, the metalation of ethyl 3-fluorobenzoate (**31c**) with TMP_2Fe (**30**) leads to the fully ferrated arene at 25 °C within 3 h. Subsequent reaction with benzyl chloride affords the substituted diphenylmethane **32d** in 85% yield (entry 4).

Table 7: Metalation of aromatics and heteroaromatics using TMP-bases of Mn, La and Fe.

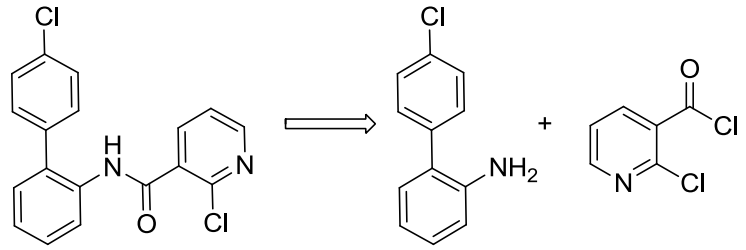
entry	substrate	TMP-base (conditions)	electrophile (conditions)	product, yield (%)[a]
1		$TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$		
	31a	**28**, 0 °C, 0.5 h	-30–25 °C, 12 h[b]	**32a** (96)
2	**31a**	$TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$		
	7	**29**, -35 °C, 0.5 h	-35–25 °C, 12 h	**32b** (80)
3		**29**		
	31b	-20 °C, 0.75 h	-20–25 °C, 12 h	**32c** (80)
4		$TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$		
	31c	**30**, 25 °C, 3 h	25 °C, 12 h	**32d** (85)

[a] Isolated yield of analytically pure product. [b] After transmetalation with CuCN·2LiCl (20%).

4. Selective Mg Insertion into Substituted Mono- and Di-Chloro Arenes in the Presence of LiCl. A new Preparation of Boscalid.

4.1. Introduction

The use of substituted aryl chlorides as starting materials for the preparation of organometallic intermediates is of interest since they are inexpensive and usually commercially available (compared to the corresponding aryl iodides or bromides). Of special interest is the preparation of Grignard reagents derived from substituted di- or trichloro-arenes. Such organometallics may react further with various electrophiles and provide aromatic derivatives of biological interest such as boscalid (**33**) which controls different plant pathogens in horticultural crops.[83a] A retrosynthesis of boscalid (**33**) requires an efficient preparation of the aniline (**34**). The nicotinyl chloride (**35**) is readily available (Scheme 37).[83] The biphenyl (**34**) may be readily prepared using a 4-chloro-substituted Grignard reagent.



33: Boscalid **34** **35**

Scheme 37: Retrosynthesis of boscalid (**33**).

Several procedures starting from chloro-substituted aromatics affording the corresponding Grignard reagents have already been described.[84] The use of Rieke-Mg which is prepared from

[83] (a) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (b) Glasnov, T. N.; Kappe, C. O. *Adv. Synth. Catal.* **2010**, *352*, 3089. (c) Felpin, F.-X.; Fouquet, E.; Zakri, C. *Adv. Synth. Catal.* **2009**, *351*, 649. (d) Wetzel, A.; Ehrhardt, V.; Heinrich, M. R. *Angew. Chem.* **2008**, *120*, 9270. (d) Spivey, A. C.; Tseng, C.-C.; Hannah, J. P.; Gripton, C. J. G.; de Fraine, P.; Parr, N. J.; Scicinski, J. J. *Chem. Commun.* **2007**, 2926. (e) Eicken, K.; Goetz, N.; Harreus, A.; Ammermann, E.; Lorenz, G.; Rang, H. (BASF SE, Ludwigshafen), European Patent EP0545099, **1993**.

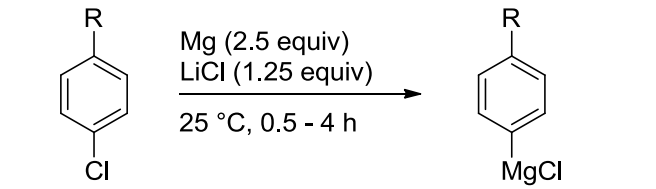
[84] (a) Ramsden, H. E.; Balint, A. E.; Whitford, W. R.; Walburn, J. J.; Cserr, R. *J. Org. Chem.* **1957**, *22*, 1202. (b) Sell, M. S.; Hanson, M. V.; Rieke, R. D. *Synth. Commun.* **1994**, *24*, 2379. (c) Review: Lai, Y.-H. *Synthesis*, **1981**, 585.

$MgCl_2$ and lithium naphthalenide (20 mol%) undergoes insertion to various aryl halides under especially mild conditions.[12]

Recently, a new LiCl-mediated Mg insertion into aryl and heteroaryl chlorides was described in the literature.[14] The presence of LiCl considerably facilitates the Mg insertion and allows the use of low reaction temperatures in large-scale preparations of organomagnesium reagents. Furthermore, LiCl is an inexpensive salt which may often also be used in catalytic amounts (30–50 mol%).

4.2. Results and Discussions

The reaction of various 4-substituted chloro arenes of type **36** with Mg (2.5 equiv) and LiCl (1.25 equiv) is complete within a few hours at 25 °C (Scheme 38). Control experiments performed without LiCl showed much lower rates for the magnesium insertion. Interestingly, 1,4-dichlorobenzene (**36a**) affords selectively the mono-insertion magnesium reagent **37a** in 74% yield.[85] Also, the aryl chlorides **36b**,**c** bearing a F- or an OTIPS-substituent in *para* position undergo clean insertion reactions leading to the desired organomagnesium compounds **37b**,**c** in 64–65% yield.



36a: R = Cl
36b: R = F
36c: R = OTIPS

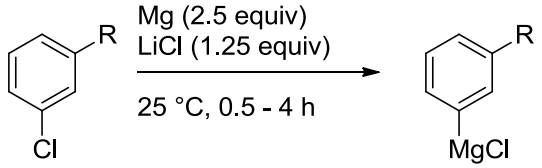
37a: R = Cl; 74%
37b: R = F; 65%
37c: R= OTIPS; 64%

Scheme 38: Mg insertion into *para*-substituted aryl chlorides (**36a-c**).

Similarly, 3-substituted aryl chlorides of type **38** react with Mg turnings and LiCl to give the Grignard reagents **39a-c** (Scheme 39). The reaction conversions are complete within 0.5–4 h. Therefore, (3-chlorophenyl)magnesium chloride **39a**, (3-fluoro-phenyl)magnesium chloride **39b**

[85] The yields of the Grignard reagents were determined by titration using I_2: Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.

and (3-((triisopropyl-silyl)oxy)phenyl)magnesium chloride **39c** are prepared from the *meta* substituted aryl chlorides **38a-c** in 60–74% yield.

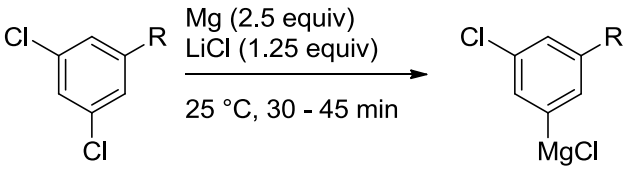


38a: R = Cl
38b: R = F
38c: R = OTIPS

39a: R = Cl; 72%
39b: R = F; 60%
39c: R= OTIPS; 74%

Scheme 39: Mg insertion into *meta*-substituted aryl chlorides (**38a-c**).

Additionally, the magnesium insertion into substituted 1,3-dichlorobenzenes of type **40** is performed in less than 1 h (Scheme 40). The magnesium reagents substituted with a chlorine, fluorine or (triisopropyl-silyl)oxy group **41a-c** are obtained in 67–80% yield. Double magnesium insertion in 1,3,5-trichlorobenzene is not observed.



40a: R = Cl
40b: R = F
40c: R = OTIPS

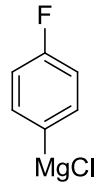
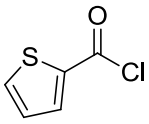
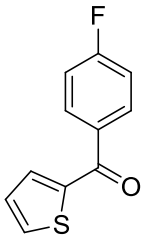
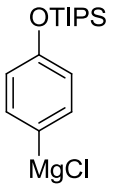
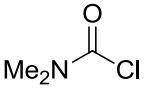
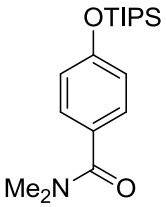
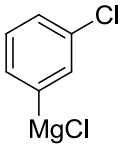
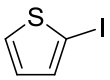
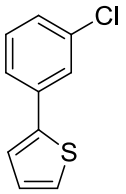
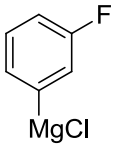
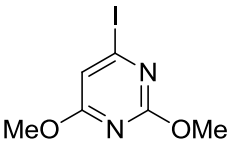
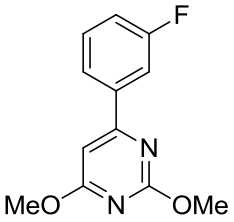
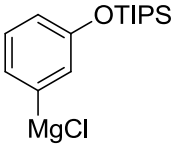
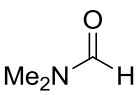
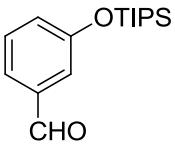
41a: R = Cl; 73%
41b: R = F; 67%
41c: R= OTIPS; 80%

Scheme 40: Mg insertion in *meta*-substituted 1,3-dichloroarenes (**40a-c**).

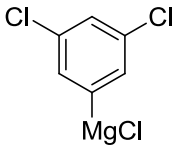
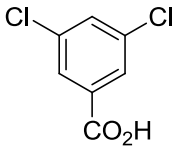
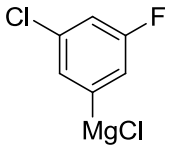
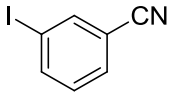
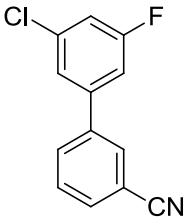
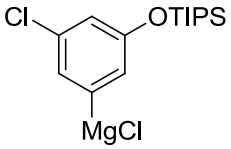
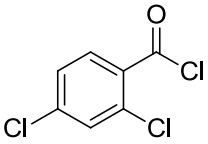
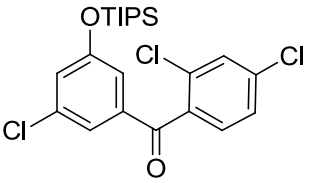
The freshly prepared magnesium reagents react with the usual electrophiles (Table 8). Thus, acylation of **37b** in the presence of CuCN·2LiCl (1.1 equiv) with thiophene-2-carbonyl chloride (**42a**) gives the ketone **43a** in 73% yield (entry 1). The reaction of (4-((triisopropylsilyl)oxy)phenyl)-magnesium chloride **37c** with dimethylcarbamoyl chloride (**42b**) yields the amide **43b** in 81% yield (entry 2). Pd-catalyzed cross-coupling reactions of (3-chloro-phenyl)-magnesium chloride **39a** or (3-fluorophenyl)-magnesium chloride **39b** with heteroaryl iodides (**42c,d**) afford the heterocycles **43c** and **d** in 74–85% yield (entries 3, 4). Formylation

using DMF (**42e**) or addition of CO_2[86] (**42f**) to **39c** or **41a** provides 3-((triisopropylsilyl)-oxy)benzaldehyde **43e** or 3,5-dichlorobenzoic acid **43f** in 96 and 99% yield, respectively (entries 5 and 6).

Table 8: Trapping of the Mg reagents with various electrophiles.

entry	Grignard reagent (h)[a]	electrophile	product, yield[b]
1			
	37b (2)	**42a**	**43a**: 73%[c]
2			
	37c (4)	**42b**	**43b**: 81%
3			
	39a (0.75)	**42c**	**43c**: 85%[d,e]
4			
	39b (4)	**42d**	**43d**: 74%[d,e]
5			
	39c (3)	**42e**	**43e**: 96%

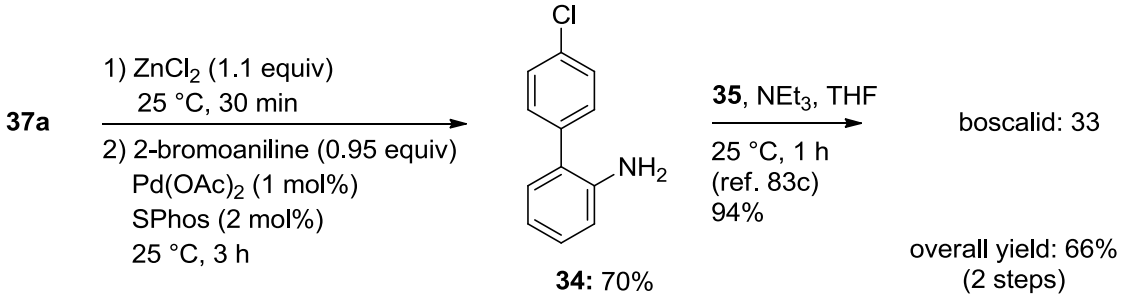
[86] Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.

6			
	41a (0.5)	**42f**	**43f**: 99%
7			
	41b (0.75)	**42g**	**43g**: 91%[d,e]
8			
	41c (0.75)	**42h**	**43h**: 80%[c]

[a] Reaction time at 25 °C. [b] Isolated yield of analytically pure product. [c] 1.1 equiv of CuCN·2LiCl was used. [d] After transmetalation with $ZnCl_2$. [e] 3 % $Pd(dba)_2$ and 6 % $P(o\text{-furyl})_3$ were used.

The Pd-catalyzed cross-coupling reaction of 3-iodobenzonitrile (**42g**) with **41b** yields the biaryl **43g** in 91% yield (entry 7). Copper-catalyzed acylation of **41c** with 2,4-dichlorobenzoyl chloride (**42h**) leads to the ketone **43h** in 80% yield (entry 8). Negishi cross-coupling[61,87] of (4-chlorophenyl)zinc chloride (obtained after transmetalation of **37a** with $ZnCl_2$) with 2-bromoaniline affords 4'-chloro-(1,1'-biphenyl)-2-amine **34** in 70% yield, which can be used as precursor for the synthesis of boscalid (**33**) (Scheme 41).[83]

[87] (a) Manolikakes, G.; Muñoz Hernandez, C.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422. (b) Manolikakes, G.; Schade, M. A.; Muñoz Hernandez, C.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765.



Scheme 41: Synthesis of 4'-chloro-(1,1'-biphenyl)-2-amine **34.**

The use of SPhos[88] as catalyst accelerates the Pd-catalyzed cross-coupling reaction, and avoids therefore the need to protect the amino function.[87]

[88] Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.

5. Stereoselective Synthesis of Polyfunctional Tetrasubstituted Thioethers *via* a Carbocupration of Alkynyl Sulfides with Aryl and Benzylic Diorganozincs

5.1. Introduction

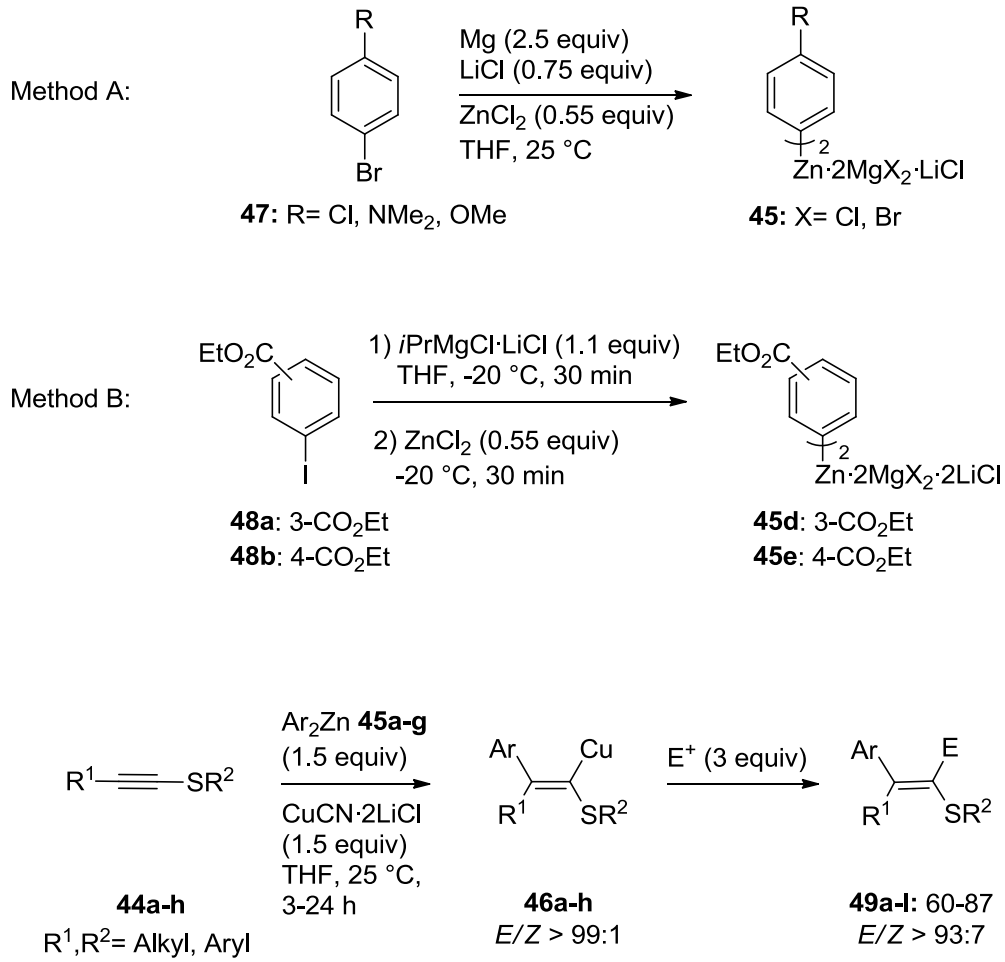
The stereoselective synthesis of tetrasubstituted olefins is of particular interest, since these carbon fragments are present in many natural products and drugs like Tamoxifen (see 3.3). The carbometalation of substituted alkynes constitutes an excellent stereoselective synthesis of such unsaturated molecules.[46] A variety of carbometalation reactions using copper, magnesium, boron and tin reagents have been reported. Recently, a stereoselective carbometalation of alkynes using organozinc reagents and catalytic amounts of cobalt dibromide was also described (see A.4).[52] Organometallic zinc compounds are important reagents in organic synthesis, due to their high functional group compatibility. Furthermore, they can be transmetalated stoichiometrically with copper(I)-salts providing highly reactive organocopper reagents which readily undergo carbometalation reactions.[51]

5.2. Results and Discussions

5.2.1. Carbocupration of Thioether-Substituted Alkynes

The readily prepared alkenyl thioethers (**44a-i**) undergo a smooth carbocupration with copper-zinc reagents ArCu(CN)ZnAr[51], prepared by mixing Ar_2Zn (**45a-g**) with CuCN·2LiCl[10] at 25 °C within 8–16 h leading to the expected alkenylcopper compounds (**46a-i**, Scheme 42) with excellent diastereoselectivity (*E/Z* > 99:1) as shown by GC-analysis of the crude hydrolyzed reaction mixture. Various functional groups can be tolerated in the alkynyl side chain, such as a cyanide, a dimethylamino group or a bromide. The functionalized diarylzinc reagents of type **45** are prepared either by Mg insertion to aryl bromides of type **47** in the presence of $ZnCl_2$ (0.55 equiv; Method A) or by an I/Mg-exchange using *i*PrMgCl·LiCl as in the case of the aryl iodides **48a** and **48b** followed by a transmetalation with $ZnCl_2$ (0.55 equiv; Method B). The resulting alkenylcopper reagents (**46a-i**) react with various electrophiles affording alkenyl thioethers **49a-n**

in 57–91% yield and *E*/*Z*-ratios > 87:13. Some loss of stereoselectivity is however observed during the quenching step.

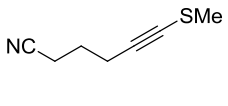
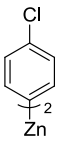
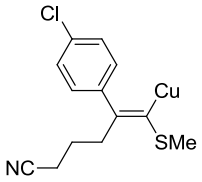
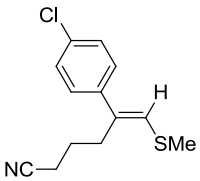
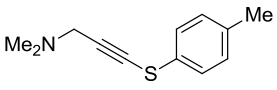
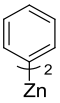
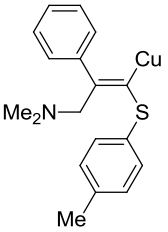
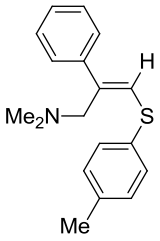
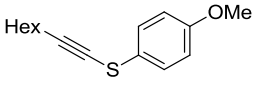
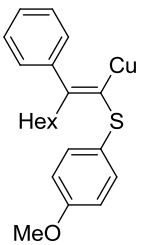
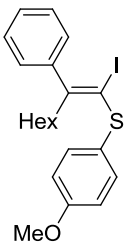


Scheme 42: Preparation of diarylzinc reagents and their use in carbocupration reactions of alkynyl sulfides.

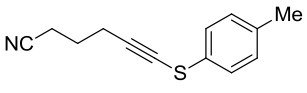
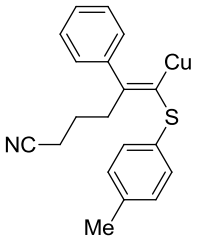
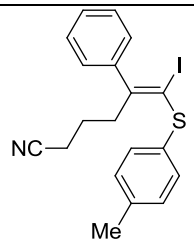
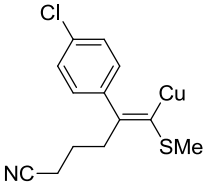
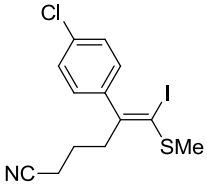
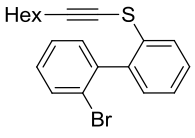
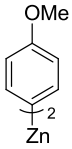
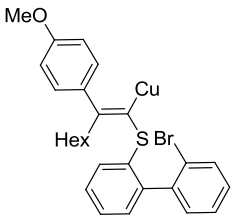
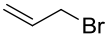
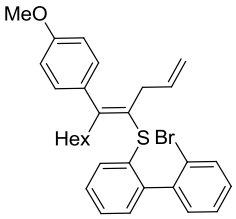
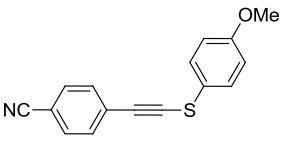
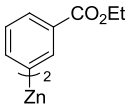
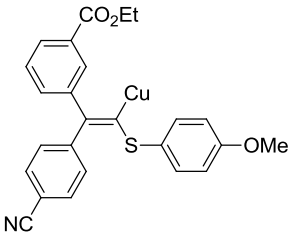
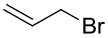
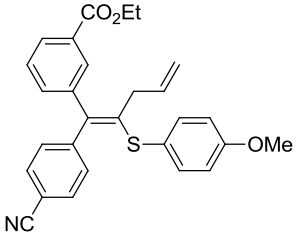
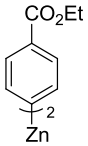
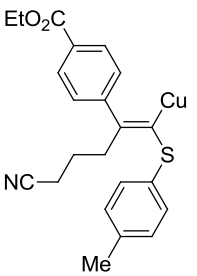
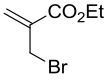
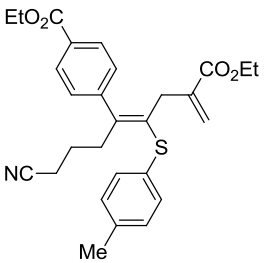
Thus, the reaction bis(4-chlorophenyl)zinc (**45a**) with the alkynyl thioether (**44a**) in the presence of CuCN·2LiCl (1.5 equiv) provides the alkenylcopper intermediate **46a** at 25 °C within 16 h. Its subsequent quenching with H_2O leads to the thioether **49a** in 80% yield; *E*/*Z* = 97:3 (Table 9, entry 1). Similarly, the hydrolysis of the alkenylcopper compound **46b**, obtained after a carbocupration with Ph_2Zn (**45b**) in the presence of CuCN·2LiCl, affords the thioether **49b** in 70% yield; *E*/*Z* = 99:1 (entry 2). Iodolysis of the copper species **46a,c,d** leads to the alkenyl iodides **49c-e** in 65–80% yield with an excellent *E*/*Z*-ratio (entries 3–5). Furthermore, the alkynes **44d-f** undergo smooth carbocupration at 25 °C within 8–24 h with *meta*- or *para*-substituted organocopper reagents bearing an ester- or a methoxy-group, obtained after transmetalation of the

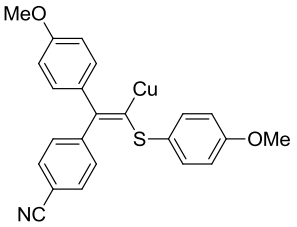
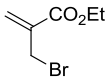
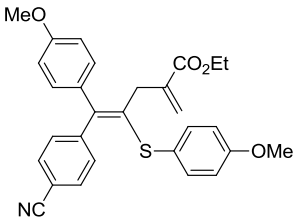
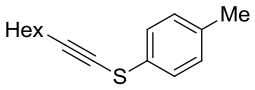
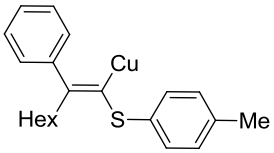
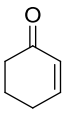
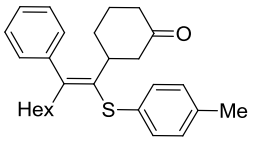
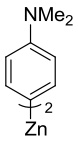
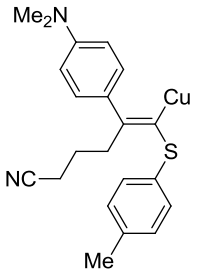
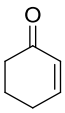
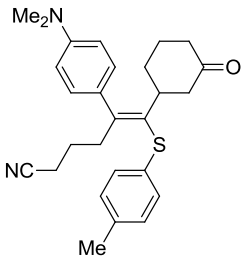
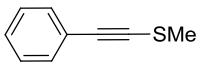
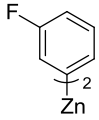
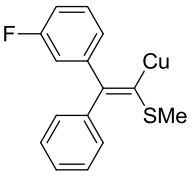
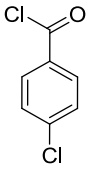
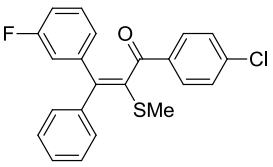
diorganozinc reagents (**45c-e**) with CuCN·2LiCl. The resulting copper intermediates (**46d-f),** react with allyl bromide or ethyl (2-bromomethyl)acrylate[63] furnishing the allylated alkenes **49f-i** in 65–87% yield; *E/Z* > 93:7 (entries 6–9). Trapping the carbometalated alkynes **46d,g** with cyclohex-2-enone in the presence of trimethylsilylchloride[89] afford the Michael adducts **49j,k** in 60-80% yield with an excellent *E/Z*-ratio of 99:1 (entries 10-11). Finally, the alkyne **44h** is carbocuprated with bis(3-fluorophenyl)zinc (**45g**) within 8 h at 25 °C. Its subsequent acylation with 4-chlorobenzoyl chloride gives the desired ketone **49l** in 66% yield; *E/Z* = 93:7 (entry 13).

Table 9: Carbocupration of alkynes and reaction with electrophiles.

entry	alkyne of type **44**	zinc-reagent[a] (time)[b]	copper-intermediate of type **46**	E^+	product, yield[c]
1				H_2O	
	44a	**45a** (16	**46a**		**49a**: 80% (*E/Z* = 97:3)
2				H_2O	
	44b	**45b** (17	**46b**		**49b**: 70% (*E/Z* = 99:1)
3		**45b**		I_2	
	44c	(15 h)	**46c**		**49c**: 80% (*E/Z* = 99:1)

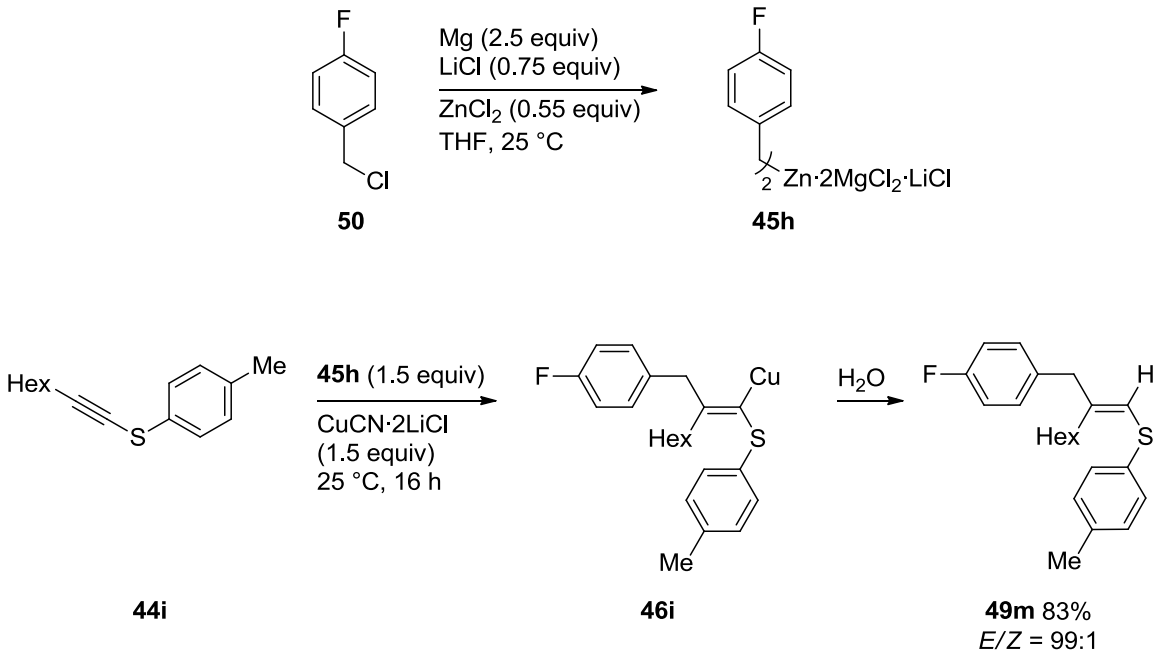
[89] (a) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029. (b) Bourgain-Commerçon, M.; Foulon, J.-P.; Normant, J. F. *J. Organomet. Chem.* **1982**, *228*, 321.

4		**45d**		I_2	
	44d	(8 h)	**46d**		**49d:** 65% (*E*/*Z* = 99:1)
5	**44a**	**45a**		I_2	
		(16 h)	**46a**		**49e**: 70% (*E*/*Z* = 99:1)
6					
	44e	**45c** (8 h)	**46e**		**49f**: 84% (*E*/*Z* = 99:1)
7					
	44f	**45d** (8 h)	**46f**		**49g**: 87% (*E*/*Z* = 93:7)
8	**44d**				
		45e (8 h)	**46d**		**49h**: 65% (*E*/*Z* = 93:7)

9	**44f**	**45c** (8 h)			 **49i**: 80% (*E*/*Z* = 93:7)
10	 **44g**	**45b** (16 h)	 **46g**		 **49j**: 80% (*E*/*Z* = 99:1)[d]
11	**44d**	 **45f** (8 h)	 **46d**		 **49k**: 60% (*E*/*Z* = 99:1)[e]
12	 **44h**	 **45g** (8 h)	 **46h**		 **49l**: 66% (*E*/*Z* = 93:7)[f]

[a] $2MgX_2 \cdot 2LiCl$ has been omitted for the sake of clarity; X = Cl, Br. [b] Reaction time for the carbometalation at 25 °C. First, the zinc reagent (1.5. equiv) was transmetalated using CuCN·2LiCl (1.5 equiv, -20 °C, 30 min). [c] Isolated yield of analytically pure product. *E*/*Z*-ratio determined by 2D-NMR. [d] TMSCl (7.5 equiv) was used.

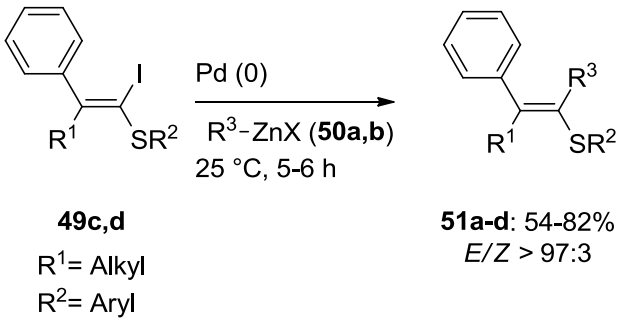
Besides arlyzincs, it is also possible to use bis-benzylic zinc reagents.[52] Thus, bis(4-fluorobenzyl)zinc (**45h**, 1.5 equiv) is obtained by Mg insertion to 4-fluorobenzyl chloride (**50**) in the presence of $ZnCl_2$ (0.55 equiv). The carbometalation reaction of the resulting diorganozinc reagent (**45h**) with the alkynyl thioether (**44i**) in the presence of CuCN·2LiCl (1.5 equiv) provides the alkenylcopper intermediate **46i** at 25 °C within 16 h. Its subsequent hydrolysis leads to the benzylic thioether **49m** in 83% yield; *E*/*Z* = 99:1 (Scheme 43).



Scheme 43: Preparation of the dibenzylzinc reagent (**45h**) and carbocupration of alkynyl sulfide **44i**.

5.2.2. Pd-Catalyzed Cross-Coupling of Alkenyl Iodides

The resulting alkenyl iodides (**49c,d**), obtained by a carbocupration-iodolysis sequence, can be further used as electrophiles in Pd-catalyzed cross-coupling reactions (Scheme 44).[90]



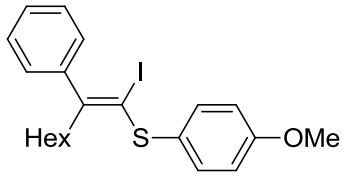
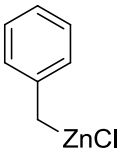
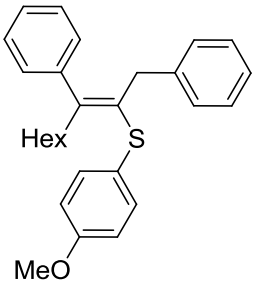
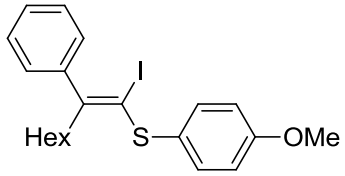
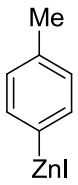
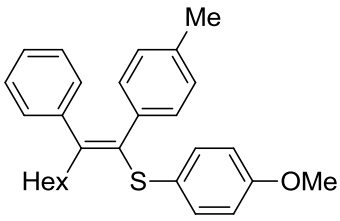
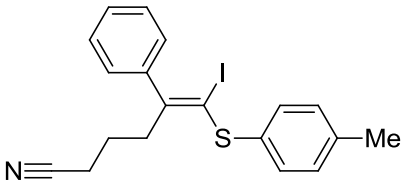
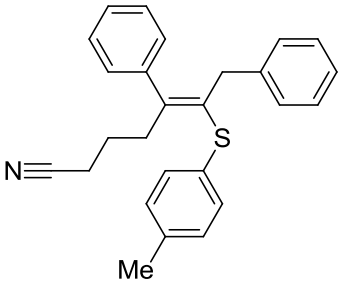
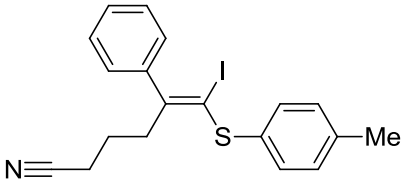
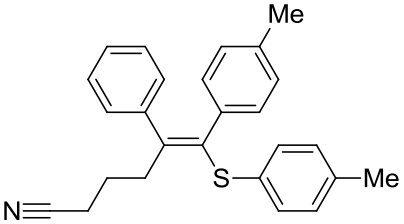
Scheme 44: Pd-catalyzed cross-coupling reaction of the vinylic iodides **47c,d**.

Negishi cross-coupling[61] reaction of the alkenyl iodide **49c** using $Pd(OAc)_2$ (2%), SPhos (4%) and benzylzinc chloride (**51a**, 1.5 equiv) affords the alkenyl thioether **52a** in 77% yield; *E/Z* = 98:2

[90] Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299.

(Table 10, entry 1). The alkenyl sulfide **52b** is obtained by using $Pd(dba)_2$ (3%), $P(o\text{-furyl})_3$[62] (6%) and *p*-tolylzinc iodide (**51b**, 1.5 equiv) within 5 h at 25 °C in 54% yield; *E/Z* = 97:3 (entry 2). The Pd-catalyzed cross-coupling reaction of **49d** with benzylzinc chloride (**51a**) or *p*-tolylzinc iodide (**51b**) leads exclusively to the alkenes **52c-d** in 76-82% yield (*E/Z* = 99:1, entries 3-4).

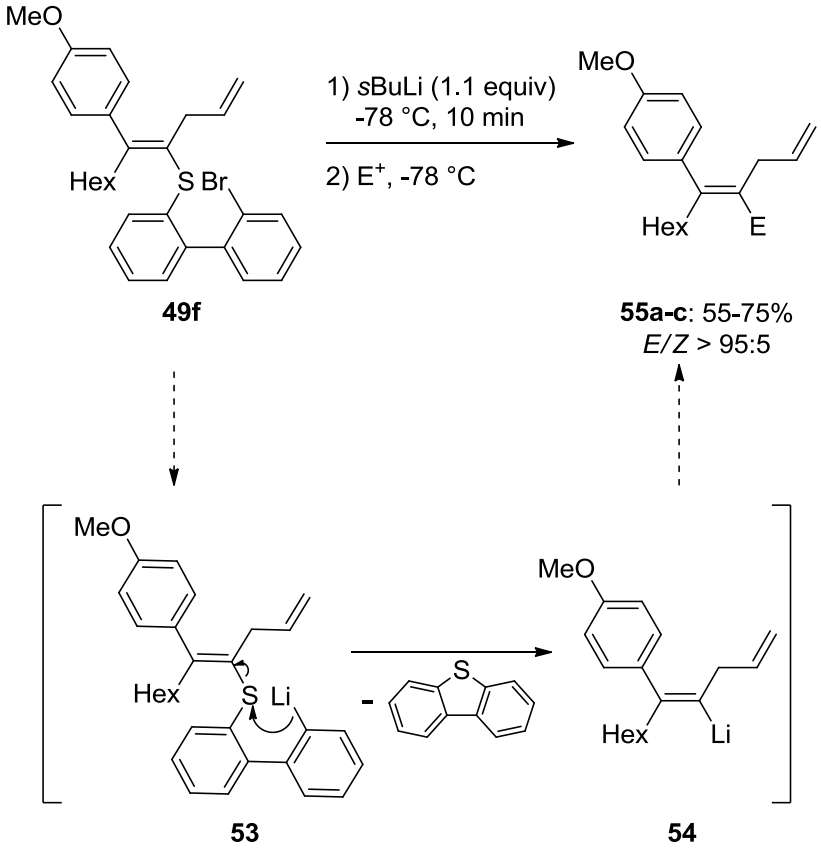
Table 10: Pd-catalyzed cross-coupling of the alkenyl iodides **49c,d** with zinc reagents at 25 °C.

entry	alkenyl iodide	zinc reagent (time)	product, yield (%)[a,b]
1			
	49c	**51a** (6 h)[c]	**52a**: 77% (*E/Z* = 98:2)
2			
	49c	**51b** (5 h)[d]	**52b**: 54% (*E/Z* = 97:3)
3		**51a**	
	49d	(6 h)[d]	**52c**: 76% (*E/Z* = 99:1)
4		**51b**	
	49d	(5 h)[d]	**52d**: 82% (*E/Z* = 99:1)

[a] Isolated yield of analytically pure product. [b] *E/Z*-ratio determined by 2D-NMR. [c] 2% $Pd(OAc)_2$ and 4% SPhos were used. [d] 3% $Pd(dba)_2$ and 6% $P(o\text{-furyl})_3$ were used.

5.2.3. Ring-Closing Rearrangement by a Sulfur/Lithium exchange

The reaction of the functionalized thioether (**49f**) with *s*BuLi affords the expected Br/Li exchange intermediate (**53**) at -78 °C (Scheme 45).[91] This compound undergoes a sulfur/Li exchange reaction at -78 °C within 10 min accompanied by the loss of dibenzothiophene, furnishing the alkenyl Li-species of type **54**. Thus, the lithiated alkene (**54**) reacts with various electrophiles affording tetrasubstituted olefins (**55a-c**) in 55-75% yield; *E/Z* > 95:5 (Table 11).

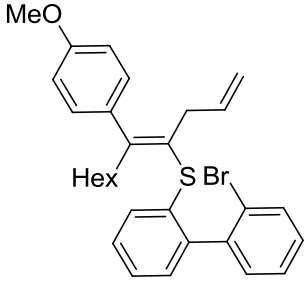
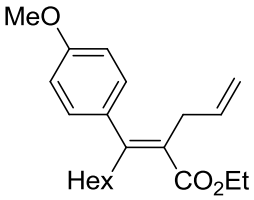
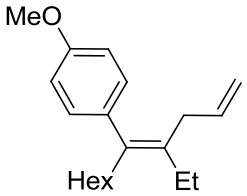
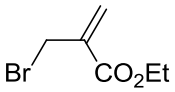
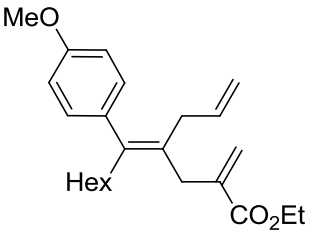


Scheme 45: Ring-closing rearrangement of the thioether **49f**.

The lithiated compound **54** reacts with ethyl chloroformate or ethyl iodide at -78 °C within 15 min furnishing the tetrasubstituted olefins **55a,b** in 55-75% yield; *E/Z* > 95:5 (entries 1 and 2). Subsequent transmetalation of **54** with $ZnCl_2$ and CuCN·2LiCl followed by the reaction with ethyl (2-bromomethyl)acrylate[63] leads to the allylic alkene **55c** in 55% yield; *E/Z* = 99:1 (entry 3).

[91] Stoll, A.; Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 606.

Table 11: Ring-closing rearrangement of the thioether **49f** and subsequent reaction with electrophiles.

entry	thioether	electrophile	product, yield (%)[a,b]
1	 **49f**	Cl-CO_2Et (-78 °C, 15 min)	 **55a**: 55% (*E*/*Z* = 95:5)
2	**49f**	EtI (-78 °C, 10 min)	 **55b**: 75% (*E*/*Z* = 99:1)
3	**49f**	 (-78 to 0 °C, 3 h)[c]	 **55c**: 55% (*E*/*Z* = 99:1)

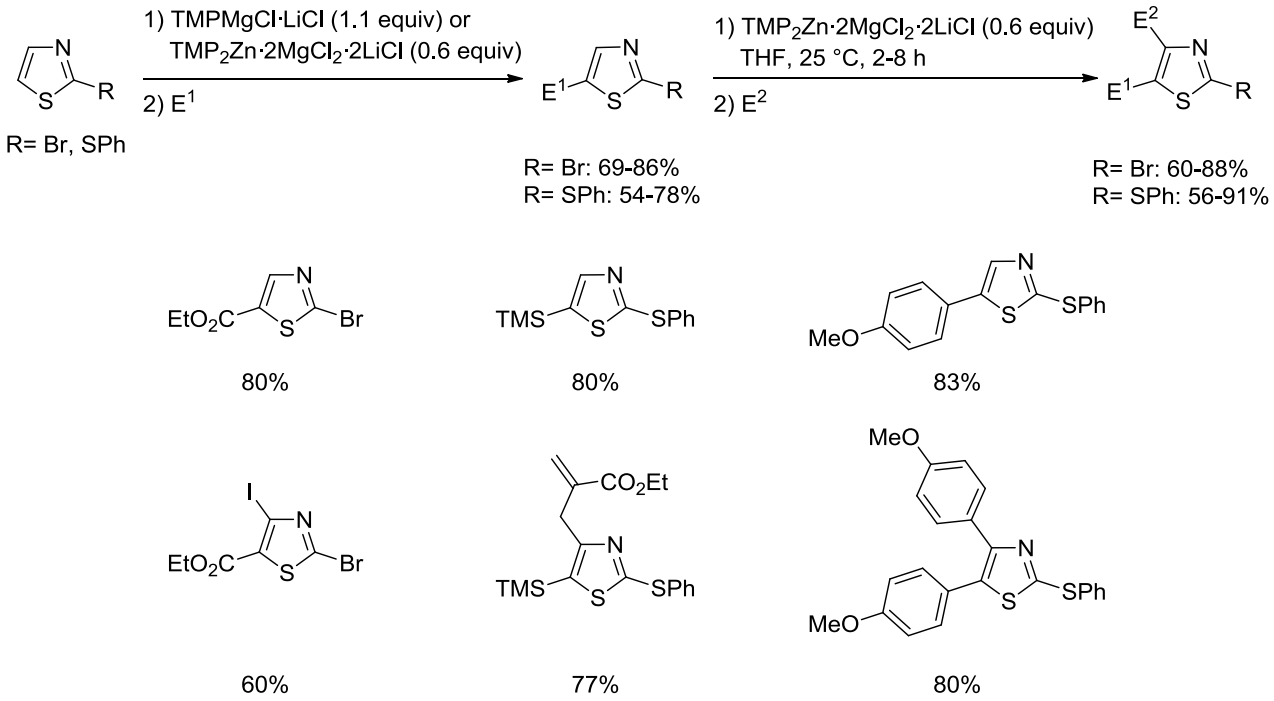
[a] Isolated yield of analytically pure product. [b] *E*/*Z*-ratio determined by 2D-NMR. [c] After transmetalation with $ZnCl_2$ (1.1 equiv) and further transmetalation with CuCN·2LiCl (1.1 equiv).

6. Summary and Outlook

This work was focused on the metalation and full functionalization of the thiazole scaffold. Furthermore, various zincated heterocycles were aminated using $PhI(OAc)_2$ as oxidant, also on large scale synthesis. Additionally, various aromatics were functionalized using TMP-manganese, -lanthanum or –iron-bases. Moreover, the Mg insertion in the presence of LiCl into mono- and polychlorinated arenes was investigated. Finally, a novel Cu(I)-mediated carbometalation reaction using functionalized diorganozinc reagents was developed.

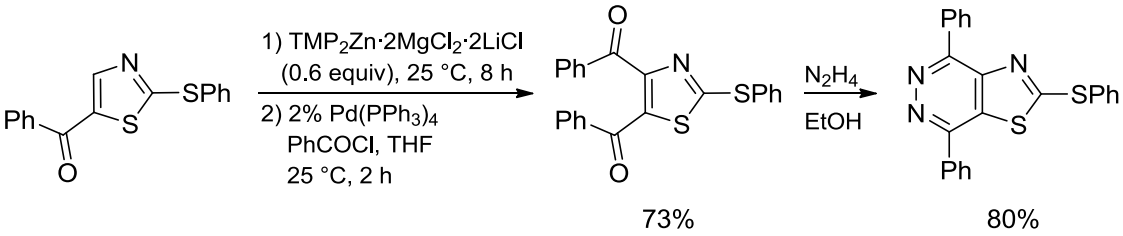
6.1. Regioselective Functionalization of the Thiazole Scaffold using TMPMgCl·LiCl and $TMP_2Zn·2MgCl_2·2LiCl$

In summary, the full functionalization of the thiazole core using the highly reactive TMP-bases TMPMgCl·LiCl (**2**) or $TMP_2Zn·2MgCl_2·2LiCl$ (**3**) was described. After functionalization at the 5-position with various electrophiles, a selective zincation at the 4-position of the heterocycle was achieved. Electrophilic trapping led to a broad range of highly functionalized trisubstituted thiazoles (Scheme 46).



Scheme 46: Full functionalization of the thiazole scaffold.

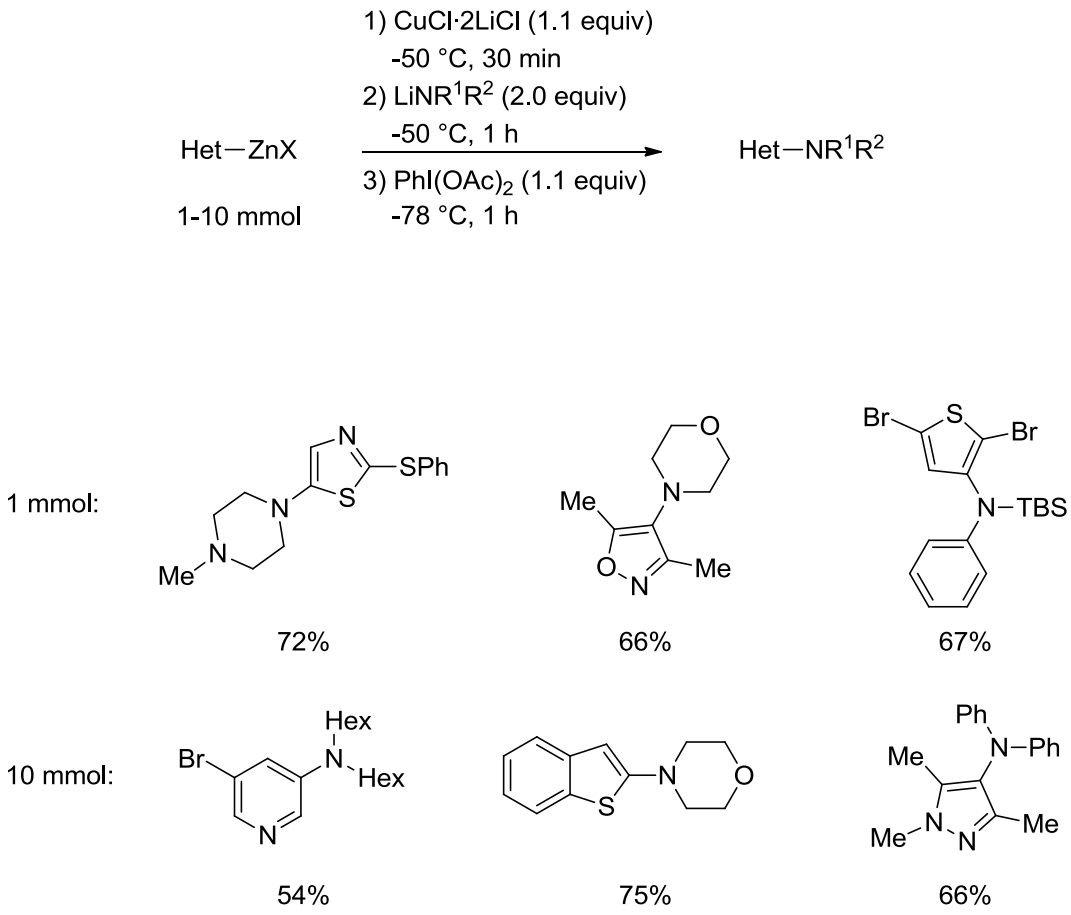
As an extension of this project, a ring closure was perfomed using hydrazine hydrate affording the functionalized thiazolopyridazine in 80% (Scheme 47).



Scheme 47: Synthesis of a functionalized thiazolopyridazine.

6.2. Oxidative Amination of Heteroaromatic Zinc Reagents Mediated by $PhI(OAc)_2$

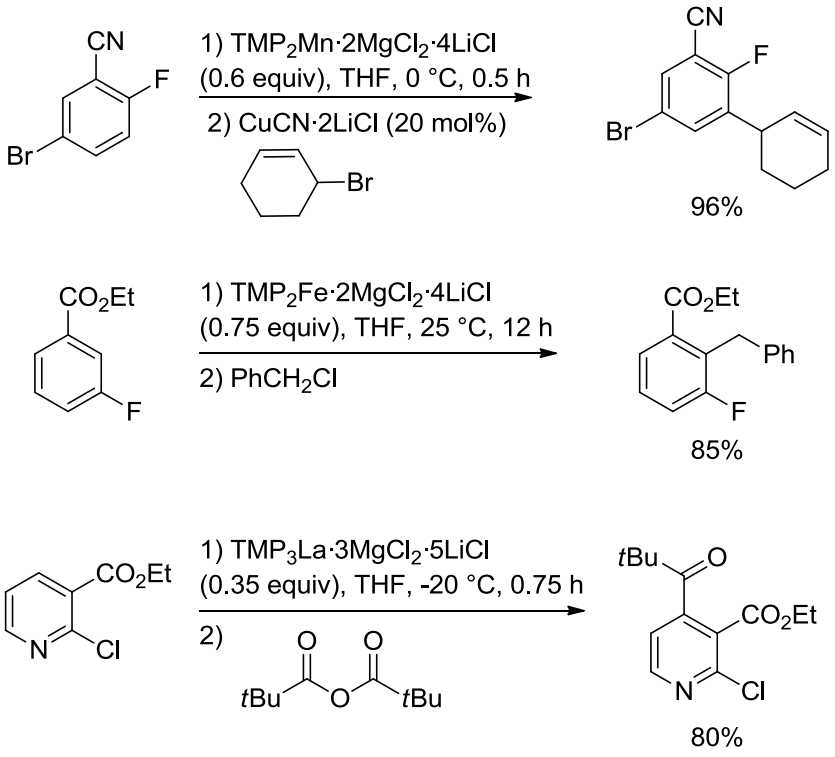
The Cu(I)-mediated oxidative amination reaction was extended to various zincated heterocycles prepared by directed metalation using TMP-bases, Mg insertion in the presence of LiCl and $ZnCl_2$ or by addition of a $ZnCl_2$ solution to a preformed magnesium reagent. Additionally, we found that these amination reactions can be scaled up easily (Scheme 48).



Scheme 48: Oxidative amination reaction.

6.3. Efficient Preparation of Polyfunctional Organometallics *Via* Directed *Ortho*-Metalation Using TMP-Bases of La, Mn and Fe

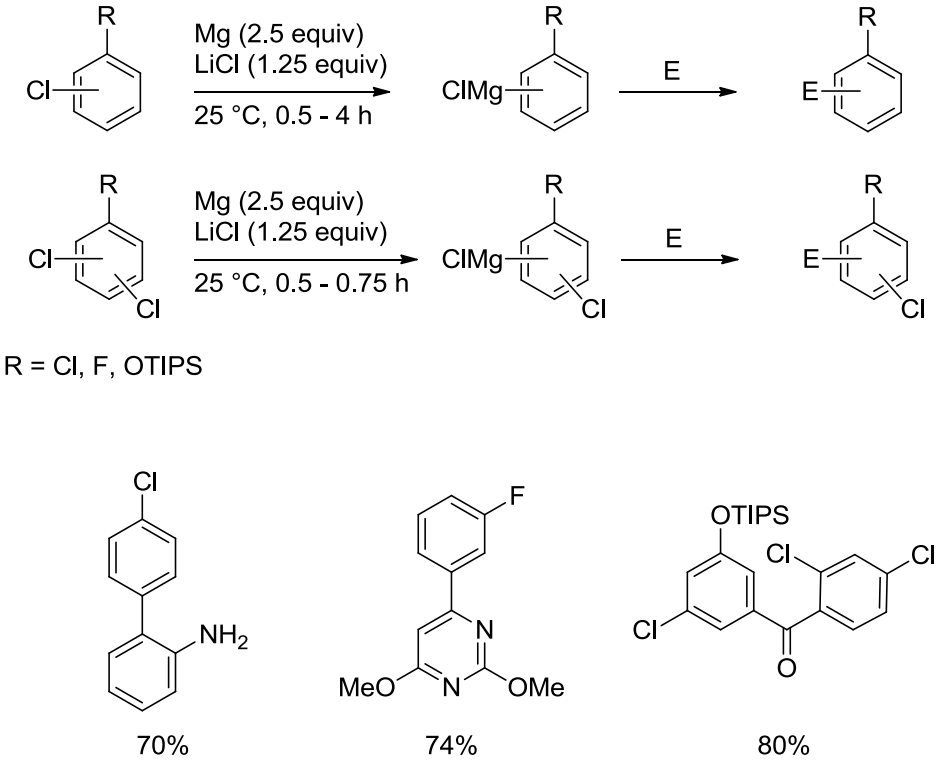
It was shown that the use of the bases $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$, $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ or $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ smoothly led to the corresponding organometallics. The reactions were carried out in large scale and in the presence of functional groups like esters or cyano groups. Efficient and atom economical reactions with electrophiles provided the desired products in very good to excellent yield (Scheme 49).



Scheme 49: Metalation of aromatics and heteroaromatics using TMP-bases of Mn, Fe and La and subsequent functionalization with electrophiles.

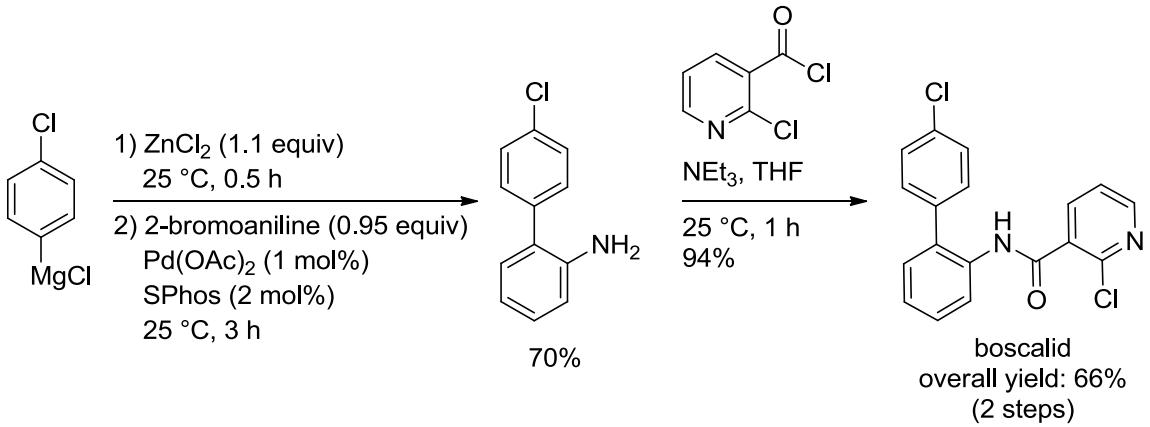
6.4. Selective Mg Insertion into Substituted Mono- and Di-Chloro Arenes in the Presence of LiCl. A new Preparation of Boscalid.

An efficient and practical Mg insertion into substituted aryl chlorides in the presence of LiCl using commercial magnesium turnings, leading to the corresponding Grignard reagents in 60–80% yield, was developed (Scheme 50).



Scheme 50: Mg insertion into substituted mono- and di-chloro arenes in the presence of LiCl.

Various trapping reactions with different electrophiles led to products which can be applied for instance to the synthesis of boscalid (Scheme 51).

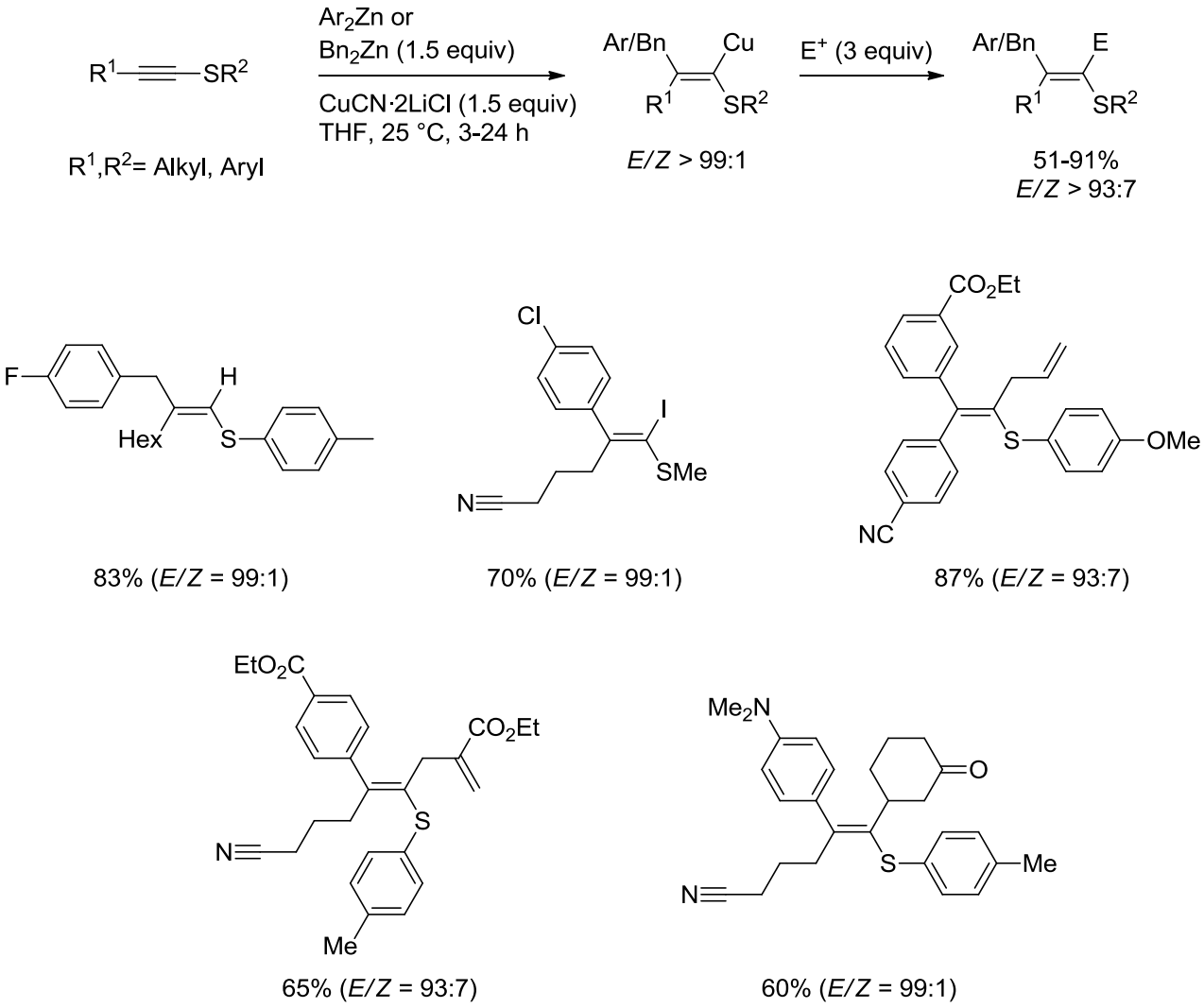


Scheme 51: Synthesis of boscalid in 2 steps.

Furthermore, this method gives an environmentally friendly access to simple substituted aryl scaffolds starting from inexpensive aryl chlorides, which is of great use for the chemical and pharmaceutical industry.

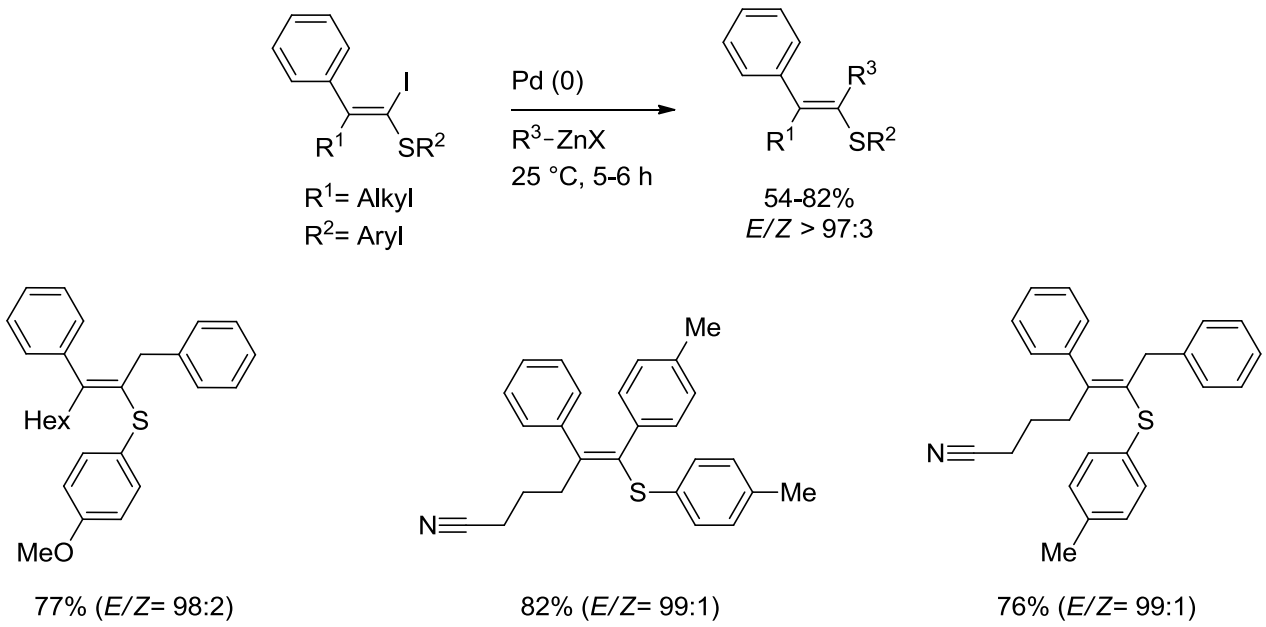
6.5. Stereoselective Synthesis of Polyfunctional Tetrasubstituted Thioethers *via* a Carbocupration of Alkynyl Sulfides with Aryl and Benzylic Diorganozincs

Finally, a novel Cu(I)-mediated carbometalation reaction was developed using alkynyl sulfides and functionalized aryl- or benzylic diorganozinc reagents prepared by Mg insertion into aryl bromides in the presence of $ZnCl_2$ (0.55 equiv) or by an I/Mg-exchange using *i*PrMgCl·LiCl in the case of aryl iodides. Trapping reactions with various electrophiles yielded highly stereoselectively tetrasubstituted thioethers in good to very good yields; *E*/*Z* = 93:7 up to 99:1 (Scheme 52).



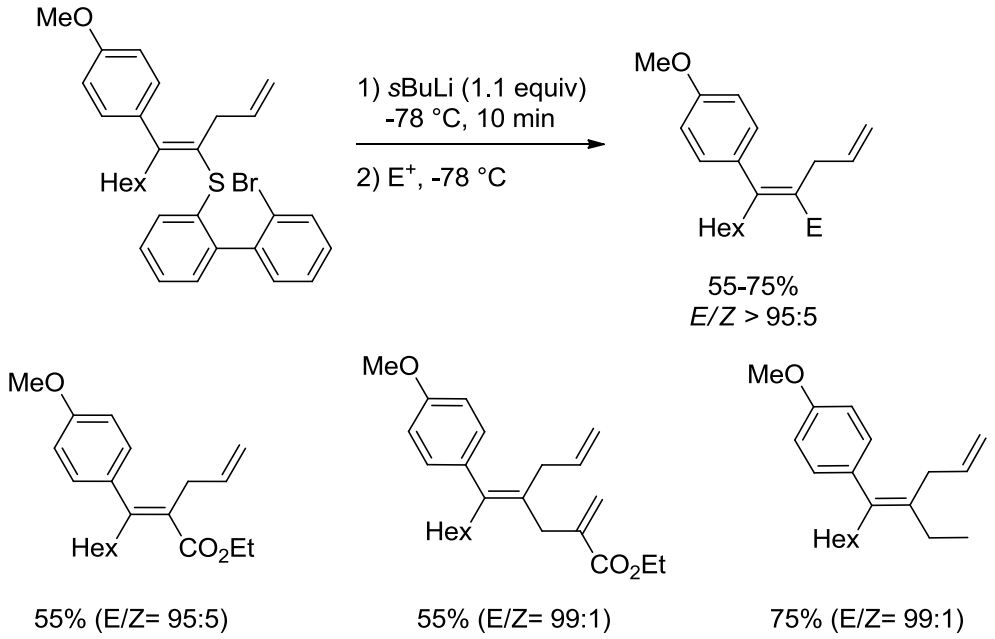
Scheme 52: Carbocupration of alkynyl sulfides with diorganozinc reagents.

Additionally, the resulting alkenyl iodides were used as electrophiles in Pd-catalyzed cross-coupling reactions with aryl- or benzylzinc reagents (Scheme 53).



Scheme 53: Cross-coupling of alkenyl iodides with aryl- or benzylzinc reagents.

Finally the thioether-substituent was removed by a ring-closing rearrangement using *s*BuLi leading to tetrasubstituted alkenes (Scheme 54).



Scheme 54: Ring-closing rearrangement leading to tetrasubstituted alkenes.

C. EXPERIMENTAL SECTION

1. General Considerations

All reactions were carried out with magentic stirring under argon atmosphere in flame-dried glassware if not indicated otherwise. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use.

1.1. Solvents

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

CH_2Cl_2 was continuously refluxed and freshly destilled from P_2O_5.

EtOH was treated with phtalic anhydride (23 g/L) and sodium, heated to reflux for 6 h and distilled.

Et_2O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

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

Triethylamin was dried over KOH and distilled.

Solvents from chromatography were distilled prior to use.

1.2. Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use.

Following compounds were prepared according to literature procedures:

sulfonothioate derivatives[92], organozinc reagents[17].

Reactions were monitored by gas chromatography (GC, GC/MS) or thin layer chromatography (TLC). The completion of deprotonation was determined *via* quenching of the reaction aliquots with iodine. Microwave reactions were performed in sealed reaction vessels under argon atmosphere with a high powered, focused microwave (Biotage initiator™ 2.5).

[92] Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343.

***i*PrMgCl·LiCl** solution in THF was purchased from Chemetall.

***n*BuLi** solution in hexane was purchased from Chemetall.

TMPMgCl·LiCl was prepared according to literature procedure (ref 28a).

$TMP_2Zn·2MgCl_2·2LiCl$ was prepared according to literature procedure (ref 33a).

$TMP_2Mn·2MgCl_2·4LiCl$ was prepared according to literature procedure (ref 78).

$TMP_2Fe·2MgCl_2·4LiCl$ was prepared according to literature procedure (ref 79).

$TMP_3La·3MgCl_2·5LiCl$ was prepared according to literature procedure (ref 80).

$ZnCl_2$ solution (1.0 M) was prepared by drying $ZnCl_2$ (27.3 g, 200 mmol) in *Schlenk*-flask under high vacuum at 150 °C for 4 h. After cooling to 25 °C, THF (200 mL) was added and the suspension was left stirring until the salt was completely dissolved.

CuCN·2LiCl solution (1.0 M) was prepared by drying CuCN (7.2 g, 80 mmol) and LiCl (6.8 g, 160 mmol) in a *Schlenk*-flask under high vacuum at 150 °C for 4 h. After cooling to 25 °C, THF (80 mL) was added and the suspension was left stirring until the salt was completely dissolved.

$MnCl_2·2LiCl$ solution (1.0 M) was prepared by drying LiCl (6.8 g, 160 mmol) in a *Schlenk*-flask under high vacuum at 150 °C for 3 h. After cooling to 25 °C, $MnCl_2$ (10.1 g, 80 mmol, 99% pure) was added under inert atmosphere inside a glove-box. The *Schlenk*-flask was further heated to 130 °C for 3 h under high vacuum, cooled to 25 °C and charged with THF (80 mL) under argon with vigorious stirring. The mixture was stirred for at least 24 h at 25 °C.

$FeCl_2·2LiCl$ solution (1.0 M) was prepared by drying LiCl (4.7 g, 110 mmol) in a *Schlenk*-flask under high vacuum at 150 °C for 3 h. After cooling to 25 °C, $FeCl_2$ (6.34 g, 50 mmol, 98% pure) was added under inert atmosphere inside a glove-box. The *Schlenk*-flask was further heated to 130 °C for 3 h under high vacuum, cooled to 25 °C and charged with THF (80 mL) under argon and wrapped in aluminium foil to protect it from light. The suspension was left stirring until the salt was completely dissolved (ca. 6 h).

CuCl·2LiCl solution (1.0 M) was prepared by drying LiCl (1.7 g, 40 mmol) in a *Schlenk*-flask under high vacuum at 150 °C for 3 h. After cooling to 25 °C under argon, CuCl (1.98 g, 20 mmol, 99.5% Cu) was added under inert atmosphere inside a glove-box. The *Schlenk*-flask was further heated to 130 °C for 5 h under high vacuum, cooled to 25 °C (*ca.* 1h), charged with

freshly distilled THF (20 mL) under argon and wrapped in aluminium foil to protect it from light. The mixture was vigorously stirred until all solid went in solution (*ca.* 2 h).

1.3. Content Determination of Organometallic Reagents

Organozinc and organomagnesium reagents were titrated against I_2 in a 0.5 M LiCl solution in THF.[85]

Organolithium reagents were titrated agains menthol using 1,10-phenanthroline as indicator in THF.[93]

TMP derived Mg, Zn, La, Mn and Fe bases were titrated agains benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.[94]

1.4. Chromatography

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

Thin layer chromatography (TLC) was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm.

1.5. Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of $CHCl_3$ (δ_H: 7.25, δ_C: 77.0). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet) as well as br (broad). The stereochemistry of new compounds was determined by 2D-NMR experiments (NOESY, COESY, HSQC, HMBC).

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

[94] Hammett, L. P.; Walden, G. H.; Edmonds, S. M. *J. Am. Chem. Soc.* **1934**, *56*, 1092.

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with a electron energy of 70 eV.

For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890/MSD 5973 was used.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. The absorption bands are reported in wavenumbers (cm^{-1}).

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

2. Typical procedures (TP)

2.1. Typical procedure for the metalation with TMPMgCl·LiCl (TP1)

In a dry and argon-flushed Schlenk-flask equipped with a septum and a magnetic stirring bar, the starting material was dissolved in THF (1 M solution). Then, TMPMgCl·LiCl (1.1 equiv) was dropwise added at –40 °C and stirred at this temperature for 0.5 h. The metalation progress was monitored by GC analysis of the reaction aliquots, which where quenched with iodine using tetradecane as internal standard.

2.2. Typical procedure for the metalation with $TMP_2Zn·2MgCl_2·2LiCl$ (TP2)

In a dry and argon-flushed Schlenk-flask equipped with a septum and a magnetic stirring bar, the starting material was dissolved in THF (1 M solution). Then, $TMP_2Zn·2MgCl_2·2LiCl$ (1.2 equiv) was dropwise added at 25 °C and stirred at this temperature for the indicated time. The metalation progress was monitored by GC analysis of the reaction aliquots, which where quenched with iodine using tetradecane as internal standard.

2.3. Typical Procedure for the TMS-deprotection with Bu_4NF (TP3)

In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the starting material was dissolved in THF (1 M solution). Then, Bu_4NF (1.1 equiv) dissolved in

THF (1 M solution) was dropwise added at 25 °C and stirred at this temperature for the indicated time. The deprotection progress was monitored by GC analysis of the reaction aliquots, which where quenched with sat. NH_4Cl sol. using tetradecane as internal standard.

2.4. Typical Procedure for the TMS-deprotection with ICl (TP4)

In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the starting material was dissolved in acetonitrile (1 M solution). Then, ICl (5 equiv) was dropwise added at –50 °C and and the resulting solution was warmed to 25 °C for the indicated time. The deprotection progress was monitored by GC analysis of the reaction aliquots, which where quenched with sat. $Na_2S_2O_3$ sol. using tetradecane as internal standard.

2.5. Typical Procedure for the Cu(I)-mediated amination of zincated heterocycles (TP5)

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with the starting material and THF (1 M solution). To the resulting mixture was added dropwise $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1.3 mL, 1.68 M in THF, 0.55 mmol) and stirred for the indicated time. Then, CuCl·2LiCl (1.1 mL, 1 M in THF, 1.1 mmol) was added dropwise at -50 °C under argon and the mixture was stirred for 30 min. The lithium amide (2 mmol, 1 M in THF) was added dropwise to the resulting cuprate, and the mixture was stirred for 1 h at –50 °C. The reaction mixture was cooled to –78 °C, then a solution of $PhI(OAc)_2$ (354 mg, 1.1 mmol) in dry THF (10 mL) was added slowly over a period of 60 min. The reaction mixture was then warmed to –50 °C and stirred for additional 3 h. Diethyl ether (100 mL) was poured into the crude reaction mixture. The organic phase was washed with 2×10 mL portions of aqueous NH_4OH (2 M) and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography yielded the product.

2.6. Typical procedure for the Cu(I)-mediated amination of zincated heterocylces obtained by Mg insertion in the presence of $ZnCl_2$ and LiCl (TP6)

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (104 mg, 2.5 mmol) and dried under vacuum at 130 °C for 1 h under vacuum. Then, $ZnCl_2$ (135 mg, 1 mmol) was added and also dried under vacuum at 450 °C for 5 min. After cooling to ambient temperature, magnesium turnings (61 mg, 2.5 mmol) and THF (5 mL) were added and activated with diisobutylaluminum hydride (0.1 mL, 0.1 M in THF, 0.01 mmol). The starting material (1 mmol) was added in one portion and the resulting mixture was stirred for the indicated time and then cannulated to a new *Schlenk*-flask for the reaction with an amine. CuCl·2LiCl (1.1 mL, 1 M in THF, 1.1 mmol) was added dropwise at –50 °C under argon and the mixture was stirred for 30 min. The lithium amide was added dropwise to the resulting cuprate, and the mixture was stirred for 1 h at –50 °C. The reaction mixture was cooled to -78 °C, then a solution of $PhI(OAc)_2$ (354 mg, 1.1 mmol) in dry THF (10 mL) was added slowly over a period of 60 min. The reaction mixture was then warmed to –50 °C and stirred for 3 h. Diethyl ether (100 mL) was poured into the crude reaction mixture. The organic phase was washed with 2×10 mL portions of aqueous NH_4OH (2 M) and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography yielded the pure product.

2.7. Typical Procedure for the Mg insertion into aryl chlorides (TP7)

A dry and argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with LiCl (530 mg, 12.5 mmol) and heated with a heat gun under high vacuum for 10 min. Magnesium turnings (608 mg, 25 mmol) and THF (10 mL) were added and the magnesium was activated with 1,2-dibromoethane (1 drop per mmol). After 5 min of stirring, 10 mmol of the aryl chloride was added and the reaction mixture was stirred for the indicated time at 25 °C. GC analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk flask and the yield was determined by iodometric titration.

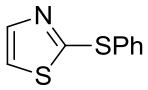
2.8. Typical procedure for the carbocupration of alkynyl sulfides with functionalized diorganozinc reagents (TP8)

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with the diorganozinc reagent of type $R_2Zn{\cdot}2MgX_2{\cdot}LiCl$ (1.5 equiv) and cooled to -20 C. CuCN·2LiCl (1.5 equiv) was dropwise added and the resulting mixture was stirred for 30 min. Then, the alkynyl sulfide was added, warmed to 25 °C and stirred for the indicated time. The carbocupration progress was monitored by GC analysis of the reaction aliquots, which where quenched with sat. NH_4Cl sol. using dodecane as internal standard.

3. Synthetic procedures

3.1. Regioselective Functionalization of the Thiazole Scaffold using TMPMgCl·LiCl and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$

2-(Phenylthio)-1,3-thiazole (5)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 2-bromothiazole (**4**) (1.64 g, 10 mmol) and THF (10 mL). To the resulting mixture was dropwise added *i*PrMgCl·LiCl (**1**, 8.3 mL, 1.3 M in THF, 11 mmol) at –40 °C and stirred for 0.5 h. *S*-Phenylbenzenethiosulfonate (2.8 g, 11 mmol) was added at –40 °C and the mixture was stirred for 0.5 h. The reaction mixture was quenched with sat. NH_4Cl sol. (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 5:1) yielded **5** (1.78 g, 92%) as yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.77 (d, J = 3.33 Hz, 1H), 7.67 (d, J = 3.52 Hz, 1H), 7.62–7.60 (m, 2H), 7.49–7.46 (m, 3H).

13C-NMR (75 MHz, DMSO) δ: 163.7, 143.3, 132.9, 130.9, 129.8, 129.4, 121.9.

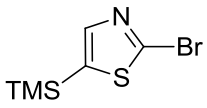
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 3058, 1582, 1474, 1440, 1384, 1328, 1302, 1278, 1152, 1052, 1036, 1014, 1000, 916, 866, 842, 740, 712, 702, 688, 642, 626, 610.

MS (EI, 70 eV): *m/z* (%) = 194 (13), 193 (41), 192 (20), 191 (100), 165 (12), 101 (12), 58 (17), 44 (10), 43 (17).

HRMS (EI): calcd. for $C_9H_7NS_2$: 193.0020, found: 193.0004 (M^+).

3.1.1. Functionalization of the thiazole scaffold at the 5-position

2-Bromo-5-(trimethylsilyl)thiazole (7a)



Prepared according to TP1 from 2-bromothiazole (**4**) (3.3 g, 20 mmol). Then, TMSCl (5.6 mL, 44 mmol) was added to **4a** at –50 °C and the resulting mixture was stirred for 0.5 h. The reaction mixture was quenched with sat. NH_4Cl sol. (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 19:1) yielded **7a** (4.02 g, 85%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.57 (s, 1H), 0.32 (s, 9H).

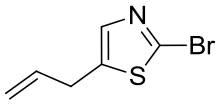
^{13}C-NMR ($CDCl_3$, 75 MHz,): δ = 148.2, 140.3, 138.6, -0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 1484, 1368, 1252, 1144, 1000, 832, 756, 740, 700, 648, 624, 596.

MS (EI, 70 eV): *m/z* (%) = 237 (96), 235 (M^+, 100), 224 (28), 223 (45), 222 (50), 221 (47), 117 (32), 116 (45), 115 (41), 73 (30).

HRMS (EI): calcd. for $C_6H_{10}BrNSSi$: 234.9487, found: 234.9484 (M^+).

5-Allyl-2-bromothiazole (7b)



Prepared according to TP2 from 2-bromothiazole (**4**) (1.6 g, 10 mmol) [metalation conditions: 25 °C, 0.5 h], CuCN·2LiCl (2 mL, 20 mol%) was dropwise added at 0 °C followed by allyl bromide (1.0 mL, 12 mmol). The resulting solution was stirred for 1 h (0 to 25 °C). The reaction

mixture was quenched with sat. NH_4Cl sol. (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 50:1) yielded **7b** (1.40 g, 69%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.27 (t, J = 1.11 Hz, 1H), 5.97–5.84 (m, 1H), 5.20–5.12 (m, 2H), 3.52–3.49 (m, 2H).

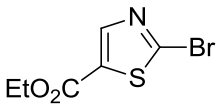
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 141.3, 139.8, 134.6, 134.3, 117.6, 31.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 1640, 1525, 1482, 1408, 1387, 1300, 1141, 1000, 919, 866, 841, 744, 734, 722, 695, 649, 632.

MS (EI, 70 eV): *m/z* (%) = 205 (47), 204 (30), 203 (M^+-^{79}Br, 50), 202 (25), 178 (15), 176 (15), 124 (60), 98 (49), 97 (100), 71 (14), 69 (10), 66 (14), 65 (16), 53 (12), 45 (19), 44 (19), 41 (12).

HRMS (EI): calcd. for C_6H_6BrNS: 202.9404, found: 202.9406 (M^+).

Ethyl 2-bromothiazole-5-carboxylate (7c)

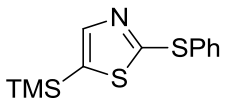


Prepared according to TP1 from 2-bromothiazole (**4**) (1.64 g, 10 mmol), ethyl cyanoformate (1.5 mL, 15 mmol) was added at –40 °C and stirred for 0.5 h warming to 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 5:1) yielded **7c** (1.88 g, 80%) as a colorless oil.

Analytical data matches the literature.[95]

[95] Kessler, U.; Ranadheera, C.; Joubert, M.; Giethlen, B.; Garrido, F. WO 2010128163, **2010**.

2-(Phenylthio)-5-(trimethylsilyl)thiazole (8a)



Prepared according to TP1 from 2-(phenylthio)thiazole (**5**) (4.83 g, 25 mmol), TMSCl (7.0 mL, 55 mmol) was added at –50 °C. The mixture was stirred for 0.5 h. The reaction mixture was quenched with sat. NH_4Cl sol. (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **8a** (5.30 g, 80%) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.80 (s, 1H), 7.67–7.64 (m, 2H), 7.52–7.48 (m, 3H), 0.23 (s, 9H).

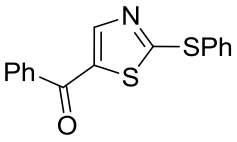
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 169.9, 149.5, 133.9, 133.9, 130.6, 130.1, 130.1, -0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 1474, 1440, 1370, 1252, 1152, 1036, 1014, 1000, 834, 750, 738, 702, 688, 644, 624, 604.

MS (EI, 70 eV): *m/z* (%) = 266 (22), 265 (M^+, 87), 264 (89), 250 (19), 167 (19), 115 (100), 73 (17), 43 (14).

HRMS (EI): calcd. for $C_{12}H_{15}NS_2Si$: 265.0415, found: 265.0401 (M^+).

Phenyl(2-(phenylthio)thiazol-5-yl)methanone (8b)



Prepared according to TP2 from 2-(phenylthio)thiazole (**5**) (967 mg, 5 mmol) [metalation conditions: 25 °C, 2 h]. Then, $Pd(PPh_3)_4$ (116 mg, 2 mol%) was added to **5b** followed by benzoyl chloride (2.25 mL, 7.5 mmol). The resulting solution was stirred for 1 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (20 mL) and the resulting mixture was extracted with diethyl ether (3×50 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 5:1) yielded **8b** (937 mg, 63%) as a yellow solid.

mp (°C): 87–89.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.03 (s, 1H), 7.81–7.77 (m, 2H), 7.72–7.69 (m, 2H), 7.61–7.44 (m, 6H).

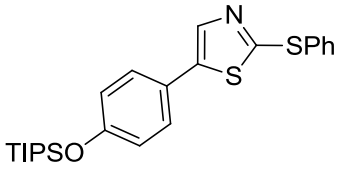
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 186.4, 178.2, 149.4, 138.9, 137.4, 135.2, 132.7, 130.9, 130.3, 129.3, 128.8, 128.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 3060, 2966, 2924, 1626, 1598, 1574, 1502, 1472, 1354, 1320, 1306, 1294, 1276, 1164, 1130, 1052, 1024, 868, 792, 750, 708, 688, 650.

MS (EI, 70 eV): *m/z* (%) = 298 (20), 297 (M^+, 83), 296 (100), 105 (23), 77 (26).

HRMS (EI): calcd. for $C_{16}H_{11}NOS_2$: 297.0282, found: 297.0275 (M^+).

2-(Phenylthio)-5-(4-((triisopropylsilyl)oxy)phenyl)thiazole (8c)



Prepared according to TP2 from 2-(phenylthio)thiazole (**5**) (387 mg, 2 mmol) [metalation conditions: 25 °C, 2 h]. Then, $Pd(dba)_2$ (35 mg, 3 mol%) and P(*o*-furyl)$_3$ (28 mg, 6 mol%) were added to **5b** followed by (4-iodophenoxy)triisopropylsilane (903 mg, 2.4 mmol). The resulting solution was stirred for 3 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **8c** (764 mg, 87%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.74 (s, 1H), 7.64–7.59 (m, 2H), 7.42–7.37 (m, 3H), 7.32–7.27 (m, 2H), 6.87–6.82 (m, 2H), 1.30–1.18 (m, 3H), 1.10–1.05 (m, 18H).

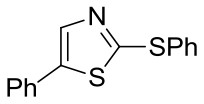
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 156.5, 141.2, 137.5, 133.3, 132.3, 129.7, 129.3, 127.9, 127.8, 123.8, 120.4, 17.9, 12.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944, 2866, 1602, 1528, 1488, 1462, 1440, 1390, 1264, 1172, 1040, 1012, 998, 906, 882, 832, 754, 734, 686, 660.

MS (EI, 70 eV): *m/z* (%) = 443 (14), 442 (27), 441 (M^+, 100), 399 (12), 370 (29), 343 (11), 342 (49), 328 (32), 171 (26), 170 (37), 163 (17).

HRMS (EI): calcd. for $C_{24}H_{31}NOS_2Si$: 441.1616, found: 441.1612 (M^+).

5-Phenyl-2-(phenylthio)thiazole (8d)



Prepared according to TP2 from 2-(phenylthio)thiazole (**5**) (967 mg, 5 mmol) [metalation conditions: 25 °C, 2 h]. Then, $Pd(dba)_2$ (86 mg, 3 mol%) and P(*o*-furyl)$_3$ (70 mg, 6 mol%) were added to **5b** followed by iodobenzene (1.22 g, 6 mmol). The resulting solution was stirred for 1 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (20 mL) and the resulting mixture was extracted with diethyl ether (3×50 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **8d** (1.08 g, 95%) as a yellow solid.

mp (°C): 57–59.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 8.15 (2, 1H), 7.67–7.65 (m, 2H), 7.55–7.49 (m, 5H), 7.40–7.35 (m, 2H), 7.33–7.29 (m, 1H).

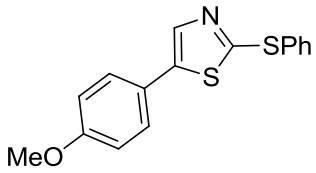
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 163.2, 140.1, 139.4, 133.2, 130.9, 130.2, 130.1, 129.8, 129.2, 128.4, 126.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3050, 1471, 1439, 1385, 1294, 1152, 1037, 1029, 854, 754, 744, 702, 690, 685.

MS (EI, 70 eV): *m/z* (%) = 270 (20), 269 (M^+, 100), 268 (85), 134 (13).

HRMS (EI): calcd. for $C_{15}H_{11}NS_2$: 269.0333, found: 269.0323 (M^+).

5-(4-Methoxyphenyl)-2-(phenylthio)thiazole (8e)



Prepared according to TP2 from 2-(phenylthio)thiazole (**5**) (967 mg, 5 mmol) [metalation conditions: 25 °C, 2 h]. Then, $Pd(dba)_2$ (86 mg, 3 mol%) and P(*o*-furyl)$_3$ (70 mg, 6 mol%) were added to **5b** followed by 1-iodo-4-methoxybenzene (1.40 g, 6 mmol). The resulting solution was stirred for 3 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (20 mL) and the resulting mixture was extracted with diethyl ether (3×50 mL). The combined organic layer was

dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 5:1) yielded **8e** (1.24 g, 83%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.74 (s, 1H), 7.65–7.60 (m, 2H), 7.42–7.33 (m, 5H), 6.90–6.85 (m, 2H), 3.80 (s, 3H).

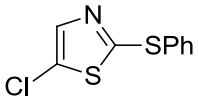
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.1, 159.8, 141.0, 137.7, 133.3, 132.3, 129.7, 129.3, 127.8, 123.6, 114.5, 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936, 2835, 1605, 1573, 1530, 1490, 1463, 1440, 1418, 1391, 1304, 1280, 1246, 1178, 1158, 1112, 1031, 1015, 1000, 964, 824, 794, 753, 741, 688.

MS (EI, 70 eV): *m/z* (%) = 300 (21), 299 (M^+, 100), 298 (46), 149 (24), 132 (22), 121 (11).

HRMS (EI): calcd. for $C_{16}H_{13}NOS_2$: 299.0439, found: 299.0430 (M^+).

5-Chloro-2-(phenylthio)thiazole (8f)



Prepared according to TP1 from 2-(phenylthio)thiazole (**5**) (967 mg, 5 mmol). Then, 1,1,2-trichloro-1,2,2-trifluoroethane (0.72 mL, 6 mmol) was added at –50 °C and the mixture was stirred for 4 h. The reaction mixture was quenched with sat. NH_4Cl sol. (20 mL) and the resulting mixture was extracted with diethyl ether (3×50 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/CH_2Cl_2; 10:1) yielded **8f** (606 mg, 54%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.62–7.58 (m, 2H), 7.46 (s, 1H), 7.45–7.39 (m, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.9, 141.1, 134.5, 133.9, 130.9, 129.9, 129.9.

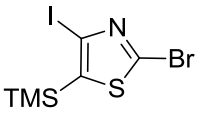
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 1489, 1475, 1440, 1395, 1034, 1006, 999, 840, 747, 734, 702, 688, 643.

MS (EI, 70 eV): *m/z* (%) = 229 (26), 228 (45), 227 (M^+, 64), 226 (100), 109 (18), 92 (18), 89 (11), 77 (12), 51 (11).

HRMS (EI): calcd. for $C_9H_6ClNS_2$: 226.9630, found: 226.9619 (M^+).

3.1.2. Functionalization of the thiazole scaffold at the 4-position

2-Bromo-4-iodo-5-(trimethylsilyl)thiazole (9a)



Prepared according to TP2 from 2-bromo-5-(trimethylsilyl)thiazole (**7a**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, a solution of iodine (508 mg, 2 mmol) in THF (2 mL) was added and the resulting solution was stirred for 10 min at 25 °C. The reaction mixture was quenched with sat. $Na_2S_2O_3$ sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 39:1) yielded **9a** (308 mg, 85%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 0.41 (s, 9H).

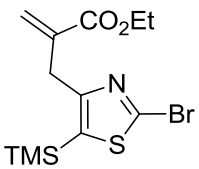
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 140.0, 139.9, 99.3, -0.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 1428, 1364, 1248, 1152, 1012, 992, 832, 796, 748, 696, 664, 628, 572, 524.

MS (EI, 70 eV): *m/z* (%) = 363 (37), 361 (M^+-^{79}Br, 39), 349 (12), 348 (100), 347 (12), 346 (90), 241 (32), 139 (10), 137 (11), 114 (25).

HRMS (EI): calcd. for $C_6H_9BrINSSi$: 360.8453, found: 360.8468 (M^+).

Ethyl 2-((2-bromo-5-(trimethylsilyl)thiazol-4-yl)methyl)acrylate (9b)



Prepared according to TP2 from 2-bromo-5-(trimethylsilyl)thiazole (**7a**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, CuCN·2LiCl (0.2 mL, 20 mol%) was added to **7ab** at 0 °C followed by ethyl 2-(bromomethyl)acrylate (232 mg, 1.2 mmol). The resulting solution was warmed to 25 °C and stirred for 5 h. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined

organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **9b** (249 mg, 72%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 6.28 (d, *J* = 1.19 Hz, 1H), 5.28 (d, *J* = 1.19 Hz, 1H), 4.21 (q, *J* = 7.15 Hz, 2H), 3.77 (d, *J*= 1.55 Hz, 2H), 1.29 (t, *J* = 7.15 Hz, 3H), 0.31 (s, 9H).

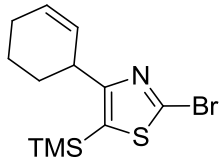
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 166.6, 159.1, 138.5, 138.4, 133.7, 126.5, 60.8, 33.7, 14.2, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 1711, 1632, 1489, 1427, 1407, 1329, 1292, 1251, 1191, 1133, 1095, 1025, 1003, 935, 899, 836, 751, 695, 655, 633, 613.

MS (EI, 70 eV): *m/z* (%) = 349 (16), 347 (M^+-^{79}Br, 15), 320 (22), 318 (21), 306 (12), 304 (28), 303 (63), 302 (18), 301 (59), 277 (11), 276 (20), 275 (31), 274 (25), 273 (22), 260 (16), 258 (11), 75 (85), 73 (100).

HRMS (EI): calcd. for $C_{12}H_{18}BrNO_2SSi$: 347.0011, found: 347.0006 (M^+).

2-Bromo-4-(cyclohex-2-en-1-yl)-5-(trimethylsilyl)thiazole (9c)



Prepared according to TP2 from 2-bromo-5-(trimethylsilyl)thiazole (**7a**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, CuCN·2LiCl (0.2 mL, 20 mol%) was added to **7ab** at 0 °C followed by 3-bromocyclohex-1-ene (242 mg, 1.5 mmol). The resulting solution was warmed to 25 °C and stirred for 2 h. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **9c** (242 mg, 77%) as a clear oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 5.87–5.80 (m, 1H), 5.58–5.53 (m, 1H), 3.58–3.49 (m, 1H), 2.20–1.84 (m, 5H), 1.69–1.57 (m, 1H), 0.32 (s, 9H).

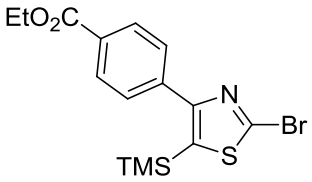
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 167.0, 138.2, 131.1, 128.7, 128.5, 39.7, 30.2, 24.6, 22.0, 0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 1678, 1488, 1400, 1283, 1251, 1002, 890, 834, 750, 722, 706, 694, 668, 636, 627, 617.

MS (EI, 70 eV): *m/z* (%) = 318 (13), 317 (59), 316 (24), 315 (M^+-^{79}Br, 66), 314 (11), 302 (24), 300 (24), 289 (36), 288 (57), 287 (33), 286 (43), 276 (16), 274 (17), 263 (20), 261 (18), 251 (13), 249 (12), 248 (16), 246 (15), 237 (19), 236 (100).

HRMS (EI): calcd. for $C_{12}H_{18}BrNSSi$: 315.0113, found: 315.0106 (M^+).

Ethyl 4-(2-bromo-5-(trimethylsilyl)thiazol-4-yl)benzoate (9d)



Prepared according to TP2 from 2-bromo-5-(trimethylsilyl)thiazole (**7a**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added to **7ab** followed by ethyl 4-iodobenzoate (304 mg, 1.1 mmol). The resulting solution was stirred for 4.5 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **9d** (307 mg, 70%) as a white solid.

mp (°C): 87–88.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.09–8.07 (m, 2H), 7.62–7.60 (m, 2H), 4.38 (q, *J* = 7.14 Hz, 2H), 1.40 (t, *J* = 7.14 Hz, 3H), 0.22 (s, 9H).

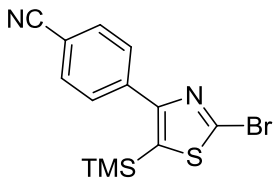
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 166.2, 161.0, 140.2, 139.0, 134.7, 130.4, 129.4, 128.9, 61.1, 14.3, 0.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2992, 1708, 1612, 1464, 1416, 1368, 1316, 1300, 1276, 1244, 1176, 1108, 1060, 984, 840, 760, 716, 676, 664, 624, 556, 528.

MS (EI, 70 eV): *m/z* (%) = 386 (19), 385 (100), 384 (18), 383 (M^+-^{79}Br, 90), 370 (13), 368 (11), 354 (26), 352 (22), 340 (21), 338 (12), 326 (33), 324 (30), 299 (10), 298 (24), 296 (62), 295 (14), 282 (19), 280 (18), 191 (18), 115 (14), 109 (31), 73 (32).

HRMS (EI): calcd. for $C_{15}H_{18}BrNO_2SSi$: 383.0011, found: 382.9996 (M^+).

4-(2-Bromo-5-(trimethylsilyl)thiazol-4-yl)benzonitrile (9e)



Prepared according to TP2 from 2-bromo-5-(trimethylsilyl)thiazole (**7a**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added to **7ab** followed by 4-iodobenzonitrile (252 mg, 1.2 mmol). The resulting solution was stirred for 15 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **9e** (239 mg, 71%) as a white solid.

mp (°C): 98–99.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.71–7.66 (m, 4H), 0.24 (s, 9H).

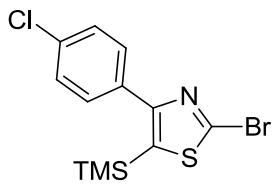
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 159.8, 140.3, 139.5, 135.6, 132.0, 129.6, 118.6, 112.3, 0.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2228, 1604, 1512, 1460, 1412, 1380, 1252, 1120, 1008, 988, 836, 748, 676, 632, 568, 548, 520.

MS (EI, 70 eV): *m/z* (%) = 339 (16), 338 (100), 337 (16), 336 (M^+-^{79}Br, 92), 324 (25), 323 (48), 322 (71), 321 (40), 320 (63), 217 (27), 216 (47), 216 (25), 108 (17), 73 (22).

HRMS (EI): calcd. for $C_{13}H_{13}BrN_2SSi$: 335.9752 found: 335.9759 (M^+).

2-Bromo-4-(4-chlorophenyl)-5-(trimethylsilyl)thiazole (9f)



Prepared according to TP2 from 2-bromo-5-(trimethylsilyl)thiazole (**7a**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added to **7ab** followed by 1-chloro-4-iodobenzene (286 mg, 1.2 mmol). The

resulting solution was stirred for 4 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 100:1) yielded **9f** (218 mg, 63%) as a yellow solid.

mp (°C): 62–63.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.47 (d, J = 8.29 Hz, 2H), 7.37 (d, J = 8.29 Hz, 2H), 0.21 (s, 9H).

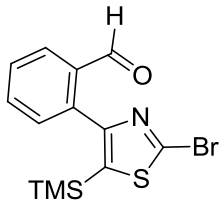
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 160.9, 138.8, 134.6, 134.4, 133.7, 130.3, 128.3, 0.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 3057, 2978, 2926, 2230, 1719, 1579, 1554, 1481, 1431, 1386, 1375, 1315, 1104, 1040, 836, 795, 746, 718, 691, 662.

MS (EI, 70 eV): *m/z* (%) = 349 (16), 348 (10), 347 (55), 345 (M^+-^{79}Br, 38), 337 (28), 336 (17), 335 (100), 227(25), 226 (10), 225 (63), 113 (14), 73 (22).

HRMS (EI): calcd. for $C_{12}H_{13}BrClNSSi$: 344.9410, found: 344.9389 (M^+).

2-(2-Bromo-5-(trimethylsilyl)thiazol-4-yl)benzaldehyde (9g)



Prepared according to TP2 from 2-bromo-5-(trimethylsilyl)thiazole (**7a**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added to **7ab** followed by 2-iodobenzaldehyde (278 mg, 1.2 mmol). The resulting solution was stirred for 5 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **9g** (239 mg, 70%) as an orange oil.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 9.84 (s, 1H), 7.99 (dd, J = 7.75 Hz, 1H), 7.62–7.59 (m, 1H), 7.54 (t, J = 7.63 Hz, 1H), 7.38 (dd, J = 7.63 Hz, 1H), 0.06 (s, 9H).

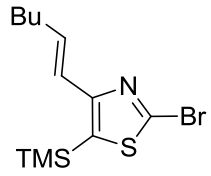
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 191.1, 158.0, 139.0, 139.0, 136.6, 135.0, 133.2, 131.3, 129.4, 127.7, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 1695, 1597, 1501, 1451, 1399, 1292, 1250, 1194, 1159, 1083, 998, 834, 817, 755, 742, 695, 650, 636, 623.

MS (EI, 70 eV): *m/z* (%) = 339 (M^+-^{79}Br, 18), 338 (16), 313 (13), 312 (32), 311 (100), 310 (31), 309 (91), 268 (24), 266 (26), 260 (62), 252 (45), 250 (48), 188 (16), 187 (20), 171 (16), 129 (16), 115 (22), 111 (18), 109 (12), 102 (15), 99 (13), 97 (27), 95 (18), 89 (12), 85 (36), 83 (26), 81 (17), 73 (62), 71 (48), 69 (28), 57 (62), 56 (12), 55 (30), 45 (14), 43 (39), 41 (20).

HRMS (EI): calcd. for $C_{13}H_{14}BrNOSSi$: 338.9749, found: 338.9757 (M^+).

(*E*)-2-Bromo-4-(hex-1-en-1-yl)-5-(trimethylsilyl)thiazole (9h)



Prepared according to TP2 from 2-bromo-5-(trimethylsilyl)thiazole (**7a**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(PPh_3)_4$ (23 mg, 2 mol%) was added to **7ab** followed by (*E*)-1-iodohex-1-ene (314 mg, 1.5 mmol). The resulting solution was stirred for 5 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 150:1) yielded **9h** (128 mg, 65%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 6.69–6.65 (m, 1H), 6.32–6.29 (m, 1H), 2.23–2.19 (m, 2H), 1.48–1.43 (m, 2H), 1.39–1.33 (m, 2H), 0.91 (t, *J* = 7.18 Hz, 3H), 0.34 (s, 9H).

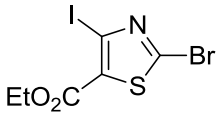
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 159.6, 138.7, 136.2, 131.1, 122.5, 32.5, 31.1, 22.2, 13.9, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 1469, 1418, 1289, 1265, 1251, 1003, 964, 834, 756, 732, 695, 679, 657, 624.

MS (EI, 70 eV): *m/z* (%) = 319 (39), 317 (M^+-^{79}Br, 32), 304 (13), 302 (11), 291 (16), 290 (91), 289 (14), 288 (75), 276 (34), 275 (11), 274 (34), 262 (14), 249 (12), 248 (16), 246 (12), 239 (12), 238 (52), 111 (11), 97 (14), 85 (15), 83 (16), 73 (100), 71 (22), 69 (20), 59 (12), 57 (30), 55 (21).

HRMS (EI): calcd. for $C_{12}H_{20}BrNSSi$: 317.0269, found: 317.0266 (M^+).

Ethyl 2-bromo-4-iodothiazole-5-carboxylate (9i)



Prepared according to TP2 from ethyl 2-bromothiazole-5-carboxylate (**7c**) (236 mg, 1 mmol) [metalation conditions: 25 °C, 2 h]. Then, a solution of iodine (508 mg, 2 mmol) in THF (2 mL) was added and the resulting solution was stirred for 10 min at 25 °C. The reaction mixture was quenched with sat. $Na_2S_2O_3$ sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **9i** (169 mg, 60%) as a white solid.

mp (°C): 106–109.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.36 (q, J = 7.00 Hz, 2H), 1.37 (t, J = 7.05 Hz, 3H).

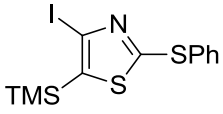
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 159.1, 142.8, 131.4, 101.1, 62.3, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3414, 2978, 1711, 1478, 1466, 1376, 1250, 1181, 1120, 1082, 1027, 883, 831, 806, 754, 668.

MS (EI, 70 eV): *m/z* (%) = 363 (100), 361 (M^+-^{79}Br, 96), 335 (75), 333 (74), 319 (18), 318 (88), 318 (18), 316 (85), 391 (26), 290 (12), 289 (27), 288 (11), 183 (58), 180 (13), 178 (13), 127 (14), 125 (14), 122 (14), 110 (19), 82 (45), 57 (13), 45 (13).

HRMS (EI): calcd. for $C_6H_5BrINO_2S$: 360.8269, found: 360.8257 (M^+).

4-Iodo-2-(phenylthio)-5-(trimethylsilyl)thiazole (10a)



Prepared according to TP2 from 2-(phenylthio)-5-(trimethylsilyl)thiazole (**8a**) (265 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, a solution of iodine (508 mg, 2 mmol) in THF (2 mL) was added and the resulting solution was stirred for 10 min at 25 °C. The reaction mixture was quenched with sat. $Na_2S_2O_3$ sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated

under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **10a** (339 mg, 86%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.65–7.62 (m, 2H), 7.46–7.41 (m, 3H), 0.34 (s, 9H).

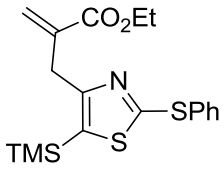
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.1, 135.1, 134.5, 130.7, 130.1, 129.9, 100.8, –0.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 1424, 1364, 1248, 1160, 1050, 990, 834, 800, 748, 704, 686, 626.

MS (EI, 70 eV): *m/z* (%) = 393 (13), 392 (19), 391 (M^+, 100), 390 (11), 376 (32), 265 (11), 264 (48), 241 (36), 167 (23), 114 (23), 109 (10), 77 (15), 73 (21).

HRMS (EI): calcd. for $C_{12}H_{14}INS_2Si$: 390.9382, found: 390.9375 (M^+).

Ethyl 2-((2-(phenylthio)-5-(trimethylsilyl)thiazol-4-yl)methyl)acrylate (10b)



Prepared according to TP2 from 2-(phenylthio)-5-(trimethylsilyl)thiazole (**8a**) (265 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, CuCN·2LiCl (0.2 mL, 20 mol%) was added to **8ab** at 0 °C followed by ethyl 2-(bromomethyl)acrylate (232 mg, 1.2 mmol). The resulting solution was warmed to 25 °C and stirred for 1.5 h. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **10b** (302 mg, 77%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.62–7.57 (m, 2H), 7.40–7.37 (m, 3H), 6.26 (q, *J* = 1.37 Hz, 1H), 5.26 (q, *J* = 1.76 Hz, 1H), 4.20 (q, *J* = 7.24 Hz, 2H), 3.75 (t, *J* = 1.66 Hz, 2H), 1.27 (t, *J* = 7.14 Hz, 3H), 0.23 (s, 9H).

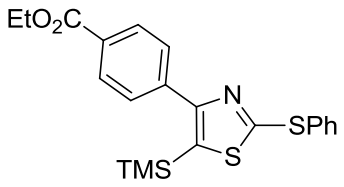
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) =168.6, 166.6, 159.3, 138.7, 133.7, 131.9, 129.7, 129.6, 129.4, 126.2, 60.7, 33.7, 14.2, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 1712, 1632, 1582, 1476, 1402, 1296, 1250, 1192, 1134, 1022, 950, 904, 836, 746, 690, 634.

MS (EI, 70 eV): *m/z* (%) = 379 (16), 378 (30), 377 (M^+, 100), 362 (32), 354 (15), 349 (11), 348 (38), 334 (32), 333 (14), 332 (28), 331 (52), 306 (15), 305 (42), 304 (89), 303 (22), 302 (11), 290 (18), 260 (12), 110 (19), 109 (12), 77 (13), 75 (60), 73 (80), 44 (55).

HRMS (EI): calcd. for $C_{18}H_{23}NO_2S_2Si$: 377.0939, found: 377.0933 (M^+).

Ethyl 4-(2-(phenylthio)-5-(trimethylsilyl)thiazol-4-yl)benzoate (10c)



Prepared according to TP2 from 2-(phenylthio)-5-(trimethylsilyl)thiazole (**8a**) (265 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added to **8ab** followed by ethyl 4-iodobenzoate (304 mg, 1.1 mmol). The resulting solution was stirred for 3 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **10c** (372 mg, 91%) as a yellow solid.

mp (°C): 69–71.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.09–8.05 (m, 2H), 7.70–7.64 (m, 3H), 7.63–7.61 (m, 1H), 7.44–7.39 (m, 3H), 4.37 (q, J = 7.00 Hz, 2H), 1.39 (t, J = 7.05 Hz, 3H), 0.14 (s, 9H).

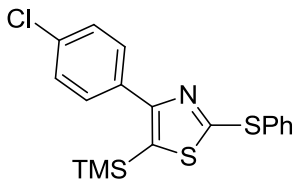
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 169.6, 166.2, 161.2, 141.0, 134.1, 131.3, 130.5, 130.0, 129.7, 129.7, 129.2, 128.9, 60.9, 14.2, 0.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 1716, 1608, 1458, 1408, 1304, 1256, 1174, 1124, 1114, 1100, 1044, 1022, 1016, 994, 830, 780, 762, 744, 708, 686, 660, 632.

MS (EI, 70 eV): *m/z* (%) = 415 (14), 414 (29), 413 (M^+, 100), 412 (28), 326 (11), 325 (10), 263 (21), 73 (20).

HRMS (EI): calcd. for $C_{21}H_{23}NO_2S_2Si$: 413.0939, found: 413.0934(M^+).

4-(4-Chlorophenyl)-2-(phenylthio)-5-(trimethylsilyl)thiazole (10d)



Prepared according to TP2 from 2-(phenylthio)-5-(trimethylsilyl)thiazole (**8a**) (265 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added to **8ab** followed by 1-chloro-4-iodobenzene (286 mg, 1.2 mmol). The resulting solution was stirred for 6 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **10d** (268 mg, 73%) as a yellow solid.

mp (°C): 109–111.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.70–7.66 (m, 2H), 7.51–7.41 (m, 5H), 7.38–7.34 (m, 2H), 0.14 (s, 9H).

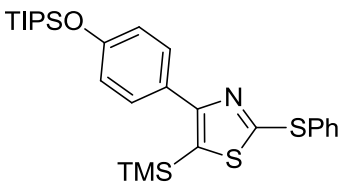
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 169.6, 161.2, 135.2, 134.2, 134.2, 131.1, 130.4, 129.8, 129.7, 129.7, 128.2, 0.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 1458, 1440, 1402, 1264, 1252, 1090, 1042, 1024, 1014, 992, 832, 822, 756, 748, 728, 696, 686, 664, 630.

MS (EI, 70 eV): *m/z* (%) = 378 (13), 377 (44), 376 (40), 375 (M^+, 100), 374 (34), 362 (16), 360 (32), 227 (29), 226 (13), 225 (73), 167 (17), 73 (36).

HRMS (EI): calcd. for $C_{18}H_{18}ClNS_2Si$: 375.0338, found: 375.0347 (M^+).

2-(Phenylthio)-4-(4-((triisopropylsilyl)oxy)phenyl)-5-(trimethylsilyl)thiazole (10e)



Prepared according to TP2 from 2-(phenylthio)-5-(trimethylsilyl)thiazole (**8a**) (265 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg,

6 mol%) were added to **8ab** followed by (4-iodophenoxy)triisopropylsilane (450 mg, 1.2 mmol). The resulting solution was stirred for 20 h at 40 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 50:1) yielded **10e** (390 mg, 76%) as a white solid.

mp (°C): 57–59.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.69–7.66 (m, 2H), 7.45–7.37 (m, 5H), 6.92–6.87 (m, 2H), 1.32–1.22 (m, 3H), 1.10 (d, J = 6.63 Hz, 18H), 0.13 (s, 9H).

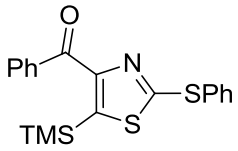
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 168.7, 162.6, 156.3, 134.0, 131.9, 130.3, 129.7, 129.7, 129.5, 128.5, 119.5, 17.9, 12.6, 0.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944, 2231, 1619, 1573, 1461, 1448, 1388, 1369, 1241, 1142, 1105, 1006, 942, 836, 786, 773, 761, 736, 715.

MS (EI, 70 eV): *m/z* (%) = 515 (16), 514 (29), 513 (M^+, 79), 472 (18), 471 (31), 470 (100), 442 (22), 335 (17), 307 (15), 207 (19), 73 (19).

HRMS (EI): calcd. for $C_{27}H_{39}NOS_2Si_2$: 513.2012, found: 513.2007 (M^+).

Phenyl(2-(phenylthio)-5-(trimethylsilyl)thiazol-4-yl)methanone (10f)



Prepared according to TP2 from 2-(phenylthio)-5-(trimethylsilyl)thiazole (**8a**) (265 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(PPh_3)_4$ (23 mg, 2 mol%) was added to **8ab** followed by benzoyl chloride (0.45 mL, 1.5 mmol). The resulting solution was stirred for 3 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **10f** (288 mg, 72%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.15 (dd, J = 8.35 Hz, 2H), 7.70–7.67 (m, 2H), 7.56–7.53 (m, 1H), 7.47–7.43 (m, 1H), 0.32 (s, 9H).

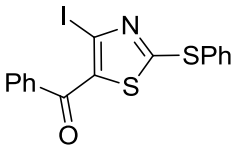
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 188.1, 168.8, 158.8, 145.9, 137.4, 134.4, 132.7, 131.1, 130.8, 129.9, 129.9, 128.0, –0.25.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2952, 2898, 1716, 1648, 1596, 1448, 1406, 1286, 1248, 1214, 1178, 1058, 1024, 1000, 972, 836, 812, 746, 728, 686, 658, 642, 622.

MS (EI, 70 eV): *m/z* (%) = 369 (M^+, 3), 356 (13), 355 (24), 354 (100), 145 (18).

HRMS (EI): calcd. for $C_{19}H_{19}NOS_2Si$: 369.0677, found: 369.0665 (M^+).

(4-Iodo-2-(phenylthio)thiazol-5-yl)(phenyl)methanone (10g)



Prepared according to TP2 from phenyl(2-(phenylthio)thiazol-5-yl)methanone (**8b**) (297 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, a solution of iodine (508 mg, 2 mmol) in THF (2 mL) was added and the resulting solution was stirred for 10 min at 25 °C. The reaction mixture was quenched with sat. $Na_2S_2O_3$ sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 5:1) yielded **10g** (296 mg, 70%) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.80–7.76 (m, 2H), 7.72–7.69 (m, 2H), 7.66–7.61 (m, 1H), 7.60–7.54 (m, 3H), 7.52–7.48 (m, 2H).

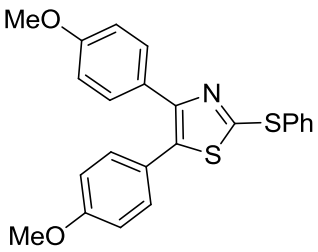
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 186.6, 175.3, 137.3, 135.0, 134.4, 133.4, 131.4, 130.7, 129.1, 128.7, 128.2, 105.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944, 2231, 1619, 1573, 1461, 1448, 1388, 1369, 1241, 1142, 1105, 1006, 942, 836, 786, 773, 761, 736, 715.

MS (EI, 70 eV): *m/z* (%) = 425 (11), 424 (20), 423 (M^+, 100), 422 (19), 298 (12), 297 (33), 296 (65), 121 (18), 109 (13), 105 (52), 77 (44), 51 (11).

HRMS (EI): calcd. for $C_{16}H_{10}INOS_2$: 422.9249, found: 422.9249 (M^+).

4,5-Bis(4-methoxyphenyl)-2-(phenylthio)thiazole (10h)



Prepared according to TP2 from 5-(4-methoxyphenyl)-2-(phenylthio)thiazole (**8e**) (299 mg, 1 mmol) [metalation conditions: 25 °C, 8 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added to **8eb** followed by 1-iodo-4-methoxybenzene (281 mg, 1.2 mmol). The resulting solution was stirred for 3 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 5:1) yielded **10h** (324 mg, 80%) as a white solid.

mp (°C): 100–102.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.73–7.69 (m, 2H), 7.52–7.48 (m, 3H), 7.37–7.33 (m, 2H), 7.18–7.14 (m, 2H), 6.90–6.84 (m, 4H), 3.72 (s, 3H), 3.72 (s, 3H).

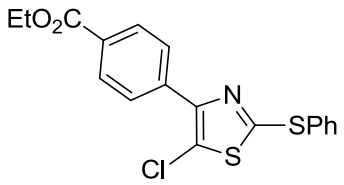
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 161.9, 159.3, 158.9, 149.1, 133.6, 132.2, 130.6, 130.5, 130.1, 130.0, 129.6, 126.3, 122.8, 114.4, 113.7, 55.1, 55.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3050, 2998, 2835, 1605, 1572, 1512, 1482, 1470, 1439, 1290, 1242, 1218, 1180, 1048, 1031, 1008, 842, 830, 792, 753, 735, 724, 715, 706, 688, 655, 628.

MS (EI, 70 eV): *m/z* (%) = 406 (28), 405 (M^+, 95), 404 (18), 300 (27), 299 (100), 298 (56), 255 (30), 238 (48), 223 (15), 211 (18), 208 (17), 151 (17), 149 (48), 132 (31), 121 (20), 113 (17), 81 (14), 77 (21), 71 (15), 69 (26), 57 (27), 55 (25), 44 (35), 43 (20), 41 (21).

HRMS (EI): calcd. for $C_{23}H_{19}NO_2S_2$: 405.0857, found: 405.0848 (M^+).

Ethyl 4-(5-chloro-2-(phenylthio)thiazol-4-yl)benzoate (10i)



Prepared according to TP2 from 5-chloro-2-(phenylthio)thiazole (**8f**) (228 mg, 1 mmol) [metalation conditions: 25 °C, 2 h]. Then, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added to **8fb** followed by ethyl 4-iodobenzoate (304 mg, 1.1 mmol). The resulting solution was stirred for 1 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **10i** (331 mg, 88%) as a yellow solid.

mp (°C): 87–88.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.11–8.08 (m, 2H), 8.03–8.00 (m, 2H), 7.68–7.65 (m, 2H), 7.47–7.42 (m, 3H), 4.38 (q, J = 7.02 Hz, 2H), 1.39 (t, J = 7.12 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 166.1, 164.2, 149.0, 136.4, 134.5, 130.3, 130.1, 130.0, 130.0, 129.5, 127.9, 121.5, 61.0, 14.3.

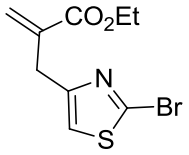
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 1705, 1607, 1471, 1433, 1408, 1364, 1314, 1265, 1173, 1101, 1045, 1028, 1014, 863, 841, 776, 754, 701, 691, 660.

MS (EI, 70 eV): *m/z* (%) = 378 (12), 377 (45), 376 (39), 376 (M^+, 100), 371 (48), 332 (25), 195 (17), 167 (11), 165 (14), 85 (24), 71 (30), 69 (11), 57 (33), 43 (22).

HRMS (EI): calcd. for $C_{18}H_{14}ClNO_2S_2$: 375.0154, found: 375.0147 (M^+).

3.1.3. Deprotection of the TMS-group with Bu_4NF or ICl

Ethyl 2-((2-bromothiazol-4-yl)methyl)acrylate (11a)



Prepared according to TP 3 from ethyl 2-((2-bromo-5-(trimethylsilyl)thiazol-4-yl)methyl)acrylate (**9b**) (348 mg, 1 mmol) [deprotection conditions: 25 °C, 10 min]. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **11a** (220 mg, 80%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.90 (t, J = 0.83 Hz, 1H), 6.27–6.26 (m, 1H), 5.61 (q, J = 1.39 Hz, 1H), 4.16 (q, J = 7.10 Hz, 2H), 3.74–3.73 (m, 2H), 1.23 (t, J = 7.05 Hz, 3H).

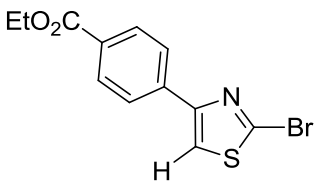
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.3, 154.4, 137.4, 135.1, 127.3, 118.6, 60.8, 33.9, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3094, 2984, 1698, 1606, 1476, 1408, 1368, 1264, 1218, 1180, 1126, 1114, 1054, 1024, 1012, 860, 834, 756, 698, 664.

MS (EI, 70 eV): *m/z* (%) = 277 (16), 275 (M^+, 15), 232 (34), 231 (100), 230 (33), 229 (94), 204 (21), 203 (77), 202 (66), 201 (21), 122 (42), 97 (62), 71 (12), 53 (14), 45 (31).

HRMS (EI): calcd. for $C_9H_{12}BrNO_2S$: 274.9616, found: 274.9611 (M^+).

Ethyl 4-(2-bromothiazol-4-yl)benzoate (11b)



Prepared according to TP 3 from ethyl 4-(2-bromo-5-(trimethylsilyl)thiazol-4-yl)benzoate (**9d**) (384 mg, 1 mmol) [deprotection conditions: 25 °C, 10 min]. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether

(3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **11b** (281 mg, 90%) as a white solid.

mp (°C): 99–100.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.10–8.06 (m, 2H), 7.93–7.89 (m, 2H), 7.52 (s, 1H), 4.39 (q, J = 7.05 Hz, 2H), 1.40 (t, J = 7.17 Hz, 3H).

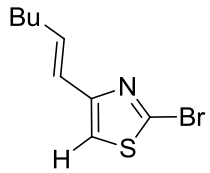
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.2, 154.7, 137.0, 136.3, 130.4, 130.1, 126.0, 117.9, 61.1, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3094, 2984, 1698, 1606, 1476, 1408, 1368, 1264, 1218, 1180, 1126, 1114, 1054, 1024, 1012, 860, 834, 756, 698, 664.

MS (EI, 70 eV): *m/z* (%) = 313 (62), 312 (14), 311 (M^+, 60), 285 (32), 283 (28), 269 (17), 268 (100), 267 (17), 266 (98), 240 (19), 161 (10), 159 (30), 89 (16).

HRMS (EI): calcd. for $C_{12}H_{10}BrNO_2S$: 310.9616, found: 310.9611 (M^+).

(*E*)-2-Bromo-4-(hex-1-en-1-yl)thiazole (11c)



Prepared according to TP 3 from ethyl (*E*)-2-bromo-4-(hex-1-en-1-yl)-5-(trimethylsilyl)thiazole (**9h**) (318 mg, 1 mmol) [deprotection conditions: 25 °C, 10 min]. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 100:1) yielded **11c** (209 mg, 85%) as a white solid.

mp (°C): 65-66.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.85 (s, 1H), 6.63–6.53 (m, 1H), 6.32–6.26 (m, 1H), 2.23–2.16 (m, 2H), 1.49–1.29 (m, 4H), 0.9 (t, J = 7.19 Hz, 3H).

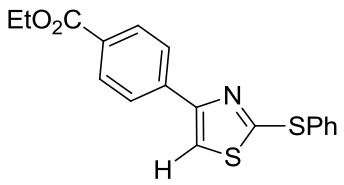
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 154.8, 135.7, 135.6, 121.8, 116.0, 32.3, 31.1, 22.2, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944, 2231, 1619, 1573, 1461, 1448, 1388, 1369, 1241, 1142, 1105, 1006, 942, 836, 786, 773, 761, 736, 715.

MS (EI, 70 eV): *m/z* (%) = 242 (M^+, 7), 227 (11), 175 (8), 174 (57), 147 (16), 146 (65), 134 (9), 133 (100), 132 (19), 65 (6).

HRMS (EI): calcd. for $C_{15}H_{18}N_2O$: 242.1419, found: 242.1412 (M^+).

Ethyl 4-(2-(phenylthio)thiazol-4-yl)benzoate (12)



Prepared according to TP 3 from ethyl 4-(2-(phenylthio)-5-(trimethylsilyl)thiazol-4-yl)benzoate (**10c**) (413 mg, 1 mmol) [deprotection conditions: 25 °C, 10 min]. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **12** (273 mg, 85%) as a white solid.

mp (°C): 124–125.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.09–8.05 (m, 2H), 7.95–7.91 (m, 2H), 7.71–7.65 (m, 2H), 7.47–7.65 (m, 4H), 4.38 (q, J = 7.21 Hz, 2H), 1.40 (t, J = 7.17 Hz, 3H).

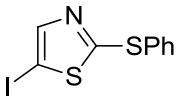
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 167.3, 166.3, 154.9, 137.9, 134.3, 131.2, 130.1, 130.0, 129.9, 129.9, 126.1, 115.5, 61.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976, 1698, 1606, 1574, 1472, 1428, 1366, 1310, 1266, 1246, 1198, 1174, 1122, 1106, 1070, 1046, 1022, 1014, 862, 834, 782, 754, 728, 710, 692, 668, 664.

MS (EI, 70 eV): *m/z* (%) = 342 (21), 341 (M^+, 100), 340 (49), 312 (15), 296 (18), 161 (20).

HRMS (EI): calcd. for $C_{18}H_{15}NO_2S_2$: 341.0544, found: 341.0548 (M^+).

5-Iodo-2-(phenylthio)thiazole (13a)



Prepared according to TP 4 from 2-(phenylthio)-5-(trimethylsilyl)thiazole (**8a**) (133 mg, 0.5 mmol) [deprotection conditions: –50 °C to 25 °C, 3 h]. The reaction mixture was quenched with sat. $Na_2S_2O_3$ sol. (10 mL) ant the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 6:1) yielded **13a** (123 mg, 77%) as a yellow solid.

mp (°C): 53–54.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.86 (s, 1H), 7.65–7.62 (m, 2H), 7.52–7.48 (m, 3H).

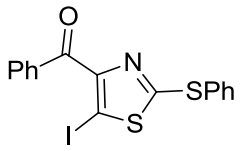
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 169.1,151.0, 133.7, 130.3, 130.2, 130.2, 74.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 1468, 1439, 1375, 1250, 1137, 1041, 1022, 957, 838, 758, 750, 736, 702, 686, 638.

MS (EI, 70 eV): *m/z* (%) = 320 (16), 319 (M^+, 100), 318 (65), 192 (62), 135 (12), 109 (37), 89 (45), 77 (19), 74 (42), 65 (17), 59 (66), 57 (12), 45 (47), 43 (11), 41 (13).

HRMS (EI): calcd. for $C_9H_6INS_2$: 318.8986, found: 318.8980 (M^+).

(5-Iodo-2-(phenylthio)thiazol-4-yl)(phenyl)methanone (13b)



Prepared according to TP 4 from phenyl(2-(phenylthio)-5-(trimethylsilyl)thiazol-4-yl)methanone (**10f**) (3 g, 8 mmol) [deprotection conditions: –50 °C to 25 °C, 5 h]. The reaction mixture was quenched with sat. $Na_2S_2O_3$ sol. (20 mL) and the resulting mixture was extracted with diethyl ether (3×50 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **13b** (3.1 g, 92%) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.91–7.89 (m, 2H), 7.70–7.68 (m, 2H), 7.64–7.60 (m, 1H), 7.55–7.47 (m, 5H).

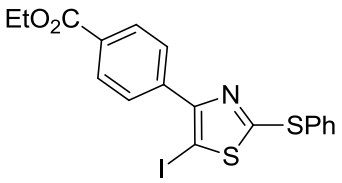
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 187.2, 170.2, 153.9, 136.2, 134.3, 133.3, 130.6, 130.3, 130.1, 129.3, 128.3, 82.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3055, 1642, 1592, 1472, 1439, 1424, 1415, 1272, 1249, 1212, 1179, 1049, 1030, 1020, 1012, 959, 943, 791, 753, 736, 721, 705, 689, 678, 650, 614.

MS (EI, 70 eV): *m/z* (%) = 424 (23), 423 (M^+, 96), 298 (12), 297 (26), 296 (78), 268 (18), 165 (16), 159 (12), 133 (18), 128 (78), 127 (44), 121 (14), 110(34), 109 (70), 89 (11), 78 (34), 77 (100), 66(11), 65(13), 50 (14), 44 (10).

HRMS (EI): calcd. for $C_{16}H_{10}INOS_2$: 422.9248, found: 422.9243 (M^+).

Ethyl 4-(5-iodo-2-(phenylthio)thiazol-4-yl)benzoate (13c)



Prepared according to TP 4 from ethyl 4-(2-(phenylthio)-5-(trimethylsilyl)thiazol-4-yl)benzoate (**10c**) (2.1 g, 5 mmol) [deprotection conditions: –50 °C to 25 °C, 7 h]. The reaction mixture was quenched with sat. $Na_2S_2O_3$ sol. (20 mL) and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **13c** (3.1 g, 92%) as a yellow solid.

mp (°C): 112–113.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 8.05–8.02(m, 2H), 7.99–7.96 (m, 2H), 7.74–7.72 (m, 2H), 7.59–7.52 (m, 3H), 4.33 (q, *J* = 7.15 Hz, 2H), 1.32 (t, *J* = 7.12 Hz, 3H).

^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 170.6, 165.3, 155.9, 138.0, 134.4, 130.7, 130.4, 129.6, 129.4, 129.2, 128.6, 72.1, 60.9, 14.2.

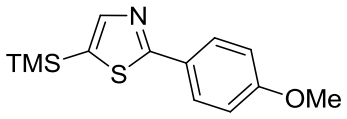
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976, 1694, 1659, 1608, 1461, 1440, 1412, 1406, 1387, 1367, 1305, 1277, 1172, 1117, 1096, 1068, 1039, 1016, 1004, 964, 864, 838, 774, 755, 710, 696, 688, 676, 651.

MS (EI, 70 eV): *m/z* (%) = 469 (12), 468 (20), 467 (M^+, 100), 341 (14), 340 (24), 268 (17), 206 (14), 205 (94), 177 (19), 160 (27), 132 (22).

HRMS (EI): calcd. for $C_{18}H_{14}INO_2S_2$: 466.9511, found: 466.9507 (M^+).

3.1.4. Synthesis of the products 14-16

2-(4-Methoxyphenyl)-5-(trimethylsilyl)thiazole (14)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, 2-(phenylthio)-5-(trimethylsilyl)thiazole (**8a**) (133 mg, 0.5 mmol) was dissolved in 0.5 mL THF. Then, $Ni(acac)_2$ (3.2 mg, 2.5 mol%), DPEphos (2,2'-bis(diphenylphosphino)diphenyl diethyl ether; 13 mg, 5 mol%) and (4-methoxyphenyl)zinc chloride (prepared by adding *i*PrMgCl·LiCl (1.5 mmol) to a 1.0 M solution of 1-iodo-4-methoxybenzene in THF (176 mg, 0.75 mmol) at 25 °C and stirring for 1 h and further transmetalation with $ZnCl_2$ (0.75 mL, 1.0 M in THF) at 25 °C for 10 min) were added at 25 °C and stirred at this temperature for 4 h. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 9:1) yielded **14** (112 mg, 85%) as a white solid.

mp (°C): 56-58**.**

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.89 (d, J = 8.75 Hz, 2H), 7.78 (s, 1H), 6.93 (d, J = 8.75 Hz, 2H), 3.83 (s, 3H), 0.35 (s, 9H).

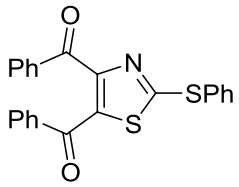
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.8, 161.1, 149.1, 131.8, 128.2, 126.7, 114.3, 55.4, -0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 1606, 1520, 1482, 1410, 1306, 1242, 1185, 1106, 1028, 970, 827, 749, 696, 633.

MS (EI, 70 eV): *m/z* (%) = 264 (13), 263 (M^+, 58), 248 (43), 116 (10), 115 (100), 73 (22).

HRMS (EI): calcd. for $C_{13}H_{17}NOSSi$: 263.0800, found: 263.0808 (M^+).

(2-(Phenylthio)thiazole-4,5-diyl)bis(phenylmethanone) (15)



Prepared according to TP2 from phenyl(2-(phenylthio)thiazol-5-yl)methanone (**8b**) (595 mg, 2 mmol) [metalation conditions: 25 °C, 8 h], $Pd(PPh_3)_4$ (46 mg, 2 mol%) was added followed by benzoyl chloride (0.9 mL, 3 mmol). The resulting solution was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 5:1) yielded **15** (586 mg, 82%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.87–7.84 (m, 2H), 7.77–7.74 (m, 2H), 7.62–7.59 (m, 2H), 7.54–7.48 (m, 4H), 7.47–7.41 (m, 1H), 7.39–7.34 (m, 2H), 7.29–7.24 (m, 2H).

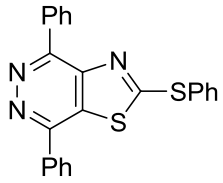
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 187.9, 187.1, 173.1, 155.0, 139.3, 137.3, 136.3, 135.3, 133.4, 133.3, 131.0, 130.4, 130.0, 129.5, 128.8, 128.4, 128.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944, 2231, 1619, 1573, 1461, 1448, 1388, 1369, 1241, 1142, 1105, 1006, 942, 836, 786, 773, 761, 736, 715.

MS (EI, 70 eV): *m/z* (%) = 403 (13), 402 (28), 401 (M^+, 93), 400 (13), 325 (14), 324 (61), 297 (13), 296 (59), 153 (19), 133 (10), 105 (100), 77 (82), 51 (15).

HRMS (EI): calcd. for $C_{23}H_{15}NO_2S_2$: 401.0544, found: 401.0541 (M^+).

4,7-Diphenyl-2-(phenylthio)thiazolo[4,5-*d*]pyridazine (16)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, (2-(phenylthio)thiazole-4,5-diyl)bis(phenylmethanone) (**15**) (314 mg, 0.78 mmol) was dissolved in 2 mL ethanol. Then, N_2H_4 (0.15 mL, 5 mmol) was added dropwise at 25 °C and stirred at this temperature for 5 min. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was dried

($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (CH_2Cl_2/EtOH; 20:1) yielded **16** (310 mg, 80%) as a yellow solid.

mp (°C): 193–195.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.58–8.55 (m, 2H), 8.00–7.97 (m, 2H), 7.77–7.74 (m, 2H), 7.61–7.44 (m, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 178.2, 152.9, 151.0, 149.8, 136.5, 135.6, 135.1, 134.8, 131.4, 130.4, 130.2, 129.9, 129.8, 128.9, 128.3, 128.3, 127.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 1523, 1440, 1413, 1382, 1351, 1074, 1017, 846, 773, 753, 693, 681, 667, 608.

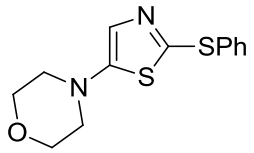
MS (EI, 70 eV): *m/z* (%) = 399 (12), 398 (28), 397 (M^+, 78), 396 (15), 322 (14), 321 (25), 320 (100), 293 (15), 289 (30), 288 (95), 261 (22), 234 (13), 202 (14), 189 (24), 127 (12), 121 (33), 109 (11), 105 (11), 77 (29), 69 (11), 57 (18), 55 (16), 44 (24), 43 (11), 41 (12).

HRMS (EI): calcd. for $C_{23}H_{15}N_3S_2$: 397.0707, found: 397.0704 (M^+).

3.2. Oxidative amination of heteroaromatic zinc reagents mediated by $PhI(OAc)_2$

3.2.1. Amination products obtained by metalation with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$

4-(2-Phenylsulfanylthiazol-5-yl)-morpholine (20a)



Prepared according to TP2 from 2-(phenylthio)thiazole (164 mg, 1 mmol) [metalation conditions: 25 °C, 2 h] and reaction with *N*-lithium morpholide (**18a**, 2 mmol; prepared by adding *n*BuLi (2 mmol) to a 0.5 M solution of morpholine in THF (174 mg, 2 mmol) at 0 °C and stirring for 30 min) according to TP5. Purification by flash chromatography (pentane/diethyl ether; 2:1; Al_2O_3 III) yielded **20a** (209 mg, 75%) as yellow oil.

^{1}H-NMR (C_6D_6, 300 MHz): δ (ppm) =7.48–7.44 (m, 2H), 7.00–6.88 (m, 3H), 6.85 (s, 1H), 3.28–3.25 (m, 4H), 2.44–2.41 (m, 4H).

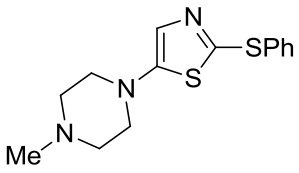
^{13}C-NMR (C_6D_6, 75 MHz): δ (ppm) = 158.1, 147.1, 135.3, 130.9, 129.2, 128.0, 123.2, 65.5, 51.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2969, 2919, 2900, 2853, 1738, 1728, 1505, 1477, 1473, 1444, 1439, 1402, 1375, 1365, 1293, 1257, 1223, 1217, 1115, 1081, 1068, 1057, 1037, 1023, 997, 929, 897, 784, 739, 687, 638, 633, 605.

MS (EI, 70 eV): *m/z* (%) = 279 (15), 278 (M^+, 100), 245 (9).

HRMS (EI): calcd. for $C_{13}H_{14}N_2OS_2$: 278.0548, found: 278.0538 (M^+).

1-Methyl-4-[2-(phenylthio)-1,3-thiazol-5-yl]piperazine (20b)



Prepared according to TP2 from 2-(phenylthio)thiazole (164 mg, 1 mmol) [metalation conditions: 25 °C, 2 h] and reaction with lithium *N*-methylpiperazide (**18b**, 2 mmol, prepared by adding *n*BuLi to a 1.0 M solution of *N*-methylpiperazine (200 mg, 2 mmol) in THF at 0 °C and stirring for 30 min) according to TP5. Purification by flash chromatography (pentane/diethyl ether; 2:1; Al_2O_3 III) yielded **20b** (210 mg, 72%) as a yellow oil.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.50-7.45 (m, 2H), 6.96-6.86 (m, 4H), 2.65 (t, *J* = 5.3 Hz, 4H), 1.95 (t, *J* = 5.3 Hz, 4H), 1.93 (s, 3H).

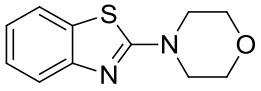
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 158.6, 146.6, 135.9, 130.9, 129.4, 127.7, 123.5, 54.1, 51.6, 46.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936, 2798, 1716, 1582, 1506, 1478, 1448, 1404, 1375, 1341, 1329, 1292, 1238, 1206, 1143, 1083, 1074, 1023, 1006, 970, 942, 888, 812, 791, 738, 689.

MS (EI, 70 eV): *m/z* (%) = 293 (9), 292 (17), 291 (M^+, 100), 206 (21), 70 (22), 43 (10).

HRMS (EI): calcd. for $C_{14}H_{17}N_3S_2$: 291.0864, found: 291.0861 (M^+).

2-Morpholin-4-yl-benzothiazole (20c)



Prepared according to TP2 from benzothiazole (135 mg, 1 mmol) [metalation conditions: 25 °C, 1 h] and reaction with lithium morpholide (**18a**, 2 mmol; prepared by adding *n*BuLi (2 mmol) to a 0.5 M solution of morpholine in THF (174 mg, 2 mmol) at 0 °C and stirring for 30 min) according to TP5. Purification by flash chromatography (pentane/diethyl ether; 2:1; Al_2O_3 III) yielded **20c** (161 mg, 73 %) as colorless solid.

mp (°C): 129–130.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.63–7.56 (m, 2H), 7.34–7.26 (m, 1H), 7.13–7.05 (m, 1H), 3.81 (t, J = 5.2 Hz, 4H), 3.61 (t, J = 5.3 Hz, 4H).

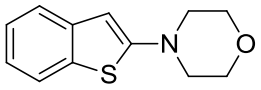
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 169.0, 152.5, 130.6, 126.1, 121.7, 120.8, 119.3, 66.3, 48.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2969, 2959, 2914, 2854, 1738, 1593, 1562, 1531, 1455, 1439, 1377, 1341, 1289, 1269, 1241, 1228, 1159, 1111, 1068, 1031, 1016, 945, 911, 858, 754, 727, 698, 656.

MS (EI, 70 eV): *m/z* (%) = 221 (11), 220 (M^+, 100), 219 (11), 189 (12), 175 (11), 163 (84), 162 (24), 136 (10), 135 (41), 108 (13), 95 (11).

HRMS (EI): calcd. for $C_{11}H_{12}N_2OS$: 220.0670, found: 220.0667 (M^+).

4-Benzo[*b*]thiophen-2-yl-morpholine (20d)



Prepared according to TP2 from benzothiophene (135 mg, 1 mmol) [metalation conditions: 25 °C, 24 h) and reaction with *N*-lithium morpholide (**18a**, 2.0 mmol; prepared by adding *n*BuLi (2 mmol) to a 0.5 M solution of morpholine in THF (174 mg, 2 mmol) at 0 °C and stirring for 30 min) according to TP5. Purification by flash chromatography (pentane/diethyl ether; 20:1; Al_2O_3 III) yielded **20d** (160 mg, 73 %) as a colorless solid.

mp (°C): 180-182.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.44–7.40 (m, 2H), 7.18–7.14 (m, 1H), 6.97–6.93 (m, 1H), 5.90 (s, 1H), 3.33 (t, *J* = 4.89 Hz, 2H), 2.70 (t, *J* = 4.89 Hz, 2H).

^{13}C-NMR (C_6D_6, 100MHz): δ (ppm) = 157.7, 140.7, 132.9, 124.5, 121.6, 121.5, 121.0, 99.4, 65.7, 50.6.

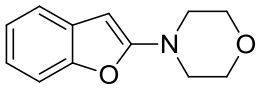
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1556, 1528, 1454, 1437, 1375, 1316, 1303, 1264, 1250, 1220, 1211, 1187, 1166, 1117, 1065, 1032, 1024, 1013, 933, 901, 869, 781, 744, 723, 653.

MS (EI, 70 eV): *m/z* (%) = 220 (12), 219 (M^+, 100), 161 (50), 160 (14).

HRMS (EI): calcd. for $C_{12}H_{13}NOS$: 219.0718, found: 219.0712 (M^+).

Large scale (10 mmol): 1.65 g, 75%

4-Benzofuran-2-yl-morpholine (20e)



Prepared according to TP2 from benzofuran (118 mg, 1 mmol) [metalation conditions: 100 °C, 60 min in a microwave] and reaction with *N*-lithium morpholide (**18a**, 2 mmol; prepared by adding *n*BuLi (2 mmol) to a 0.5 M solution of morpholine in THF (174 mg, 2 mmol) at 0 °C and stirring for 30 min) according to TP5. Purification by flash chromatography (pentane/diethyl ether; 3:1; Al_2O_3 III) yielded **20e** (122 mg, 60%) as a white solid.

mp (°C): 123–125.

^{1}H-NMR (C_6D_6, 300 MHz): δ (ppm) = 7.37–7.27 (m, 2H), 7.18–7.12 (m, 1H), 7.02–6.97 (m, 1H), 5.19 (d, *J* = 0.97 Hz, 1H), 3.41–3.38 (m, 4H), 2.83–2.80 (m, 4H).

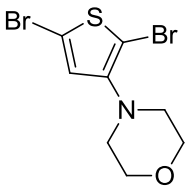
^{13}C-NMR (C_6D_6, 75 MHz): δ (ppm) = 161.0, 150.8, 130.4, 122.8, 120.6, 118.3, 109.7, 79.8, 66.1, 47.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2968, 2911, 2892, 2855, 1738, 1728, 1595, 1582, 1467, 1455, 1448, 1428, 1394, 1374, 1368, 1345, 1332, 1309, 1302, 1269, 1254, 1231, 1214, 1206, 1171, 1161, 1114, 1098, 1077, 1066, 1057, 1047, 1027, 1008, 971, 925, 894, 880, 851, 788, 752, 748, 725, 694, 665, 619, 610.

MS (EI, 70 eV): *m/z* (%) = 204 (14), 203 (M^+, 100), 146 (11), 145 (47), 138 (11), 95 (11), 81 (12), 55 (11), 44 (16).

HRMS (EI): calcd. for $C_{12}H_{13}NO_2$: 203.0946, found: 203.0938 (M^+).

4-(2,5-Dibromothiophen-3-yl)morpholine (20f)



Prepared according to TP2 from 2,5-dibromothiophene (242 mg, 1 mmol) [metalation conditions: 100 °C, 60 min in a microwave] and reaction with *N*-lithium morpholide (**18a**, 2.0 mmol; prepared by adding *n*BuLi (2 mmol) to a 0.5 M solution of morpholine in THF (174 mg, 2 mmol) at 0 °C and stirring for 30 min) according to TP5. Purification by flash chromatography (pentane/diethyl ether; 7:1) yielded **20f** (229 mg, 70 %) as a colorless solid.

mp (°C): 77–79.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.13 (s, 1H), 3.67–3.64 (m, 4H), 2.94–2.92 (m, 4H,).

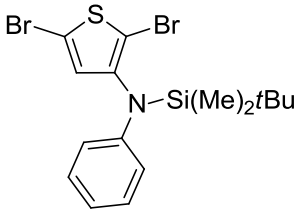
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 150.3, 125.7, 110.0, 96.7, 66.6, 51.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 2858, 2833, 1542, 1488, 1456, 1446, 1436, 1414, 1380, 1365, 1344, 1330, 1281, 1262, 1198, 1162, 1114, 1080, 1066, 1030, 1010, 982, 955, 935, 922, 865, 834, 806, 784, 759, 751, 697, 665, 650, 636, 626, 618, 612, 604.

MS (EI, 70 eV): *m/z* (%) = 328 (36), 326 (76), 325 (10), 324 (M^+, 37), 270 (50), 269 (14), 268 (100), 267 (17), 266 (49), 247 (16), 245 (14), 111 (10), 97 (18), 85 (10), 83 (15), 71 (13), 69 (11), 57 (17), 42 (18).

HRMS (EI): calcd for $C_8H_9{}^{79}Br_2NOS$ = 324.8772, found: 324.8771 (M^+).

(*Tert*-butyldimethylsilanyl)-(2,5-dibromothiophen-3-yl)phenylamine (20g)



Prepared according to **TP1** from 2,5-dibromothiophene (242 mg, 1 mmol) [reaction conditions: deprotonation with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at 100 °C for 60 min in a microwave] and lithium (*tert*-butyl-dimethyl-silanyl)-phenyl-amide (**18c**, 2 mmol, prepared by adding *n*BuLi to a 0.5 M solution of (*tert*-butyl-dimethyl-silanyl)-phenyl-amine (414 mg, 2 mmol) in THF at -20 °C

and stirring for 30 min). Purification by flash chromatography (pentane; Al_2O_3 III) yielded **20g** (300 mg, 67 %) as a colorless oil.

^{1}H-NMR (C_6D_6, 300 MHz): δ (ppm) = 7.08–7.03 (m, 2H), 6.97–6.94 (m, 2H), 6.83–6.78 (m, 1H), 6.77 (s, 1H), 0.87 (s, 9H), 0.15 (s, 6H).

^{13}C-NMR (C_6D_6, 75 MHz):): δ (ppm) = 148.2, 126.1, 132.2, 128.7, 121.9, 121.5, 110.1, 109.7, 27.4, 19.8, -2.6.

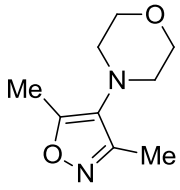
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2929, 2886, 2857, 1471, 1462, 1409, 1390, 1360, 1303, 1252, 1220, 1188, 1175, 1067, 1048, 1004, 938, 833, 818, 777, 690, 678, 670, 624, 613.

MS (EI, 70 eV): *m/z* (%) = 449 (6), 447 (11), 445 (M^+, 5), 392 (22), 390 (41), 388 (19), 312 (18), 311 (100), 310 (30), 309 (85), 308 (15), 139 (10), 85 (11), 73 (28), 71 (13), 57 (17).

HRMS (EI): calcd. for $C_{16}H_{21}Br_2NSSi$: 444.9531, found: 444.9534 (M^+).

3.2.2. Amination products obtained by Mg insertion in the presence of $ZnCl_2$ and LiCl

4-(3,5-Dimethylisoxazol-4-yl)morpholine (25a)



Prepared according to **TP7** from 4-Bromo-3,5-dimethyl-isoxazole (**22a**, 176 mg, 1 mmol, stirring for 40 min) and lithium diphenyl amide *N*-lithium morpholide (**18a**, 2 mmol; prepared by adding *n*BuLi (2 mmol) to a 0.5 M solution of morpholine in THF (174 mg, 2 mmol) at 0 °C and stirring for 30 min). Purification by flash chromatography (pentane/diethyl ether; 1:1) yielded **25a** (120 mg, 66%) as a yellow oil.

^{1}H-NMR (C_6D_6, 300 MHz): δ (ppm) = 3.79 (t, *J* = 4.6 Hz, 4H), 2.97 (t, *J* = 4.6 Hz, 4H), 2.40 (s, 3H), 2.27(s, 3H).

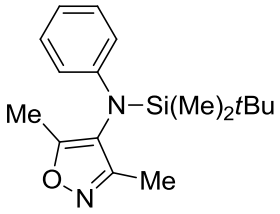
^{13}C-NMR (C_6D_6, 75 MHz): δ (ppm) = 161.4, 158.2, 127.2, 67.6, 52.0, 11.6, 10.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2853, 1631, 1450, 1422, 1384, 1373, 1318, 1297, 1264, 1214, 1113, 1069, 1051, 1030, 923, 917, 884, 844, 706.

MS (EI, 70 eV): *m/z* (%) = 182 (M^+, 28), 154 (10), 141 (27), 98 (61), 85 (12), 71 (28), 69 (11), 68 (15), 54 (13), 42 (100), 40 (32).

HRMS (EI): calcd. for $C_9H_{14}N_2O_2$: 182.1055, found: 182.1049 (M^+).

(*Tert*-butyldimethylsilanyl)-(3,5-dimethylisoxazol-4-yl)phenylamine (25b)



Prepared according to **TP7** from 4-bromo-3,5-dimethyl-isoxazole (**22a**, 176 mg, 1 mmol) and lithium (*tert*-butyl-dimethyl-silanyl)-phenyl-amide (**18c**, 2 mmol, prepared by adding *n*BuLi to a 0.5 M solution of (*tert*-butyl-dimethyl-silanyl)-phenyl-amine (414 mg, 2 mmol) in THF at -20 °C and stirring for 30 min). Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **25b** (182 mg, 60 %) as yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.16–7.14 (m, 2H), 6.88–6.83 (m, 3H), 2.31 (s, 3H), 2.09 (s, 3H), 0.96 (s, 9H), 0.21 (s, 6H).

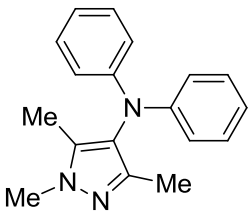
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 164.7, 160.3, 148.7, 128.8, 123.6, 120.9, 120.4, 27.9, 19.9, 11.3, 9.9, -2.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2855, 1594, 1490, 1472, 1440, 1419, 1276, 1260, 1249, 1241, 1215, 1030, 948, 891, 876, 858, 836, 821, 802, 772, 746, 706, 691, 681, 633.

MS (EI, 70 eV): *m/z* (%) = 302 (M^+, 23), 246 (20), 245 (96), 204 /19), 161 (17), 137 (21), 126 (15), 111 (24), 109 (17), 103 (29), 101 (58), 99 (16), 97 (35), 95 (22), 85 (40), 83 (30), 73 (100), 71 (51), 69 (28), 56 (20), 55 (24), 37 (27).

HRMS (EI): calcd. for $C_{17}H_{26}N_2OSi$: 302.1814, found: 302.1822 (M^+).

Diphenyl(1,3,5-trimethyl-1*H*-pyrazol-4-yl)amine (25c)



Prepared according to **TP7** from 4-bromo-1,3,5-trimethyl-1*H*-pyrazole (**22b**, 189 mg, 1 mmol, stirring for 30 min) and lithium diphenyl amide (**18d**, 2 mmol, prepared by adding *n*BuLi to a 0.5 M solution of diphenylamine (338 mg, 2 mmol) in THF at –20 °C and stirring for 30 min at

0 °C). Purification by flash chromatography (pentane/diethyl ether; 1:1) yielded **25c** (208 mg, 66 %) as a yellow solid.

mp (°C): 78–80.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.25–7.20 (m, 4H), 7.07–7.03 (m, 4H), 6.94–6.89 (m, 2H), 3.76 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 146.9, 145.1, 136.1, 129.0, 123.8, 121.1, 120.2, 36.4, 11.5, 9.2.

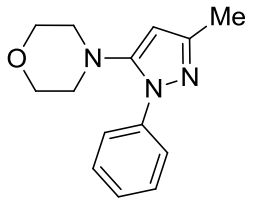
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2919, 1584, 1482, 1457, 1448, 1386, 1373, 1322, 1287, 1276, 1198, 1170, 1153, 1116, 1075, 1037, 1025, 998, 983, 959, 916, 890, 831, 755, 712, 693, 644, 638, 628, 620, 605.

MS (EI, 70 eV): *m/z* (%) = 278 (18), 277 (M^+, 100), 56 (14).

HRMS (EI): calcd. for $C_{18}H_{19}N_3$: 277.1579, found: 277.1574 (M^+).

Large scale (10 mmol): 1.8 g, 65%.

4-(5-Methyl-2-phenyl-2H-pyrazol-3-yl)morpholine (25d)



Prepared according to **TP7** from 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole (**22c**, 193 mg, 1 mmol, stirring for 1 h) and *N*-lithium morpholide (**18a**, 2 mmol; prepared by adding *n*BuLi (2 mmol) to a 0.5 M solution of morpholine in THF (174 mg, 2 mmol) at 0 °C and stirring for 30 min). Purification by flash chromatography (pentane/diethyl ether; 7:1; Al_2O_3 III) yielded **25d** (163 mg, 67 %) as a yellow solid.

mp (°C): 68–69.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.74–7.72 (m, 2H), 7.45–7.41 (m, 2H), 7.27–7.23 (m, 1H), 5.79 (s, 1H), 3.61–3.59 (m, 4H), 2.74 -2.72 (m, 4H), 2.13 (s, 3H).

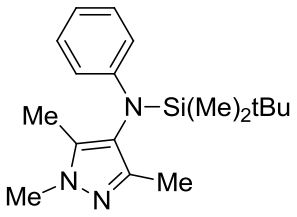
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 152.2, 148.3, 140.4, 129.5, 126.6, 122.4, 94.9, 66.1, 51.6, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2848, 2821, 1589, 1554, 1503, 1456, 1445, 1429, 1387, 1370, 1358, 1287, 1266, 1252, 1162, 1114, 1070, 1020, 909, 854, 848, 794, 746, 690, 675, 659, 648.

MS (EI, 70 eV): *m/z* (%) = 257 (12), 256 (14), 243 (M^+, 27), 239 (10), 186 (16), 184 (12), 150 (24), 102 (19), 98 (11), 97 (13), 85 (22), 83 (31), 71 (17), 69 (14), 60 (15), 57 (20), 55 (17), 44 (100), 43 (18), 41 (10).

HRMS (EI): calcd. for $C_{14}H_{17}N_3O$: 243.1372, found: 243.1362 (M^+).

(*Tert*-butyldimethylsilanyl)phenyl-(1,3,5-trimethyl-1H-pyrazol-4-yl)amine (25e)



Prepared according to **TP7** from 4-bromo-1,3,5-trimethyl-1*H*-pyrazole (**22b**, 190 mg, 1 mmol, stirring for 30 min) and lithium (*tert*-butyldimethylsilanyl)phenyl amide (**18c**, 2 mmol, prepared by adding *n*BuLi to a 0.5 M solution of (*tert*-butyldimethylsilanyl)phenylamine (414 mg, 2 mmol) in THF at -20 °C and stirring for 30 min). Purification by flash chromatography (pentane/Et_2O; 20:1) yielded **25e** (208 mg, 66 %) as a yellow solid.

mp (°C): 59–61

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.12–7.08 (m, 2H), 6.80–6.75 (m, 3H), 3.71 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 0.97 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H).

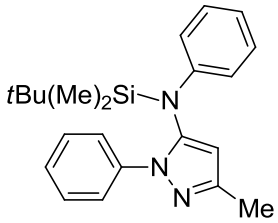
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 150.2, 145.6, 136.0, 128.4, 125.1, 119.3, 119.2, 36.5, 28.2, 20.1, 11.8, 9.7, -2.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2946, 2927, 2855, 1595, 1488, 1476, 1468, 1384, 1374, 1363, 1295, 1253, 1221, 1182, 1151, 941, 886, 834, 823, 805, 775, 756 (vs), 710, 700, 684, 660, 620.

MS (EI, 70 eV): *m/z* (%) = 315 (M^+, 33), 259 (21), 258 (100).

HRMS (EI): calcd. for $C_{18}H_{29}N_3Si$: 315.2131, found: 315.2130 (M^+).

(*Tert*-butyldimethylsilanyl)-(5-methyl-2-phenyl-2H-pyrazol-3-yl)phenyl-amine (25f)



Prepared according to **TP7** from 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole (**22c**, 193 mg, 1 mmol, stirring for 1 h) and lithium (*tert*-butyldimethylsilanyl)phenyl amide (**18c**, 2 mmol, prepared by adding *n*BuLi to a 0.5 M solution of (*tert*-butyl-dimethyl-silanyl)-phenyl-amine (414 mg, 2 mmol) in THF at –20 °C and stirring for 30 min). Purification by flash chromatography (pentane/diethyl ether; 10:1) yielded **25f** (207 mg, 57 %) as a yellow solid.

mp (°C): 107–108.

^{1}H-NMR ($CDCl_3$, 300 MHz,): δ (ppm) = 7.31–7.24 (m, 5H), 7.21–7.15 (m, 2H), 6.95 -6.88 (m, 3H), 6.12 (s, 1H), 2.37 (s, 3H), 0.87 (s, 9H), 0.00 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 148.5, 148.4, 145.3, 139.1, 128.8, 128.5, 126.9, 124.5, 121.2, 120.8, 106.3, 27.4, 20.3, 14.4, –2.7.

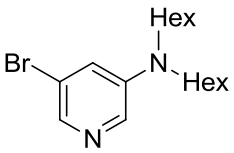
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 2852, 1596, 1548, 1498, 1488 1466, 1442, 1415, 1388, 1378, 1362, 1254, 1233, 1184, 1176, 1157, 1027, 1010, 997, 934, 906, 886, 867, 838, 822, 804, 794, 784, 758, 750, 722, 690, 666, 660, 627, 615.

MS (EI, 70 eV): *m/z* (%) = 363 (M^+, 10), 307 (22), 306 (100).

HRMS (EI): calcd. for $C_{22}H_{29}N_3Si$: 363.2131, found: 363.2130 (M^+).

3.2.3. Large Scale Amination Reactions

(5-Bromo-pyridin-3-yl)-dihexyl-amine (27a)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 3,5-dibromopyridine (**26**, 2.36 g, 10 mmol). After cooling to 0 °C, *i*PrMgCl·LiCl

(**1**, 9.0 mL, 1.24 M in THF, 11 mmol) was added dropwise and stirred for 30 min. at this temperature and for further 30 min at 25 °C. Then, THF (10 mL) was added and the resulting solution was stirred for additional 10 min at 25 °C. After cooling to 0 °C, $ZnCl_2$ (5.5 mL, 1.0 M in THF, 5.5 mmol) was added and the mixture was stirred for 30 min at this temperature. CuCl·2LiCl (11 mL, 1.0 M in THF, 11 mmol) was added dropwise at –50 °C and the resulting mixture was stirred for additional 30 min at –50 °C. Lithium dihexylamide (**18e**, 20 mmol, prepared by adding *n*BuLi to a 0.5 M solution of dihexylamine (3.71 g, 20 mmol) in THF at -20 °C and stirring for 30 min at 0 °C) was added dropwise to the resulting cuprate, and the mixture was stirred for 1 h at –50 °C. The reaction mixture was cooled to –78 °C, then a solution of $PhI(OAc)_2$ (3.54 g, 11 mmol) in dry THF (100 mL) was added slowly over a period of 60 min. The reaction mixture was then warmed to –50 °C and stirred for 3 h. diethyl ether (300 mL) was poured into the crude reaction mixture. The organic phase was washed with 2×100 mL portions of aqueous NH_4OH (2.0 M) and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether; 20:1) yielded **27a** (1.85 g, 54 %) as yellow oil.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 8.24 (d, *J* = 1.96 Hz, 1H), 8.11 (d, *J* = 2.74 Hz, 1H), 6.97 (t, *J* = 1.96 Hz, 1H), 2.81 (t, *J* = 7.63 Hz, 4H), 1.30–1.16 (m, 8H), 1.13–0.98 (m, 8H), 0.86 (t, *J* = 7.23 Hz, 6H).

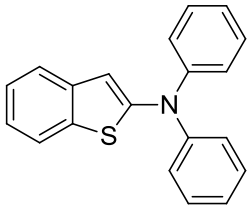
^{13}C-NMR (C_6D_6, 100 MHz,): δ (ppm) = 144.8, 137.2, 133.1, 121.1, 119.4, 50.3, 31.5, 26.7, 26.5, 26.4, 22.6, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2926, 2870, 2856, 1572, 1533, 1465, 1428, 1368, 1255, 1242, 1228, 1213, 1176, 1164, 1135, 1106, 992, 837, 822, 797, 725, 697, 657.

MS (EI, 70 eV): *m/z* (%) = 342 (15), 340 (M^+, 16), 272 (12), 271 (88), 270 (13), 269 (100), 201 (46), 199 (47), 187 (15), 185 (16), 43 (23).

HRMS (EI): calcd. for $C_{17}H_{29}BrN_2$: 340.1514, found: 340.1509 (M^+).

Benzo[*b*]thiophen-2-yldiphenylamine (27b)



Prepared according to TP2 from benzothiophene (**21b**, 135 mg, 10 mmol) [metalation conditions: 25 °C, 24 h] and reaction with *N*-lithium diphenylamide (**18d**, 20 mmol; prepared by adding *n*BuLi (20 mmol) to a 1.0 M solution of diphenylamine in THF (3.38 g, 20 mmol) at -20 °C and stirring for 5 min and further stirring at 0 °C for 30 min) according to TP5. Purification by flash chromatography (pentane; Al_2O_3 III) yielded **27b** (18.1 g, 60 %) as a colorless solid.

mp (°C): 134-136.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.37–7.30 (m, 2H), 7.16–7.10 (m, 4H), 7.05–6.98 (m, 6H), 6.88–6.81 (m, 2H), 6.63 (s, 1H).

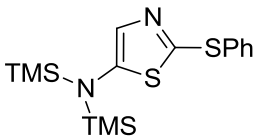
^{13}C-NMR (C_6D_6, 100 MHz,): δ (ppm) = 151.9, 147.6, 139.4, 136.1, 129.2, 124.3, 123.6, 123.5, 123.3, 122.3, 122.0, 114.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1586, 1562, 1530, 1518, 486, 1458, 1436, 1418, 1316, 1292, 1276, 1250, 1241, 1172, 1158, 761, 750, 726, 695, 688.

MS (EI, 70 eV): *m/z* (%) = 302 (23), 301 (M^+, 100), 300 (18), 223 (12), 197 (29), 121 (13), 77 (10).

HRMS (EI): calcd. for $C_{20}H_{15}NS$: 301.0925, found: 301.0919 (M^+).

5-(1,1,1,3,3,3-Hexamethyl-disilazan-2-yl)-2-phenylsulfanyl-thiazole (27d)



Prepared according to **TP2** from 2-(phenylthio)-1,3-thiazole (**5**, 1.64 g, 10 mmol) [metalation conditions: 25 °C, 2 h] and reaction with $LiN(SiMe_3)_2$ (**18f**, 20 mmol, 20 mL, 1 M in THF) according to TP5. Purification by flash chromatography (pentane/diethyl ether; 19:1; Al_2O_3 III) yielded **27d** (2.22 g, 63%) as yellow oil.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.48–7.46 (m, 2H), 7.06 (s, 1H), 6.97–6.90 (m, 3H), 0.00 (s, 18H).

^{13}C-NMR (C_6D_6, 100 MHz,): δ (ppm) = 156.6, 150.9, 138.1, 137.3, 133.5, 132.2, 129.9, 129.2, 128.1, 1.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 1514, 1500, 1477, 1440, 1403, 1377, 1273, 1251, 1150, 1141, 1016, 922, 874, 840, 819, 739, 701, 686, 624.

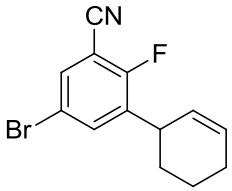
MS (EI, 70 eV): *m/z* (%) = 354 (18), 353 (28), 352 (M^+, 100), 337 (23), 243 (32), 206 (11), 116 (22), 73 (84), 45 (10).

HRMS (EI): cald. for $C_{15}H_{24}N_2S_2Si_2$: 352.0919, found: 352.0912 (M^+).

3.3. Efficient Preparation of Polyfunctional Organometallics *Via* Directed *Ortho*-Metalation Using TMP-Bases of La, Mn and Fe

3.3.1. Metalation with $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$

5-Bromo-2-fluoro-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carbonitrile (32a)



In a dry argon-flushed 100 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum 5-bromo-2-fluorobenzonitrile (**31a**; 3.0 g, 15 mmol) was dissolved in THF (15 mL). This solution was cooled to 0 °C, then $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**28**; 0.34 M in THF, 26.4 mL, 9.0 mmol) was dropwise added and stirred at this temperature for 0.5 h. The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 3.0 mL) and 3-bromocyclohexene (1.95 mL, 15.0 mmol) were then added dropwise and the reaction mixture was allowed to warm up slowly to 25 °C overnight. The reaction was then quenched with a sat. NH_4Cl (60 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether 50:1) yielded **32a** (4.03 g, 96%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.12–8.10 (m, 1H), 7.66–7.63 (m, 1H), 6.00–5.95 (m, 1H), 5.59–5.55 (m, 1H), 3.73–3.68 (m, 1H), 2.08–1.90 (m, 3H), 1.65–1.46 (m, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 159.9 (d, *J* = 256.4 Hz), 137.3 (d, *J* = 5.7 Hz), 136.1 (d, *J* = 14.9 Hz), 133.7, 130.3, 126.8, 116.6 (d, *J* = 3.8 Hz), 112.9, 102.3 (d, *J* = 17.3 Hz), 34.1, 29.3, 24.2, 20.2.

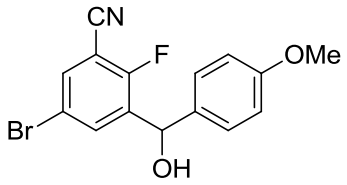
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 2862, 2239, 1458, 1448, 1325, 1314, 1294, 1274, 1261, 1248, 1230, 1222, 1199, 952, 925, 920, 870, 775, 766, 742, 723, 700, 681, 636, 614.

MS (EI, 70 eV): *m/z* (%) = 282 (11), 281 (51), 280 (M^+, 9), 279 (49), 266 (38), 264 (32), 251 (11), 227 (14), 225 (15), 200 (22), 185 (32), 184 (12), 173 (15), 172 (100), 171 (28), 159 (43), 158 (29), 152 (23), 145 (21), 144 (10), 67 (29), 54 (69), 41 (28).

HRMS (EI): calcd. for $C_{13}H_{11}BrFN$: 279.0059, found: 279.0055 (M^+).

3.3.2. Metalation with $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$

5-Bromo-2-fluoro-3-(hydroxy(4-methoxyphenyl)methyl)benzonitrile (32b)



In a dry argon-flushed 100 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum 5-bromo-2-fluorobenzonitrile (**31a**; 3 g, 15 mmol) was dissolved in THF (15 mL). The solution was cooled to -35 °C, then $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**30**; 0.35 M in THF, 13 mL, 4.6 mmol) was dropwise added and stirred at this temperature for 0.5 h. After addition of 4-methoxy-benzaldehyde (1.77 g, 1.6 mL, 13 mmol) the reaction mixture was allowed to warm up slowly to 25 °C over night. The reaction was then quenched with sat. NaCl (60 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether 5:1) yielded **32b** (4.03 g, 80%) as a colorless solid.

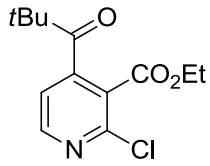
mp (°C): 124–126.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 8.10–8.04 (m, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.30 (d, *J* = 4.5 Hz, 1H), 5.90 (d, *J* = 4.5 Hz, 1H), 3.7 (s, 3H).

^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 158.7, 158.6 (d, *J* = 257.2 Hz), 136.3 (d, *J* = 13.8 Hz), 135.5 (d, *J* = 5.4 Hz), 134.6, 134.3, 127.7, 116.7 (d, *J* = 3.5 Hz), 113.8, 112.7, 102.3(d, *J* = 16.9 Hz), 67.4 (d, *J* =1.9 Hz), 55.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3513, 2241, 1608, 1511, 1460, 1440, 1368, 1304, 1284, 1246, 1208, 1191, 1177, 1058, 1024, 866, 843, 829, 820, 786, 758, 718, 665, 644, 634, 627, 614.
MS (EI, 70 eV): *m/z* (%) = 337 (39), 336 (M^+, 14), 335 (41), 228 (16), 226 (18), 137 (63), 135 (11), 109 (100), 77 (10).
HRMS (EI): calcd. $C_{15}H_{11}BrFNO_2$: 334.9957, found: 334.9954 (M^+).

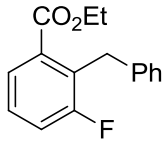
2-Chloro-4-(2,2-dimethyl-propionyl)-nicotinic acid ethyl ester (32c)



In a dry argon-flushed 100 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum ethyl 2-chloro-nicotinate (**31b**; 2.79 g, 15 mmol) was dissolved in THF (15 mL). The solution was cooled to -20 °C, then $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**30**; 0.35 M in THF, 13 mL, 4.6 mmol) was dropwise added and stirred at this temperature for 0.75 h. After addition of 2,2-dimethylpropanoic anhydride (3.04 mL, 15.0 mmol the reaction mixture was allowed to warm up slowly to 25 °C over night. The reaction mixture was then quenched with sat. NaCl (60 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether 5:1) yielded **32c** (3.24 g, 80%) as a yellow oil.
^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 8.59 (d, *J* = 5.07 Hz, 1H), 7.67 (d, *J* = 5.07 Hz, 1H), 4.27 (q, *J* = 7.21 Hz, 2H), 1.24 (t, *J* = 7.21 Hz, 3H), 1.19 (s, 9H).
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 209.3, 164.6, 152.6, 151.7, 150.1, 126.0, 119.8, 62.8, 44.4, 27.2, 14.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2977, 727, 1696, 1574, 1538, 1479, 1463, 1449, 1394, 1380, 1364, 1271, 1222, 1185, 1127, 1096, 1065, 1042, 999, 854, 832, 796, 777, 768, 744, 705, 626.
MS (EI, 70 eV): *m/z* (%) = 213 (16), 212 (20), 186 (27), 183 (100), 113 (11), 57 (21).
HRMS (EI): calcd. for $C_{13}H_{16}ClNO_3$: 269.0819, found: 269.0808 (M^+).

3.3.3. Metalation with $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$

2-Benzyl-3-fluoro-benzoic acid ethyl ester (32d)



In a dry argon-flushed 100 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum ethyl 3-fluoro benzoate (**31c**; 2.52 g, 15.0 mmol) was dissolved in THF (15 mL). Then, $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**3**; 0.53 M in THF, 21.2 mL, 11.25 mmol) was added dropwise at 25 °C and stirred at this temperature for 3 h. Then, benzylchloride (2.28 g, 2.1 mL, 18 mmol) was dropwise added and the reaction mixture was allowed to stirr at 25°C overnight. The reaction was then quenched with a mixture of sat. NH_4Cl (60 mL) and HCl (2 M, 25 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether 10:1) yielded **32d** (3.3 g, 85%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.75–7.72 (m, 1H), 7.35–7.17 (m, 7H), 4.48 (d, *J* = 1.9 Hz, 2H), 4.34 (q, *J* = 7.3 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 186.7 (d, *J* = 3.4 Hz), 161.5 (d, *J* = 245 Hz), 139.9, 132.5 (d, *J* = 4.1 Hz), 129.0 (d, *J* = 17.0 Hz), 128.3 (d, *J* = 1.0 Hz), 128.1, 127.4 (d, *J* = 8.8 Hz), 126.1 (d, *J* = 3.6 Hz), 125.8, 118.8 (d, *J* = 23.7 Hz), 61.1, 30.9 (d, *J* = 4.6 Hz), 14.1.

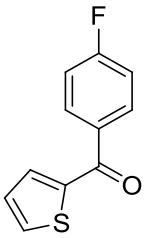
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3030, 2982, 2938, 1718, 1604, 1583, 1496, 1452, 1391, 1367, 1259, 1215, 1182, 1172, 1159, 1132, 1112, 1096, 1075, 1025, 969, 912, 865, 843, 829, 798, 785, 755, 730, 720, 695, 640.

MS (EI, 70 eV): *m/z* (%) = 258 (M^+, 3), 213 (22), 212 (100), 183 (21), 151 (10).

HRMS (EI): calcd. for $C_{16}H_{15}FO_2$: 258.1056, found: 258.1059 (M^+).

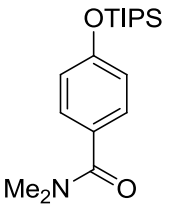
3.4. Selective Mg Insertion into Substituted Mono- and Di-Chloro Arenes in the Presence of LiCl

(4-Fluorophenyl)(thiophen-2-yl)-methanone (43a)



Freshly prepared and titrated (4-fluoro-phenyl)magnesium chloride (**37b**) (1.59 mL, 1 mmol) prepared according to TP7 (2 h, 0.63 M, 65%), was transmetalated with CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol) at -20 °C and stirred for 30 min. After addition of thiophene-2-carbonyl chloride (117 mg, 0.8 mmol) the resulting solution was stirred for 30 min at this temperature. The reaction was then quenched with sat. NH_4Cl (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography (isohexane/diethyl ether 50:1) yielded **43a** (151 mg, 73%) as a white solid.
Analytical data matches the literature.[96]

***N*,*N*-Dimethyl-4-((triisopropylsilyl)-oxy)benzamide (43b)**



Freshly prepared and titrated (4-((triisopropylsilyl)oxy)phenyl)magnesium chloride (**37c**) (1.56 mL, 1 mmol) prepared according to TP7 (4 h, 0.64 M, 64%), was added dimethylcarbamoyl chloride (86 mg, 0.8 mmol) at -20 °C and stirred for 30 min. The reaction was then quenched with sat. NH_4Cl (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. Purification by

[96] Zhao, W.; Carreira, E. M. *Chem. Eur. J.* **2007**, *13*, 2671.

flash chromatography (isohexane/diethyl ether 10:1) yielded **43b** (260 mg, 81%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.33–7.29 (m, 2H), 6.88–6.84 (m, 2H), 3.03 (s, 6H), 1.31–1.20 (m, 3H), 1.08 (d, J = 7.24 Hz, 18H).

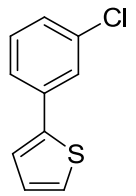
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 171.6, 157.3, 129.0, 128.7, 119.5, 36.4 (br), 17.8, 12.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944, 2867, 1634, 1604, 1514, 1490, 1463, 1387, 1261, 1168, 1102, 1078, 1013, 997, 908, 882, 845, 766, 752, 709, 684, 675.

MS (EI, 70 eV): *m/z* (%) = 321 (M^+, 22), 279 (18), 278 (100), 277 (12), 250 (39), 222 (57), 208 (18), 110 (25), 103 (19), 72 (88).

HRMS (EI): calcd. for $C_{18}H_{31}NO_2Si$: 321.2124, found: 321.2118 (M^+).

2-(3-Chlorophenyl)thiophene (43c)



Freshly prepared and titrated (3-chlorophenyl)magnesium chloride (**39a**) (1.33 mL, 1 mmol) prepared according to TP7 (45 min, 0.75 m, 72%), was transmetalated with $ZnCl_2$ (1 M in THF, 1.1 mL, 1.1 mmol) at 25 °C. After addition of 2-iodothiophene (168 mg, 0.8 mmol), $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) the resulting solution was stirred for 1 h at 25 °C. The reaction mixture was then quenched with sat. NH_4Cl (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography (isohexane) yielded **43c** (165 mg, 85%) as a colorless solid.

mp (°C): 25-26.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.58–7.57 (m, 1H), 7.48–7.44 (m, 1H), 7.30–7.28 (m, 3H), 7.24–7.20 (m, 1H), 7.06 (dd, J =, 4.98 Hz, J = 3.59 Hz, 1H).

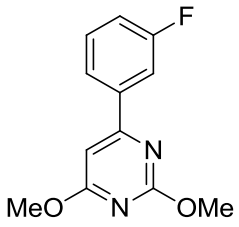
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 142.7, 136.1, 134.8, 130.1, 128.1, 127.3, 125.9, 125.5, 124.0, 123.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3104, 3066, 3035, 1932, 1856, 1794, 1658, 1589, 1563, 1529, 1479, 1466, 1419, 1256, 1215, 1172, 1078, 1056, 979, 874, 856, 826, 774, 763, 752, 734, 693, 680.

MS (EI, 70 eV): *m/z* (%) = 196 (36), 195 (12), 194 (M^+, 100), 159 (13), 149 (16), 115 (32).

HRMS (EI): calcd. for $C_{10}H_7ClS$: 193.9957, found: 193.9952 (M^+).

4-(3-Fluorophenyl)-2,6-dimethoxy-pyrimidine (43d)



Freshly prepared and titrated (3-fluoro-phenyl)magnesium chloride (**39b**) (1.56 mL, 1 mmol) prepared according to TP7 (4 h, 0.64 M, 60%), was transmetalated with $ZnCl_2$ (1 M in THF, 1.1 mL, 1.1 mmol) at 25 °C. After addition of 4-iodo-2,6-dimethoxypyrimidine (213 mg, 0.8 mmol), $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) the resulting solution was stirred for 3 h at 25 °C. The reaction mixture was then quenched with sat. NH_4Cl (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography (isohexane/diethyl ether 10:1) yielded **43d** (173 mg, 74%) as a light yellow solid.

mp (°C): 53–54.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.79–7.75 (m, 2H), 7.44–7.37 (m, 1H), 7.17–7.11 (m, 1H), 6.74 (s, 1H), 4.07 (s, 3H), 4.00 (s, 3H).

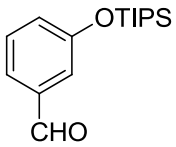
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.7, 165.5, 164.5 (d, *J* = 2.8 Hz), 163.1 (d, *J* = 246 Hz), 139.1 (d, *J* = 7.85 Hz), 130.1 (d, *J* = 8.13 Hz), 122.5 (d, *J* = 2.8 Hz), 117.4 (d, *J* = 21.6 Hz), 114.0 (d, *J* = 23 Hz), 97.4, 54.8, 53.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1}= 3080, 2954, 2361, 1567, 1481, 1462, 1352, 1258, 1242, 1199, 1160, 1099, 1018, 982, 922, 886, 825, 802, 784, 777, 706, 662.

MS (EI, 70 eV): *m/z* (%) = 235 (18), 234 (M^+, 100), 233 (74), 219 (18), 205 (23), 204 (56), 203 (13), 189 (24), 163 (16), 146 (15).

HRMS (EI): calcd. for $C_{12}H_{11}FN_2O_2$: 234.0805, found: 234.0808 (M^+).

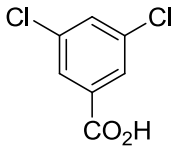
3-((Triisopropylsilyl)oxy)-benzaldehyde (43e)



Freshly prepared and titrated (3-((triisopropylsilyl)oxy)phenyl)magnesium chloride (**39c**) (1.45 mL, 1 mmol) prepared according to TP7 (3 h, 0.69 M, 74%), was added *N*,*N*-dimethylformamide (80 mg, 1.1 mmol) at -20 °C and stirred for 30 min. The reaction was then quenched with sat. NH_4Cl (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography (isohexane/diethyl ether 20:1) yielded **43e** (267 mg, 96%) as a yellow oil.

Analytical data matches the literature.[97]

3,5-Dichlorobenzoic acid (43f)



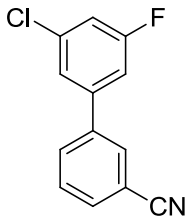
Freshly prepared and titrated (3,5-dichlorophenyl)-magnesium chloride (**41a**)(1.54 mL, 1 mmol) prepared according to TP7 (30 min, 0.65 M, 73%), was to a flask filled with dry $CO_{2(g)}$. Then, dry $CO_{2(g)}$ was bubbled through the reaction mixture (ca. 5 min) until a balloon attached to the reaction flask by a short length rubber tubing and a needle adapter was inflated. The reaction mixture was stirred for 1 h at 25 °C and then diluted with diethyl ether (15 mL) and extracted with sat. aq. $NaHCO_3$ (3×20 mL). The combined aq. phases were carefully acidified with HCl (5 mL) until pH<5 and extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo* to give **43f** (189 mg, 99%) as a yellow solid.

Analytical data matches the literature.[98]

[97] Joncour, A.; Liu, J. M.; Décor, A.; Thoret, S.; Wdzieczak-Bakala, J.; Bignon, J.; Baudoin, O. *ChemMedChem* **2008**, *3*, 1731.

[98] Heiss, C.; Marzi, E.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 4625.

3'-Chloro-5'-fluoro-(1,1'-biphenyl)-3-carbonitrile (43g)



Freshly prepared and titrated (3-chloro-5-fluorophenyl)magnesium chloride (**41b**) (1.49 mL, 1 mmol) prepared according to TP7 (45 min, 0.67 M, 67%), was transmetalated with $ZnCl_2$ (1 M in THF, 1.1 mL, 1.1 mmol) at 25 °C. After addition of 3-iodobenzonitrile (183 mg, 0.8 mmol), $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) the resulting solution was stirred for 2 h at 25 °C. The reaction mixture was then quenched with sat. NH_4Cl (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography (isohexane/diethyl ether 10:1) yielded **43g** (211 mg, 91%) as a colorless solid.

mp (°C): 118–120.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.81–7.74 (m, 2H), 7.70–7.66 (m, 1H), 7.60–7.54 (m, 1H), 7.34–7.33 (m, 1H), 7.17–7.11 (m, 2H).

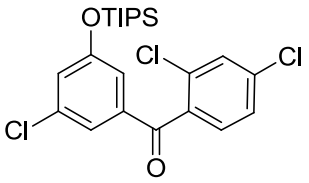
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.9 (d, J = 250 Hz), 141.9 (d, J = 8.7 Hz), 139.9, 135.8 (d, J = 11 Hz), 131.8, 131.3, 130.5, 129.9, 123.2, 118.2, 116.0 (d, J = 25 Hz), 113.4, 112.6 (d, J =, 23 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 307, 2362, 2338, 2231, 1588, 1574, 1444, 1396, 1324, 1308, 1276, 1202, 1175, 1164, 10094, 1069, 945, 916, 890, 866, 837, 791, 748, 694, 680.

MS (EI, 70 eV): *m/z* (%) = 233 (32), 231 (M^+, 100), 196 (17), 195 (22), 169 (13), 43 (28).

HRMS (EI): calcd. for $C_{13}H_7ClFN$: 231.0251, found: 231.0245 (M^+).

(3-Chloro-5-((triisopropylsilyl)oxy)-phenyl)(2,4-dichlorophenyl)methanone (43h)



Freshly prepared and titrated (3-chloro-5-((triisopropylsilyl)-oxy)phenyl)magnesium chloride (**41c**) (1.43 mL, 1 mmol) prepared according to TP7 (45 min, 0.70 M, 80%), was transmetalated with CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol) at -20 °C and stirred for 30 min. After addition of 2,4-dichlorobenzoyl chloride (168 mg, 0.8 mmol) the resulting solution was stirred for 30 min at this temperature. The reaction mixture was then quenched with sat. NH_4Cl (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography (isohexane/diethyl ether 50:1) yielded **43h** (366 mg, 80%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.48 (d, J =1.66 Hz, 1H), 7.38–7.35 (m, 1H), 7.32–7.27 (m, 2H), 7.14–7.09 (m, 2H), 1.28–1.16 (m, 3H), 1.07 (d, J = 7.24 Hz, 18H).

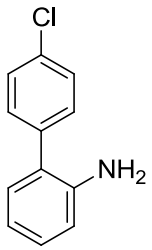
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 192.8, 157.2, 138.5, 137.0, 136.3, 135.3, 132.5, 130.1, 130.1, 127.2, 125.5, 122.6, 119.2, 17.8, 12.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2946, 2867, 1718, 1606, 1595, 1566, 1501, 1453, 1433, 1398, 1318, 1254, 1199, 1137, 1112, 1065, 1025, 999, 964, 921, 880, 854, 799, 762, 738, 688.

MS (EI, 70 eV): *m/z* (%) = 458 (M^+, 8), 417 (43), 416 (23), 415 (98), 414 (43), 413 (100), 389 (17), 387 (53), 385 (51), 356 (38), 354 (41), 279 (13), 251 (25), 249 (37), 174 (58), 173 (84), 95 (44), 79 (14), 44 (15), 41 (17).

HRMS (EI): calcd. for $C_{22}H_{27}Cl_3O_2Si$: 456.0846, found: 458.0842 (M^+).

4'-Chloro-(1,1'-biphenyl)-2-amine (34)



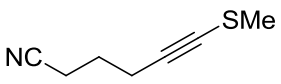
Freshly prepared and titrated (4-chlorophenyl)-magnesium chloride (**37a**) (25 mL, 19.3 mmol) prepared according to TP7 (30 min, 0.77 M, 70%), was transmetalated with $ZnCl_2$ (1 M in THF, 19.3 mL, 19.3 mmol) and then slowly added to a 1 M premixed solution of 2-bromoaniline (3.15 g, 18.3 mmol), $Pd(OAc)_2$ (45 mg, 1 mol%), SPhos (164 mg, 1 mol%) in THF (19 mL). The resulting solution was stirred for 3 h at 25 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (150 mL) and the resulting mixture was extracted with diethyl ether (3×150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography (CH_2Cl_2) yielded **34** (2.75 g, 70%) as a yellow solid.

Analytical data matches the literature.[99]

3.5. Stereoselective Synthesis of Polyfunctional Tetrasubstituted Thioethers *via* a Carbocupration of Alkynyl Sulfides with Aryl and Benzylic Diorganozincs

3.5.1. Starting Materials

6-(Methylthio)hex-5-ynenitrile (44a)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 5-hexynenitrile (2.3 g, 25 mmol) in THF (13 mL). *n*BuLi (12 mL, 30 mmol) was

[99] Glasnov, T. N.; Kappe, C. O. *Adv. Synth. Catal.* **2010**, *352*, 3089.

slowly added at -78 °C and stirred for 1.5 h. Then, dimethyl disulfide (2.7 mL, 30 mmol) was dropwise added at this temperature, and the resulting mixture was allowed to warm up to -20 °C overnight. The reaction mixture was quenched with sat. Na_2CO_3 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 50:1) yielded **44a** (1 g, 30%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 2.52–2.45 (m, 4H), 2.36–2.35 (m, 3H), 1.90–1.81 (m, 2H)

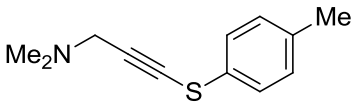
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 119.2, 89.9, 72.6, 24.6, 19.2, 19.1, 16.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2247, 1735, 1452, 1424, 1312, 978, 960, 765.

MS (EI, 70 eV): *m/z* (%) = 139 (M^+, 65), 124 (21), 98 (12), 97 (28), 85 (100), 84 (33), 71 (10), 70 (19), 69 (18), 45 (14).

HRMS (EI): calcd. for C_7H_9NS: 139.0456, found: 139.0450 (M^+).

***N*,*N*-Dimethyl-3-[(4-methylphenyl)thio]prop-2-yn-1-amine (44b)**



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with *N*,*N*-dimethylprop-2-yn-1-amine (2.5 g, 30 mmol) in THF (15 mL) and cooled to -78 °C. Then, *n*BuLi (13 mL, 32 mmol) was slowly added at -78 °C and the resulting mixture was stirred for 1 h. Then, *p*-tolyl disulfide (8.1 g, 33 mmol) was added at this temperature, and the resulting mixture was allowed to warm up to 25 °C overnight. The reaction mixture was quenched with sat. Na_2CO_3 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether: 1:50 + 2 vol-% NEt_3) yielded **44b** (4 g, 65%) as an orange oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.34–7.31 (m, 2H), 3.49 (s, 2H), 2.27 (s, 3H), 2.19 (m, 6H).

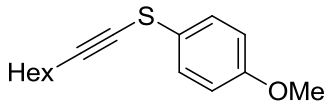
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 136.3, 130.1, 128.4, 125.9, 95.3, 70.0, 48.4, 43.6, 20.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2940, 2861, 2821, 2772, 1492, 1451, 1354, 1322, 1260, 1181, 1156, 1084, 1074, 1038, 1016, 1009, 837, 801, 670.

MS (EI, 70 eV): *m/z* (%) = 206 (13), 205 (M^+, 69), 204 (53), 172 (39), 162 (38), 161 (100), 147 (45), 129 (17), 128 (23), 117 (60), 115 (18), 114 (30), 91 (46), 42 (12).

HRMS (EI): calcd. for $C_{12}H_{15}NS$: 205.0925, found: 205.0922 (M^+).

1-Methoxy-4-(oct-1-yn-1-ylthio)benzene (44c)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with oct-1-yne (2.2 g, 20 mmol) in THF (15 mL) and cooled to -78 °C. Then, *n*BuLi (8.8 mL, 20 mmol) was slowly added at -78 °C and the resulting mixture was stirred for 2 h. 1,1'-Disulfanediylbis(4-methoxybenzene) (6.1 g, 22 mmol, in 20 mL THF) was added at this temperature, and the resulting mixture was allowed to warm up to 25 °C overnight. The reaction mixture was quenched with sat. Na_2CO_3 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane+ 2 vol-% NEt_3) yielded **44c** (3 g, 60%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 7.38– 7.33 (m, 2H), 6.91–6.86 (m, 2H), 3.81 (s, 3H), 2.41 (t, *J* = 7.05, 2H), 1.63–1.30 (m, 8H), 0.93–0.88 (m, 3H).

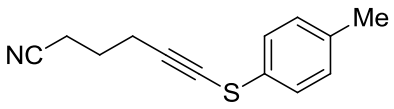
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 158.7, 128.3, 124.0, 114.9, 98.4, 66.0, 55.4, 31.3, 28.6, 28.6, 22.5, 20.3, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2857, 1593, 1492, 1462, 1289, 1243, 1174, 1032, 1006, 820, 725, 637, 623.

MS (EI, 70 eV): *m/z* (%) = 249 (14), 248 (M^+, 100), 179 (14), 177 (19), 146 (17), 140 (44), 139 (21), 133 (44), 67 (14).

HRMS (EI): calcd. for $C_{15}H_{20}OS$: 248.1234, found: 243.1231 (M^+).

6-[(4-Methylphenyl)thio]hex-5-ynenitrile (44d)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with hex-5-ynenitrile (2.9 g, 30 mmol) in THF (15 mL) and cooled to -78 °C. Then, *n*BuLi (14.4 mL, 36 mmol) was slowly added at -78 °C and the resulting mixture was stirred for 1.5 h. Then, *p*-tolyl disulfide (8.1 g, 33 mmol) was added at this temperature, and the resulting mixture was allowed to warm up to 25 °C overnight. The reaction mixture was quenched with sat. Na_2CO_3 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane) yielded **44d** (3.2 g, 50%) as an orange oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.34–7.30 (m, 2H), 7.23–7.19 (m, 2H), 2.60–2.56 (m, 4H), 2.28 (s, 3H), 1.86–1.79 (m, 2H).

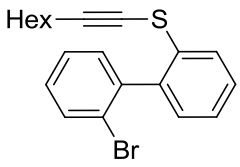
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 136.2, 130.1, 128.5, 125.8, 120.0, 98.0, 66.0, 24.0, 20.5, 18.8, 15.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2942, 2922, 2248, 1491, 1452, 1425, 1400, 1308, 1210, 1182, 1117, 1084, 1016, 803.

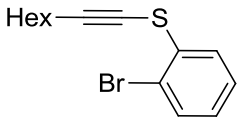
MS (EI, 70 eV): *m/z* (%) = 216 (14), 215 (M^+, 100), 161 (41), 117 (44), 115 (13), 91 (14).

HRMS (EI): calcd. for $C_{13}H_{13}NS$: 215.0769, found: 215.0762 (M^+).

2'-Bromobiphenyl-2-yl oct-1-yn-1-yl sulfide (44e)



A) Synthesis of 1-bromo-2-(oct-1-yn-1-ylsulfanyl)benzene



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-octyne (1.1 g, 10 mmol) in THF (10 mL). *n*BuLi (4.4 mL, 11 mmol) was slowly added at -78 °C and the resulting solution was stirred for 2 h. Then, 1,1'-disulfanediylbis(2-bromobenzene) (4.1 g, 11 mmol) was added at this temperature and the resulting mixture was stirred for 3 h warming up to 25 °. The reaction mixture was quenched with sat. Na_2CO_3 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane) yielded **1-bromo-2-(oct-1-yn-1-ylsulfanyl)benzene** (2.2 g, 75%) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.65–7.62 (m, 2H), 7.50–7.46 (m, 1H), 7.23–7.19 (m, 1H), 2.51 (t, *J* = 6.92 Hz, 2H), 1.58–1.50 (m, 2H), 1.42–1.35 (m, 2H), 1.26–1.27 (m, 4H), 0.87–0.83 (m, 3H).

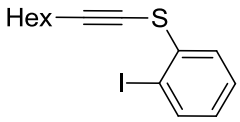
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 134.0, 132.8, 128.8, 128.0, 126.2, 118.4, 102.9, 63.3, 30.7, 28.0, 27.9, 22.0, 19.5, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2928, 2856, 1575, 1446, 1428, 1255, 1104, 1036, 1018, 743, 726, 710.

MS (EI, 70 eV): *m/z* (%) = 298 (50), 296 (M^+, 45), 229 (20), 227 (31), 225 (11), 190 (14), 188 (25), 188 (14), 183 (25), 181 (26), 175 (16), 174 (42), 173 (19), 160 (14), 149 (17), 148 (95), 147 (100), 146 (20), 145 (13), 141 (27), 115 (12), 109 (51), 108 (20), 108 (14), 107 (17), 102 (32), 93 (14), 81 (14), 79 (33), 71 (23), 69 (12), 67 (70), 55 (13), 44 (10), 44 (15).

HRMS (EI): calcd. for $C_{14}H_{17}BrS$: 296.0234, found: 296.0225 (M^+).

B) Synthesis of 1-iodo-2-(oct-1-yn-1-ylsulfanyl)benzene



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-bromo-2-(oct-1-yn-1-ylsulfanyl)benzene (2.9 g, 10 mmol) and cooled to -20 °C. *i*PrMgCl·LiCl (17 mL, 11 mmol) was added at -20 °C and the resulting mixture was stirred for 10 h warming slowly to 0 °C. Then, a solution of I_2 (5.6 g, 22 mmol) in THF (20 mL) was added and stirred at this temperature for 15 min. The reaction mixture was quenched with sat. $Na_2S_2O_3$ (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **1-iodo-2-(oct-1-yn-1-ylsulfanyl)benzene** (2.1 g, 60%) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.81 (dd, J = 7.80 Hz, 1H), 7.63–7.60 (m, 1H), 7.52–7.47 (m, 1H), 7.04–7.00 (m, 1H), 2.51–2.48 (m, 2H), 1.57–1.50 (m, 2H), 1.42–1.35 (m, 2H), 1.30–1.25 (m, 4H), 0.87–0.83 (m, 3H).

^{13}C-NMR (DMSO, 100 MHz): δ (ppm) =139.2, 137.6, 129.3, 127.9, 125.6, 102.6, 94.0, 65.0, 30.7, 28.0, 27.9, 22.0, 19.5, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2926, 2856, 1568, 1558, 1440, 1424, 1378, 1324, 1254, 1094, 1036, 1008, 938, 742, 702, 644.

MS (EI, 70 eV): *m/z* (%) = 344 (M^+, 90), 275 (23), 273 (20), 236 (39), 174 (15), 173 (17), 148 (43), 147 (100), 146 (31), 141 (25), 128 (13), 109 (47), 109 (16), 108 (17), 108 (19), 102 (22), 81 (15), 79 (27), 71 (16), 69 (13), 67 (58), 57 (14), 55 (19), 43 (13), 41 (17).

HRMS (EI): calcd. for $C_{14}H_{17}IS$: 344.0096, found: 344.0101 (M^+).

C) A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with *i*PrMgCl·LiCl (9.4 mL, 12.6 mmol) and cooled to -20 °C. 1,2-Dibromobenzene (2.8 g, 12 mmol) was slowly added at this temperature and stirred at -15 °C for 2 h. Then, $ZnCl_2$ (12 mL, 12.6 mmol, 1 M in THF) was added and the resulting mixture was stirred at this temperature for 20 min. The resulting zinc-solution was cannulated to a new *Schlenk*-flask equipped with 1-iodo-2-(oct-1-yn-1-ylsulfanyl)benzene (2.8 g, 12 mmol, 1 M in THF), $Pd(dba)_2$ (115 mg, 1 mol%) and P(*o*-furyl)$_3$ (93 mg, 2 mol%) and stirred at 50 °C for 5 h. The reaction mixture was then quenched with sat. NH_4Cl (100 mL) and the resulting mixture

was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (pentane + 2 vol-% NEt_3) to give **44e** (3.6 g, 80%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.82–7.79 (m, 1H), 7.71–7.67 (m, 1H), 7.47–7.35 (m, 2H), 7.31–7.24 (m, 3H), 7.16–7.13 (m, 1H), 2.24 (t, J = 6.93 Hz, 2H), 1.65–1.56 (m, 2H), 1.50–1.40 (m, 2H), 1.36–1.29 (m, 4H), 0.94–0.89 (m, 3H).

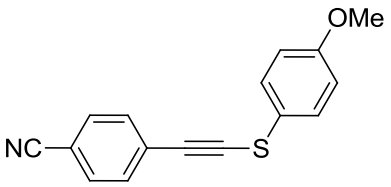
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 139.8, 138.4, 133.5, 132.8, 131.2, 129.8, 129.7, 128.8, 127.3, 125.8, 125.7, 123.8, 100.6, 64.6, 31.3, 28.6, 22.5, 20.3, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 2952, 2926, 2855, 1582, 1561, 1453, 1434, 1421, 1377, 1324, 1159, 1118, 1078, 1052, 1035, 1027, 1002, 942, 748, 729, 686, 658.

MS (EI, 70 eV): *m/z* (%) = 372 (M^+, 5), 294 (20), 293 (100), 221 (11), 184 (21).

HRMS (EI): calcd. for $C_{20}H_{21}BrS$: 372.0547, found: 372.0539 (M^+).

4-{[(4-Methoxyphenyl)thio]ethynyl}benzonitrile (44f)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 4-ethynylbenzonitrile (1.3 g, 10 mmol) in THF (15 mL) and cooled to -78 °C. Then, *i*PrMgCl·LiCl (8.8 mL, 11 mmol) was slowly added at -78 °C and the resulting mixture was stirred for 30 min. S-(4-methoxyphenyl)benzenesulfonothioate (3.1 g, 11 mmol, in 10 mL THF) was added at this temperature, and the resulting mixture was allowed to warm up to 25 °C overnight. The reaction mixture was quenched with sat. Na_2CO_3 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane+ 2 vol-% NEt_3) yielded **44f** (1.7 g, 65%) as an yellow solid.

mp (°C): 88–90.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.59–7.57 (m, 2H), 7.50–7.47 (m, 2H), 7.44–7.40 (m, 2H), 6.94–6.90 (m, 2H), 3.81 (s, 3H).

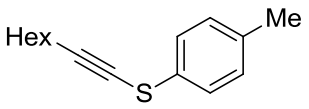
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 159.4, 132.0, 131.4, 129.7, 127.9, 121.7, 118.5, 115.2, 111.1, 94.5, 83.6, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2844, 2224, 2168, 1590, 1570, 1492, 1466, 1458, 1442, 1408, 1288, 1244, 1172, 1120, 1106, 1022, 850, 828, 808, 622.

MS (EI, 70 eV): *m/z* (%) = 266 (16), 265 (M^+, 100), 250 (48), 222 (14).

HRMS (EI): calcd. for $C_{16}H_{11}NOS$: 265.0561, found: 265.0556 (M^+).

1-Methyl-4-(oct-1-yn-1-ylthio)benzene (44g)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-octyne (2.8 g, 25 mmol) in THF (25 mL). *n*BuLi (11 mL, 27 mmol) was slowly added at -78 °C and stirred for 2 h. Then, *p*-tolyl disulfide (6.9 g, 28 mmol) was added at this temperature, and the resulting mixture was allowed to warm up to 25 °C overnight. The reaction mixture was quenched with sat. Na_2CO_3 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane) yielded **44g** (3.2 g, 55%) as a colorless oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.31–7.27 (m, 2H), 7.21–7.17 (m, 2H), 2.45 (t, *J* = 7.02 Hz, 2H), 2.27 (s, 3H), 1.54–1.47 (m, 2H), 1.40–1.33 (m, 2H), 1.29–1.22 (m, 4H), 0.87–0.83 (m, 3H).

^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 136.0, 130.0, 128.9, 125.5, 100.2, 64.4, 30.7, 28.0, 27.9, 22.0, 20.4, 19.5, 13.9.

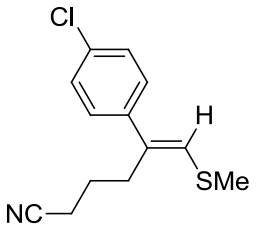
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2927, 2857, 1492, 1465, 1456, 1085, 1017, 801, 725.

MS (EI, 70 eV): *m/z* (%) = 233 (18), 232 (M^+, 100), 203 (19), 190 (20), 163 (53), 162 (16), 161 (73), 156 (15), 148 (22), 147 (22), 135 (25), 130 (38), 129 (29), 128 (22), 124 (50), 123 (14), 117 (63), 109 (23), 105 (16), 91 (42), 71 (13), 67 (45), 65 (18).

HRMS (EI): calcd. for $C_{15}H_{20}S$: 232.1286, found: 232.1266 (M^+).

3.5.2. Tetrasubstituted Thioethers

(5*E*)-5-(4-Chlorophenyl)-6-(methylthio)hex-5-enenitrile (49a)



Prepared according to TP8 from 6-(methylthio)hex-5-ynenitrile (**44a**) (209 mg, 1.5 mmol) and bis(4-chlorophenyl)zinc (**45a**, 5.7 mL, 2.3 mmol) [carbometalation conditions: 25 °C, 16 h]. Then, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (25% in H_2O) = 4:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 9:1 + 2 vol-% NEt_3) yielded **49a** (201 mg, 80%, *E/Z* = 97:3) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.30–7.26 (m, 2H), 7.24–7.20 (m, 2H), 6.28 (s, 1H), 2.72–2.69 (m, 2H), 2.38 (s, 3H), 2.31 (t, *J* = 7.24, 2H), 1.81–1.73 (m, 2H).

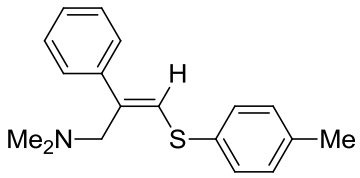
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 138.7, 134.5, 132.9, 128.8, 128.4, 126.8, 119.4, 30.3, 23.6, 17.4, 16.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2869, 2246, 1585, 1557, 1491, 1424, 1398, 1321, 1166, 1091, 1010, 960, 803, 712, 646.

MS (EI, 70 eV): *m/z* (%) = 253 (35), 252 (13), 251 (M^+, 100), 199 (20), 197 (51), 195 (30), 163 (16), 149 (24), 115 (11).

HRMS (EI): calcd. for $C_{13}H_{14}ClNS$: 251.0535, found: 251.0534 (M^+).

(Dimethyl((2*Z*)-3-((4-methylphenyl)thio)-2-phenylprop-2-en-1-yl)amine (49b)



Prepared according to TP8 from *N*,*N*-dimethyl-3-[(4-methylphenyl)thio]prop-2-yn-1-amine (**44b**) (205 mg, 1.0 mmol) and diphenylzinc (**45b**, prepared by transmetalation of freshly titrated PhMgCl (4.2 mL, 1.43 M, 6 mmol) with $ZnCl_2$/LiCl (3 mL, 3 mmol) at 25 °C for 10 min) [carbometalation conditions: 25 °C, 17 h]. Then, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (25% in H_2O) = 4:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 5:1 + 2 vol-% NEt_3) yielded **49b** (198 mg, 70%, *E*/*Z* = 99:1) as a colorless oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.52–7.49 (m, 2H), 7.34–7.29 (m, 4H), 7.25–7.16 (m, 3H), 6.74 (s, 1H), 3.44 (s, 2H), 2.28 (s, 3H), 2.15 (s, 6H).

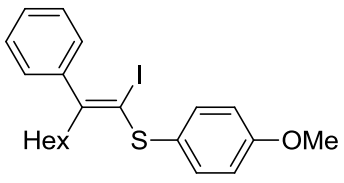
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 140.0, 137.0, 136.3, 132.0, 130.0, 129.0, 128.2, 127.0, 126.0, 125.7, 58.7, 44.7, 20.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2970, 2939, 2854, 2814, 2764, 1588, 1564, 1491, 1454, 1442, 1364, 1259, 1176, 1092, 1054, 1041, 1015, 976, 852, 823, 803, 767, 748, 694.

MS (EI, 70 eV): *m/z* (%) = 283 (M^+, 54), 161 (13), 160 (100), 158 (15), 91 (11), 58 (80).

HRMS (EI): calcd. for $C_{18}H_{21}NS$: 283.1395, found: 283.1399 (M^+).

1-(((1*Z*)-1-Iodo-2-phenyloct-1-en-1-yl)thio)-4-methoxybenzene (49c)



Prepared according to TP8 from 1-methoxy-4-(oct-1-yn-1-ylthio)benzene (**44c**) (994 mg, 4 mmol) and diphenylzinc (**45b**, prepared by transmetalation of fresh titrated PhMgCl (8.4 mL, 1.43 M, 12 mmol) with $ZnCl_2$/LiCl (6 mL, 6 mmol) at 25 °C for 10 min) [carbometalation conditions: 25 °C, 15 h]. Then, the reaction mixture was cooled to -40 °C and a 1 M solution of I_2

(5 g, 20 mmol) in THF was added. The solution was stirred for 10 min at this temperature. The reaction mixture was quenched with sat. $Na_2S_2O_3$ (150 mL) and the resulting mixture was extracted with diethyl ether (3×150 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **49c** (1.44 g, 80%, *E/Z* = 99:1) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.40–7.36 (m, 2H), 7.33–7.28 (m, 3H), 7.18–7.16 (m, 2H), 7.02–6.98 (m, 2H), 3.77 (s, 3H), 2.83 (d, *J* = 7.19 Hz, 2H), 1.30–1.17 (m, 8H), 0.81–0.77 (m, 3H).

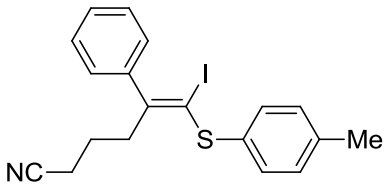
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 159.6, 158.3, 146.0, 132.5, 128.7, 128.1, 128.0, 126.6, 115.5, 90.4, 55.7, 37.3, 31.4, 28.5, 27.9, 22.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2924, 2854, 1592, 1491, 1452, 1440, 1286, 1242, 1179, 1171, 1072, 1031, 825, 773, 746, 698, 639, 621.

MS (EI, 70 eV): *m/z* (%) = 452 (M^+, 16), 325 (17), 241 (31), 226 (12), 186 (12), 185 (100), 147 (15), 143 (14), 139 (82), 121 (19), 115 (11), 91 (17), 43 (12).

HRMS (EI): calcd. for $C_{21}H_{25}IOS$: 452.0671, found: 452.0673 (M^+).

(5*Z*)-6-Iodo-6-((4-methylphenyl)thio)-5-phenylhex-5-enenitrile (49d)



Prepared according to TP8 from 6-[(4-methylphenyl)thio]hex-5-ynenitrile (**44d**) (431 mg, 2 mmol) and diphenylzinc (**45b**, prepared by transmetalation of fresh titrated PhMgCl (4.2 mL, 1.43 M, 6 mmol) with $ZnCl_2$/LiCl (3 mL, 3 mmol) at 25 °C for 10 min) [carbometalation conditions: 25 °C, 8 h]. Then, the reaction mixture was cooled to -40 °C and a 1 M solution of I_2 (2.5 g, 10 mmol) in THF was added. The solution was stirred for 10 min at this temperature. The reaction mixture was quenched with sat. $Na_2S_2O_3$ (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 1:1 + 2 vol-% NEt_3) yielded **49d** (273 mg, 65%, *E/Z* = 99:1) as a white solid.

mp (°C): 75–77.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.43–7.32 (m, 3H), 7.29–7.24 (m, 6H), 2.94–2.46 (m, 2H), 2.52–2.46 (m, 2H), 2.30 (s, 3H), 1.59–1.51 (m, 2H).

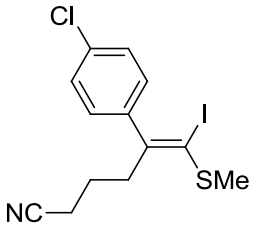
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 157.4, 144.9, 136.9, 131.9, 130.0, 129.5, 128.3, 127.8, 127.7, 120.1, 89.2, 35.7, 23.5, 20.7, 15.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2243, 1489, 1453, 1441, 1430, 1074, 831, 802, 762, 752, 729, 700, 675.

MS (EI, 70 eV): *m/z* (%) = 419 (M^+, 12), 293 (20), 292 (100), 275 (27), 225 (27), 224 (67), 223 (10), 103 (10).

HRMS (EI): calcd. for $C_{19}H_{18}INS$: 419.0205, found: 419.0198 (M^+).

(5*Z*)-5-(4-Chlorophenyl)-6-iodo-6-(methylthio)hex-5-enenitrile (49e)



Prepared according to TP8 from 6-(methylthio)hex-5-ynenitrile (**44a**) (209 mg, 1.5 mmol) and bis(4-chlorophenyl)zinc (**45a**, 5.7 mL, 2.3 mmol) [carbometalation conditions: 25 °C, 16 h]. Then, the reaction mixture was cooled to -40 °C and a 1 M solution of I_2 (1.9 g, 7.5 mmol) in THF was added. The solution was stirred for 10 min at this temperature. The reaction mixture was quenched with sat. $Na_2S_2O_3$ (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 5:1 + 2 vol-% NEt_3) yielded **49e** (264 mg, 70%, *E/Z* = 99:1) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.35 (d, *J* = 8.22 Hz, 2H), 7.05 (d, *J* = 8.22 Hz, 2H), 2.92–2.88 (m, 2H), 2.35 (s, 3H), 2.31 (t, *J* = 7.24, 2H), 1.72–1.64 (m, 2H).

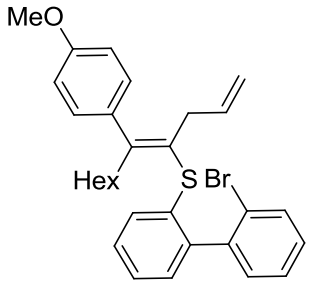
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 151.2, 143.8, 133.8, 129.4, 128.8, 119.0, 96.9, 36.1, 23.7, 22.7, 16.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2858, 2246, 1594, 1482, 1452, 1421, 1395, 1167, 1088, 1013, 969, 835, 809, 784, 719, 649, 618.

MS (EI, 70 eV): *m/z* (%) = 377 (M^+, 12), 252 (39), 251 (19), 250 (100), 202 (13), 181 (16), 175 (26), 167 (21), 162 (13), 137 (12).

HRMS (EI): calcd. for $C_{13}H_{13}ClINS$: 376.9502, found: 376.9490 (M^+).

2-(((1*E*)-1-Allyl-2-(4-methoxyphenyl)oct-1-en-1-yl)thio)-2'-bromobiphenyl (49f)



Prepared according to TP8 from 2'-bromobiphenyl-2-yl oct-1-yn-1-yl sulfide (**44e**) (373 mg, 1 mmol) and bis(4-methoxyphenyl)zinc (**45c**, 4 mL, 1.5 mmol) [carbometalation conditions: 25 °C, 8 h]. Then, the reaction mixture was cooled to -40 °C and allyl bromide (0.29 mL, 3 mmol) was added. The solution was stirred for 30 min at this temperature followed by 30 min at 0 °C. The reaction mixture was quenched with sat. NH_4Cl/NH_3 (25% in H_2O) = 4:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **49f** (438 mg, 84%, *E/Z* = 99:1) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.68 (d, *J* = 7.92 Hz, 1H), 7.41–7.16 (m, 7H), 7.00 (d, *J* = 8.51 Hz, 2H), 6.85 (d, *J* = 8.66 Hz, 2H), 5.79–5.65 (m, 1H), 4.90–4.75 (m, 2H), 3.80 (s, 3H), 2.71 (d, *J* = 6.16 Hz, 2H), 2.46 (d, *J* = 4.11 Hz, 2H), 1.28–1.15 (m, 8H), 0.81 (t, *J* = 6.53 Hz, 3H).

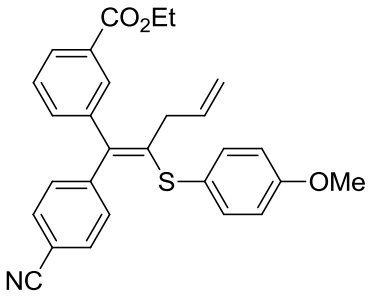
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 158.4, 149.6, 141.9, 141.4, 136.6, 136.5, 135.1, 134.2, 132.6, 131.5, 130.4, 129.8, 129.1, 129.0, 128.3, 127.5, 126.9, 125.8, 123.9, 115.4, 113.4, 107.5, 55.2, 38.3, 37.1, 31.6, 29.0, 28.1, 22.5, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2926, 2855, 1582, 1561, 1453, 1434, 1421, 1377, 1323, 1159, 1118, 1078, 1052, 1027, 1002, 942, 863, 748, 729, 686, 658.

MS (EI, 70 eV): *m/z* (%) = 523 (26), 522 (78), 521 (26), 520 (M^+, 70), 442 (24), 441 (65), 216 (10), 215 (55), 187 (35), 186 (18), 185 (19), 184 (15), 174 (14), 173 (87), 171 (11), 161 (46), 159 (23), 158 (12), 147 (20), 145 (13), 121 (100).

HRMS (EI): calcd. for $C_{30}H_{33}BrOS$: 520.1435, found: 520.1432 (M^+).

Ethyl 3-{(1*Z*)-1-(4-cyanophenyl)-2-[(4-methoxyphenyl)thio]penta-1,4-dien-1-yl}benzoate (49g)



Prepared according to TP8 from 4-{[(4-methoxyphenyl)thio]ethynyl}benzonitrile (**44f)** (265 mg, 1 mmol) and bis[3-(ethoxycarbonyl)phenyl]zinc (**45d**, prepared by adding *i*PrMgCl·LiCl (3 mmol) to a 1.0 M solution of ethyl 3-iodobenzoate in THF (828 mg, 3 mmol) at -20 °C and stirring for 0.5 h and further transmetalation with $ZnCl_2$ (1.5 mL, 1.5 mmol) at -20 °C for 10 min)) [carbometalation conditions: 25 °C, 8 h]. Then, the reaction mixture was cooled to -40 °C and allyl bromide (0.29 mL, 3 mmol) was added. The solution was stirred for 30 min at this temperature followed by 30 min at 0 °C. The reaction mixture was quenched with sat. NH_4Cl/NH_3 (25% in H_2O) = 4:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 19:1 + 2 vol-% NEt_3) yielded **49g** (395 mg, 87%, *E/Z* = 93:7) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.88–7.85 (m, 1H), 7.82–7.78 (m, 3H), 7.53–7.48 (m, 4H), 7.37–7.33 (m, 2H), 6.95–6.91 (m, 2H), 5.80–5.70 (m, 1H), 5.05–5.02 (m, 1H), 4.92–4.87 (m, 1H), 4.28 (q, *J* = 7.06 Hz, 2H), 3.74 (s, 3H), 2.80 (d, *J* = 6.17 Hz, 2H), 1.28 (t, *J* = 7.17 Hz, 3H).

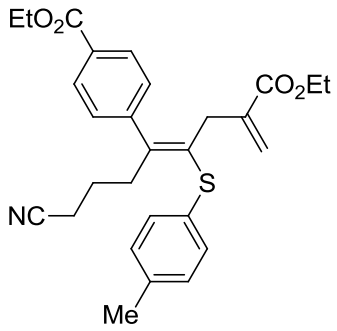
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 165.3, 159.3, 146.5, 140.9, 140.0, 135.7, 134.7, 134.4, 133.5, 132.2, 130.3, 130.1, 129.2, 129.0, 128.2, 122.5, 118.7, 116.7, 114.9, 109.8, 60.8, 55.2, 35.9, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 2978, 2904, 2836, 2226, 1714, 1592, 1572, 1492, 1462, 1406, 1366, 1284, 1244, 1222, 1172, 1104, 1082, 1026, 914, 826, 764, 740, 708, 636, 628.

MS (EI, 70 eV): *m/z* (%) = 457 (10), 456 (36), 455 (M^+, 100), 140 (21), 139 (10).

HRMS (EI): calcd. for $C_{28}H_{27}NO_4S$: 455.1555, found: 455.1563 (M^+).

Ethyl 4-((1*E*)-1-(3-cyanopropyl)-4-(ethoxycarbonyl)-2-((4-methylphenyl)thio)penta-1,4-dien-1-yl)benzoate (49h)



Prepared according to TP8 from 6-[(4-methylphenyl)thio]hex-5-ynenitrile (**44d**) (215 mg, 1 mmol) and bis[4-(ethoxycarbonyl)phenyl]zinc (**45e**, prepared by adding *i*PrMgCl·LiCl (3 mmol) to a 1 M solution of ethyl 4-iodobenzoate in THF (828 mg, 3 mmol) at -20 °C and stirring for 0.5 h and further transmetalation with $ZnCl_2$ (1.5 mL, 1.5 mmol) at -20 °C for 10 min) [carbometalation conditions: 25 °C, 8 h]. Then, the reaction mixture was cooled to -40 °C and ethyl 2-(bromomethyl)acrylate (580 mg, 3 mmol) was added. The solution was stirred for 30 min at this temperature followed by 30 min at 0 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 1:1 + 2 vol-% NEt_3) yielded **49h** (273 mg, 65%, *E/Z* = 93:7) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.96–7.93 (m, 2H), 7.41–7.38 (m, 2H), 7.23–7.15 (m, 4H), 6.09 (d, *J* = 0.98 Hz, 1H), 5.51 (d, *J* = 1.17 Hz, 1H), 4.3 (q, *J* = 7.11 Hz, 2H), 3.94 (q, *J* = 7.04Hz, 2H), 2.89–2.85 (m, 4H), 2.48–2.45 (m, 2H). 2.28 (s, 3H), 1.57–1.50 (m, 2H), 1.30 (t, *J* = 7.04, 3H), 1.09 (t, *J* = 7.04, 3H).

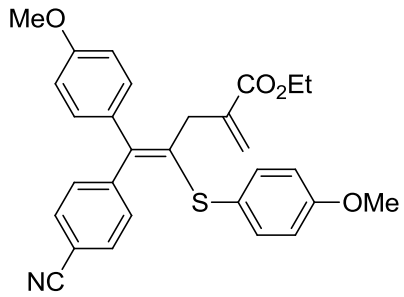
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 165.6, 165.3, 145.6, 145.5, 136.8, 136.6, 130.5, 129.9, 129.8, 129.2, 128.9, 128.9, 128.1, 126.1, 120.2, 60.7, 60.3, 35.0, 34.4, 23.5, 20.6, 15.9, 14.1, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2936, 1711, 1631, 1606, 1492, 1447, 1403, 1367, 1271, 1221, 1176, 1138, 1102, 1018, 947, 862, 808, 780, 712.

MS (EI, 70 eV): *m/z* (%) = 477 (M^+, 20), 365 (25), 355 (11), 354 (51), 352 (11), 351 (12), 309 (21), 308 (100), 286 (23), 285 (11), 284 (35), 281 (11), 280 (55), 279 (33), 262 (15), 241 (13), 239 (17), 238 (72), 213 (17), 196 (10), 195 (15), 167 (12), 165 (11), 157 (12), 153 (12), 143 (11), 141 (11), 129 (15), 128 (13), 124 (19), 115 (12), 91 (15), 86 (18).

HRMS (EI): calcd. for $C_{28}H_{31}NO_4S$: 477.1974, found: 477.1970 (M^+).

Ethyl (4*E*)-5-(4-cyanophenyl)-5-(4-methoxyphenyl)-4-((4-methoxyphenyl)thio)-2-methylenepent-4-enoate (49i)



Prepared according to TP8 4-{[(4-methoxyphenyl)thio]ethynyl}benzonitrile (**44f**) (265 mg, 1 mmol) and bis(4-methoxyphenyl)zinc (**45c**, 4 mL, 1.5 mmol) [carbometalation conditions: 25 °C, 8 h]. Then, the reaction mixture was cooled to -40 °C and ethyl 2-(bromomethyl)acrylate (580 mg, 3 mmol) was added. The solution was stirred for 30 min at this temperature followed by 30 min at 0 °C. The reaction mixture was quenched with sat. NH_4Cl/NH_3 (25% in H_2O) = 4:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 1:1 + 2 vol-% NEt_3) yielded **49i** (388 mg, 80%, *E/Z* = 93:7) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.81–7.78 (m, 2H), 7.49–7.48 (m, 2H), 7.26–7.11 (m, 2H), 6.91–6.87 (m, 4H), 6.20 (d, *J* = 0.88 Hz, 1H), 5.71 (d, *J* = 0.88 Hz, 1H), 3.98 (q, *J* = 7.20 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.09 (s, 2H), 1.09 (t, *J* = 7.17 Hz, 3H).

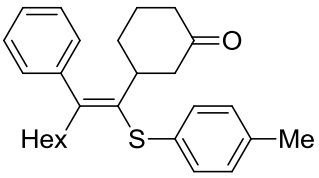
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 165.5, 159.2, 158.5, 147.0, 142.2, 136.6, 134.4, 132.6, 132.6, 132.1, 130.1, 129.6, 126.3, 122.6, 118.7, 114.7, 113.9, 109.6, 60.3, 55.2, 55.0, 33.6, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2836, 2226, 1712, 1630, 1604, 1592, 1508, 1492, 1462, 1442, 1426, 1402, 1368, 1284, 1242, 1172, 1136, 1106, 1028, 944, 828, 808, 752, 640, 618.

MS (EI, 70 eV): *m/z* (%) = 487 (11), 486 (33), 485 (M^+, 100), 347 (14), 346 (63), 345 (50), 318 (18), 317 (32), 316 (75), 273 (12), 272 (23), 140 (28), 139 (19).

HRMS (EI): calcd for $C_{29}H_{27}NO_4S$: 485.1661, found: 485.1651 (M^+).

3-((1*E*)-1-((4-Methylphenyl)thio)-2-phenyloct-1-en-1-yl)cyclohexanone (49j)



Prepared according to TP8 from 1-methyl-4-(oct-1-yn-1-ylthio)benzene (**44g**) (465 mg, 2 mmol) and diphenylzinc (prepared by transmetalation of fresh titrated PhMgCl (**45b**, 4.2 mL, 1.43 M, 6 mmol) with $ZnCl_2$/LiCl (3 mL, 3 mmol) at 25 °C for 10 min) [carbometalation conditions: 25 °C, 10 h]. Then, the reaction mixture was cooled to -40 °C and a premixed solution of TMSCl (2.24 mL, 17.5 mmol) and cyclohex-2-en-1-one (0.68 mL, 7 mmol) was added. The solution was stirred for at this temperature and slowly warmed to 0 °C over night. The reaction mixture was quenched with sat. NH_4Cl/NH_3 (25% in H_2O) = 4:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 5:1 + 2 vol-% NEt_3) yielded **49j** (651 mg, 80%, *E/Z* = 99:1) as a colorless oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.43–7.39 (m, 2H), 7.34–7.27 (m, 1H), 7.21–7.18 (m, 4H), 7.15–7.13 (m, 2H), 2.73–2.65 (m, 1H), 2.61–2.51 (m, 3H), 2.25 (s, 3H), 2.22–2.17 (m, 1H), 1.99–1.91 (m, 2H), 1.85–1.79 (m, 1H), 1.73–1.66 (m, 1H), 1.55–1.52 (m, 1H), 1.24–1.15 (m, 1H), 1.10–1.00 (m, 8H), 0.74–0.71 (m, 3H).

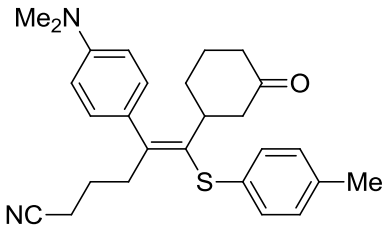
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 209.7, 153.0, 144.8, 140.9, 134.4, 133.9, 130.7, 129.8, 128.5, 127.3, 127.3, 126.0, 45.8, 44.1, 37.0, 30.9, 29.5, 28.4, 26.7, 24.3, 21.8, 20.4, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2926, 2856, 1712, 1597, 1490, 1446, 1352, 1316, 1258, 1222, 1183, 1117, 1080, 1016, 803, 777, 702.

MS (EI, 70 eV): *m/z* (%) = 407 (27), 406 (M^+, 100), 335 (19), 283 (14), 91 (12).

HRMS (EI): calcd. for $C_{27}H_{34}OS$: 406.2330, found: 406.2321 (M^+).

(5*E*)-5-[4-(Dimethylamino)phenyl]-6-[(4-methylphenyl)thio]-6-(3-oxocyclohexyl)hex-5-enenitrile (49k)



Prepared according to TP8 from 6-[(4-methylphenyl)thio]hex-5-ynenitrile (**44d**) (217 mg, 1 mmol) and bis[4-(dimethylamino)phenyl]zinc (**45f**, 3.6 mL, 1.5 mmol) [carbometalation conditions: 25 °C, 8 h]. Then, the reaction mixture was cooled to -40 °C and a premixed solution of TMSCl (1.12 mL, 8.7 mmol) and cyclohex-2-en-1-one (0.34 mL, 3.5 mmol) was added. The solution was stirred for at this temperature and slowly warmed to 0 °C over night. After 8 h the reaction mixture was quenched with sat. NH_4Cl/NH_3 (25% in H_2O) = 4:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 1:1 + 2 vol-% NEt_3) yielded **49k** (260 mg, 60%, *E/Z* = 99:1) as a yellow oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.18–7.13 (m, 4H), 7.07–7.04 (m, 2H), 6.76–6.72 (m, 2H), 2.91 (s, 6H), 2.72–2.62 (m, 2H), 2.57–2.51 (m, 1H), 2.29 (t, *J* = 7.14 Hz, 2H), 2.26 (s, 3H), 2.23–2.18 (m, 1H), 2.02–1.92 (m, 2H), 1.88–1.82 (m, 1H), 1.77–1.67 (m, 1H), 1.58–1.54 (m, 1H), 1.35–1.22 (m, 4H).

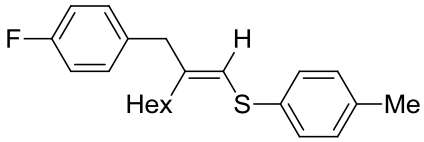
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 209.9, 151.9, 149.5, 134.4, 134.0, 130.9, 129.9, 128.2, 127.1, 125.9, 120.3, 112.0, 45.9, 45.7, 44.1, 36.1, 29.5, 24.3, 23.3, 20.5, 15.8, 11.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 2860, 2804, 1708, 1608, 1518, 1490, 1446, 1350, 1258, 1222, 1196, 1116, 1082, 1062, 946, 820, 804, 736.

MS (EI, 70 eV): *m/z* (%) = 433 (29), 432 (M^+, 100), 309 (17), 251 (10).

HRMS (EI): calcd. for $C_{27}H_{32}N_2OS$: 432., 2235, found: 432.2232 (M^+).

1-Fluoro-4-(2-hexyl-3-((4-methylphenyl)thio)prop-2-en-1-yl)benzene (49m)



Prepared according to TP8 from 1-methyl-4-(oct-1-yn-1-ylthio)benzene (**44i**) (232 mg, 1 mmol) and bis(4-fluorobenzyl)zinc (**45h**, 3.9 mL, 1.5 mmol) [carbometalation conditions: 25 °C, 16 h]. Then, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (25% in H_2O) = 4:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 9:1 + 2 vol-% NEt_3) yielded **49m** (284 mg, 83%, *E/Z* = 99:1) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.20–7.08 (m, 6H), 7.00–6.94 (m, 2H), 5.89 (s, 1H), 3.41 (s, 2H), 2.31 (s, 3H), 2.20–2.16 (m, 2H), 1.42–1.23 (m, 8H), 0.89–0.85 (m, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 161.5 (d, *J* = 244.2 Hz), 143.9 (d, *J* = 0.77 Hz), 135.9, 134.8 (d, *J* = 3.07 Hz), 133.3, 130.4 (d, *J* = 8.06 Hz), 129.7, 128.7, 119.5, 115.2 (d, *J* = 21.5 Hz), 42.4, 31.7, 31.6, 29.2, 27.7, 22.6, 20.9, 14.1.

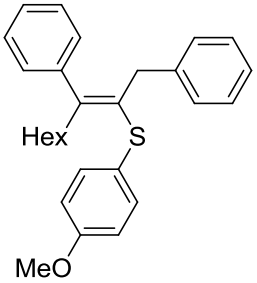
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2926, 2856, 1722, 1600, 1508, 1492, 1466, 1220, 1156, 1092, 1016, 820, 804, 758, 734.

MS (EI, 70 eV): *m/z* (%) = 343 (23), 342 (M^+, 100), 147 (17), 135 (13), 109 (31).

HRMS (EI): calcd. for $C_{22}H_{27}FS$: 342.1817, found: 342.1809 (M^+).

3.5.3. Pd-Catalyzed Cross-Coupling of Alkenyl Iodides

1-(((1*E*)-1-Benzyl-2-phenyloct-1-en-1-yl)thio)-4-methoxybenzene (52a)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, 1-(((1*Z*)-1-iodo-2-phenyloct-1-en-1-yl)thio)-4-methoxybenzene (**49c**) (452 mg, 1 mmol) was dissolved in 1 mL THF. Then, $Pd(OAc)_2$ (4.5 mg, 2 mol%), SPhos (16.4 mg, 4 mol%) and benzylzinc chloride (**51a**, 1.36 mL, 1.19 M, 1.5 mmol) were added at 0 °C, warmed to 25 °C and stirred at this temperature for 6 h. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **52a** (112 mg, 77%, *E/Z* = 98:2) as a colorless oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.37–7.32 (m, 3H), 7.29–7.25 (m, 2H), 7.23–7.11 (m, 7H), 6.91–6.88 (m, 2H), 3.73 (s, 3H), 3.26 (s, 2H), 2.80–2.76 (m, 2H), 1.28–1.17 (m, 8H), 0.81–0.78 (m, 3H).

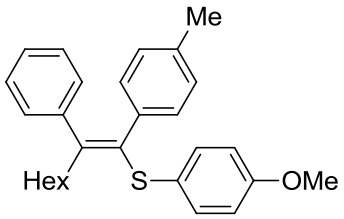
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 159.0, 147.5, 141.9, 139.6, 132.8, 129.7, 128.8, 128.6, 128.5, 128.3, 127.5, 126.3, 124.9, 115.3, 55.6, 46.1, 36.6, 31.4, 28.8, 27.8, 22.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2925, 2854, 1592, 1492, 1462, 1452, 1440, 1286, 1243, 1179, 1171, 1073, 1031, 825, 773, 747, 698.

MS (EI, 70 eV): *m/z* (%) = 417 (21), 416 (M^+, 75), 206 (15), 205 (25), 191 (11), 140 (22), 139 (46), 129 (14), 121 (10), 117 (11), 115 (17), 91 (100), 43 (15), 41 (10).

HRMS (EI): calcd. for $C_{28}H_{32}OS$: 416.2174, found: 416.2167 (M^+).

1-Methoxy-4-(((1*E*)-1-(4-methylphenyl)-2-phenyloct-1-en-1-yl)thio)benzene (52b)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, 1-(((1*Z*)-1-iodo-2-phenyloct-1-en-1-yl)thio)-4-methoxybenzene (**49c**) (181 mg, 0.4 mmol) was dissolved in 0.5 mL THF. Then, $Pd(dba)_2$ (7 mg, 3 mol%), P(*o*-furyl)$_3$ (5.6 mg, 6 mol%) and *p*-tolylzinc iodide (**51b**, 0.9 mL, 0.67 M, 0.6 mmol) were added at 0 °C, warmed to 25 °C and stirred at this temperature for 5 h. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **52b** (90 mg, 54%, *E*/*Z* = 97:3) as a colorless oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.14–7.01 (m, 7H), 6.90–6.87 (m, 2H), 6.75–6.71 (m, 4H), 3.63 (s, 3H), 2.96 (t, *J* = 7.04 Hz, 2H), 2.05 (s, 3H), 1.29–1.19 (m, 8H), 0.83–0.79 (m, 3H).

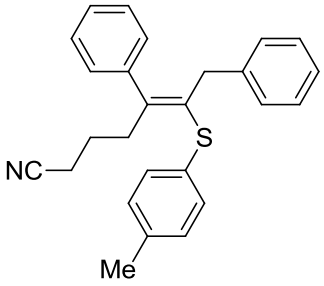
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 163.3, 163.3, 151.8, 147.2, 141.6, 140.5, 137.0, 135.6, 134.2, 133.0, 133.0, 131.5, 130.0, 119.6, 60.2, 44.7, 42.7, 36.2, 33.6, 33.0, 27.2, 25.7, 19.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2855, 1593, 1491, 1462, 1441, 1285, 1243, 1179, 1172, 1104, 1032, 821, 804, 766, 698, 640.

MS (EI, 70 eV): *m/z* (%) = 417 (31), 416 (M^+, 100), 237 (16), 181 (13), 173 (19), 159 (11), 131 (18), 117 (20), 105 (31), 91 (18).

HRMS (EI): calcd for $C_{28}H_{32}OS$: 416.2174, found: 416.2162 (M^+).

(5*E*)-6-[(4-Methylphenyl)thio]-5,7-diphenylhept-5-enenitrile (52c)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, (5*Z*)-6-iodo-6-((4-methylphenyl)thio)-5-phenylhex-5-enenitrile (**49d**) (105 mg, 0.25 mmol) was dissolved in 0.5 mL THF. Then, $Pd(dba)_2$ (4.3 mg, 3 mol%), P(*o*-furyl)$_3$ (3.5 mg, 6 mol%) and benzylzinc chloride (**51a**, 0.32 mL, 1.19 M, 0.38 mmol) were added at 0 °C, warmed to 25 °C and stirred at this temperature for 6 h. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 5:1 + 2 vol-% NEt_3) yielded **52c** (73 mg, 76%, *E/Z* = 99:1) as a colorless oil.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.42–7.38 (m, 2H), 7.33–7.29 (m, 3H), 7.21–7.10 (m, 7H), 6.90–6.87 (m, 2H), 3.31 (s, 2H), 2.90-2.86 (m, 2H), 2.48–2.44 (m, 2H), 2.28 (s, 3H), 1.58–1.50 (m, 2H).

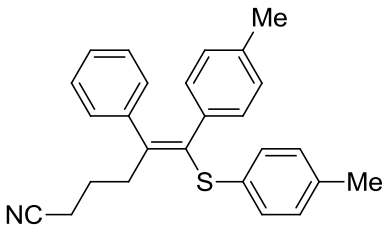
^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 147.6, 141.1, 139.3, 136.5, 131.2, 130.4, 130.2, 130.1, 129.0, 128.6, 128.5, 128.5, 127.8, 126.4, 120.8, 38.6, 35.8, 24.0, 21.0, 16.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 3025, 2921, 2246, 1600, 1491, 1452, 1262, 1210, 1180, 1083, 1017, 918, 806, 774, 748, 698, 620.

MS (EI, 70 eV): *m/z* (%) = 384 (27), 383 (M^+, 100), 260 (12), 259 (11), 258 (22), 232 (10), 224 (12), 206 (17), 205 (28), 191 (15), 182 (15), 141 (12), 124 (13), 115 (11), 91 (51), 44 (11).

HRMS (EI): calcd. for $C_{26}H_{25}NS$: 383.1708, found: 383.1699 (M^+).

(5*E*)-6-(4-Methylphenyl)-6-[(4-methylphenyl)thio]-5-phenylhex-5-enenitrile (52d)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, (5*Z*)-6-iodo-6-((4-methylphenyl)thio)-5-phenylhex-5-enenitrile (**49d**) (126 mg, 0.3 mmol) was dissolved in 0.5 mL THF. Then, $Pd(dba)_2$ (5.2 mg, 3 mol%), P(*o*-furyl)$_3$ (4.2 mg, 6 mol%) and *p*-tolylzinc iodide (**51b**, 0.6 mL, 0.67 M, 0.4 mmol) were added at 0 °C, warmed to 25 °C and stirred at this temperature for 5 h. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether = 5:1 + 2 vol-% NEt_3) yielded **52d** (94 mg, 82%, *E/Z* = 99:1) as a white solid.

mp (°C): 70–71.

^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 7.18–7.07 (m, 7H), 6.99–6.94 (m, 4H), 6.76–6.73 (m, 2H), 3.08–3.04 (m, 2H), 2.50–2.47 (m, 2H), 2.15 (s, 3H), 2.05 (s, 3H), 1.59–1.52 (m, 2H).

^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 146.3, 141.3, 136.3, 135.6, 135.5, 132.0, 130.8, 130.4, 129.5, 129.3, 129.1, 128.0, 127.9, 126.7, 120.4, 36.7, 23.9, 20.6, 20.5, 16.0.

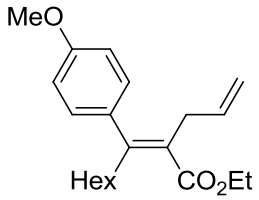
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2922, 2854, 1727, 1491, 1454, 1441, 1278, 1114, 1080, 1019, 870, 820, 804, 766, 753, 701, 681, 638.

MS (EI, 70 eV): *m/z* (%) = 384 (37), 383 (M^+, 100), 261 (17), 260 (83), 233 (17), 219 (41), 206 (22), 205 (20), 204 (22), 191 (20), 182 (18), 168 (20), 141 (17), 117 (15), 105 (17), 91 (23), 83 (22), 69 (28), 58 (20), 57 (35), 44 (17), 43 (18), 43 (50), 41 (23).

HRMS (EI): calcd. for $C_{26}H_{25}NS$: 383.1708, found: 383.1694 (M^+).

3.5.4. Ring-Closing Rearrangement by a Sulfur/Lithium-Exchange

Ethyl (2*E*)-2-allyl-3-(4-methoxyphenyl)non-2-enoate (55a)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, 2-(((1*E*)-1-allyl-2-(4-methoxyphenyl)oct-1-en-1-yl)thio)-2'-bromobiphenyl (**49f**) (235 mg, 0.45 mmol) was dissolved in 6 mL THF and cooled to -78 °C. Then, *s*BuLi (0.4 mL, 0.6 mmol) was added and the reaction mixture was stirred for 10 min. Then, ethyl chloroformate (0.08 mL, 0.5 mmol) was added and the solution was stirred for 15 min. The reaction mixture was quenched with sat. NH_4Cl sol. (5 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **55a** (82 mg, 55%, *E/Z* = 95:5) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.10–7.07 (m, 2H), 6.95–6.92 (m, 2H), 5.76–5.66 (m, 1H), 4.98–4.90 (m, 2H), 4.15 (t, *J* = 7.04 Hz, 2H), 3.75 (s, 3H), 2.79 (d, *J* = 5.87 Hz, 2H), 1.22 (t, *J* = 7.14 Hz, 3H), 1.19–1.12 (m, 8H), 0.81–0.78 (m, 3H).

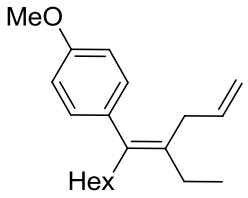
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 169.1, 158.9, 148.7, 136.4, 132.9, 129.0, 127.6, 116.1, 114.1, 60.4, 55.5, 36.1, 35.5, 31.4, 28.9, 28.1, 22.4, 14.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2928, 2858, 1712, 1608, 1510, 1462, 1442, 1366, 1284, 1244, 1208, 1176, 1134, 1112, 1080, 1032, 1010, 994, 912, 834, 810, 752, 700, 668.

MS (EI, 70 eV): *m/z* (%) = 331 (18), 330 (M^+, 100), 329 (20), 285 (45), 260 (40), 257 (40), 245 (55), 227 (41), 214 (52), 199 (34), 199 (43), 187 (36), 186 (52), 185 (37), 173 (57), 172 (50), 171 (67), 159 (28), 158 (24), 147 (19), 145 (20), 134 (22), 128 (22), 121 (78), 108 (26).

HRMS (EI): calcd. for $C_{21}H_{30}O_3$: 330.2195, found: 330.2179 (M^+).

1-[(1*Z*)-2-ethyl-1-hexylpenta-1,4-dien-1-yl]-4-methoxybenzene (55b)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, 2-(((1*E*)-1-allyl-2-(4-methoxyphenyl)oct-1-en-1-yl)thio)-2'-bromobiphenyl (**49f**) (185 mg, 0.35 mmol) was dissolved in 4 mL THF and cooled to -78 °C. Then, *s*BuLi (0.3 mL, 0.4 mmol) was added and the reaction mixture was stirred for 10 min. Then, iodethane (109 mg, 0.7 mmol) was added and the solution was stirred for 15 min. The reaction mixture was quenched with sat. NH_4Cl sol. (5 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **55b** (75 mg, 75%, *E/Z* = 88:12) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.03–7.01 (m, 2H), 6.86–6.83 (m, 2H), 5.75–5.68 (m, 1H), 4.97–4.92 (m, 2H), 3.82 (s, 3H), 2.61 (d, *J* = 6.31 Hz, 2H), 2.32 (t, *J* = 7.14 Hz, 2H), 2.18 (q, *J* = 7.50 Hz, 2H), 1.31–1.20 (m, 8H), 1.05 (t, *J* = 7.55 Hz, 3H), 0.86 (m, *J* = 7.14 Hz, 3H).

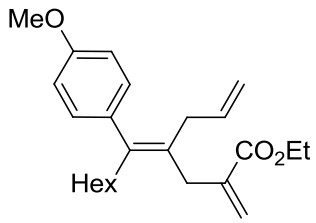
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 157.7, 137.8, 136.8, 136.0, 134.6, 129.7, 114.8, 113.2, 55.1, 37.1, 34.2, 31.8, 29.3, 28.4, 23.8, 22.6, 14.1, 13.4

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2926, 2872, 2856, 1636, 1608, 1508, 1458, 1442, 1374, 1286, 1242, 1174, 1104, 1038, 994, 908, 832, 810, 742, 704.

MS (EI, 70 eV): *m/z* (%) = 287 (15), 286 (M^+, 61), 257 (24), 202 (17), 201 (100), 187 (29), 184 (35), 174 (11), 173 (55), 172 (13), 161 (15), 160 (15), 159 (40), 158 (16), 147 (14), 145 (13), 128 (13), 121 (65), 115 (13), 91 (13), 57 (13), 55 (12), 43 (16), 43 (14), 41 (15).

HRMS (EI): calcd. for $C_{20}H_{30}O$: 286.2297, found: 286.2290 (M^+).

Ethyl (4*E*)-4-allyl-5-(4-methoxyphenyl)-2-methyleneundec-4-enoate (55c)



In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, 2-(((1*E*)-1-allyl-2-(4-methoxyphenyl)oct-1-en-1-yl)thio)-2'-bromobiphenyl (**49f**) (107 mg, 0.2 mmol) was dissolved in 6 mL THF and cooled to -78 °C. Then *s*BuLi (0.27 mL, 0.22 mmol) was added and the reaction mixture was stirred for 10 min. After transmetalation to $ZnCl_2$ (0.22 mL, 0.22 mmol) at -78 °C for 10 min, CuCN·2LiCl (0.22 mL, 0.22 mmol) was added and the resulting solution was stirred for 30 min. Then, ethyl 2-(bromomethyl)acrylate (58 mg, 0.3 mmol) was added and the mixture was stirred for 2 h warming up to 0 °C. The reaction mixture was quenched with sat. NH_4Cl sol. (10 mL) and the resulting mixture was extracted with diethyl ether (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane+ 2 vol-% NEt_3) yielded **55c** (41 mg, 55%, *E/Z* = 90:10) as a yellow oil.

^{1}H-NMR (C_6D_6, 600 MHz): δ (ppm) = 7.12–7.10 (m, 2H), 6.87–6.84 (m, 2H), 6.46 (q, *J* = 1.65 Hz, 1H), 5.84–5.77 (m, 1H), 5.63 (q, *J* = 1.74 Hz, 1H), 5.08–5.03 (m, 2H), 4.09 (t, *J* = 7.14 Hz, 2H), 3.52 (t, *J* = 1.78 Hz, 2H), 3.38 (s, 3H), 2.78 (d, *J* = 6.31 Hz, 2H), 2.45–2.41 (m, 2H), 1.41–1.36 (m, 2H), 1.27–1.16 (m, 6H), 1.04 (t, *J*= 7.14 Hz, 3H), 0.87 (t, *J*= 7.14 Hz, 3H).

^{13}C-NMR (C_6D_6, 150 MHz): δ (ppm) = 166.8, 158.5, 140.9, 139.1, 137.3, 135.1, 129.5, 129.3, 128.0, 124.0, 115.4, 113.6, 60.4, 54.4, 37.8, 34.8, 32.8, 31.8, 29.3, 28.3, 22.7, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 1716, 1608, 1510, 1464, 1283, 1243, 1175, 1134, 1034, 944, 833.

MS (EI, 70 eV): *m/z* (%) = 370 (M^+, 100), 285 (20), 257 (48), 239 (49), 211 (27), 185 (25), 173 (27), 172 (15), 171 (20), 159 (15), 147 (12), 122 (24), 121 (100), 59 (14), 43 (14), 41 (15).

HRMS (EI): calcd. for $C_{24}H_{34}O_3$: 370.2508, found: 370.2504 (M^+).

D. APPENDIX

CURRICULUM VITAE

PERSONAL INFORMATIONS

Name: Cora Dunst

Date of Birth: September 20th 1983

Place of Birth: Starnberg, Germany

PUBLICATIONS

1. Cora Dunst, Albrecht Metzger, Elena Zaburdaeva, Paul Knochel, „Stereoselective Synthesis of Polyfunctional Tetrasubstituted Alkenyl Thioethers *via* a Carbocupration of Alkynyl Sulfides with Aryl and Benzylic Diorganozincs“, *Synthesis, accepted*.

2. Cora Dunst, Paul Knochel, „Regioselective Functionalization of the Thiazole Scaffold using TMPMgCl·LiCl and $TMP_2Zn·2MgCl_2·2LiCl$”, *J. Org. Chem* **2011**, *76*, 6972.

3. Cora Dunst, Paul Knochel, „Selective Mg Insertion into Substituted Mono- and Di-Chloro Arenes in the Presence of LiCl. A new Preparation of Boscalid”, *Synlett* **2011,** *14*, 2064.

4. Marcel Kienle, Andreas J. Wagner, Cora Dunst, Paul Knochel, „Preparation of Heterocyclic Amines by an Oxidative Amination of Zinc Organometallics Mediated by CuI: A New Oxidative Cycloamination for the Preparation of Annulated Indole Derivatives”, *Chem. Asian J.* **2011**, *6*, 517.

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