Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
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Preparation and Applications of Benzylic Zinc Chlorides. Lewis-Acid Promoted Additions of Organomagnesium and Organozinc Reagents to Carbonyl Derivatives. Transition Metal-Catalyzed Cross-Coupling Reactions With Methylthio-Substituted N-Heterocycles.

von

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe bearbeitet.

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Albrecht Metzger

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1. Gutachter: Prof. Dr. Paul Knochel
2. Gutachter: Prof. Dr. Thomas Carell

Mündliche Prüfung am 18. Mai 2010

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Parts of this Ph.D. thesis have been published

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To Teresa, my love!

Table of Contents

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
Bn	benzyl
br	broad
Bu	butyl
n-Bu	*n*-butyl
s-Bu	*s*-butyl
t-Bu	*t*-butyl
calc.	calculated
conc.	concentrated
c-Hex	cyclohexyl
δ	chemical shifts in parts per million
d	doublet
dba	*trans,trans*-dibenzylideneacetone
DMF	*N,N*-dimethylfomamide
DMAP	4-(dimethylamino)pyridine
DMSO	dimethyl sulfoxide
dppe	diphenylphosphinoethane
dppp	diphenylphosphinopropane
DPE-Phos	bis(2-diphenylphosphino-phenyl)ether
E	electrophile
EI	electron-impact
ESI	electrospray ionization
equiv	equivalent
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
IR	infra-red
J	coupling constant (NMR)
M	Molarity
m	meta
m	multiplet
Me	methyl
Met	metal
min	minute
mmol	millimole
M.p.	melting point
MS	mass spectroscopy
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
i-Pr	iso-propyl
q	quartet
R	organic substituent
rt	room temperature
sat.	saturated
s	singulet
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TP	typical procedure
Ts	4-toluenesulfonyl

A. INTRODUCTION

1. Overview

Since the groundbreaking synthesis of urea by Friedrich Wöhler and the development of the elementary analysis by Justus von Liebig in the 19th century, organic chemistry underwent fundamental progress. Some milestones that should be mentioned are the development of nuclear magnetic resonance spectroscopy which became a very powerful analytical method for organic chemists helping to determinate organic structures and to understand the way how organic reactions proceed.[1] During the last years, large progress was achieved in the field of asymmetric synthesis[2] as well as in organometallic chemistry[3] for which several Nobel prizes have been awarded. Since there is an intensive need of new agrochemicals and materials as well as novel pharmaceuticals for mankind due to the permanent changes in environment and healthcare a consistent development of new synthetic methods is needed which fulfill requirements for fast adoption into the chemical community. For example, new reagents should have some desirable properties like an excellent selectivity and reactivity combined with low costs, environmental-friendliness and a high functional group tolerance. Furthermore, the transformation of organic molecules should occur in an atom-economic fashion.[4] Organometallic chemistry has the potential to fulfill these requirements. For the last decades, a large range of metals were applied in synthetic organic chemistry to solve ongoing problems.[3] The reactivity of organometallics strongly depends on the character of the metal-carbon bond providing many possibilities for tuning the wanted organometallic reagents.[5] For instance, organolithium compounds show excellent reactivity towards numerous electrophiles.[6] However, a low selectivity is observed due to the ionic character of the lithium carbon bond. On the other hand, organoboron reagents are well established organometallics due to their air- and moisture stability which is a result of the almost covalent carbon-boron bond.[7] These compounds show a high functional group tolerance. However, for the transformation with different electrophiles the lack of the reactivity of organoboron compounds must be overcome by transmetalations with appropriate catalysts and often the formation of boronates as well as harsh reaction conditions are required. Moreover, the

[1] P. J. Hore, *Nuclear Magnetic Resonance*, Oxford University Press: Oxford, **1995**.
[2] (a) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008; (b) S. Kobayashi, M. Sugiura, *Adv. Synth. Catal.* **2006**, *348*, 1496.
[3] (a) *Handbook of Functionalized Organometallics*; P. Knochel, Ed., Wiley-VCH: Weinheim, **2005**; (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., A. de Meijere, F. Diederich, Wiley-VCH: Weinheim, **2004**.
[4] B. M. Trost, *Science* **1991**, *254*, 1471.
[5] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.
[6] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596.
[7] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

toxicological properties of these organometallics are not absolutely user-friendly. Another class of stable organometallics having an exceptional functional group tolerance are organoindium reagents. The research field of these organometallics is permanently growing, but major drawbacks for industrial applications are the methods of preparation, in which expensive indium metal or salts are used.[8]

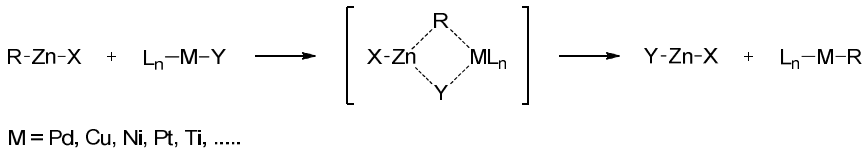
2. Preparation of Functionalized Organozinc Reagents

2.1. Introduction

Organozinc reagents are known for more than 150 years. The first preparation of diethylzinc was reported by Frankland who synthesized it in summer 1848 by the reaction of finely granulated zinc and ethyl iodide.[9] Below 150 °C, no reaction occurred but at around 200 °C the ethyl iodide-zinc reaction proceeded with 'tolerable rapidity'. A colourless mobile liquid together with white crystals were obtained. Over the years, the potential of these organozinc reagents for synthetic applications has found only few interest due to the meanwhile established organomagnesium reagents by Grignard[10] and moreover due to the accessibility of organolithium reagents. These organometallics show a significant higher reactivity towards various electrophiles and therefore, organozincs were only used for Reformatsky- (zinc enolates)[11] and Simmons-Smith reactions (cyclopropanations)[12] due to the easier handling of the involved organometallic reagents. On the other hand, organolithium and –magnesium reagents show a significantly lower functional group tolerance than organozinc reagents and this fact was long ignored by the synthetic community. The moderate reaction of organometallic zinc compound is due to the more covalent character of the carbon-zinc bond in comparison with the related lithium and magnesium organometallics.[5,13] This strong metal-carbon bond can be seen as a great advantage because functionalized organozincs are stable at temperatures where a decomposition of the corresponding organolithium and -magnesium reagents normally occurs.[14] However, as a result of the high energy of the empty d-orbital at the zinc center no participation of organozinc reagents in

[8] (a) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; (b) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236; (c) S. Araki, T. Hirashita, *Comprehensive Organometallic Chemistry III*, Vol. 9, P. Knochel, Ed., Pergamon Press: Oxford, **2007**; (d) J. Auge, N. Lubin-Germain, J. Uziel, *Synthesis* **2007**, 1739.
[9] E. Frankland, *Liebigs Ann. Chem.* **1848**, *71*, 171 and 213; D. Seyferth, *Organometallics* **2001**, *20*, 2940.
[10] V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322.
[11] (a) A. Fürstner, *Angew. Chem. Int. Ed.* **1993**, *32*, 164; (b) S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210.
[12] H. E. Simmons, T. L. Cairns, A. Vladiuchick, C. M. Hoiness, *Org. React.* **1972**, *20*, 1.
[13] I. Antes, G. Frenking, *Organometallics* **1995**, *14*, 4263.
[14] *Handbook of Grignard Reagents*, G. S. Silverman, P. E. Rakita, Eds., Marcel Dekker: New York, **1996**.

common organic reactions is observed. A milestone in this field was the discovery of a range of possible transmetalation reactions of organozinc compounds with various transition-metal salts.[15] Due to the empty, energetically low p-orbitals at the zinc center, an interaction with the d-orbitals of the transition metal occurs resulting in the formation of a highly reactive intermediate (Scheme 1).[16]



Scheme 1: Transmetalation reaction of organozinc reagents with various transition metal salts.

In other words, organozinc reagents which show an exceptional functional group tolerance react with almost all kinds of electrophiles in the presence of the appropriate catalyst. Since these discoveries, an absolute breakthrough has occurred in the field of organozinc chemistry.[17] Organozinc reagents can be divided into three major classes, namely organozinc halides (RZnX), diorganozincs (R^1ZnR^2) and zincates ($R^1R^2R^3ZnM$; M often Li or MgX). Furthermore, the more ionic character the carbon-zinc bond is (more negative charge is located at the carbon attached to the zinc ion), the more reactive are the corresponding zinc reagents, as illustrated in Scheme 2.

$$RZnX < R_2Zn < R_3ZnMgX < R_3ZnLi$$

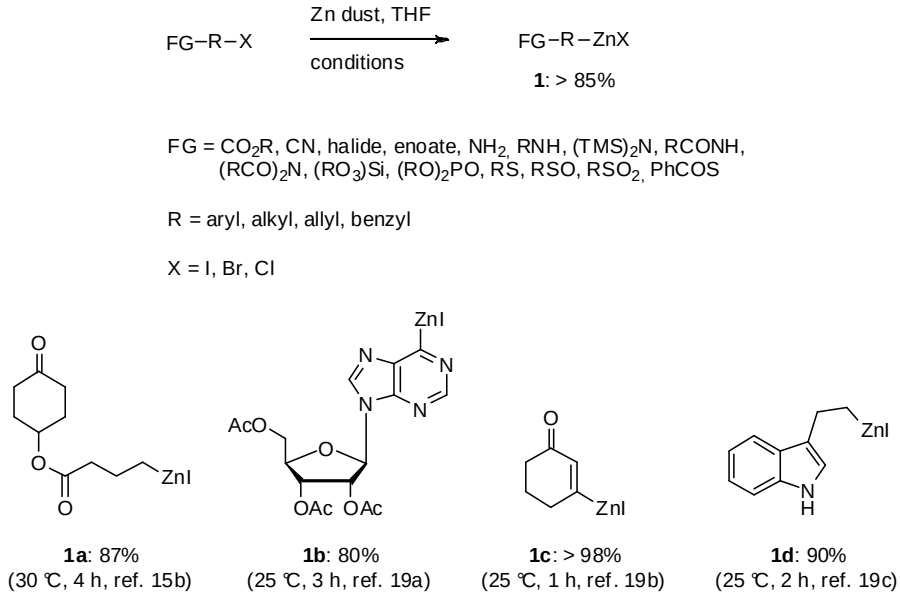
$$\text{alkynyl} < \text{alkyl} < \text{alkenyl} \sim \text{aryl} < \text{benzyl} < \text{allyl}$$

Scheme 2: Reactivity series of organozinc reagents.

[15] (a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 571; (b) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[16] (a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117; (b) P. Knochel, M. J. Rozema, C. E. Tucker, C. Retherford, M. Furlong, S. AchyuthaRao, *Pure Appl. Chem.* **1992**, *64*, 361.
[17] (a) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417; (b) P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel, *Handbook of Functionalized Organometallics*; P. Knochel, Ed., Wiley-VCH: Weinheim, **2005**; (c) P. Knochel, J. J. Almena Perea, P. Jones, *Tetrahedron* **1998**, *54*, 8275; (d) *Organozinc Reagents*, P. Knochel, P. Jones, Eds., Oxford University Press: New York, **1999**; (e) P. Knochel, F. Langer, M. Rottländer, T. Stüdemann, *Chem. Ber.* **1997**, *130*, 387; (f) P. Knochel, S. Vettel, C. Eisenberg, *Appl. Organomet. Chem.* **1995**, *9*, 175.

2.2. Direct zinc insertion into organic halides using zinc metal

The most general preparation method for functionalized organozinc halides (**1**) is the direct insertion of zinc metal into organic halides in THF. Using this method, almost any functional group is tolerated (Scheme 3). Only a few groups such as an azide or a nitro function which can accept an electron from the zinc surface hamper the preparation of the related organozinc compounds. Furthermore, to achieve good insertion results, the activation of the zinc metal is essential due to the oxide layer covering the zinc surface. Typically, 1,2-dibromoethane (5 mol%, reflux, 1 min) followed by TMSCl (1 mol%, reflux, 1 min) were used to activate the zinc metal for the insertion.[18]

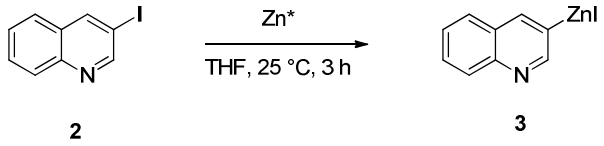


Scheme 3: Preparation of functionalized organozinc reagents by the direct insertion of zinc metal into the corresponding iodides.

A broad range of polyfunctional organozincs are easily accessible by the method described above.[19] The insertion of zinc dust into a sp^2-carbon-iodide bond is generally problematic and therefore higher reaction temperatures or polar cosolvents are necessary.[20] Alternatively, the reduction of zinc chloride by lithium naphthalenide in THF provides highly reactive zinc metal

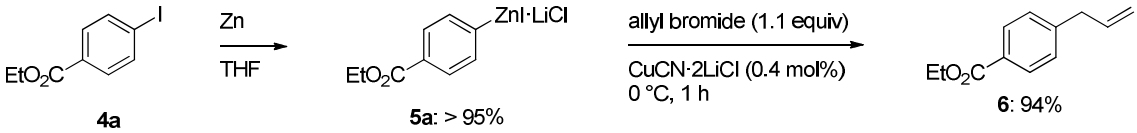
[18] (a) M. Gaudemar, *Bull. Soc. Chim. Fr*. **1962**, *5*, 974; (b) E. Erdik, *Tetrahedron* **1987**, *43*, 2203.
[19] (a) T. M. Stevenson, B. Prasad, J. Citineni, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8375; (b) P. Knochel, C. Janakiram, *Tetrahedron* **1993**, *49*, 29; (c) H. P. Knoess, M. T. Furlong, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1991**, *56*, 5974.
[20] T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413.

(Zn*),[21] which can, for example, insert into 3-iodoisoquinoline (**2**) providing the corresponding zinc reagent **3** (Scheme 4).[22]



Scheme 4: Preparation of heteroarylzinc reagent **3** by insertion of highly active Zn*-metal.

Since highly active Zn* decomposes over time and, moreover, two equivalents lithium naphthalenide are required for its preparation, an efficient and very simple new method for the direct zinc insertion into aromatic bromides and iodides was demonstrated which overcomes all the previously mentioned drawbacks. Thus, the reaction of ethyl 4-iodobenzoate (**4a**) with zinc dust at 70 °C for 24 h did not provide the expected arylzinc iodide **5a**. Contrary, performing the insertion in the presence of stoichiometric amounts of LiCl furnished the desired zinc compound **5a** within 24 h at 25 °C in more than 95% yield (Scheme 5).[23] Subsequent allylation reaction provided the benzoate **6** within 1 h in 94% yield.

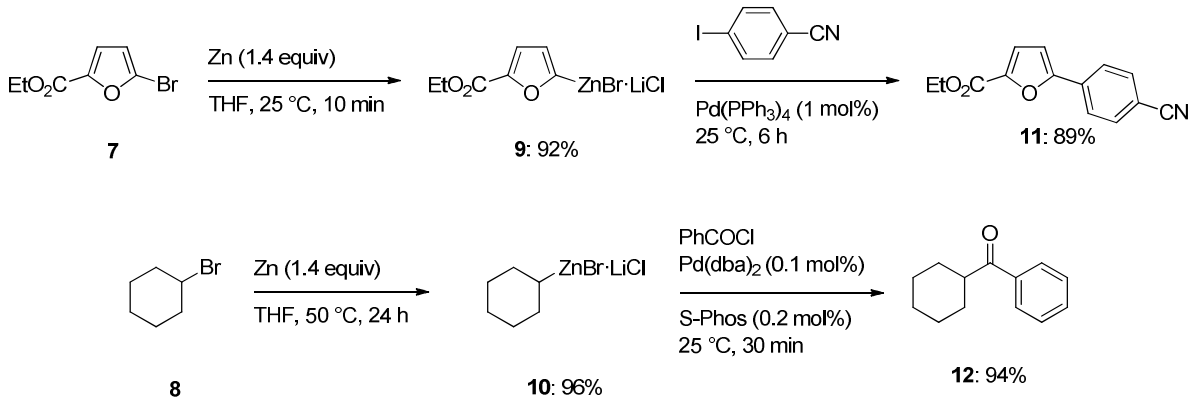


by using Zn (2.0 equiv) at 70 °C, 24 h: < 5%
by using Zn·LiCl (1.4 equiv) at 25 °C, 24 h: > 98%

Scheme 5: Preparation of 4-(ethoxycarbonyl)phenylzinc iodide (**5a**) in the absence and in the presence of stoichiometric amounts of LiCl.

Similarly, the bromo-substituted furan **7** as well as bromocyclohexane (**8**) were converted to the corresponding organozinc reagents **9**-**10** and provided after a Pd-catalyzed cross-coupling with 4-iodobenzonitrile as well as after a acylation with benzoyl chloride the expected products **11**and **12** in 89-94% yield (Scheme 6).

[21] (a) R. D. Rieke, *Science* **1989**, *246*, 1260; (b) M. V. Hanson, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; (c) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323; (d) M. V. Hanson, R. D. Rieke, *J. Am. Chem. Soc.* **1995**, *117*, 1445; (e) R. D: Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925.
[22] T. Sakamoto, Y. Kondo, N. Murata, H. Yamanaka, *Tetrahedron* **1993**, *49*, 9713.
[23] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

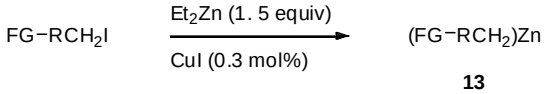


Scheme 6: Preparation of heteroaromatic aryl- and secondary alkylzinc bromides **9** and **10**.

It can be envisioned that due to the influence of LiCl, the prepared organozinc halide is highly soluble in THF and is easily released from the metal surface. This allows a rapid reaction of additional organohalides with zinc and the deactivation is not favored.

2.3. The iodine-zinc exchange reaction

Diorganozinc reagents are more reactive than organozinc halides.[5] Besides the typical preparation of diorganozincs by transmetalation of organolithium or -magnesium reagents using one half-equivalent of zinc salt,[24] a practical way for their preparation is the iodine-zinc exchange reaction using diethylzinc leading to functionalized zinc reagents of the type $(FG\text{-}R)_2Zn$ (**13**; Scheme 7).[25] One major advantage, compared to the transmetalations described above, is the functional group tolerance. Catalytic amounts of copper(I)-salts are necessary to achieve good exchange reactions.[26]



Scheme 7: Cu(I)-catalyzed iodine-zinc exchange reaction.

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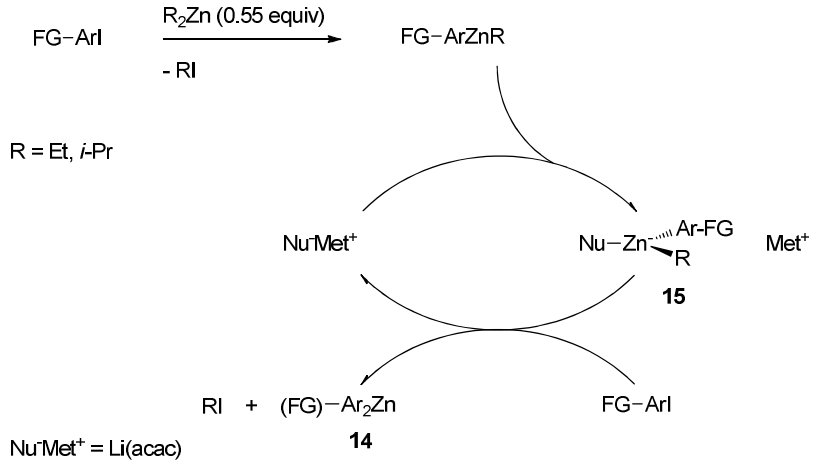
[24] K. Nützel, *Methoden der Organischen Chemie, Metallorganische Verbindungen Be, Mg, Ca, Sr, Ba, Zn, Cd*, Vol. 13/2a, Thieme: Stuttgart, **1973**.

[25] Diorganozinc reagents can be also prepared by boron-zinc exchange, see: (a) P. Knochel, A. Boudier, L. O. Bromm, E. Hupe, J. A. Varela, A. Rodriguez, C. Koradin, T. Bunlaksananusorn, H. Laaziri, F. Lhermitte, *Pure Appl. Chem.* **2000**, *72*, 1699; (b) P. Knochel, E. Hupe, W. Dohle, D. M. Lindsay, V. Bonnet, G. Queguiner, A. Boudier, F. Kopp, S. Demay, N. Seidel, M. I. Calaza, V. A. Vu, I. Sapountzis, T. Bunlaksananusorn, *Pure Appl. Chem.* **2002**, *74*, 11.

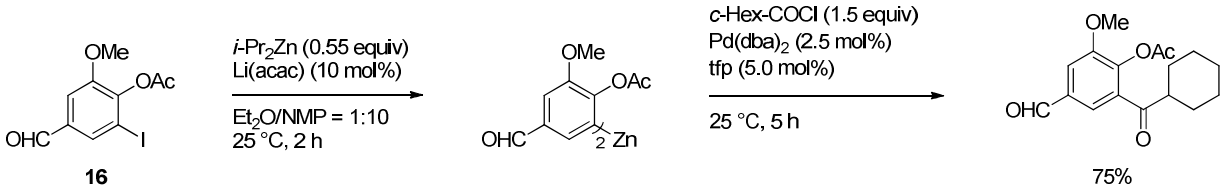
[26] (a) M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956; (b) M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115.

The aforementioned exchange reaction is limited to alkyl iodides. Therefore, a Li(acac) catalyzed novel iodine-zinc exchange was developed using aryl iodides and diisopropylzinc (Scheme 8).[27] This new reaction provides access to functionalized diarylzinc reagents of type **14**.



Scheme 8: Li(acac)-catalyzed iodine-zinc exchange with aromatic iodides furnishing diarylzincs.

The reaction is performed in a Et_2O:NMP mixture at 25 °C. The use of Li(acac) is crucial to promote the transfer of the second alkyl group R and the proposed intermediated **15** is shown as an "ate-complex" which can be seen in analogy to the known boranate-complex in the Suzuki cross-coupling reaction.[28] Several sensitive functional groups can be tolerated during this exchange as exemplarily shown in Scheme 9.



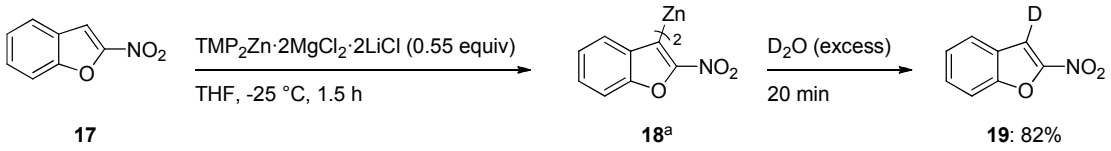
Scheme 9: Selective I/Zn-exchange reaction on aromatic iodide **16** followed by an acylation.

2.4. Preparation of highly functionalized arylzinc reagents by directed metalations

Recently, the preparation of the mild and chemoselective base $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ was reported.[29] Using this base, an efficient and convenient access to functionalized diarylzinc reagents is possible. The Lewis acid LiCl is responsible for the excellent solubility of both the

[27] F. F: Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[28] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
[29] (a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; (b) Z. Dong, G. C. Clososki, S. H. Wunderlich, A. Unsinn, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 457.

base and the formed diarylzincs. Moreover, $MgCl_2$ leads to the high reactivity of the base in analogy to the presented iodine-zinc exchange presented above. Thus, the reaction of the nitro-substituted benzofuran **17** with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ provided the desired heterodiarylzinc compound **18** which led to the deuterated product **19** in 82% yield (Scheme 10).

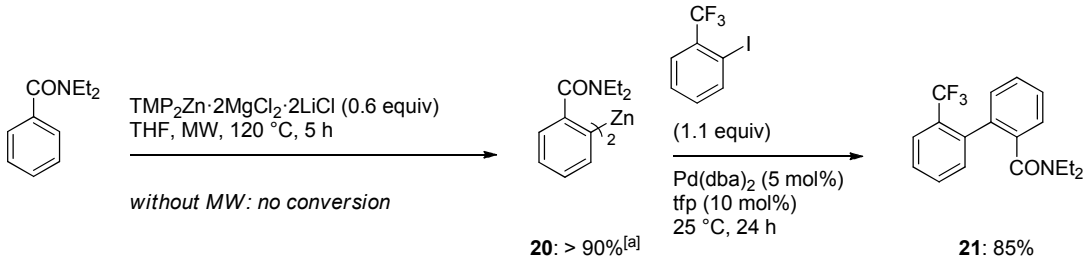


17 **18**[a] **19**: 82%

[a] Complexed salts have been omitted for the sake of clarity

Scheme 10: Preparation of diarylzinc reagent **18** by using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$.

Due to the thermal stability and functional group tolerance of organozinc reagents even at higher temperatures, [30] difficult substrates for directed metalation can be converted to the expected diarylzinc compounds using microwave techniques, as shown for *N*,*N*-diethylbenzamide which provided the corresponding zinc reagent **20** within 5 h (Scheme 11).[31] Subsequent Pd-catalyzed cross-coupling led to the biphenyl **21** in 85% yield.



20: > 90%[a] **21**: 85%

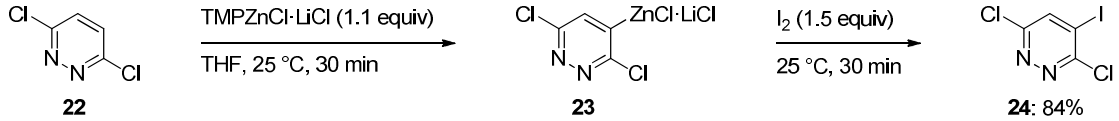
[a] Complexed salts have been omitted for the sake of clarity

Scheme 11: Preparation of bisarylzinc reagent **20** using microwave irradiation.

However, using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$, only unsatisfactory results in terms of reaction selectivity and yield are obtained with some electron-poor heteroaromatics. Therefore, a more selective base ($TMPZnCl \cdot LiCl$) was developed which showed, in contrast to the previously demonstrated base a very good chemoselectivity towards functionalized heterocycles even at

[30] P. Walla, C. O. Kappe, *Chem. Commun.* **2004**, 564.
[31] S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.

ambient temperatures.[32] Moreover, this new base allows a direct way for the preparation of functionalized aryl- and heteroarylzinc halides. By using TMPZnCl·LiCl, 3,6-dichloropyridazine (**22**) was zincated within 30 min providing the corresponding heteroarylzinc chloride **23** which led to the expected iodinated pyridazine **24** in 84% yield.

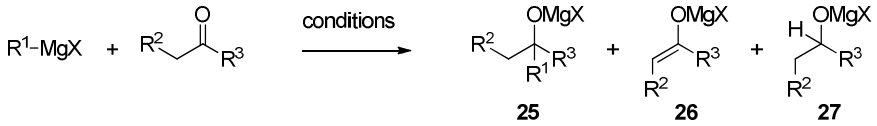


Scheme 12: Direct metalation of 3,6-dichloropyridazine (**22**) using the mild base TMPZnCl·LiCl to provide the corresponding heteroaryl zinc chloride **23**.

[32] (a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; (b) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.

3. Lewis-Acid Promoted Additions of Functionalized Organomagnesium and Organozinc Reagents to Carbonyl Derivatives

The additions of lithium or magnesium organometallics to aldehydes, ketones and imines are highly important carbon-carbon bond formation reactions.[33] Grignard reagents show a significantly higher functional group tolerance than the corresponding lithium counterparts and therefore their use became more and more frequent over the last years.[34] However, such 1,2-additions to enolizable ketones are often complicated if sterically hindered or unreactive Grignard reagents are used (Scheme 13). In these cases, the formation of the tertiary alcohol **25** proceeds along with several side reactions such as enolization (leading to **26**) or β-hydride transfer (leading to the secondary alcohol **27**).



Scheme 13: Possible products of the reaction of a Grignard reagent with enolizable ketones.

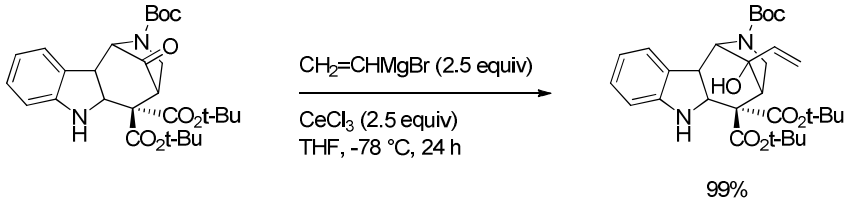
The formation of byproducts **26** and **27** can be considerably reduced by using a Lewis acid activation of the ketone. Lanthanide halides[35] such as $CeCl_3$ introduced by Imamoto have proven to be especially effective. In the presence of $CeCl_3$, the 1,2-addition reaction of a Grignard reagent to a ketone is favored and the formation of byproducts of type **26** and **27** is

[33] (a) *The Chemistry of Organolithium Compounds*, Z. Rappoport, I. Marek, Eds., Wiley, Chichester, **2004**; (b) B. J. Wakefield, *The Chemistry of Organolithium Compounds*, Pergamon Press: New York, **1974**; (c) R. Noyori, M. Kitamura, *Angew. Chem. Int. Ed.* **1991**, *30*, 49; (d) K. Tomioka, I. Inoue, M. Shindo, K. Koga, *Tetrahedron Lett.* **1990**, *31*, 6681; (e) *The Chemistry of Organomagnesium Compounds*; Z. Rappoport, I. Marek, Eds., Wiley, Chichester, **2008**; (f) M. R. Luderer, W. F. Bailey, M. R. Luderer, J. D. Fair, R. J. Dancer, M. B. Sommer, *Tetrahedron: Asymmetry*, **2009**, *20*, 981; (g) J. M. Mallan, R. L. Bebb, *Chem. Rev.* **1969**, *69*, 693; (h) *Grignard Reagents - New Developments*, H. G. Richey, Jr., Ed., Wiley: Chichester, **2000**.

[34] (a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; (b), A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; (c) F. Kopp, I. Sapountzis, P. Knochel, *Synlett* **2003**, 885; (d) Dietmar Seyferth, *Organometallics*, **2009**, *28*, 1598; (e) J. J. Eisch, *Organometallics*, **2002**, *21*, 5439; (f) A. Wolan, Y. Six, *Tetrahedron* **2010**, *66*, 15.

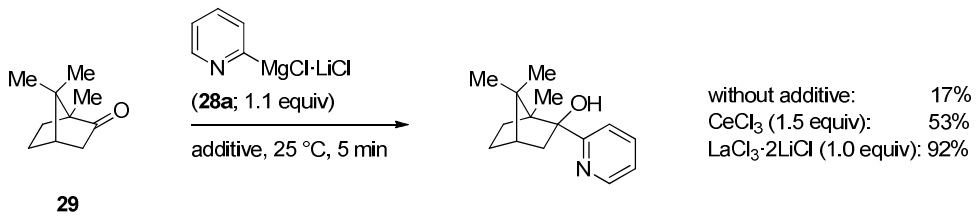
[35] For selected reviews on the use of lanthanide derivatives, see: (a) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 7140; (b) V. Nair, A. Deepth, *Tetrahedron* **2009**, *65*, 10745; (c) G. A. Molander, *Chem. Rev.* **1992**, *92*, 29; (d) G. A. Molander, J. A. C. Romero, *Chem. Rev.* **2002**, *102*, 2161; (e) T. J. Boyle, L. A. M. Ottley, *Chem. Rev.* **2008**, *108*, 1896; (f) G. A. Molander, *Pure Appl. Chem.* **2000**, *72*, 1757; (g) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227; (h) P. G. Steel, *J. Chem. Soc., Perkin Trans. 1* **2001**, *21*, 2727; (i) For an selected article about the reduction of ketones in the presence of lanthanide halides, see: J.-L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226.

reduced.[36] A recent example using $CeCl_3$ for the addition of a Grignard reagent to a ketone is demonstrated in the reaction sequence in Scheme 14 to provided an precursor for the total synthesis of (±)-actinophyllic acid.[37]



Scheme 14: Application of $CeCl_3$ in natural product synthesis.

Two explanations are commonly used to describe the influence of $CeCl_3$ in these addition reactions. On the one hand lanthanide salts activate in a Lewis-acid fashion the ketone due to the oxophilic behavior of these salts. On the other hand, a transmetalation of the Grignard reagent to the lanthanide salt is possible. The resulting organolanthanides are less basic and therefore a deprotonation of alpha-acidic ketones should not occur.[38] Recently, the preparation of THF-soluble $LaCl_3 \cdot 2LiCl$ complex has been reported.[39] It was found that this complex is highly efficient in improving the addition of Grignard reagents to ketones and imines (Scheme 15).



Scheme 15: Addition of pyridylmagnesium chloride (**28a**) to camphor (**29**) in the presence of different lanthanide salts.

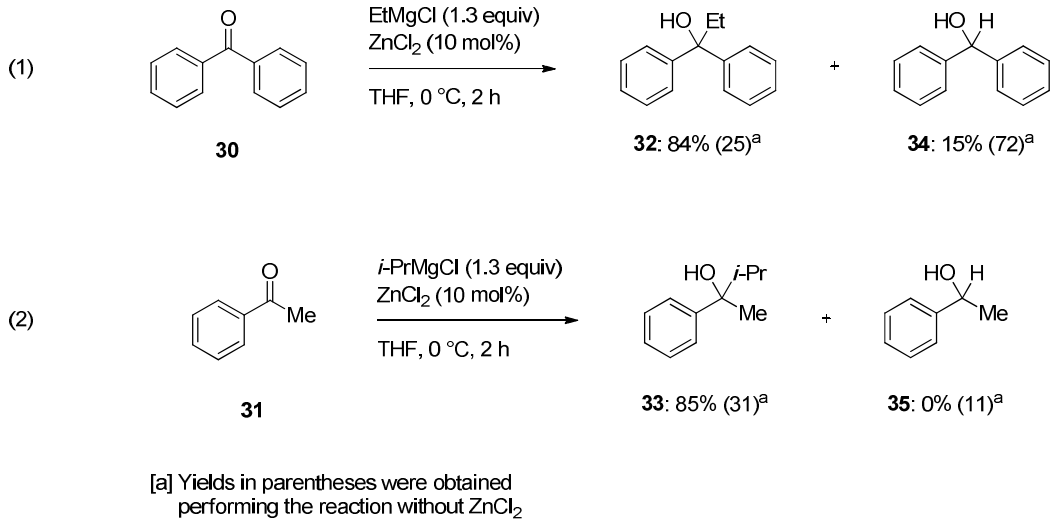
[36] (a) T. Imamoto, Y. Sugiyura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233; (b) T. Imamoto, *Pure and Appl. Chem.* **1990**, *62*, 747; (c) T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, Y. Kamiya, *J. Am. Chem. Soc.* **1989**, *111*, 4392; (d) S. Panev, V. Dimitrov, *Tetrahedron: Asymmetry* **2000**, *11*, 1517; (e) D. A. Conlon, D. Kumke, C. Moeder, M. Hardiman, G. Hutson, L. Sailer, *Adv. Synth. Catal.* **2004**, *346*, 1307.

[37] (a) C. L. Martin, L. E. Overman, J. M. Rohde, *J. Am. Chem. Soc.* **2008**, *130*, 7568; (b) For another example using $CeCl_3$ in natural product synthesis, see: Q. Wang, C. Chen, *Org. Lett.* **2008**, *10*, 1223.

[38] (a) M. Badioli, R. Ballini, M. Bartolacci, G. Bosica, E. Torregiani, E. Marcantoni, *J. Org. Chem.* **2002**, *67*, 8938; (b) H.-J. Liu, K.-S. Shia, X. Shang, B.-Y. Zhu, *Tetrahedron* **1999**, *55*, 3803; (c) V. Dimitrov, K. Kostova, M. Genov, *Tetrahedron Lett.* **1996**, *37*, 6787; (d) T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, M. Yokoyama, *J. Org. Chem.* **1984**, *49*, 3904.

[39] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

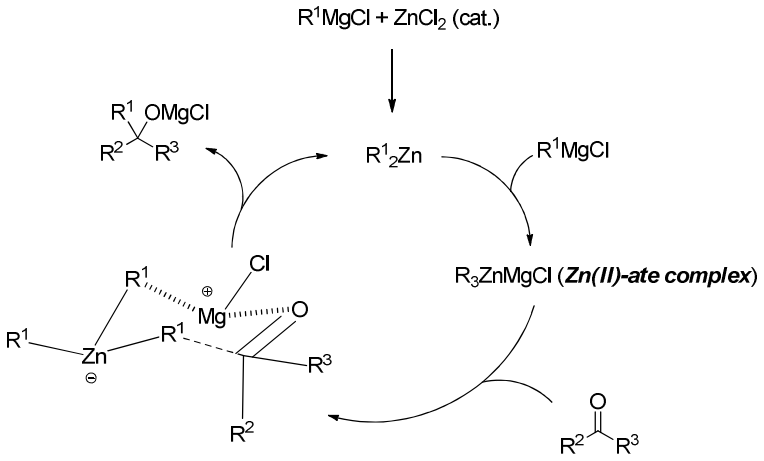
Furthermore, the direct alkylation of benzophenone (**30**) with Grignard reagents in the presence of a catalytic amount of $ZnCl_2$ (10 mol%) was very recently reported (equation 1, Scheme 16).[40] Moreover, isopropylation of acetophenone (**31**) proceeds along the same way (equation 2). Interestingly, by using a catalytic amount of $ZnCl_2$ the addition of alkylmagnesium reagents to ketones **30** and **31** led to the tertiary alcohols **32-33** without significant formation of reduction products **34** and **35**.



Scheme 16: Addition of alkylmagnesium reagents to ketones in the presence of $ZnCl_2$ (cat.).

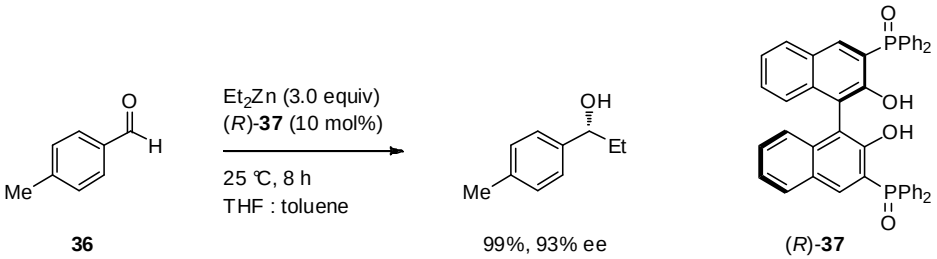
These results were explained by assuming that the addition of an organomagnesium reagent to a carbonyl derivative in the presence of catalytic amounts of $ZnCl_2$ proceeds via a catalytic cycle including a six-membered transition state (Scheme 17). First, a active Zn(II)-ate complex is formed by the reaction of the Grignard reagent with $ZnCl_2$ followed by the addition to the ketone. Therefore, the $[MgCl]^+$-moiety coordinates to the carbonyl group followed by the attack of $[R_2Zn\text{-}R]^-$ and finally release of the adduct and regeneration of the active zinc intermediate.

[40] (a) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998; (b) M. Hatano, S. Suzuki, K. Ishihara, *Synlett* **2010**, 321; (c) M. Hatano, T. Miyamoto, K. Ishihara, *Curr. Org. Chem.* **2007**, *11*, 127; (d) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647; (e) M. Hatano, K. Ishihara, *Acid Catalysis in Modern Organic Synthesis*, *Vol. 1*, H. Yamamoto, K. Ishihara, Eds., Wiley-VCH: Weinheim, **2008**.



Scheme 17: Proposed catalytic cycle for the addition of organomagnesium reagents to ketones in the presence of catalytic amounts of $ZnCl_2$.

The addition of organozinc reagents to carbonyl derivatives is widely studied, mainly in the field of asymmetric synthesis. Common ways for the preparation of dioorganozincs are transmetalation reactions of the corresponding lithium- or magnesium reagents with zinc salts or hydroboration of an olefin and subsequent boron zinc exchange.[25] Then, the additions of these zinc organometallics to aldehydes,[41] ketones,[42] or aldimines[43] proceed often in the presence of a chiral ligand as exemplarily shown in Scheme 18.



Scheme 18: Addition of Et_2Zn to benzaldehyde **36** in the presence of the chiral ligand **37**.

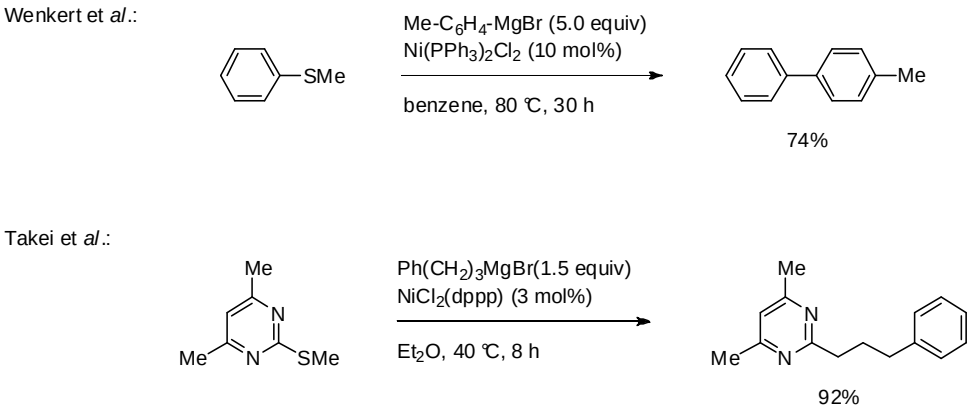
[41] (a) For selected reviews, see: L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757; (b), K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833; (c) See also: J. Rudolph, M. Lormann, C. Bolm, S. Dahmen, *Adv. Synth. Catal.* **2005**, *347*, 1361; (d) C. Bolm, N. Hermanns, J. P. Hildebrand, K Muniz, *Angew. Chem. Int. Ed.* **2000**, *39*, 3465; (e) M. Hatano, T. Miyamoto, K. Ishihara, *Adv. Synth. Catal.* **2005**, *347*, 1561; (f) L. Salvi, J. G. Kim, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 12483; (g) C. E. Tucker, P. Knochel, *J. Am. Chem. Soc.* **1991**, *113*, 9888; (h) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1979**, *62*, 1701; (i) M. Hatano, T. Miyamoto, K. Ishihara, *J. Org. Chem.* **2006**, *71*, 6474; (j) W.-S. Huang, L. Pu, *J. Org. Chem.* **1999**, *64*, 4222; (k) J. L. von dem Bussche-Hünnefeld, D. Seebach, *Tetrahedron Lett.* **1992**, *33*, 5719; (l) P. Wipf, W. Xu, *Tetrahedron Lett.* **1994**, *35*, 5197.

[42] (a) V. J. Forrat, O. Prieto, D. J. Ramon, M. Yus, *Chem. Eur. J.* **2006**, *12*, 4431; (b) M. Hatano, T. Miyamoto, K. Ishihara, *Org. Lett.* **2007**, *9*, 4535; (c) K. Yearick, C. Wolf, *Org. Lett.* **2008**, *10*, 3915.

[43] (a) For a selected review, see: K. Yamada, K. Tomioka, *Chem. Rev.* **2001**, *101*, 757; (b) See also: K. P. Chiev, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry* **2002**, *13*, 2205.

4. Transition Metal-Catalyzed Cross-Coupling Reactions of Functionalized Organometallics With Unsaturated Thioethers

The transition metal-catalyzed cross-coupling reactions of unsaturated thioethers as well as thiols with Grignard reagents have been pioneered by *Wenkert* and *Takei* in 1979.[44, 45] They represent attractive methods for converting a carbon-sulfur bond into a carbon-carbon bond (Scheme 19).



Scheme 19: Nickel-catalyzed cross-couplings reported by *Wenkert* and *Takei* in 1979.

Based on these first results, *Fukuyama* and especially *Liebeskind* and co-workers could extremely extend the scope of this cross-coupling reaction leading to a general ketone synthesis. Thus, functionalized thioesters **38** and **39** were converted to the corresponding ketones **40**-**41** using organozinc reagents or organoboronic acids in a palladium-catalyzed cross-coupling reaction (Scheme 20).[46]

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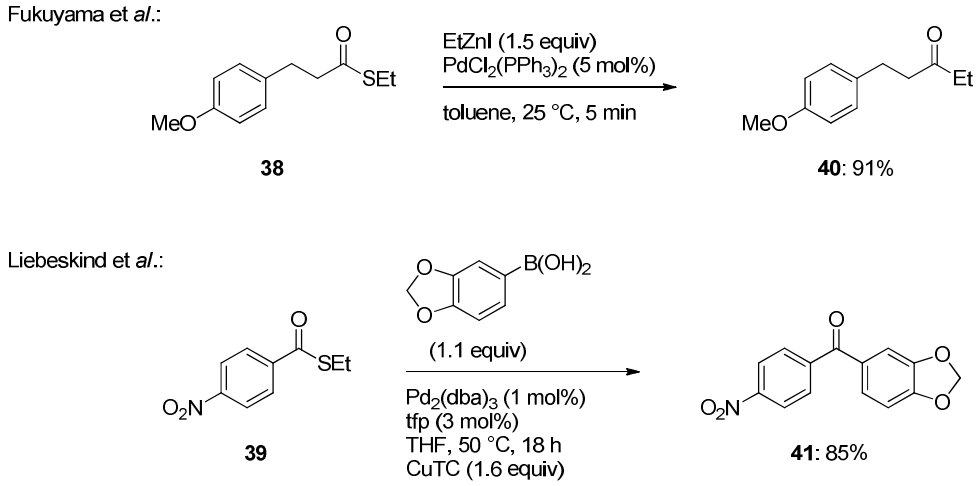
[44] (a) E. Wenkert, T. W. Ferreira, E. L. Michelotti, *J. Chem. Soc.,Chem. Commun.* **1979**, 637; (b) H. Okamura, M. Miura, H. Takei, *Tetrahedron Lett.* **1979**, *20*, 43; (c) H. Takei, M. Miura, H. Sugimura, H. Okamura, *Chem. Lett.* **1979**, *8*, 1447; (d) E. Wenkert, T. W. Ferreira, *J. Chem. Soc., Chem. Commun.* **1982**, 840; (e) E. Wenkert, M. E. Shepard, A. T. McPhail, *J. Chem. Soc., Chem. Commun.* **1986**, 1390; (f) E. Wenkert, D. Chianelli, *J. Chem. Soc., Chem. Commun.* **1991**, 627.

[45] For selected reviews, see: (a) S. R. Dubbaka, P. Vogel, *Angew. Chem. Int. Ed.* **2005**, *44*, 7674; (b) H. Prokopcova, C. O. Kappe, *Angew. Chem. Int. Ed.* **2009**, *48*, 2276.

[46] (a) H. Tokuyama, S. Yokoshima, T. Yamashita, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 3189; (b) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000,** *122*, 11260; (c) J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997,** *119*, 12376; (d) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 3229; (e) J. M. Villalobos, J. Srogl, L. S. Liebeskind, *J. Am. Chem. Soc.* **2007,** *129*, 15734; (f) L. S. Liebeskind, H. Yang, H. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 1417; (g) Y. Yu, L. S. Liebeskind, *J. Org. Chem.* **2004**, *69*, 3554; (h) C. L. Kusturin, L. S. Liebeskind, W. L. Neumann, *Org. Lett.* **2002**, *4*, 983.

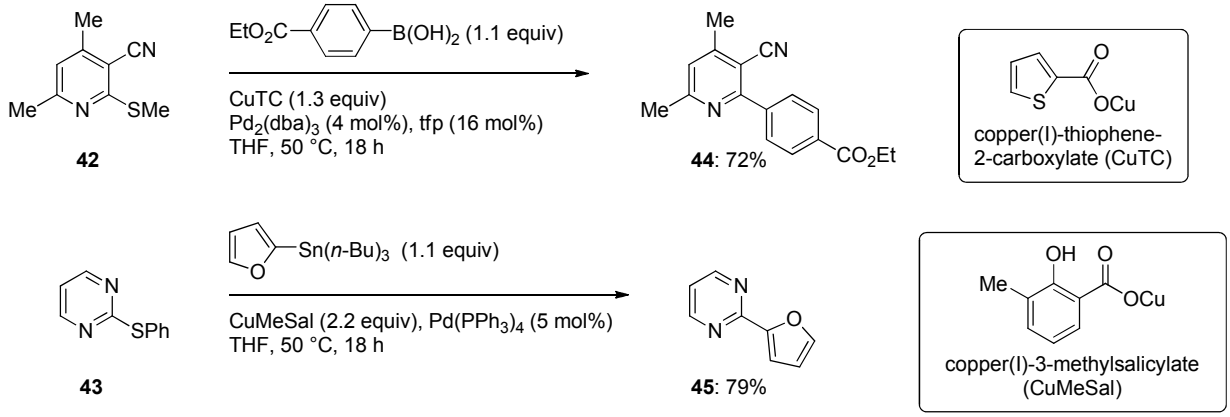


Scheme 20: Ketone synthesis using thioesters and various organometallic reagents in Pd-catalyzed cross-coupling reactions.

Furthermore, organostannanes [47] as well as organoindium reagents [48] were also used as nucleophilic partners for the direct synthesis of ketones starting from the corresponding thioesters.

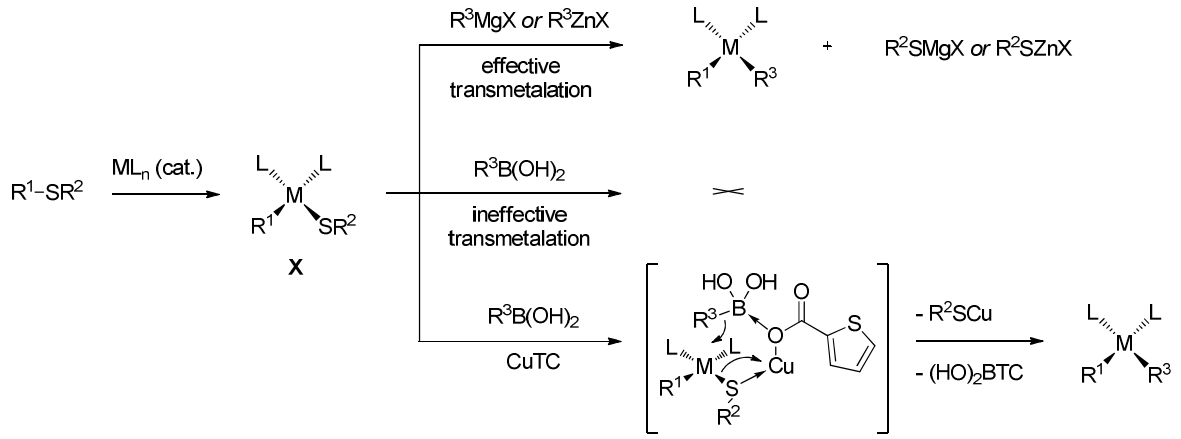
More recently, this Pd-catalyzed reaction was used in modified ways to couple organoboronic acids[49] or organostannanes[50] with heteroaromatic thioethers **42** and **43** (Scheme 21). To perform these cross-couplings stoichiometric amounts of Cu(I)-salts are also necessary. The expected heterobiphenyls **44**-**45** were obtained in good yields.

[47] R. Wittenberg, J. Srogl, M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 3033.
[48] B. W. Fausett, L. S. Liebeskind, *J. Org. Chem.* **2005**, *70*, 4851.
[49] (a) L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979; (b) S. Oumouch, M. Bourotte, M. Schmitt, J.-J. Bourguignon, *Synthesis* **2005**, 25; (c) A. Aguilar-Aguilar, E. Pena-Cabrera, *Org. Lett.* **2007**, *9*, 4163; (d) A. Lengar, C. O. Kappe, *Org. Lett.* **2004**, *6*, 771; (e) H. Prokopcova, C. O. Kappe, *J. Org. Chem.* **2007**, *72*, 4440; (f) W. van Rossom, W. Maes, L. Kishore, M. Ovaere, L. van Meervelt, W. Dehaen, *Org. Lett.* **2008**, *10*, 585; (g) K. Itami, D. Yamazaki, J. Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 15396; (h) C. Kusturin, L. S. Liebeskind, H. Rahman, K. Sample, B. Schweitzer, J. Srogl, W. L. Neumann, *Org. Lett.* **2003**, *5*, 4349.
[50] M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 801.



Scheme 21: Pd-catalyzed cross-couplings of organoboronic acids and organostannanes with thioether-substituted heterocycles.

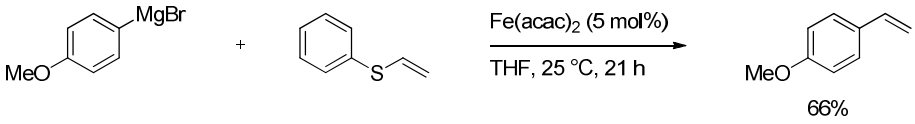
An explanation for the success of these cross-couplings using organomagnesium or -zinc reagents is an efficient transmetalation step towards the intermediate **46** which is promoted by the formation of an 'ate' intermediate due to the high reactivity of Grignard reagents or, in the case of organozinc compounds, by the polarization of the palladium-sulfur bond due to the thiophilicity of the zinc cation (Scheme 22).[49a] On the other hand, to ensure a "base-free" transmetalation in the case of organoboronic acids, the Cu(I)-carboxylate plays an important role due to the polarisation of the Pd-S bond and moreover the activation of the trivalent boron by coordination of the carboxylate anion to the boron species.



Scheme 22: Explanation for the need of Cu(I)-carboxylates in palladium-catalyzed cross-couplings of organoboronic acids with thioethers as well as thioesters.

Beside the known Ni-catalyzed cross-couplings of vinyl sulfides with organomagnesium reagents,[44b, d] cross-coupling reactions of alkenyl sulfides with Grignard reagents in the presence

of an iron catalyst were recently reported leading to functionalized styrenes (Scheme 23).[51]

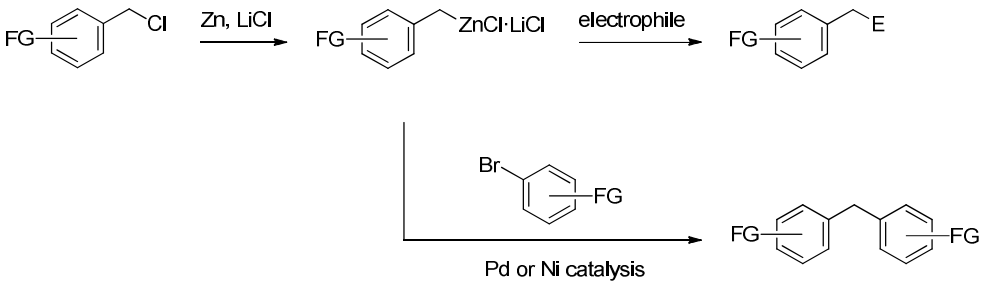


Scheme 23: Iron-catalyzed cross-coupling of 4-methoxyphenylmagnesium bromide with phenyl vinyl sulfide leading to methoxy-4-vinylbenzene.

[51] K. Itami, S. Higashi, M. Mineno, J. Yoshida, *Org. Lett.* **2005**, *7*, 1219.

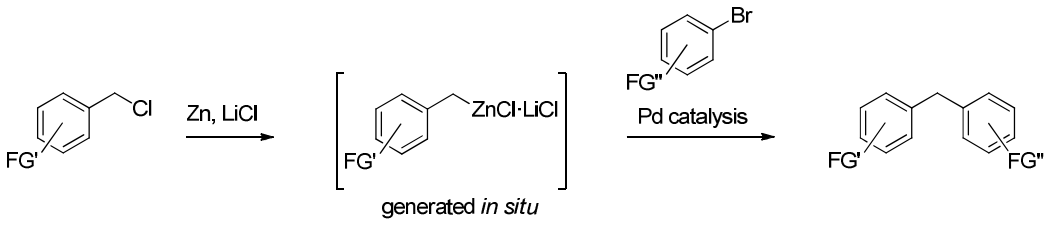
5. Objectives

Organozinc reagents are an important class of organometallics.[16] However, the preparation of benzylic zinc reagents is still problematic and normally low temperatures are required to avoid the formation of homo-coupling products. Moreover, due to various difficulties, cheap benzylic chlorides are only rarely used to date for the preparation of the corresponding benzylic zinc reagents. The aim of the first project was the preparation of highly functionalized benzylic zinc chlorides by direct zinc insertion in the presence of LiCl into the corresponding benzylic chlorides as well as reaction with common electrophiles (Scheme 24). Furthermore, the transition metal-catalyzed cross-couplings of benzylic zinc chlorides with various electrophiles leading to the important class of diarylmethanes were investigated.



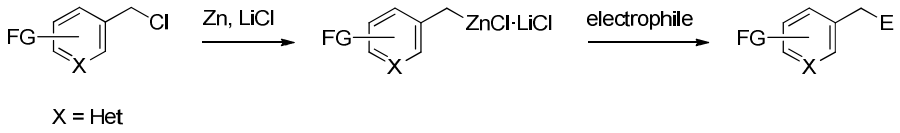
Scheme 24: Preparation of benzylic zinc chlorides and reaction with common electrophiles as well as transition metal-catalyzed cross-couplings.

Furthermore, an *in situ* preparation of benzylic zinc chlorides and subsequent cross-coupling reaction with electrophiles under transition metal catalysis in a one-pot procedure was performed.



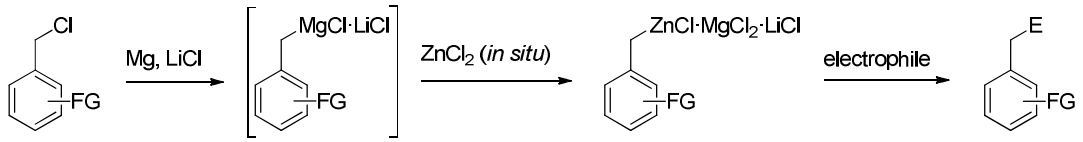
Scheme 25: *In situ* generation of benzylic zinc chlorides followed by Pd-catalyzed cross-coupling reactions.

Additionally, the preparation of heterobenzylic zinc chlorides was investigated (Scheme 26).



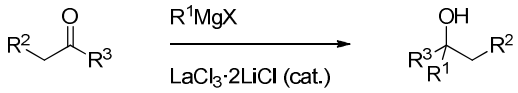
Scheme 26: Preparation of heterobenzylic zinc chlorides.

Moreover, the preparation of benzylic zinc chlorides was extended to the direct insertion of magnesium into benzylic chlorides in the presence of $ZnCl_2$ and LiCl and subsequent reaction with different electrophiles (Scheme 27).



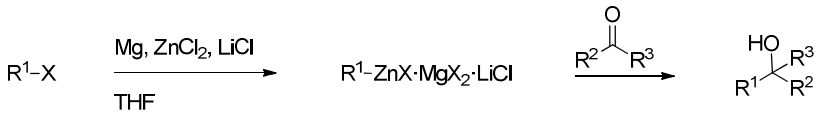
Scheme 27: Preparation of benzylic zinc chlorides by direct insertion of magnesium in the presence of $ZnCl_2$ and LiCl into benzylic chlorides.

Lanthanide halides are often used to support an efficient addition of Grignard reagents to enolizable ketones. However, $CeCl_3$ and $LaCl_3 \cdot 2LiCl$ have been used so far only in a stoichiometric fashion. Therefore, in a second project, the addition of functionalized magnesium reagents to carbonyl derivatives in the presence of catalytic amounts of $LaCl_3 \cdot 2LiCl$ was investigated (Scheme 28).



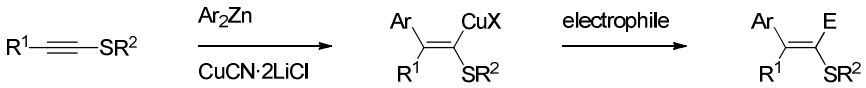
Scheme 28: Addition of Grignard reagents to ketones in the presence of $LaCl_3 \cdot 2LiCl$ (cat.).

Since functionalized organozinc reagents are only rarely used towards the addition to carbonyl derivatives, the direct addition of highly functionalized organozinc compounds to aldehydes, ketones and carbon dioxide mediated by stoichiometric amounts of $MgCl_2$ was developed (Scheme 29).



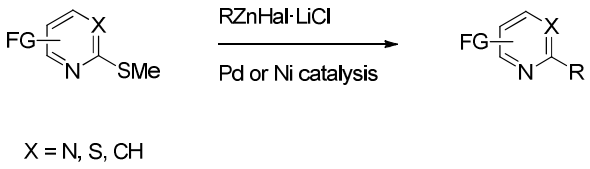
Scheme 29: Addition of functionalized organozinc reagents to carbonyl derivatives.

As a further project, a novel Cu(I)-mediated direct carbometalation reaction was developed using thioether-substituted alkynes and functionalized diarylzinc reagents, which gave access to tetra-substituted alkenes (Scheme 30).



Scheme 30: Cu(I)-mediated carbometalation using diarylzinc reagents.

Due to the facile introduction of thioether-groups to heterocycles as advantage compared to halogen substituents, the aim of the fourth project was the transition metal-catalyzed cross-couplings of methylthio-substituted N-heterocycles with functionalized organozinc reagents (Scheme 31).



Scheme 31: Pd- or Ni-catalyzed cross-coupling reactions of heterocyclic thioethers with functionalized organozinc compounds.

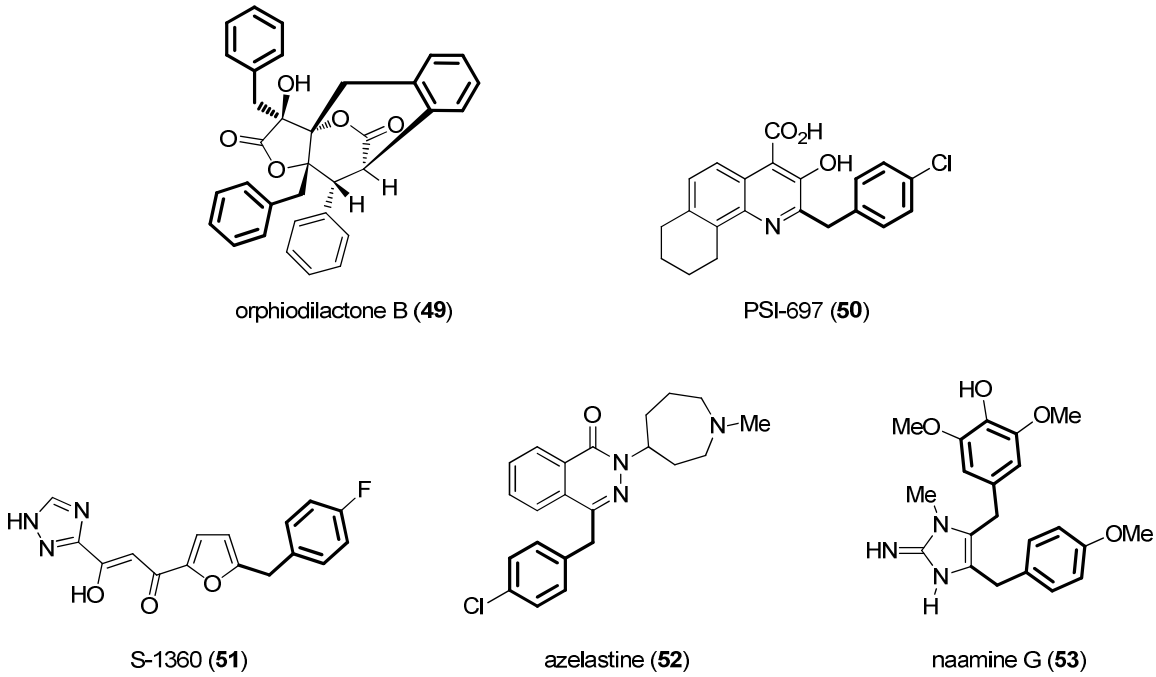
B. RESULTS AND DISCUSSION

1. Preparation and Applications of Benzylic Zinc Chlorides

1.1. Preparation of functionalized benzylic zinc chlorides by LiCl-mediated zinc insertion into benzylic chlorides

1.1.1. Introduction

Benzylic groups are widespread moieties in organic chemistry. They are extensively used as protecting groups in the total synthesis of complex structures.[52] Besides, in numerous biologically active compounds as well as pharmaceuticals, benzylic groups are important structural motives.



Scheme 32: Presence of benzylic moieties in natural products and pharmaceuticals.

Orphiodilactone B (**49**) is a complex molecule with a unique carbon skeleton bearing three benzylic groups (Scheme 32).[53] It was isolated from the orphiuroid *Ophiocoma scolopendrina*. Cytotoxic activity of Orphiodilactone B (**49**) against P388 murine leukemia cells was demonstrated. PSI-697 (**50**), another benzylic derivative, is a potential candidate for the treatment

[52] (a) T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis, 3rd ed.*, Wiley: New York, **1999**; (b) F. A. Luzzio, J. Chen, *J. Org. Chem.* **2008**, *73*, 5621; (c) H. Lam, S. E. House, G. B. Dudley, *Tetrahedron Letters* **2005**, *46*, 3283; (d) G. A. Eller, W. Holzer, *Heterocycles* **2004**, *63*, 2537.
[53] R. Ueoka, T. Fujita, S. Matsunaga, *J. Org. Chem.* **2009**, *74*, 4396.

of atherothrombotic vascular events and is already in clinical development.[54] Its structural scaffold is based on quinoline salicylic acid and contains a benzylic group in 2-position. As inhibitor for HIV integrase and viral replication, 2,4-diketobutanoic acid derivatives are attractive molecules for pharmaceutical applications.[55] S-1360 (**51**), containing a oxotriazole moiety and a 2-(4-fluorobenzyl)furan, is a molecule which also entered clinical development. Azelastine (**52**), a phthalazine derivative bearing a 4-chlorobenzyl group, is widely used as anti-histaminic agent.[56] Finally, the alkaloid naamine G (**53**) which was isolated from the sponge *Leucetta chagosensis* shows strong antifungal activity against phytopathogenic fungus *Cladosporium herbarum*.[57] Moreover, naamine G (**53**) exhibits cytotoxicity against human cervix carcinoma (HeLa) cell lines. Two substituted benzylic groups combined with a 2-aminoimidazole moiety constitutes the main structure of naamine G (**53**). Due to the common usage of the benzylic group in organic synthesis it would be advantageous to have benzylic organometallic reagents in hand with a high functional group tolerance as well as an easy high yielding preparation, long-time stability and good toxicological properties.

Benzylic lithium reagents show very high reactivity due to the strong ionic character of the carbon-lithium bond. Therefore, the functional group tolerance of these organometallic reagents is low.[58] If benzylic lithium reagents are prepared by a metal-halogen exchange reaction, formation of the Wurtz-coupling product occurs even at very low temperatures.[59] The direct metalation reaction can be complicated because strong bases are required and, therefore, ring metalation products can be obtained.[60] Benzylic magnesium reagents show a slightly higher functional group tolerance but a simple preparation of these organometallics and suppression of side reactions (Wurtz coupling product) is still problematic.[61] In 2006, a new and easy

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[54] N. Kaila, K. Janz, A. Huang, A. Moretto, S. DeBernardo, P. W. Bedard, S. Tam, V. Clerin, J. C. Keith, Jr., D. H. H. Tsao, N. Sushkova, G. D. Shaw, R. T. Camphausen, R. G. Schaub, Q. Wang, *J. Med. Chem.*, **2007**, *50*, 40.

[55] T. Kawasuji, T. Yoshinaga, A. Sato, M. Yodo, T. Fujiwara, R. Kiyama, *Bioorg. Med. Chem.* **2006**, *14*, 8430 (and references cited therein).

[56] F. Horak, U. P. Zieglmayer, *Expert Rev. Clin. Immunol.* **2009**, *5*, 659.

[57] (a) Z. Jin, *Nat. Prod. Rep.* **2005**, *22*, 196; (b) W. Hassan, R. Edrada, R. Ebel, V. Wray, A. Berg, R. van Soest, S. Wiryowidagdo, P. Proksch, *J. Nat. Prod.* **2004**, *67*, 817.

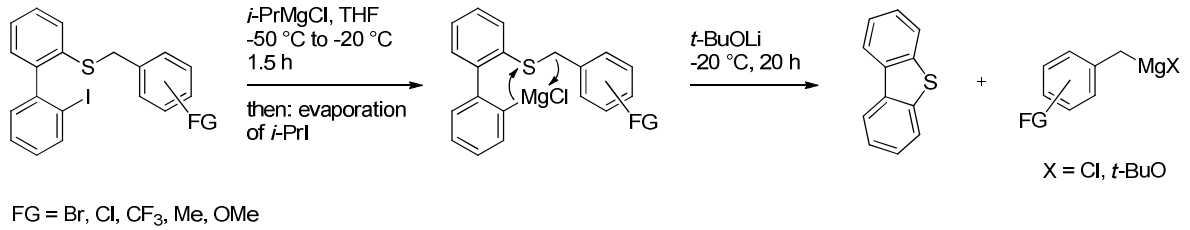
[58] (a) J. N. Reed, *Science of Synthesis*, V. Snieckus, Ed., **2006**, *8a*, 329; (b) B. J. Wakefield, *Organolithium Methods*, Academic Press: New York, **1988**; (c) S. L. Hargreaves, B. L. Pilkington, S. E. Russell, P. A. Worthington, *Tetrahedron Lett.* **2000**, *41*, 1653.

[59] W. E. Parham, L. D. Jones, Y. A. Sayed, *J. Org. Chem.* **1976**, *41*, 1184.

[60] J. L. Wardell, *Preparation and Use in Organic Synthesis of Organolithium and Group IA Organometallics; The Chemistry of the Metal-Carbon Bond. The Chemistry of Functional Groups*, Vol. 4, .S. Patai, Ed., Wiley: New York, **1987**.

[61] (a) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674; (b) R. A. Benkeser, D. C. Snyder, *J. Org. Chem.* **1982**, *47*, 1243; (c) K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis, A. Sexton, *J. Org.* Chem. **1991**, *56*, 698; (d) S.

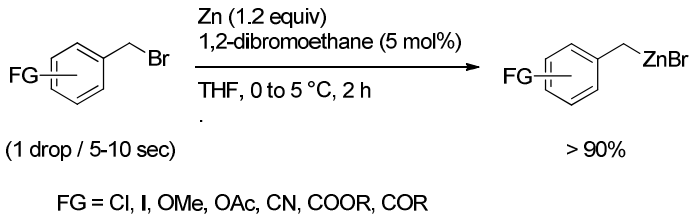
preparation for benzylic magnesium reagents was demonstrated using a sulfur-magnesium exchange (Scheme 33).[62]



Scheme 33: Preparation of benzylic magnesium reagents through a sulfur-magnesium exchange.

One major disadvantage of benzylic magnesium reagents is still the intolerance towards sensitive functions like esters, nitriles or ketones.

Functionalized benzylic zinc halides play a unique role since the high reactivity of corresponding benzylic lithium and magnesium compounds preclude the presence of most functional groups in these organometallics. Benzylic zinc reagents can be prepared by the direct zinc insertion into benzylic bromides, mesylates and phosphates. During the insertion of zinc (activated using 1,2-dibromoethane) into benzylic bromides, the temperature for the insertion must be kept strictly between 0 to 5 °C to avoid the formation of homo-coupling products (Scheme 34). [63, 64]



Scheme 34: Preparation of benzylic zinc bromides.

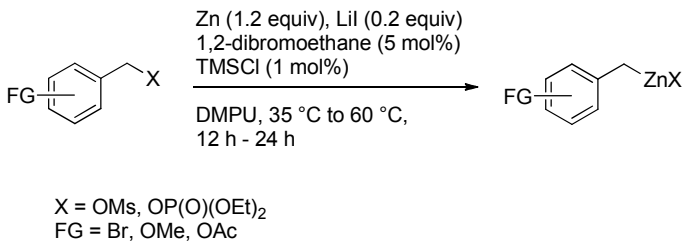
Harvey, P. C. Junk, C. L. Raston, G. Salem, *J. Org. Chem.* **1988**, *53*, 3134; (e) C. L. Raston, G. Salem, *J. Chem. Soc., Chem. Commun.* **1984**, 1702; (f) C. L. Raston, S. Harvey, *J. Chem. Soc., Chem. Commun.* **1988**, 652.

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

[63] (a) S. C. Berk, M. C. P. Yeh, N. Jeong, P. Knochel, *Organometallics* **1990**, *9*, 3053; (b) S. C. Berk, P. Knochel, M. C. P. Yeh, *J. Org. Chem.* **1988**, *53*, 5791; (c) M. Yuguchi, M. Tokuda, K. Orito, *J. Org. Chem.* **2004**, *69*, 908; (d) J. X. Wang, Y. Fu, Y. L. Hu, *Chin. Chem. Lett.* **2002**, *5*, 405; (e) H. Stadtmüller, B. Greve, K. Lennick, A. Chair, P. Knochel, *Synthesis* **1995**, 69; (f) C. Gosmini, Y. Rollin, C. Cebehenne, E. Lojou, V. Ratovelomanana, J. Perichon, *Tetrahedron Lett.* **1994**, 35, 5637.

[64] 1,2-Dibromoethane and TMSCl are used for the zinc activation; see also (ref 18).

To perform the zinc insertion into benzylic mesylates or phosphates in the presence of a lithium halide (LiBr or LiI), elevated temperatures and the use of polar cosolvents are required (Scheme 35).[65, 66]

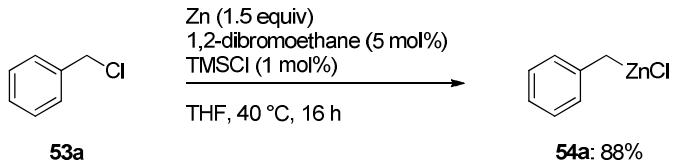


Scheme 35: Preparation of benzylic zinc mesylates and -phosphates.[64]

1.1.2. Direct zinc insertion into benzylic chlorides in the presence of LiCl

The above mentioned drawbacks hamper a more general application of zinc organometallics.[67] Recently, it has been reported that LiCl considerably facilitates the rate of zinc insertion.[23, 68] Therefore, this new method was applied to the preparation of benzylic zinc reagents using cheap benzylic chlorides, commercially available zinc dust and LiCl.[69] The activation of zinc dust was generally performed using 1,2-dibromoethane (5 mol%) and TMSCl (1 mol%).[64] As a comparative example the insertion of zinc dust into benzyl chloride (**53a**) was examined in the absence (Scheme 36) and in the presence of LiCl (Scheme 37).

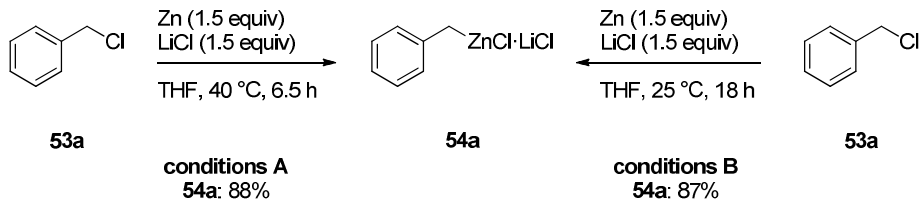
[65] C. Jubert, P. Knochel, *J. Org. Chem.* **1992**, *57*, 5425.
[66] For alternative preparation methods of benzylic zinc reagents, see: (a) via fragmentation reaction: C. Piazza, N. Millot, P. Knochel, *J. Organomet. Chem.* **2001**, *624*, 88; (b) via homologation of triorganozincates: T. Harada, T. Kaneko, T. Fujiwara, A. Oku, *J. Org. Chem.* **1997**, *62*, 8966.
[67] For the use of benzylic zinc reagents in organic synthesis, see: (a) S. Klein, I. Marek, J.-F. Normant, *J. Org. Chem.* **1994**, *59*, 2925; (b) M. Rottländer, P. Knochel, *Tetrahedron Lett.* **1997**, *38*, 1749; (c) A. M. Egorov, *J. Phys. Org. Chem.* **2006**, *19*, 664; (d) D. Huang, J.-X. Wang, *Synlett* **2007**, 2272; (e) A. Paul Krapcho, D. J. Waterhouse, A. Hammach, R. Di Domenico, E. Menta, A. Oliva, S. Spinelli, *Synth. Commun.* **1997**, *27*, 781; (f) T. J. Anderson, D. A. Vicic, *Organometallics* **2004**, *23*, 623; (g) J.-X. Wang, K. Wang, L. Zhao, H. Li, Y. Fu, Y. Hu, *Adv. Synth. Catal.* **2006**, *348*, 1262; (h) Y. Fellahi, D. Mandin, P. Dubois, J. E. Ombetta-Goka, J. Guenzet, J. P. Chaumont, Y. Frangin, *Eur. J. Med. Chem.* **1996**, *31*, 77; (i) J.-X. Wang, Y. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 2757; (j) S. N. Thorn, T. Gallagher, *Synlett* **1997**, 185; (k) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 185; (l) G. Wu, Z.-W. Cai, M. S. Bednarz, O. R. Kocy, A. V. Gavai, J. D. Godfrey, Jr., W. N. Washburn, M. A. Poss, P. M. Sher, *J. Comb. Chem.* **2005**, *7*, 99.
[68] N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.
[69] 1 mol benzyl chloride: 3.86 €; 1 mol LiCl: 7.44 €; 1 mol benzyl bromide: 76.58 €; Sigma-Aldrich, 2010.



Scheme 36: Preparation of benzylzinc chloride (**54a**) in the absence of LiCl.

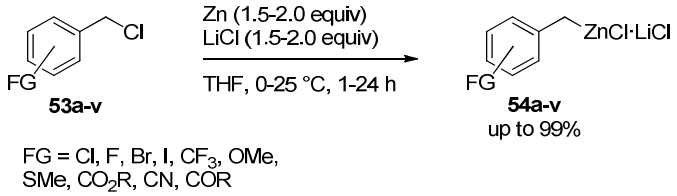
The preparation of benzylzinc chloride (**54a**) by the direct insertion of zinc dust into benzyl chloride (**53a**) in the absence of LiCl must be performed at an elevated temperature (40 °C) and full conversion is achieved only after 16 h.

In contrast, the zinc insertion[64] into benzyl chloride (**53a**) in the presence of LiCl proceeded easily within 6.5 h at 40 °C or at 25 °C within 18 h without the formation of significant amounts of homo-coupling products (< 5%; Scheme 37). The use of stoichiometric amounts of LiCl is essential for a fast zinc insertion.



Scheme 37: Preparation of benzylzinc chloride (**54a**) in the presence of LiCl either at 40 °C or at 25 °C.

A range of functionalized benzylic zinc chlorides was easily prepared by this new method and numerous functional groups are tolerated during the formation of the benzylic zinc reagents (Scheme 38).[70]

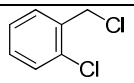
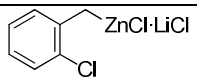
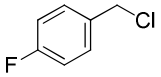
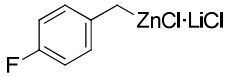
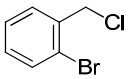
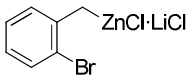
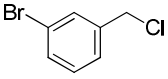
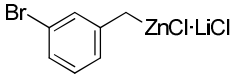
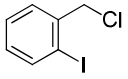
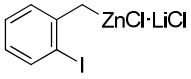
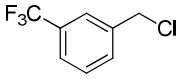
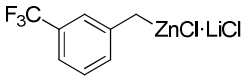


Scheme 38: Preparation of benzylic zinc reagents of type **54** by the direct insertion of zinc dust into the corresponding benzylic chlorides of type **53** in the presence of LiCl.

[70] For an investigation of the formation of organozincate anions using ESI-spectroscopy, see: K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771.

Thus, the addition of 2-chlorobenzyl chloride (**53b**, 1.0 equiv) to zinc dust (1.5 equiv) and LiCl (1.5 equiv) at 0 °C followed by 2 h of stirring at 25 °C provided almost quantitatively 2-chlorobenzylzinc chloride **54b** (in 99% yield as determined by iodometric titration, entry 1 Table 1).[71] 4-Fluorobenzyl chloride **53c** was smoothly converted to the corresponding benzylic zinc chloride **54c** within 24 h at 25 °C in 87% yield (entry 2). Furthermore, treatment of 2-bromobenzyl chloride **53d** with commercially available zinc dust in the presence of LiCl at ambient temperature led to the related benzylic zinc reagent **54d** in 92% yield (entry 3). Related bromo-, iodo- and (trifluoromethyl)-substituted benzylic chlorides **53e-g** reacted smoothly under these conditions leading to the benzylic zinc reagents **54e-g** in 94-99% yield (entries 4-6).

Table 1: Preparation of halogen-substituted benzylic zinc chlorides of type **54**.

Entry	Benzylic chloride	Time (h)[a]	Benzylic zinc chloride	Yield (%)[b]
1	 **53b**	2	 **54b**	99[c]
2	 **53c**	24	 **54c**	87[d]
3	 **53d**	2	 **54d**	92[c]
4	 **53e**	4	 **54e**	95[c]
5	 **53f**	2	 **54f**	99[c]
6	 **53g**	9	 **54g**	94[c]

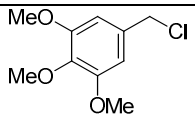
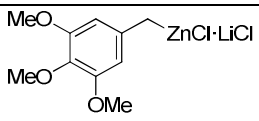
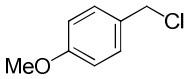
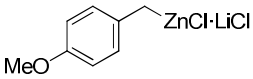
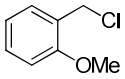
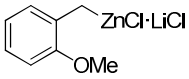
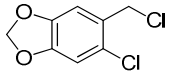
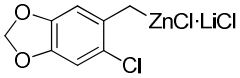
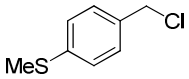
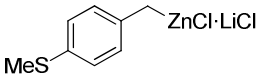
[a] Reaction time at 25 °C. [b] Yield determined by iodometric titration. [c] Zn (1.5 equiv), LiCl (1.5 equiv) were used. [d] Zn (2.0 equiv), LiCl (2.0 equiv) were used.

Even electron-rich benzylic chlorides reacted with zinc dust and LiCl under the standard protocol affording the expected benzylic zinc chlorides although electron-donor substituted benzylic chlorides are often prone to carbocation-induced side-reactions.[72] Under the mild reaction

[71] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
[72] (a) I. Lee, *J. Phys. Org. Chem.* **1996**, *9*, 661; (b) D. Stadler, A. Goeppert, G. Rasul, G. A. Olah, G. K. S. Prakash, T. Bach, *J. Org. Chem.* **2009**, *74*, 312; (c) S. T. A. Berger, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2007**, *129*, 9753.

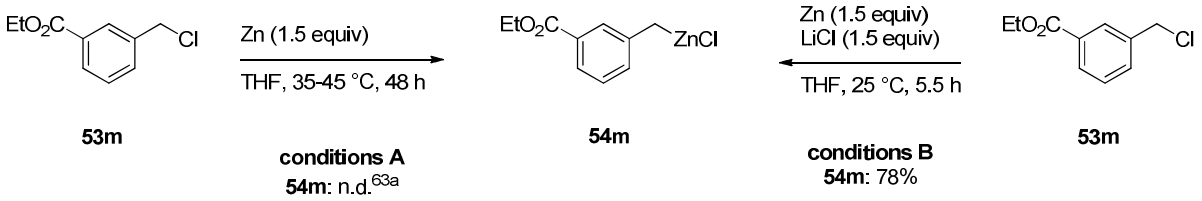
conditions, these side reactions are normally disfavored. Thus, 3,4,5-trimethoxybenzyl chloride (**53h**) was easily converted within 3.5 h at 25 °C (zinc dust 2.0 equiv, LiCl 2.0 equiv) to the corresponding benzylic zinc compound **54h** in 78% yield (entry 1 of Table 2). Similarly, the reaction of 4-methoxybenzyl chloride (**53i**) and 2-methoxybenzyl chlorides (**53j**) furnished readily the related benzylic zinc chlorides **54i-j** in 73% respectively 92% yield (entries 2-3). Also, the electron-rich benzylic chlorides **53k-l** led smoothly to the related zinc compound **54k** and **54l** within 1-2 h (Zn 1.5 equiv, LiCl 1.5 equiv) in 77-93% yield (entries 4-5).

Table 2: Preparation of electron-donor substituted benzylic zinc chlorides (**54h-l**).

Entry	Benzylic chloride	Time (h)[a]	Benzylic zinc chloride	Yield (%)[b]
1	 **53h**	3.5	 **54h**	78[c]
2	 **53i**	6.5	 **54i**	73[d]
3	 **53j**	4.5	 **54j**	92[d]
4	 **53k**	1	 **54k**	93[d]
5	 **53l**	2	 **54l**	77[d, e]

[a] Reaction time at 25 °C. [b] Yield determined by iodometric titration. [c] Zn (2.0 equiv), LiCl (2.0 equiv) were used. [d] Zn (1.5 equiv), LiCl (1.5 equiv). [e] 7% of the homo-coupling product was observed.

The effect of LiCl on the rate of the zinc insertion into benzylic chlorides has been well studied in the case of 3-(ethoxycarbonyl)benzyl chloride (**53m**). In the absence of LiCl the insertion reaction must be performed at 35-45 °C for 48 h (comditions A, Scheme 39). In the presence of LiCl (1.5 equiv) 3-(ethoxycarbonyl)benzylzinc chloride (**54m**) is smoothly prepared within 5.5 h at 25 °C without the formation of significant amounts of homo-coupling products (< 5%; conditions B).



Scheme 39: Preparation of 3-(ethoxycarbonyl)benzylzinc chloride (**54m**) by the insertion of zinc dust into benzylic chloride **53m** in the absence or in the presence of LiCl.

The reaction time can be shortened to 3.5 h and the yield of the benzylic zinc reagent **54m** can be improved to 85% if two equivalents of zinc dust and LiCl are used (entry 1 of Table 3). Also the *para*-substituted 4-(ethoxycarbonyl)benzyl chloride **53n** is readily converted to 4-(ethoxycarbonyl)benzylzinc chloride (**54n**) within 1 h in 64% yield (entry 2). Similarly, cyano groups are tolerated by this new method. Thus, 3-cyanobenzyl chloride (**53o**) and 4-cyanobenzyl chloride (**53p**) were smoothly converted to the corresponding benzylic zinc chlorides **54o** and **54p** in 2 h respectively 3 h in 83-93% yield (entries 3 and 4). Various benzylic zinc reagents bearing a keto group in the *meta*-position have also been prepared. The reactions of the benzylic chlorides **53q-s** with zinc dust at 25 °C provided easily the desired zinc reagents **54q-s** in 64-72% yield (entries 5-7).

Table 3: Preparation of ester-, cyano- and keto-substituted benzylic zinc chlorides of type **54m-s.**

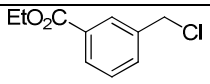
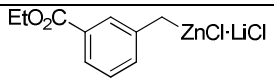
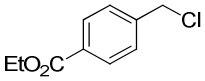
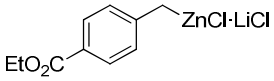
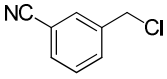
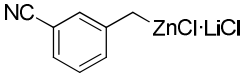
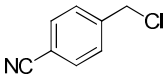
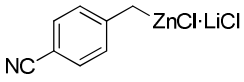
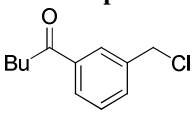
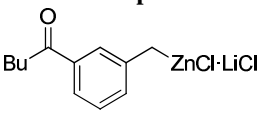
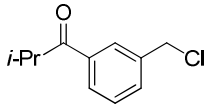
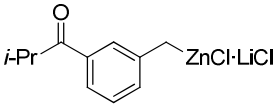
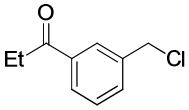
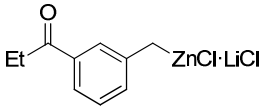
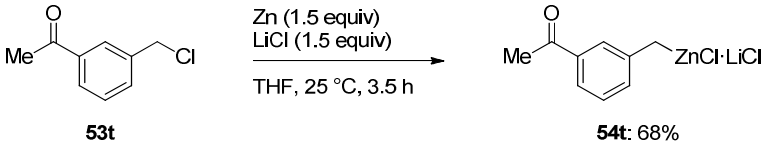
Entry	Benzylic chloride	Time (h)[a]	Benzylic zinc chloride	Yield (%)[b]
1	 **53m**	3.5	 **54m**	85[c]
2	 **53n**	1	 **54n**	64[c]
3	 **53o**	3	 **54o**	93[d]
4	 **53p**	2	 **54p**	83[d]
5	 **53q**	3.5	 **54q**	72[d]

Table 3 continued

6	 **53r**	9	 **54r**	64[d]
7	 **53s**	3	 **54s**	72[d]

[a] Reaction time at 25 °C. [b] Yield determined by iodometric titration. [c] Zn (2.0 equiv), LiCl (2.0 equiv) were used. [d] Zn (1.5 equiv), LiCl (1.5 equiv) were used.

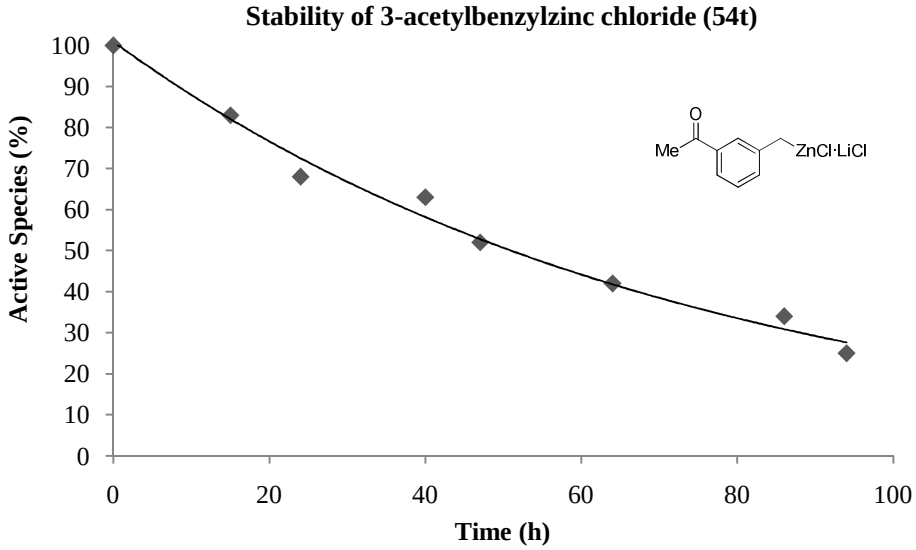
Even the acetyl-substituted benzylic chloride **53t** was converted to the expected benzylic zinc reagent **54t** within 3.5 h at 25 °C (Scheme 40).



53t **54t**: 68%

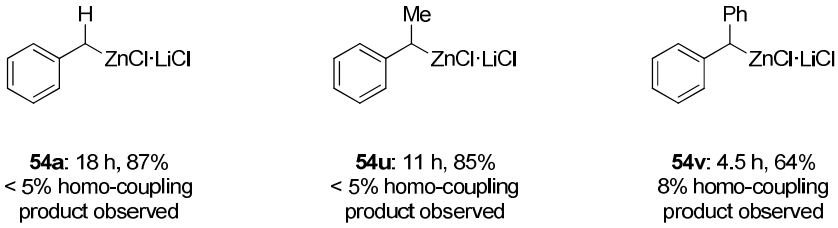
Scheme 40: Preparation of 3-acetylbenzylzinc chloride (**54t**).

Remarkably, the keto group present in the benzylic zinc chlorides **54q-t** is quite stable with respect to enolization. The 3-propionylbenzylzinc chloride (**54s**) has a half-life of one month at 25 °C and the acetyl-substituted benzylic zinc **54t** is stable for several days ($t_{1/2}$ = 2 days, 25 °C, Scheme 41).



Scheme 41: Stability of 3-acetylbenzylzinc chloride (**54t**).

Moreover, secondary benzylic zinc chlorides can also be prepared (Scheme 42). Thus, addition of 1-chloroethylbenzene to zinc dust (1.5 equiv) and LiCl (1.5 equiv) at 25 °C gave the desired zinc compound **54u** in 85% yield. Benzhydryl chloride furnished the expected secondary benzylic zinc chloride **54v** in 64% yield under the standard reaction conditions. In contrast, cumyl chloride (a tertiary benzylic chloride) did not afford the corresponding zinc species due to competitive elimination.

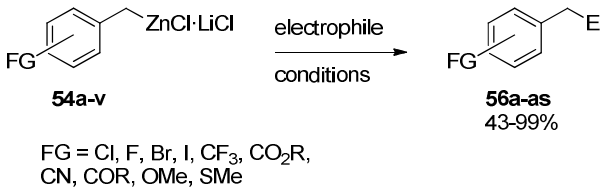


Scheme 42: Preparation of benzylzinc chloride (**54a**) and secondary benzylic zinc chlorides **54u**-**v** at 25 °C.

Comparison of the different insertion times shows that the better the second substituent in the benzylic position stabilizes the benzylic radical, the shorter is the time for the insertion. More noteworthy, the yield of the zinc reagent drops as the stability of the benzylic radical increases due to the formation of homo-coupling product.

1.1.3. Reaction of functionalized benzylic zinc chlorides with various electrophiles

These new benzylic zinc chlorides were treated with various electrophiles leading to a range of polyfunctional products of type **56** (Scheme 43 and Table 4 - Table 7).

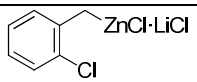
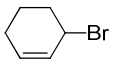
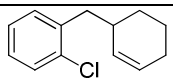
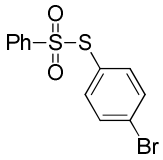
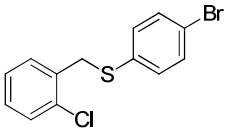
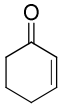
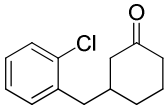
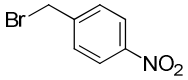
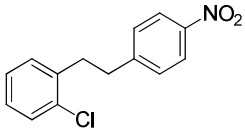


Scheme 43: Reactions of various benzylic zinc chlorides of type **54** with a variety of electrophiles leading to polyfunctional products of type **56**.

The benzylic zinc reagent **54b** was subject to a range of useful reactions with electrophiles (Table 4). Thus, the copper(I)-catalyzed reaction of 2-chlorobenzylzinc chloride (**54b**; 1.0 equiv) with 3-

bromocyclohex-1-ene (**55a**; 1.3 equiv) at 0 °C, catalyzed with CuCN·2LiCl,[15b] led to the product **56a** in 94% yield (entry 1). Then, **54b** (1.0 equiv) reacted with *S*-(4-bromophenyl) benzenesulfonothioate[73] (**57a**; 0.8 equiv) at 25 °C in 1 h to give the expected thioether **56b** in 89% yield (entry 2). Also, copper (I)-mediated 1,4-addition of cyclohex-2-enone (**58a**; 0.8 equiv) with CuCN·2LiCl (1.0 equiv) and TMSCl[74] (2.0 equiv) furnished the Michael adduct **56c** in 93% yield (entry 3). The copper(I)-catalyzed reaction with 4-nitrobenzyl bromide (**59a**; 0.8 equiv) provided the nitro compound **56d** in 89% yield (entry 4). Furthermore, the Pd-catalyzed cross-coupling reaction[75] of ethyl 4-iodobenzoate (**4a**; 0.8 equiv) in the presence of $Pd(PPh_3)_4$ (2 mol%) as catalyst at 60 °C gave the expected diarylmethane derivative **56e** in 97% yield in 5 h (entry 5). A copper(I)-mediated acylation reaction of 2-chlorobenzylzinc chloride (**54a**) with acetyl chloride (**60a**) led to the ketone **56f** in 89% yield (entry 6) and the addition of **54a** to 2-chlorobenzaldehyde (**61a**) furnished the benzylic alcohol **56g** in 87% yield on a 20 mmol scale reaction (entry 7).

Table 4: Reactions of halogen-substituted benzylic zinc reagents **54b-g** with various electrophiles.

Entry	Benzylic zinc chloride	Electrophile	Temperature (°C) / Time (h)	Product	Yield (%)[a]
1	 **54b**	 **55a**	25/ 1.5	 **56a**	94[b]
2	**54b**	 **57a**	25 / 1	 **56b**	89
3	**54b**	 **58a**	-40 to 25 / 15	 **56c**	93[c]
4	**54b**	 **59a**	0 / 3	 **56d**	89[b]

[73] K. Fujiki, N. Tanifuji, Y. Sasaki, T. Yokoyama, *Synthesis* **2002**, 343.
[74] E. Nakamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 5181.
[75] (a) Q. Mingxing, E. Negishi, *Tetrahedron Lett.* **2005**, *46*, 2927; (b) E. Metay, Q. Hu, E. Negishi, *Org. Lett.* **2006**, *8*, 5773; (c) E. Negishi, M. Qian, F. Zeng, L. Anastasia, D. Babinski, *Org. Lett.* **2003**, *5*, 1597.

Table 4 continued

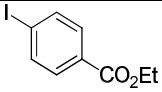
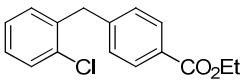
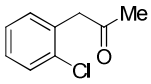
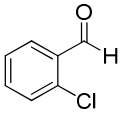
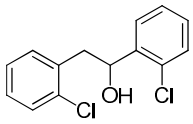
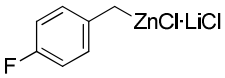
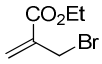
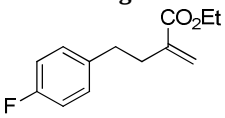
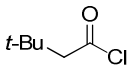
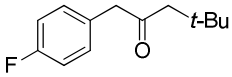
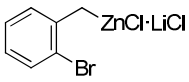
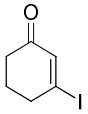
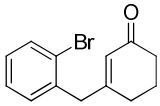
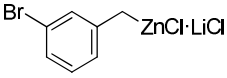
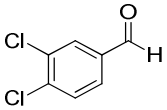
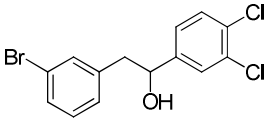
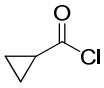
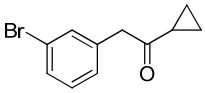
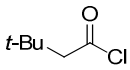
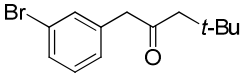
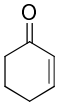
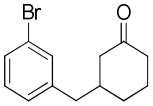
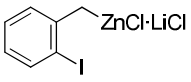
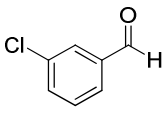
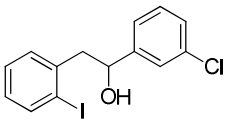
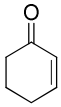
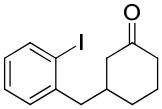
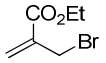
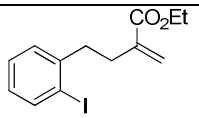
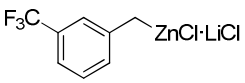
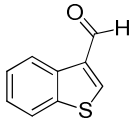
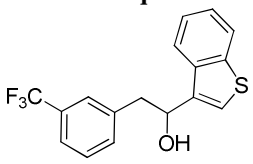
5	**54b**	 **4a**	60 / 5	 **56e**	97[d]
6	**54b**	 **60a**	-40 to 25 / 13.5	 **56f**	89[c]
7	**54b**	 **61a**	0 / 3	 **56g**	87[e]
8	 **54c**	 **55b**	-60 to 0 / 2	 **56h**	93[b]
9	**54c**	 **60b**	-40 to 25 / 15	 **56i**	95[c]
10	 **54d**	 **58b**	-60 to 0 / 15	 **56j**	96[c]
11	 **54e**	 **61b**	25 / 17	 **56k**	98
12	**54e**	 **60c**	-40 to 0 / 18	 **56l**	92[c]
13	**54e**	 **60b**	-60 to -20 / 15	 **56m**	96[c]
14	**54e**	 **58a**	-40 to 25 / 16	 **56n**	91[c, f]
15	 **54f**	 **61c**	25 / 5	 **56o**	87
16	**54f**	 **58a**	-40 to 25 / 15	 **56p**	72[c]

Table 4 continued

17	**54f**	 **55b**	-60 to 0 / 1	 **56q**	86[b]
18	 **54g**	 **61d**	25 / 6	 **56r**	86

[a] Yield of isolated analytically pure product. [b] Reaction performed in the presence of catalytic amounts of CuCN·2LiCl. [c] Stoichiometric amounts of CuCN·2LiCl and, in the case of 1,4-additions, TMSCl were used. [d] $Pd(PPh_3)_4$ (2 mol%) was used. [e] Reaction performed on a 20 mmol scale. [f] Reaction performed on a 5 mmol scale.

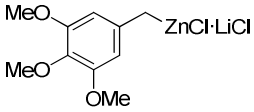
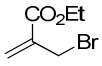
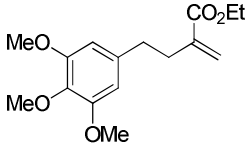
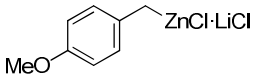
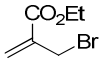
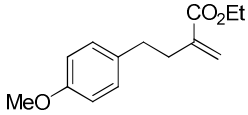
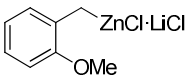
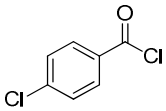
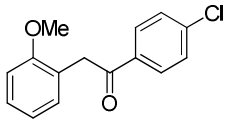
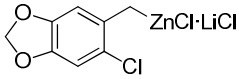
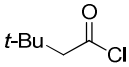
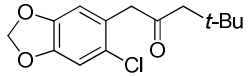
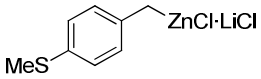
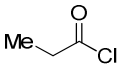
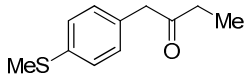
4-Fluorobenzylzinc chloride (**54c**) reacted in a Cu(I)-catalyzed allylation using ethyl (2-bromomethyl)acrylate [76] (**55b**) and in a Cu(I)-mediated acylation with 3,3-dimethylbutyryl chloride (**60b**; 0.7 equiv) to the functionalized products **56h-i** (entries 8-9). The 2-bromo-substituted benzylic zinc chlorides **54d** furnished with 3-iodocyclohex-2-enone (**58b**) the 3-substituted cyclohex-2-enone **56j** in 96% yield within 15 h (entry 10). The high reactivity of benzylic zinc chlorides allowed an efficient addition to benzaldehydes *in the absence of any catalyst*. Thus, the benzylic alcohol **56k** was obtained by the reaction of 3-bromobenzylzinc chloride (**54e**) with 3,4-dichlorobenzaldehyde (**61b**; 98% yield; entry 11). Moreover, Cu(I)-mediated reactions of **54e** with cyclopropylcarbonyl chloride (**60c**), 3,3-dimethylbutyryl chloride (**60b**) and cyclohex-2-enone (**58a**) provided the functionalized ketones **56l-n** in 91-96% yield (entries 12-14). According to the reaction procedures described above, the 2-iodo-substituted benzylic zinc chloride **54f** reacted with various electrophiles (**61c**, **58a**, **55b**) to the expected products **56o-q** in 72-87% (entries 15-17). Finally, addition of 3-(trifluoromethyl)benzylzinc chloride **54g** with benzothiophene-3-carbaldehyde (**61d**) furnished the heterocyclic benzylic alcohol **56r** in 86% yield (entry 18).

Also, electron-rich benzylic zinc chlorides such as **54h-l** reacted smoothly with a range of electrophiles. Thus, the trimethoxy-substituted benzylic zinc chloride **54h** underwent a smooth allylation with ethyl (2-bromomethyl)acrylate (**55b**; 0.8 equiv) in 1 h to give the allylated derivative **56s** in 98% yield (entry 1 of Table 5). In an analogous manner, 4-methoxybenzylzinc chloride (**54i**) was allylated to afford the acrylate **56t** in 97% yield (entry 2). After transmetalation using CuCN·2LiCl, acylation reaction of the electron-rich benzylic zinc chloride

[76] (a) J. Villieras, M. Rambaud, *Synthesis* **1982**, *11*, 924; (b) J. Villieras, M. Rambaud, *Org. Synth*. **1988**, *66*, 220.

54j with the acid chloride **60d** led to the desired ketone **56u** within 21 h in 99% yield (entry 3). Similarly, 6-chloro-1,3-benzodioxol-5-ylmethylzinc chloride (**54k**) was readily acylated with 3,3-dimethylbutyryl chloride (**60b**) providing the product **56v** in 93% yield (entry 4). 4-(Methylthio)benzylzinc chloride (**54l**) was also converted into the corresponding ketone **56w** (71%; entry 5) in 4 h by using propionyl chloride (**60e**; 0.8 equiv) in the presence of CuCN·2LiCl (0.5 equiv).

Table 5: Reactions of electron-rich benzylic zinc reagents **54h-l** with different electrophiles.

Entry	Benzylic zinc chloride	Electrophile	Temperature (°C) / Time (h)	Product	Yield (%)[a]
1	 **54h**	 **55b**	-60 to 0 / 1	 **56s**	98[b]
2	 **54i**	 **55b**	-40 to 0 / 1	 **56t**	97[b]
3	 **54j**	 **60d**	-40 to 25 / 21	 **56u**	99[c]
4	 **54k**	 **60b**	-60 to 25 / 15	 **56v**	93[c]
5	 **54l**	 **60e**	0 to 25 / 4	 **56w**	71[c]

[a] Yield of isolated analytically pure product. [b] Catalytic amounts of CuCN·2LiCl were used. [c] Stoichiometric amounts of CuCN·2LiCl were used.

Benzylic zinc reagents **54m-n** bearing an ester function in *meta*- or *para*-position reacted smoothly with various electrophiles. Thus, the reaction with 4-bromobenzaldehyde (**61e**; 0.8 equiv) furnished the benzylic alcohol **56x** in 91% yield (entry 1 of Table 6). Also, a copper(I)-mediated 1,4-addition of 3-(ethoxycarbonyl)benzylzinc chloride (**54m**) to cyclohex-2-enone (**58a**; 0.8 equiv) with CuCN·2 LiCl (1.0 equiv) and TMSCl (2.0 equiv) led to the Michael adduct **56y** in 97% yield (entry 2). Furthermore, reaction of **54m** with thiophene-3-carbaldehyde (**61f**) and *S*-methyl methanesulfonothioate (**57b**) provided the functionalized products **56z-aa** in 88% yield (entries 3-4). A Cu(I)-mediated acylation reaction of **54n** with the acid choride **60d** led

to the desired ketone **56ab** in 43% yield (entry 5). The use of the benzylic zinc reagent **54o**, which bears a cyano group on the aromatic ring, towards a Pd-catalyzed cross-coupling reaction with 3-iodoanisole (**4b**; 0.8 equiv) provided the diarylmethane **56ac** in 88% yield (entry 6). This benzylic zinc reagent was used to prepare various ketones in 78-97% yield (**56ad-ae**; entries 7 and 8). Smooth reaction of the *para*-cyano-substituted benzylic zinc chloride **54p** with ethyl (2-bromomethyl)acrylate (**55b**) and *S*-(4-fluorophenyl) benzenesulfonothioate (**57c**) furnished the acrylate **56af** and the thioether **56ag** (81-95%, entries 9-10).

Table 6: Reactions of ester, cyano and keto-substituted benzylic zinc reagents **54m-t** with various electrophiles.

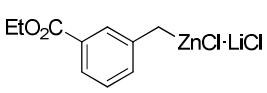
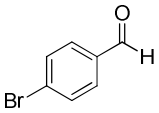
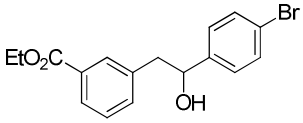
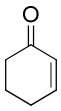
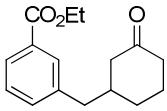
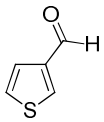
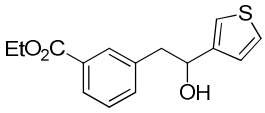
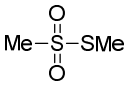
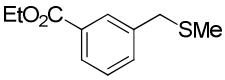
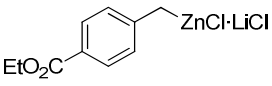
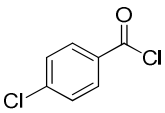
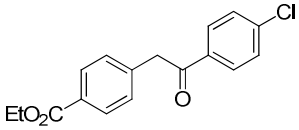
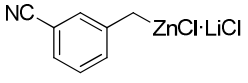
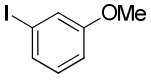
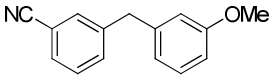
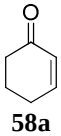
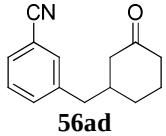
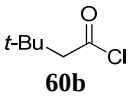
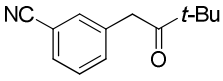
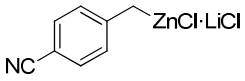
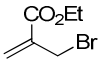
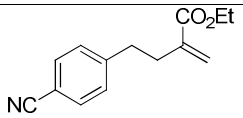
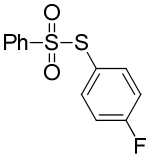
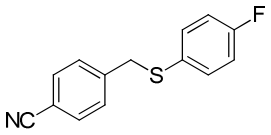
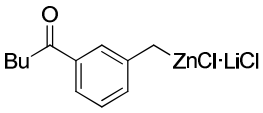
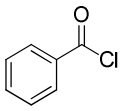
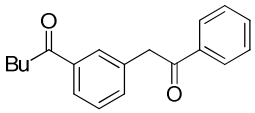
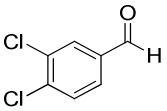
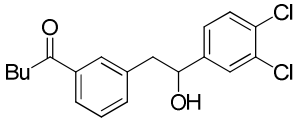
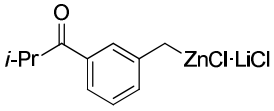
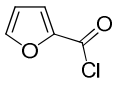
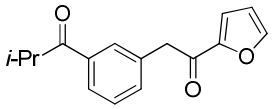
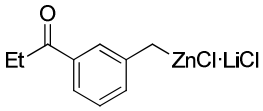
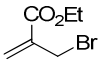
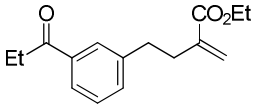
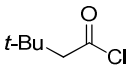
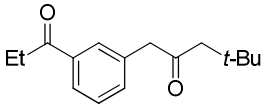
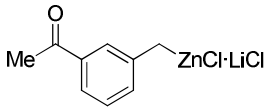
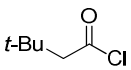
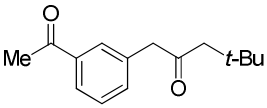
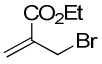
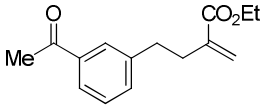
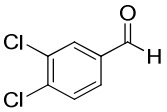
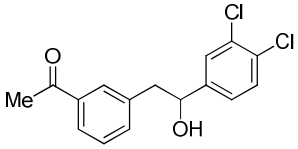
Entry	Benzylic zinc chloride	Electrophile	Temperature (°C) / Time (h)	Product	Yield (%)[a]
1	 **54m**	 **61e**	25 / 4.5	 **56x**	91
2	**54m**	 **58a**	-40 to 25 / 15	 **56y**	97[b]
3	**54m**	 **61f**	25 / 22	 **56z**	88
4	**54m**	 **57b**	25 / 25	 **56aa**	88
5	 **54n**	 **60d**	-40 to 25 / 20	 **56ab**	43[b]
6	 **54o**	 **4b**	60 / 5	 **56ac**	88[c]
7	**54o**	 **58a**	-40 to 25 / 15	 **56ad**	97[b]
8	**54o**	 **60b**	-60 to -20 / 15	 **56ae**	78[b]

Table 6 continued

9	 **54p**	 **55b**	-60 to 0 / 1	 **56af**	81[d, e]
10	**54p**	 **57c**	25 / 1.5	 **56ag**	95
11	 **54q**	 **60f**	-20 / 15	 **56ah**	85[b]
12	**54q**	 **61b**	25/ 5.5	 **56ai**	95
13	 **54r**	 **60g**	-40 to 25 / 20	 **56aj**	51[b]
14	 **54s**	 **55b**	-60 to 0 / 1	 **56ak**	92[d]
15	**54s**	 **60b**	-60 to -20 / 15	 **56al**	69[b]
16	 **54t**	 **60b**	-60 to -20 / 15	 **56am**	74[b]
17	**54t**	 **55b**	-60 to 0 / 1	 **56an**	97[d]
18	**54t**	 **61b**	25 / 3	 **56ao**	82

[a] Yield of isolated analytically pure product. [b] Stoichiometric amounts of CuCN·2LiCl and, in the case of 1,4-additions, TMSCl were used. [c] $Pd(PPh_3)_4$ (2 mol%) was used. [d] Reaction performed in the presence of catalytic amounts of CuCN·2LiCl. [e] Reaction performed on a 8 mmol scale.

Notably, the keto group on the benzylic zinc reagents is compatible with various reactions such as allylation, acylation and nucleophilic attack on an aldehyde. Thus, the products **56ah-al** were obtained in 51-95% yield after reactions with various electrophiles (entries 11-15). A Cu(I)-mediated reaction of the acetyl-substituted benzylic zinc reagent **54t** with 3,3-dimethylbutyryl chloride (**60b**) as well as a Cu(I)-catalyzed allylation using ethyl (2-bromomethyl)acrylate (**55b**) furnished the highly functionalized products **56am-an** in 74-97% yield (entries 16-17). Finally, the addition of 3-acetylbenzylzinc chloride (**54t**) to 3,4-dichlorobenzaldehyde (**61b**) *in the absence of any catalyst* provided the benzylic alcohol **56ao** within 3 h at 25 °C (82%; entry 18).

By the copper(I)-mediated acylation reaction of benzylzinc chloride (**54a**) with benzoyl chloride (**60f**) benzyl phenyl ketone (**56ap**) was easily prepared in 92% yield (entry 1 of Table 7). Furthermore, benzylzinc chloride (**54a**) was allylated with ethyl (2-bromomethyl)acrylate (**55b**; 0.8 equiv) to give the expected unsaturated ester **56aq** (93%; entry 2). Acylation is also possible with the secondary benzylic zinc reagent **54u**. Thus, reaction of **54u** with 3,3-dimethylbutyryl chloride (**60b**; 0.7 equiv) in the presence of CuCN·2LiCl (1.0 equiv) gave the ketone **56ar** in 96% yield (entry 3). Also the secondary benzylic zinc reagent **54v** is readily converted into the corresponding α,β-unsaturated ester **56as** in 96% yield by allylic substitution reaction using ethyl (2-bromomethyl)acrylate (**55b**; entry 4).

Table 7: Reactions of benzylzinc chloride (**54a**) and secondary benzylic zinc reagents **54u-v** with different electrophiles.

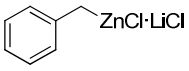
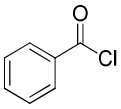
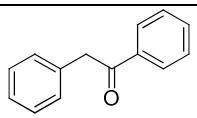
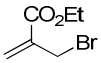
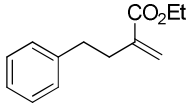
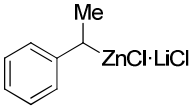
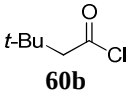
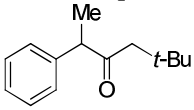
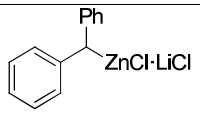
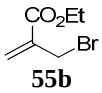
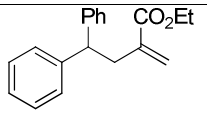
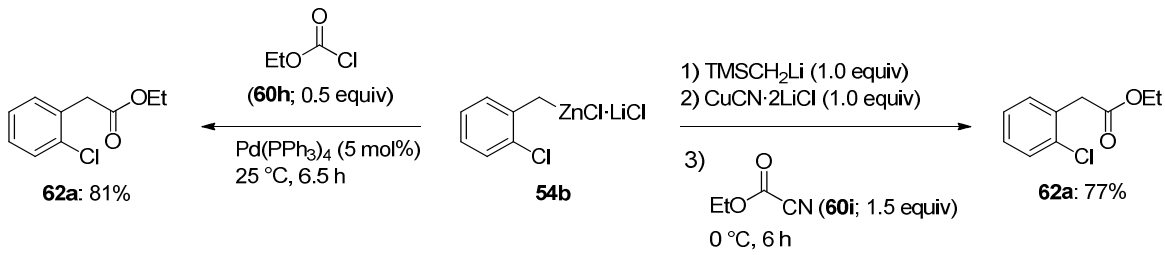
Entry	Benzylic zinc chloride	Electrophile	Temperature (°C) / Time (h)	Product	Yield (%)[a]
1	 **54a**	 **60f**	-40 to 25 / 20	 **56ap**	92[b, c]
2	**54a**	 **55b**	-60 to 0 / 1	 **56aq**	93[d]
3	 **54u**	 **60b**	-60 to 25 / 15	 **56ar**	96[b]

Table 7 continued

4	 **54v**	 **55b**	-60 to 0 / 1	 **56as**	96[d]

[a] Yield of isolated analytically pure product. [b] Stoichiometric amounts of CuCN·2LiCl were used. [c] 12 mmol scale. [d] Reaction performed in the presence of catalytic amounts of CuCN·2LiCl.

Benzylic zinc reagents can also be used to prepare phenyl acetic acid derivatives which are useful intermediates and targets in pharmaceutical research.[77] Two possible ways have been explored (Scheme 44). The first is a Pd-catalyzed acylation[78] with ethyl chloroformate (**60h**) as an electrophile. Alternatively, a copper(I)-mediated acylation with ethyl cyanoformate (**60i**) as the electrophilic species was developed. Thus, Pd-catalyzed acylation of the benzylic zinc chloride **54b** with ethyl chloroformate (**60h**) in the presence of $Pd(PPh_3)_4$ (5 mol%) at 25 °C in 6.5 h led to the phenylacetic acid ethyl ester **62a** in 81% yield. To perform the copper(I)-mediated reaction, it was essential to prepare the mixed diorganozinc compound of the type $ArCH_2ZnCH_2SiMe_3$[79] by adding $TMSCH_2Li$ at -30 °C to **54b**. After transmetalation to copper with CuCN·2LiCl and the addition of Mander's reagent[80] (ethyl cyanoformate; **60i**), the expected ethyl phenylacetic ester **62a** was obtained in 77% yield.



Scheme 44: Preparation of phenylacetic acid derivative **62a** by either Pd-catalyzed or copper(I)-mediated acylation reaction.

In a similar manner, the phenylacetic acid derivative **62b** was smoothly prepared by the Pd-catalyzed reaction of 3-(ethoxycarbonyl)benzylzinc chloride (**54m**) with ethyl chloroformate (**60h**) on a 10 mmol scale (76%, entry 1 of Table 8).

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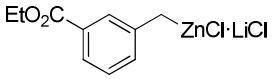
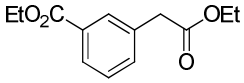
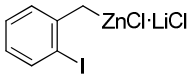
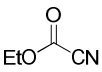
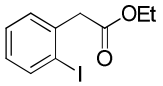
[77] A. Garcia Martinez, A. Herrera Fernandez, D. Molero Vilchez, M. L. Laordon Gutiérrez, L. R. Subramanian, *Synlett* **1993**, 229 (and references cited therein).
[78] E. Negishi, V. Bagheri, S. Chatterjee, F.-T. Luo, J. A. Miller, A. T. Stoll, *Tetrahedron Lett.* **1983**, *24*, 5181.
[79] $ArCH_2ZnCl$ is not reactive enough and the mixed reagent $ArCH_2ZnCH_2SiMe_3$ gives better results; see also: S. Berger, F. Langer, C. Lutz, P. Knochel, T. A. Mobley, C. K. Reddy, *Angew. Chem. Int. Ed.* **1997**, *36*, 1496.
[80] L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1983**, *24*, 5425.

Table 8: Preparation of phenylacetic acid derivatives of type **62**.

Entry	Benzylic zinc chloride	Electrophile	Temperature (°C) / Time (h)	Product	Yield (%)[a]
1	 **54m**	 **60h**	25 / 6	 **62b**	76[b, c]
2	 **54f**	 **60i**	0 / 6	 **62c**	59[d]

[a] Yield of isolated analytically pure product. [b] $Pd(PPh_3)_4$ (2.5 mol%) was used. [c] Reaction performed in a 10 mmol scale. [d] After transmetalation using $LiCH_2TMS$, stoichiometric amounts of $CuCN \cdot 2LiCl$ were used; reaction scale: 5 mmol.

Furthermore, copper(I)-mediated acylation reaction of 2-iodobenzylzinc chloride (**54f**) with ethyl cyanoformate (**60i**) led to the phenylacetic ester derivative **62c** in 59% yield (entry 2).

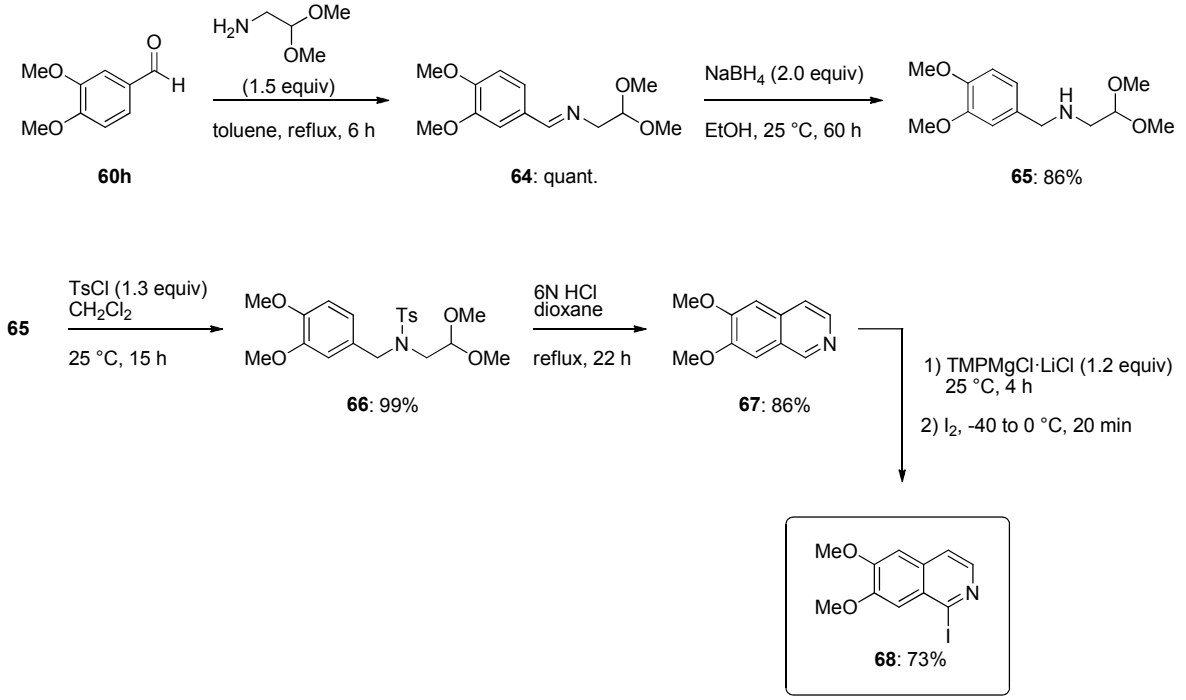
1.1.4. Synthesis of papaverine

As an application, the alkaloid papaverine (**63**; 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline) was synthesized. Papaverine[81] is primarily used for the treatment of vasospasm[81k] and was isolated from *Papaver somniferum* in 1848.[81l]

The synthesis started with a condensation reaction of 3,4-dimethoxybenzaldehyde (**60h**) with aminoacetaldehyde dimethylacetal to provide the imine **64** within 6 h in quantitative yield (Scheme 45). Reduction of **64** led to the benzylic amine **65** in 86% yield. Protection of the amino function using tosyl chloride furnished the sulfonamide **66** in 99% yield. Subsequent Pomeranz-Fritsch reaction provided 6,7-dimethoxyisoquinoline (**67**) within 22 h in 86% yield.[82]

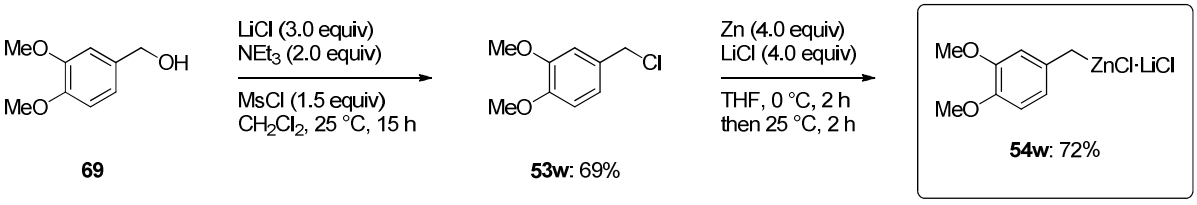
[81] (a) H. P. Schmauder, D. Gröger, H. Grüner, D. Lohmann, *Pharmazie* **1988**, *43*, 313; (b) A. Buzas, J.-Y. Merour, G. Lavielle, *Heterocycles* **1985**, *23*, 2561; (c) I. D. Rae, P. M. Simmonds, *Aust. J. Chem.* **1987**, *40*, 915; (d) A. R. de Lera, S. Aubourg, R. Suau, L. Castedo, *Heterocycles* **1987**, *26*, 675; (e) N. P. Peet, G. L. Karrick, R. J. Barbuch, *J. Heterocycl. Chem.* **1987**, *24*, 715; (f) J. R. Falck, S. Manna, *J. Org. Chem.* **1981**, *46*, 3742; (g) A. Pictet, M. Finkelstein, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 1979; (h) F. D. Popp, W. E. McEwen, *J. Am. Chem. Soc.* **1957**, *79*, 3773; (i) C. D. Gilmore, K. M. Allan, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 1558; (j) R. Hirsenkorn, *Tetrahedron Lett.* **1991**, *32*, 1775; (k) H.-M. Liu, Y.-K. Tu, *J. Clin. Neurosci.* **2002**, *9*, 561; (l) For the isolation of papaverine: G. Merck, *Liebigs Ann. Chem.* **1848**, *66*, 125.

[82] (a) A. Ioanaviciu, S. Antony, Y. Pommier, B. L. Staker, L. Stewart, M. Cushman, *J. Med. Chem.* **2005**, *48*, 4803; (b) D. L. Boger, C. E. Brotherton, M. D. Kelley, *Tetrahedron* **1981**, *37*, 5181; (c) J. B. Henderickson, C. Rodriguez, *J. Org. Chem.* **1983**, *48*, 3344; (d) N. Saito, C. Tanaka, T. Satomi, C. Oyama, A. Kubo, *Chem. Pharm. Bull.* **2004**, *52*, 282.



Scheme 45: Preparation of 2-iodo-6,7-dimethoxyisoquinoline (**68**).

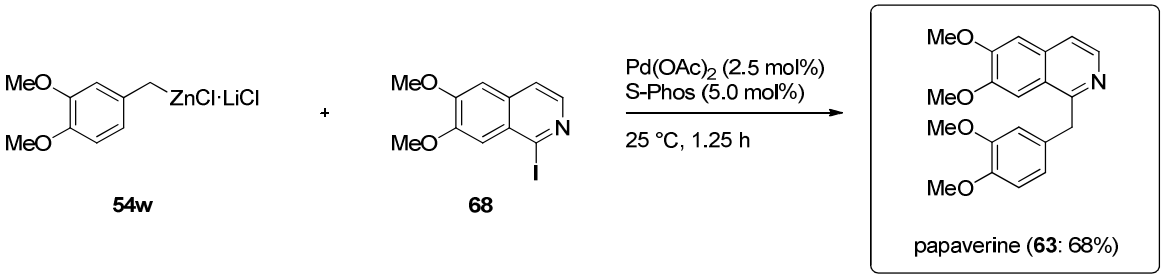
Magnesiation of **67** with TMPMgCl·LiCl[83] (TMP = 2,2,6,6-tetramethylpiperidyl) at 25 °C for 4 h, followed by iodolysis provided the iodo-substituted isoquinoline **68** in 73% yield. The preparation of the second intermediate for the papaverine synthesis started with the conversion of 3,4-dimethoxybenzyl alcohol (**69**) to the corresponding benzylic chloride **53w** (Scheme 46). Thus, reaction of **69** with LiCl, NEt_3 and mesyl chloride furnished the chloride **53w** in 69% yield within 15 h. Direct zinc insertion into **53w** in the presence of LiCl within 4 h provided 3,4-dimethoxybenzylzinc chloride (**54w**) in 72% yield. In order to receive a good yield of **54w**, it was crucial to use four equivalents of zinc and LiCl for the zinc insertion.



Scheme 46: Preparation of 3,4-dimethoxybenzylzinc chloride (**54w**).

[83] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.

The last step for the papaverine (**63**) synthesis included a Pd-catalyzed cross-coupling reaction of the benzylic zinc chloride **54w** and iodo-substituted isoquinoline **68** using $Pd(OAc)_2$ (2.5 mol%) and S-Phos[84] (5.0 mol%) as catalytic system (Scheme 47). Thus, papaverine (**63**) was provided within 1.25 h at 25 °C in 68% yield over 8 steps (longest linear sequence: 6 steps).[85]



Scheme 47: Synthesis of papaverine (**63**) by Pd-catalyzed cross-coupling reaction.

1.2. Efficient Nickel-catalyzed cross-coupling reactions of benzylic zinc chloride with aromatic halides

1.2.1. Introduction

Diarylmethanes are important subunits in organic synthesis as well as in pharmaceutically important molecules and therefore recently received a lot of attention.[86] By example, beclobrate (**69**) is a potent triglyceride- and cholesterol-lowering substance (Scheme 48).[87] Moreover, *N*,*N*-diethyl-2-[(4-phenylmethyl)phenoxy]ethanamine·hydrochloride (DPPE) (**70**) is a specific ligand for the anti-estrogen binding site (AEBS) and is now in clinical phase III trials for the treatment of chemotherapeutically refractive cancers.[88]

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[84] (a) M. D. Charles, P. Schultz, S. L. Buchwald, *Org. Lett*. **2005**, *7*, 3965; (b) K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman, S. L. Buchwald, *Angew. Chem. Int. Ed*. **2006**, *45*, 6523; (c) T. E. Barder, S. L. Buchwald, *Org. Lett*. **2004**, *6*, 2649.

[85] The copper-catalyzed cross-coupling with the magnesiated isoquinoline (**67**) and 3,4-dimethoxybenzyl chloride (**53w**) did not provide the expected papaverine (**63**).

[86] (a) T. A. Chappie, J. M. Humphrey, M. P. Allen, K. G. Estep, C. B. Fox, L. A. Lebel, S. Liras, E. S. Marr, F. S. Menniti, J. Pandit, C. J. Schmidt, M. Tu, R. D. Williams, F. V. Yang, *J. Med. Chem.* **2007**, *50*, 182; (b) L.-W. Hsin, C. M. Dersch, M. H. Baumann, D. Stafford, J. R. Glowa, R. B. Rothman, A. E. Jacobson, K. C. Rice, *J. Med. Chem.* **2002**, *45*, 1321; (c) P. D. Leeson, J. C. Emmett, V. P. Shah, G. A. Showell, R. Novelli, H. D. Prain, M. G. Benson, D. Ellis, N. J. Pearce, A. H. Underwood, *J. Med. Chem.* **1989**, *32*, 320; (d) J. S. Wai, M. S. Egbertson, L. S. Payne, T. E. Fisher, M. W. Embrey, L. O. Tran, J. Y. Melamed, H. M. Langford, J. P. Guare, Jr, L. Zhuang, V. E. Grey, J. P. Vacca, M. K. Holloway, A. M. Naylor-Olsen, D. J. Hazuda, P. J. Felock, A. L. Wolfe, K. A. Stillmock, W. A. Schleif, L. J. Gabryelski, S. D. Young, *J. Med. Chem.* **2000**, *43*, 4923.

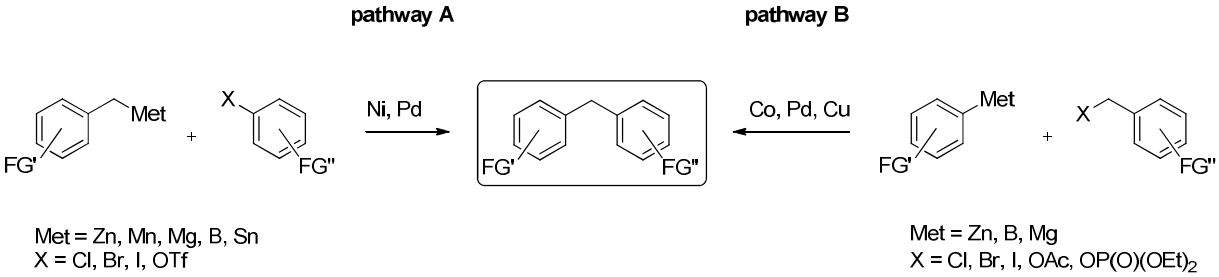
[87] (a) C. Wanner, H. Wieland, P. Schollmeyer, W. H. Hörl, *Eur. J. Clin. Pharmacol.* **1991**, *40*, 85; (b) J. Kischel, I. Jovel, K. Mertins, A. Zapf, M. Beller, *Org. Lett.* **2006**, *8*, 19.

[88] (a) M. Poirot, P. De Medina, F. Delarue, J.-J. Perie, A. Klaebe, J.-C. Faye, *Bioorg. Med. Chem.* **2000**, *8*, 2007; (b) C. C. Teo, O. L. Kon, K. Y. Sim, S. C. Ng, *J. Med. Chem.* **1992**, *35*, 1330.

beclobrate (**69**) DPPE (**70**)

Scheme 48: Selected diarylmethane derivatives.

A common way for the preparation of various diarylmethane derivatives is the addition of an organometallic species to functionalized benzaldehydes followed by subsequent reduction.[89] Alternative ways for their formations are on the one hand transition-metal catalyzed reactions of a benzylic organometallic reagent and an aromatic halide (pathway A, Scheme 49).[90] On the other hand, aromatic organometallics can be cross-coupled under transition metal catalysis with benzylic halides leading to functionalized diarylmethanes (pathway B, Scheme 49).[91]



Scheme 49: Preparation of diarylmethane derivatives by various possible cross-couplings.

Since the first reported cross-coupling reaction of benzylic zinc bromides under Ni catalysis[92] only a few examples for diarylmethane synthesis have been reported using benzylic zinc halides under transition metal catalysis.[58c, 93]

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[89] (a) Y.-Q. Long, X.-H. Jiang, R. Dayam, T. Sanchez, R. Shoemaker, S. Sei, N. Neamati, *J. Med. Chem.* **2004**, *47*, 2561; (b) X. Wu, A. K. Mahalingam, M. Alterman, *Tetrahedron Lett.* **2005**, *46*, 1501.

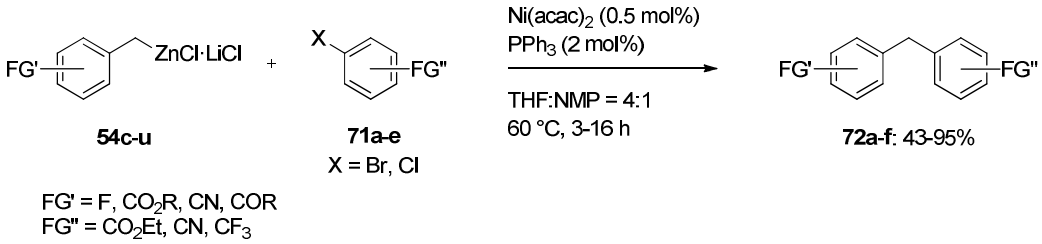
[90] (a) Y. Suh, J. Lee, S.-H. Kim, R. D. Rieke, *J. Organomet. Chem.* **2003**, *684*, 20; (b) S. Y. Park, M. Kang, J. E. Yie, J. M. Kim, I.-M. Lee, *Tetrahedron Lett.* **2005**, *46*, 2849; (c) A. Flaherty, A. Trunkfield, W. Barton, *Org. Lett.* **2005**, *7*, 4975; (d) A. Garcia Martinez, J. Osio Barcina, M. del Rosario Colorado Heras, A. de Fresno Cerezo, *Org. Lett.* **2000**, *2*, 1377.

[91] (a) M. Amatore, C. Gosmini, *Chem. Commun.* **2008**, 5019; (b) C. C. Kofink, P. Knochel, *Org. Lett.* **2006**, *8*, 4121; (c) R. Kuwano, M. Yokogi, *Chem. Commun.* **2005**, 5899; (d) L. Chahen, H. Doucet, M. Santelli, *Synlett* **2003**, 1668; (e) S. Langle, M. Abarbri, A. Duchene, *Tetrahedron Lett.* **2003**, *44*, 9255; (f) B. P. Bandgar, S. V. Bettigeri, J. Phopase, *Tetrahedron Lett.* **2004**, *45*, 6959; (g) S. M. Nobre, A. L. Monteiro, *Tetrahedron Lett.* **2004**, *45*, 8225.

[92] E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821.

1.2.2. Ni-catalyzed cross-coupling reactions with benzylic zinc chlorides using $Ni(acac)_2/PPh_3$

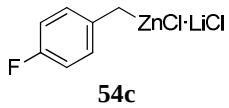
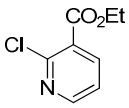
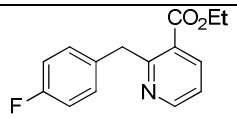
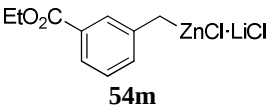
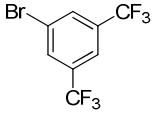
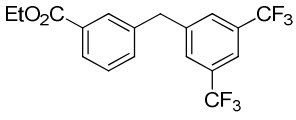
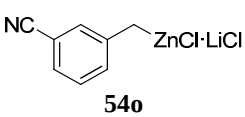
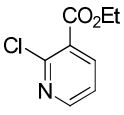
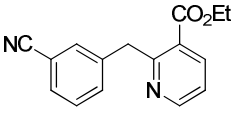
Nickel catalysts are significantly cheaper than palladium catalysts. Therefore, a cross-coupling reaction of benzylic zinc chlorides of type **54** with aromatic bromides and chlorides of type **71a-e** based on nickel as catalytic source was developed (Scheme 50).



Scheme 50: Nickel-catalyzed cross couplings of benzylic zinc chlorides with aromatic halides.

By screening of several catalytic systems, $Ni(acac)_2$ (0.5 mol%) combined with PPh_3 (2 mol%) in a THF:NMP = 4:1 mixture at 60 °C was found to be the most efficient system.[94] Using this cheap and convenient catalytic system, it was possible to synthesize various functionalized diarylmethanes of type **72** (Table 9).

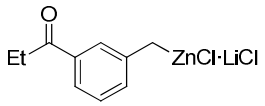
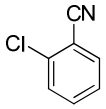
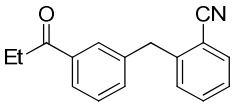
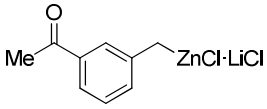
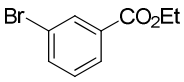
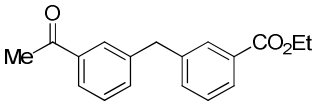
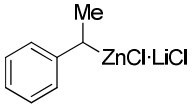
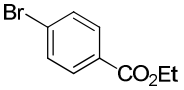
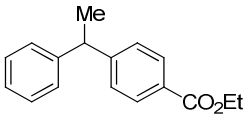
Table 9: Reaction of functionalized benzylic zinc chlorides with various aromatic and hetereo-aromatic bromides and chlorides under Nickel catalysis.

Entry	Benzylic zinc chloride	Electrophile	Time (h)[a]	Product	Yield (%)[b]
1	 **54c**	 **71a**	3	 **72a**	78
2	 **54m**	 **71b**	4	 **72b**	45
3	 **54o**	 **71a**	4	 **72c**	43

[93] (a) J. E. Utas, B. Olofsson, B. Akermark, *Synlett* **2006**, 1965; (b) B. Betzemeier, P. Knochel, *Angew. Chem. Int. Ed.* **1997**, *36*, 2623; c) For a review of the activation of benzylic derivatives by Pd-catalysis, see: B. Liegault, J.-L. Renaud, C. Bruneau, *Chem. Soc. Rev.* **2008**, *37*, 290.

[94] Screening of the catalytic systems was done by M. A. Schade. For further information, see: Ph.D. thesis M. A. Schade, Ludwig-Maximilians-University, Munich.

Table 9 continued

4	 **54s**	 **71c**	6	 **72d**	71
5	 **54t**	 **71d**	16	 **72e**	51
6	 **54u**	 **71e**	12	 **72f**	95

[a] Reaction time for the Ni-catalyzed cross-couplings at 60 °C. [b] Yield of isolated analytically pure product.

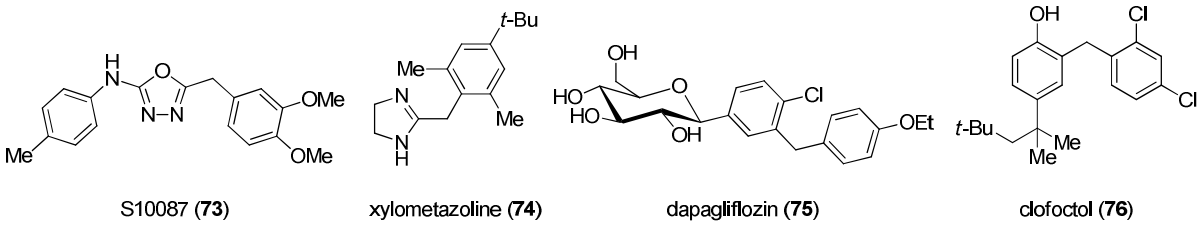
Thus, the Ni-catalyzed cross coupling reaction of 4-fluorobenzylzinc chloride (**54c**) with ethyl 2-chloronicotinate (**71a**) furnished the heterodiarylmethane **72a** within 3 h in 78% yield (entry 1 of Table 1). A smooth reaction of 3-(ethoxycarbonyl)benzylzinc chloride (**54m**) with the aromatic bromide **71b** led to the trisubstituted diarylmethane **72b** in 45% yield (entry 2). Similarly, 3-cyanobenzylzinc chloride (**54o**) provided after Ni-catalyzed cross-coupling reaction with ethyl 2-chloronicotinate (**71a**) the nicotinic acid derivative **72c** in 43% yield (entry 3). Furthermore, the benzylic zinc reagent **54s** reacted with 2-chlorobenzonitrile (**71c**) within 6 h giving the keto-substituted diarylmethane derivate **72d** in 71% yield (entry 4). In an analogous manner, 3-acetylbenzylzinc chloride (**54t**) readily provided after easily cross-coupling reaction with ethyl 3-bromobenzoate (**71d**) the expected product **72e** in 51% yield. Finally, Ni-catalyzed cross-coupling reaction of the secondary benzylic zinc reagent **54u** with ethyl 4-bromobenzoate (**71e**) led to the diarylmethane compound **72f** in 95% yield (entry 6).

1.3. Pd-catalyzed cross-couplings of benzylic zinc chlorides with unsaturated bromides bearing relatively acidic protons

Several bioactive substances bear relatively acidic functions like amines and alcohols combined with the benzyl moiety (Scheme 51). For example, the oxadiazole amine derivative *S10087* (**73**) containing a dimethoxy-substituted benzylic group is a known library substance showing anti-HIV activity.[95] Moreover, xylometazoline (**74**) acts as vasoconstrictor. [96] Its structural backbone

[95] G. Barreiro, J. T. Kim, C. R. W. Guimaraes, C. M. Bailey, R. A. Domaoal, L. Wang, K. S. Anderson, W. L. Jorgensen, *J. Med. Chem.* **2007**, *50*, 5324.

is based on a benzylimidazoline containing a secondary amine function. Dapagliflozin (**75**) is a new potent inhibitor for the treatment of type 2 diabetes that contains a sugar scaffold condensed with a functionalized diarylmethane motive.[97] Finally, clofoctol (**76**), a benzylic phenol derivative, is widely used as antibacterial.[98]

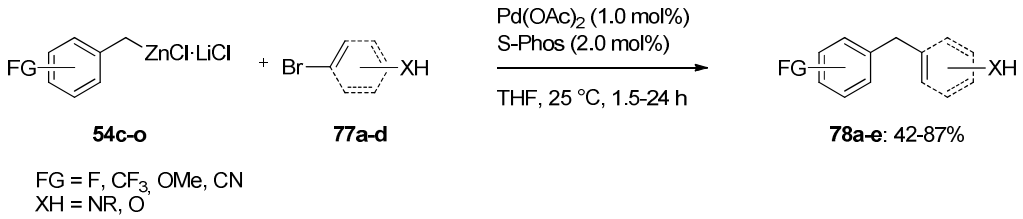


Scheme 51: Bioactive substances containing relatively acidic protons and the benzyl moiety.

To construct such molecules these sensitive functions are usually protected. Therefore, a classical natural product synthesis often contains several protection and deprotection steps which lengthen the linear sequence and cause additional costs and chemical waste. Although organoboronic acids are common reagents for cross-coupling reactions with organic halides bearing sensitive acidic functions[99] due to their air-stability as well as their commercial availability, there are still several disadvantages related to these organometallics. One is their tendency to form non-stoichiometric admixtures of boroxines. Moreover, harsher reaction conditions are required for organoboron compounds than for the related Negishi cross-couplings.[100] Recently, it was shown that benzylic zinc reagents posses remarkably low basicity.[101] Therefore, Pd-catalyzed cross-coupling reactions using benzylic zinc chlorides of type **54c** with unsaturated bromides in the presence of an amino- as well as an alcohol function were successfully performed (Scheme 52).

---

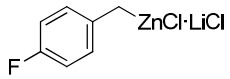
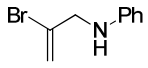
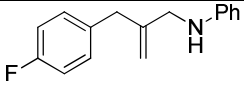
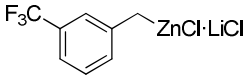
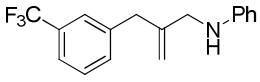
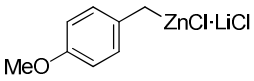
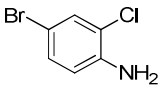
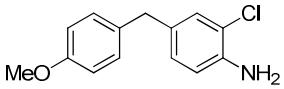
[96] A. G. van Velzen, A. J. H. P. van Riel, C. Hunault, T. E. van Riemsdijk, I. de Vries, J. Meulenbelt, *Clin. Toxicol.* **2007**, *45*, 290.
[97] W. Meng, B. A. Ellsworth, A. A. Nirschl, P. J. McCann, M. Patel, R. N. Girotra, G. Wu, P. M. Sher, E. P. Morrison, S. A. Biller, R. Zahler, P. P. Deshpande, A. Pullockaran, D. L. Hagan, N. Morgan, J. R. Taylor, M. T. Obermeier, W. G. Humphreys, A. Khanna, L. Discenza, J. G. Robertson, A. Wang, S. Han, J. R. Wetterau, E. B. Janovitz, O. P. Flint, J. M. Whaley, W. N. Washburn, *J. Med. Chem.* **2008**, *51*, 1145.
[98] M. Del Tacca, R. Danesi, S. Senesi, M. Gasperini, A. Mussi, C. A. Angeletti, *J. Antimicrob. Chemother.* **1987**, *19*, 679.
[99] E. Bey, S. Marchais-Oberwinkler, M. Negri, P. Kruchten, A. Oster, T. Klein, A. Spadaro, R. Werth, M. Frotscher, B. Birk, R. W. Hartmann, *J. Med. Chem.* **2009**, *52*, 6724.
[100] Selected publication highlighting problems using organoboronic reagents: T. Watanabe, N. Miyaura, A. Suzuki, *Synlett* **1992**, 207.
[101] G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765.



Scheme 52: Pd-catalyzed cross-couplings of benzylic zinc reagents with unsaturated halides bearing relatively acidic protons.

Thus, reaction of 4-fluorobenzylzinc chloride (**54c**) with *N*-(2-bromoprop-2-en-1-yl)aniline (**77a**) provided the cross-coupling product **78a** within 24 h in 61% yield without prior protection of the aniline function (entry 1 of Table 10). Similarly, 3-(trifluoromethyl)benzylzinc chloride (**54g**) led to the aniline derivative **78b** in 87% yield (entry 2). Smooth Pd-catalyzed cross-coupling reaction of 4-methoxybenzylzinc chloride (**54i**) with 4-bromo-2-chloroaniline (**77b**) provided the desired diarylmethane **78c** in 77% yield (entry 3).

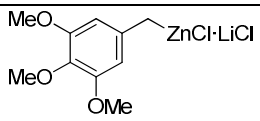
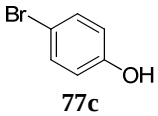
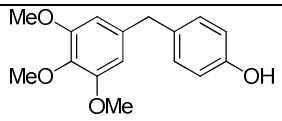
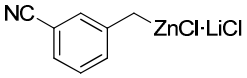
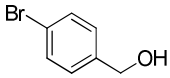
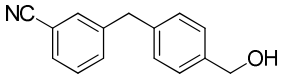
Table 10: Cross-couplings of benzylic zinc reagents with various bromo-aniline derivatives.

Entry	Benzylic zinc chloride	Electrophile	Time (h)[a]	Product	Yield (%)[b]
1	 **54c**	 **77a**	24	 **78a**	61
2	 **54g**	**77a**	8	 **78b**	87
3	 **54i**	 **77b**	6.25	 **78c**	77

[a] All reactions were performed at 25 °C. [b] Yield of isolated analytically pure product.

This protocol allowed also the tolerance of more acidic functions than the amine function present in anilines. Thus, cross-coupling reaction of the benzylic zinc reagent **54h** with 4-bromophenol (**77c**) provided the expected product in 42% yield (entry 1 of Table 11). Furthermore, 3-cyanobenzylzinc chloride (**54o**) was smoothly reacted with 4-bromobenzyl alcohol (**77d**) within 1.5 h leading to the desired product **78e** in 84% yield (entry 2).

Table 11: Cross-couplings of benzylic zinc reagents with different alcohol derivatives.

Entry	Benzylic zinc chloride[a]	Electrophile	Time (h)[b]	Product	Yield (%)[c]
1	 **54h**	 **77c**	1.5	 **78d**	42
2	 **54o**	 **77d**	1.5	 **78e**	84

[a] The benzylic zinc reagent was slowly added over a period of 90 min using a syringe pump. [b] All reactions were performed at 25 °C. [c] Yield of isolated analytically pure product.

1.4. Palladium-catalyzed one-pot reaction of *in situ* generated benzylic zinc chlorides with aromatic bromides

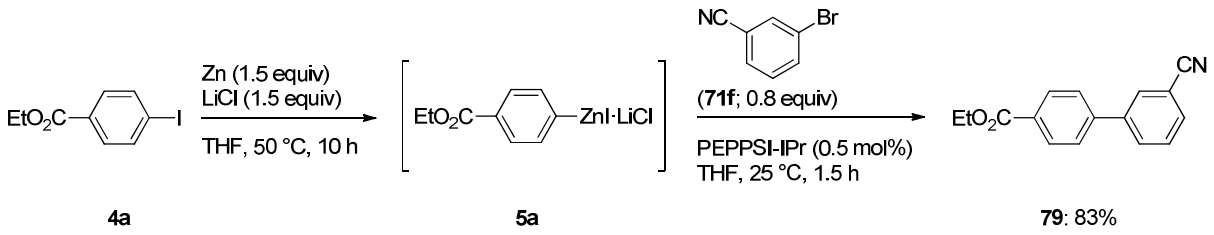
1.4.1. Introduction

Transition metal-catalyzed reactions are among the most important reactions for carbon-carbon bond formation.[3b] Especially, palladium-catalyzed reactions have found numerous applications.[102] One of the main advantages for the Suzuki cross-coupling reaction is the use of air and moisture stable boronic acids and their derivatives. On the other hand, an important limitation of these boronic compounds is their preparation requiring the corresponding magnesium or lithium species which limits the presence of functional groups.[103] Organozinc reagents display much higher reactivity in Pd-catalyzed cross-coupling reactions.[104] Moreover, these reagents can be prepared in the presence of sensitive functional groups. A major drawback of these organometallics is the instability towards air and moisture.[16]

In initial experiments, ethyl 4-iodobenzoate (**4a**; 1.0 equiv) was treated with zinc dust (1.5 equiv) and LiCl (1.5 equiv) in THF. [105] The zinc reagent **5a** was obtained within 10 h at 50 °C (> 98% conversion, Scheme 53). Then, 3-bromobenzonitrile (**71f**; 0.8 equiv) and PEPPSI-IPr [106] (0.5 mol %) were added. After 1.5 h of reaction time at 25 °C, ethyl 3'-cyanobiphenyl-4-

[102] J. Tsuji, *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*, Wiley: New York, **1995**.
[103] (a) N. Miyaura, *Advances in Metal-Organic Chemistry*, Vol. 6, L. S. Liebeskind, Ed., JAI: London, **1998**, 187; (b) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; (c) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.
[104] E. Negishi, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., A. de Meijere, F. Diederich, Eds., Wiley-VCH: Weinheim, **2004**.
[105] The experiment was performed by Dr. Shohei Sase and Milica Jaric and is given here for the sake of completeness. For further information, see: diploma thesis M. Jaric, LMU Munich, **2007**.
[106] PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropylphenyl-imidazolium derivative.

carboxylate (**79**) was obtained in 83% isolated yield *without prior removal of the excess of zinc powder*.



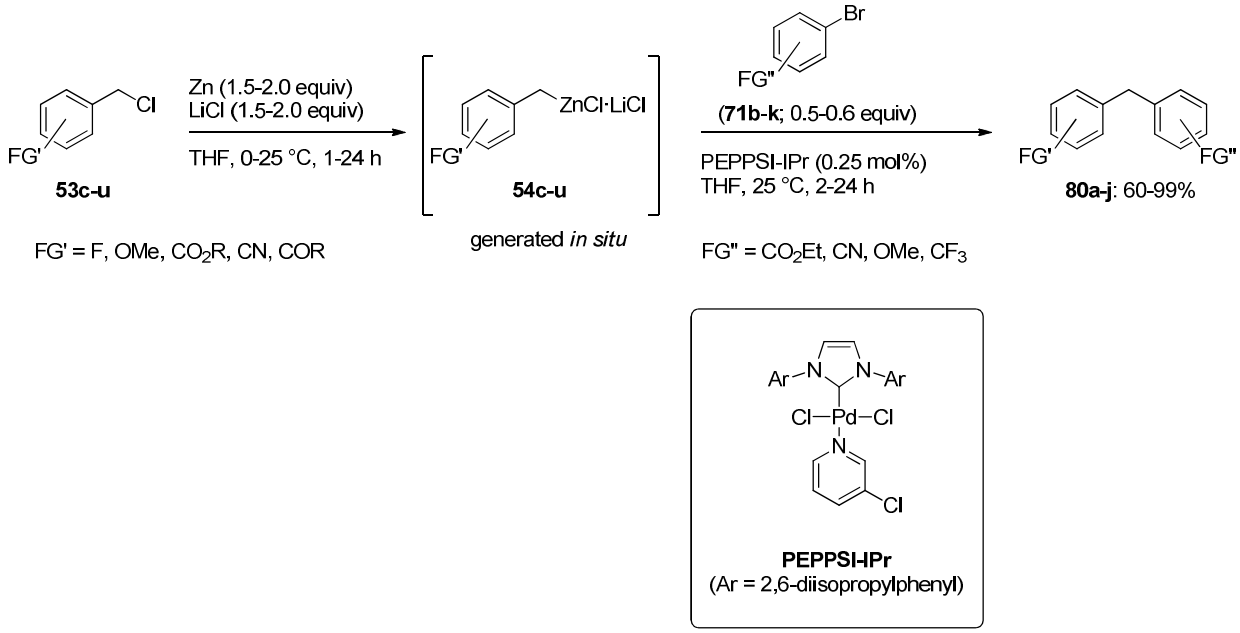
Scheme 53: Preliminary experiments of one-pot Negishi cross-coupling reaction using the palladium catalyst PEPPSI-IPr.

The palladium catalyst PEPPSI-IPr, introduced by Organ, displays a broader applicability compared to common catalysts like $Pd(PPh_3)_4$.[107] This catalyst is easily synthesized and air-stable. Moreover, shorter reaction times and higher yields are generally observed.

1.4.2. PEPPSI-IPr catalyzed cross-coupling reactions of benzylic zinc chlorides with aryl bromides in the presence of zinc dust

The preparation of functionalized benzylic zinc chlorides of type **54** and subsequent cross-coupling reactions in a one-pot fashion facilitates the handling of these water and air-sensitive organozinc intermediates. *In situ* generated polyfunctional benzylic zinc reagents **54c-u** obtained by the addition of zinc and LiCl to the corresponding benzylic chlorides **53c-u** smoothly underwent Pd(0)-catalyzed cross-coupling reactions with aryl bromides **71b-k** in the presence of PEPPSI-IPr as catalyst (Scheme 54).

[107] (a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; (b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Eur. J. Chem.* **2006**, *12*, 4749; (c) For the use of PEPPSI-IPr, see also: (i) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443; (ii) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150; (iii) G. Shore, S. Morin, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2008**, *14*, 1351; (iv) C. Valente, S. Baglione, D. Candito, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2008**, 735.



Scheme 54: Cross-couplings of benzylic zinc chlorides with aromatic bromides using PEPPSI-IPr.

Very low catalyst loadings are sufficient (0.25 mol%) to perform these cross-coupling reactions. Thus, 4-fluorobenzyl chloride (**53c**) was readily converted to the corresponding benzylic zinc intermediate **54c** within 24 h at 25 °C. Subsequent cross-coupling reaction with methyl 2-bromobenzoate (**71g**; 0.5 equiv) furnished the desired diarylmethane **80a** in 96% yield (entry 1 of Table 12). Similarly, reaction of 3,4,5-trimethoxybenzyl chloride (**53h**) with zinc dust (1.5 equiv) and LiCl provided the desired benzylic zinc reagent **54h** within 4 h (entry 2). Pd-catalyzed cross-coupling with 4-bromobenzonitrile (**71h**) led to the expected product **80b** in 99% yield. Moreover, 3-(ethoxycarbonyl)- as well as 3-cyano-substituted benzylic chlorides **53m-o** were smoothly converted to the corresponding benzylic zinc chlorides **54m-o** which led, after Pd-catalyzed cross-couplings with different aromatic bromides **71b** and **71i**, to the diarylmethanes **80c-d** (entry 3 and 4). Several keto-functions present on benzylic chlorides can be tolerated by this protocol. Thus, direct zinc insertion into 3-pentanoylbenzyl chloride (**53q**) provided the desired benzylic zinc chloride intermediate **54q**. After one-pot Pd-catalyzed cross-coupling with ethyl 3-bromobenzoate (**71d**), the disubstituted diarylmethane **80e** was obtained within 2 h in 92% yield (entry 5). Similarly, 3-propionylbenzyl chloride (**53s**) led to 3'-propionylbiphenyl-4-carbonitrile (**80f**) in 79% yield (entry 6). In an analogous manner, 3-acetylbenzyl chloride (**53t**) was smoothly converted to the corresponding zinc intermediate **54t** by direct zinc insertion within

4 h. Subsequent cross-couplings in a one-pot fashion with either 1-bromo-3-(trifluoromethyl)benzene (**71j**), ethyl 4-bromobenzoate (**71e**) or 1-bromo-3-methoxybenzene (**71k**) led to the desired diarylmethanes **80g-i** in 60-94% yield (entries 7-9). Finally, the secondary benzylic chloride **53u** was easily converted to the corresponding secondary benzylic zinc intermediate **54u** which provided after Pd-catalyzed cross-coupling reaction with 4-bromobenzonitrile (**71h**) the expected 1,1-diarylethane derivative **80j** in 94% yield (entry 10).

Table 12: PEPPSI-IPr catalyzed cross-coupling reaction of *in situ* generated benzylic zinc chlorides **54** with aromatic bromides **71** at 25 °C.

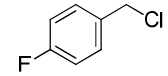
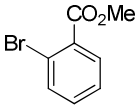
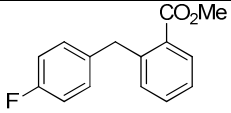
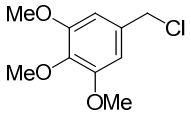
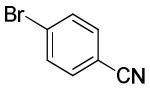
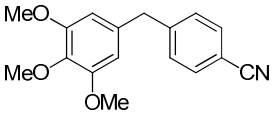
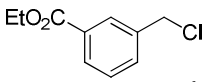
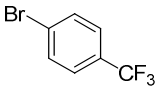
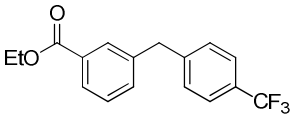
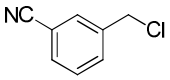
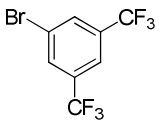
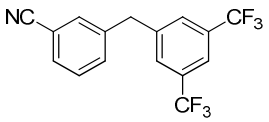
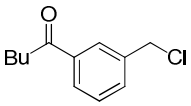
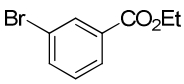
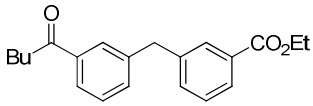
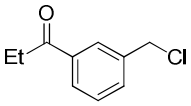
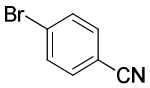
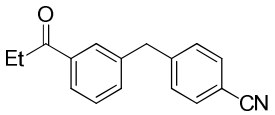
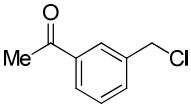
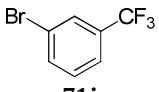
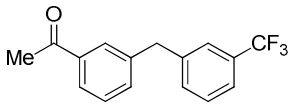
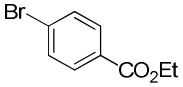
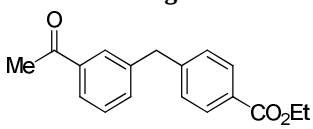
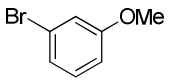
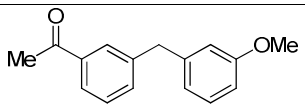
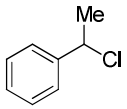
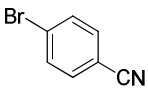
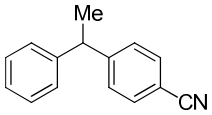
Entry	Benzylic chloride[a]	Electrophile	Time (h)[b]	Product	Yield (%)[c]
1	 **53c** (25 °C, 24 h)	 **71g**	24	 **80a**	96[d]
2	 **53h** (25 °C, 4 h)	 **71h**	15	 **80b**	99[e]
3	 **53m** (25 °C, 4 h)[f]	 **71i**	4	 **80c**	94[d]
4	 **53o** (25 °C, 3.5 h)	 **71b**	15.5	 **80d**	85[d]
5	 **53q** (25 °C, 4 h)	 **71d**	2	 **80e**	92[e]
6	 **53s** (25 °C, 4 h)	 **71h**	2	 **80f**	79[e]
7	 **53t** (25 °C, 4 h)	 **71j**	5	 **80g**	86[e]
8	**53t**	 **71e**	2	 **80h**	94[e]

Table 12 continued

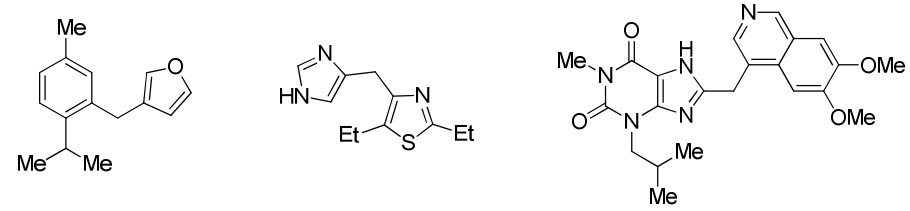
9	**53t**	 **71k**	5	 **80i**	60[e]
10	 **53u** (25 °C, 15 h)	 **71h**	8	 **80j**	94[d]

[a] Reaction conditions for the zinc insertion are given using Zn (1.5 equiv), LiCl (1.5 equiv). [b] Reaction time for the Pd-catalyzed cross-couplings at 25 °C. [c] Yield of isolated analytically pure product. [d] 0.6 equivalents of the electrophile were used. [e] 0.5 equivalents of the electrophile were used. [f] Zn (2.0 equiv), LiCl (2.0 equiv) were used for the insertion step.

1.5. Preparation of diheterobenzylic zinc reagents and heterobenzylic zinc chlorides

1.5.1. Introduction

The heteromethylene group is also a present motive in several natural products as well as in lead structures for pharmaceuticals and therefore an interesting research target is the preparation of heterobenzylic zinc reagents (Scheme 55).



Tsitsikammafuran (**81**) RWJ 37210 (**82**) isoquinolylmethyl derivative **83**

Scheme 55: Heterobenzylic groups present in various bioactive compounds.

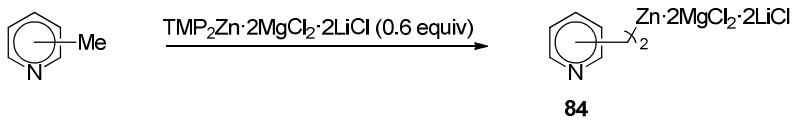
Thus, Tsitsikammafuran (**81**), extracted from *Dysidea* sponge in a very low yield (0.8 mg, 0.0004% dry wt. of sponge), bears a heterobenzylic furan scaffold.[108] Furthermore, lead structure RWJ 3720 (**82**) is a potent antinociceptive agent which showed a good binding at the α_{2D} adrenergic receptor (K_i = 18 nM).[109] Also the isoquinolylmethyl derivate **83** was found to be a

[108] K. L. McPhail, D. E. A. Rivett, D. E. Lack, M. T. Davies-Coleman, *Tetrahedron* **2000**, *56*, 9391.
[109] (a) T. M. Ross, M. C. Jetter, M. E. McDonnell, R. E. Boyd, Charlene D. Connelly, R. P. Martinez, M. A. Lewis, E. E. Codd, R. B. Raffa, A. B. Reitz, *J. Med. Chem.* **2000**, *43*, 1423; (b) R. E. Boyd, C. Royce Rasmussen, J. B. Press, R. B. Raffa, E. E. Codd, C. D. Connelly, Q. S. Li, R. P. Martinez, M. A. Lewis, H. R. Almond, A. B. Reitz, *J. Med. Chem.* **2001,** *44*, 863.

highly active inhibitor of human platelet phosphodiesterase 5 (PDE5).[110] It structural motive is based on a heterobenzylic isoquinoline group attached to a dihydropurindione core.

1.5.2. Preparation of heterobenzylic zinc reagents and further reactions

Heterobenzylic zinc reagents were prepared by two different methods. The first possibility for the preparation of these zinc reagents was the direct metalation using the mild base $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$.[29, 111] Therefore, methyl-substituted heteroaromatics were smoothly deprotonated to furnish the heterobenzylic zinc reagent **84** (Scheme 56). However, to succeed in the formation of the heterobenzylic zinc reagent it is crucial that the methyl group is in activated position to the nitrogen atom (2- or 4-position of the pyridine ring).



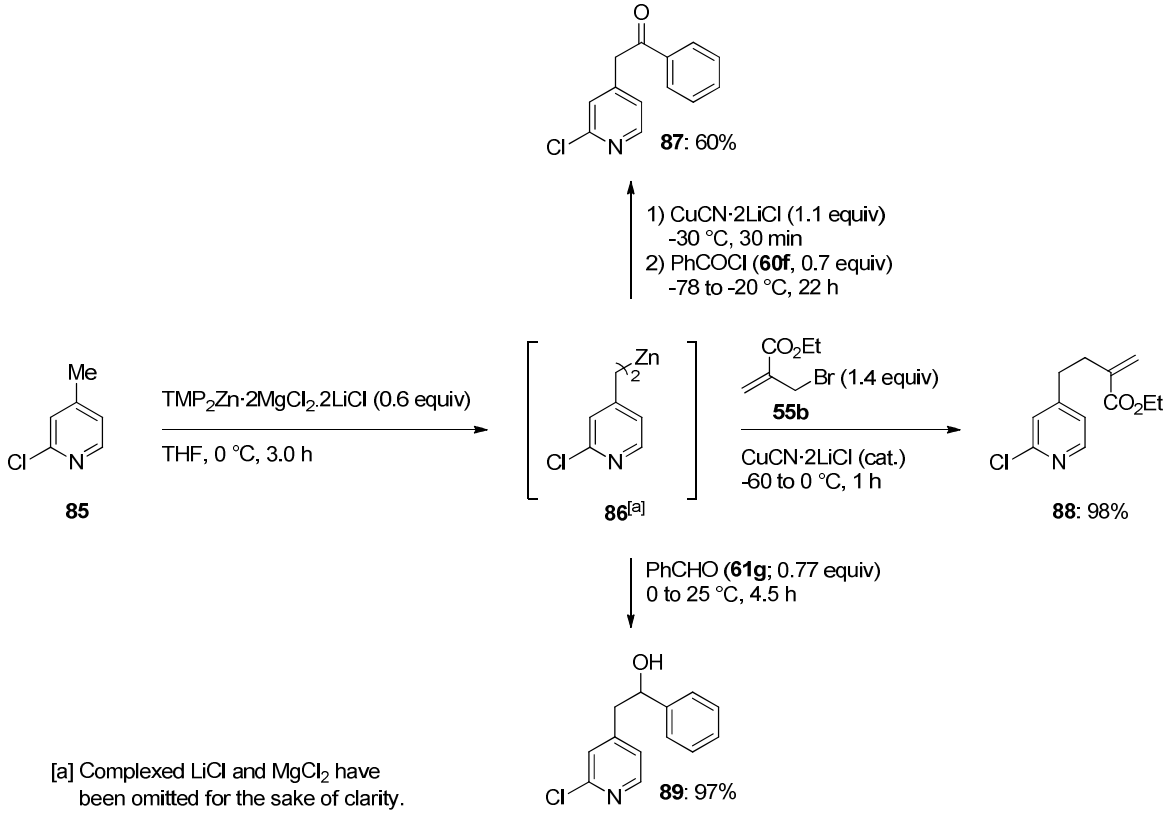
84

Scheme 56: General preparation of bis-heterobenzylic zinc reagents by direct metalation using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$.

Thus, 2-chloro-4-methylpyridine (**85**) was easily metalated using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (0.6 equiv) within 3 h at 0 °C (Scheme 57). Transmetalation of the bis-heterobenzylic zinc reagent **86** with $CuCN \cdot 2LiCl$ and subsequent acylation using benzoyl chloride (**60f**) furnished the heterocyclic ketone **87** in 60%. Moreover, the zinc reagent **86** was smoothly allylated with ethyl (2-bromomethyl)acrylate (**55b**) under Cu(I)-catalysis to provide the desired product **88** in 98% yield.

[110] N. J. Arnold, R. Arnold, D. Beer, G. Bhalay, S. P. Collingwood, S. Craig, N. Devereux, M. Dodds, A. R. Dunstan, R. A. Fairhurst, D. Farr, J. D. Fullerton, A. Glen, S. Gomez, S. Haberthuer, J. D. I. Hatto, C. Howes, D. Jones, T. H. Keller, B. Leuenberger, H. E. Moser, I. Muller, R. Naef, P. A. Nicklin, D. A. Sandham, K. L. Turner, M. F. Tweed, S. J. Watson, M. Zurini, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2376.

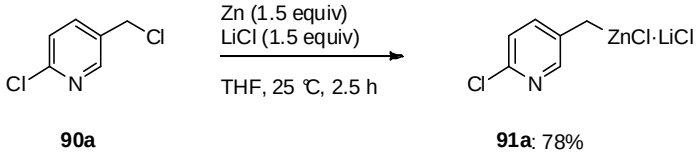
[111] For metalation of picoline derivatives, see: (a) T. Kaminski, P. Gros, Y. Fort, *Eur. J. Org. Chem.* **2003**, 3855; (b) F. A. Davis, J. Y. Melamed, S. S. Sharik, *J. Org. Chem.* **2006**, *71*, 8761.



Scheme 57: Preparation of bis[(2-chloropyridin-4-yl)methyl]zinc (**86**) and subsequent reactions with different electrophiles.

Also a direct addition of the pyridyl-substituted zinc reagent **86** to benzaldehyde (**61g**) *in the absence of any catalyst* led to the heterobenzylic alcohol **89** within 4.5 h in 97% yield.

However, the preparation of heterobenzylic zinc reagents by direct metalation reaction with $TMP_2Zn \cdot 2MgCl_2 \cdot LiCl$ totally fails in the case of unactivated methyl group such as in the case of 3-picoline.[112] Therefore, a zinc insertion into heterobenzyl chlorides was developed. Thus, direct zinc insertion in the presence of LiCl into 2-chloro-5-(chloromethyl)pyridine (**90a**) led smoothly to the corresponding heterobenzylic zinc chloride **91a** within 2.5 h in 78% yield (Scheme 58).

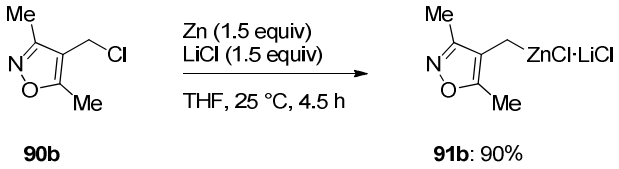


Scheme 58: Preparation of (6-chloropyridin-3-yl)methylzinc chloride (**91a**).[18]

[112] For metalation of 3-picoline derivatives with strong bases, see: (a) A. D. Miller, R. Levine, *J. Org. Chem.* **1959**, *24*, 1364; (b) M. Albrecht, C. Riether, *Synlett* **1995**, 309; (c) E. D. Kaiser, J. D. Petty, *Synthesis* **1975**, 705.

The chloro-substituent in 2 position is absolutely crucial for the formation of the heterobenzylic zinc reagent **91a**. Direct zinc insertion into (3-chloromethyl)pyridine led only to decomposition probably due to direct alkylation reactions of the starting material.

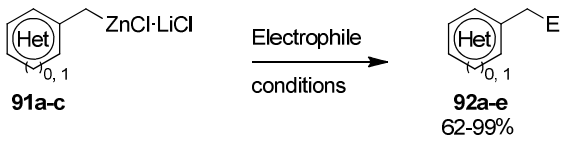
Moreover, reaction of 4-(chloromethyl)-3,5-dimethylisoxazole (**90b**) with commercially available zinc dust in the presence of LiCl provided the expected heterobenzylic zinc reagent **91b** within 4.5 h in 90% yield (Scheme 59).



90b **91b**: 90%

Scheme 59: Preparation of (3,5-dimethylisoxazol-4-yl)methylzinc chloride (**91b**).[18]

These new heterobenzylic zinc reagents, prepared by direct zinc insertion into the corresponding heterobenzylic chlorides were reacted with various electrophiles.

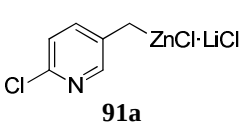
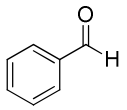
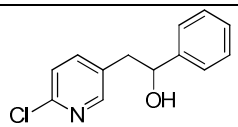
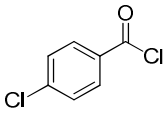
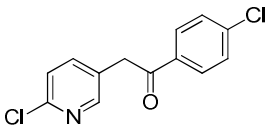
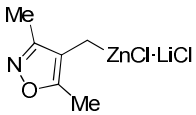
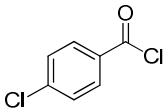
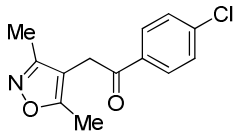
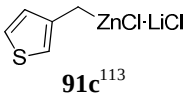
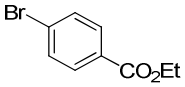
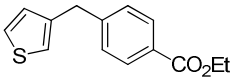


91a-c **92a-e** 62-99%

Scheme 60: Reaction of heterobenzylic zinc reagents with various electrophiles.

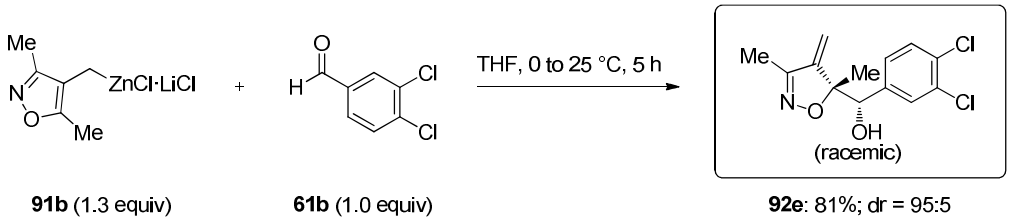
Thus, reaction of (6-chloropyridin-3-yl)methylzinc chloride (**91a**) with benzaldehyde (**61g**) led to the heterobenzylic alcohol **92a** in 99% yield (entry 1 of Table 13). Moreover, Cu(I)-mediated acylation with 4-chlorobenzoyl chloride (**60d**) furnished the ketone **92b** in 62% yield (entry 2). Similarly, (3,5-dimethylisoxazol-4-yl)methylzinc chloride (**91b**) reacted with 4-chlorobenzoyl chloride (**60d**) to provide the desired isoxazole **92v** within 27 h in 81% yield (entry 3). Smooth Pd-catalyzed cross-coupling reaction of (3-thienylmethyl)zinc chloride (**91c**) with ethyl 4-bromobenzoate (**71e**) led to the diarylmethane derivative **92d** in 65% yield (entry 4).

Table 13: Reaction of heterobenzylic zinc reagents **91a-c** with various electrophiles

Entry	Heterobenzylic zinc chloride	Electrophile	Temperature (°C) / Time (h)	Product	Yield (%)[a]
1	 **91a**	 **61g**	0 to 25 / 17	 **92a**	99
2	**91a**	 **60d**	-40 to 25 / 20	 **92b**	62[b]
3	 **91b**	 **60d**	-40 to 25 / 27	 **92c**	81[b]
4	 **91c**[113]	 **71e**	18 / 25	 **92d**	65[c]

[a] Yield of isolated analytically pure product. [b] Stoichiometric amounts of CuCN·2LiCl were used. [c] $Pd(OAc)_2$ (2.0 mol%) and S-Phos (4.0 mol%) were used.

Interestingly, reaction of (3,5-dimethylisoxazol-4-yl)methylzinc chloride (**91c**) with 3,4-dichlorobenzaldehyde (**61b**) did not provide the expected addition product. In fact, the heterobenzylic zinc reagent **91b** reacted equally to the known chemistry of allylic zinc reagents[114] as well as similarly to special examples of benzylic zinc compounds [115] and heterobenzylic copper derivatives[116] and provided the alcohol **92e** within 5 h in 81% yield (Scheme 61).



91b (1.3 equiv) **61b** (1.0 equiv) **92e**: 81%; dr = 95:5

Scheme 61: Preparation of the benzylic alcohol **92e** by the direct addition of (3,5-dimethylisoxazol-4-yl)methylzinc chloride (**91b**) to 3,4-dichlorobenzaldehyde (**61b**).

[113] For the preparation of (3-thienylmethyl)zinc chloride (**91c**) as well as additional reaction conditions, see. A. J. Wagner, Ph.D. thesis, LMU Munich.
[114] H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376.
[115] (a) I. Klement, K. Lennick, C. E. Tucker, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 4623; (b) V. F. Raaen, J. F. Eastham, *J. Am. Chem. Soc.* **1960**, *82*, 1349.
[116] A. Sidduri, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1993**, *58*, 2694.

The configuration of the alcohol **92e** was confirmed by X-ray analysis and an ORTEP plot is presented in Figure 1.

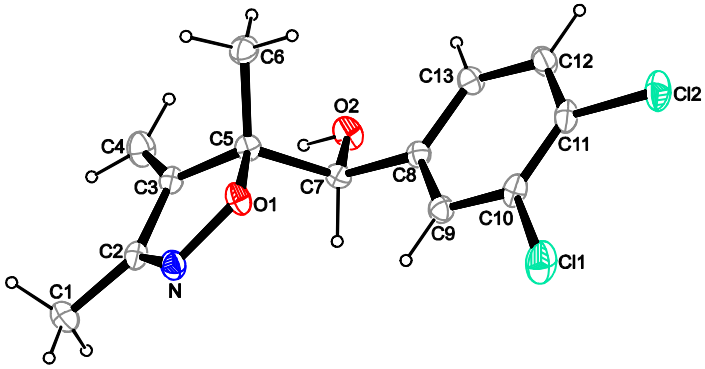


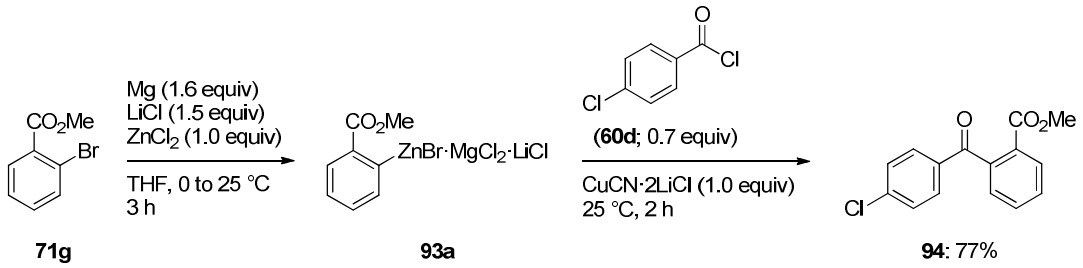
Figure 1: ORTEP representation of the alcohol **92e**.

1.6. Preparation of benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of $ZnCl_2$ and LiCl

1.6.1. Introduction

In 2008, a mild and easy preparation of arylmagnesium reagents by the direct insertion of magnesium in the presence of LiCl into halogen-substituted aromatics was reported.[117] This work extended considerably the previously documented preparation and applications of Grignard reagents.[118] However, there were also some limitations. Mainly, in the case of an ester group attached to an aromatic bromide, the method described above needed to be modified. Therefore, stoichiometric amounts of $ZnCl_2$ were added to transmetalate *in situ* the formed Grignard reagent to the corresponding organozinc halide. Thus, methyl 2-bromobenzoate (**71g**) reacted with magnesium powder in the presence of $ZnCl_2$ and LiCl to furnish the desired organozinc reagent **93a** which was subsequently acylated with the acid chloride **60d** providing the benzophenone **94** in 77% yield (Scheme 62).[119]

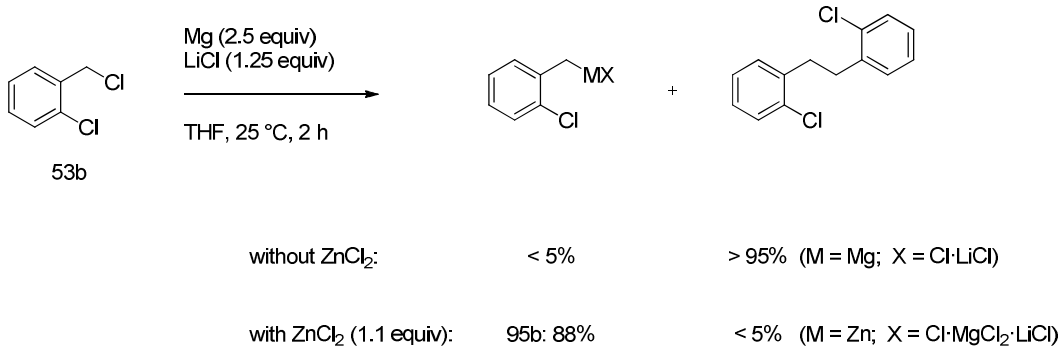
[117] F. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[118] (a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; (b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.
[119] F. M. Piller, A. Metzger, M. A. Schade, B. H. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.



Scheme 62: Preparation of the ester-substituted aryl zinc reagent **93a** and subsequent acylation reaction with benzoyl chloride **60d**.

1.6.2. Preparation of benzylic zinc chlorides by the Mg/$ZnCl_2$/LiCl method

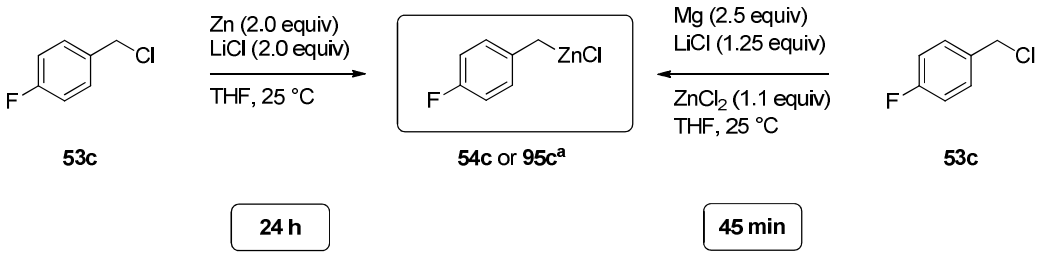
This mild method was adapted for the preparation of benzylic organometallics. Thus, reaction of 2-chlorobenzyl chloride (**53b**) with magnesium turnings in the presence of LiCl led only to large amount of Wurtz-coupling product (Scheme 63). Only traces of the benzylic magnesium reagent were formed. In strong contrast, by performing the insertion reaction in the presence of stoichiometric amounts of $ZnCl_2$, 2-chlorobenzylzinc chloride·$MgCl_2$ (**95b**) is readily formed and the amount of homo-coupling product is below 5%. Moreover, it has to be pointed out that no activation of the magnesium is required.



Scheme 63: Influence of $ZnCl_2$ for the preparation of benzylic zinc chlorides of type **95**.

In contrast to the previously described insertion method into benzylic chlorides using zinc dust and LiCl (chapter 1, p. 23 ff.), the magnesium insertion in the presence of zinc chloride and lithium chloride allows shorter insertion times due to the use of a more strongly reducing metal and proceeds at a lower temperature. Thus, direct zinc insertion (Zn powder; 2.0 equiv) in the presence of LiCl (2.0 equiv) into 4-fluorobenzyl chloride (**53c**) furnished the corresponding benzylic zinc chloride **54c** after a reaction time of 24 h at 25 °C. On the other hand, direct

magnesium insertion (Mg turnings; 2.5 equiv) into benzylic chloride **53c** in the presence of $ZnCl_2$ (1.1 equiv) and LiCl (1.25 equiv) in THF resulted in complete conversion to the zinc reagent **95c** within 45 min at 25 °C (Scheme 64).

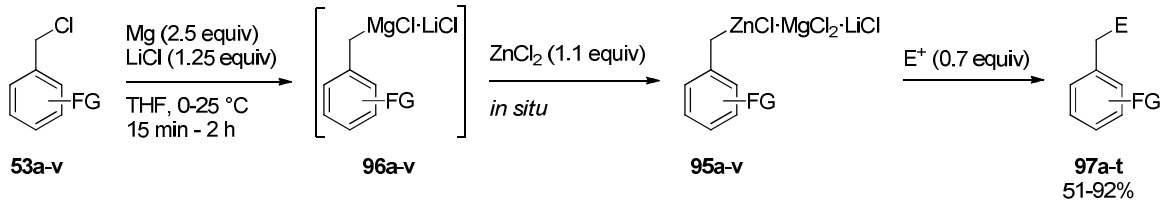


[a] = Complexed salts (LiCl and $MgCl_2$) have been omitted for the sake of clarity.

Scheme 64: Comparison of the preparation times for 4-fluorobenzylzinc chloride (**54c** or **95c**) either by the Zn/LiCl method or by the Mg/$ZnCl_2$/LiCl method.

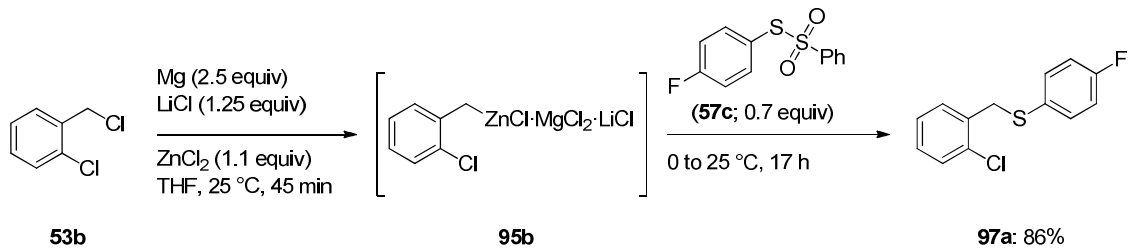
Furthermore, by using 0.5 equivalents of $ZnCl_2$, this alternative method allows the preparation of bisbenzylic zinc reagents of the type $(ArCH_2)_2Zn$.

Ranges of functionalized benzylic zinc reagents of type **95** have been successfully prepared by this new procedure described above, using commercially available benzylic chlorides of type **53** and magnesium turnings in the presence of $ZnCl_2$ and LiCl. These reactions proceed via intermediate benzylic magnesium compounds **96**, which are *in situ* transmetalated to the corresponding benzylic zinc chlorides of type **95**. Subsequent reactions of the functionalized benzylic zinc reagents **95** with various electrophiles (E^+) provided a range of benzylic derivatives of type **97** (Scheme 65).



Scheme 65: General procedure for the preparation of benzylic zinc chlorides by the Mg/$ZnCl_2$/LiCl method and subsequent reactions of these organometallics with common electrophiles.

In a typical experiment, the reaction of 2-chlorobenzyl chloride (**53b**) with magnesium turnings (2.5 equiv), $ZnCl_2$ (1.1 equiv) and LiCl (1.25 equiv) easily occurred at 25 °C within 45 min providing the benzylic zinc reagent **95b**. Its subsequent reaction with *S*-(4-fluorophenyl) benzenesulfonothioate (**57c**; 0.7 equiv) led to the asymmetrically substituted sulfide **97a** within 17 h in 86% yield (Scheme 66).



Scheme 66: Insertion of magnesium into 2-chlorobenzyl chloride (**53b**) in the presence of $ZnCl_2$ and LiCl and subsequent reaction with benzenesulfonothioate **57c**.

Similarly, allylation of the zinc reagent **95c** with ethyl (2-bromomethyl)acrylate (**55b**) provided the unsaturated ester **97b** in 77% yield (entry 1 of Table 14). As mentioned above, 4-fluorobenzyl chloride (**53c**) is readily converted to the corresponding benzylic zinc reagent **95c** within 45 min. Addition of **95c** to 4-bromobenzaldehyde (**61e**) gave the benzylic alcohol **97c** in 51% yield (entry 2). 3-(Trifluoromethyl)benzyl chloride (**53g**) was converted to the benzylic zinc organometallic **95g** within 30 min at 25 °C. Reaction with 2-chlorobenzaldehyde (**61a**) or *S*-(3-cyanobenzyl) benzenesulfonothioate (**57d**) gave the benzylic alcohol **97d** and, respectively, the dibenzylic sulfide **97e** in 85-86% yield (entries 3 and 4). Also, electron-rich benzylic chlorides are converted to the corresponding zinc reagents without the formation of homo-coupling products. Thus, 3,4,5-trimethoxybenzylzinc chloride **95h** was obtained after reaction of 3,4,5-trimethoxybenzyl chloride (**53h**) with magnesium, $ZnCl_2$ and LiCl (25 °C, 1 h). Cu(I)-mediated treatment with 4-chlorobenzoyl chloride (**60d**) provided the ketone **97f** in 56% yield (entry 5). Moreover, 4-methoxybenzyl chloride (**53i**) was readily converted to the expected benzylic zinc chloride **95i** within 2 h and subsequent reaction with (*S*)-(4-bromophenyl) benzenesulfonothioate (**57a**) yielded the sulfide **97g** in 88% (entry 6). Similarly, 2-methoxybenzyl chloride (**53j**) reacted under standard conditions to provide the corresponding benzylic zinc chloride **95j** within 45 min. Its copper(I)-mediated acylation with cyclopropanecarbonyl chloride (**60c**) as well as reaction with 3-chlorobenzaldehyde (**61c**) furnished the desired products **97h-i** in 89-92% yield (entries 7

and 8). Furthermore, the direct magnesium insertion in the presence of $ZnCl_2$ and LiCl into (4-methylthio)benzyl chloride (**53l**) led to the thioether-substituted benzylic zinc chloride **95l** within 1.5 h reaction time at 25 °C. Subsequent addition to 4-bromobenzaldehyde (**61e**) or Cu(I)-mediated addition to 3-iodocyclohex-2-enone (**58b**) provided the alcohol **97j** as well as the substituted cyclohex-2-enone **97k** in 62-82% yield (entries 9 and 10).

Table 14: Preparation of benzylic zinc chlorides **95** by the Mg/$ZnCl_2$/LiCl method and their subsequent reaction with various electrophiles (part 1).

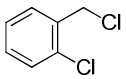
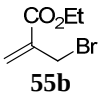
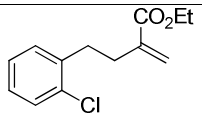
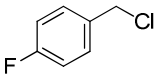
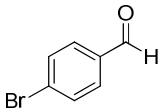
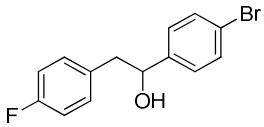
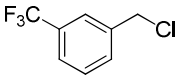
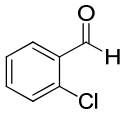
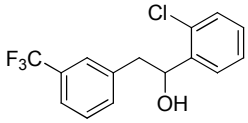
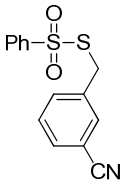
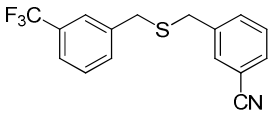
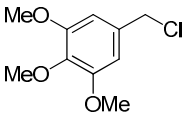
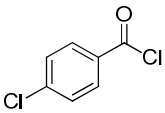
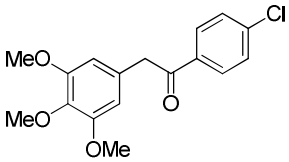
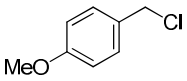
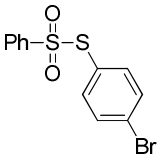
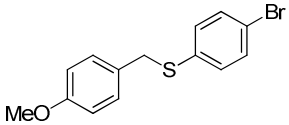
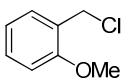
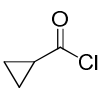
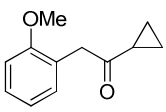
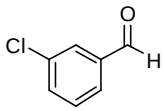
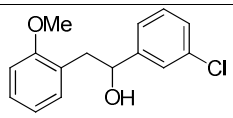
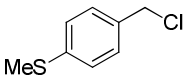
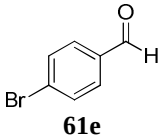
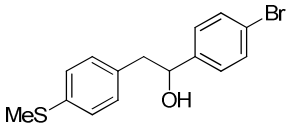
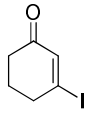
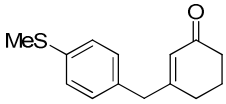
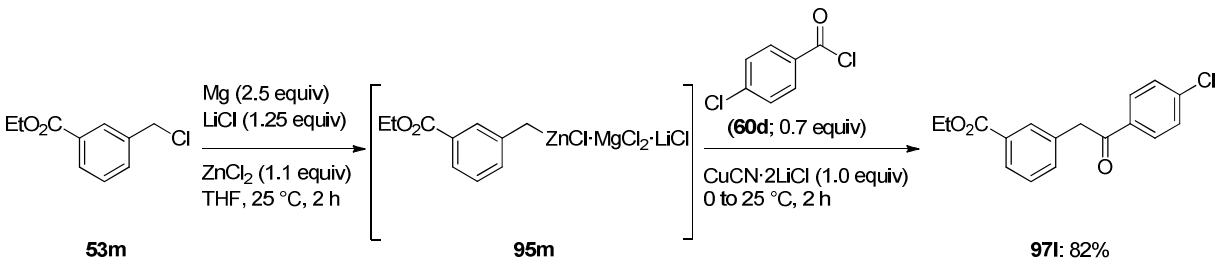
Entry	Benzylic zinc chloride[a]	Electrophile	Conditions[b]	Product	Yield (%)[c]
1	 **53b** (0.75 h)	 **55b**	25 / 0.75	 **97b**	77[d]
2	 **53c** (0.75 h)	 **61e**	25 / 2	 **97c**	51
3	 **53g** (0.5 h)	 **61a**	25 / 1	 **97d**	85
4	**53g** (0.5 h)	 **57d**	25 / 2	 **97e**	86
5	 **53h** (1.0 h)	 **60d**	-20 to 25 / 2	 **97f**	56[e]
6	 **53i** (2.0 h)	 **57a**	25 / 17	 **97g**	88
7	 **53j** (1.0 h)	 **60c**	-20 to 25 / 6.5	 **97h**	89[e]

Table 14 continued

8	**53j** (1.0 h)	 **61c**	25 / 4	 **97i**	92
9	 **53l** (1.5 h)	 **61e**	25 / 2	 **97j**	82
10	**53l** (1.5 h)	 **58b**	-40 to 0 / 18	 **97k**	62[f]

[a] Reaction time for the insertion step at 25 °C. [b] Temperature (°C) / time (h) for the reaction step with the electrophile. [c] Yield of isolated analytically pure product. [d] The reaction was performed in the presence of catalytic amounts of CuCN·2LiCl. [e] Stoichiometric amounts of CuCN·2LiCl were used. [f] Stoichiometric amounts of CuCN·2LiCl and TMSCl were used.

Sensitive functional groups are also tolerated by this method. Thus, the reaction of 3-(ethoxycarbonyl)benzyl chloride (**53m**) with Mg/$ZnCl_2$/LiCl at 25 °C for 2 h provided the corresponding zinc reagent **95m**. Its copper(I)-mediated reaction with 4-chlorobenzoyl chloride (**60d**), as a representative acid chloride, led to the benzylic ketone **97l** in 82% yield (Scheme 67).



Scheme 67: Insertion of magnesium into 3-(ethoxycarbonyl)benzyl chloride (**53m**) in the presence of $ZnCl_2$ and LiCl and subsequent Cu(I)-mediated acylation reaction.

Moreover, Pd-catalyzed cross-coupling reaction of **95m** with 4-iodoanisole (**4c**) using PEPPSI-IPr (0.25 mol%) as catalyst led to the expected product **97m** in 78% yield (entry 1 of Table 15). Additionally, the zinc reagent **95m** smoothly reacted with *S*-(4-chlorophenyl) benzenesulfonothioate (**57e**) to furnish the sulfide **97n** within 2 h in 67% yield (entry 2). Analogously, a cyano function is tolerated as well. Thus, 3-cyanobenzyl chloride (**53o**) was cleanly converted to the corresponding zinc reagent **95o** within 2 h at 25 °C and a copper(I)-catalyzed allylation of the latter with ethyl (2-bromomethyl)acrylate (**55b**) provided the desired

acrylate **97o** (79%; entry 3). Similarly, reaction with 3,4-dichlorobenzaldehyde (**61b**) and Cu(I)-mediated 1,4-addition to 3-iodocyclohex-2-enone (**58b**) led to the expected products **97p** and **97q** in 77-83% yield (entries 4 and 5). Furthermore, reaction of benzyl chloride (**53a**) under standard conditions led to benzylzinc chloride (**95a**) at 25 °C in 2 h. Then, reaction with *S*-(4-methoxyphenyl) benzenesulfonothioate (**57f**) provided the sufide **97r** in 78% yield (entry 6). Analogous to the reaction times for the direct LiCl-mediated zinc insertion into secondary benzylic chlorides **53u-v**, the direct magnesium insertion in the presence of $ZnCl_2$ and LiCl into secondary benzylic chlorides **53u-v** proceeded also faster than the magnesium insertion into benzyl chloride (**53a**; see also Scheme 42). Thus, 1-(chloroethyl)benzene (**53**u) or 1,1-diphenylchloromethane (**53v**) are smoothly converted to the corresponding secondary benzylic zinc reagents **95u-v** within 30 min to 1 h. Subsequent reaction with 4-bromobenzaldehyde (**61e**) or Cu(I)-mediated acylation with acetyl chloride (**60a**) yielded the adducts **97s** and **97t** in 68-70% yield (entries 7 and 8).

Table 15: Preparation of benzylic zinc chlorides **95** by the Mg/$ZnCl_2$/LiCl method and their subsequent reaction with various electrophiles (part 2).

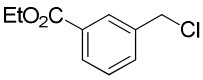
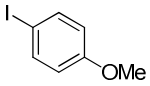
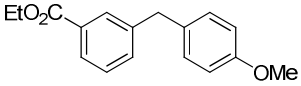
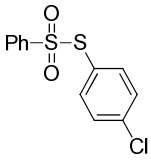
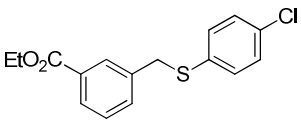
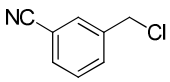
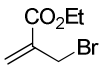
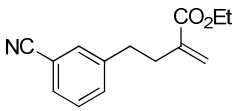
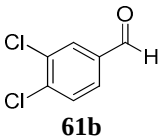
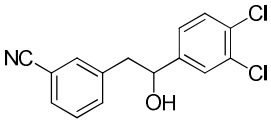
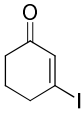
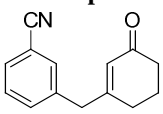
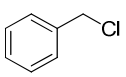
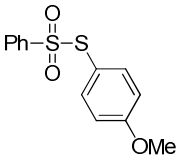
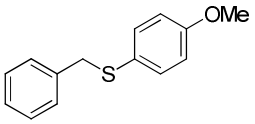
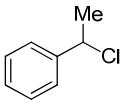
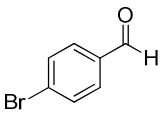
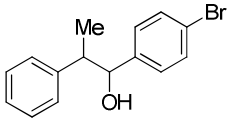
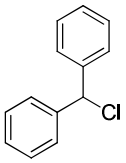
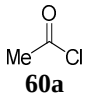
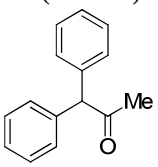
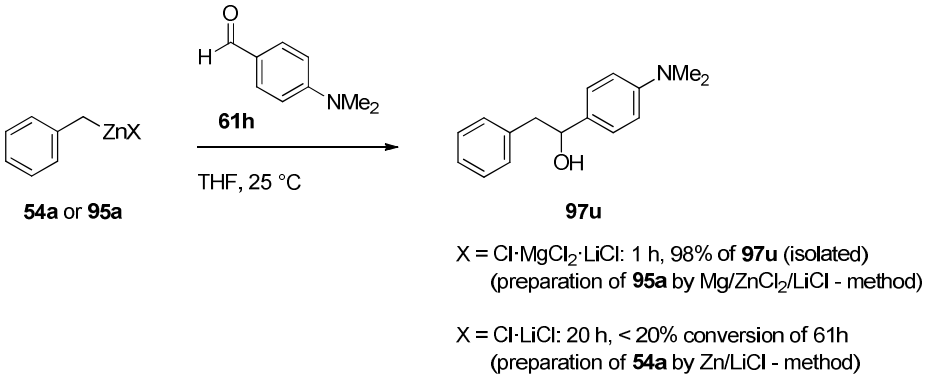
Entry	Benzylic zinc chloride[a]	Electrophile	Conditions[b]	Product	Yield (%)[c]
1	 **53m** (2.0 h)	 **4c**	25 / 21	 **97m**	78[d]
2	**53m** (2.0 h)	 **57e**	25 / 2	 **97n**	67
3	 **53o** (2.0 h)	 **55b**	25 / 1	 **97o**	79[e]
4	**53o** (2.0 h)	 **61b**	25 / 2	 **97p**	83
5	**53o** (2.0 h)	 **58b**	-60 to 0 / 18	 **97q**	77[f]

Table 15 continued

6	 **53a** (2.0 h)	 **57f**	25 / 13	 **97r**	78
7	 **53u** (1.0 h)	 **61e**	25 / 2	 **97s** (dr = 2:1)	70
8	 **53v** (0.5 h at 0 °C)	 **60a**	-20 to 10 / 24	 **97t**	68[g]

[a] Reaction time for the insertion step at 25 °C. [b] Temperature (°C) / time (h) for the reaction step with the electrophile. [c] Yield of isolated analytically pure product. [d] The reaction is performed in the presence of PEPPSI-IPr (0.25 mol%). [e] The reaction is performed in the presence of catalytic amounts of CuCN·2LiCl. [f] Stoichiometric amounts of CuCN·2LiCl and TMSCl were used. [g] Stoichiometric amounts of CuCN·2LiCl were used.

This *in situ* method (Mg, $ZnCl_2$, LiCl) also has the advantage of producing more reactive benzylic zinc reagents due to the *in situ* generation of $MgCl_2$, which accelerates the addition to carbonyl derivatives. Thus, for benzylzinc chloride (**95a**) generated by using Mg/$ZnCl_2$/LiCl method, the reaction with electron-rich 4-(dimethylamino)benzaldehyde (**61h**) led to the desired benzylic alcohol **97u** in 98% isolated yield after a reaction time of only 1 h at 25 °C (Scheme 68). In contrast, by generating **54a** via the Zn/LiCl-method, the addition to benzaldehyde **61h** did not provide the expected product **97u** in any appreciable amount. Only 20% conversion of the aldehyde **61h** was observed after a reaction time of 20 h at 25 °C.



Scheme 68: Different reactivity of benzylzinc chloride (**54a** or **95a**) depending on its preparation.

2. Lewis-Acid Promoted Additions of Functionalized Organomagnesium and Organozinc Reagents to Carbonyl Derivatives

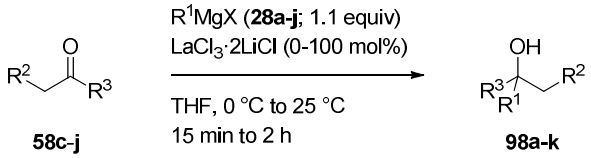
2.1. Addition of Grignard reagents to ketones in the presence of catalytic amounts of $LaCl_3 \cdot 2LiCl$

2.1.1. Introduction

As mentioned in the general introduction, $CeCl_3$ is commonly used to activate carbonyl groups towards the attack of an organomagnesium reagent. However, the low solubility of $CeCl_3$ in THF requires the use of stoichiometric amounts of this relatively expensive salt. The general problem of insolubility of the lanthanide salt is elegantly solved by using the THF-soluble complex $LaCl_3 \cdot 2LiCl$. Recently, this method was applied to the synthesis of tryptamines and related heterocycles.[120, 121] However, $LaCl_3 \cdot 2LiCl$ has been used so far only in stoichiometric amounts, while a catalytic version of this reaction would be highly appreciable considering industrial applications of this methodology.[122]

2.1.2. $LaCl_3 \cdot 2LiCl$-catalyzed addition of organomagnesium reagents to enolizable ketones

A comparative study of the use of $LaCl_3 \cdot 2LiCl$ in stoichiometric and catalytic amounts for 1,2-addition reactions of various Grignard reagents to ketones was investigated (Scheme 2).



Scheme 69: Addition of Grignard reagents (**28a-j**) to ketones (**58c-j**) in the presence of variable amount of $LaCl_3 \cdot 2LiCl$.

Therefore, organomagnesium reagents of type **28** were added to ketones of type **58** premixed with either 100 mol% or 30 mol% of $LaCl_3 \cdot 2LiCl$ or in the absence of the lanthanum salt. Lowering the amount of $LaCl_3 \cdot 2LiCl$ below 30 mol% often resulted in heterogeneous reaction mixtures. Thus, the reaction of cyclohexylmagnesium bromide (**28b**) with the easily enolizable

[120] (a) K. C. Nicolaou, A. Krasovskiy, U. Majumder, V. E. Trepanier, D. Y.-K. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 3690; (b) K. C. Nicolaou, A. Krasovskiy, V. E. Trepanier, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* **2008**, *47*, 4217.

[121] For the prepartion of aryl- and heteroaryl-lanthanum reagents by directed ortho-metalation reactions, see: S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3260.

[122] The addition of Grignard reagents to imines requires only 10 mol% of $LaCl_3 \cdot 2LiCl$. An isolated example of the addition of PhMgBr to camphor using 10 mol% of $LaCl_3 \cdot 2LiCl$ has also been reported (ref. 39).

ketone **58c** in the presence of one equivalent of $LaCl_3 \cdot 2LiCl$ provided the tertiary alcohol **98a** in 93% yield (entry 1 of Table 16). By using 30 mol% of $LaCl_3 \cdot 2LiCl$ a similar yield (87%) was achieved. Without the addition of $LaCl_3 \cdot 2LiCl$ only 33% of the alcohol **98a** was isolated.

Table 16: Addition of Grignard reagents to different ketones in the presence of $LaCl_3 \cdot 2LiCl$.

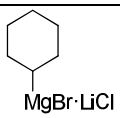
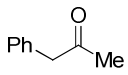
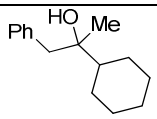
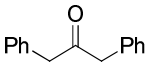
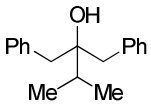
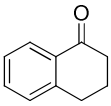
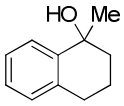
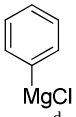
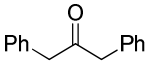
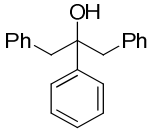
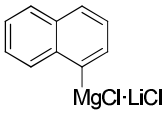
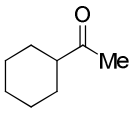
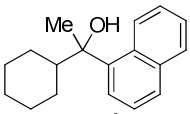
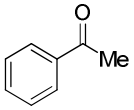
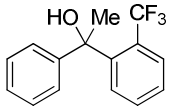
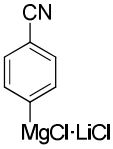
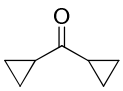
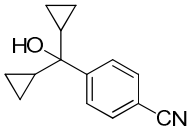
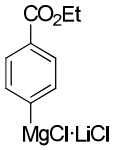
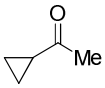
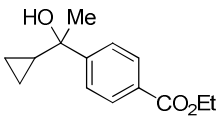
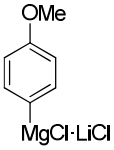
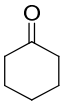
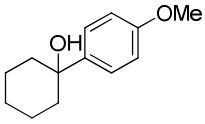
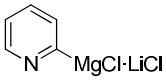
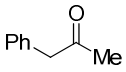
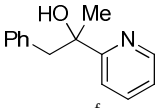
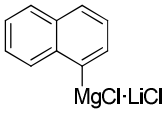
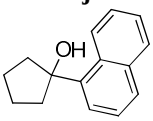
Entry	Grignard reagent	Ketone	Product	Yield (%)[a] in the presence of variable amounts of $LaCl_3 \cdot 2LiCl$		
				100 mol%	30 mol%	0 mol%
1	 **28b**[c]	 **58c**	 **98a**	93	87	33[b]
2	*i*-PrMgCl **28c**[d]	 **58d**	 **98b**	86	65	<3
3	MeMgCl **28d**[d]	 **58e**	 **98c**	95	94	69
4	 **28e**[d]	 **58d**	 **98d**	97	93	67[b]
5	 **28f**[e]	 **58f**	 **98e**[f]	76	66	22
6	 **28g**[e]	 **30**	 **98f**	72	72	13
7	 **28h**[e]	 **58g**	 **98g**	77	84	87
8	 **28i**[e]	 **58h**	 **98h**	76	83	81

Table 16 continued

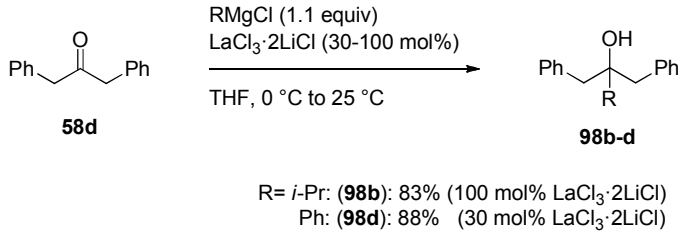
9	 **28j**[e]	 **58i**	 **98i**	73	74	84
10	 **28a**[e]	 **58c**	 **98j**[f]	71	67	22
11	 **28f**[e]	 **58j**	 **98k**	59	65	75

[a] Yield of isolated analytically pure product. [b] Yields determined by ^{1}H-NMR. [c] The Grignard reagent was prepared by direct magnesium insertion in the presence of LiCl according to ref.117. [d] The Grignard reagent is commercially available. [e] The Grignard reagent was prepared by halogen-magnesium exchange reaction using *i*-PrMgCl·LiCl according to ref. 118. [f] Experiments were performed by Dr. Andrei Gavryushin and are given here for the sake of completeness.

The reaction of the secondary alkylmagnesium reagent *i*-PrMgCl (**28c**) with 1,3-diphenylacetone (**58d**) is strongly influenced by the addition of $LaCl_3 \cdot 2LiCl$. Thus, the alcohol **98b** was obtained in 86% with stoichiometric amount of $LaCl_3 \cdot 2LiCl$ and in 65% yield in the presence of 30 mol% of $LaCl_3 \cdot 2LiCl$ (entry 2). In the absence of $LaCl_3 \cdot 2LiCl$, only traces of the alcohol **98b** were obtained due to the occurrence of competing reduction and enolization reactions. With MeMgCl (**28d**) which does not possess β-hydrogen atoms, similar yields were obtained regardless of the amount of the lanthanum salt added (entry 3). Reaction of phenylmagnesium chloride (**28e**) with the enolizable ketone **58d** led to the desired alcohol **98d** in 93-97% in the presence of either 30 or 100 mol% of $LaCl_3 \cdot 2LiCl$ (entry 4). Without $LaCl_3 \cdot 2LiCl$, a yield of 67% was achieved. In the reaction of naphthylmagnesium chloride (**28f**) with the less sterically hindered cyclohexyl methyl ketone (**58f**), the influence of $LaCl_3 \cdot 2LiCl$ is relatively strong (entry 5). The uncatalyzed reaction afforded the product **98e** in 22% yield, in the presence of 30 mol% of $LaCl_3 \cdot 2LiCl$ a yield of 66% was obtained. Using stoichiometric amounts of $LaCl_3 \cdot 2LiCl$ led to the product **98e** in 76% yield. In the absence of a catalyst, sterically hindered Grignard reagents do not react satisfactorily with ketones bearing acidic protons. Thus, reaction of 2-(trifluoromethyl)phenylmagnesium chloride (**28g**) and acetophenone (**30**) furnished the corresponding alcohol **98g** in 72% yield only in the presence of $LaCl_3 \cdot 2LiCl$, independently on whether 100 or 30 mol% were used (entry 6). A poor yield of **98f** (13%) was observed in the absence of $LaCl_3 \cdot 2LiCl$. Treatment of dicyclopropyl ketone (**58g**), cyclopropyl methyl ketone (**58h**) and cyclohexanone (**58i**) with various

organomagnesium reagents **28h-j** led to the desired alcohols **98g-i** in similar yields almost regardless of the $LaCl_3 \cdot 2LiCl$ amount (entries 7-9). However, the positive influence of $LaCl_3 \cdot 2LiCl$ was well demonstrated in the case of heteroaromatic organomagnesium compounds such as 2-pyridylmagnesium chloride (**28a**; entry 10). Its reaction with ketone **58c** led to the desired alcohol **98j** in 71% yield only in the presence of $LaCl_3 \cdot 2LiCl$. Using electron-rich arylmagnesium reagent **28f** and enolizable ketone **58j** the alcohol **98k** was obtained in lower yields with $LaCl_3 \cdot 2LiCl$ than without the use of $LaCl_3 \cdot 2LiCl$ (entry 11). These results show that for the addition of electron-rich organomagnesium species the influence of $LaCl_3 \cdot 2LiCl$ on the product yield can be negative.

An upscaling of the above described procedure gave satisfactory results (Scheme 70). The reaction of ketone **58d** either with secondary alkylmagnesium reagent **28c** in the presence of $LaCl_3 \cdot 2LiCl$ (100 mol%) or with aryl magnesium reagent **28e** in the presence of $LaCl_3 \cdot 2LiCl$ (30 mol%) furnished the expected alcohols **98b** and **98d** in 83-88% yield.

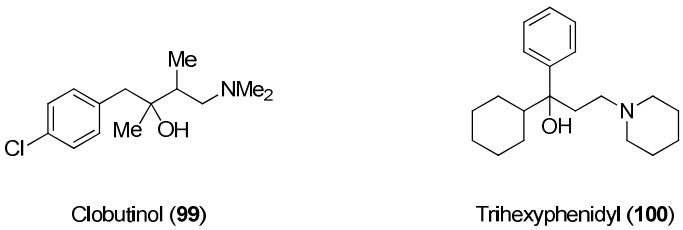


Scheme 70: Upscaled reaction (20 mmol) of ketone **58d** with either *i*-PrMgCl (**28c**) using 100 mol% of lanthanum salt or PhMgCl (**28e**) using 30 mol% of $LaCl_3 \cdot 2LiCl$.

2.2. Addition of functionalized organozinc reagents to aldehydes, ketones and carbon dioxide under mediation of $MgCl_2$

2.2.1. Introduction

The alcohol function is an important structural motive and present in many natural products as well as in pharmaceuticals demonstrated examplarily in the racemic antitussive agent clobutinol (**99**)[123] and the antiparkinsonian compound trihexyphenidyl (**100**; Scheme 71).[124] One of the most common approaches towards the synthesis of alcohols is the addition of organometallic reagents to ketones or aldehydes.[33]



Clobutinol (**99**) Trihexyphenidyl (**100**)

Scheme 71: Presence of the alcohol function in various pharmaceuticals.

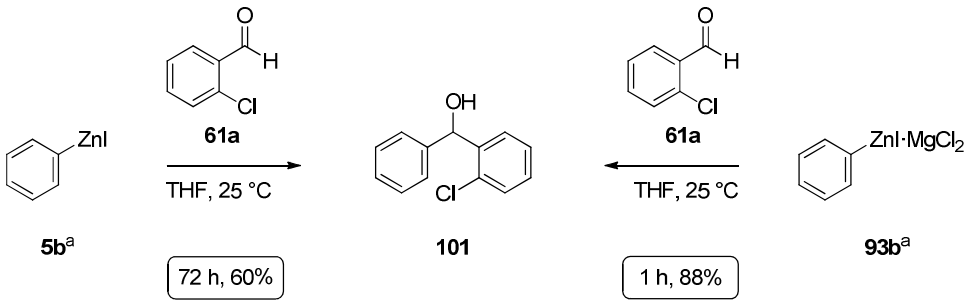
Organozinc reagents are versatile tools in organic synthesis.[17] Their intrinsic moderate reactivity towards electrophiles can be dramatically increased by transmetalations with catalytic amounts of various transition metal complexes.[125] However, for reactions with a ketone or an aldehyde such transmetalations are less appropriate. In these cases, a Lewis-acid complexation[126] of the carbonyl group is usually a more suitable activation.[127] As already mentioned in the general introduction, the addition of organozinc reagents to carbonyl derivatives has widely been investigated. However, one major drawback is the fact that diorganozinc reagents have to be used due to the higher reactivity compared to organozinc halides. Moreover, these organozinc reagents have to be used in large excess, usually one to four equivalents, to achieve completeness of the

[123] C. Bellocq, R. Wilders, J.-J. Schott, B. Louerat-Oriou, P. Boisseau, H. Le Marec, D. Escande, I. Baro, *Mol. Pharmacol.* **2004**, *66*, 1093.
[124] (a) T. D. Sanger, A. Bastian, J. Brunstrom, D. Damiano, M. Delgado, L. Dure, D. Gaebler-Spira, A. Hoon, J. W. Mink, S. Sherman-Levine, L. J. Welty, *J. Child Neurol*. **2007**, *22*, 530; (b) A. Giachetti, E. Giraldo, H. Ladinsky, E. Montagna, *Br. J. Pharmac.* **1986**, *89*, 83.
[125] For selected example, see: (a) J. Shi, X. Zeng, E. Negishi, *Org. Lett.* **2003**, *5*, 1825; (b) A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Org. Lett.* **2005**, *7*, 4871; (c) M. C. P. Yeh, P. Knochel, L. E. Santa, *Tetrahedron Lett.* **1988**, *29*, 3887; (d) C. K. Reddy, P. Knochel, *Angew. Chem. Int. Ed.* **1996**, *35*, 1700; (e) I. Kazmierski, M. Bastienne, C. Gosmini, J.-M. Paris, J. Périchon, *J. Org. Chem.* **2004**, *69*, 936; (f) Y. Tamaru, T. Nakamura, M. Sakaguchi, H. Ochiai, Z. Yoshida, *J. Chem. Soc., Chem. Commun.* **1988**, 610; (g) D. Seebach, A. K. Beck, B. Schmidt, Y. M. Wang, *Tetrahedron* **1994**, *50*, 4363.
[126] (a) J. G. Kim, P. J. Walsh, *Angew. Chem. Int. Ed.* **2006**, *45*, 4175; (b) H. Li, P. J. Walsh, *J. Am. Chem Soc.* **2005**, *127*, 8355; (c) S.-J. Jeon, H. Li, P. J. Walsh, *J. Am. Chem Soc.* **2005**, *127*, 16416.
[127] (a) H. Yamamoto, In *Lewis-Acids in Organic Synthesis*, Vol. 2, Wiley-VCH: Weinheim, **2000**; (b) see also ref. 40.

reactions. Furthermore, the functional group tolerance is low due to the problems in the preparation methods of these organozincs species. As presented in chapter 1.6. (p. 58 ff), benzylic zinc chlorides prepared by the direct insertion of magnesium into benzylic chlorides in the presence of zinc chloride and lithium chloride showed a significantly higher rate for the addition to carbonyl derivatives. This result is explained due to the presence of magnesium chloride which is generated *in situ* during the preparation of the zinc reagent (Scheme 68).Therefore, the addition of functionalized aryl-, alkyl- and benzylic zinc reagents, prepared by the Mg/$ZnCl_2$/LiCl method, to various carbonyl derivatives was investigated.[128]

2.2.2. Addition of functionalized organozinc reagents to carbonyl derivatives

Thus, the addition of PhZnI (**5b**) prepared by the insertion of zinc dust in the presence of LiCl into iodobenzene,[23] to 2-chlorobenzaldehyde (**61a**) required 72 h at 25 °C to reach completion and afforded (2-chlorophenyl)(phenyl)methanol (**101**) in 60% yield (Scheme 72). In contrast, by using PhZnI·$MgCl_2$ (**93b**) prepared by the reaction of iodobenzene with magnesium turnings, $ZnCl_2$ and LiCl,[117] a complete conversion was obtained within 1 h at 25 °C. The desired alcohol **101** was obtained in 88% yield. The presence of $MgCl_2$ (1.0 equiv) is responsible for this dramatic rate acceleration.[129]

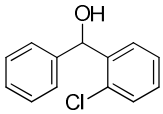


Scheme 72: Comparison of the reactivity of phenylzinc idodide (**5b**) and phenylzinc iodide·$MgCl_2$ (**93b**) towards the addition to 2-chlorobenzaldehyde (**61a**).

[128] For a crystal structure of PhZnBr·$MgCl_2$ obtained after transmetalation of PhMgBr with $ZnCl_2$, see: L. Jin, C. Liu, J. Liu, F. Hu, Y. Lan, A. S. Batsanov, J. A. K. Howard, T. B. Marder, A. Lei, *J. Am. Chem. Soc.* **2009**, *131*, 16656.
[129] (a) For Mg-salt enhanced reactivity of organometallic reagents, see: L. A. Paquette, *Encyclopedia of Reagents for Organic Synthesis*, Vol. 5, Wiley-VCH: New York, **1995**; (b) B. Marx, E. Henry-Basch, P. Fréon, *C. R. Chim.* **1967**, *264*, 527.

Also, by external addition of $MgCl_2$[130] to phenylzinc iodide (**5b**) or 2-chlorobenzaldehyde (**61a**), the addition rate is improved. Thus, premixing of $MgCl_2$ with phenylzinc iodide (**5b**) followed by the addition to 2-chlorobenzaldehyde (**61a**) provided the alcohol **101** within 2 h in 79% yield (Table 17). Furthermore, addition reaction of zinc reagent **5b** to a premixed solution of $MgCl_2$ with 2-chlorobenzaldehyde (**61a**) under similar reaction conditions led to the expected product within 2 h in 78% yield.

Table 17: Reaction of phenylzinc iodide (**5b**) with 2-chlorobenzaldehyde (**61a**) under mediation of additionally added $MgCl_2$.

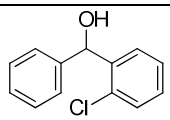
Entry	Zinc reagent	Additive	Time (h)[a]	Product	Yield (%)[b]
1	PhZnI·LiCl **5b**	$MgCl_2$ (premixed with zinc reagent **61a**)	2	 **101**	79
2	**5b**	$MgCl_2$ (premixed with aldehyde **61a**	2	**101**	78

[a] Reaction time at 25 °C. [b] Yield of isolated analytically pure product.

It is known that in the case of Grignard reagents the counterion plays an important role towards the addition reaction to carbonyl groups.[131] Therefore, the reaction described above was investigated regarding the influence of the zinc counterion. Thus, addition of phenylzinc chloride·$MgCl_2$ (**93c**) to 2-chlorobenzaldehyde (**61a**) provided the alcohol **101** in 60 min in 86% yield (entry 1 of Table 18). Reaction of PhZnBr·$MgCl_2$ (**93d**) with aldehyde **61a** led to full conversion in 30 min and provided the expected product in 93% yield (entry 2). As already demonstrated in Scheme 72, reaction of PhZnI·$MgCl_2$ (**93b**) with aldehyde **61a** furnished the desired alcohol **101** in 60 min in 88% (entry 3).

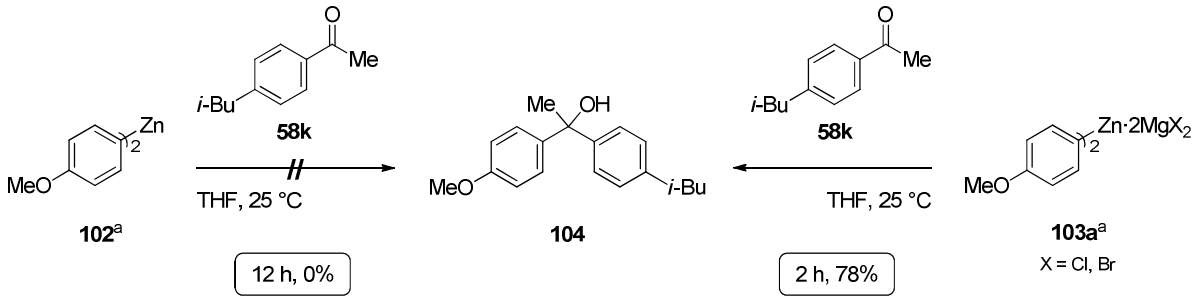
[130] $MgCl_2$ was freshly prepared as 0.5 M solution in THF by the reaction of magnesium turnings with 1,2-dichloroethane.
[131] M. T. Reetz, N. Harmat, R. Mahrwald, *Angew. Chem. Int. Ed.* **1992**, *31*, 342.

Table 18: Addition of various phenylzinc halides complexed with $MgCl_2$ to 2-chlorobenzaldehyde (**61a**).

Entry	Zinc reagent	Time (min)[a]	Product	Yield (%)[b]
1	$PhZnCl \cdot MgCl_2 \cdot LiCl$ **93c**	60	 **101**	86
2	$PhZnBr \cdot MgCl_2 \cdot LiCl$ **93d**	30	**101**	93
3	$PhZnI \cdot MgCl_2 \cdot LiCl$ **93b**	60	**101**	88

[a] Reaction time at 25 °C. [b] Yield of isolated analytically pure product.

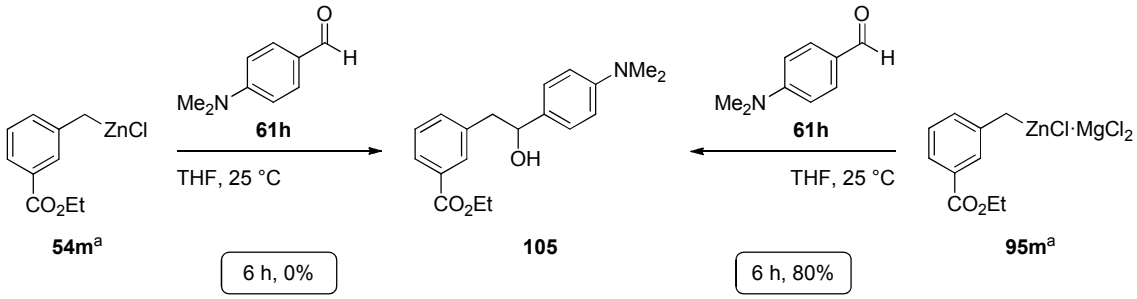
Diorganozinc reagents are more reactive than organozinc halides[132] and these reagents were found particularly well suited for addition reactions to ketones. The reaction of bis(4-methoxyphenyl)zinc (**102**) prepared from 4-bromoanisole (*n*-BuLi, -78 °C, 2 h; then $ZnCl_2$ (0.5 equiv)) to 4-isobutylacetophenone (**58k**) does not proceed (25 °C, 12 h). However, the corresponding diarylzinc reagent (**103a**) which was prepared by direct insertion of magnesium into 4-bromoanisole in the presence of LiCl and 0.5 equivalents of $ZnCl_2$ underwent a smooth addition to the ketone **58k** within 2 h at 25 °C and provided the tertiary alcohol **104** in 78% yield (Scheme 73). It is noteworthy that both Ar-groups are transferred to the ketone in the addition reaction.[133, 134]



Scheme 73: Addition of diarylzinc reagents **102** and **103a** to ketone **58k** in the presence or absence of $MgCl_2$.

[132] S. Matsubara, T. Ikeda, K. Oshima, K. Utimoto, *Chem. Lett.* **2001**, *30*, 1226.
[133] This experiment was performed by Sebastian Bernhardt and is given here for the sake of completeness.
[134] For further informations, see: Ph.D. thesis S. Bernhardt, LMU Munich.

Functionalized benzylic zinc reagents show the same behaviour and the addition of the ester-substituted benzylic zinc reagent **54m** prepared by the insertion of zinc dust in the presence of LiCl into 3-(ethoxycarbonyl)benzyl chloride (**53m**) to the aldehyde **61h** did not proceed at 25 °C (Scheme 74). Heating of the reaction mixture at 50 °C for 14 h only led to a conversion of 60%. In strong contrast, by using the same zinc reagent complexed with $MgCl_2$ (**95m**) and prepared by the reaction of 3-(ethoxycarbonyl)benzyl chloride (**53m**) with magnesium turnings in the presence of $ZnCl_2$ and LiCl, a full conversion was achieved within 6 h at 25 °C and the secondary alcohol **105** was isolated in 80% yield. Bisbenzylic zinc reagents of type **106** $(ArCH_2)_2Zn \cdot 2MgCl_2$ can also be prepared, as already discussed in chapter 1.6. and used for efficient addition reactions.

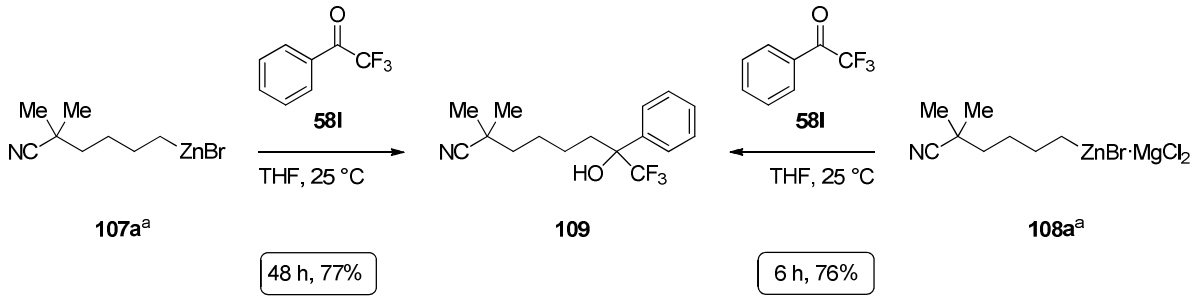


[a] Complexed LiCl has been omitted for the sake of clarity.

Scheme 74: Addition of benzylic zinc chlorides **54m** and **95m** to benzaldehyde **61h**.

Finally, the functionalized alkylzinc reagent **107a** (no $MgCl_2$ present) and **108a** (complexed with $MgCl_2$) showed a similar reactivity difference.[135] Thus, the reaction of **107a** with trifluoromethyl phenyl ketone (**58l**) required 48 h at 25 °C, whereas by using **108a**, a complete conversion is reached within 6 h at 25 °C leading to the tertiary alcohol **109** in 76-77% yield (Scheme 75).

[135] For the preparation of alkylzinc reagents by the direct insertion of magnesium into alkyl bromides in the presence of $ZnCl_2$ and LiCl, see: T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, in press.



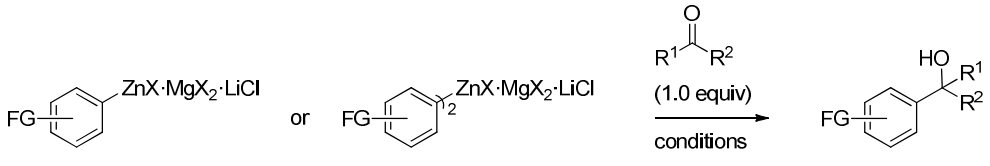
[a] Complexed LiCl has been omitted for the sake of clarity.

Scheme 75: Addition of cyano-substituted alkylzinc reagents **107a** and **108a** to ketone **58l**.

These $MgCl_2$-mediated addition reactions have an excellent reaction scope (Table 19 and Table 20). Thus, tolylzinc iodide·$MgCl_2$ (**93e**) added at 25 °C to 4-cyanobenzaldehyde (**61i**) within 13 h affording the alcohol **110a** in 73% yield (entry 1 of Table 19). Electron-rich heteroarylzinc reagent **93f** added to benzaldehyde **61i** furnishing the heterobenzylic secondary alcohol **110b** in 98% yield (entry 2). Interestingly, a copper-free acylation reaction is possible. Thus, the electron-rich arylzinc reagent 4-(trimethylsilyl)phenylzinc bromide·$MgCl_2$ (**93g**) reacted with 4-chlorobenzoyl chloride (**60d**) leading to the benzophenone derivative **110c** in 81% yield (entry 3). As indicated above (Scheme 73), it is advantageous to use bisarylzinc derivative of type **103** ($Ar_2Zn·2MgX_2·2LiCl$; 0.6 equiv; X = Cl, Br).[134] In these cases, both aryl-groups are transferred in the carbonyl addition reaction. Thus, the reaction of bis(2-trifluoromethylphenyl)zinc·$2MgX_2$ (**103b**; X = Cl, Br) proceeded smoothly with the heterocyclic aldehyde **61j** and furnished the pyridyl alcohol **110d** in 82 % yield (entry 4). Furthermore, the addition of the electron-poor zinc reagent **103c** to the aldehyde **61k** led to the desired alcohol **110e** in 85% yield (entry 5). The addition of bis(4-methoxyphenyl)zinc·$2MgX_2$ (**103a**; X = Cl, Br) to 4-cyanoacetophenone (**58m**) provided the tertiary alcohol **110f** within 1 h in 62% yield (entry 6). The electron-rich arylzinc reagent bis(4-trimethylsilylphenyl)zinc·$2MgX_2$ (**103d**; X = Cl, Br) reacted with 4-cyanobenzaldehyde (**61i**) and the benzhydryl alcohol **110g** was obtained in almost quantitative yield (entry 7). Furthermore, bis(4-*N*,*N*-dimethylaminophenyl)zinc·$2MgX_2$ (**103e**; X = Cl, Br) reacted with dicyclopropyl ketone (**58g**) in 24 h leading to the desired product **110h** (74%; entry 8). Also, bis(2-*N*,*N*-dimethylaminophenyl)zinc·$2MgX_2$ (**103f**; X = Cl, Br) reacted smoothly with the benzaldehyde **61l** providing the alcohol **110i** within 3 h reaction time in 93% yield (entry 9). The bis(5-pyrazolyl)zinc species **103g** as well as the bis(1,2-oxazol-4-

yl)zinc compound **103h** added to various substituted benzaldehydes providing heterocyclic secondary alcohols (**110j-m**) in 76-91% yield (entries 10-13).

Table 19: Addition of aryl- and heteroarylzinc reagents of type **93** and **103** to various carbonyl derivatives.



93e-g (1.2 equiv) **103a-h** (0.6 equiv) **110a-m** 62-98%

FG = Me, CF_3, Cl, OMe, TMS, NMe_2; X = Cl, Br, I; R^1 = aryl, alkyl; R^2 = H, alkyl, Cl

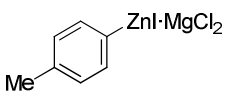
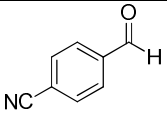
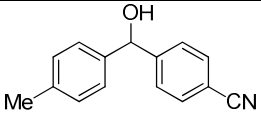
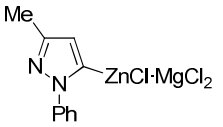
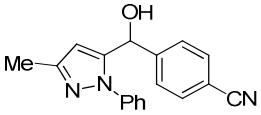
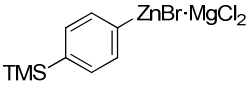
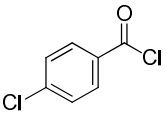
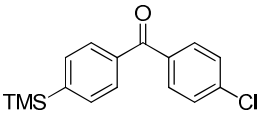
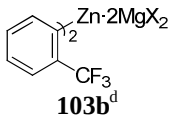
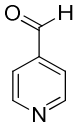
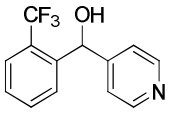
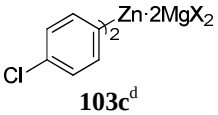
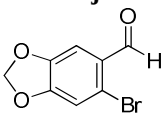
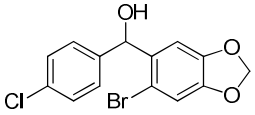
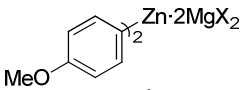
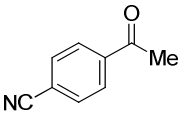
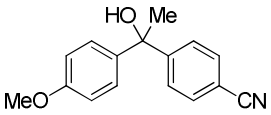
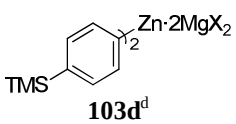
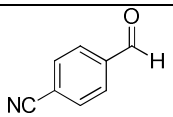
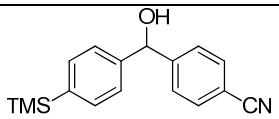
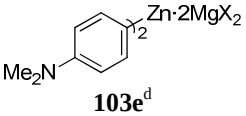
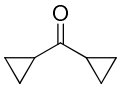
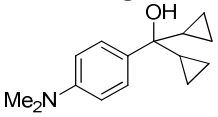
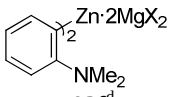
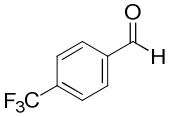
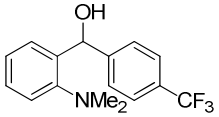
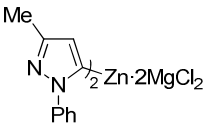
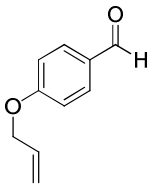
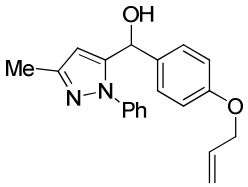
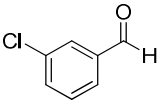
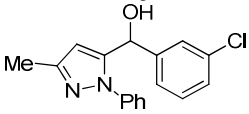
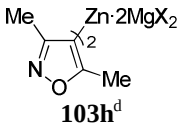
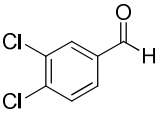
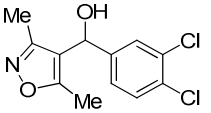
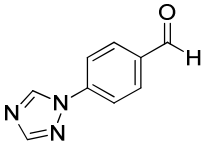
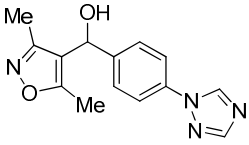
Entry	Zinc reagent[a]	Carbonyl derivative	Time (h)[b]	Product	Yield (%)[c]
1	 **93e**	 **61i**	13	 **110a**	73
2	 **93f**	**61i**	10	 **110b**	98
3	 **93g**	 **60d**	18[e]	 **110c**	81
4	 **103b**[d]	 **61j**	8	 **110d**	82
5	 **103c**[d]	 **61k**	10	 **110e**	85
6	 **103a**[d]	 **58m**	1	 **110f**	62

Table 19 continued

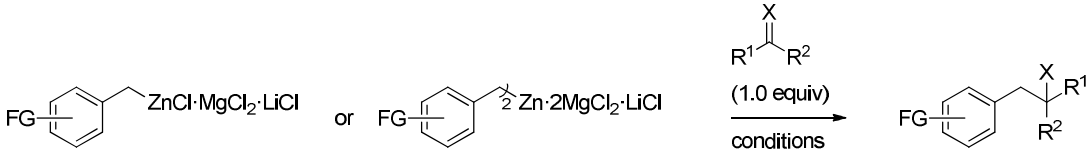
7	 **103d**[d]	 **61i**	6	 **110g**	95
8	 **103e**[d]	 **58g**	24[e]	 **110h**	74
9	 **103f**[d]	 **61l**	3	 **110i**	93
10	 **103g**	 **61m**	15	 **110j**	91
11	**103g**	 **61c**	6	 **110k**	80
12	 **103h**[d]	 **61b**	24	 **110l**	83
13	**103h**[d]	 **61n**	14	 **110m**	76

[a] Complexed LiCl has been omitted for the sake of clarity. [b] All reactions are performed at 25 °C unless otherwise indicated. [c] Isolated yield of analytically pure product. [d] X = Cl, Br. [e] Reaction performed at 50 °C.

Benzylic zinc reagents are similarly activated by the presence of $MgCl_2$. Thus, electron-poor 4-fluorobenzylzinc chloride·$MgCl_2$ (**95c**) added to α-tetralone (**58e**) and acetophenone **58m** providing the products **111a-b** in 74-80% yield (entries 1 and 2 of Table 20). Moreover, addition of zinc reagent **95c** to benzophenone **58n** provided the tertiary alcohol **111c** in 78% yield (entry 3). 4-Methoxybenzylzinc chloride·$MgCl_2$ (**95i**) reacted well with 4-(dimethylamino)benzaldehyde (**61h**) and 4-acetylbenzonitrile (**58m**) furnishing the benzylic alcohols **111d-e** in 74-99% yield (entries 4 and 5). The ester-substituted benzylic zinc reagent **95m** smoothly added within 16 h to trifluoromethyl phenyl ketone (**58l**) leading to the alcohol

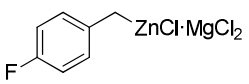
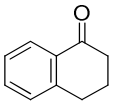
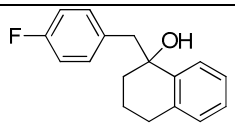
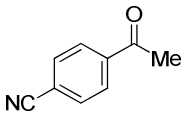
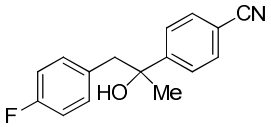
111f in 87% yield (entry 6). Instead of using benzylic zinc chlorides of type **95** ($ArCH_2ZnCl \cdot MgCl_2$; 1.2 equiv) it is also possible to use bisbenzylic zinc compounds of type **106** ($(ArCH_2)_2Zn \cdot 2MgCl_2$; 0.6 equiv). Usually, both benzylic groups are transferred to the electrophile. Recently, it has been reported that both aryl *N*-(2-pyridylsulfonyl)aldimines and Cu(II)-catalysis are required for adding various zinc reagents.[136] However, the presence of $MgCl_2$ allows a direct addition of organozincs to *N*-tosylimines. Thus, the reaction of bis(3-(ethoxycarbonyl)benzyl)zinc·$2MgCl_2$ (**106a**) with the *N*-tosylimine **61o** affords the expected *N*-tosylamine derivative **111g** in 86% yield within 24 h at 25 °C (entry 7). Furthermore, the benzylic zinc reagent **106a** added to 4-fluorophenylmethyl ketone (**58o**; 50 °C, 24 h) leading to the tertiary alcohol **111h** in 68% yield (entry 8). Electron-rich methoxy-substituted benzylic zinc reagent **106b** reacted well with dicyclopropyl ketone (**58g**) within 1 h at 25 °C and furnished the benzylic alcohol **111i** within 1 h at 25 °C in 84% yield (entry 9).

Table 20: Addition of benzylic zinc reagents of type **95** and **106** to different carbonyl derivatives.



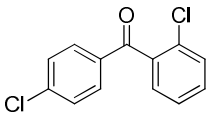
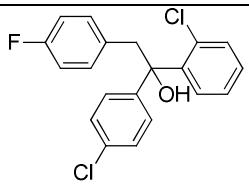
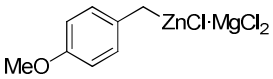
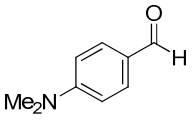
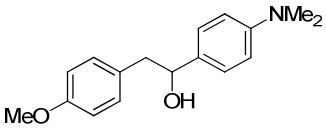
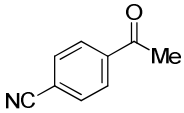
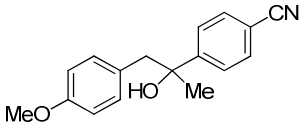
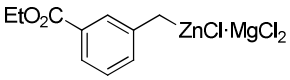
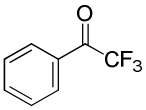
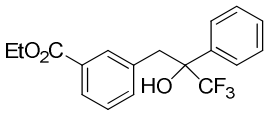
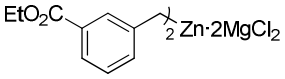
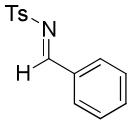
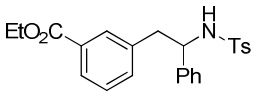
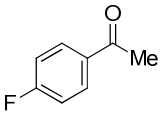
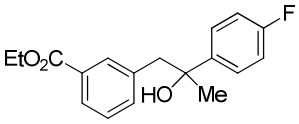
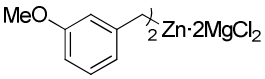
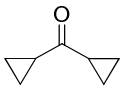
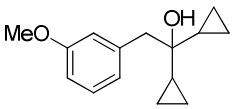
95c-m (1.2 equiv) **106a-b** (0.6 equiv) **111a-i** 68-99%

FG = F, OMe, CO_2Et X = O, N; R^1 = aryl, alkyl; R^2 = alkyl, aryl, H

Entry	Zinc reagent[a]	Carbonyl derivative	Time (h)[b]	Product	Yield (%)[c]
1	 **95c**	 **58e**	9	 **111a**	74
2	**95c**	 **58m**	15	 **111b**	80

[136] (a) J. Esquivias, R. G. Arrayas, J. C. Carretero, *Angew. Chem. Int. Ed.* **2007**, *46*, 9257; (b) A. Cote, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 2771; (c) Using benzylic zinc reagent **95m** (1.2 equiv) under similar reaction conditions led to 90% conversion of the aldimine **61n**.

Table 20 continued

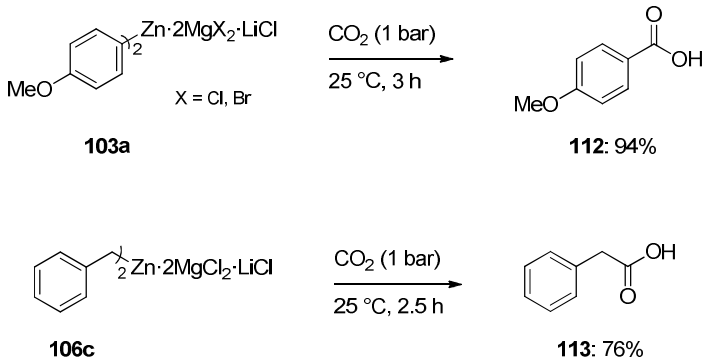
3	**95c**	 **58n**	48	 **111c**	78
4	 **95i**	 **61h**	1	 **111d**	99
5	**95i**	 **58m**	14	 **111e**	74
6	 **95m**	 **58l**	16	 **111f**	87
7	 **106a**	 **61o**	24	 **111g**	86
8	**106a**[d]	 **58o**	24[e]	 **111h**	68
9	 **106b**	 **58g**	1	 **111i**	84

[a] Complexed LiCl has been omitted for the sake of clarity. [b] All reactions are performed at 25 °C unless otherwise indicated. [c] Isolated yield of analytically pure product. [d] 1.2 Equivalents were used. [e] Reaction performed at 50 °C.

Remarkably, the presence of $MgCl_2$ allows the addition of aryl and benzylic zinc reagents to CO_2 (1 bar) at 25 °C in THF without the need of a polar solvent[137] or transition metal catalysis.[138] Thus, bis(4-methoxyphenyl)zinc·2MgX_2 (**103a**; X = Cl, Br) added in THF to CO_2 (1 bar, 25 °C,

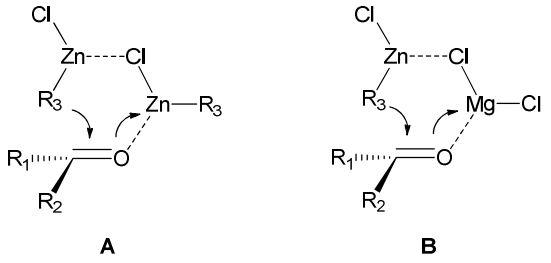
[137] K. Kobayashi, Y. Kondo, *Org. Lett.* **2009**, *11*, 2035.
[138] C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 7826.

3 h) providing 4-methoxybenzoic acid (**112**) in 94% yield (Scheme 76).[139] Furthermore, reaction of bis(benzylzinc)·2$MgCl_2$ (**106c**) with CO_2 led to phenylacetic acid (**113**) in 76% yield.



Scheme 76: Preparation of carboxylic acids **112** and **113** by the direct reaction of organozinc reagents **103** and **106** with carbon dioxide under mediation of $MgCl_2$.

The acceleration effect of $MgCl_2$ may be rationalized by the following explanations. The usual 6-membered transition state (**A**) is modified by the presence of $MgCl_2$ (Scheme 77).[140] Thus, the organozinc regent R^3ZnCl which complexes the carbonyl group, is replaced by $MgCl_2$ (see the transition state **B**). Since $MgCl_2$ is a stronger Lewis-acid than the zinc compound R^3ZnCl, a more effective activation of the carbonyl group towards the addition of the zinc reagent is expected.



Scheme 77: Proposed $MgCl_2$-modified six membered transition state for the addition of R^3ZnCl to carbonyl reagents (R^1R^2CO).

The results described above showed that the addition of an organometallic reagent to a carbonyl group depends not only on the reactivity of the carbon-metal bond, but also on a Lewis-acid

[139] In a comparative experiment, performed by S. Bernhardt and given here for the sake of completeness, 4-MeO(C_6H_4)ZnBr·$MgCl_2$·LiCl added to carbon dioxide within 6 h reaction time under similar reaction conditions to reach full conversion of the zinc reagent; see ref. 134.

[140] (a) C. Lambert, F. Hampel, P. von R. Schleyer, *Angew. Chem. Int. Ed.* **1992**, *31*, 1209; (b) M. Uchiyama, S. Nakamura, T. Ohwada, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 10897.

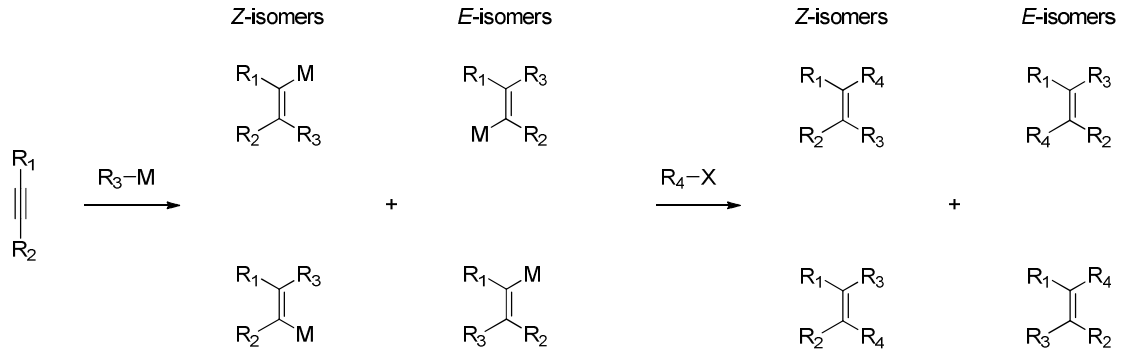
activation of this carbonyl group. Both of these effects should be considered for predicting the addition rates of organometallics. Similar synergetic effects have been reported.[141,142]

[141] E. Negishi, *Chem. Eur. J.* **1999**, *5*, 411.
[142] (a) Y. N. Belokon, W. Clegg, R. W. Harrington, C. Young, M. North, *Tetrahedron* **2007,** *63*, 5287; (b) Y. N. Belokon, *Pure Appl. Chem.* **1992**, *64*, 1917; (c) Y. N. Belokon, W. Clegg, R. W. Harrington, V. I. Maleev, M. North, M. O. Pujol, D. L. Usanov, C. Young, *Chem. Eur. J.* **2009**, *15*, 2148.

3. Carbocupration of Alkynes With Functionalized Diorganozinc Reagents

3.1. Introduction

The stereo- and regioselective formation of tetrasubstituted olefins is still a challenge in the field of organic chemistry.[143] One major way to obtain these substances is the direct carbometalation of alkynes. Several possible products can be formed as illustrated in Scheme 78.



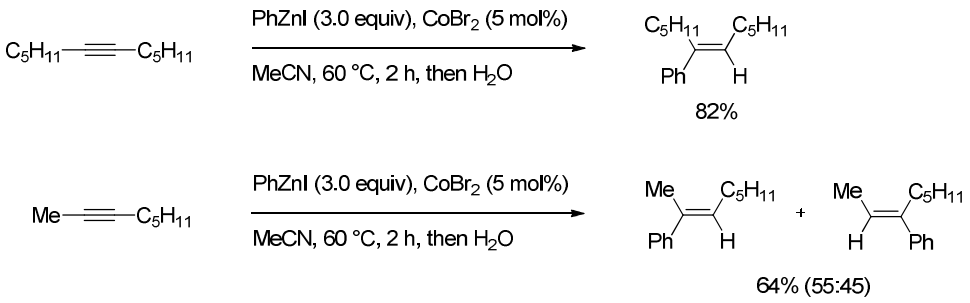
Scheme 78: Possible isomers obtained by carbometalation reactions of alkynes.

A range of carbometalation reactions is known today mainly involving copper, magnesium, tin and boron reagents.[144] Recently, it was shown that arylzinc reagents were used for carbometalation reactions of alkynes in the presence of catalytic amounts of cobalt dibromide.[145] In this work the use of symmetrical alkynes is mainly described. In the case of unsymetrically substituted alkynes without directing group, the selectivity of the regioisomers decreases (Scheme 79).

[143] (a) J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841; (b) O. Reiser, *Angew. Chem. Int. Ed.* **2006**, *45*, 2838; (c) K. Itami, T. Nokami, Y. Ishimura, K. Mitsudo, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2001,** *123*, 11577; (d) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; (e) D. Hamels, P. M. Dansette, E. A. Hillard, S. Top, A. Vessieres, P. Herson, G. Jaouen, D. Mansuy, *Angew. Chem. Int. Ed.* **2009**, *48*, 9124; (f) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128; (g) A. Abramovitch, I. Marek, *Eur. J. Org. Chem.* **2008**, 4924; (h) I. Marek, *Chem. Eur. J.* **2008**, *14*, 7460.

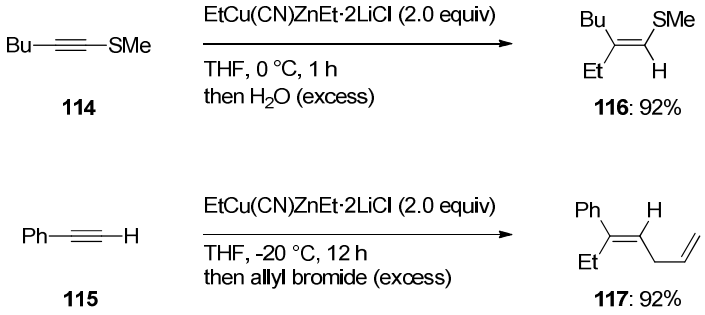
[144] (a) A. B. Flynn, W. W. Ogilvie, *Chem. Rev.* **2007**, *107*, 4698; (b) C. Zhou, R. C. Larock, *Org. Lett.* **2005**, *7*, 259; (c) H. Oda, M. Morishita, K. Fugami, H. Sano, M. Kosugi, *Chem. Lett.* **1996**, *25*, 811; (d) K. Itami, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670; (e) R. B. Miller, M. I. Al-Hassan, *J. Org. Chem.* **1985**, *50*, 2121.

[145] K. Murakami, H. Yorimitsu, K. Oshima, *Org. Lett.* **2009**, *11*, 2373.



Scheme 79: Arylzincation of alkynes by cobalt catalysis.

Furthermore, functionalized organozinc reagents can be transmetalated with stoichiometric amounts of copper(I)- salts providing highly reactive organocopper reagents which were used for carbometalation reactions of alkynes **114** and **115** and, after subsequent reaction of the intermediate vinylic cuprate with different electrophiles, substituted olefins **116** and **117** were obtained (Scheme 80).[146]

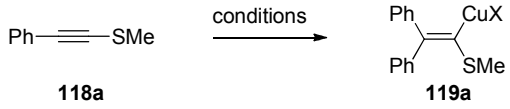


Scheme 80: Copper(I)-mediated carbometalation reactions on various acetylenes with alkylzincs.

3.2. Carbocupration reaction on thioether-substituted alkynes

Copper(I)-mediated carbocupration reactions using arylzinc reagents are less investigated probably due to the difficulties in the preparation method of the organozincs. Since functionalized arylzinc reagents are readily available, these reagents were used in carbometalation reactions. A comparative study was performed showing the influence of the preparation method of the zinc reagent on the following carbocupration (Scheme 81).

[146] (a) S. A. Rao, P. Knochel, *J. Am. Chem. Soc.* **1991**, *113*, 5735; (b) A. Sidduri, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 7579; (c) A. Levin, A. Basheer, I. Marek, *Synlett* **2010**, 329; (d) C. Meyer, I. Marek, G. Courtemanche, J.-F. Normant, *Tetrahedron* **1994**, *50*, 11665; (e) For a nickel-catalyzed carbozincation of alkynes, see: T. Stüdemann, P. Knochel, *Angew. Chem. Int. Ed.* **1997**, *36*, 93.



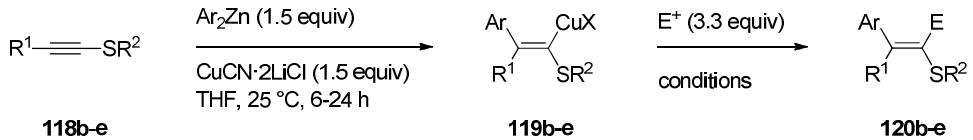
PhZnI·LiCl (**5b**; 3.0 equiv) — conversion of **118a**: < 10%
CuCN·2LiCl (1.5 equiv) — (25 °C, 23 h)

$Ph_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**103i**; 1.5 equiv) — full conversion of **118a**
CuCN·2LiCl (1.5 equiv) — (25 °C, 23 h)

Scheme 81: Influence of $MgCl_2$ on the carbometalation of alkyne **118a** with phenylzinc reagents.

Thus, the transmetalation of PhZnI (**5b**, 3.0 equiv) which was prepared by the direct insertion into phenyliodide in the presence of LiCl with CuCN·2LiCl (1.5 equiv) provided the corresponding arylcopper reagent which did not react with alkyne **118a** (1.0 equiv). On the other hand, the related organocopper compound prepared by the reaction of CuCN·2LiCl (1.5 equiv) with $Ph_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**103i**, 1.5 equiv; prepared by transmetalation using PhMgCl (3.0 equiv) and $ZnCl_2 \cdot LiCl$ solution (1.5 equiv)) smoothly led to the vinylic copper intermediate **119a** within 23 h at 25 °C.[147] One can say that in the presence of stoichiometric amounts of $MgCl_2$ the carbometalation reaction occurs. Having this novel reaction in hand, several thioether-substituted alkynes were subjected to copper(I)-mediated carbometalation reaction with functionalized diorganozinc reagents.

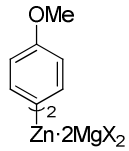
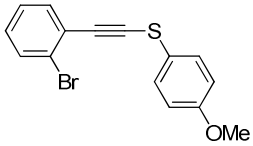
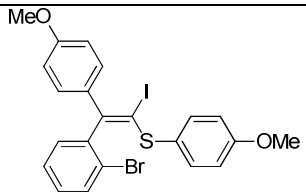
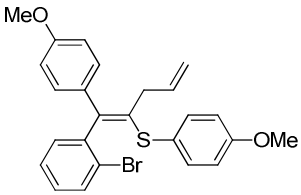
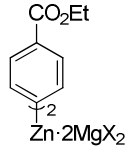
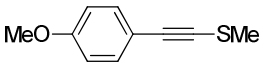
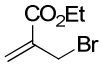
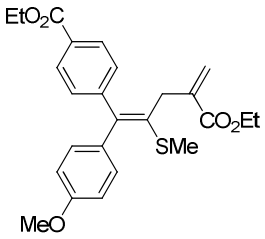
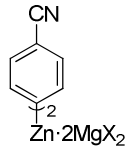
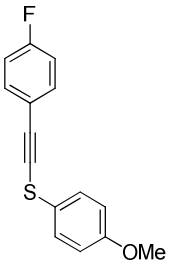
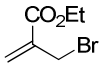
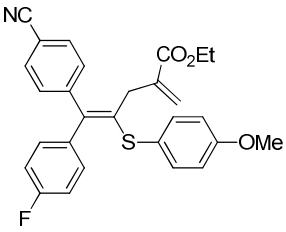
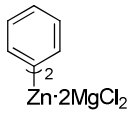
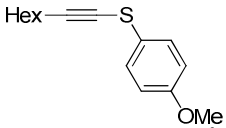
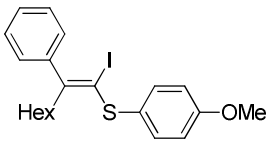
Table 21: Carbocupration of thioether-substituted alkynes with functionalized diarylzinc reagents.



118b-e — **119b-e** — **120b-e** 51-91%

R^1, R^2 = Alkyl, Aryl

[147] For the use of vinylic sulfides, see: (a) A. Sabarre, J. Love, *Org. Lett.* **2008**, *10*, 3941; (b) H. Kuniyasu, A. Ohtaka, T. Nakazono, M. Kinomoto, H. Kurosawa, *J. Am. Chem. Soc.* **2000,** *122*, 2375; (c) M. Su, W. Yu, Z. Jin, *Tetrahedron Lett.* **2001**, *42*, 3771; (d) P. A. Magriotis, T. J. Doyle, K. D. Kim, *Tetrahedron Lett.* **1990**, *31*, 2541; (e) S. Kanemura, A. Kondoh, H. Yorimitsu, K. Oshima, *Sythesis* **2008**, 2659; (f) N. Taniguchi, *Tetrahedron* **2009**, *65*, 2782.

Entry	Zinc reagent[a]	Alkyne[b]	Electrophile[c]	Product[d]	Yield (%)[e]
1	 **103a**	 **118b** (25 °C, 6 h)	I_2 (-40 °C, 10 min)	 **120b** (E/Z = 99:1)[e]	82
2	**103a**	**118b** (25 °C, 6 h)	allyl bromide (-60 to 0 °C, 1 h)	 **120c** (E/Z = 99:1)[e]	91
3	 **103j**	 **118c** (25 °C, 24 h)[d]	 **55b** (-40 to 0 °C, 1 h)	 **120d** (E/Z = 94:6)[e]	68
4	 **103k**	 **118d** (25 °C, 16 h)[d]	 **55b** (-60 to -20 °C, 2 h)	 **120e** (E/Z = 68:32)[e]	51
5	 **103i**	 **118e** (25 °C, 15 h)[d]	I_2 (-40 °C, 10 min)	 **120f** (E/Z = 96:4)[e]	80[148]

[a] LiCl has been omitted for the sake of clarity; X = Cl, Br. [b] Reaction conditions for the carbometalation step. First, the zinc reagent (1.5 equiv) was transmetalated using CuCN·2LiCl (1.5 equiv; -20 °C, 15 min). [c] Conditions for the reaction with the electrophile. [d] *E*/*Z*-ratio determined by 2D-NMR. [e] Yield of isolated analytically pure product.

Thus, the reaction of bis(4-methoxyphenyl)zinc·2MgX (**103a**; 1.5 equiv; X = Cl, Br) with the alkyne **118b** (1.0 equiv) in the presence of CuCN·2LiCl (1.5 equiv) provided the vinylic copper

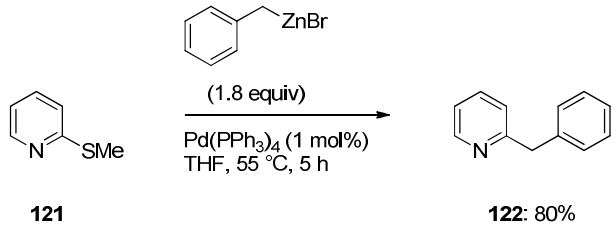
[148] The experiment was performed by Cora Dunst and is given here for the sake of completeness. For further informations, see: Ph.D. thesis Cora Dunst, LMU Munich.

intermediate **119b** within 6 h at 25 °C. Its subsequent reaction with iodine led to the vinylic iodide **120b** in 82% yield with an excellent *E*/*Z*-ratio determined by 2D-NMR (entry 1 of Table 21). Similarly, the copper species **119b** was smoothly allylated using allyl bromide providing the alkene **120c** in 91% yield (E/Z-ration = 99:1, entry 2). Furthermore, the alkyne **118c** was prone to stereoselective Cu(I)-mediated carbometalation reaction using the ester-substituted arylzinc reagent **103j** and provided the expected olefin **120d** after allylation reaction with ethyl (2-bromomethyl)acrylate (**55b**) in 68% yield (entry 3). The fluoro-substituted acetylene **118d** was used in the carbometalation reaction with bis(4-cyanophenyl)zinc·2MgX_2 (**104k**; X = Cl, Br) and the desired vinyl sulfide **120e** was obtained in 51% yield with an *E*/*Z*-ration of 68:32 (entry 4). Finally, the alkylacetylene **118e** underwent smooth carbometalation with bis(phenyl)zinc·$MgCl_2$ (**104k**) and led to the vinylic iodide **120f** in 80% yield (entry 5).

4. Transition Metal-Catalyzed Cross-Coupling Reactions of Functionalized Organozinc Reagents With Methylthio-Substituted N-Heterocycles

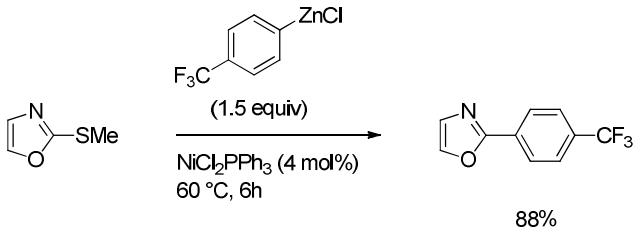
4.1. Introduction

Transformation of a carbon-sulfur bond into a carbon-carbon bond via transition metal catalysis is an efficient tool in organic synthesis, as shown in the introduction. Nevertheless, organozinc reagents are rarely used for such cross-couplings. One of the first documented examples for the Pd-catalyzed reaction of heterocyclic thioethers with organozinc reagents was the reaction of methylthio-substituted pyridine **121** with benzylzinc bromide in the presence of $Pd(PPh_3)_4$ at elevated temperatures leading to the heterodiarylmethane **122** (Scheme 82).[149]



Scheme 82: Palladium-catalyzed cross-coupling reaction of benzylzinc bromide with 2-(methylthio)pyridine (**121**) at elevated temperatures.

Very recently, it was shown that the functionalization of oxazoles was achieved by Pd- or Ni-catalyzed reactions of methylthio-substituted oxazoles using arylzinc reagents (Scheme 83).[150]



Scheme 83: Ni-catalyzed cross-coupling reaction for the functionalization of oxazole derivatives.

[149] (a) M. E. Angiolelli, A. L. Casalnuovo, T. P. Selby, *Synlett* **2000**, 905; (b) J. Srogl, W. Liu, D. Marshall, L. S. Liebeskind, *J. Am. Chem. Soc.* **1999**, *121*, 9449; (c) For Pd-catalyzed reactions of organozinc reagents with thioimidates, see: (i) I. Ghosh, P. A. Jacobi, *J. Org. Chem.* **2002**, *67*, 9304; (ii) W. P. Roberts, I. Ghosh, P. A. Jacobi, *Can. J. Chem.* **2004**, *82*, 279; (iii) D. M. Mans, W. H. Pearson, *J. Org. Chem.* **2004**, *69*, 6419; (d) For cross-coupling reactions of vinyl sulfides with benzylic and allylic zinc reagents under nickel catalysis, see: Y. Baba, A. Toshimitsu, S. Matsubara, *Synlett* **2008**, 2061.

[150] K. Lee, C. M. Counceller, J. P. Stambuli, *Org. Lett.* **2009**, *11*, 1457.

4.2. Palladium-catalyzed cross-coupling reactions of functionalized organozinc reagents with methylthio-substituted N-heterocycles

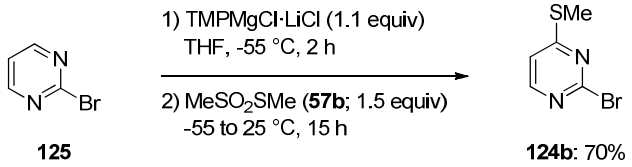
It can be difficult to introduce a halogen substituent to heterocyclic systems. Therefore, the use of the methylthio-group for cross-couplings has a great advantage due to the easy introduction of this group as well as the long-time stability of thioether-substituted heterocycles.[151] The classical way to prepare methylthio-substituted heterocycles are condensation reactions of for example thiourea with 1,3-dioxo systems followed by methylation of the resulting thiol.[152] Alternatively, substitution reactions of a heteroaromatic halogen using NaSMe in DMF are possible.[153] Thus, 3-chloro-6-methoxypyradazine (**123**) was converted to the expected methylthio-product **124a** in 69% yield (Scheme 84).

123 **124a**: 69%

Scheme 84: Preparation of methylthio-substituted pyridazine **124a** by classical substitution reaction.

Also, by using the selective bases TMPMgCl·LiCl or TMP_2Mg·2LiCl several heterocycles can be easily metalated and reacted with various sulfonothioates in order to introduce the thioether moiety to the heterocyclic system.[83, 154] Thus, 2-bromopyridine (**125**) was reacted with TMPMgCl·LiCl and subsequent reaction with *S*-methyl methanesulfonothioate (**57b**) led to the desired methylthio-substituted pyrimidine **124b** in 70% yield (Scheme 85).[155]

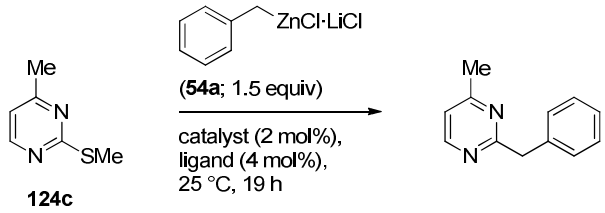
[151] For reactions of organomagnesium as well as organozinc reagents with tetramethylthiuram disulfide, see: (a) A. Krasovskiy, A. Gavryushin, P. Knochel, *Synlett* **2005**, 2691; (b) A. Krasovskiy, A. Gavryushin, P. Knochel, *Synlett* **2006**, 792.
[152] (a) D. G. Crosby, R. V. Berthold, H. E. Johnson, *Org. Synth.* **1963**, *43*, 68; (b) L. Bethge, D. V. Jarikote, O. Seitz, *Bioorg. Med. Chem.* **2008**, *16*, 114; (c) J. E. Arguello, L. C. Schmidt, A. B. Penenory, *Org. Lett.* **2003**, *5*, 4133.
[153] (a) L. Testaferri, M. Tiecco, M. Tingoli, D. Bartoli, A. Massoli, *Tetrahedron* **1985**, *41*, 1373; (b) B. A. Johns, K. S. Gudmundsson, E. M. Turner, S. H. Allen, V. A. Samano, J. A. Ray, G. A. Freeman, F. L. Boyd, Jr., C. J. Sexton, D. W. Selleseth, K. L. Creech, K. R. Moniri, *Bioorg. Med. Chem.* **2005**, *13*, 2397.
[154] (a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; (b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; (c) G. Chauviere, B. Bouteille, B. Enanga, C. de Albuquerque, S. L. Croft, M. Dumas, J. Perie, *J. Med. Chem.* **2003**, *46*, 427.
[155] M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497.



Scheme 85: Preparation of methylthio-substituted pyrimidine (**124b**) by metalation procedures.

Furthermore, the catalytic system for the Pd-catalyzed cross-coupling of organozinc reagents with heterocyclic thioethers was optimized to perform this reaction at ambient temperature. Thus, the reaction of benzylzinc chloride (**54a**) with 4-methyl-2-(thiomethyl)pyrimidine (**124c**) in the absence of any catalyst led to no conversion of the pyrimidine **124c** (entry 1 of Table 22). Using $PdCl_2$(dppe) as well as $Pd(dba)_2$/tfp no conversion of the pyrimidine **124c** was observed too (entries 2 and 3). By using PEPPSI-IPr, the cross-coupling took place and after 19 h only 27% starting material was left (entry 4). The best catalytic system for the cross-coupling of organozinc reagents with heterocyclic thioethers was found to be $Pd(OAc)_2$/S-Phos (entry 5).[84] Additionally, is was observed that these cross-couplings can also be performed using a cheap nickel catalyst. Thus, reaction of pyrimidine **124c** with benzylzinc chloride (**54a**) using $NiCl_2(PPh)_2$ led to full conversion of the heterocyclic species **124c** within 12 h at 60 °C (entry 6).

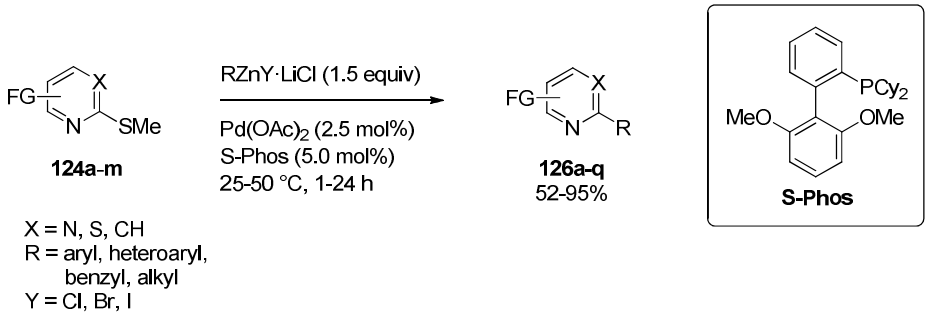
Table 22: Screening of various transition-metal-ligand systems for the cross-coupling of methylthio-substituted pyrimidine **124c** with benzylzinc chloride (**54a**).



Entry	Catalyst (2 mol%)	Ligand (4 mol%)	Conversion[a]
1	-	-	0
2	$PdCl_2$	dppe	0
3	$Pd(dba)_2$	tfp	<5
4	PEPPSI-IPr	-	73
5	$Pd(OAc)_2$	S-Phos	93
6	$NiCl_2$	PPh	95 (60 °C, 12 h)

[a] Conversions were determined by GC-analysis of a hydrolyzed reaction aliquot using tetradecane as internal standard.

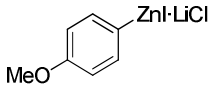
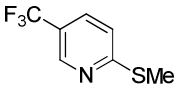
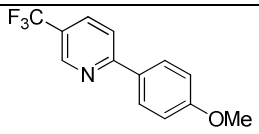
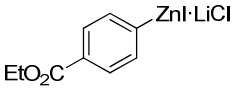
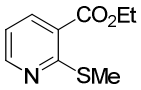
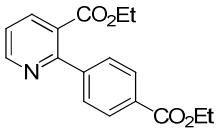
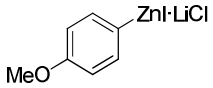
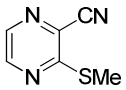
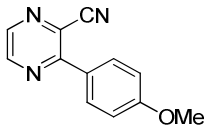
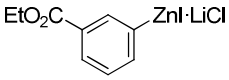
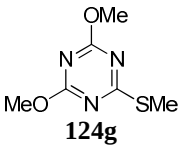
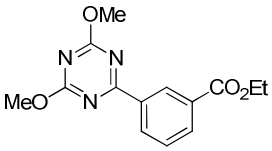
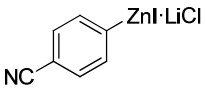
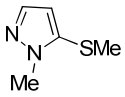
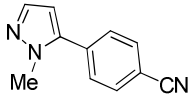
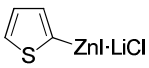
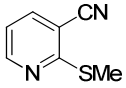
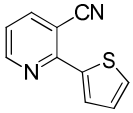
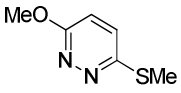
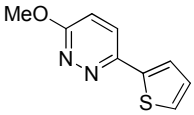
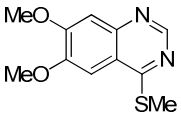
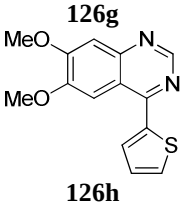
Having a robust catalytic system in hand, several organozinc reagents were reacted with different methylthio-substituted heterocyclic compounds. These cross-couplings were mainly performed at 25 °C (Scheme 86).



Scheme 86: Pd-catalyzed cross-coupling reactions of functionalized organozinc reagents with methylthio-substituted N-heterocycles.

Thus, the reaction of 4-methoxyphenylzinc iodide (**5c**) with 2-(methylthio)-5-(trifluoromethyl)pyridine (**124d**) provided the cross-coupling product **126a** in 95% yield (entry 1 of Table 23). Smooth cross-coupling of the nicotinic acid derivative **124e** with 4-(ethoxycarbonyl)phenylzinc iodide (**5a**) led to the heterocyclic diester **126b** in 67% yield (entry 2) Cyano-substituted pyrazine **124f** was smoothly converted to the substituted pyrazine **126c** in 57% yield (entry 3). Furthermore, electron-rich triazines underwent the cross-coupling as well. Thus, dimethoxy-substituted triazine **124g** reacted with 3-(ethoxycarbonylphenyl)zinc iodide (**5d**) furnishing the triazine **126d** in 84% yield (entry 4). Furthermore, Pd-catalyzed cross-coupling of the substituted pyrazole **124h** with 4-cyanophenylzinc iodide (**5e**) led to the expected product **126e** in 52% yield (entry 5). Moreover, heterocyclic zinc reagents readily participate in the cross-coupling under these conditions. Thus, 2-thienylzinc iodide (**5f**) reacted with the substituted pyridine **124i** and pyridazine **124a** as well as the quinazoline **124j** leading to the heterocyclic biphenyls **126f**-**h** in 91-95% yields (entries 6-8).

Table 23: Reaction of aromatic and heteroaromatic zinc reagents (**5**) with methylthio-substituted N-heterocycles (**124**) under palladium catalysis.

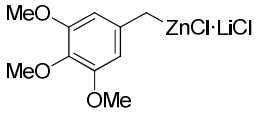
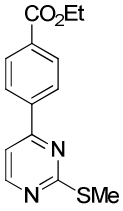
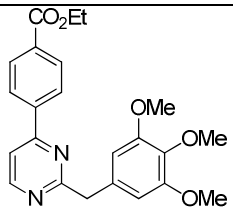
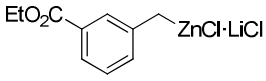
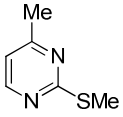
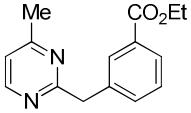
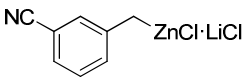
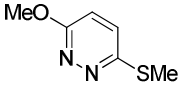
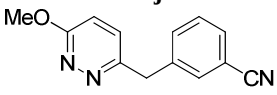
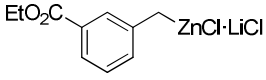
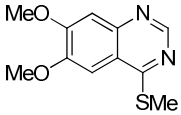
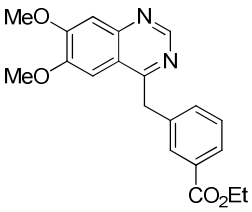
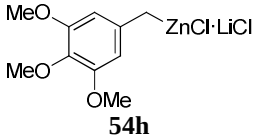
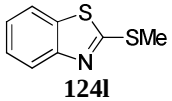
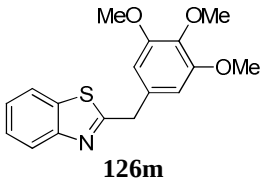
Entry	Aryl- and heteroarylzinc reagent	Electrophile	Time (h)[a]	Product	Yield (%)[b]
1	 **5c**	 **124d**	1	 **126a**	95
2	 **5a**	 **124e**	6	 **126b**	67
3	 **5c**	 **124f**	5	 **126c**	57
4	 **5d**	 **124g**	21	 **126d**	84
5	 **5e**	 **124h**	1.5[c]	 **126e**	52
6	 **5f**	 **124i**	18	 **126f**	93
7	**5f**	 **124a**	5[c]	 **126g**	91
8	**5f**	 **124j**	10	 **126h**	95

[a] The reaction time for the Pd-catalyzed cross-coupling is given. All reactions were performed at 25 °C unless otherwise indicated. [b] Yield of isolated analytically pure product. [c] The reaction was performed at 50 °C.

These Pd-catalyzed cross-coupling reactions proceed also well with benzylic zinc reagents of type **54**. Thus, reaction of 3,4,5-trimethoxybenzylzinc chloride (**54h**) with the ester-substituted pyrimidine **124k** afforded the 2-benzylated pyrimidine **126i** in 88% yield (entry 1 of Table 24).

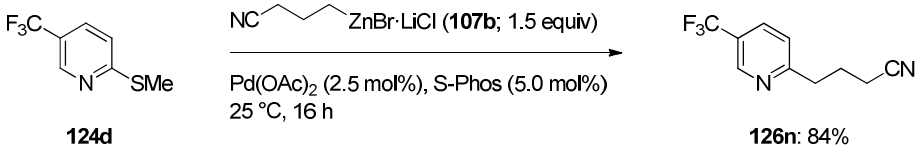
Smooth cross-coupling reaction of the functionalized pyrimidine **124c** with 3-(ethoxycarbonyl)benzylzinc chloride (**54m**) provided the heterocyclic diarylmethane **126j** (73%, entry 2). Similarly, pyridazine **124a** and quinazoline **124j** underwent also efficient cross-couplings with various benzylic zinc reagents bearing an ester or a nitrile group furnishing the desired products **126k-l** in 71-78% yield (entries 3 and 4). Moreover, methylthio-substituted benzothiazole **124l** provided, after Pd-catalyzed cross-coupling reaction with 3,4,5-trimethoxybenzylzinc chloride (**54h**), easily the desired product **126m** within 16 h reaction time in 70% yield (entry 5).

Table 24: Reaction of benzylic zinc reagents (**54**) with methylthio-substituted N-heterocycles (**124**) under palladium catalysis.

Entry	Benzylic zinc chloride	Electrophile	Time (h)[a]	Product	Yield (%)[b]
1	 **54h**	 **124k**	1.5	 **126i**	88
2	 **54m**	 **124c**	24	 **126j**	73
3	 **54o**	 **124a**	14[c]	 **126k**	71
4	 **54n**	 **124j**	12[c]	 **126l**	78
5	 **54h**	 **124l**	16	 **126m**	70

[a] Reaction time for the Pd-catalyzed cross-coupling is given. All reactions were performed at 25 °C unless otherwise indicated. [b] Yield of isolated analytically pure product. [c] The reaction was performed at 50 °C.

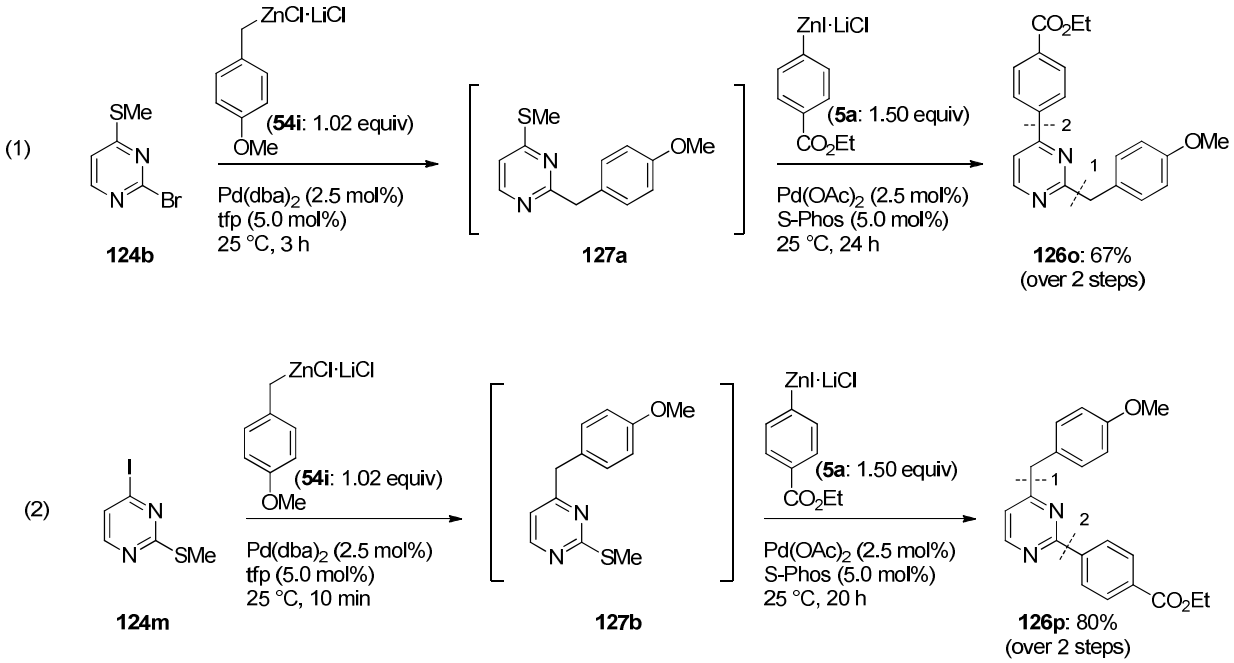
The scope of this Pd-catalyzed cross-coupling reaction was extended to alkylzinc reagents. Thus, 3-cyanopropylzinc bromide (**107b**) reacted with trifluoromethyl-substituted pyridine **124d** providing the pyridine **126n** within 16 h at 25 °C in 84% yield (Scheme 87).



124d **126n**: 84%

Scheme 87: Cross-coupling reaction of 3-cyanopropylzinc bromide (**107b**) with 2-(methylthio)-5-(trifluoromethyl)pyridine (**124d**) at 25 °C.

A selective bis-functionalization of pyrimidines in positions 2 and 4 can be achieved. Cross-coupling occurs first in position 2 or 4 depending on the substrate. Thus, the reaction of 2-bromo-4-(methylthio)pyrimidine (**124b**) with 4-methoxybenzylzinc chloride (**54i**) proceeded rapidly in the presence of $Pd(dba)_2$/tfp leading to intermediate **127a** (25 °C, 3 h; equation 1, Scheme 88).



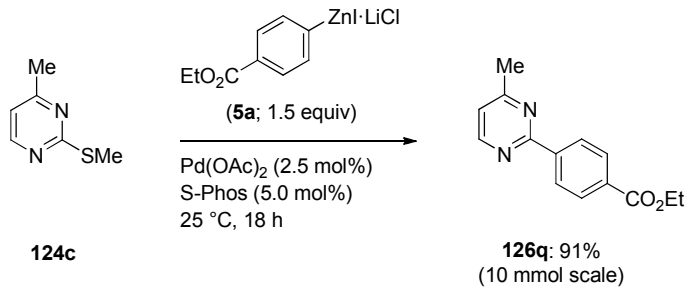
124b **127a** **126o**: 67% (over 2 steps)

124m **127b** **126p**: 80% (over 2 steps)

Scheme 88: Selective one-pot cross-couplings of 2-bromo-4-(methylthio)pyrimidine (**124b**) or 4-iodo-2-(methylthio)pyrimidine (**124m**) using $Pd(dba)_2$/tfp and *in situ* $Pd(OAc)_2$/S-Phos.

After a direct addition of a second catalyst system ($Pd(OAc)_2$/S-Phos) to the reaction mixture, a second cross-coupling occurred with 4-(ethoxycarbonyl)phenylzinc iodide (**5a**) providing the 2,4-disubstituted pyrimidine **126o** in 68% overall yield. Alternatively, 4-iodo-2-(methylthio)pyrimidine (**124m**) was converted into the regioisomeric 2,4-disubstituted pyrimidine **126p** by performing first a cross-coupling with 4-methoxybenzylzinc chloride (**54i**) using $Pd(dba)_2$/tfp (25 °C, 10 min; leading to **127b**) followed by a second cross-coupling with the arylzinc reagent **5a** in the presence of $Pd(OAc)_2$/S-Phos (25 °C, 20 h). The pyrimidine **126p** was obtained in 80% overall yield in this one-pot double cross-coupling sequence (equation 2).

This Pd-catalyzed cross-coupling reaction can be easily scaled up. Thus, 10 mmol scale reaction of the ester-substituted arylzinc iodide **5a** with the methylthio-substituted pyrimidine **124c** led to the heterocyclic biphenyl **126q** within 18 h at 25 °C in 91% yield (Scheme 89).

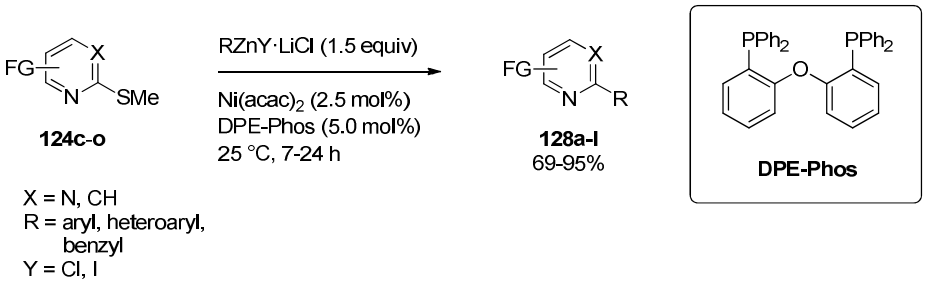


Scheme 89: Cross-coupling reaction of arylzinc iodide **5a** with pyrimidine (**124c**) under palladium catalysis on a 10 mmol scale.

4.3. Nickel-catalyzed cross-coupling reactions of functionalized organozinc reagents with methylthio-substituted N-heterocycles

During the screening of the catalytic system for the palladium catalyzed cross-coupling reaction of methylthio-substituted N-heterocycles with organozinc reagents it was found, that this cross-coupling can be also performed under nickel catalysis (entry 6 of Table 22), lowering the catalyst system cost. Therefore, an optimization of the nickel catalytic systems was performed.[156] It was found that by using $Ni(acac)_2$ (2.5 mol%) and DPE-Phos[157] (5.0 mol%) a broad reaction scope was achieved and the cross-couplings could be completed in 7-24 h at 25 °C (Scheme 90).

[156] The screening of the nickel/ligand catalytic systems was performed by Laurin Melzig. For further information, see also: Ph.D. thesis Laurin Melzig, LMU Munich.
[157] DPE = bis(2-diphenylphosphinophenyl)ether.



Scheme 90: Ni-catalyzed cross-coupling reactions of functionalized organozinc reagents with methylthio-substituted N-heterocycles at 25 °C.

Thus, the cross-coupling proceeded well with a range of functionalized aryl- and heteroarylzinc reagents. The reaction of ethyl 2-(methylthio)nicotinate (**124e**) with 3-(ethoxycarbonyl)phenylzinc iodide (**5d**) provided the functionalized pyridine **128a** in 91% yield (entry 1 of Table 25). Similarly, 2-(methylthio)nicotinonitrile (**124i**) reacted with 4-(ethoxycarbonyl)phenylzinc iodide (**5a**) leading to the heterocyclic biphenyl **128b** in 69% yield (entry 2). Electron-poor zinc reagents **5d**-**e** bearing an ester or a nitrile function readily reacted with 4-methyl-2-(methylthio)pyrimidine **124c** leading to the functionalized pyrimidines **128c**-**d** in 73-95% yield (entries 3 and 4). Furthermore, 3-(ethoxycarbonyl)phenylzinc iodide (**5d**) reacted smoothly with the 2-(methylthio)pyrazine (**124n**) and 6,7-dimethoxy-4-(methylthio)quinazoline (**124j**) leading to the polyfunctional heterocycles **128e** and **128f** in 74-80% yield (entries 5 and 6). The reaction of trifluoromethyl-substituted triazine **124o** with 2-thienylzinc iodide (**5f**) gave the triazine **128g** in 94% yield (entry 7). Using this method, it was possible to prepare the anti-inflammatory agent[158] **128h** in 87% yield by cross-coupling reaction of the 2,4,6-substituted triazine **124g** with the heteroarylzinc reagent **5f** (entry 8). The reaction protocol was also applied to benzylic zinc reagents of type **54**. Thus, the 2-(methylthio)-5-(trifluoromethyl)-substituted pyridine **124d** reacted with 3-(ethoxycarbonyl)benzylzinc chloride (**54m**) furnishing the expected product **128i** in 74% yield (entry 9). Similarly, the pyridine **124i** and the pyrimidine **124c** were cross-coupled with benzylic zinc reagents bearing a chloro-substituent as well as a sensitive nitrile group leading to the heterocyclic diarylmethanes **128j**-**k** in 69-94% yield (entries 10-11).

[158] (a) R. Menicagli, S. Samaritani, G. Signore, F. Vaglini, L. Dalla Via, *J. Med. Chem.* **2004**, *47*, 4649; (b) C. Dianzani, M. Collino, M. Gallicchio, S. Samaritani, G. Signore, R. Menicagli, R. Fantozzi, *J. Pharm. Pharmacol.* **2006**, *58*, 219; (c) S. Samaritani, G. Signore, C. Malanga, R. Menicagli, *Tetrahedron* **2005**, *61*, 4475.

Table 25: Reaction of aromatic, heteroaromatic and benzylic zinc reagents (**5** and **54**) with methylthio-substituted N-heterocycles (**124**) under nickel catalysis.

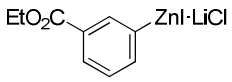
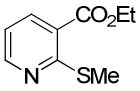
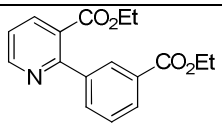
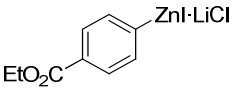
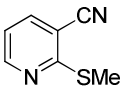
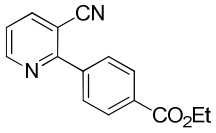
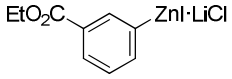
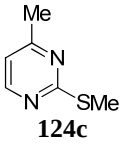
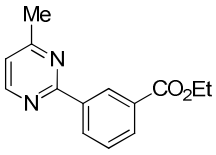
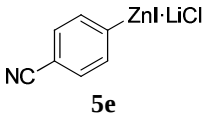
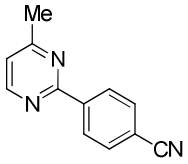
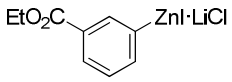
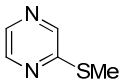
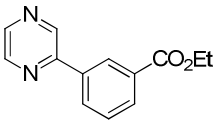
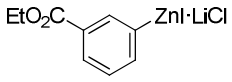
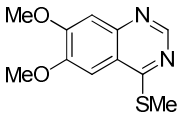
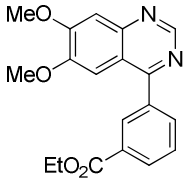
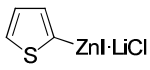
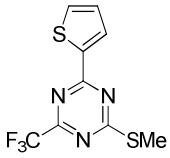
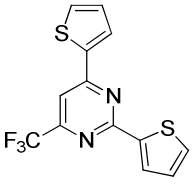
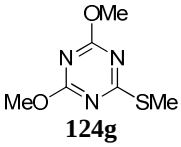
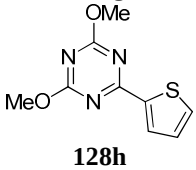
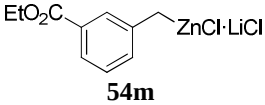
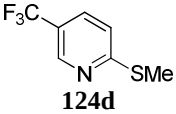
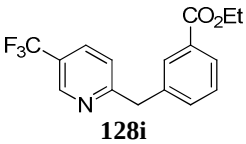
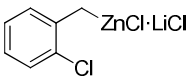
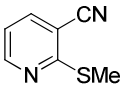
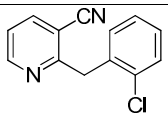
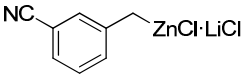
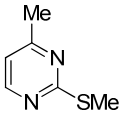
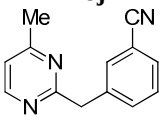
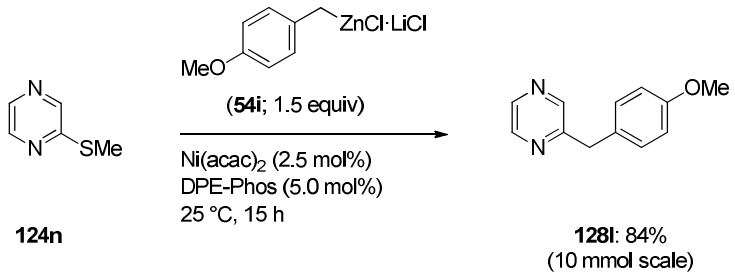
Entry	Zinc reagent	Electrophile	Time (h)[a]	Product	Yield (%)[b]
1	 **5d**	 **124e**	14	 **128a**	91
2	 **5a**	 **124i**	18	 **128b**	69
3	 **5d**	 **124c**	12	 **128c**	95
4	 **5e**	**124c**	18	 **128d**	73
5	 **5d**	 **124n**	14	 **128e**	74
6	 **5d**	 **124j**	18	 **128f**	80
7	 **5f**	 **124o**	16	 **128g**	94
8	**5f**	 **124g**	16	 **128h**	87
9	 **54m**	 **124d**	24	 **128i**	74

Table 25 continued

10	 **54b**	 **124i**	24	 **128j**	69
11	 **54o**	 **124c**	7	 **128k**	94

[a] Reaction time for the Ni-catalyzed cross-coupling reaction at 25 °C is given. [b] Yield of isolated analytically pure product.

Finally, this Ni-catalyzed cross-coupling reaction was scaled up. Thus, reaction of 4-methoxybenzylzinc chloride (**54i**) with the 2-(methylthio)pyrazine **124n** provided the heterocyclic diarylmethane **128l** within 15 h at 25 °C in 84% yield.



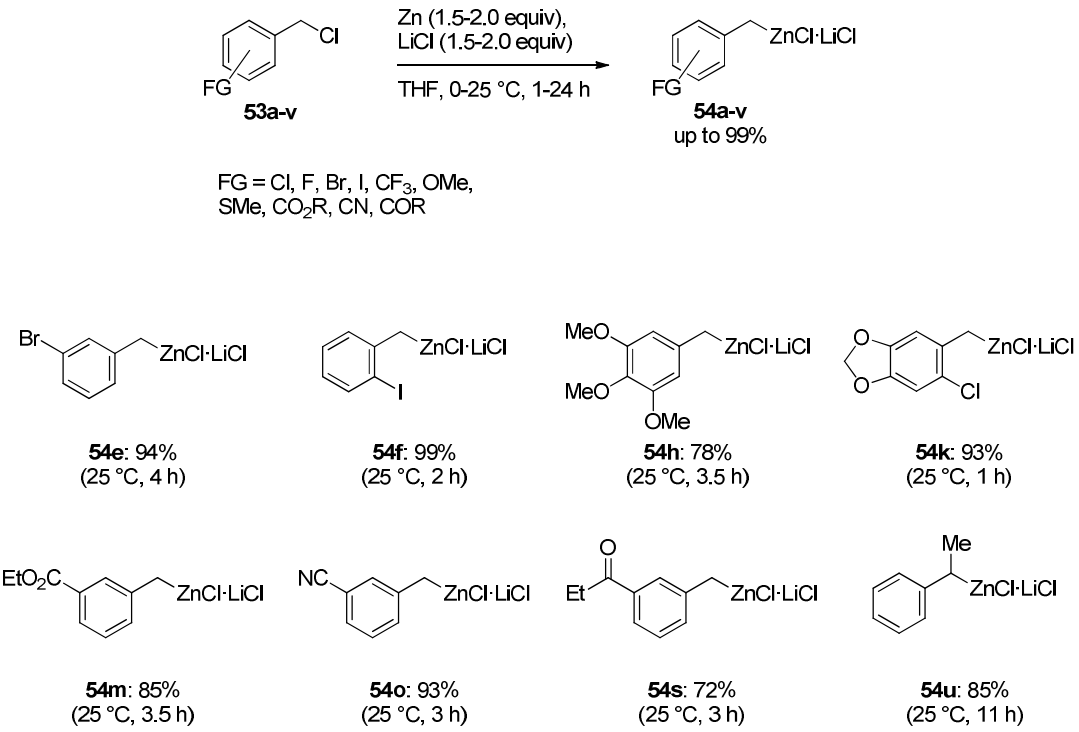
Scheme 91: Cross-coupling reaction of 4-methoxybenzylzinc chloride (**54i**) with 2-(methylthio)pyrazine (**124n**) under nickel catalysis on a 10 mmol scale.

5. Summary and Outlook

This work was focused on the preparations and applications of benzylic zinc chlorides. Furthermore, the Lewis acid promoted additions of organomagnesium and organozinc reagents to carbonyl derivatives were investigated. Additionally, a novel Cu(I)-mediated carbometalation reaction using functionalized arylzinc reagents was developed. Finally, mild and convenient transition metal-catalyzed cross-couplings of thioether-substituted N-heterocycles with organozinc compounds were studied.

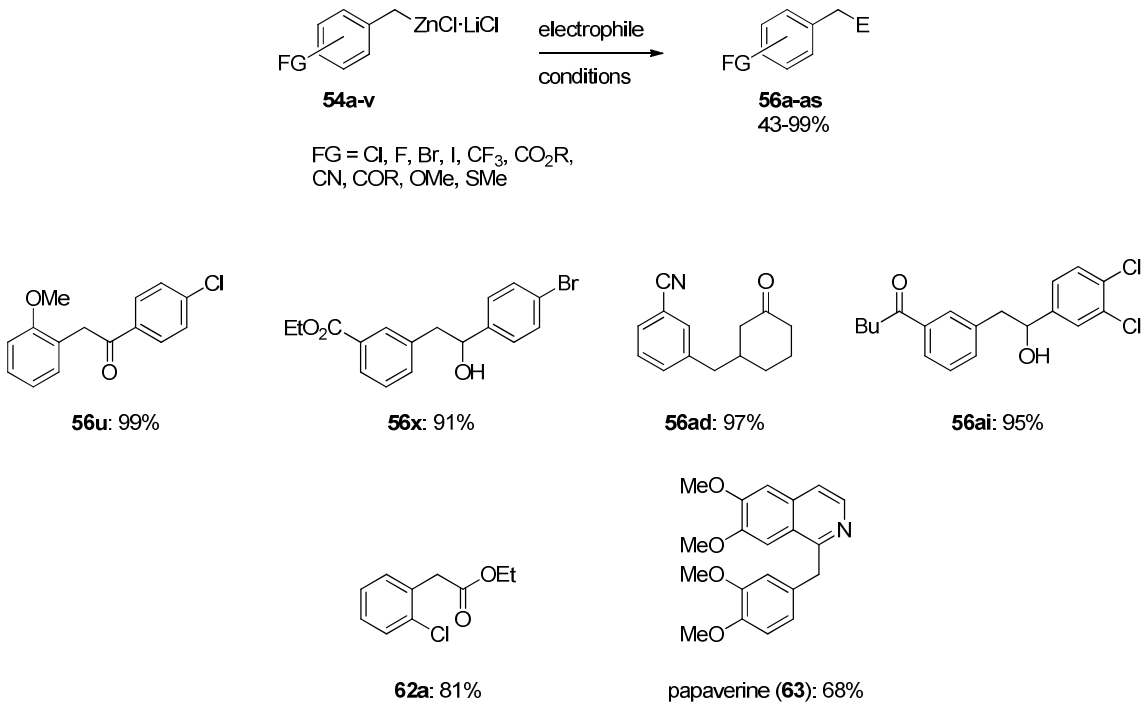
5.1. Preparation and applications of benzylic zinc chlorides

In summary, the LiCl-mediated direct insertions of commercially available zinc dust into benzylic chlorides under mild conditions was explored. The desired highly functionalized benzylic zinc chlorides are easily accessible in excellent yields and are normally storable over months without significant loss of reactivity (Scheme 92).



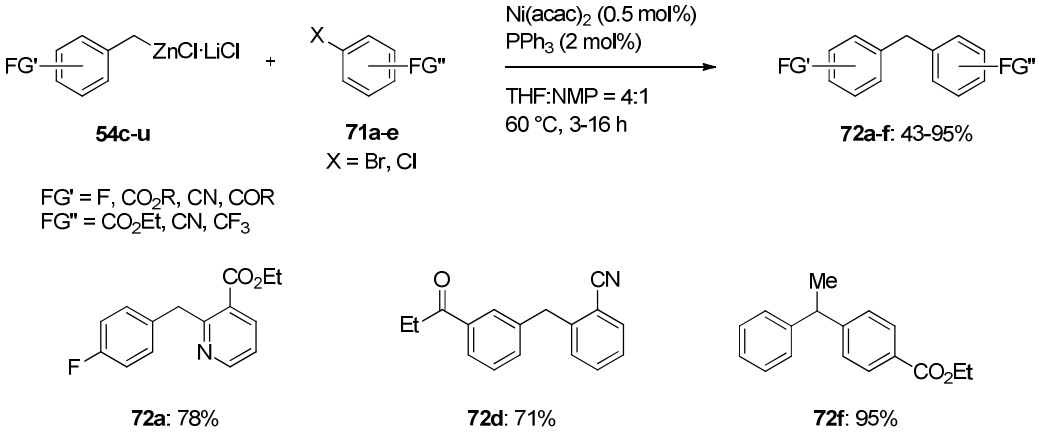
Scheme 92: Preparation of functionalized benzylic zinc chlorides.

These novel benzylic zinc reagents were reacted with various electrophiles leading to polyfunctionalized products (Scheme 93). Moreover, it was possible to establish an easy access to phenylacetic acid derivative as well as the alkaloid papaverine (Scheme 93).



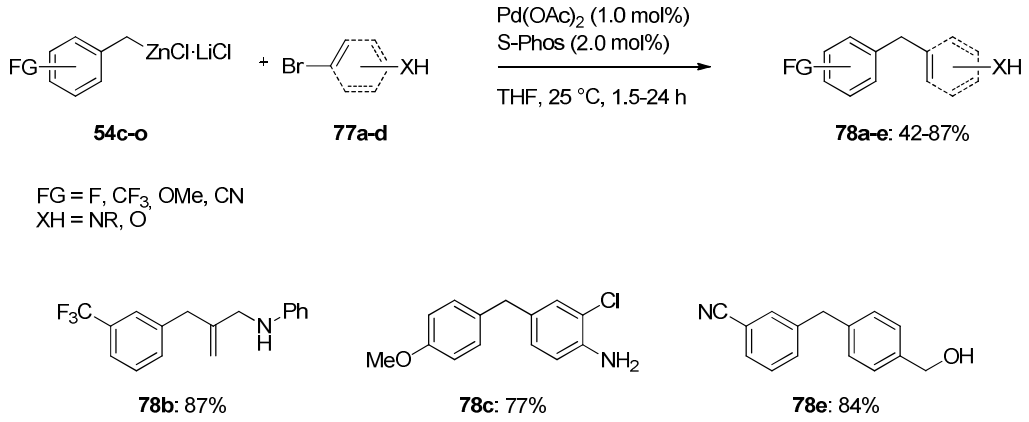
Scheme 93: Reaction of benzylic zinc chlorides with different electrophiles leading to polyfunctionalized products.

Furthermore, benzylic zinc reagents were prone to Ni-catalyzed cross-coupling reactions providing the important class of diarylmethanes (Scheme 94).



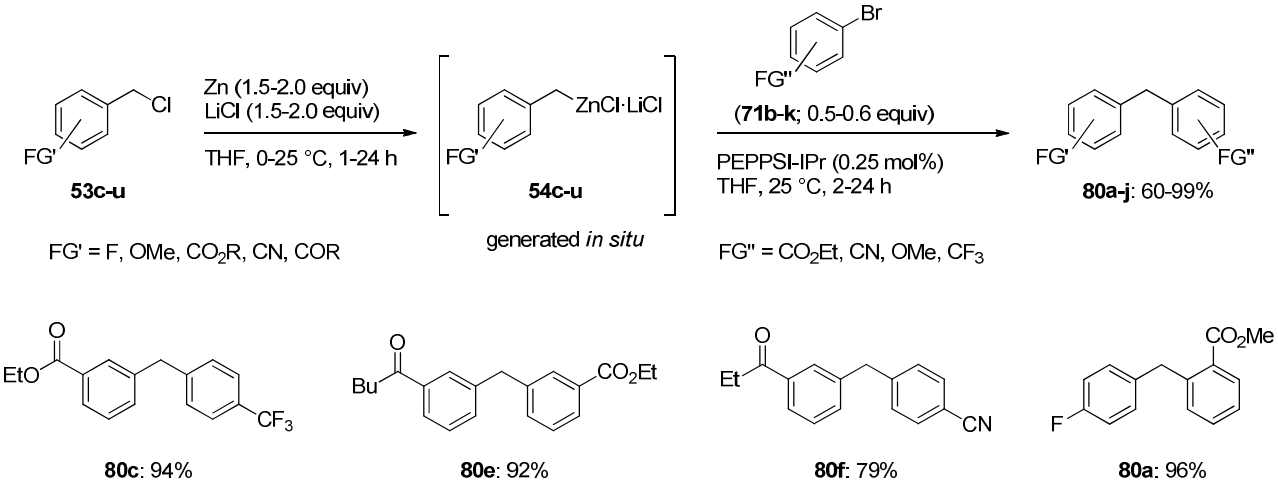
Scheme 94: Ni-catalyzed cross-couplings of benzylic zinc chlorides with aromatic halides.

Additionally, benzylic zinc chlorides underwent smooth Pd-catalyzed cross-couplings with unsaturated bromides bearing free amino or alcohol function without previous protections (Scheme 95).



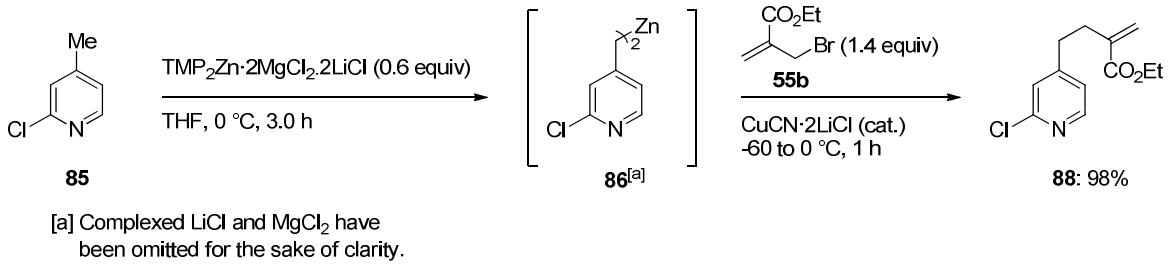
Scheme 95: Pd-catalyzed cross-couplings of benzylic zinc reagents with unsaturated bromides bearing acidic protons.

The preparation of benzylic zinc chlorides and their transition metal-catalyzed cross-couplings were modified to a one-pot procedure providing an easy access to diarylmethanes without the handling of air and moisture sensitive zinc compounds.



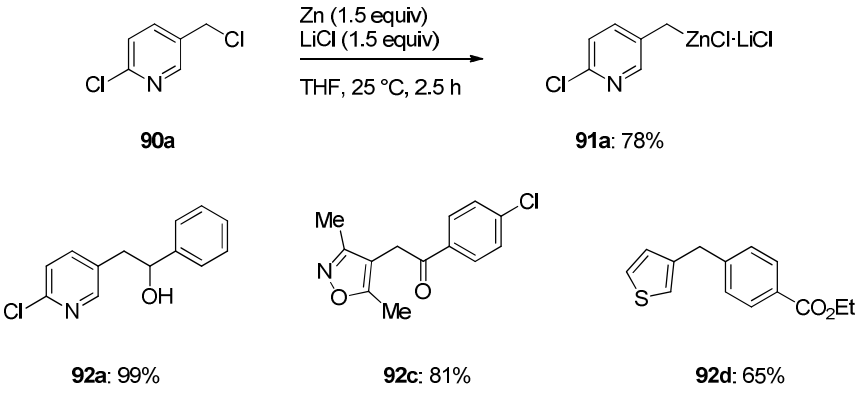
Scheme 96: Pd-catalyzed cross-couplings of *in situ* generated benzylic zinc chloride with aromatic bromides in the presence of residual zinc dust.

Furthermore, heterobenzylic zinc reagents were prepared by metalation reactions of methyl-substituted heterocycles using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (Scheme 97).



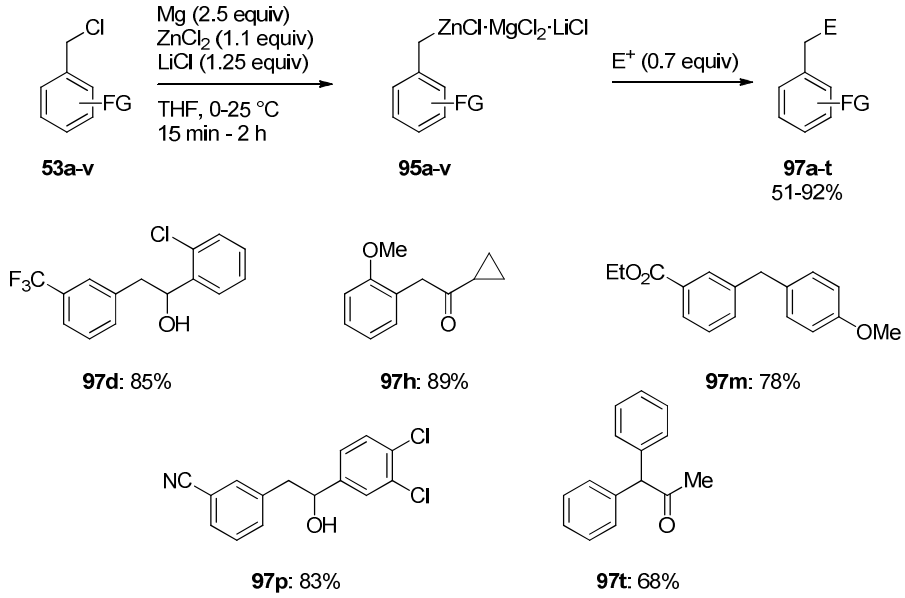
Scheme 97: Application of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ to prepare heterobenzylic zinc reagents.

Alternatively, the direct insertion of zinc dust into heterobenzylic chlorides in the presence of LiCl was examined giving an access to heterobenzylic zinc reagent as exemplarily shown in Scheme 98. Analogously, these zinc reagents were reacted with different electrophiles providing polyfunctional heterocyclic products.



Scheme 98: Preparation of heterobenzylic zinc reagents by direct zinc insertion into heterobenzylic chlorides and reactions thereof with various electrophiles.

Furthermore, benzylic zinc chlorides were smoothly prepared by the direct insertion of magnesium into benzylic chlorides in the presence of $ZnCl_2$ and LiCl. Their subsequent reactions with different electrophiles led to highly functionalized products (Scheme 99).

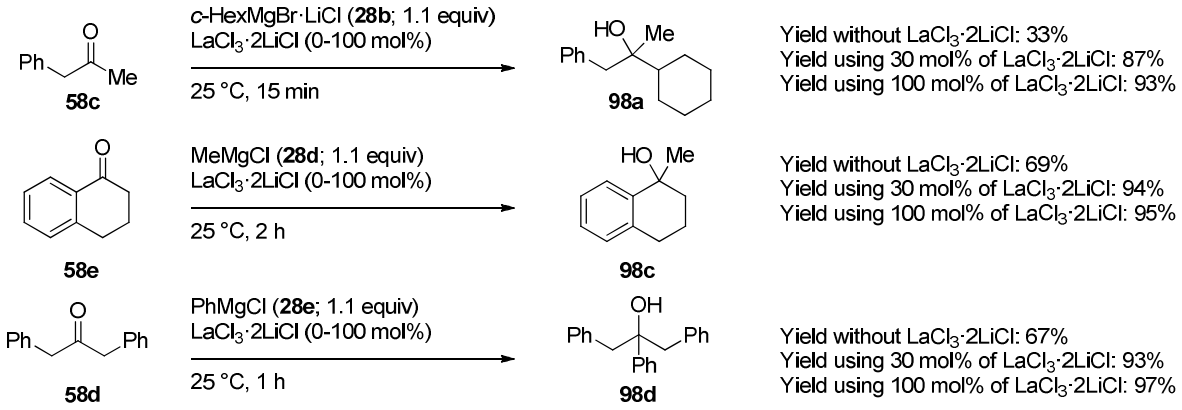


Scheme 99: Preparation of benzylic zinc chlorides by Mg insertion into benzylic chlorides in the presence of $ZnCl_2$/LiCl and subsequent reactions with various electrophiles.

The previously described methods can be extended to the preparation of benzylic aluminum and benzylic manganese reagents by direct metal insertion as well as by the insertion of magnesium into benzylic chlorides in the presence of the corresponding metal salt which should provide new benzylic organometallics having different chemical properties.

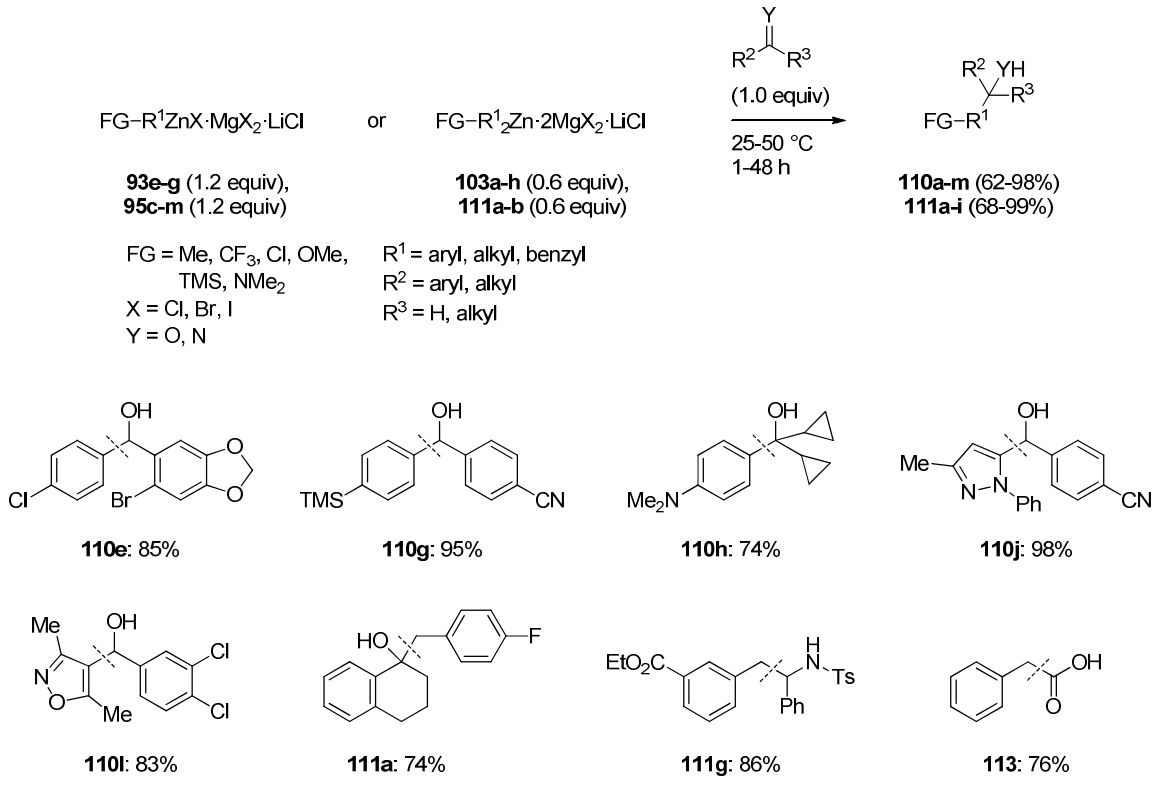
5.2. Lewis-acid promoted additions of functionalized organomagnesium and organozinc reagents to carbonyl derivatives

It was demonstrated that by using the THF-soluble complex $LaCl_3 \cdot 2LiCl$ in a catalytic fashion organomagnesium reagents easily add to enolizable ketones to provide the expected alcohols in similar yields to when using $LaCl_3 \cdot 2LiCl$ in stoichiometric amounts (Scheme 100).



Scheme 100: Addition of Grignard reagents to enolizable ketones in the presence of catalytic amounts of $LaCl_3 \cdot 2LiCl$.

Furthermore, it was demonstrated that functionalized organozinc reagents add to aldehydes, ketones and even carbon dioxide in the presence of stoichiometric amounts of $MgCl_2$ under mild conditions (Scheme 101).

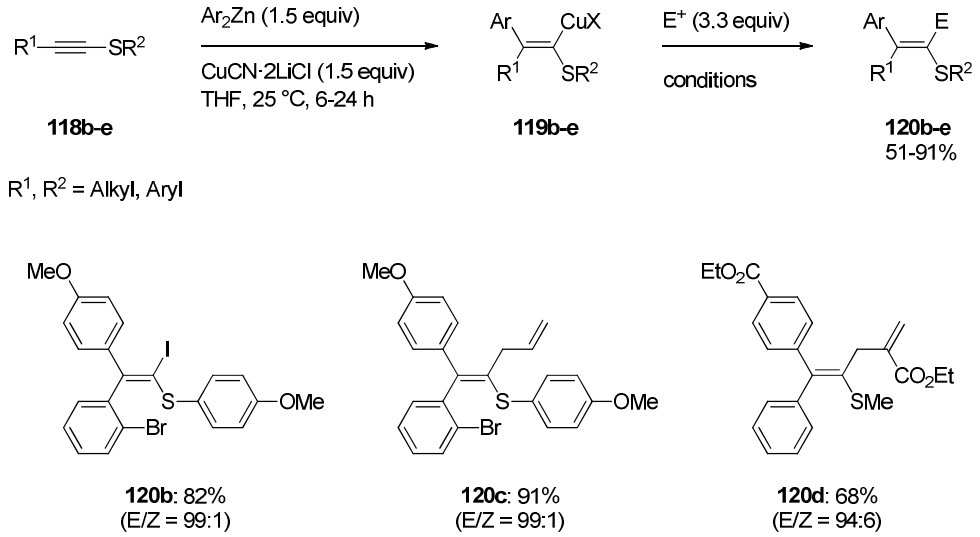


Scheme 101: Addition of functionalized organozinc reagents to carbonyl derivatives in the presence of stoichiometric amounts of $MgCl_2$.

The catalytic use of $LaCl_3 \cdot 2LiCl$ for the addition of a Grignard reagent to a ketone can be extended to a catalytic use of the lanthanum salt for reductions of 1,4-systems having a positive influence for industrial processes. Furthermore, the addition of zinc organometallics to carbonyl derivatives should be performed in the presence of various magnesium or aluminum salts to change the reaction scope. Also the addition of organozinc reagents to carbonyl derivatives in the presence of a chiral ligand should be investigated. Moreover, this method can find important applications in the pharmaceutical and agrochemical industry due to the high functional group tolerance of the utilized zinc reagents which is normally not given for the corresponding Grignard compounds.

5.3. Carbocupration of alkynes with functionalized diorganozinc reagents

A novel Cu(I)-mediated carbometalation reaction was developed using thioether-substituted alkynes and functionalized diarylzinc reagents (Scheme 102). The reaction proceeds in very good stereo- and regioselectivity providing tetrasubstituted olefins in good yields.

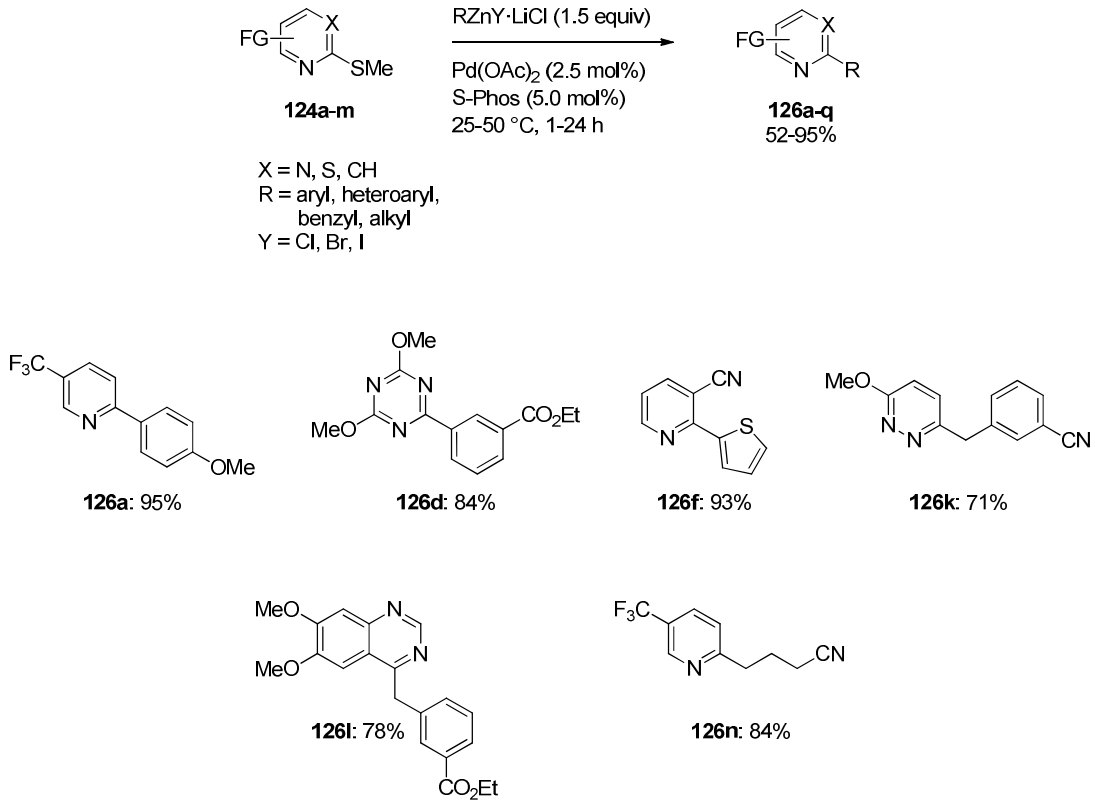


Scheme 102: Carbometalation reactions on thioether-substituted alkynes.

As an extension of this method the use of benzylic zinc reagents as well as various alkynes bearing directing groups should be possible.

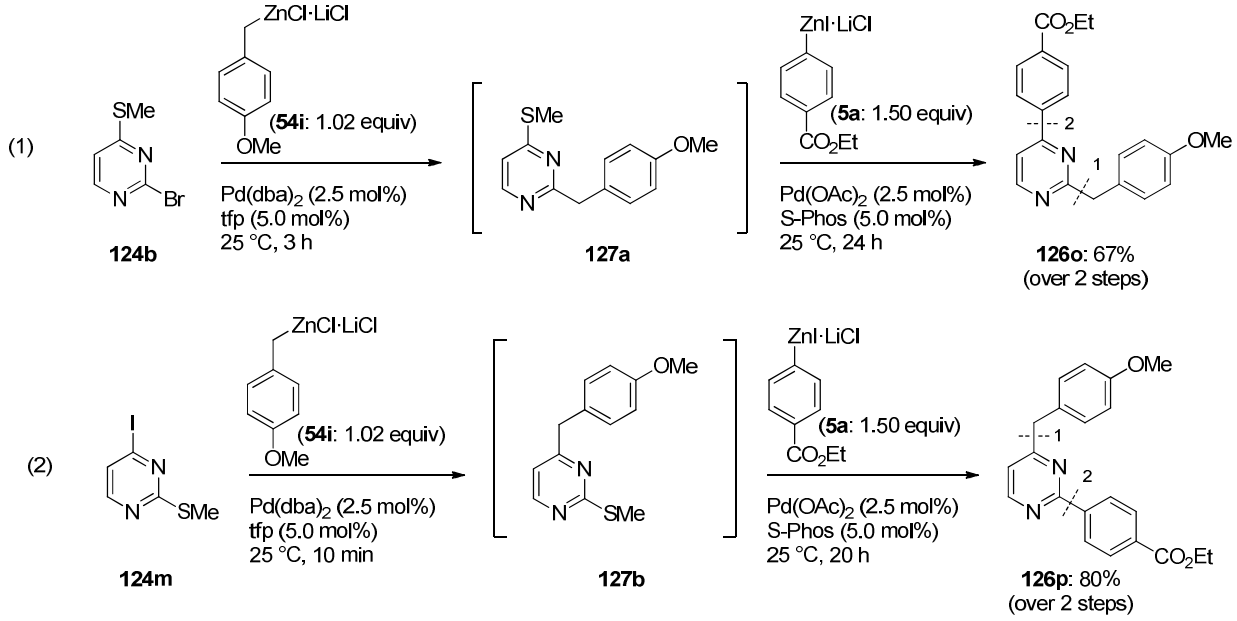
5.4. Transition metal-catalyzed cross-coupling reactions of functionalized organozinc reagents with methylthio-substituted N-heterocycles

A mild Pd-catalyzed cross-coupling reaction of organozinc reagents with N-heterocycles was studied. Numerous methylthio-substituted N-heterocycles were used as electrophiles and the coupling products were generally obtained in good to excellent yields (Scheme 103).



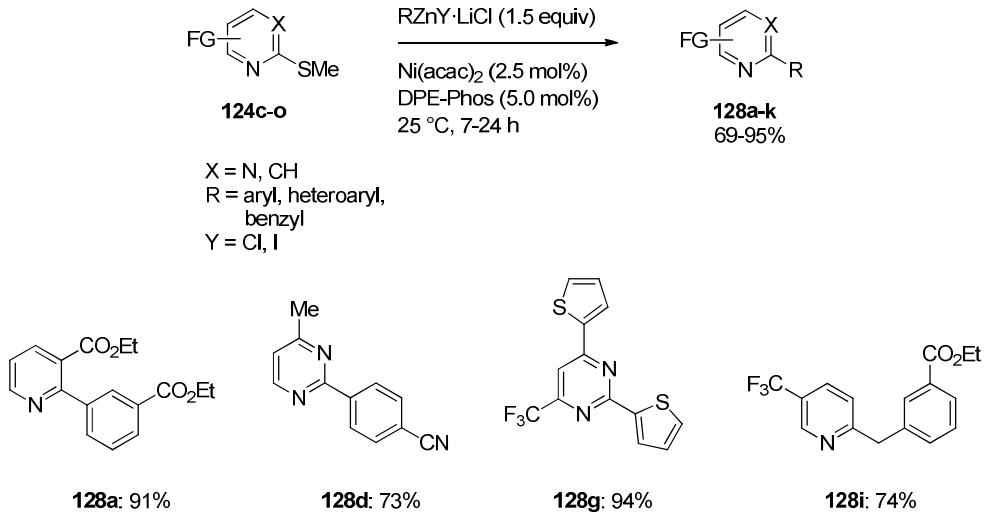
Scheme 103: Pd-catalyzed cross-couplings of organozinc reagents with heterocyclic thioethers.

Furthermore, selective one-pot cross-coupling procedures were developed.



Scheme 104: Selective Pd-catalyzed cross-coupling reactions of organozinc halides with pyrimidines bearing a halogen and a thioether substituent.

The method was extended to Nickel-catalyzed cross-coupling reactions of functionalized organozinc reagents with methylthio-substituted N-heterocycles. All reactions could be performed at ambient temperature. Moreover, the reaction scope is similar to the Pd-catalyzed cross-couplings (Scheme 105).



Scheme 105: Ni-catalyzed cross-couplings of organozinc reagents with heterocyclic thioethers.

These methods allow smooth cross-couplings of highly functionalized organozinc reagents with stable thioether-substituted N-heterocycles and they can find several applications in fields where the cross-couplings of halogen-substituted heterocycles are not possible due to the instability of the starting materials as well as the difficulties in their preparations.

C. EXPERIMENTAL SECTION

1. General Considerations

All reactions were carried out with magnetic stirring and, if the reagents were air or moisture sensitive, in flame-dried glassware under argon. Syringes which were used to transfer reagents and solvents were purged with argon prior to use.

1.1. Solvents

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

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.

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

EtOH was treated with phthalic anhydride (25 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.

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

Pyridine was dried over KOH and distilled

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

Toluene was predried over $CaCl_2$ and distilled from CaH_2.

Triethylamine was dried over KOH and distilled

Solvents for column chromatography were distilled prior to use.

1.2. Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use. Following compounds were prepared according to literature procedures: 3-(ethoxycarbonyl)benzyl chloride,[63a] sulfonothioate derivatives,[73] 2-iodocyclohex-2-en-1-one, [159] ethyl (2-bromomethyl)- acrylate,[76] (2-bromoprop-2-en-1-yl)phenylamine, [160] 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine, [161] 6,7-dimethoxy-4-(methylthio)quinazoline,[161]

[159] M. E. Krafft, J. W. Cran, *Synlett* **2005**, 1263.
[160] J. Barluenga, F. Foubelo, F. J. Fananas, M. Yus; *J. Chem. Soc. Perkin Trans 1* **1989**, 553
[161] A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228.

1-methyl-5-(methylthio)-1*H*-pyrazole, [162] ethyl 4-[2-(methylthio)pyrimidin-4-yl]benzoate, [163] 2-bromo-4-(methylthio)pyrimidine,[155] 4-iodo-2-(methylthio)pyrimidine, [164] 2-(methylthio)-4-(2-thienyl)-6-(trifluoromethyl)pyrimidine.[165]

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

***i*-PrMgCl** solution in THF was purchased from Chemetall

PhMgCl solution in THF was purchased from Chemetall

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

TMPMgCl·LiCl was prepared according to a literature procedure (ref. 83).

$TMP_2Zn·2MgCl_2·2LiCl$ was prepared according to a literature procedure (ref. 29a).

CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a *Schlenk*-tube under vacuum at 140 °C for 5 h. After cooling, 80 mL dry THF were added and stirring was continued until the salt was dissolved.

$ZnCl_2$ solution (1.00 M) was prepared by drying $ZnCl_2$ (100 mmol, 136 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL dry THF were added and stirring was continued until the salt was dissolved.

LiCl solution (0.5 M) was prepared by drying LiCl (100 mmol, 4.23 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 200 mL dry THF were added and stirring was continued until the salt was dissolved.

$ZnCl_2$/LiCl solution (1.1/1.5 M) was prepared by drying LiCl (15.9 g, 375 mmol) and $ZnCl_2$ (37.5 g, 275 mmol) under high vacuum (1 mbar) for 5 h at 140 °C. After cooling to 25 °C, dry THF (250 mL) was added and stirring was continued until the salts were dissolved.

1.3. Content determination of organometallic reagents

Organzinc and organomagnesium reagents were titrated against I_2 in a 0.5 M LiCl solution in THF.[71]

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[162] C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326.

[163] (a) Ethyl 4-[2-(methylthio)pyrimidin-4-yl]benzoate was obtained as chemical gift from Dr. M. Mosrin and is herewith gratefully acknowledged; (b) See also: (i) C. Gosmini, J. Y. Nedelec, J. Perichon, *Tetrahedron Lett.* **2000**, 41, 201; (ii) C. J. Rohbogner, S. H. Wunderlich, G. C. Clososki, P. Knochel, *Eur. J. Org. Chem.* **2009**, 1781.

[164] A. J. Majeed, O. Antonsen, T. Benneche, K. Undheim, *Tetrahedron* **1989**, *45*, 993.

[165] A. F. C Flores, L. Pizzuti, S. Brondani, M. Rossato, N. Zanatta, M. A. P Martins, *J. Braz. Chem. Soc.* **2007**, *18*, 1316.

Organolithium reagents were titrated against menthol using 1,10-phenanthroline as indicator in THF.

TMPMgCl·LiCl and **$TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$** were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

1.4. Chromatography

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

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

- $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).

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 appreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) as well as br (broad).

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an 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. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. 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 preparation of benzylic zinc chlorides by LiCl-mediated direct zinc insertion into benzylic chlorides (TP1)

A Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.5–2.0 equiv). The flask was heated with a heat gun (400 °C) for 10 min under high vacuum. After cooling to 25 °C, the flask was flushed with argon (3 times). Zinc dust (1.5–2.0 equiv) was added followed by THF. 1,2-Dibromoethane was added (5 mol%) and the reaction mixture was heated until ebullition occurs. After cooling to 25 °C, trimethylsilyl chloride (1 mol%) was added and the mixture was heated again until ebullition occurs. The benzylic chloride (1.0 equiv) was added at the required temperature (usually 25 °C) as a solution in THF (usually 4 M). When capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of > 98%, the Schlenk-flask was centrifuged for 75 min at 2000 rpm or the reaction mixture was allowed to settle down for some hours. The yield of the resulting benzylic zinc chloride was determined by iodiometric titration.[71]

2.2. Typical procedure for the reaction of benzylic zinc chlorides with aldehydes (TP2)

In a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, the aldehyde (1.0 equiv) was dissolved in THF at 0 °C and the benzylic zinc chloride (1.3 equiv) was added dropwise. The resulting solution was allowed to warm to 25 °C and was stirred for the required time. Then, sat. aq. NH_4Cl (20 mL) solution was added. The phases were separated and the aq. layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected alcohols.

2.3. Typical procedure for the reaction of benzylic zinc chlorides with acid chlorides (TP3)

Into a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, $CuCN \cdot 2LiCl$ solution (1.4 equiv) was added: Then, the desired benzylic zinc chloride (1.4 equiv) was added dropwise at -25 °C. The resulting reaction mixture was stirred for 15 min at this temperature. Then, the solution was cooled to the required temperature and the acid chloride (1.0 equiv) was added dropwise. The reaction mixture was stirred for the given time and allowed to warm to 25 °C. Then, a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 was added, the

phases were separated and the aq. layer was extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected ketones.

2.4. Typical procedure for the reaction of benzylic zinc chlorides with unsaturated ketones (TP4)

Into a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, CuCN·2LiCl solution (1.25 equiv) was added. Then, the desired benzylic zinc chloride (1.25 equiv) was added dropwise at -25°C. The resulting reaction mixture was stirred for 15 min at this temperature. Then, the solution was cooled to the required temperature and a mixture of the unsaturated ketone (1.0 equiv), trimethylsilyl chloride (2.5 equiv) and THF was added dropwise. The reaction mixture was stirred for the given time and allowed to reach 25 °C. Then, a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 was added. The phases were separated and the aq. layer was extracted with Et_2O (3 x 100 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected ketones.

2.5. Typical procedure for the Ni-catalyzed cross-coupling reactions of benzylic zinc chlorides with aromatic halides (TP5)

In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the aromatic bromide or chloride (2.00 mmol, 1.0 equiv) was dissolved in NMP (0.4 mL) and PPh_3 (0.1 mL, 0.04 mmol, 0.4 M in THF, 2 mol%) was added. Then, $Ni(acac)_2$ (0.1 mL, 0.01 mmol, 0.1 M in THF, 0.5 mol%) was added. After the addition of the corresponding benzylic zinc reagent (2.40 mmol, 1.2 equiv), the reaction mixture was warmed to 60 °C and stirred for the given time until GC-analysis showed full conversion of the electrophile. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with Et_2O (3 times). The combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The product was purified by flash column chromatography.

2.6. Typical procedure for the Pd-catalyzed cross-coupling reaction with a bromo-aniline (TP6)

A dry and argon flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with the bromo-aniline (1.0 equiv), $Pd(OAc)_2$ (1 mol%), S-Phos (2 mol%) and THF. After stirring the reaction mixture for 5 min, the zinc reagent was added. The reaction mixture was stirred for the given time at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with Et_2O (3 times). The combined organic phases were washed with an aq. thiourea solution and dried over $MgSO_4$. Purification of the crude residue obtained after evaporation of the solvents by flash column chromatography yielded the desired product.

2.7. Typical procedure for the Pd-catalyzed cross-coupling reaction with a bromo-alcohol (TP7)

A dry and argon flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with the bromo-alcohol (1.0 equiv), $Pd(OAc)_2$ (1 mol%), S-Phos (2 mol%) and THF. After stirring the reaction mixture for 5 min, the zinc reagent was added slowly over 90 min using a syringe pump at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with Et_2O (3 times). The combined organic phases were washed with an aq. thiourea solution and dried ($MgSO_4$). Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the desired product.

2.8. Typical procedure for the one-pot Negishi cross-coupling reaction (TP8)

A Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (1.5 equiv). The flask was heated with a heat gun (400 °C) for 10 min under high vacuum. After cooling to 25 °C, the flask was flushed with argon (3 times). Zinc dust (1.5 equiv) was added followed by THF. 1,2-Dibromoethane was added (5 mol%) and the reaction mixture was heated to ebullition for 15 s. After cooling to 25 °C, trimethylsilyl chloride (1 mol%) was added and the mixture was heated to ebullition for 15 s. The benzylic chloride (1.0 equiv) was added at the required temperature (usually 25 °C) as a solution in THF (usually 4 M). When capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of > 98%, the aromatic bromide was added, followed by PEPPSI-IPr. The reaction mixture was stirred at 25 °C until GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of > 98%. Then, sat. aq. NH_4Cl solution was added (20 mL). The phases were

separated and the aq. layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography afforded the expected diarylmethanes.

2.9. Typical procedure for preparation of benzylic zinc chlorides by magnesium insertion in the presence of $ZnCl_2$ and LiCl (TP9)

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with magnesium turnings (122 mg, 5.00 mmol). LiCl (5.00 mL, 2.50 mmol, 0.5 M in THF) and $ZnCl_2$ (2.20 mL, 2.20 mmol, 1.00 M in THF) were added. The benzylic chloride (2.00 mmol) was added in one portion at the given temperature. The reaction mixture was stirred for the given time and then canulated to a new *Schlenk*-flask for the reaction with an electrophile.

2.10. Typical procedure for the addition of organomagnesium reagents to carbonyl derivatives in the presence of variable amounts of $LaCl_3 \cdot 2LiCl$ (TP10)

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with the carbonyl derivative (1 equiv) in $LaCl_3 \cdot 2LiCl$ solution (1 equiv) and the reaction mixture was stirred for 1 h. Then, the organomagnesium reagent (1.1 equiv) was added dropwise at 0 °C. The reaction mixture was stirred for the given time at the required temperature until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl solution and extracted with Et_2O (3 times). The combined organic phases were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected alcohols.

2.11. Typical procedure for the preparation of zinc reagents using Mg and $ZnCl_2$/LiCl solution (TP11)

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with magnesium turnings (2.5 equiv). Then, $ZnCl_2$/LiCl (1.1/1.5 M) solution was added (1 mL / mmol for the preparation of organozinc reagents of type $RZnX \cdot MgX_2 \cdot LiCl$ (X = Cl, Br); 0.5 mL / mmol for the preparation of diorganozinc reagents of type $R_2Zn \cdot 2MgX_2 \cdot LiCl$ (X = Cl, Br)). The organic halide (1.0 equiv) was added dropwise as a solution in THF using a water cooling bath to keep the temperature below 30 °C. The reaction mixture was stirred for the given time until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the

supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask through a syringe filter. The concentration of the zinc reagent was determined by iodometric titration.

2.12. Typical procedure for the addition of organozinc reagents of type $RZnX \cdot MgX_2 \cdot LiCl$ or diorganozinc reagents of type $R_2Zn \cdot 2MgX_2 \cdot LiCl$ to carbonyl derivatives (TP12)

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with the carbonyl derivative (1.5 mmol) in THF (1 mL). Then, the organozinc reagent $RZnX \cdot MgX_2 \cdot LiCl$ (1.8 mmol, 1.2 equiv; X = Cl, Br) or the diorganozinc reagent $R_2Zn \cdot 2MgX_2 \cdot LiCl$ (0.9 mmol, 0.6 equiv; X = Cl, Br) was added dropwise. The reaction mixture was stirred for the given time until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected products.

2.13. Typical procedure for the addition of organozinc reagents to carbon dioxide (TP13)

A *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was flame-dried under high vacuum. After cooling to 25 °C, the flask was filled with dry $CO_{2(g)}$ and the organozinc reagent (typically 1.0 mmol for Ar_2Zn or $(ArCH_2)_2Zn$) was added. 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 the given time and temperature until the zinc reagent had been completely consumed (quenching of reaction aliquots with I_2 and GC-analysis). The reaction mixture was diluted with Et_2O (20 mL) and sat. aq. $NaHCO_3$ (30 mL) was added. After filtration, the organic phase was separated and extracted with sat. aq. $NaHCO_3$ (3 x 30 mL). The combined aq. phases were carefully acidified with HCl (5 M) until pH < 5 and extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* provided the corresponding carboxylic acids.

2.14. Typical procedure for the Pd-catalyzed cross-coupling reaction of organozinc reagents with methylthio-substituted N-heterocycles (TP14)

In a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, the aromatic thioether (1.00 mmol), $Pd(OAc)_2$ (2.5 mol%) and S-Phos (5.0 mol%) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (1.5 mmol) was added dropwise and the reaction mixture was stirred for the given time at the required temperature until GC-analysis of a hydrolyzed aliquot showed full consumption of the electrophile. The reaction mixture was quenched with sat. aq. Na_2CO_3 solution and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected products.

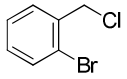
2.15. Typical procedure for the Ni-catalyzed cross-coupling reaction of organozinc reagents with methylthio-substituted N-heterocycles (TP15)

In a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, the aromatic thioether (1.00 mmol), $Ni(acac)_2$ (2.5 mol%) and DPE-Phos (5.0 mol%) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (1.5 mmol) was added dropwise and the reaction mixture was stirred for the given time at 25 °C until GC-analysis of a hydrolyzed aliquot showed full consumption of the electrophile. The reaction mixture was quenched with sat. aq. Na_2CO_3 solution and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected products.

3. Preparation and Applications of Benzylic Zinc Chlorides

3.1. Prepartion of the starting materials

2-Bromobenzyl chloride (53d)



To a solution of LiCl (2.54 g, 60.0 mmol, dried for 10 min under high vacuum at 400 °C using a heat gun) in THF (50 mL) was added 2-bromobenzyl alcohol (3.74 g, 20.0 mmol) at 0 °C. Then, NEt_3 (5.56 mL, 40.0 mmol) was added dropwise, followed by mesyl chloride (2.32 mL, 30.0 mmol). The reaction mixture was allowed to reach 25 °C within 15 h. Then, CH_2Cl_2 (300 mL) was added and the solution was washed with water (3 x 250 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the benzylic chloride **53d** (3.67 g, 89%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.58 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.48 (dd, *J* = 7.4 Hz, 1.6 Hz, 1H), 7.35-7.28 (m, 1H), 7.22-7.15 (m, 1H), 4.70 (s, 2H).

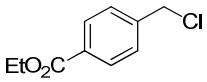
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 136.6, 133.1, 130.8, 130.0, 127.8, 124.1, 46.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060 (w), 2968 (w), 1588 (w), 1570 (w), 1470 (m), 1438 (m), 1280 (w), 1264 (m), 1210 (w), 1046 (w), 1026 (s), 820 (m), 762 (m), 728 (vs), 672 (s), 656 (m), 570 (m).

MS (EI, 70 eV): m/z (%) = 204 (M^+, 25), 171 (98), 169 (100), 90 (22), 84 (15), 63 (11).

HRMS (C_7H_6BrCl): calc.: 203.9341; found: 203.9339.

4-(Ethoxycarbonyl)benzyl chloride (53n)



N,N-Dimethylpyridin-4-amine (305 mg, 2.50 mmol) was dissolved in ethanol (4 mL) and pyridine (7.5 mL) at 0 °C. 4-(Chloromethyl)benzoyl chloride (9.45 g, 50.0 mmol, in 2.5 mL Et_2O) was added dropwise. Then, the reaction mixture was warmed to 25 °C and added to a dilute HCl/Et_2O mixture = 1:1 (200 mL). The phases were separated and the organic layer was washed successively with H_2O (100 mL) and brine (100 mL), then dried over $MgSO_4$. Evaporation of the solvents *in vacuo* afforded the benzylic chloride **53n** (9.51 g, 96%) as a pale yellow liquid which was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.06-7.98 (m, 2H), 7.47-7.41 (m, 2H), 4.59 (s, 2H), 4.37 (q, *J* = 7.0 Hz, 2H), 1.38 (q, *J* = 7.2 Hz, 3H).

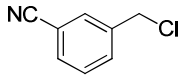
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.0, 142.1, 130.4, 129.9, 128.4, 61.1, 45.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 1712 (s), 1614 (w), 1578 (w), 1446 (w), 1414 (w), 1368 (m), 1306 (w), 1270 (vs), 1178 (m), 1100 (vs), 1020 (s), 920 (w), 856 (w), 804 (m), 772 (m), 710 (vs), 676 (m), 622 (w).

MS (EI, 70 eV): m/z (%) = 198 (M^+, 11), 170 (29), 163 (12), 155 (28), 153 (100), 135 (26), 89 (19).

HRMS ($C_{10}H_{11}ClO_2$): calc.: 198.0448; found: 198.0446.

3-Cyanobenzyl chloride (53o)



LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min). 3-(Bromomethyl)benzonitrile (9.80 g, 50.0 mmol) was added followed by THF (100 mL) at 0 °C. The reaction mixture was refluxed for 5 h. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over $MgSO_4$ followed by the evaporation of the solvents *in vacuo*. Again, LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min) and the crude product was added followed by THF (100 mL) at 0 °C. The reaction mixture was refluxed for 5 h. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over $MgSO_4$ followed by the evaporation of the solvents *in vacuo*. Once again, LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min) and the crude product was added followed by THF (100 mL) at 0 °C. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over $MgSO_4$ followed by the evaporation of the solvents *in vacuo*. Purification by flash chromatography (short column, silica gel, pentane / Et_2O = 9:1) afforded the benzylic chloride **53o** (7.47 g, 99%) as a white solid.

M.p. (°C): 73-75.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.70-7.65 (m, 1H), 7.65-7.57 (m, 2H), 7.52-7.43 (m, 1H), 4.58 (s, 2H).

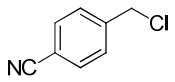
^{13}C-NMR (300 MHz, $CDCl_3$): δ / ppm = 138.8, 132.8, 131.9, 131.9, 129.6, 118.2, 112.9, 44.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060 (w), 2227 (m), 1584 (w), 1484 (m), 1445 (m), 1275 (m), 1240 (m), 1153 (m), 930 (w), 907 (m), 894 (w), 804 (s), 718 (m), 701 (vs), 679 (vs).

MS (EI, 70 eV): m/z (%) = 151 (M^+, 100), 117 (17), 116 (83), 89 (45), 63 (11).

HRMS (C_8H_6ClN): calc.: 151.0189; found: 151.0183.

4-Cyanobenzyl chloride (53p)



LiCl (1.40 g, 33.0 mmol) was dried (high vacuum, heat gun ca. 400 °C, 10 min). 4-(Bromomethyl)benzonitrile (2.16 g, 11.0 mmol) was added followed by THF (20 mL) at 25 °C. The reaction mixture was refluxed for 12 h. The resulting suspension was transferred into a separation funnel, washed with water (1 x 50 mL) and dried over $MgSO_4$ followed by filtration and evaporation of the solvents *in vacuo*. Again, LiCl (1.40 g, 33.0 mmol) was dried (high vacuum, heat gun ca. 400 °C, 10 min) and the crude product was added followed by THF (20 mL) at 0 °C. The reaction mixture was refluxed for 12 h. The resulting suspension was transferred into a separation funnel, washed with water (1 x 50 mL) and dried over $MgSO_4$ followed by the evaporation of the solvents *in vacuo*. Purification by flash chromatography (short column, silica gel, pentane / Et_2O = 5:1) afforded the benzylic chloride **53p** (1.62 g, 97%) as a white solid.

M.p. (°C): 84-85.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.64 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 4.59 (s, 2H).

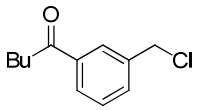
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 142.4, 132.5, 129.2, 118.4, 112.2, 45.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2228 (m), 1416 (m), 1290 (m), 1266 (m), 1212 (m), 848 (s), 830 (s), 740 (m), 708 (m), 660 (vs).

MS (EI, 70 eV): m/z (%) = 151 (M+, 61), 116 (100), 71 (14), 59 (11).

HRMS (C_8H_6ClN): calc.: 151.0189; found: 151.0184.

3-Pentanoylbenzyl chloride (53q)



Butylmagnesium chloride (12.2 mL, 18.0 mmol, 1.48 M in THF/toluene) was added to $ZnCl_2$ (18.8 mL, 18.8 mmol, 1.00 M in THF) at -25 °C. The mixture was stirred for 30 min. CuCN·2LiCl (19.5 mL, 19.5 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched with 60 mL of a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1. The phases were separated and the organic layer was extracted with 60 mL of a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1. The combined aqueous layers were extracted with Et_2O (3 x 250 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 2:1) afforded the benzylic chloride **53q** (2.89 g, 91%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.97-7.95 (m, 1H), 7.90 (dt, *J* = 7.7 Hz, 1.3 Hz, 1H), 7.60-7.56 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 4.62 (s, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 1.77-1.66 (m, 2H), 1.47-1.34 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

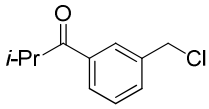
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 200.2, 138.3, 137.8, 133.1, 129.3, 128.3, 128.3, 45.9, 38.7, 26.6, 22.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957 (m), 2931 (w), 2871 (w), 1717 (w), 1682 (s), 1443 (w), 1260 (m), 1233 (w), 1199 (w), 1179 (m), 1162 (m), 1109 (w), 1036 (w), 790 (w), 760 (w), 704 (vs), 654 (m).

MS (EI, 70 eV): m/z (%) = 210 (M^+, 6), 175 (13), 170 (19), 168 (54), 155 (33), 154 (12), 153 (100), 125 (25), 89 (18).

HRMS ($C_{12}H_{15}ClO$): calc.: 210.0811; found: 210.0798.

3-Isobutyrylbenzyl chloride (53r)



$ZnCl_2$ solution (18.8 mL, 18.8 mmol, 1.00 M in THF) was added to *i*-PrMgCl·LiCl (11.3 mL, 18.0 mmol, 1.59 M in THF) at -10 °C. The mixture was stirred for 30 min. CuCN·2LiCl (19.5 mL,

19.5 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched with 100 mL of a mixture of sat. aqueous NH_4Cl / NH_3 (25% in H_2O) = 2:1. The layers were separated and the organic layer was extracted with 100 mL of a mixture of sat. aqueous NH_4Cl / NH_3 (25% in H_2O) = 2:1. The combined aqueous layers were extracted with Et_2O (3 x 250 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the ketone **53r** (2.91 g, 98%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.97-7.94 (m, 1H), 7.91-7.86 (m, 1H), 7.60-7.55 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 4.62 (s, 2H), 3.62-3.46 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 6H).

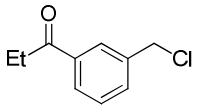
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 203.9, 138.1, 136.6, 132.8, 129.1, 128.3, 128.2, 45.6, 35.4, 19.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972 (w), 2934 (w), 2874 (w), 1682 (s), 1604 (w), 1586 (w), 1466 (w), 1444 (w), 1384 (w), 1270 (w), 1242 (m), 1186 (w), 1148 (m), 1104 (w), 1090 (w), 1022 (m), 996 (m), 924 (w), 808 (w), 702 (vs), 674 (m), 644 (m).

MS (EI, 70 eV): m/z (%) = 196 (M+, 37), 161 (62), 154 (100), 125 (29), 118 (28), 89 (94).

HRMS ($C_{11}H_{13}ClO$): calc.: 196.0655; found: 196.0656.

3-Propionylbenzyl chloride (53s)



Ethylmagnesium bromide (21.2 mL, 18.0 mmol, 0.85 M in *t*-BuOMe) was added to $ZnCl_2$ (18.8 mL, 18.8 mmol, 1.00 M in THF) at -25 °C. The mixture was stirred for 30 min. CuCN·2LiCl (19.5 mL, 19.5 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched with 60 mL of a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1. The phases were separated and the organic layer was extracted with 60 mL of a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1. The combined aqueous layers were extracted with Et_2O (3 x 250 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash

chromatography (silica gel, pentane / Et_2O = 1:1) afforded the benzylic chloride **53s** (2.89 g, 94%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.98-7.95 (m, 1 H), 7.90 (dt, *J* = 7.7 Hz, 1.3 Hz, 1H), 7.60-7.56 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 4.62 (s, 2H), 3.00 (t, *J* = 7.3 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

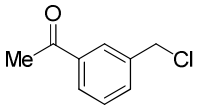
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 200.5, 138.3, 137.6, 133.1, 129.3, 128.2, 128.2, 45.9, 32.1, 8.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 1682 (s), 1604 (w), 1586 (w), 1444 (w), 1378 (w), 1350 (m), 1270 (w), 1242 (s), 1184 (m), 1164 (s), 974 (m), 786 (m), 704 (vs).

MS (EI, 70 eV): m/z (%) = 182 (M^+, 7), 153 (100), 147 (14), 125 (27), 90 (14), 89 (19), 44 (16).

HRMS ($C_{10}H_{11}ClO$): calc.: 182.0498; found: 182.0472.

3-Acetylbenzyl chloride (54t)



Methylmagnesium chloride (7.03 mL, 18.0 mmol, 2.56 M in THF) was added to $ZnCl_2$ (18.8 mL, 18.8 mmol, 1.00 M in THF) at -10 °C. The mixture was stirred for 30 min. CuCN·2LiCl (19.5 mL, 19.5 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched with 60 mL of a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1. The phases were separated and the organic layer was extracted with 60 mL of a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1. The combined aqueous layers were extracted with Et_2O (3 x 250 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the benzylic chloride **53t** (2.46 g, 97%) as colourless liquid.

^{1}H-NMR (600 MHz, C_6D_6): δ / ppm = 7.74-7.71 (m, 1H), 7.58 (dt, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.12-7.04 (m, 1H), 6.93 (t, *J* = 7.7 Hz, 1H), 4.02 (s, 2H), 2.06 (s, 3H).

^{13}C-NMR (150 MHz, C_6D_6): δ / ppm = 196.0, 138.2, 137.9, 132.8, 128.9, 128.4, 128.2, 45.5, 26.1.

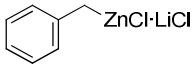
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1680 (vs), 1604 (m), 1586 (w), 1440 (m), 1428 (m), 1356 (s), 1280 (s), 1258 (s), 1192 (s), 1174 (m), 976 (w), 956 (w), 798 (m), 702 (vs), 688 (s).

MS (EI, 70 eV): m/z (%) = 168 (M^+, 3), 164 (13), 153 (17), 149 (100), 121 (17), 65 (19), 43 (19).

HRMS (C_9H_9ClO): calc.: 168.0342; found: 168.0317.

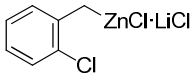
3.2. Preparation of benzylic zinc chlorides by LiCl-mediated zinc insertion into benzylic chlorides

Benzylzinc chloride (54a)



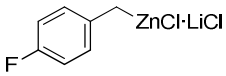
According to **TP1** benzyl chloride (**53a**) (2.53 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 20 h at 25 °C. After centrifugation iodometric titration of **54a** indicates a yield of 87%.

2-Chlorobenzylzinc chloride (54b)



According to **TP1** 2-chlorobenzyl chloride (**53b**; 3.22 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 15 min at 0 °C followed by 1.75 h at 25 °C. After centrifugation iodometric titration of **54b** indicates a yield of 99%.

4-Fluorobenzylzinc chloride (54c)

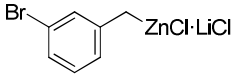


According to **TP1** 4-fluorobenzyl chloride (**53c**; 2.17 g, 15.0 mmol, in 4 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 3.5 mL THF (activation: $BrCH_2CH_2Br$ (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 24 h at 25 °C. After centrifugation iodometric titration of **54c** indicates a yield of 87%.

2-Bromobenzylzinc chloride (54d)

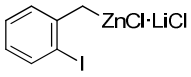
According to **TP1** 2-bromobenzyl chloride (**53d**; 3.39 g, 16.5 mmol, in 4 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.05 g, 24.8 mmol) and zinc dust (1.62 g, 24.8 mmol) in 4.3 mL THF (activation: $BrCH_2CH_2Br$ (0.07 mL, 5 mol%), TMSCl (0.02 mL,1 mol%)). The reaction mixture was stirred for 10 min at 0 °C followed by 110 min at 25 °C. After centrifugation iodometric titration of **54d** indicates a yield of 92%.

3-Bromobenzylzinc chloride (54e)



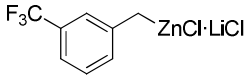
According to **TP1** 3-bromobenzyl chloride (**53e**; 4.11 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 3.5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 4 h at 25 °C. After centrifugation iodometric titration of **54e** indicates a yield of 95%.

2-Iodobenzylzinc chloride (54f)



According to **TP1** 2-iodobenzyl chloride (**53f**; 5.05 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 20 min at 0 °C followed by 100 min at 25 °C. After centrifugation iodometric titration of **54f** indicates a yield of 99%.

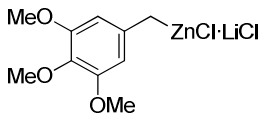
3-(Trifluoromethyl)benzylzinc chloride (54g)



According to **TP1** 3-(trifluoromethyl)benzyl chloride (**53g**; 2.92 g, 15.0 mmol, in 4 mL THF) was added dropwise at 25 °C to a suspension of LiCl (954 mg, 22.5 mmol) and zinc dust (1.47 g, 22.5 mmol) in 3.5 mL THF (activation: $BrCH_2CH_2Br$ (0.07 mL, 5 mol%), TMSCl (0.02 mL,

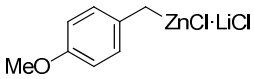
1 mol%)). The reaction mixture was stirred for 9 h at 25 °C. After centrifugation iodometric titration of **54g** indicates a yield of 94%.

3,4,5-Trimethoxybenzylzinc chloride (54h)



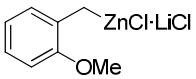
According to **TP1** 3,4,5-trimethoxybenzyl chloride (**53h**; 2.71 g, 12.5 mmol, solution in 3 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.06 g, 25.0 mmol) and zinc dust (1.64 g, 25.0 mmol) in 3.5 mL THF (activation: $BrCH_2CH_2Br$ (0.05 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The ice bath was removed and the reaction mixture was stirred for 3 h at 25 °C. After centrifugation iodometric titration of **54h** indicates a yield of 78%.

4-Methoxybenzylzinc chloride (54i)



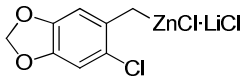
According to **TP1** 4-methoxybenzyl chloride (**53i**; 1.57 g, 10.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (636 mg, 15.0 mmol) and zinc dust (981 mg, 15.0 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.04 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 6.5 h at 25 °C. After centrifugation, iodometric titration of **54i** indicates a yield of 73%.

2-Methoxybenzylzinc chloride (54j)



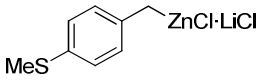
According to **TP1** 2-methoxybenzyl chloride (**53j**; 2.35 g, 15.0 mmol, in 4 mL THF) was added dropwise at 25 °C to a suspension of LiCl (954 mg, 22.5 mmol) and zinc dust (1.47 g, 22.5 mmol) in 3.5 mL THF (activation: $BrCH_2CH_2Br$ (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 4.5 h at 25 °C. After centrifugation iodometric titration of **54j** indicates a yield of 92%.

6-Chloro-1,3-benzodioxol-5-ylmethylzinc chloride (54k)



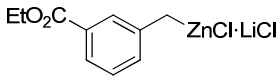
According to **TP1** 6-chloro-1,3-benzodioxol-5-ylmethyl chloride (**53k**; 4.10 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The ice bath was removed and the reaction mixture was stirred for 1 h at 25 °C. After centrifugation iodometric titration of **54k** indicates a yield of 93%.

4-(Methylthio)benzylzinc chloride (54l)



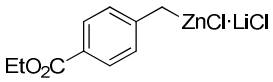
According to **TP1** 4-(methylthio)benzyl chloride (**53l**, 2.59 g, 15.0 mmol, in 3 mL THF) was added dropwise at 0 °C to a suspension of LiCl (954 mg, 22.5 mmol) and zinc dust (1.47 g, 22.5 mmol) in 4.5 mL THF (activation: $BrCH_2CH_2Br$ (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 2 h at 25 °C. After centrifugation, iodometric titration of **54l** indicates a yield of 77%.

3-(Ethoxycarbonyl)benzylzinc chloride (54m)



According to **TP1** 3-(ethoxycarbonyl)benzyl chloride (**53m**; 3.97 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.70 g, 40.0 mmol) and zinc dust (2.62 g, 40.0 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation iodometric titration of **54m** indicates a yield of 85%.

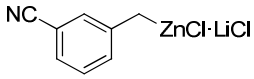
4-(Ethoxycarbonyl)benzylzinc chloride (54n)



According to **TP1** 4-(ethoxycarbonyl)benzyl chloride (**53n**; 1.99 g, 10.0 mmol, in 2.5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (848 mg, 20.0 mmol) and zinc dust (1.31 g, 20.0 mmol) in 2.5 mL THF (activation: $BrCH_2CH_2Br$ (0.04 mL, 5 mol%), TMSCl (0.01 mL,

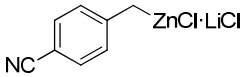
1 mol%)). The reaction mixture was stirred for 10 min at 0 °C followed by 50 min at 25 °C. After centrifugation iodometric titration of **54n** indicates a yield of 64%.

3-Cyanobenzylzinc chloride (54o)



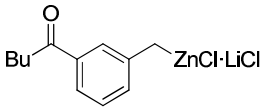
According to **TP1** 3-cyanobenzyl chloride (**53o**; 3.03 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The ice bath was removed and the reaction mixture was stirred for 3 h at 25 °C. After centrifugation iodometric titration of **54o** indicates a yield of 93%.

4-Cyanobenzylzinc chloride (54p)



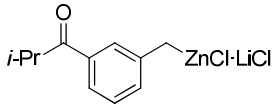
According to **TP1** 4-cyanobenzyl chloride (**53p**; 1.57 g, 10.4 mmol, in 3 mL THF) was added dropwise at 0 °C to a suspension of LiCl (660 mg, 15.6 mmol) and zinc dust (1.02 g, 15.6 mmol) in 2 mL THF (activation: $BrCH_2CH_2Br$ (0.05 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 2 h at 25 °C. After centrifugation iodometric titration of **54p** indicates a yield of 83%.

3-Pentanoylbenzylzinc chloride (54q)



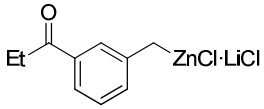
According to **TP1** 3-pentanoylbenzyl chloride (**53q**; 4.21 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation iodometric titration of **54q** indicates a yield of 72%.

3-Isobutyrylbenzylzinc chloride (54r)



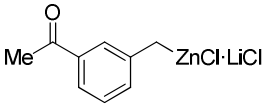
According to **TP1** 3-isobutyrylbenzyl chloride (**53r**; (2.18 g, 10.9 mmol, in 3 mL THF) was added dropwise at 25 °C to a suspension of LiCl (699 mg, 16.5 mmol) and zinc dust (1.08 g, 16.5 mmol) in 2.5 mL THF (activation: $BrCH_2CH_2Br$ (0.05 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 9 h at 25 °C. After centrifugation iodometric titration of **54r** indicates a yield of 64%.

3-Propionylbenzylzinc chloride (54s):



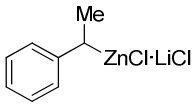
According to **TP1** 3-propionylbenzyl chloride (**53s**; 2.01 g, 11.0 mmol, in 3.5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (0.70 g, 16.5 mmol) and zinc dust (1.08 g, 16.5 mmol) in 3 mL THF (activation: $BrCH_2CH_2Br$ (0.05 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 3 h at 25 °C. After centrifugation iodometric titration of **54s** indicates a yield of 72%.

3-Acetylbenzylzinc chloride (54t)



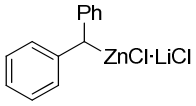
According to **TP1** 3-acetylbenzyl chloride (**54t**; 1.85 g, 11.0 mmol, in 2.5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (0.70 g, 16.5 mmol) and zinc dust (1.08 g, 16.5 mmol) in 3 mL THF (activation: $BrCH_2CH_2Br$ (0.05 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation iodometric titration of **54t** indicates a yield of 68%.

1-Phenylethylzinc chloride (54u)



According to **TP1** 1-phenylethyl chloride (**53u**; 2.81 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: $BrCH_2CH_2Br$ (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The ice bath was removed and the reaction mixture was stirred for 11 h at 25 °C. After centrifugation iodometric titration of **54u** indicates a yield of 85%.

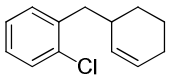
(Diphenylmethyl)zinc chloride (54v)



According to **TP1** 1,1'-(chloromethylene)dibenzene (**53v**; 3.04 g, 15.0 mmol, in 4 mL THF) was added dropwise at 0 °C to a suspension of LiCl (954 mg, 22.5 mmol) and zinc dust (1.47 g, 22.5 mmol) in 3.5 mL THF (activation: $BrCH_2CH_2Br$ (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 15 min at 0 °C followed by 4.5 h at 25 °C. After centrifugation iodometric titration of **54v** indicates a yield of 64%. (8% of the homo-coupling product was observed.

3.3. Preparation of the title compounds

1-Chloro-2-(cyclohex-2-en-1-ylmethyl)benzene (56a)



3-Bromocyclohexene (**55a**; 419 mg, 2.60 mmol) was added to 2-chlorobenzylzinc chloride (**54b**; 1.23 mL, 2.00 mmol, 1.62 M in THF) at 0 °C followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The mixture was stirred for 1.5 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (3 x 5 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane) afforded the cyclohexene **56a** (389 mg, 94%) as a colourless liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.33 (dd, *J* = 7.7 Hz, 1.3 Hz, 1H), 7.20-7.11 (m, 3H), 5.72-5.68 (m, 1H), 5.58-5.54 (m, 1H), 2.77-2.72 (m, 1H), 2.69-2.65 (m, 1H), 2.51-2.43 (m, 1H), 2.02-1.96 (m, 2H), 1.77-1.66 (m, 2H), 1.55-1.47 (m, 1H), 1.33-1.27 (m, 1H).

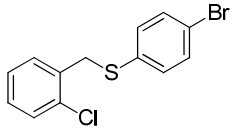
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 138.5, 134.3, 131.4, 131.0, 129.5, 127.5, 127.3, 126.4, 40.0, 35.4, 28.8, 25.4, 21.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3017 (m), 2922 (s), 2857 (m), 2834 (m), 1473 (s), 1446 (m), 1439 (m), 1052 (m), 1032 (m), 746 (vs), 718 (m), 683 (m), 665 (m).

MS (EI, 70 eV): m/z (%) = 208 (M^+, 9), 206 (31), 125 (22), 82 (12), 81 (24), 80 (100), 79 (24).

HRMS ($C_{13}H_{15}Cl$): calc.: 206.0862; found: 206.0840.

1-{[(4-Bromophenyl)thio]methyl}-2-chlorobenzene 4-bromophenyl 2-chlorobenzyl sulphide (56b)



To a solution of *S*-(4-bromophenyl) benzenesulfonothioate (**57a**; 658 mg, 2.00 mmol) in THF (4 mL) at 25 °C was added 2-chlorobenzylzinc chloride (**54b**; 1.55 mL, 2.4 mmol, 1.55 M in THF). The reaction mixture was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane) afforded the sulfide **56b** (559 mg, 89%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.40-7.33 (m, 3H), 7.23-7.10 (m, 5H), 4.18 (s, 2H).

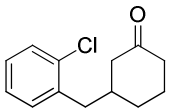
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 134.8, 134.8, 134.1, 132.4, 131.9, 130.6, 129.7, 128.7, 126.8, 120.9, 37.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1567 (w), 1471 (vs), 1442 (s), 1386 (m), 1235 (w), 1090 (s), 1068 (m), 1051 (s), 1037 (s), 1006 (vs), 804 (s), 757 (s), 741 (vs), 728 (s), 698 (m), 681 (s), 666 (m).

MS (EI, 70 eV): m/z (%) = 316 (35), 314 (50), 312 (M^+, 100), 127 (15), 125 (26), 107 (43), 98 (15), 90 (13), 89 (40), 63 (20).

HRMS ($C_{13}H_{10}BrClS$): calc.: 311.9375; found: 311.9366.

3-(2-Chlorobenzyl)cyclohexanone (56c)



According to **TP4** a mixture of cyclohex-2-en-1-one (**58a**; 480 mg, 5.00 mmol) and TMSCl (1.60 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.30 mL, 6.30 mmol, 1.00 M in THF) and 2-chlorobenzylzinc chloride (**54b**; 3.83 mL, 6.24 mmol, 1.63 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the ketone **56c** (1.03 g, 93%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.33-7.27 (m, 1H), 7.18-7.05 (m, 3H), 2.81-2.62 (m, 2H), 2.38-1.94 (m, 6H), 1.89-1.78 (m, 1H), 1.66-1.48 (m, 1H), 1.47-1.32 (m, 1H).

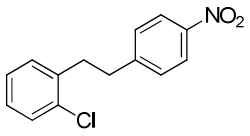
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 211.4, 137.5, 134.4, 131.5, 129.9, 128.0, 126.9, 47.9, 41.6, 40.6, 39.6, 31.2, 25.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936 (w), 2864 (w), 1708 (vs), 1476 (m), 1444 (m), 1348 (w), 1312 (w), 1224 (m), 1128 (w), 1052 (m), 1036 (m), 748 (vs), 680 (s), 596 (w).

MS (EI, 70 eV): m/z (%) = 222 (M^+, 3), 187 (39), 186 (23), 164 (18), 142 (19), 130 (10), 129 (24), 127 (11), 125 (28), 115 (16), 97 (87), 91 (29), 89 (14), 69 (100), 55 (46), 44 (15), 41 (58).

HRMS ($C_{13}H_{15}ClO$): calc.: 222.0811; found: 222.0800.

1-Chloro-2-[2-(4-nitrophenyl)ethyl]benzene (56d)



To a solution of 4-nitrobenzyl bromide (**59a**; 594 mg, 2.75 mmol) in 2.7 mL THF at 0 °C was added successively 2-chlorobenzylzinc chloride (**54b**; 2.17 mL, 3.3 mmol, 1.62 M in THF) and CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The mixture was stirred for 3 h at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (5 x 5 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the diarylethane **56d** (643 mg, 89%) as a white solid.

M.p. (°C): 67-68.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.14-8.11 (m, 2H), 7.38-7.34 (m, 1H), 7.32-7.29 (m, 2H), 7.18-7.13 (m, 2H), 7.09-7.06 (m, 1H), 3.07-3.00 (m, 4H).

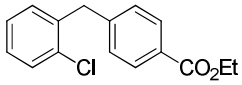
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 149.3, 146.7, 138.2, 134.1, 130.7, 129.9, 129.6, 128.1, 127.1, 123.9, 36.0, 35.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932 (w), 2854 (w), 1596 (m), 1509 (s), 1470 (m), 1457 (m), 1444 (m), 1334 (m), 1313 (m), 1256 (m), 1107 (m), 1049 (m), 1036 (m), 829 (s), 750 (vs), 698 (s).

MS (EI, 70 eV): m/z (%) = 263 (11), 261 (M^+, 29), 127 (33), 125 (100), 89 (13).

HRMS ($C_{14}H_{12}ClNO_2$): calc.: 261.0557; found: 261.0560.

Ethyl 4-(2-chlorobenzyl)benzoate (56e)



To a solution of ethyl 4-iodobenzoate (**4a**; 690 mg, 2.50 mmol) in 2.5 mL THF at 25 °C was added successively 2-chlorobenzylzinc chloride (**54b**; 1.96 mL, 3.00 mmol, 1.53 M in THF) and $Pd(PPh_3)_4$ (69 mg, 2 mol%). The resulting reaction mixture was heated to 60 °C for 5 h. After cooling to 25 °C the reaction mixture was diluted with Et_2O (5 mL) and quenched with sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (5 x 5 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the diarylmethane **56e** (667 mg, 97%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.06-8.01 (m, 3H), 7.46-7.42 (m, 1H), 7.34-7.28 (m, 2H), 7.27-7.18 (m, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.21 (s, 2H), 1.44 (t, *J* = 7.2 Hz, 3H).

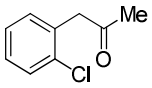
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.8, 145.0, 138.0, 134.5, 131.3, 130.0, 129.9, 129.1, 128.9, 128.2, 127.2, 61.1, 39.5, 14.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 1712 (vs), 1610 (m), 1473 (w), 1443 (m), 1415 (m), 1366 (w), 1271 (vs), 1177 (m), 1103 (s), 1050 (m), 1039 (m), 1020 (m), 747 (s).

MS (EI, 70 eV): m/z (%) = 276 (23), 275 (15), 274 (M^+, 77), 248 (10), 246 (30), 239 (13), 232 (38), 231 (17), 230 (100), 211 (21), 203 (12), 201 (32), 167 (20), 166 (39), 165 (67).

HRMS ($C_{16}H_{15}ClO_2$): calc.: 274.0671; found: 274.0748.

1-(2-Chlorophenyl)acetone (56f)



According to **TP3** acetyl chloride (**60a**; 166 mg, 2.11 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.00 mL, 3.00 mmol, 1.00 M in THF) and 2-chlorobenzylzinc chloride (**54b**; 1.96 mL, 3.00 mmol, 1.53 M in THF) at –40 °C. The reaction mixture was allowed to reach 25 °C within 13.5 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (30 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the ketone **56f** (315 mg, 89%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.41-7.34 (m, 1H), 7.26-7.16 (m, 3H), 3.83 (s, 2H), 2.19 (s, 3H).

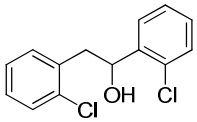
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 204.9, 134.4, 132.9, 131.6, 129.5, 128.6, 127.0, 48.3, 29.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060 (vw), 3001 (vw), 2907 (vw), 1720 (s), 1474 (m), 1444 (m), 1410 (m), 1356 (m), 1323 (m), 1219 (w), 1158 (s), 1127 (w), 1053 (s), 1040 (m), 746 (vs), 716 (m), 682 (s), 631 (m).

MS (EI, 70 eV): m/z (%) = 168 (M^+, 5), 141 (11), 133 (44), 125 (32), 91 (8), 89 (14), 59 (6), 42 (100).

HRMS (C_9H_9ClO): calc.: 168.0342; found: 168.0329.

1,2-Bis(2-chlorophenyl)ethanol (56g)



According to **TP2** 2-chlorobenzylzinc chloride (**54b**; 18.0 mL, 28.1 mmol, 1.56 M in THF) was reacted with 2-chlorobenzaldehyde (**61a**; 2.81 g, 20.0 mmol, in 10 mL THF) at 0 °C. After 3 h, the reaction mixture was quenched with sat. aq. NH_4Cl (200 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 7:1) afforded the benzylic alcohol **56g** (4.67 g, 87%) as a white solid.

M.p. (°C): 86-88.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.68-7.62 (m, 1H), 7.46-7.20 (m, 7H), 5.50 (dd, *J* = 8.8 Hz, 4.1 Hz, 1H), 3.33 (dd, *J* = 13.9 Hz, 4.1 Hz, 1H), 3.11 (dd, *J* = 13.7 Hz, 8.9 Hz, 1H), 2.07 (s, 1H).

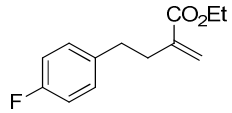
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.1, 135.5, 134.6, 132.0 (double), 129.6, 129.4, 128.6, 128.1, 127.3, 127.1, 126.7, 70.2, 41.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3332 (w), 3257 (w), 2939 (w), 1572 (w), 1473 (m), 1442 (m), 1433 (m), 1346 (w), 1176 (w), 1123 (w), 1056 (m), 1047 (s), 1030 (s), 996 (m), 758 (vs), 746 (vs), 723 (s), 699 (s), 680 (m), 628 (m), 585 (m), 558 (s), 555 (s).

MS (EI, 70 eV): m/z (%) = 266 (M^+, 1), 178 (7), 143 (34), 141 (100), 128 (18), 126 (58), 113 (15), 91 (16), 77 (48).

HRMS ($C_{14}H_{12}Cl_2O$): calc.: 266.0265; found: 266.0251.

Ethyl 2-[2-(4-fluorophenyl)ethyl]acrylate (56h)



To a solution of ethyl (2-bromo)methylacrylate (**55b**; 965 mg, 5.00 mmol) in 3 mL THF at -60 °C was added 4-fluorobenzylzinc chloride (**54c**; 4.12 mL, 6.00 mmol, 1.45 M in THF) followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 1.5 h, followed by stirring at 0 °C for additional 30 min. Workup as usual and purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the acrylate **56h** (1.03 g, 93%) as colourless liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.14-7.10 (m, 2H), 6.97-6.92 (m, 2H), 6.15-6.13 (m, 1H), 5.47-5.45 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.79-2.72 (m, 2H), 2.61-2.54 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H).

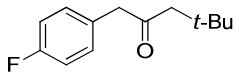
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 167.0, 161.3 (d, $^1J_{C-F}$ = 243.7 Hz), 139.9, 137.0 (d, $^4J_{C-F}$ = 3.1 Hz), 129.8 (d, $^3J_{C-F}$ = 7.6 Hz), 125.2, 115.0 (d, $^2J_{C-F}$ = 21.0 Hz), 60.6, 34.1, 34.0, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932 (w), 2984 (w), 1632 (w), 1304 (m), 524 (m), 944 (m), 1028 (m), 1092 (m), 1156 (m), 820 (s), 1132 (s), 1220 (s), 1184 (s), 1712 (s), 1508 (s).

MS (EI, 70 eV): m/z (%) = 222 (M^+, 5), 209 (9), 176 (13), 148 (7), 109 (100), 101 (8), 83 (6).

HRMS ($C_{13}H_{15}FO_2$): calc.: 222.1056; found: 222.1032.

1-(4-Fluorophenyl)-4,4-dimethylpentan-2-one (56i)



According to **TP3** 3,3-dimethylbutyryl chloride (**60b**; 377 mg, 2.80 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.92 mL, 3.92 mmol, 1.00 M in THF) and 4-fluorobenzylzinc chloride (**54c**; 2.69 mL, 3.93 mmol, 1.46 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 4:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the ketone **56i** (555 mg, 95%) as a pale yellow liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.15-7.10 (m, 2H), 7.02-6.97 (m, 2H), 3.36 (s, 1H), 2.35 (s, 1H), 1.00 (s, 9H).

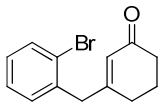
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 207.8, 162.1 (d, $^1J_{C-F}$ = 245.1 Hz), 131.2 (d, $^3J_{C-F}$ = 8.1 Hz), 130.1 (d, $^4J_{C-F}$ = 3.4 Hz), 115.7 (d, $^2J_{C-F}$ = 21.6 Hz), 54.4, 51.2, 31.3, 29.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956 (m), 1712 (s), 1508 (vs), 1364 (m), 1352 (m), 1220 (vs), 1160 (m), 1084 (m), 1064 (m), 824 (m), 780 (m), 524 (m).

MS (EI, 70 eV): m/z (%) = 208 (M^+, 3), 109 (53), 99 (60), 71 (17), 57 (100), 43 (13), 42 (16).

HRMS ($C_{13}H_{17}FO$): calc.: 208.1263; found: 208.1261.

3-(2-Bromobenzyl)cyclohex-2-en-1-one (56j)



According to **TP4** 3-iodocyclohex-2-en-1-one (**58b**; 666 mg, 3.00 mmol) was added dropwise at –60 °C to a mixture of CuCN·2LiCl (3.90 mL, 3.90 mmol, 1.00 M in THF) and 2-bromobenzylzinc chloride (**54d**; 2.52 mL, 3.90 mmol, 1.55 M in THF). The reaction mixture was allowed to reach slowly 0 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 2:1) afforded the unsaturated ketone **56j** (779 mg, 96%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.55 (dd, *J* = 8.0 Hz, 1.3 Hz, 1H), 7.29-7.22 (m, 1H), 7.19-7.07 (m, 2H), 5.68-5.64 (m, 1H), 3.65 (s, 2H), 2.40-2.29 (m, 4H), 2.05-1.94 (m, 2H).

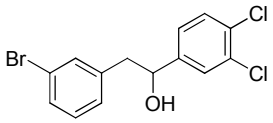
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.6, 163.3, 136.6, 133.1, 131.2, 128.7, 127.6, 127.0, 125.1, 43.9, 37.3, 29.7, 22.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054 (vw), 2944 (w), 2926 (w), 2887 (w), 2868 (w), 2823 (vw), 1664 (vs), 1627 (m), 1567 (w), 1470 (m), 1426 (m), 1371 (m), 1348 (m), 1323 (m), 1245 (m), 1190 (m), 1131 (w), 1023 (s), 967 (m), 884 (m), 749 (vs), 659 (s).

MS (EI, 70 eV): m/z (%) = 264 (M^+, 53), 235 (55), 185 (50), 15 (66), 129 (100), 115 (14), 90 (12), 67 (24).

HRMS ($C_{13}H_{13}BrO$): calc.: 264.0150; found: 264.0142.

2-(3-Bromophenyl)-1-(3,4-dichlorophenyl)ethanol (56k)



According to **TP2** 3-bromobenzylzinc chloride (**54e**; 1.72 mL, 2.68 mmol, 1.56 M in THD) was reacted with 3,4-dichlorobenzaldehyde (**61b**; 361 mg, 2.1 mmol, in 1.5 mL THF). After 17 h the reaction mixture was quenched with sat. aq. NH_4Cl solution. Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the alcohol **56k** (699 mg, 98%) as a white solid.

M.p. (°C): 64-65.

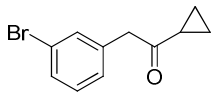
^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.43 (d, *J* = 2.0 Hz, 1H), 7.41-7.34 (m, 3H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.12 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 4.81 (dd, *J* = 8.4 Hz, 4.6 Hz, 1H), 2.96-2.85 (m, 2H), 2.09 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 143.6, 139.6, 132.6, 132.4, 131.5, 130.4, 130.1, 130.0, 128.1, 127.8, 125.1, 122.6, 73.8, 45.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3288 (m), 1564 (m), 1470 (s), 1424 (m), 1202 (m), 1128 (m), 1070 (s), 1046 (s), 1026 (s), 998 (s), 884 (s), 782 (vs), 668 (vs).

HRMS (ESI; $C_{15}H_{12}BrCl_2O_3$): calc.: 388.9352 ($[M+HCO_2]^-$); found: 388.9360 ($[M+HCO_2]^-$).

2-(3-Bromophenyl)-1-cyclopropylethanone (56l)



According to **TP3** cyclopropanecarbonyl chloride (**60c**; 320 mg, 3.07 mmol) was added dropwise to a mixture of CuCN·2LiCl (4.2 mL, 4.2 mmol, 1.00 M in THF) and 3-bromobenzylzinc chloride (**54e**; 2.75 mL, 4.2 mmol, 1.53 M in THF) at -40 °C. The reaction mixture was allowed to reach

0 °C within 18 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the ketone **56l** (675 mg, 92%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.42-7.35 (m, 2H), 7.23-7.10 (m, 2H), 3.79 (s, 2H), 2.00-1.89 (m, 1H), 1.08-1.00 (m, 2H), 0.91-0.83 (m, 2H).

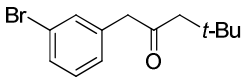
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 207.3, 136.5, 132.5, 130.1, 130.0, 128.2, 122.6, 49.9, 20.2, 11.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} =3007 (w), 1693 (s), 1593 (w), 1567 (m), 1474 (m), 1428 (m), 1379 (s), 1205 (m), 1066 (vs), 1021 (m), 997 (m), 900 (m), 886 (m), 816 (m), 787 (m), 766 (s), 695 (s), 681 (m), 670 (m), 664 (m), 600 (m), 568 (m), 565 (m).

MS (EI, 70 eV): m/z (%) = 238 (M^+, 4), 168 (7), 90 (8), 69 (100), 59 (6), 45 (5), 44 (16), 40 (21).

HRMS ($C_{11}H_{11}BrO$): calc.: 237.9993; found: 237.9983.

1-(3-Bromophenyl)-4,4-dimethylpentan-2-one (56m)



According to **TP3** 3,3-dimethylbutyryl chloride (**60b**; 581 mg, 4.32 mmol) was added dropwise to a mixture of CuCN·2LiCl (6.02 mL, 6.02 mmol, 1.00 M in THF) and 3-bromobenzylzinc chloride (**54e**; 1.72 mL, 6.02 mmol, 1.53 M in THF) at -60 °C. The reaction mixture was allowed to reach -20 °C overnight and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the ketone **56m** (1.11 g, 96%) as a pale yellow liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.40-7.37 (m, 1H), 7.33-7.32 (m, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.11-7.08 (m, 1H), 3.62 (s, 2H), 2.35 (s, 2H), 1.00 (s, 9H).

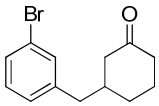
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 206.9, 136.4, 132.5, 130.1, 130.0, 128.2, 122.6, 54.3, 51.3, 31.1, 29.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2868 (m), 1596 (m), 1188 (m), 1222 (m), 996 (m), 1428 (m), 1350 (m), 1568 (m), 2954 (m), 668 (s), 1364 (s), 696 (s), 1474 (s), 772 (s), 1072 (vs), 1714 (vs).

MS (EI, 70 eV): m/z (%) = 268 (M^+, 6), 180 (16), 169 (16), 99 (100), 90 (15), 71 (14), 57 (79).

HRMS ($C_{13}H_{17}BrO$): calc.: 268.0463; found: 268.0457.

3-(3-Bromobenzyl)cyclohexanone (56n)



According to **TP4** a mixture of cyclohex-2-en-1-one (**58a**; 480 mg, 5.00 mmol) and TMSCl (1.60 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.25 mL, 6.25 mmol, 1.00 M in THF) and 3-bromobenzylzinc chloride (**56e**; 4.08 mL, 6.25 mmol, 1.53 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 16 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (60 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the ketone **56n** (1.22 g, 91%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.36-7.30 (m, 1H), 7.29-7.25 (m, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.07-7.00 (m, 1H), 2.65-2.50 (m, 2H), 2.43-2.17 (m, 3H), 2.12-1.94 (m, 3H), 1.91-1.79 (m, 1H), 1.70-1.52 (m, 1H), 1.43-1.28 (m 1H).

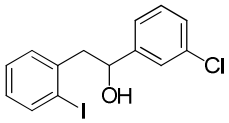
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 211.0, 141.7, 132.0, 129.9, 129.3, 127.7, 122.4, 47.6, 42.5, 41.3, 40.6, 30.8, 25.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926 (m), 1707 (vs), 1565 (m), 1473 (m), 1447 (m), 1424 (m), 1224 (m), 1070 (m), 997 (m), 857 (m), 778 (m), 753 (m), 696 (m), 668 (m).

MS (EI, 70 eV): m/z (%) = 266 (M^+, 31), 210 (38), 208 (38), 170 (12), 129 (26), 115 (12), 97 (100), 90 (16), 69 (70), 55 (38), 40 (37).

HRMS ($C_{13}H_{15}BrO$): calc.: 266.0306; found: 266.0297.

1-(3-Chlorophenyl)-2-(2-iodophenyl)ethanol (56o)



According to **TP2** 2-iodobenzylzinc chloride (**54f**; 1.28 mL, 1.96 mmol, 1.53 M in THF) was reacted with 3-chlorobenzaldehyde (**61c**; 211 mg, 1.5 mmol, in 1.5 mL THF). After 5 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 to 7:3) afforded the alcohol **56o** (470 mg, 87%) as a pale yellow solid.

M.p. (°C): 68-70.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.86 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.46-7.44 (m, 1H), 7.30-7.24 (m, 4H), 7.18 (dd, *J* = 7.5 Hz, 1.8 Hz, 1H), 6.96-6.93 (m, 1H), 5.01-4.97 (m, 1H), 3.17-3.13 (m 1H), 3.08-3.03 (m, 1 H), 1.92 (d, *J* = 3.3 Hz, 1H).

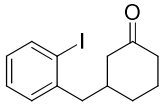
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 145.7, 140.4, 139.7, 134.4, 131.3, 129.7, 128.7, 128.3, 127.8, 125.9, 123.9, 100.9, 72.8, 50.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3322 (w), 3252 (w), 1596 (w), 1575 (w), 1468 (m), 1435 (m), 1198 (m), 1055 (s), 1015 (s), 884 (m), 783 (s), 746 (s), 725 (s), 695 (vs).

MS (EI, 70 eV): m/z (%) = 358 (M^+, 1), 218 (100), 142 (8), 141 (27), 77 (13).

HRMS ($C_{14}H_{12}ClIO$): calc.: 357.9621; found: 357.9629.

3-(2-Iodobenzyl)cyclohexanone (56p)



According to **TP4** a mixture of cyclohex-2-en-1-one (**58a**; 480 mg, 5.00 mmol) and TMSCl (1.60 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.30 mL, 6.30 mmol, 1.00 M in THF) and 2-iodobenzylzinc chloride (**54f**; 4.81 mL, 6.25 mmol, 1.30 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the ketone **56p** (1.13 g, 72%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.80 (dd, *J* = 7.8 Hz, 1.2 Hz, 1 H), 7.28-7.22 (m, 1H), 7.13-7.09 (m, 1H), 6.91-6.85 (m, 1H), 2.82-2.64 (m, 2H), 2.43-1.98 (m, 6H), 1.95-1.83 (m, 1H), 1.70-1.53 (m, 1H), 1.53-1.37 (m, 1H).

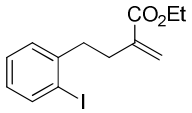
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 211.3, 142.2, 139.7, 130.4, 128.1 (overlap), 101.0, 47.6, 47.2, 41.4, 39.5, 30.9, 25.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933 (m), 2863 (m), 1706 (vs), 1466 (m), 1446 (m), 1224 (m), 1008 (s), 744 (s), 646 (m).

MS (EI, 70 eV): m/z (%) = 314 (M^+, 9), 217 (18), 188 (13), 187 (100), 1269 (15), 115 (16), 97 (66), 91 (22), 89 (12), 69 (72), 55 (34), 41 (33).

HRMS ($C_{13}H_{15}IO$): calc.: 314.0168; found: 314.0166.

Ethyl 2-[2-(2-iodophenyl)ethyl]acrylate (56p)



2-Iodobenzylzinc chloride (**54f**; 3.92 mL, 6.00 mmol, 1.53 M in THF) was added to a solution of ethyl (2-bromomethyl)acrylate (**55b**; 965 mg, 5.00 mmol) in 3 mL THF at -60 °C followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 9:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 1 vol-% NEt_3) afforded the acrylate **56p** (1.42 g, 86%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.80 (d, *J* = 6.9 Hz, 1H), 7.32-7.14 (m, 2H), 6.93-6.81 (m, 1H), 6.17 (s, 1H), 5.53 (d, *J* = 1.4 Hz, 1H), 4.22 (d, *J* = 7.2 Hz, 2H), 2.95-2.85 (m, 2H), 2.63-2.54 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H).

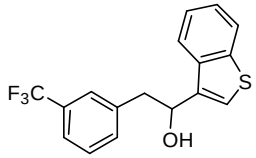
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.0, 143.9, 139.7, 139.4, 129.6, 128.3, 127.8, 125.5, 100.4, 60.7, 39.9, 32.4, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057 (vw), 2978 (w), 2932 (w), 2903 (vw), 2868 (vw), 1711 (vs), 1629 (m), 1562 (w), 1465 (m), 1368 (m), 1299 (m), 1251 (m), 1240 (m), 1180 (vs), 1136 (vs), 1102 (m), 1027 (m), 1010 (s), 943 (m), 814 (m), 747 (vs), 717 (m), 645 (s).

MS (EI, 70 eV): m/z (%) = 330 (M^+, 2), 217 (100), 175 (14), 157 (12), 131 (13), 129 (51), 90 (26), 64 (6).

HRMS ($C_{13}H_{15}IO_2$): calc.: 330.0117; found: 330.0110.

1-(1-Benzothien-3-yl)-2-[3-(trifluoromethyl)phenyl]-ethanol (56r)



According to **TP2** 3-(trifluoromethyl)benzylzinc chloride (**54g**; 1.39 mL, 2.09 mmol, 1.50 M in THF) was reacted with benzothiophene-3-carbaldehyde (**61d**; 260 mg, 1.60 mmol, in 0.5 mL THF) at 0 °C. The ice-bath was removed. After 6 h, the reaction mixture was quenched with sat. aq. NH_4Cl (50 mL). The phases were separated and the aq. layer was extracted with CH_2Cl_2

(3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the benzylic alcohol **56r** (441 mg, 86%) as a yellow oil.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.68-7.64 (m, 1H), 7.59-7.55 (m, 1H), 7.39 (s, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.20-7.15 (m, 1H), 7.12-7.07 (m, 1H), 6.92-6.88 (m, 1H), 6.86 (t, *J* = 7.7 Hz, 1H), 6.78-6.76 (m 1H), 4.68 (t, *J* = 6.3 Hz, 1H), 2.79 (d, *J* = 6.2 Hz, 2H), 1.24 (s, 1H).

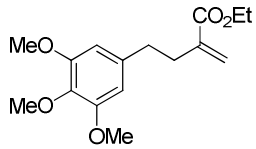
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 141.3, 139.7, 139.2, 137.5, 133.2 (q, $^4J_{C\text{-}F}$ = 1.2 Hz), 130.6 (q, $^2J_{C\text{-}F}$ = 31.7 Hz), 128.7, 126.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 125.0 (q, $^1J_{C\text{-}F}$ = 272.5 Hz), 124.7, 124.2, 123.4 (q, *J* = 3.8 Hz), 123.2, 122.6, 122.6, 70.5, 43.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2970 (w), 2919 (w), 1739 (m), 1450 (m), 1428 (m), 1365 (m), 1326 (s), 1217 (m), 1201 (m), 1160 (s), 1118 (vs), 1098 (s), 1072 (s), 797 (m), 761 (s), 732 (s), 701 (s), 657 (s).

MS (EI, 70 eV): m/z (%) = 322 (M^+, 2), 240 (2), 164 (100), 135 (21), 91 (8).

HRMS ($C_{17}H_{13}F_3OS$): calc.: 322.0639; found: 322.0630.

Ethyl 2-[2-(3,4,5-trimethoxyphenyl)ethyl]acrylate (56s)



To a solution of ethyl (2-bromomethyl)acrylate (**55b**; 579 mg, 3.00 mmol) in 1.5 mL THF at -60 °C was added 3,4,5-trimethoxybenzylzinc chloride (**54h**; 7.40 mL, 3.75 mmol, 0.51 M in THF) followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (3 x 20 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 7:1) afforded the acrylate **56s** (867 mg, 98%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 6.36 (s, 2H), 6.11 (s, 1H), 5.48 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 6H), 3.77 (s, 3H), 2.73–2.63 (m, 2H), 2.62-2.51 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

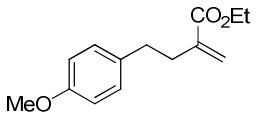
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.3, 153.3, 140.3, 137.5, 136.4, 125.3, 105.6, 61.0, 60.8, 56.2, 35.6, 34.2, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936 (w), 2840 (w), 1712 (m), 1588 (m), 1508 (m), 1456 (m), 1420 (m), 1332 (m), 1236 (s), 1184 (s), 1120 (vs), 1008 (m), 944 (m), 820 (m).

MS (EI, 70 eV): m/z (%) = 294 (M^+, 31), 182 (20), 181 (100), 148 (7), 121 (9).

HRMS ($C_{16}H_{22}O_5$): calc.: 294.1467; found: 294.1457.

Ethyl 2-[2-(4-methoxyphenyl)ethyl]acrylate (**56t**)



To a solution of ethyl 2-bromomethylacrylate (**55b**; 772 mg, 4.00 mmol) in THF (2 mL) at -40 °C was added 4-methoxybenzylzinc chloride (**54i**; 7.19 mL, 5.00 mmol, 0.70 M in THF) followed by CuCN·2LiCl (0.01 mL, 1.00 M in THF). The reaction mixture was stirred at -40 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (3 x 50 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the acrylate **56t** (0.91 g, 97%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.14-7.06 (m, 2H), 6.86–6.79 (m, 2H), 6.15-6.13 (m, 1H), 5.49-5.46 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.78–2.69 (m, 2H), 2.62-2.53 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

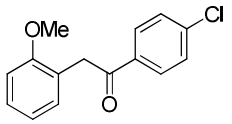
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.1, 157.8, 140.2, 133.5, 129.3, 125.0, 113.7, 60.6, 55.2, 34.1, 34.0, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936 (w), 1712 (s), 1612 (m), 1512 (vs), 1300 (m), 1244 (vs), 1176 (vs), 1132 (s), 1104 (m), 1032 (s), 944 (m), 816 (s), 520 (m).

MS (EI, 70 eV): m/z (%) = 234 (M^+, 50), 189 (31), 161 (12), 121 (100), 115 (10), 91 (25), 77 (30).

HRMS ($C_{14}H_{18}O_3$): calc.: 234.1256; found: 234.1233.

1-(4-Chlorophenyl)-2-(2-methoxyphenyl)ethanone (56u)



According to **TP3** 4-chlorobenzoyl chloride (**60d**; 411 mg, 2.35 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.29 mL, 3.29 mmol, 1.00 M in THF) and 2-methoxybenzylzinc chloride (**54i**; 2.19 mL, 3.29 mmol, 1.50 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 21 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 14:1) afforded the ketone **56u** (605 mg, 99%) as a white solid.

M.p. (°C): 56-57.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.99-7.94 (m, 2H), 7.44-7.38 (m, 2H), 7.29-7.22 (m, 1H), 7.16 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H), 6.95-6.85 (m, 2H), 4.23 (s, 2H), 3.78 (s, 3H).

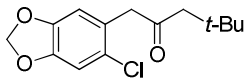
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 196.8, 157.0, 139.2, 135.2, 130.9, 129.8, 128.8, 128.5, 123.4, 120.7, 110.6, 55.4, 39.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2988 (w), 2954 (w), 2940 (w), 2912 (w), 2832 (w), 1692 (vs), 1590 (s), 1494 (s), 1466 (m), 1398 (m), 1334 (s), 1288 (m), 1238 (vs), 1208 (s), 1196 (s), 1174 (m), 1110 (s), 1086 (s), 1026 (s), 992 (s), 816 (vs), 766 (vs), 758 (vs), 568 (m).

MS (EI, 70 eV): m/z (%) = 260 (M^+, 19), 141 (31), 139 (100), 121 (22), 111 (14), 91 (24).

HRMS ($C_{15}H_{13}ClO_2$): calc.: 260.0604; found: 260.0599.

1-(6-Chloro-1,3-benzodioxol-5-yl)-4,4-dimethylpentan-2-one (56v)



According to **TP3** 3,3-dimethylbutyryl chloride (**60b**; 377 mg, 2.80 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.92 mL, 3.92 mmol, 1.00 M in THF) and 6-chloro-1,3-benzodioxol-5-ylmethylzinc chloride (**54k**; 2.80 mL, 3.92 mmol, 1.40 M in THF) at -60 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 95:5) afforded the ketone **56v** (703 mg, 93%) as a pale yellow liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 6.84 (s, 1H), 6.63 (s, 1H), 5.95 (s, 2H), 3.70 (s, 2H), 2.38 (s, 2H), 1.02 (s, 9H).

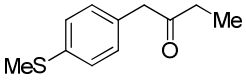
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 206.5, 147.4, 146.7, 126.0, 125.7, 110.9, 109.8, 101.7, 54.3, 49.2, 31.0, 29.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952 (m), 2904 (w), 1716 (m), 1504 (s), 1480 (vs), 1364 (m), 1248 (s), 1232 (s), 1120 (s), 1036 (vs), 984 (m), 932 (s), 840 (s), 724 (w), 684 (w).

MS (EI, 70 eV): m/z (%) = 268 (77), 171 (76), 169 (50), 110 (23), 99 (100), 71 (65), 57 (43), 41 (33).

HRMS ($C_{14}H_{17}ClO_3$): calc.: 268.0866; found: 268.0855.

1-[4-(Methylthio)phenyl]butan-2-one (**56w**)



According to **TP3** propanoyl chloride (**60e**; 95.3 mg, 1.03 mmol, in 0.5 mL THF) was added dropwise at -20 °C to a mixture of CuCN·2LiCl (0.50 mL, 0.50 mmol, 1.00 M in THF) and 4-(methylthio)benzylzinc chloride (**54l**; 0.85 mL, 1.20 mmol, 1.42 M in THF). The reaction mixture was stirred at 0 °C and slowly warmed to 25 °C within 4 h. Then, a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL) was added and the phases were separated. The aq. layer was extracted with Et_2O (5 x 20 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the ketone **56w** (143 mg, 71%) as a white solid.

M.p. (°C): 42-43.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.23-7.19 (m, 2H), 7.13-7.10 (m, 2H), 3.63 (s, 2H) 2.46 (q, *J* = 7.3 Hz, 2H), 2.46 (s, 3H), 1.02 (t, *J* = 7.3 Hz, 3H).

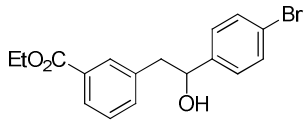
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 208.8, 137.0, 131.3, 129.8, 127.0, 49.2, 35.2, 16.0, 7.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2937 (w), 2922 (w), 2903 (w), 1711 (vs), 1601 (w), 1496 (s), 1456 (m), 1438 (m), 1413 (s), 1378 (m), 1351 (m), 1317 (m), 1111 (s), 1098 (m), 1087 (m), 1038 (s), 1020 (m), 993 (m), 969 (m), 959 (m), 866 (m), 823 (m), 803 (vs), 725 (m), 667 (m).

MS (EI, 70 eV): m/z (%) = 194 (M^+, 26), 137 (100), 122 (11), 57 (10).

HRMS ($C_{11}H_{14}OS$): calc.: 194.0765; found: 194.0747.

Ethyl 3-[2-(4-bromophenyl)-2-hydroxyethyl]benzoate (56x)



According to **TP2** 3-(ethoxycarbonyl)benzylzinc chloride (**54m**; 4.10 mL, 5.33 mmol, 1.30 M in THF) was reacted with 4-bromobenzaldehyde (**61e**; 775 mg, 4.2 mmol, in 3 mL THF). After 4.5 h the reaction mixture was quenched with sat. aq. NH_4Cl solution. Purification by flash chromatography (silica gel, pentane / Et_2O = 7:3) afforded the alcohol **56x** (1.33 g, 91%) as a white solid.

M.p. (°C): 65-66.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.92-7.90 (m, 1H), 7.86-7.85 (m, 1H), 7.47-7.44 (m, 2H), 7.37-7.30 (m, 2H), 7.22-7.19 (m, 2H), 4.91-4.87 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.04-3.01 (m, 2H), 1.97 (d, *J* = 3.1 Hz, 1H), 1.39 (t, *J* = 7.2 Hz, 3H).

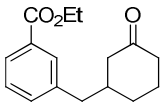
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 166.5, 142.5, 137.9, 134.1, 131.5, 130.7, 130.4, 128.5, 127.9, 127.6, 121.5, 74.6, 61.0, 45.6, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3466 (w), 1704 (s), 1682 (s), 1484 (m), 1446 (m), 1400 (m), 1366 (m), 1278 (s), 1200 (s), 1108 (s), 1066 (s), 1024 (s), 1004 (s), 746 (vs), 698 (s).

MS (EI, 70 eV): m/z (%) = 348 (M^+, <1), 164 (100), 136 (29), 135 (13), 118 (10), 92 (10), 91 (16), 90 (11), 78 (10), 77 (20).

HRMS ($C_{17}H_{17}BrO_3$): calc.: 348.0361; found: 348.0372.

Ethyl 3-[(3-oxocyclohexyl)methyl]benzoate (56y)



According to **TP4** a mixture of cyclohex-2-en-1-one (**58a**; 480 mg, 5.0 mmol) and TMSCl (1.60 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.30 mL, 6.30 mmol, 1.0 M in THF) and 3-(ethoxycarbonyl)benzylzinc chloride (**54m**; 4.46 mL, 6.24 mmol, 1.40 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 5:1 to 1:1) afforded the cyclohexanone **56y** (1.26 g, 97%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.82-7.78 (m, 1H), 7.74-7.72 (m, 1H), 7.28-7.24 (m, 1H), 7.24-7.21 (m, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.63-2.53 (m, 2H), 2.28-2.21 (m, 2H), 2.20-2.13 (m, 1H), 2.01-1.89 (m, 3H), 1.79-1.73 (m, 1H), 1.57-1.47 (m, 1H), 1.33-1.25 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H).

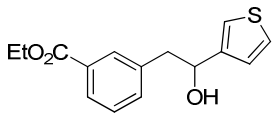
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 211.2, 166.7, 140.0, 133.7, 130.8, 130.2, 128.6, 127.7, 61.1, 47.8, 42.9, 41.5, 40.9, 31.0, 25.2, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936 (w), 1708 (vs), 1444 (m), 1368 (w), 1276 (vs), 1196 (s), 1108 (s), 1024 (m), 864 (w), 748 (s), 700 (m), 672 (w).

MS (EI, 70 eV): m/z (%) = 260 (M^+, 30), 215 (36), 214 (79), 164 (26), 129 (39), 121 (83), 115 (20), 97 (80), 91 (33), 69 (100), 55 (46), 41 (50).

HRMS ($C_{16}H_{20}O_3$): calc.: 260.1412; found: 260.1386.

Ethyl 3-[2-hydroxy-2-(3-thienyl)ethyl]benzoate (56z)



According to **TP2** 3-(ethoxycarbonyl)benzylzinc chloride (**54m**; 3.07 mL, 3.90 mmol, 1.27 M in THF) was reacted with 3-thiophencarbaldehyde (**61f**; 337 mg, 3.00 mmol, in 1.5 mL THF) at 0 °C. After 22 h at 25 °C, the reaction mixture was quenched with sat. aq. NH_4Cl (50 mL). The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the benzylic alcohol **56z** (730 mg, 88%) as a pale yellow solid.

M.p. (°C): 44-46.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.94-7.82 (m, 2H), 7.37-7.26 (m, 3H), 7.14-7.08 (m, 1H), 7.09-7.03 (m, 1H), 4.99 (dd, *J* = 6.9 Hz, 6.4 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.16-3.00 (m, 2H), 2.22 (s, 1H), 1.37 (t, *J* = 7.2 Hz, 3H).

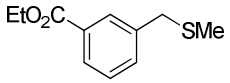
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.6, 145.0, 138.2, 134.0, 130.5, 130.4, 128.3, 127.7, 126.1, 125.5, 120.9, 71.2, 60.9, 44.8, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3350 (w), 3267 (w), 3100 (w), 2980 (w), 2924 (w), 1711 (vs), 1605 (w), 1587 (w), 1472 (w), 1443 (m), 1363 (m), 1279 (s), 1261 (s), 1196 (s), 1106 (s), 1060 (s), 1029 (s), 922 (m), 853 (s), 792 (s), 757 (s), 727 (vs), 673 (m).

MS (EI, 70 eV): m/z (%) = 276 (M^+, 1), 231 (13), 164 (100), 136 (42), 118 (12), 113 (35), 91 (18), 85 (22).

HRMS ($C_{15}H_{16}O_3S$): calc.: 276.0820; found: 276.0817.

Ethyl 3-[(methylthio)methyl]benzoate (56aa)



3-(Ethoxycarbonyl)benzylzinc chloride (**54m**; 1.82 mL, 2.40 mmol, 1.32 M in THF) was added dropwise to *S*-methyl methanethiosulfonate (**57b**; 254 mg, 2.01 mmol) at 25 °C. After 25 h, the reaction mixture was quenched with sat. aq. NH_4Cl (25 mL). The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane) afforded the thioether **56aa** (370 mg, 88%) as a yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.98-7.88 (m, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 2H), 1.98 (s, 3H), 1.38 (q, *J* = 7.2 Hz, 3H).

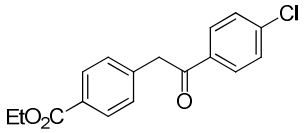
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 138.7, 133.2, 130.7, 129.8, 128.5, 128.2, 61.0, 38.0, 14.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979 (w), 2914 (w), 1713 (vs), 1605 (w), 1587 (w), 1442 (m), 1366 (m), 1303 (m), 1277 (vs), 1236 (s), 1190 (s), 1102 (s), 1078 (s), 1021 (m), 912 (w), 863 (w), 818 (w), 761 (m), 730 (s), 714 (m), 699 (s), 682 (m).

MS (EI, 70 eV): m/z (%) = 210 (M^+, 28), 181 (11), 163 (100), 135 (18), 119 (39), 91 (12), 77 (6).

HRMS ($C_{11}H_{14}O_2S$): calc.: 210.0715; found: 210.0711.

Ethyl 4-[2-(4-chlorophenyl)-2-oxoethyl]benzoate (56ab)



According to **TP3** 4-chlorobenzoyl chloride (**60d**; 350 mg, 2.00 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.60 mL, 2.60 mmol, 1.00 M in THF) and 4-(ethoxycarbonyl)benzylzinc chloride (**54n**; 2.20 mL, 2.60 mmol, 1.18 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 20 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in

H_2O) = 2:1 (50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the ketone **56ab** (261 mg, 43%) as a white solid.

M.p. (°C):141-143.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.03-7.97 (m, 2H), 7.95-7.89 (m, 2H), 7.46-7.39 (m, 2H), 7.34-7.28 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.30 (s, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

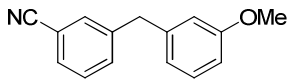
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 195.6, 166.3, 139.9, 139.2, 134.6, 129.9 (double), 129.5, 129.3, 129.0, 60.9, 45.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981 (m), 2970 (m), 2928 (m), 1739 (s), 1728 (s), 1705 (s), 1681 (vs), 1586 (m), 1489 (m), 1399 (m), 1366 (s), 1267 (s), 1229 (s), 1216 (s), 1200 (s), 1091 (s), 1022 (s), 1015 (m), 992 (s), 930 (m), 875 (m), 824 (s), 797 (m), 758 (vs), 725 (s).

MS (EI, 70 eV): m/z (%) = 302 (M^+, 1), 257 (8), 141 (31), 139 (100), 111 (13).

HRMS ($C_{17}H_{15}ClO_3$): calc.: 302.0710; found: 302.0716.

3-(3-Methoxybenzyl)benzonitrile (56ac)



To a solution of 3-iodoanisole (**4b**; 585 mg, 2.5 mmol) in 2.0 mL THF at 25 °C was added successively 3-cyanobenzylzinc chloride (**54o**; 2.03 mL, 3.00 mmol, 1.48 M in THF) and $Pd(PPh_3)_4$ (139 mg, 5.0 mol%). The resulting reaction mixture was heated to 60 °C for 5 h. After cooling to 25 °C, the reaction mixture was diluted with Et_2O (5 mL) and quenched with sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (5 x 5 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the diarylmethane **56ac** (492 mg, 88%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.51-7.34 (m, 4H), 7.26-7.20 (m, 1H), 6.81-6.67 (m, 3H), 3.97 (s, 2H), 3.78 (s, 3H).

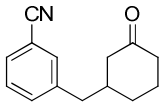
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2, 142.7, 141.2, 133.6, 132.6, 130.2, 130.0, 129.5, 121.5, 119.2, 115.2, 112.8, 112.0, 55.4, 41.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2937 (w), 2228 (s), 1596 (s), 1582 (s), 1488 (s), 1453 (m), 1435 (m), 1257 (vs), 1151 (m), 1048 (s), 779 (m), 741 (m), 686 (s).

MS (EI, 70 eV): m/z (%) = 224 (15), 223 (M^+, 100), 222 (12), 208 (13), 190 (10).

HRMS ($C_{15}H_{13}NO$): calc.: 223.0997; found: 223.0988.

3-(3,3-Dimethyl-2-oxobutyl)benzonitrile (56ad)



According to **TP4** a mixture of cyclohex-2-en-1-one (**58a**; 480 mg, 5.00 mmol) and TMSCl (1.60 mL, 12.5 mmol) in THF (2 mL) was added dropwise to a mixture of CuCN·2LiCl (6.30 mL, 6.30 mmol, 1.00 M in THF) and 3-cyanobenzylzinc chloride (**54o**; 4.05 mL, 6.25 mmol, 1.55 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the cyclohexanone **56ad** (1.03 g, 97%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.53-7.46 (m, 1H), 7.43-7.32 (m, 3H), 2.73-2.57 (m, 2H), 2.42-2.18 (m, 3H), 2.14-1.95 (m, 3H), 1.90-1.79 (m, 1H), 1.71-1.53 (m, 1H), 1.45-1.29 (m, 1H).

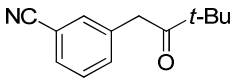
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 210.6, 140.8, 133.5, 132.5, 130.1, 129.2, 118.8, 112.5, 47.5, 42.4, 41.2, 40.5, 30.7, 24.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933 (w), 2863 (w), 2227 (m), 1706 (vs), 1582 (w), 1483 (w), 1448 (m), 1429 (w), 1346 (w), 1312 (w), 1277 (w), 1258 (w), 1225 (m), 1100 (w), 1059 (w), 912 (w), 901 (w), 866 (w), 796 (m), 753 (w), 723 (m), 691 (s), 572 (w), 558 (w).

MS (EI, 70 eV): m/z (%) = 213 (M^+, 52), 155 (78), 142 (12), 116 (28), 97 (100), 89 (15), 69 (93), 55 (45).

HRMS ($C_{14}H_{15}NO$): calc.: 213.1154; found: 213.1153.

3-(3,3-Dimethyl-2-oxobutyl)benzonitrile (56ae)



According to **TP3** 2,2-dimethylpropionyl chloride (**60b**; 225 mg, 1.87 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.6 mL, 2.6 mmol) and 3-cyanobenzylzinc chloride (**54o**; 1.9 mL, 2.6 mmol, 1.37 M in THF) at -60 °C. The reaction mixture was allowed to reach -20 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 6:1) afforded the ketone **56ae** (292 mg, 78%) as a white solid.

M.p. (°C): 39-40.

^{1}H-NMR (600 MHz, C_6D_6): δ / ppm = 7.03-7.01 (m, 1H), 6.98-6.95 (m, 2H), 6.74 (t, *J* = 7.8 Hz, 1H), 3.13 (s, 2H), 0.89 (s, 9H).

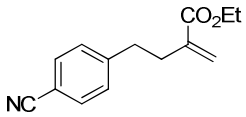
^{13}C-NMR (150 MHz, C_6D_6): δ / ppm = 209.7, 136.7, 134.0, 133.2, 130.2, 128.8, 118.9, 112.9, 44.3, 42.2, 26.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956 (m), 2226 (m), 1700 (s), 1482 (m), 1364 (m), 1330 (s), 1058 (vs), 1020 (s), 808 (m), 770 (vs), 684 (vs).

MS (EI, 70 eV): m/z (%) = 201 (M^+, <1), 117 (28), 116 (22), 85 (22), 57 (100), 41 (30).

HRMS ($C_{13}H_{15}NO$): calc.: 201.1154; found: 201.1131.

Ethyl 2-[2-(4-cyanophenyl)ethyl]acrylate (56af)



4-Cyanobenzylzinc chloride (**54p**; 6.90 mL, 10.0 mmol, 1.45 M in THF) was added to a solution of ethyl (2-bromomethyl)acrylate (**55b**; 1.54 g, 8.00 mmol) in 4 mL THF at -60 °C followed by CuCN·2LiCl (0.01 mL, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 9:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the acrylate **56af** (1.48 g, 81%) as colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.58-7.51 (m, 2H), 7.29-7.22 (m, 2H), 6.17-6.10 (m, 1H), 5.48-5.43 (m, 1H), 4.19 (d, *J* = 7.1 Hz, 2H), 2.88-2.79 (m, 2H), 2.65-2.54 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

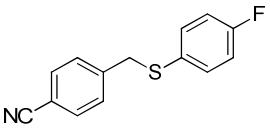
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.7, 147.0, 139.3, 132.1, 129.3, 125.6, 119.0, 109.9, 60.7, 35.0, 33.4, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983 (w), 2936 (w), 2228 (m), 1710 (vs), 1631 (w), 1608 (m), 1506 (w), 1445 (w), 1412 (w), 1369 (m), 1309 (m), 1273 (m), 1254 (m), 1184 (vs), 1135 (s), 1105 (m), 1027 (m), 947 (m), 838 (m), 820 (s), 668 (w).

MS (EI, 70 eV): m/z (%) = 229 (M^+, 12), 183 (80), 155 (35), 127 (11), 116 (100), 89 (23), 43 (15).

HRMS ($C_{14}H_{15}NO_2$): calc.: 229.1103; found: 229.1096.

_S_-(4-Fluorophenyl) (4-cyanophenyl)methanesulfono-thioate (56ag)



To *S*-(4-fluorophenyl) benzenesulfonothioate (**57c**; 644 mg, 2.40 mmol, in 1.0 mL THF) was added dropwise 4-cyanobenzylzinc chloride (**54p**; 2.30 mL, 2.88 mmol, 1.25 M in THF). The reaction mixture was stirred for 1.5 h followed by the addition of sat. aq. NH_4Cl solution at 0 °C. The phases were separated and the aq. layer was extracted with Et_2O (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 95:5) afforded the thioether **56ag** (552 mg, 95%) as a white solid.

M.p. (°C): 50-51.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.58-7.52 (m, 2H), 7.30-7.21 (m, 4H), 7.01-6.91 (m, 2H), 4.03 (s, 2H).

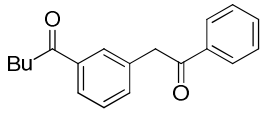
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.4 (d, $^1J_{C\text{-}F}$ = 248.2 Hz), 143.3, 134.2 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 132.2, 129.5, 129.2 (d, *J* = 3.4 Hz), 118.7, 116.1 (d, *J* = 21.9 Hz), 110.9, 40.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064 (w), 3044 (w), 2930 (w), 2856 (w), 2360 (w), 2342 (w), 2228 (m), 1862 (w), 1734 (w), 1606 (m), 1590 (w), 1506 (m), 1488 (s), 1416 (m), 1400 (m), 1298 (w), 1216 (s), 1180 (m), 1158 (m), 1104 (m), 1090 (m), 1014 (w), 968 (w), 924 (w), 904 (w), 856 (s), 812 (vs), 804 (vs), 760 (s), 712 (w), 630 (s).

MS (EI, 70 eV): m/z (%) = 243 (M^+, 35), 127 (5), 117 (8), 116 (100), 89 (9) 83 (6), 63 (2).

HRMS ($C_{14}H_{10}FNS$): calc.: 243.0518; found: 243.0513.

1-[3-(2-Oxo-2-phenylethyl)phenyl]pentan-1-one (56ah)



According to **TP3** benzoyl chloride (**60f**; 278 mg, 1.98 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.60 mL, 2.60 mmol, 1.00 M in THF) and 3-pentanoylbenzylzinc chloride (**54q**; 2.30 mL, 2.64 mmol, 1.15 M in THF) at -20 °C. The reaction mixture was stirred for 15 h at this temperature followed by quenching with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the ketone **56ah** (470 mg, 85%) as a white solid.

M.p. (°C): 33-36.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.03-8.00 (m, 2H), 7.86-7.83 (m, 2H), 7.59-7.55 (m, 1H), 7.49-7.40 (m, 4H), 4.35 (s, 2 H), 2.94 (t, *J* = 7.4 Hz, 2H), 1.73-1.67 (m, 2H), 1.43-1.35 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3H).

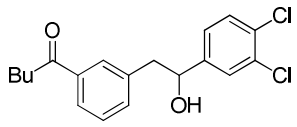
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 200.4, 197.0, 137.4, 136.4, 135.0, 134.1, 133.4, 129.2, 128.8, 128.7, 128.5, 126.7, 45.1, 38.4, 26.4, 22.4, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2932 (w), 1678 (vs), 1594 (m), 1580 (m), 1446 (m), 1328 (m), 1266 (m), 1206 (s), 1164 (m), 994 (m), 974 (m), 748 (s), 692 (vs).

MS (EI, 70 eV): m/z (%) = 280 (M^+, 6), 223 (6), 105 (100), 77 (17).

HRMS ($C_{19}H_{20}O_2$): calc.: 280.1463; found: 280.1439.

1-{3-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]phenyl}pentan-1-one (56ai)



According to **TP3** 3-pentanoylbenzylzinc chloride (**54q**; 2.40 mL, 2.59 mmol, 1.08 M in THF) was reacted with 3,4-dichlorobenzaldehyde (**61b**; 350 mg, 2.00 mmol, in 1.5 mL THF). After 5.5 h the reaction mixture was quenched with sat. aq. NH_4Cl solution. Purification by flash chromatography (silica gel, pentane / Et_2O = 2:1) afforded the alcohol **56ai** (665 mg, 95%) as a white solid.

M.p. (°C): 47-48.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84-7.80 (m, 1H), 7.75-7.72 (m, 1H), 7.45-7.30 (m, 4 H), 7.16-7.11 (m, 1H), 4.92-4.85 (m, 1H), 3.04-3.00 (m, 2H), 2.01 (t, *J* = 7.4 Hz, 2H), 2.11-1.93 (s, 1H), 1.76-1.62 (m, 2H), 1.47-1.32 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

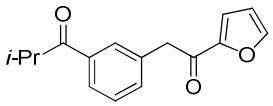
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 200.5, 143.8, 137.8, 137.4, 134.1, 132.6, 131.5, 130.4, 129.0, 128.8, 127.9, 126.7, 125.2, 73.9, 45.7, 38.4, 26.5, 22.5, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3427 (w), 2956 (m), 2930 (m), 2871 (w), 1673 (s), 1601 (w), 1583 (m), 1466 (s), 1440 (m), 1379 (m), 1319 (m), 1261 (m), 1231 (m), 1199 (m), 1179 (m), 1163 (m), 1129 (m), 1057 (s), 1028 (vs), 885 (m), 820 (s), 787 (m), 764 (m), 730 (m), 692 (s), 675 (s).

MS (EI, 70 eV): m/z (%) = 350 (M^+, <1), 293 (7), 177 (15), 176 (100), 175 (14), 119 (8).

HRMS ($C_{19}H_{20}Cl_2O_2$): calc.: 350.0840; found: 350.0839.

1-{3-[2-(2-Furyl)-2-oxoethyl]phenyl}-2-methyl-propan-1-one (56aj)



According to **TP3** 2-furoyl chloride (**60g**; 261 mg, 2.00 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.60 mL, 2.60 mmol, 1.00 M in THF) and 3-isobutyrylbenzylzinc chloride (**54r**; 2.36 mL, 2.60 mmol, 1.10 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 20 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the ketone **56aj** (259 mg, 51%) as a yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.88 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.62-7.59 (m, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.27-7.24 (m, 1H), 6.56-6.52 (m, 1H), 4.18 (s, 2H), 3.56-3.50 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 6H).

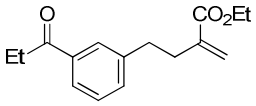
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 204.3, 186.1, 152.3, 146.7, 136.5, 134.5, 134.0, 129.5, 128.9, 127.1, 117.9, 112.5, 45.0, 35.4, 19.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3132 (vw), 2972 (w), 2934 (w), 2873 (w), 1673 (vs), 1568 (m), 1465 (s), 1439 (m), 1384 (m), 1335 (m), 1288 (m), 1235 (s), 1149 (s), 1084 (m), 1039 (m), 1019 (s), 994 (s), 912 (m), 882 (m), 836 (m), 764 (s), 734 (s), 708 (m), 685 (m), 643 (m), 594 (s), 576 (m).

MS (EI, 70 eV): m/z (%) = 256 (M^+, 10), 214 (65), 185 (21), 128 (20), 118 (11), 95 (100), 90 (20).

HRMS ($C_{16}H_{16}O_3$): calc.: 256.1099; found: 256.1097.

Ethyl 2-[2-(3-propionylphenyl)ethyl]acrylate (56ak)



To a solution of ethyl (2-bromomethyl)acrylate (**55b**; 560 mg, 2.90 mmol) in 1.5 mL THF at -60 °C was added 3-propionylbenzylzinc chloride (**54s**; 2.80 mL, 3.48 mmol, 1.25 M in THF) followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (3 x 20 mL). The combined extracts were dried over $MgSO_4$.

Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 95:5) afforded the acrylate **56ak** (694 mg, 92%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.80-7.74 (m, 2H), 7.39-7.34 (m, 2H), 6.16-6.14 (m, 1H), 5.48 (q, *J* = 1.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.98 (q, *J* = 7.1 Hz, 2H), 2.89-2.80 (m, 2H), 2.66-2.59 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H).

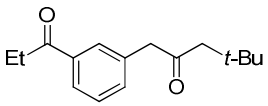
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 200.9, 167.0, 141.9, 139.8, 137.1, 133.1, 128.5, 128.0, 125.8, 125.4, 60.7, 34.8, 33.8, 31.8, 14.2, 8.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2938 (w), 1712 (vs), 1684 (vs), 1300 (m), 1240 (s), 1184 (vs), 1164 (s), 1132 (s), 1028 (m), 944 (m), 782 (s), 694 (s).

MS (EI, 70 eV): m/z (%) = 260 (M^+, 23), 232 (16), 231 (100), 214 (11), 213 (11), 185 (16), 147 (28), 129 (14), 128 (12), 118 (10), 91 (12), 90 (19), 57 (15).

HRMS ($C_{16}H_{20}O_3$): calc.: 260.1412; found: 260.1419.

4,4-Dimethyl-1-(3-propionylphenyl)pentan-2-one (56al)



According to **TP3** 3,3-dimethylbutyryl chloride (**60b**; 192 mg, 1.44 mmol) was added dropwise to a mixture of CuCN·2LiCl (1.88 mL, 1.88 mmol, 1.00 M in THF) and 3-propionylbenzylzinc chloride (**54s**; 1.76 mL, 1.88 mmol, 1.07 M in THF) at -60 °C. The reaction mixture was allowed to reach -20 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the ketone **56al** (246 mg, 69%) as a white solid.

M.p. (°C): 39.4-41.5.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.86-7.83 (m, 1H), 7.77-7.75 (m, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.37-7.35 (m, 1H), 3.73 (s, 2H), 2.99 (q, *J* = 7.3 Hz, 2H), 2.38 (s, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.00 (s, 9H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 207.2, 200.6, 137.2, 134.7, 134.0, 129.0, 128.8, 126.7, 54.4, 51.6, 31.8, 31.1, 29.7, 8.2.

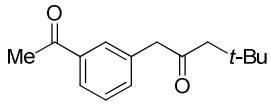
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2947 (m), 2938 (m), 2899 (w), 2867 (w), 1711 (s), 1677 (vs), 1604 (w), 1459 (m), 1440 (m), 1411 (m), 1404 (m), 1369 (m), 1364 (m), 1340 (s), 1311 (m),

1247 (m), 1235 (m), 1193 (m), 1167 (s), 1149 (m), 1085 (s), 1037 (m), 1024 (m), 983 (m), 898 (m), 778 (vs), 747 (m), 697 (vs), 647 (w), 571 (m).

MS (EI, 70 eV): m/z (%) = 246 (M^+, 2), 217 (9), 148 (23), 147 (33), 118 (11), 99 (75), 71 (18), 57 (100), 43 (11), 41 (14).

HRMS ($C_{16}H_{22}O_2$): calc.: 246.1620; found: 246.1626.

1-(3-Acetylphenyl)-4,4-dimethylpentan-2-one (56am)



According to **TP3** 3,3-dimethylbutyryl chloride (**60b**; 192 mg, 1.44 mmol) was added dropwise to a mixture of CuCN·2LiCl (1.88 mL, 1.88 mmol, 1.00 M in THF) and 3-acetylbenzylzinc chloride (**54t**; 1.68 mL, 1.88 mmol, 1.12 M in THF) at -60 °C. The reaction mixture was stirred for 15 h at -20 °C and quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 7:3) afforded the ketone **56am** (248 mg, 74%) as a pale yellow liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.85-7.82 (m, 1H), 7.75-7.74 (m, 1H), 7.43-7.40 (m, 1H), 7.38-7.36 (m, 1H), 3.73 (s, 2H), 2.58 (s, 3H), 2.37 (s, 2H), 1.00 (s, 9H).

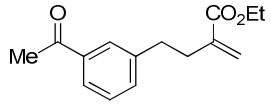
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 207.1, 197.9, 137.4, 134.7, 134.2, 129.2, 128.8, 127.0, 54.4, 51.5, 31.1, 29.6, 26.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2868 (w), 1920 (w), 1602 (w), 1584 (w), 2953 (m), 1439 (m), 790 (m), 1063 (m), 1083 (m), 1189 (m), 1713 (m), 1356 (s), 693 (s), 1269 (s), 1681 (vs).

MS (EI, 70 eV): m/z (%) = 232 (M^+, 3), 134 (18), 133 (50), 99 (100), 90 (15), 71 (17), 57 (72), 43 (27).

HRMS ($C_{15}H_{20}O_2$): calc.: 232.1463; found: 232.1447.

Ethyl 2-[2-(3-acetylphenyl)ethyl]acrylate (56an)



To a solution of ethyl 2-bromomethylacrylate (**55b**; 193 mg, 1.00 mmol) in THF (3 mL) at -60 °C was added 3-acetylbenzylzinc chloride (**54t**; 1.16 mL, 1.30 mmol, 1.12 M in THF) and CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C

for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (3 x 100 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and and purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 to 6:1) afforded the acrylate **56an** (239 mg, 97%) as colourless liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.80-7.75 (m, 2H), 7.41-7.34 (m, 2H), 6.16-6.14 (m, 1H), 5.50-5.47 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.87-2.81 (m, 2H), 2.65-2.60 (m, 2H), 2.59 (s, 3H), 1.30 (q, *J* = 7.1 Hz, 3H).

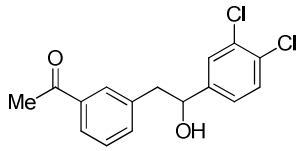
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 198.3, 167.0, 142.0, 139.8, 137.3, 133.3, 128.6, 128.2, 126.2, 125.4, 60.7, 34.8, 33.8, 26.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2931 (w), 1711 (s), 1682 (vs), 1438 (m), 1357 (m), 1300 (m), 1270 (s), 1241 (m), 1184 (vs), 1133 (s), 1114 (m), 1026 (m), 946 (m), 795 (m), 693 (s).

MS (EI, 70 eV): m/z (%) = 234 (M^+, 23), 201 (18), 200 (29), 185 (29), 157 (19), 133 (100), 129 (20), 118 (11), 90 (18), 42 (48).

HRMS ($C_{15}H_{18}O_3$): calc.: 246.1156; found: 246.1143.

1-{3-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]phenyl}-ethanone (56ao)



According to **TP2** 3-propionylbenzylzinc chloride (**54t**; 3.12 mL, 3.12 mmol, 1.00 M in THF) was reacted with 3,4-dichlorobenzaldehyde (**61b**; 420 mg, 2.40 mmol, in 2 mL THF) at 25 °C. After 3 h, the reaction mixture was quenched with sat. aq. NH_4Cl (5 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 2:1 + 1 vol-% NEt_3) afforded the benzylic alcohol **56ao** (609 mg, 82%) as a white solid.

M.p. (°C): 65-67.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84-7.80 (m, 1H), 7.77-7.75 (m, 1H), 7.45-7.31 (m, 4H), 7.16-7.11 (m, 1H), 4.89 (dd, *J* = 7.3 Hz, 6.1 Hz, 1H), 3.03 (s, 1H), 3.01 (d, *J* = 1.9 Hz, 1H), 2.57 (s, 3H), 2.11 (s, 1H).

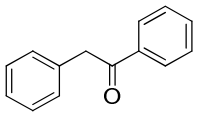
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 198.1, 143.9, 137.9, 137.4, 134.3, 132.6, 131.5, 130.4, 129.2, 128.8, 128.0, 127.0, 125.3, 73.9, 45.6, 26.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3353 (w), 2921 (w), 1676 (s), 1601 (m), 1583 (m), 1467 (m), 1438 (m), 1389 (m), 1357 (s), 1271 (s), 1189 (m), 1129 (m), 1056 (m), 1028 (s), 957 (m), 906 (m), 887 (m), 820 (s), 792 (s), 730 (s), 692 (vs), 674 (s).

MS (EI, 70 eV): m/z (%) = 308 (M+, <1), 212 (11), 174 (85), 147 (44), 135 (90), 119 (27), 111 (100), 91 (95), 75 (21), 43 (57).

HRMS ($C_{16}H_{14}Cl_2O_2$): calc.: 308.0371; found: 308.0371.

1,2-Diphenylethanone (56ap)



According to **TP3** benzoyl chloride (**60f**; 1.69 g, 12.0 mmol) was added dropwise to a mixture of CuCN·2LiCl (16.8 mL, 16.8 mmol, 1.00 M in THF) and benzylzinc chloride (**54a**; 11.1 mL, 16.8 mmol, 1.52 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 20 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the ketone **56ap** (2.17 g, 92%) as a pale yellow solid.

M.p. (°C): 55-57.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.06-7.98 (m, 2H), 7.59-7.51 (m, 1H), 7.50-7.41 (m, 2H), 7.37-7.21 (m, 5H), 4.29 (s, 2H).

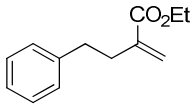
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.6, 136.6, 134.5, 133.1, 129.4, 128.6, 128.6, 128.6, 126.8, 45.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3564 (vw), 3058 (w), 3027 (w), 2922 (vw), 2904 (w), 1682 (s), 1593 (m), 1579 (m), 1496 (m), 1447 (m), 1336 (m), 1323 (m), 1216 (m), 1199 (m), 1076 (m), 1026 (m), 991 (m), 750 (s), 728 (s), 711 (m), 698 (vs), 686 (vs), 662 (s), 648 (m), 619 (m), 565 (vs).

MS (EI, 70 eV): m/z (%) = 196 (M^+, 2), 165 (5), 105 (100), 91 (13), 77 (41), 69 (6), 61 (5), 51 (8), 44 (32).

HRMS ($C_{14}H_{12}O$): calc.: 196.0888; found: 196.0872.

Ethyl 2-(2-phenylethyl)acrylate (56aq)



To a solution of ethyl 2-bromomethylacrylate (**55b**; 965 mg, 5.00 mmol) in THF (2.5 mL) at -60 °C was added benzylzinc chloride (**54a**; 3.85 mL, 6.00 mmol, 1.56 M in THF) and CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with Et_2O (3 x 100 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and and purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the acrylate **56aq** (948 mg, 93%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.33-7.24 (m, 2H), 7.23-7.15 (m, 3H), 6.18-6.14 (m, 1H), 5.52-5.47 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.85-2.76 (m, 2H), 2.67-2.58 (m, 2H), 1.32 (q, *J* = 7.2 Hz, 3H).

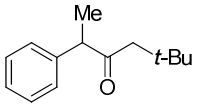
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.1, 141.4, 140.1, 128.4, 128.3, 125.9, 125.0, 60.6, 34.9, 33.9, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2932 (w), 1712 (vs), 1632 (w), 1456 (w), 1308 (m), 1240 (m), 1184 (s), 1156 (m), 1132 (s), 1028 (m), 944 (m), 748 (m), 700 (vs).

MS (EI, 70 eV): m/z (%) = 234 (M^+, 7), 158 (17), 130 (26), 91 (100), 65 (11), 57 (13).

HRMS ($C_{13}H_{16}O_2$): calc.: 204.1150; found: 204.1144.

5,5-Dimethyl-2-phenylhexan-3-one (56ar)



According to **TP3** 3,3-dimethylbutyryl chloride (**60b**; 382 mg, 2.84 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.90 mL, 3.90 mmol, 1.00 M in THF) and 1-phenylethylzinc chloride (**54u**; 2.73 mL, 3.90 mmol, 1.43 M in THF) at -60 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 95:5) afforded the ketone **56ar** (556 mg, 96%) as a colourless liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.39-7.35 (m, 2H), 7.32-7.28 (m, 1H), 7.26-7.23 (m, 2H), 3.76 (q, *J* = 6.9 Hz, 1H), 2.37 (d, *J* = 15.3 Hz, 1H), 2.23 (d, *J* = 15.5 Hz, 1H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 9H).

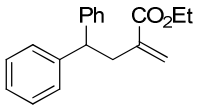
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 210.3, 140.5, 128.8, 128.0, 127.0, 54.4, 53.2, 30.9, 29.6, 17.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952 (m), 2868 (w), 1712 (s), 1492 (w), 1452 (m), 1364 (m), 1068 (w), 1044 (w), 1028 (w), 1016 (w), 912 (w), 756 (m), 700 (vs), 548 (m), 520 (w).

MS (EI, 70 eV): m/z (%) = 204 (M^+, 3), 105 (63), 99 (74), 83 (14), 79 (11), 71 (29), 69 (13), 57 (100), 55 (13), 43 (23).

HRMS ($C_{14}H_{20}O$): calc.: 204.1514; found: 204.1525.

Ethyl 2-(2,2-diphenylethyl)acrylate (56as)



(Diphenyl)methylzinc chloride (**54v**; 5.42 mL, 3.90 mmol, 0.72 M in THF) was added to a solution of ethyl (2-bromomethyl)acrylate (**55b**; 579 mg, 3.00 mmol) in THF (3 mL) at -60 °C followed by CuCN·2LiCl (0.01 mL, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 8:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the acrylate **56as** (804 mg, 96%) as colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.39-7.21 (m, 10H), 6.16-6.14 (m, 1H), 5.40-5.37 (m, 1H), 4.34 (t, *J* = 7.9 Hz, 1H), 4.26 (d, *J* = 7.2 Hz, 2H), 3.19-3.13 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

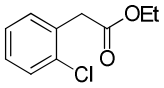
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.1, 144.0, 138.5, 128.4, 128.0, 126.8, 126.2, 60.6, 49.9, 38.0, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061 (vw), 3027 (w), 2981 (w), 2936 (vw), 1709 (s), 1630 (w), 1600 (w), 1494 (w), 1464 (w), 1450 (m), 1368 (w), 1330 (w), 1300 (m), 1231 (w), 1187 (s), 1134 (s), 1082 (w), 1028 (m), 944 (m), 863 (w), 816 (w), 788 (w), 742 (s), 697 (vs), 602 (m).

MS (EI, 70 eV): m/z (%) = 280 (M^+, 2), 235 (3), 167 (100), 165 (14), 152 (9), 128 (2), 105 (3), 77 (2).

HRMS ($C_{19}H_{20}O_2$): calc.: 280.1463; found: 280.1461

Ethyl (2-chlorophenyl)acetate (62a)



Reaction 1 using ethyl chloroformate:

To 2-chlorobenzylzinc chloride (**54b**; 2.62 mL, 4.00 mmol, 1.50 M in THF) at -30 °C was added THF (0.5 mL) followed by $Pd(PPh_3)_4$ (116 mg, 5.0 mol%). The reaction mixture was stirred for 5 min. Then, ethyl chloroformate (**60h**, 227 mg, 2.09 mmol) was added dropwise. Stirring was continued for 10 min at -30 °C followed by 6.25 h at 25 °C. The reaction mixture was quenched by adding a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 4:1 (15 mL). The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the phenylacetic acid ester **62a** (336 mg, 81%) as colourless liquid.

Reaction 2 using ethyl cyanoformate:

To 2-chlorobenzyl zinc chloride (**54b**; 0.67 mL, 1.00 mmol, 1.50 M in THF) at -30 °C was added dropwise $TMSCH_2Li$ (1.00 mL, 1.00 mmol, 1.00 M in pentane). The reaction mixture was stirred for 30 min. CuCN·2LiCl solution (1.00 mL, 1.00 mmol, 1.00 M in THF) was added dropwise and the mixture was stirred for additional 30 min. Ethyl cyanoformate (**60i**; 150 mg, 1.5 mmol) was added dropwise. Stirring was continued for 10 min at -30 °C followed by 6 h at 0 °C. The reaction mixture was quenched by adding a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (15 mL). The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the phenylacetic acid ester **62a** (152 mg, 77%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.42-7.34 (m, 1H), 7.32-7.17 (m, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

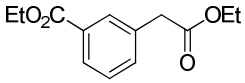
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 170.5, 134.5, 132.5, 131.4, 129.4, 128.6, 126.8, 61.0, 39.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981 (w), 1731 (vs), 1475 (m), 1445 (m), 1415 (w), 1367 (m), 1335 (m), 1279 (m), 1246 (m), 1216 (s), 1156 (vs), 1122 (m), 1053 (s), 1028 (s), 928 (w), 885 (w), 859 (w), 827 (w), 741 (vs), 681 (s), 626 (w).

MS (EI, 70 eV): m/z (%) = 198 (M^+, 4), 163 (100), 135 (23) 127 (78), 125 (35, 89 (21).

HRMS ($C_{10}H_{11}ClO_2$): calc.: 198.0448; found: 198.0462.

Ethyl 3-(2-ethoxy-2-oxoethyl)benzoate (62b)



Ethyl chloroformate (**60h**; 1.09 g, 10.0 mmol) was solved in THF (5 mL) at -30 °C. Then, $Pd(PPh_3)_4$ (290 mg, 0.25 mmol, 2.5 mol%) was added and the mixture was stirred for 10 min. 3-(Ethoxycarbonyl)benzylzinc chloride (**54m**; 9.09 mL, 12.0 mmol, 1.32 M in THF) was added dropwise. The reaction mixture was stirred for 6 h at 25 °C. Then, sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 9:1 (100 mL) was added. The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the ester **62b** (1.79 g, 76%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.96-7.91 (m, 2H), 7.49-7.45 (m, 1H), 7.41-7.35 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.65 (s, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

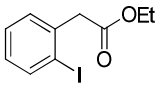
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 171.1, 166.3, 134.4, 133.7, 130.8, 130.3, 128.5, 128.3, 61.0 (double), 41.1, 14.3, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 1715 (vs), 1589 (w), 1446 (m), 1367 (m), 1278 (vs), 1251 (s), 1192 (s), 1156 (s), 1104 (s), 1081 (s), 1025 (s), 902 (w), 863 (w), 741 (s), 725 (m), 685 (m).

MS (EI, 70 eV): m/z (%) = 236 (M^+, 99), 208 (33), 192 (18), 191 (87), 164 (100), 136 (54), 135 (89), 119 (95), 77 (16), 59 (11).

HRMS ($C_{13}H_{16}O_4$): calc.: 236.1049; found: 236.1033.

Ethyl (2-iodophenyl)acetate (62c)



$TMSCH_2Li$ (5.00 mL, 5.00 mmol, 1.00 M in pentane) was added dropwise to 2-iodobenzylzinc chloride (**54f**; 3.76 mL, 5.00 mmol, 1.33 M in THF) at -30 °C, followed by THF (1 mL). The resulting mixture was stirred for 30 min. Then, $CuCN \cdot 2LiCl$ (5.00 mL, 5.00 mmol, 1.00 M in THF) was added and stirring was continued for additional 30 min. Ethyl cyanoformate (**60i**; 625 mg, 6.31 mmol) was added dropwise and the reaction mixture was stirred for 6 h at 0 °C. The reaction mixture was quenched with 30 mL of a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1. The phases were separated and the organic layer was extracted again with 30 mL of a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1. The combined aq. layers were extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the ester **62c** (859 mg, 59%) as a white solid.

M.p. (°C): 51-52.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.87-7.81 (m, 1H), 7.34-7.24 (m 2H), 6.99-6.91 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

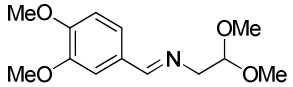
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.5, 139.5, 137.9, 130.6, 128.8, 128.4, 101.0, 61.0, 46.3, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} =2987 (w), 2944 (w), 2906 (w), 1726 (s), 1564 (w), 1469 (m), 1411 (m), 1366 (m), 1338 (s), 1277 (m), 1214 (s), 1171 (s), 1162 (s), 1113 (m), 1029 (s), 1012 (vs), 926 (m), 888 (m), 760 (s), 734 (vs), 681 (m), 647 (s), 594 (m), 574 (s).

MS (EI, 70 eV): m/z (%) = 289 (M^+, 4), 216 (100), 163 (60), 135 (96), 107 (11), 90 (54), 63 (13), 43 (10).

HRMS ($C_{10}H_{11}IO_2$): calc.: 289.9804; found: 289.9803.

***N*-[(1*E*)-(3,4-Dimethoxyphenyl)methylene]-2,2-dimethoxyethanamine (64)**



To a solution of 3,4-dimethoxybenzyaldehyde (**60h**; 8.31 g, 50.0 mmol) in 150 mL toluene was added aminoacetaldehyde dimethylacetal (8.24 mL, 76.0 mmol). The reaction mixture was refluxed for 6 h and the water was removed by using Dean–Stark apparatus. After cooling to

25 °C, the solvent was removed *in vacuo*. The yellow oil was dissolved in CH_2Cl_2 (50 mL) and washed with water (4 x 50 mL), then dried over Na_2SO_4. Evaporation of the solvents *in vacuo* gives the imine **64** (12.8 g, 100%) as a pale yellow solid which was used without further purification. The spectroscopic data match the literature.[82a]

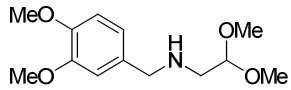
M.p. (°C): 55-56.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.18-8.17 (m, 1H), 7.41 (d, *J* = 1.9 Hz, 1H), 7.14 (dd, *J* = 8.1 Hz, 1.9 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.65 (t, *J* = 5.4 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.73 (dd, *J* = 5.4 Hz, 1.3 Hz, 2H), 3.40 (s, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.0, 151.4, 149.2, 129.3, 123.3, 110.3, 108.8, 103.9, 63.4, 55.9, 55.9, 54.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3001 (w), 2932 (w), 2912 (w), 2884 (w), 2832 (w), 1641 (s), 1600 (m), 1583 (s), 1512 (s), 1464 (s), 1444 (m), 1422 (s), 1396 (m), 1361 (m), 1334 (w), 1305 (w), 1263 (vs), 1238 (vs), 1187 (m), 1158 (s), 1137 (vs), 1092 (s), 1066 (s), 1036 (s), 1015 (vs), 996 (s), 971 (s), 959 (vs), 868 (s), 850 (m), 822 (s), 809 (s), 780 (m), 752 (s), 636 (s), 621 (s)

(3,4-Dimethoxybenzyl)(2,2-dimethoxyethyl)amine (65)



To a solution of *N*-[(1*E*)-(3,4-dimethoxyphenyl)methylene]-2,2-dimethoxyethanamine (**64**; 12.8 g, 50.0 mmol) in ethanol (50 mL) was added sodium borohydride (3.78 g, 100 mmol) and the reaction mixture was stirred for 60 h at 25 °C. Then, water (150 mL) was added carefully. The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 300 mL). The combined extracts were washed with water (3 x 300 mL), brine (1 x 300 mL) and then dried over Na_2SO_4. Evaporation of the solvents *in vacuo* gives the amine **65** (11.0 g, 86%) as a pale yellow liquid which was used without further purification. The spectroscopic data match the literature.[82a]

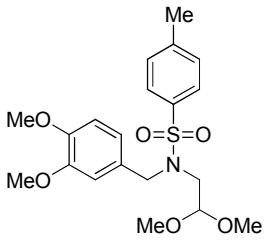
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 6.88-6.85 (m, 1H), 6.84-6.76 (m, 2H), 4.46 (t, *J* = 5.5 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (s, 2H), 3.34 (s, 6H), 2.72 (d, *J* = 5.8 Hz, 2H).

^{13}C-NMR (75Hz, $CDCl_3$): δ / ppm = 148.8, 147.9, 132.6, 120.1, 111.2, 110.9, 103.7, 55.7, 55.7, 53.7, 53.5, 50.3.

MS (EI, 70 eV): m/z (%) = 255 (M^+, 2), 180 (5), 151 (100), 107 (3), 75 (14).

HRMS ($C_{13}H_{21}NO_4$): calc.: 255.1464; found: 255.1471.

***N*-(3,4-dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (66)**



Pyridine (3.40 mL, 42.0 mmol) was added dropwise at 0 °C to a solution of 3,4-dimethoxybenzyl)(2,2-dimethoxyethyl)amine (**65**; 7.66 g, 30.0 mmol) in CH_2Cl_2 (60 mL). Tosyl chloride (7.43 g, 39.0 mmol) was added and the reaction mixture was allowed to warm to 25 °C within 15 h and then poured on sat. aq. $NaHCO_3$ solution. The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 100 mL), then dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 1:2) afforded the sulphonamide **66** (12.2 g, 99%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.74-7.68 (m, 2H), 7.30-7.24 (m, 2H), 6.73-6.71 (m, 2H), 6.66-6.64 (m, 1H), 4.38 (s, 2H), 4.33 (t, *J* = 5.4 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.23 (s, 6H), 3.18 (d, *J* = 5.4 Hz, 2H), 2.39 (s, 3H).

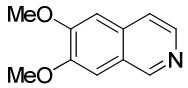
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 149.0, 148.5, 143.1, 137.7, 129.5, 128.4, 127.1, 121.0, 111.3, 110.7, 103.8, 55.8, 55.6, 54.5, 52.2, 48.3, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2935 (w), 2834 (w), 1595 (w), 1514 (s), 1438 (m), 1337 (s), 1255 (s), 1236 (s), 1155 (vs), 1066 (s), 1026 (vs), 997 (s), 911 (s), 813 (s), 760 (s), 706 (m), 658 (vs).

MS (EI, 70 eV): m/z (%) = 409 (M^+, <1), 254 (5), 151 (28), 91 (4), 75 (100).

HRMS ($C_{20}H_{27}NO_6S$): calc.: 409.1559; found: 409.1546.

6,7-Dimethoxyisoquinoline (67)



To a solution of *N*-(3,4-dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (**66**; 12.1 g, 29.5 mmol) in dioxane (280 mL) was added 6N HCl (22 mL). The reaction mixture was refluxed for 22 h. After cooling to 25 °C the solution was poured on water. The phases were separated and the aq. phase was extracted with Et_2O (2 x 250 mL), CH_2Cl_2 (3 x 250 mL). The combined aq. phases were treated with NaOH (10%) solution until pH >9. The aq. phase was extracted with Et_2O (2 x 250 mL) and CH_2Cl_2 (3 x 250 mL). The combined extracts were dried

over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, EtOAc) afforded the isoquinoline **67** (4.78 g, 86%) as a white solid.

M.p. (°C): 93-95.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.98 (s, 1H), 8.33 (d, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 5.8 Hz. 1H), 7.11 (s, 1H), 6.98 (s, 1H), 3.95 (s, 6H).

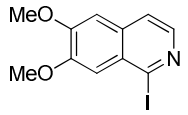
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 152.8, 150.1, 149.8, 141.8, 132.3, 124.6, 119.0, 105.1, 104.4, 55.9, 55.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3015 (w), 2836 (w), 1573 (m), 1502 (s), 1477 (s), 1459 (m), 1433 (m), 1412 (s), 1335 (s), 1248 (vs), 1206 (s), 1138 (vs), 1001 (s), 923 (s), 852 (vs), 755 (s), 632 (s).

MS (EI, 70 eV): m/z (%) = 189 (M^+, 100), 174 (11), 146 (24), 117 (8), 103 (6), 91 (6).

HRMS ($C_{11}H_{11}NO_2$): calc.: 189.0790; found: 189.0788.

1-Iodo-6,7-dimethoxyisoquinoline (68)



To a solution of 6,7-dimethoxyisoquinoline (**67**; 946 mg, 5.00 mmol) in THF (5 mL) was added TMPMgCl·LiCl (5.13 mL, 6.00 mmol, 1.17 M in THF) at 25 °C. The reaction mixture was stirred for 4 h. Iodine (1.52 g, 6.00 mmol) was dissolved in THF (3 mL) in a second flask at -40 °C. To this solution the magnesium compound was added dropwise. The solution was stirred 10 min at -40 °C, then 10 min at 0 °C. The reaction mixture was quenched by adding a mixture of sat. aq. NH_4Cl solution and sat. aq. $Na_2S_2O_3$ solution, then sat. aq. $NaHCO_3$ until pH >7. The phases were separated and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL), then dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 1:4) afforded the iodo-substituted isoquinoline **68** (1.14 g, 73%) as a pale yellow solid.

M.p. (°C): 140-141 (decomposition).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 5.6 Hz, 1H), 7.37 (d, *J* = 5.1 Hz, 1H), 7.29 (s, 1H), 6.59 (s, 1H), 4.03 (s, 3H), 4.00 (s, 3H).

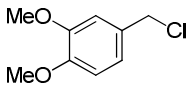
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 153.3, 151.3, 141.8, 132.4, 127.9, 124.6, 120.0, 111.0, 105.0, 56.3, 56.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936 (w), 1504 (s), 1473 (s), 1458 (s), 1431 (s), 1392 (s), 1296 (s), 1251 (s), 1226 (s), 1140 (vs), 1006 (s), 929 (s), 858 (vs), 774 (s), 671 (s).

MS (EI, 70 eV): m/z (%) = 315 (M^+, 53), 189 (12), 188 (100), 145 (3), 94 (6).

HRMS ($C_{11}H_{10}INO_2$): calc.: 314.9751; found: 314.9756.

4-(Chloromethyl)-1,2-dimethoxybenzene (53w)



To a solution of LiCl (2.54 g, 60.0 mmol, dried for 10 min under high vacuum at 400 °C using a heat gun) in THF (50 mL) was added 3,4-dimethoxybenzyl alcohol (**69**; 3.30 g, 20.0 mmol) at 0 °C. Then, NEt_3 (5.60 mL, 40.0 mmol) was added dropwise, followed by mesyl chloride (2.33 mL, 30.0 mmol). The reaction mixture was allowed to reach 25 °C within 15 h. Then, CH_2Cl_2 (300 mL) was added and the solution was washed with water (3 x 250 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the benzylic chloride **53w** (2.56 g, 69%) as a white solid.

M.p. (°C): 55-56.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 6.94-6.88 (m, 1H), 6.89 (s, 1H), 6.83-6.77 (m, 1H), 4.54 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H).

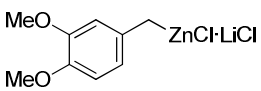
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 149.1, 149.0, 129.9, 121.0, 111.6, 110.9, 55.8, 55.8, 46.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3010 (w), 2935 (w), 2838 (w), 1593 (m), 1514 (s), 1463 (s), 1450 (m), 1437 (m), 1259 (s), 1232 (vs), 1154 (vs), 1139 (vs), 1036 (s), 1022 (vs), 848 (s), 815 (s), 685 (vs).

MS (EI, 70 eV): m/z (%) = 186 (M^+, 17), 151 (100), 107 (9), 91 (3), 77 (4).

HRMS ($C_9H_{11}ClO_2$): calc.: 186.0448; found: 186.0434.

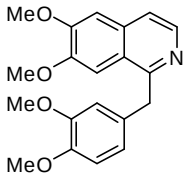
3,4,-Dimethoxybenzyl zinc chloride (54w)



According to **TP1** 3,4-dimethoxybenzyl chloride (**53w**; 933 mg, 5.00 mmol, in 2 mL THF) was added dropwise at 0 °C to a suspension of LiCl (848 mg, 20.0 mmol) and zinc dust (1.31 g,

20.0 mmol) in 2 mL THF (activation: $BrCH_2CH_2Br$ (0.02 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 2 h at 0 °C followed by stirring for 2.5 h at 25 °C. After centrifugation iodometric titration of **54w** indicates a yield of 72%.

Papaverine (63)



To a solution of 1-iodo-6,7-dimethoxyisoquinoline (**68**; 315 mg, 1.00 mmol) in THF (3 mL) was added S-Phos (20.5 mg, 0.05 mmol, 5.0 mol%), $Pd(OAc)_2$ (5.6 mg, 0.03 mmol, 2.5 mol%). Then, 3,4,-dimethoxybenzylzinc chloride (**54w**; 2.00 mL, 1.40 mmol, 0.70 M in THF) was added dropwise. The reaction mixture was stirred for 1.25 h at 25 °C, then quenched by adding a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 5:1. The phases were separated and the aq. layer was extracted with CH_2Cl_2 (5 x 50 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 1:4, + 2 vol-% NEt_3, + 2 vol-% EtOH) afforded papaverine **63** (229 mg, 68%) as pale yellow solid.

M.p. (°C): 144-146.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.35 (d, *J* = 6.0 Hz, 1H), 7.46 (d, *J* = 5.7 Hz, 1H), 7.37 (s, 1H), 7.06 (s, 1H), 6.83–6.80 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 4.58 (s, 2H), 4.00 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 157.7, 152.3, 149.7, 149.0, 147.4, 140.9, 133.4, 132.2, 122.8, 120.4, 118.6, 111.8, 111.1, 105.2, 104.1, 55.9, 55.8, 55.8, 55.7, 42.2.

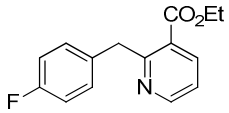
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2939 (w), 2835 (w), 1504 (vs), 1478 (s), 1463 (s), 1454 (m), 1434 (s), 1414 (s), 1257 (vs), 1232 (vs), 1202 (s), 1157 (s), 1153 (s), 1147 (s), 1139 (vs), 1075 (m), 1045 (m), 1028 (vs), 986 (s), 875 (s), 867 (m), 860 (s), 843 (s), 822 (s), 805 (m), 785 (s), 768 (m), 736 (m), 732 (m), 661 (s), 645 (m).

MS (EI, 70 eV): m/z (%) = 339 (M^+, 55), 324 (75), 308 (20), 154 (13).

HRMS ($C_{20}H_{21}NO_4$): calc.: 339.1471; found: 339.1455.

3.3 Efficient Nickel-catalyzed cross-coupling reactions of benzylic zinc chloride with aromatic halides

Ethyl 2-(4-fluorobenzyl)nicotinate (72a)



According to **TP5** 4-fluorobenzylzinc chloride (**54c**; 1.98 mL, 2.40 mmol, 1.21 M in THF) was reacted with ethyl 2-chloronicotinate (**71a**; 371 mg, 2.00 mmol in 0.4 mL NMP), PPh_3 (0.1 mL, 0.04 mmol, 0.4 M in THF) and $Ni(acac)_2$ (0.1 mL, 0.01 mmol, 0.1 M in THF). The reaction mixture was stirred for 3 h. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the ester **72a** (407 mg, 78%) as a pale yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.67 (dd, *J* = 5.0 Hz, 1.8 Hz, 1H), 8.17 (dd, *J* = 7.8 Hz, 1.9 Hz, 1H), 7.25-7.20 (m, 3H), 6.94-6.89 (m, 2H), 4.54 (s, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

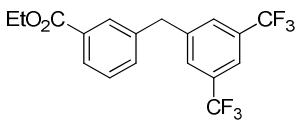
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 166.3, 161.4 (d, $^1J_{C\text{-}F}$ = 243.7 Hz), 161.0, 151.8, 138.8, 135.2 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 130.4 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 126.0, 121.3, 115.0 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 61.5, 41.4, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2988 (m), 2970 (m), 1720 (vs), 1601 (w), 1583 (w), 1568 (m), 1507 (s), 1438 (m), 1365 (s), 1296 (m), 1256 (s), 1217 (vs), 1157 (m), 1129 (s), 1094 (s), 1078 (vs), 1057 (s), 1017 (m), 860 (m), 810 (m), 790 (s), 747 (s), 607 (m).

MS (EI, 70 eV): m/z (%) = 259 (M^+, 100), 230 (61), 213 (86), 184 (70), 157 (11), 109 (11), 93 (10).

HRMS ($C_{15}H_{14}O_2NF$): calc.: 259.1009; found: 259.1006.

Ethyl 3-[3,5-bis(trifluoromethyl)benzyl]benzoate (72b)



According to **TP5** 3-(ethoxycarbonyl)benzylzinc chloride (**54m**; 1.90 mL, 2.40 mmol, 1.26 M in THF) was reacted with 1-bromo-3,5-bis(trifluoromethyl)benzene (**71b**; 586 mg, 2.00 mmol in 0.4 mL NMP), PPh_3 (0.1 mL, 0.04 mmol, 0.4 M in THF) and $Ni(acac)_2$ (0.1 mL, 0.01 mmol, 0.1 M in THF). The reaction mixture was stirred for 4 h. Purification by flash chromatography (silica gel, pentane / Et_2O = 95:5) afforded the ester **72b** (331 mg, 45%) as a white solid.

M.p. (°C): 55-57.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.96-7.93 (m, 1H), 7.90-7.88 (m, 1H), 7.73 (s, 1H), 7.62 (s, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.36-7.33 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.14 (s, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

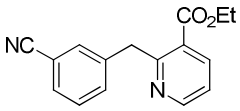
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 166.3, 142.9, 139.0, 133.2, 131.8 (q, $^2J_{C\text{-}F}$ = 33.4 Hz), 131.2, 130.0, 129.0, 128.9 (m), 128.2, 123.3 (q, $^1J_{C\text{-}F}$ = 272.6 Hz), 120.5 (m), 61.1, 41.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2989 (w), 2970 (w), 2911 (w), 1739 (m), 1712 (s), 1447 (m), 1376 (s), 1278 (vs), 1255 (s), 1205 (s), 1164 (s), 1110 (vs), 1027 (m), 930 (m), 921 (m), 868 (m), 843 (m), 752 (s), 728 (m), 708 (s), 699 (s), 682 (s).

MS (EI, 70 eV): m/z (%) = 376 (M^+, 18), 357 (11), 348 (25), 331 (100), 283 (17), 233 (15), 165 (17).

HRMS ($C_{17}H_{18}O_2$): calc.: 376.0898; found: 376.0888.

Ethyl 2-(3-cyanobenzyl)nicotinate (72c)



According to **TP5** 3-cyanobenzylzinc chloride (**54o**; 0.94 mL, 1.20 mmol, 1.27 M in THF) was reacted with ethyl 2-chloronicotinate (**71a**; 186 mg, 1.00 mmol in 0.2 mL NMP), PPh_3 (0.05 mL, 0.02 mmol, 0.4 M in THF) and $Ni(acac)_2$ (0.05 mL, 0.005 mmol, 0.1 M in THF). The reaction mixture was stirred for 4 h. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the ester **72c** (115 mg, 43%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.68 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H), 7.57-7.52 (m, 2H), 7.47-7.43 (m, 1H), 7.37-7.31 (m, 1H), 7.28 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H), 4.59 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

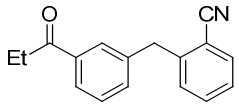
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.0, 159.9, 152.1, 141.0, 138.9, 133.7, 132.6, 129.9, 128.9, 125.7, 121.7, 119.0, 112.1, 61.6, 41.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983 (w), 2229 (m), 1717 (vs), 1581 (m), 1568 (m), 1483 (w), 1436 (m), 1366 (w), 1259 (vs), 1172 (w), 1131 (s), 1079 (vs), 1058 (s), 1016 (m), 861 (w), 823 (w), 781 (s), 742 (s), 712 (m), 689 (s).

MS (EI, 70 eV): m/z (%) = 266 (M^+, 63), 265 (100), 237 (41), 221 (33), 193 (75), 164 (14).

HRMS ($C_{16}H_{14}N_2O_2$): calc.: 266.1055; found: 266.1057.

2-(3-Propionylbenzyl)benzonitrile (72d)



According to **TP5** 3-propionylbenzylzinc chloride (**54s**; 1.63 mL, 1.80 mmol, 1.10 M in THF) was reacted with 2-chlorobenzonitrile (**71c**; 206 mg, 1.50 mmol in 0.3 mL NMP), PPh_3 (0.08 mL, 0.03 mmol, 0.4 M in THF) and $Ni(acac)_2$ (0.075 mL, 0.0075 mmol, 0.1 M in THF). The reaction mixture was stirred for 6 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the nitrile **72d** (265 mg, 71%) as a white solid.

M.p. (°C): 50-52.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.84-7.80 (m, 2H), 7.65-7.61 (m, 1H), 7.52-7.48 (m, 1H), 7.43-7.41 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.33-7.29 (m, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 4.25 (s, 2H), 2.97 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

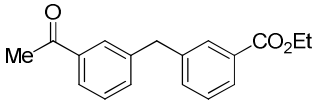
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 200.6, 144.1, 139.2, 137.3, 133.4, 133.0, 133.0, 130.0, 128.9, 128.3, 127.0, 126.4, 118.0, 112.5, 40.0, 31.8, 8.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2970 (m), 2935 (m), 2901 (m), 2224 (m), 1739 (m), 1684 (s), 1597 (m), 1488 (m), 1445 (m), 1437 (m), 1407 (m), 1375 (s), 1347 (m), 1238 (s), 1217 (m), 1163 (s), 1080 (m), 1066 (m), 1028 (m), 980 (w), 963 (m), 944 (w), 918 (m), 851 (m), 789 (s), 765 (s), 755 (vs), 711 (m), 694 (s), 647 (m), 634 (m).

MS (EI, 70 eV): m/z (%) = 249 (M^+, 2), 220 (100), 192 (10), 190 (19), 178 (9), 165 (19), 116 (4), 89 (3).

HRMS ($C_{17}H_{15}NO$): calc.: 249.1154; found: 249.1152.

Ethyl 3-(3-acetylbenzyl)benzoate (72e)



According to **TP5** 3-acetylbenzylzinc chloride (**54t**; 2.27 mL, 2.40 mmol, 1.07 M in THF, addition via syringe pump over 30 min) was reacted with ethyl 3-bromobenzoate (**71d**; 458 mg, 2.00 mmol in 0.4 mL NMP), PPh_3 (0.1 mL, 0.04 mmol, 0.4 M in THF) and $Ni(acac)_2$ (0.1 mL, 0.01 mmol, 0.1 M in THF). The reaction mixture was stirred for 16 h. Purification by flash

chromatography (silica gel, pentane / Et_2O = 4:1) afforded the ester **72e** (289 mg, 51%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.92-7.86 (m, 2H), 7.82-7.76 (m, 2H), 7.40-7.32 (m, 4H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 2H), 2.57 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

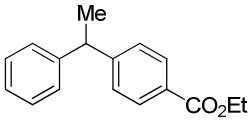
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 198.1, 166.5, 141.1, 140.7, 137.5, 133.6, 133.3, 130.9, 129.9, 128.8, 128.6, 128.5, 127.6, 126.5, 61.0, 41.5, 26.7, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981 (w), 2928 (w), 1714 (s), 1682 (s), 1602 (w), 1585 (m), 1484 (w), 1437 (m), 1392 (w), 1358 (m), 1268 (vs), 1193 (s), 1104 (s), 1081 (m), 1021 (m), 977 (w), 954 (w), 918 (w), 861 (w), 789 (m), 753 (s), 718 (s), 690 (s), 587 (s), 559 (m).

MS (EI, 70 eV): m/z (%) = 282 (M^+, 100), 268 (52), 237 (61), 194 (9), 165 (72), 152 (10), 43 (35).

HRMS ($C_{18}H_{18}O_3$): calc.: 282.1256; found: 282.1249.

Ethyl 4-(1-phenylethyl)benzoate (72f)



According to **TP5** 1-phenylethylzinc chloride (**54u**; 1.78 mL, 2.40 mmol, 1.35 M in THF) was reacted with ethyl 4-bromobenzoate (**71e**; 458 mg, 2.00 mmol in 0.4 mL NMP), PPh_3 (0.1 mL, 0.04 mmol, 0.4 M in THF) and $Ni(acac)_2$ (0.1 mL, 0.01 mmol, 0.1 M in THF). The reaction mixture was stirred for 12 h. Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the ester **72f** (485 mg, 95%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.00-7.93 (m, 2H), 7.33-7.26 (m, 4H), 7.23-7.16 (m, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 1H), 1.66 (t, *J* = 7.3 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 151.5, 145.4, 129.7, 128.5, 128.4, 127.6, 127.5, 126.3, 60.7, 44.8, 21.6, 14.3.

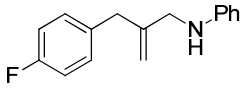
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085 (vw), 3061 (vw), 3028 (vw), 2973 (w), 2934 (vw), 2905 (vw), 2876 (vw), 1712 (s), 1610 (m), 1574 (vw), 1494 (w), 1451 (w), 1415 (w), 1391 (w), 1367 (m), 1310 (w), 1271 (vs), 1178 (m), 1102 (s), 1055 (w), 1019 (s), 980 (w), 910 (w), 857 (m), 758 (m), 738 (m), 698 (vs), 646 (w), 634 (w), 595 (w).

MS (EI, 70 eV): m/z (%) = 254 (M^+, 100), 239 (45), 209 (40), 181 (41), 165 (57), 91 (6).

HRMS ($C_{17}H_{18}O_2$): calc.: 254.1307; found: 254.1305.

3.4. Pd-catalyzed cross-couplings of benzylic zinc chlorides with unsaturated bromides bearing relatively acidic protons

***N*-[2-(4-fluorobenzyl)prop-2-en-1-yl]aniline (78a)**



According to **TP6** 4-fluorobenzylzinc chloride (**54c**, 3.34 mL, 2.40 mmol, 0.72 M in THF) was added to a solution of (2-bromo-allyl)-phenyl-amine (**77a**; 424 mg, 2.00 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL). The reaction mixture was stirred for 24 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the aniline **78a** (295 mg, 61%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.21-7.11 (m, 4H), 7.05-6.94 (m, 2H), 6.74-6.67 (m, 1H), 6.59-6.51 (m, 2H), 5.14-5.10 (m, 1H), 4.95-4.91 (m, 1H), 3.88 (s, 1H), 3.65 (s, 2H), 3.39 (s, 2H).

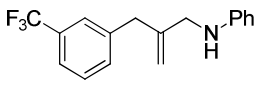
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 161.5 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 148.0, 146.0, 134.7 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 130.3 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 129.1, 117.4, 115.2 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 112.8, 112.5, 48.1, 40.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3419 (vw), 3051 (vw), 2909 (vw), 2839 (vw), 1651 (w), 1601 (s), 1504 (vs), 1432 (w), 1313 (m), 1268 (m), 1252 (m), 1218 (s), 1180 (m), 1156 (m), 1092 (m), 1071 (w), 1016 (w), 993 (w), 901 (m), 852 (m), 812 (m), 777 (m), 747 (vs), 690 (s).

MS (EI, 70 eV): m/z (%) = 241 (M^+, 100), 147 (55), 132 (28), 109 (25), 106 (72), 93 (16), 77 (25).

HRMS ($C_{16}H_{16}FN$): calc.: 241.1267; found: 241.1262.

***N*-{2-[3-(trifluoromethyl)benzyl]prop-2-en-1-yl}aniline (78b)**



According to **TP6** 3-(trifluoromethyl)benzylzinc chloride (**54g**; 1.60 mL, 2.40 mmol, 1.50 M in THF) was added to a solution of (2-bromo-allyl)-phenyl-amine (**77a**; 424 mg, 2.00 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL). The reaction

mixture was stirred for 8 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the aniline **78b** (437 mg, 87%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ / ppm = 7.51-7.46 (m, 2H), 7.43-7.38 (m, 2H), 7.17-7.12 (m, 2H), 6.72-6.68 (m, 1H), 6.65-6.52 (m, 2H), 5.17 (d, *J* = 0.9 Hz, 1H), 4.94 (d, *J* = 0.9 Hz, 1H) 3.82 (s, 1H), 3.66 (s, 2H), 3.47 (s, 2H).

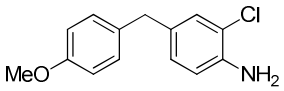
^{13}C NMR (150 MHz, $CDCl_3$): δ / ppm = 148.0, 145.3, 140.1, 132.3 (q, *J* = 1.3 Hz), 130.8 (q, $^2J_{C\text{-}F}$ = 32.1 Hz), 129.2, 128.8, 125.5 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 124.2 (q, $^1J_{C\text{-}F}$ = 272.3 Hz), 123.2 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 117.5, 113.2, 112.8, 48.1, 40.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3420 (vw), 3054 (vw), 2913 (vw), 1603 (s), 1506 (m), 1448 (w), 1327 (vs), 1161 (s), 1117 (vs), 1093 (s), 1072 (s).

MS (EI, 70 eV): m/z (%) = 291 (M^+, 100), 276 (18), 132 (29), 129 (21), 106 (95).

HRMS ($C_{17}H_{16}F_3N$): calc.: 291.1235; found: 291.1227.

2-Chloro-4-(4-methoxybenzyl)aniline (78c)



According to **TP6** 4-methoxybenzylzinc chloride (**54i**, 1.94 mL, 2.40 mmol, 1.24 M in THF) was added to a solution of 4-bromo-2-chloroaniline (**77b**; 413 mg, 2.00 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL). The reaction mixture was stirred for 6.25 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 to 3:1) afforded the aniline **78c** (381 mg, 77%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ / ppm = 7.10-7.06 (m, 2H), 7.06 (d, *J* = 1.9 Hz, 1H), 6.87 (dd, *J* = 8.1 Hz, 1.9 Hz, 1H), 6.85-6.81 (m, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 3.92 (s, 2H), 3.79 (s, 2H), 3.78 (s, 3H) .

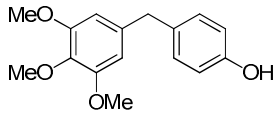
^{13}C NMR (150 MHz, $CDCl_3$): δ / ppm = 157.9, 140.9, 133.2, 132.6, 129.7, 129.4, 128.0, 119.3, 115.9, 113.9, 55.2, 39.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3465 (vw), 3062 (vw), 3029 (vw), 2983 (vw), 1707 (w), 1602 (w), 1580 (vw), 1494 (w), 1446 (m), 1369 (w), 1305 (vs), 1271 (s), 1225 (w), 1164 (s), 1124 (vs), 1095 (s), 1032 (vs), 960 (w), 928 (m), 910 (w), 883 (w), 840 (w), 766 (vs), 698 (vs).

MS (EI, 70 eV): m/z (%) = 247 (M^+, 100), 212 (69), 180 (12), 168 (12), 140 (13), 106 (17).

HRMS ($C_{14}H_{14}ClNO$): calc.: 247.0764; found: 247.0756.

4-(3,4,5-Trimethoxybenzyl)phenol (78d)



According to **TP7** 3,4,5-trimethoxybenzylzinc chloride (**54h**, 2.47 mL, 2.40 mmol, 0.97 M in THF) was slowly added over 90 min using a syringe pump to a solution of 4-bromophenol (**77c**; 346 mg, 2.00 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL) at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the phenol **78d** (232 mg, 42%) as a white solid.

M.p. (°C): 119-120.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.07-7.00 (m, 2H), 6.79-6.73 (m, 2H), 6.38 (s, 2H), 5.22 (s, 1H), 3.84 (s, 2H), 3.82 (s, 3H), 3.79 (s, 6H).

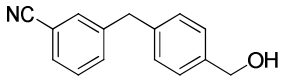
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 154.0, 153.1, 137.3, 136.0, 132.8, 129.9, 115.3, 105.7, 60.8, 56.0, 41.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3338 (w), 1612 (w), 1592 (m), 1511 (m), 1462 (m), 1444 (w), 1438 (w), 1420 (m), 1342 (w), 1318 (w), 1262 (w), 1240 (s), 1224 (m), 1189 (w), 1172 (w), 1126 (vs), 1040 (w), 1001 (m), 971 (w), 862 (w), 846 (w), 824 (m), 783 (w), 720 (vw), 669 (m).

MS (EI, 70 eV): m/z (%) = 274 (M^+, 100), 259 (19), 227 (9), 184 (8), 107 (5).

HRMS ($C_{16}H_{18}O_4$): calc.: 274.1205; found: 274.1208.

3-[4-(Hydroxymethyl)benzyl]benzonitrile (78e)



According to **TP7** 3-cyanobenzylzinc chloride (**54o**, 1.89 mL, 2.40 mmol, 1.27 M in THF) is slowly added over 90 min using a syringe pump to a solution of (4-bromophenyl)methanol (**77d**; 374 mg, 2.00 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL) at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the nitrile **78e** (375 mg, 84%) as a yellow solid.

M.p. (°C): 53-55.

^{1}H NMR (600 MHz, $CDCl_3$): δ / ppm = 7.51-7.33 (m, 4H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.65 (s, 2H), 3.99 (s, 2H), 1.95 (s, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ / ppm = 142.5, 139.3, 138.7, 133.3, 132.2, 129.9, 129.2, 129.0, 127.4, 118.8, 112.4, 64.9, 41.0.

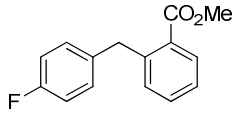
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3404 (m), 2921 (m), 2853 (m), 2228 (s), 1582 (w), 1512 (w), 1482 (m), 1419 (m), 1209 (w), 1031 (s), 1016 (s), 794 (s), 750 (m), 730 (m), 686 (vs).

MS (EI, 70 eV): m/z (%) = 223 (M^+, 80), 221 (18), 224 (12), 192 (63), 165 (41), 116 (40), 107 (100), 91 (14), 79 (35), 44 (38).

HRMS ($C_{15}H_{13}NO$): calc.: 223.0997; found: 223.0988.

3.5. Palladium-catalyzed one-pot reaction of *in situ* generated benzylic zinc chlorides with aromatic bromides

Methyl 2-(4-fluorobenzyl)benzoate (80a)



According to **TP8** – *zinc insertion*: 4-fluorobenzyl chloride (**53c**; 723 mg, 5.00 mmol), LiCl (318 mg, 7.50 mmol) and Zn (490 mg, 7.50 mmol) in THF (2.5 mL), t_1 = 25 °C for 24 h; *cross-coupling*: methyl 2-bromobenzoate (**71g**; 645 mg, 3.00 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), t_2 = 25 °C for 24 h; *work-up and purification*: extracted with Et_2O (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 98:2) to give the diarylmethane **80a** as a colourless liquid (702 mg, 96%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.90 (dd, *J* = 7.9 Hz, 1.3 Hz, 1H), 7.47-7.39 (m, 1H), 7.33-7.25 (m, 1H), 7.22-7.17 (m, 1H), 7.13-7.06 (m, 2H), 6.98-6.89 (m, 2H), 4.34 (s, 2H), 3.82 (s, 3H).

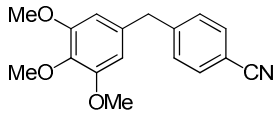
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.9, 161.2 (d, $^1J_{C\text{-}F}$ = 243.8 Hz), 142.0 (d, $^6J_{C\text{-}F}$ = 1.0 Hz), 136.5 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 132.1, 131.5, 130.8, 130.2 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 129.8, 126.4, 115.0 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 51.9, 38.8 (d, $^5J_{C\text{-}F}$ = 0.5 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952 (w), 2360 (w), 2342 (w), 1718 (vs), 1602 (m), 1576 (w), 1508 (s), 1434 (m), 1258 (vs), 1220 (s), 1192 (m), 1158 (m), 1128 (s), 1094 (s), 1076 (s), 1048 (m), 1016 (w), 966 (w), 914 (w), 844 (m), 822 (m), 802 (m), 776 (s), 732 (vs), 704 (m), 664 (m).

MS (EI, 70 eV): m/z (%) = 244 (M^+, 3), 212 (100), 183 (38), 133 (10), 109 (5), 91 (5).

HRMS ($C_{15}H_{13}FO_2$): calc.: 244.0900; found: 244.0895.

4-(3,4,5-Trimethoxybenzyl)benzonitrile (80b)



According to **TP8** – *zinc insertion*: 3,4,5-trimethoxybenzyl chloride (**53h**; 1.08 g, 5.00 mmol), LiCl (318 mg, 7.50 mmol) and Zn (490 mg, 7.50 mmol) in THF (2.5 mL), t_1 = 25 °C for 4 h; *cross-coupling*: 4-bromobenzonitrile (**71h**; 455 mg, 2.50 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), t_2 = 25 °C for 15 h; *work-up and purification*: extracted with Et_2O (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 3:1) to give the diarylmethane **80b** as a white solid (698 mg, 99%).

M.p. (°C): 60-62.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.60-7.54 (m, 2H), 7.31-7.25 (m, 2H), 6.34 (s, 2H), 3.95 (s, 2H), 3.81 (s, 3H), 3.80 (s, 6H).

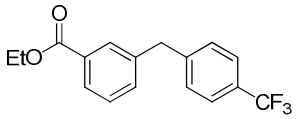
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.4, 146.5, 136.6, 134.8, 132.3, 129.5, 118.9, 110.1, 105.9, 60.8, 56.0, 42.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2990 (w), 2940 (w), 2836 (w), 2360 (w), 2342 (w), 2224 (w), 1590 (s), 1508 (m), 1500 (m), 1464 (m), 1422 (m), 1338 (w), 1324 (w), 1238 (s), 1186 (w), 1128 (vs), 1016 (w), 998 (s), 978 (m), 944 (w), 904 (w), 854 (w), 832 (m), 818 (m), 808 (m), 734 (m), 666 (m), 644 (m).

MS (EI, 70 eV): m/z (%) = 283 (M^+, 100), 268 (54), 240 (12), 225 (9), 209 (6), 166 (4), 154 (4), 127 (5), 116 (10).

HRMS ($C_{17}H_{17}NO_3$): calc.: 283.1208; found: 283.1203.

Ethyl 3-[4-(trifluoromethyl)benzyl]benzoate (80c)



According to **TP8** – *zinc insertion*: 3-(ethoxycarbonyl)benzyl chloride (**53m**; 993 mg, 5.00 mmol), LiCl (424 mg, 10.0 mmol) and Zn (654 mg, 10.0 mmol) in THF (2.5 mL), t_1 = 25 °C for 4 h; *cross-coupling*: 1-bromo-4-(trifluoromethyl)benzene (**71i**; 667 mg, 2.97 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), t_2 = 25 °C for 4 h; *work-up and purification*: extracted with CH_2Cl_2 (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 95:5) to give the diarylmethane **80c** as a colourless liquid (857 mg, 94%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.93-7.90 (m, 1H), 7.90-7.88 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.35-7.33 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

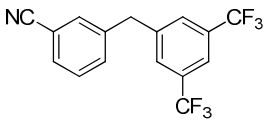
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 166.5, 144.5 (q, $^4J_{C\text{-}F}$ = 1.3 Hz), 140.2, 133.3, 130.9, 130.0, 129.1, 128.7, 128.7 (q, $^2J_{C\text{-}F}$ = 32.3 Hz), 127.7, 125.5 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 124.2 (q, $^1J_{C\text{-}F}$ = 271.9 Hz), 61.0, 41.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2985 (vw), 1715 (s), 1619 (w), 1588 (w), 1445 (w), 1418 (w), 1368 (w), 1322 (vs), 1278 (s), 1188 (m), 1161 (s), 1119 (s), 1104 (vs), 1065 (vs), 1018 (s), 939 (w), 852 (m), 816 (m), 764 (w), 742 (vs), 695 (m), 672 (m), 639 (m), 596 (m).

MS (EI, 70 eV): m/z (%) = 308 (M^+, 39), 280 (20), 263 (100), 235 (23), 215 (9), 165 (30).

HRMS ($C_{17}H_{15}F_3O_2$): calc.: 308.1024; found: 308.1022.

3-[3,5-Bis(trifluoromethyl)benzyl]benzonitrile (80d)



According to **TP8** – *zinc insertion*: 3-cyanobenzyl chloride (**53o**; 758 mg, 5.00 mmol), LiCl (318 mg, 7.50 mmol) and Zn (490 mg, 7.50 mmol) in THF (2.5 mL), t_1 = 25 °C for 3.5 h; *cross-coupling*: 1-bromo-3,5-bis(trifluoromethyl)benzene (879 mg, 3.00 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), t_2 = 25 °C for 15.5 h; *work-up and purification*: extracted with Et_2O (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 95:5 to 9:1) to give the diarylmethane **80d** as a white solid (844 mg, 85%).

M.p. (°C): 66-67.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.77 (m, 1H), 7.60 (m, 2H), 7.59-7.54 (m, 1H), 7.49-7.43 (m, 2H), 7.43-7.38 (m, 1H), 4.14 (s, 2H).

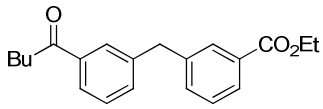
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.8, 140.2, 133.3, 132.3, 132.1 (q, $^2J_{C\text{-}F}$ = 33.3 Hz), 130.8, 129.8, 128.9 (m), 123.1 (q, $^1J_{C\text{-}F}$ = 273.1 Hz), 120.9 (m), 118.5, 113.1, 40.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3675 (w), 2989 (m), 2970 (m), 2229 (w), 1739 (s), 1374 (s), 1275 (s), 1229 (s), 1217 (s), 1165 (s), 1123 (vs), 1109 (vs), 944 (m), 911 (m), 903 (m), 881 (m), 842 (m), 804 (m), 737 (m), 726 (m), 708 (s), 692 (s), 682 (s).

MS (EI, 70 eV): m/z (%) = 329 (M^+, 100), 309 (68), 289 (13), 260 (33), 240 (30), 190 (25), 116 (8).

HRMS ($C_{16}H_9F_6N$): calc.: 329.0639; found: 329.0628.

Ethyl 3-(3-pentanoylbenzyl)benzoate (80e)



According to **TP8** – *zinc insertion:* 3-pentanoylbenzyl chloride (**53q**; 843 mg, 4.00 mmol), LiCl (254 mg, 6.00 mmol) and Zn (392 mg, 6.00 mmol) in THF (2.0 mL), t_1 = 25 °C for 4 h; *cross-coupling*: ethyl 3-bromobenzoate (**71d**; 458 mg, 2.00 mmol), PEPPSI-IPr (6.8 mg, 0.01 mmol), THF (1.0 mL), t_2 = 25 °C for 2 h; *work-up and purification*: extracted with CH_2Cl_2 (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 15:1 to 7:1) to give the diarylmethane **80e** as a colourless liquid (595 mg, 92%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.92-7.86 (m, 2H), 7.82-7.75 (m, 2H), 7.40-7.31 (m, 4H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 2H), 2.92 (t, *J* = 7.3 Hz, 2H), 1.76-1.62 (m, 2H), 1.45-1.30 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H).

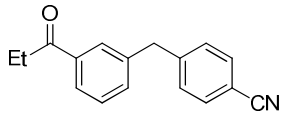
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 200.5, 166.5, 141.0, 140.7, 137.4, 133.3 (overlap), 130.8, 129.9, 128.8, 128.6, 128.3, 127.6, 126.2, 60.9, 41.5, 38.4, 26.4, 22.4, 14.3, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957 (m), 2931 (m), 2871 (w), 1714 (vs), 1681 (s), 1443 (m), 1366 (m), 1276 (vs), 1190 (s), 1159 (m), 1104 (m), 1081 (m), 1022 (m), 745 (m), 703 (m).

MS (EI, 70 eV): m/z (%) = 324 (M^+, 3), 282 (25), 267 (100), 237 (10), 236 (51), 166 (12), 165 (30), 161 (13).

HRMS ($C_{21}H_{24}O_3$): calc.: 324.1725; found: 324.1714.

4-(3-Propionylbenzyl)benzonitrile (80f)



According to **TP8** – *zinc insertion*: 3-propionylbenzyl chloride (**53s**; 365 mg, 2.00 mmol), LiCl (127 mg, 3.00 mmol) and Zn (196 mg, 3.00 mmol) in THF (1.0 mL), t_1 = 25 °C for 4 h; *cross-coupling*: 4-bromobenzonitrile (**71h**; 182 mg, 1.0 mmol), PEPPSI-IPr (3.4 mg, 0.005 mmol), THF (1.0 mL), t_2 = 25 °C for 2 h; *work-up and purification*: extracted with CH_2Cl_2 (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 7:1) to give the diarylmethane **80f** as a white solid (196 mg, 79%).

M.p. (°C): 83-84.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.83-7.71 (m, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.42-7.20 (m, 4H), 4.04 (s, 2H), 2.93 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.3 Hz, 3H).

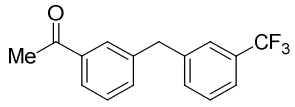
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 200.6, 146.0, 139.9, 137.4, 133.3, 132.4, 129.6, 129.0, 128.3, 126.5, 118.8, 110.3, 41.8, 31.8, 8.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2938 (w), 2227 (m), 1683 (vs), 1602 (m), 1506 (m), 1413 (m), 1349 (m), 1240 (s), 1177 (m), 1160 (s), 1020 (m), 973 (m), 859 (m), 813 (s), 783 (s), 746 (s), 695 (s).

MS (EI, 70 eV): m/z (%) = 249 (M^+, 100), 221 (26), 220 (31), 191 (42), 190 (86), 165 (75), 152 (11).

HRMS ($C_{17}H_{15}NO$): calc.: 249.1154; found: 249.1131.

1-{3-[3-(Trifluoromethyl)benzyl]phenyl}ethanone (80g)



According to **TP8** – *zinc insertion*: 3-acetylbenzyl chloride (**53t**; 674 mg, 4.00 mmol), LiCl (254 mg, 6.00 mmol) and Zn (392 mg, 6.00 mmol) in THF (2.0 mL), t_1 = 25 °C for 3 h; *cross-coupling*: 1-bromo-3-(trifluoromethyl)benzene (**71j**; 450 mg, 2.00 mmol), PEPPSI-IPr (6.8 mg, 0.01 mmol), THF (1.0 mL), t_2 = 25 °C for 5 h; *work-up and purification*: extracted with ether (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 4:1) to give the diarylmethane **80g** as a colourless liquid (476 mg, 86%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84-7.78 (m, 2H), 7.51-7.31 (m, 6H), 4.09 (s, 2H), 2.58 (s, 3H).

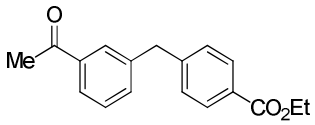
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 198.0, 141.3, 140.6, 137.6, 133.6, 132.2 (q, $^4J_{C\text{-}F}$ = 1.3 Hz), 130.9 (q, $^2J_{C\text{-}F}$ = 32.2 Hz), 129.1, 129.0, 128.6, 126.7, 125.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.1 (m, $^1J_{C\text{-}F}$ = 272.1 Hz), 123.3 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 41.5, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1682 (s), 1436 (w), 1358 (m), 1329 (s), 1268 (s), 1159 (s), 1117 (vs), 1094 (s), 1072 (vs), 915 (m), 790 (s), 749 (m), 719 (m), 701 (s), 692 (s), 655 (m).

MS (EI, 70 eV): m/z (%) = 278 (M^+, 21), 263 (100), 215 (12), 165 (23), 43 (13).

HRMS ($C_{16}H_{13}F_3O$): calc.: 278.0918; found: 278.0921.

Ethyl 4-(3-acetylbenzyl)benzoate (80h)



According to **TP8** – zinc *insertion*: 3-acetylbenzyl chloride (**53t**; 337 mg, 2.00 mmol), LiCl (127 mg, 3.00 mmol) and Zn (196 mg, 3.00 mmol) in THF (1.0 mL), t_1 = 25 °C for 3 h; *cross-coupling*: ethyl 4-bromobenzoate (**71e**; 229 mg, 1.00 mmol), PEPPSI (3.4 mg, 0.005 mmol), THF (1.0 mL), t_2 = 25 °C for 2 h; *work-up and purification*: extracted with CH_2Cl_2 (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 7:1) to give the diarylmethane **80h** as a white solid (264 mg, 94%).

M.p. (°C): 78-80.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.99-7.93 (m, 2H), 7.82-7.77 (m, 2H), 7.41-7.32 (m, 2H), 7.26-7.21 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 2H), 2.56 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H).

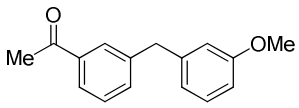
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 198.1, 166.5, 145.6, 140.8, 137.5, 133.7, 129.9, 128.9, 128.9 (overlap), 128.8, 128.6, 126.6, 60.9, 41.7, 26.7, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984 (w), 1706 (vs), 1673 (vs), 1609 (m), 1580 (m), 1478 (m), 1416 (m), 1363 (s), 1288 (s), 1274 (vs), 1194 (s), 1177 (s), 1125 (s), 1103 (s), 1021 (s), 958 (m), 920 (s), 856 (m), 792 (s), 763 (s), 720 (vs), 698 (vs).

MS (EI, 70 eV): m/z (%) = 282 (M^+, 48), 267 (100), 237 (26), 165 (20), 111 (12), 43 (11).

HRMS ($C_{18}H_{18}O_3$): calc.: 282.1256; found: 282.1234.

1-[3-(3-Methoxybenzyl)phenyl]ethanone (80i)



According to **TP8** – *zinc insertion*: 3-acetylbenzyl chloride (**53t**; 337 mg, 2.00 mmol), LiCl (127 mg, 3.00 mmol) and Zn (196 mg, 3.00 mmol) in THF (1.0 mL), t_1 = 25 °C for 3 h; *cross-coupling*: 1-bromo-3-methoxybenzene (**71k**; 187 mg, 1.00 mmol), PEPPSI-IPr (3.4 mg, 0.005 mmol), THF (1.0 mL), t_2 = 25 °C for 5 h; *work-up and purification*: extracted with CH_2Cl_2 (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 7:1) to give the diarylmethane **80i** as a white solid (145 mg, 60%).

M.p. (°C): 78-80.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84-7.74 (m, 2H), 7.43-7.33 (m, 2H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.81-6.69 (m, 3H), 4.00 (s, 2H), 3.76 (s, 3H), 2.57 (s, 3H).

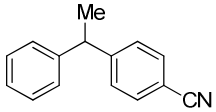
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 198.2, 159.8, 141.9, 141.5, 137.4, 133.7, 129.5, 128.7, 128.6, 126.3, 121.3, 114.8, 111.5, 55.1, 41.8, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3003 (vw), 2938 (w), 2836 (w), 1680 (s), 1598 (s), 1583 (s), 1488 (s), 1454 (m), 1434 (m), 1356 (m), 1267 (vs), 1257 (vs), 1162 (m), 1148 (s), 1047 (s), 778 (s), 740 (s), 690 (vs).

MS (EI, 70 eV): m/z (%) = 240 (M^+, 84), 226 (20), 225 (100), 197 (21), 182 (18), 165 (43), 153 (21), 44 (17), 42 (23).

HRMS ($C_{16}H_{16}O_2$): calc.: 240.1150; found: 240.1132.

Ethyl 3-[4-(trifluoromethyl)benzyl]benzoate (80j)



According to **TP8** – *zinc insertion*: (1-chloroethyl)benzene (**53u**; 703 mg, 5.00 mmol), LiCl (318 mg, 7.50 mmol) and Zn (490 mg, 7.50 mmol) in THF (1.0 mL), t_1 = 25 °C for 15 h; *cross-coupling*: 4-bromobenzonitrile (**71h**; 546 mg, 3.00 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), t_2 = 25 °C for 8 h; *work-up and purification*: extracted with CH_2Cl_2 (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et_2O = 98:2) to give the 1,1-diarylethane **80j** as a colourless liquid (586 mg, 94%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.56 (d, *J* = 8.6 Hz, 2H), 7.33-7.27 (m, 4H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 4.19 (q, *J* = 7.5 Hz, 1H), 1.64 (d, *J* = 7.2 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 151.9, 144.7, 132.2, 128.6, 128.4, 127.5, 126.6, 119.0, 109.9, 44.9, 21.4.

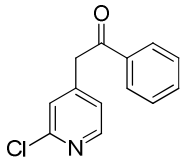
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031 (vw), 2973 (w), 2934 (w), 2876 (w), 2222 (m), 1912 (vw), 1606 (w), 1598 (w), 1502 (w), 1491 (m), 1452 (m), 1416 (w), 1374 (w), 1302 (w), 1176 (w), 1122 (w), 1086 (w), 1045 (w), 1028 (w), 1019 (w), 982 (w), 840 (s), 771 (s), 730 (s), 702 (vs), 600 (s), 559 (s).

MS (EI, 70 eV): m/z (%) = 207 (M^+, 36), 192 (100), 165 (18), 95 (5), 83 (4).

HRMS ($C_{15}H_{13}N$): calc.: 207.1048; found: 207.1038.

3.6. Preparation of diheterobenzylic zinc reagents and heterobenzylic zinc chlorides

2-(2-Chloropyridin-4-yl)-1-phenylethanone (87)



To a solution of 2-chloro-4-methylpyridine (**85**; 357 mg, 2.80 mmol) in THF (1.5 mL) was added $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (4.19 mL, 1.55 mmol, 0.37 M in THF) at 0 °C. The reaction mixture was stirred for 3 h. Then, the reaction mixture was cooled to -30 °C. CuCN·2LiCl (3.10 mL, 3.10 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for 30 min. Then, benzoyl chloride (**60f**; 281 mg, 2.00 mmol) was added at -78 °C and the reaction mixture was slowly warmed to -20 °C within 22 h. Then, a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 was added (50 mL). The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 1:4) afforded the pyridine **87** (279 mg, 60%) as a white solid.

M.p. (°C): 90-92.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.33 (d, *J* = 5.1 Hz, 1H), 8.02-7.93 (m, 2H), 7.65-7.56 (m, 1H), 7.53-7.44 (m, 2H), 7.26-7.24 (m, 1H), 7.15-7.09 (m, 1H), 4.27 (s, 2H).

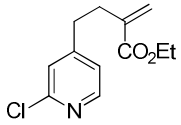
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 195.0, 151.7, 149.6, 146.7, 136.0, 133.8, 128.9, 128.4, 125.4, 123.7, 44.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062 (vw), 2914 (vw), 1688 (s), 1597 (m), 1579 (w), 1550 (w), 1446 (w), 1416 (w), 1388 (m), 1325 (m), 1290 (w), 1230 (m), 1208 (m), 1184 (w), 1124 (w), 1088 (m), 992 (m), 915 (w), 898 (w), 886 (w), 860 (w), 792 (m), 756 (vs), 722 (m), 690 (s), 674 (m).

MS (EI, 70 eV): m/z (%) = 231 (M^+, 1), 105 (100), 77 (32), 63 (1), 51 (8).

HRMS ($C_{13}H_{10}ClNO_3$): calc.: 231.0451; found: 231.0439.

Ethyl 4-(2-chloropyridin-4-yl)-2-methylidenebutanoate (88)



To a solution of 2-chloro-4-methylpyridine (**85**; 255 mg, 2.00 mmol) in THF (1 mL) was added $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (3.24 mL, 1.20 mmol, 0.37 M in THF) at 0 °C. The reaction mixture was stirred for 3 h. Then, the reaction mixture was cooled to -60 °C and ethyl 2-(bromomethyl)acrylate (**55b**; 541 mg, 2.80 mmol) was added followed by $CuCN \cdot 2LiCl$ (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred for 30 min at -60 °C and additional 30 min at 0 °C. Then, sat. aq. NH_4Cl solution (20 mL) was added. The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the pyridine **88** (472 mg, 98%) as a yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.25 (d, *J* = 5.1 Hz, 1H), 7.16-7.12 (m, 1H), 7.04-7.00 (m, 1H), 6.18-6.15 (m, 1H), 5.48 (q, *J* = 1.3 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.83-2.73 (m, 2H), 2.64-2.55 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

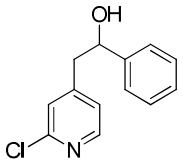
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.6, 153.7, 151.6, 149.5, 138.9, 125.9, 124.2, 122.7, 60.8, 33.9, 32.5, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 2930 (w), 1711 (vs), 1631 (w), 1593 (s), 1548 (m), 1466 (m), 1445 (w), 1386 (s), 1311 (m), 1296 (m), 1277 (m), 1256 (m), 1241 (m), 1183 (vs), 1135 (s), 1086 (s), 1028 (m), 990 (m), 945 (m), 900 (m), 875 (m), 835 (s), 818 (m), 721 (m), 711 (w), 684 (w), 635 (w).

MS (EI, 70 eV): m/z (%) = 239 (M^+, 12), 210 (18), 194 (24), 165 (100), 151 (16), 140 (12), 130 (82), 103 (16), 91 (18), 77 (20), 63 (11), 51 (15).

HRMS ($C_{12}H_{14}ClNO_2$): calc.: 239.0713; found: 239.0701.

2-(2-Chloropyridin-4-yl)-1-phenylethanol (89)



To a solution of 2-chloro-4-methylpyridine (**85**; 357 mg, 2.80 mmol) in THF (1.5 mL) was added $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (4.19 mL, 1.55 mmol, 0.37 M in THF) at 0 °C. The reaction mixture was stirred for 3 h. Then, benzaldehyde (**60g**; 228 mg, 2.15 mmol) was added and the reaction mixture was slowly warmed to 25 °C and stirred for 4.5 h. Sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 8:1 was added (10 mL). The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the pyridine **89** (485 mg, 97%) as a white solid.

M.p. (°C): 80-82.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 8.25 (dd, *J* = 5.1 Hz, 0.6 Hz, 1H), 7.38-7.27 (m, 5H), 7.25-7.19 (m, 2H), 5.43 (d, *J* = 4.7 Hz, 1H), 4.87-4.80 (m, 1H), 2.98-2.92 (m, 1H), 2.91-2.84 (m, 1H).

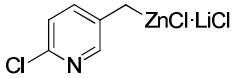
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 152.4, 149.9, 149.1, 145.0, 127.9, 126.9, 125.8, 125.0, 124.4, 72.2, 44.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3311 (w), 3063 (w), 2946 (w), 2909 (w), 2834 (vw), 1596 (s), 1547 (m), 1452 (w), 1431 (m), 1387 (s), 1332 (m), 1277 (w), 1237 (w), 1220 (w), 1204 (w), 1124 (w), 1086 (s), 1051 (vs), 1026 (m), 1010 (m), 996 (m), 918 (w), 900 (w), 888 (w), 847 (m), 816 (m), 761 (m), 752 (m), 735 (m), 717 (s), 700 (vs).

MS (EI, 70 eV): m/z (%) = 233 (M^+, <1), 215 (1), 180 (1), 127 (100), 107 (63), 79 (36).

HRMS ($C_{13}H_{12}ClNO$): calc.: 233.0607; found: 233.0595.

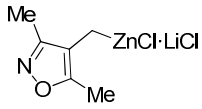
6-Chloropyridin-3-yl)methylzinc chloride (91a)



According to **TP1** 2-chloro-5-(chloromethyl)pyridine (**90a**; 1.62 g, 10.0 mmol, in 4 mL THF) was added dropwise at 0 °C to a suspension of LiCl (848 mg, 20.0 mmol) and zinc dust (1.31 g, 20.0 mmol) in THF (1 mL) (activation: $BrCH_2CH_2Br$ (0.04 mL, 5 mol%), TMSCl (0.01 mL,

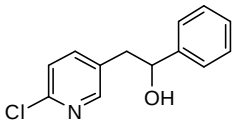
1 mol%)). The reaction mixture was stirred for 2.5 h at 25 °C. After centrifugation iodometric titration of **91a** indicates a yield of 78%.

(3,5-Dimethylisoxazol-4-yl)methylzinc chloride (91b)



According to **TP1** 4-(chloromethyl)-3,5-dimethylisoxazole (**90b**; 1.02 g, 7.00 mmol) was added dropwise at 25 °C to a suspension of LiCl (455 mg, 10.5 mmol) and zinc dust (687 mg, 10.5 mmol) in THF (3.5 mL) (activation: $BrCH_2CH_2Br$ (0.03 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 4 h at 25 °C. After centrifugation iodometric titration of **91b** indicates a yield of 90%.

2-(6-Chloropyridin-3-yl)-1-phenylethanol (92a)



According to **TP2** (6-chloropyridin-3-yl)methylzinc chloride (**91a**; 2.33 mL, 2.40 mmol, 1.03 M in THF) was reacted with benzaldehyde (**60g**; 212 mg, 2.00 mmol, in 1.0 mL THF) at 0 °C. The reaction mixture was slowly warmed to 25 °C within 17 h and was quenched with sat. aq. NaCl solution (50 mL). The phases were separated and the aq. layer was extracted with EtOAc (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the benzylic alcohol **92a** (463 mg, 99%) as a white solid.

M.p. (°C): 115-116.

^{1}H-NMR (400 MHz, DMSO): δ / ppm = 8.14 (d, *J* = 2.5 Hz, 1H), 7.63 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.37 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.34-7.27 (m, 4H), 7.25-7.19 (m, 1H), 5.40 (d, *J* = 4.5 Hz, 1H ('OH')), 4.76 (dt, *J* = 7.9, 4.8 Hz, 1H), 2.93 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.86 (dd, *J* = 13.7, 8.0 Hz, 1H).

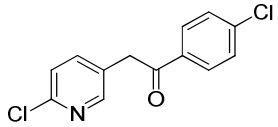
^{13}C-NMR (100 MHz, DMSO): δ / ppm = 150.5, 147.8, 144.9, 140.7, 134.0, 127.9, 126.8, 125.8, 123.3, 72.6, 41.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3346 (w), 1738 (w), 1586 (w), 1568 (m), 1459 (s), 1434 (m), 1387 (m), 1312 (m), 1215 (m), 1203 (m), 1111 (m), 1092 (m), 1076 (m), 1060 (s), 1027 (m), 826 (s), 763 (s), 738 (m), 700 (vs), 685 (s), 638 (s), 615 (m).

MS (EI, 70 eV): m/z (%) = 233 (M^+, <1), 129 (83), 107 (100), 91 (26), 79 (64), 51 (8).

HRMS ($C_{13}H_{13}ClNO$): calc.: 234.0686; found: 234.0686.

1-(4-Chlorophenyl)-2-(6-chloropyridin-3-yl)ethanone (92b)



According to **TP3** 4-chlorobenzoyl chloride (**60d**; 404 mg, 2.31 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.00 mL, 3.00 mmol, 1.00 M in THF) and (6-chloropyridin-3-yl)methylzinc chloride (**91a**; 2.42 mL, 3.00 mmol, 1.24 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 20 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the ketone **92b** (379 mg, 62%) as a white solid.

M.p. (°C): 124-125.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.25 (d, *J* = 2.4 Hz, 1H), 7.96-7.89 (m, 2H), 7.55 (dd, *J* = 8.2 Hz, 2.6 Hz, 1H), 7.48-7.42 (m, 2H), 7.30 (d, *J* = 7.7 Hz, 1H), 4.24 (s, 2H).

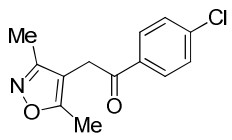
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 194.6, 150.3, 150.2, 140.2, 140.1, 134.3, 129.7, 129.2, 128.7, 124.1, 41.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3091 (vw), 1938 (vw), 1678 (s), 1586 (m), 1568 (m), 1490 (w), 1457 (s), 1401 (m), 1382 (m), 1323 (m), 1289 (m), 1248 (w), 1226 (m), 1204 (m), 1184 (m), 1169 (m), 1133 (w), 1108 (m), 1087 (s), 1026 (m), 1014 (m), 988 (s), 858 (m), 833 (vs), 820 (s), 793 (s), 741 (m), 716 (m), 635 (m), 627 (m).

MS (EI, 70 eV): m/z (%) = 265 (M^+, 5), 141 (100), 126 (4), 111 (52), 75 (14), 63 (3), 50 (3).

HRMS ($C_{13}H_9Cl_2NO$): calc.: 265.0061; found: 265.0057.

1-(4-Chlorophenyl)-2-(3,5-dimethylisoxazol-4-yl)ethanone (92c)



According to **TP3** 4-chlorobenzoyl chloride (**60d**; 350 mg, 2.00 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.80 mL, 2.80 mmol, 1.00 M in THF) and (3,5-dimethylisoxazol-4-yl)methylzinc chloride (**91b**; 2.37 mL, 2.80 mmol, 1.18 M in THF) at -40 °C. The reaction

mixture was allowed to reach 25 °C within 27 h and was quenched with a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the ketone **92c** (403 mg, 81%) as a white solid.

M.p. (°C): 139-141.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.51-7.45 (m, 2H), 7.06-7.00 (m, 2H), 3.22 (s, 2H), 1.95 (s, 3H), 1.79 (s, 3H).

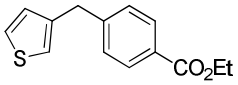
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 193.5, 166.0, 159.6, 139.7, 134.9, 129.8, 129.0, 107.3, 32.1, 10.7, 10.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930 (vw), 1687 (vs), 1647 (m), 1586 (m), 1571 (m), 1486 (w), 1455 (m), 1420 (m), 1398 (m), 1333 (m), 1263 (m), 1212 (s), 1194 (s), 1089 (s), 1015 (m), 987 (vs), 957 (m), 888 (m), 840 (s), 817 (vs), 759 (vs), 748 (vs), 692 (s).

MS (EI, 70 eV): m/z (%) = 249 (M^+, 3), 206 (40), 141 (100), 113 (17), 111 (53), 75 (19), 68 (25), 43 (20).

HRMS ($C_{13}H_{12}ClNO_2$): calc.: 249.0557; found: 249.0559.

Ethyl 4-(thiophen-3-ylmethyl)benzoate (92d)



(3-Thienylmethyl)zinc chloride (**91c**; 1.67 mL, 1.20 mmol, 0.72 M in THF) was added dropwise to a mixture of ethyl 4-bromobenzoate (**71e**; 229 mg, 1.00 mmol), $Pd(OAc)_2$ (4.5 mg, 2.0 mol%) and S-Phos (16.4 mg, 4.0 mol%) in THF (1 mL) at 25 °C. The reaction mixture was stirred for 18 h. Then, sat. aq. NH_4Cl solution (20 mL) was added. The phases were separated and the aq. layer was extracted with EtOAc (3 x 20 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the thiophene **92d** (160 mg, 65%) as a yellow liquid.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.13-8.08 (m, 2H), 6.96-6.91 (m, 2H), 6.86 (dd, *J* = 4.9 Hz, 2.9 Hz, 1H), 6.59 (dd, *J* = 4.9 Hz, 1.4 Hz, 1H), 6.54-6.51 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.58 (s, 2H), 1.03 (t, *J* = 7.1 Hz, 3H).

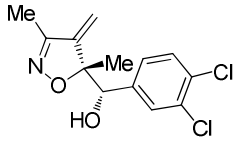
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 166.2, 146.0, 140.6, 130.1, 129.3, 129.0, 128.4, 125.9, 121.7, 60.7, 36.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3101 (vw), 2981 (w), 2906 (vw), 1713 (s), 1610 (w), 1576 (vw), 1416 (w), 1366 (w), 1275 (vs), 1176 (m), 1102 (s), 1021 (m), 942 (w), 919 (vw), 859 (w), 832 (w), 764 (m), 713 (m)..

MS (EI, 70 eV): m/z (%) = 246 (M^+, 100), 218 (10), 201 (84), 173 (77), 128 (11), 97 (20).

HRMS ($C_{14}H_{14}O_2S$): calc.: 246.0715; found: 246.0715.

3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)(phenyl)methanol (92e; rac)



According to **TP2** (3,5-dimethylisoxazol-4-yl)methylzinc chloride (**91b**; 2.49 mL, 3.03 mmol, 1.22 M in THF) was reacted with 3,4-dichlorobenzaldehyde (**61b**; 408 mg, 2.33 mmol, in 0.5 mL THF) at 0 °C. The reaction mixture was slowly warmed to 25 °C within 5 h and was quenched with sat. aq. NH_4Cl solution (20 mL). The phases were separated and the aq. layer was extracted with Et_2O (5 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1 + 1 vol-% NEt_3) afforded the racemic alcohol **92e** (541 mg, 81%, d:r = 95:5) as a white solid.

M.p. (°C): 90-92.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.49-7.46 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.25-7.20 (m, 1H), 5.33 (d, *J* = 0.8 Hz, 1H), 4.72-4.70 (m, 1H), 4.66-4.64 (s, 1H), 2.71 (s_{br}, 1H), 2.00 (s, 3H), 1.39 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 155.6, 150.3, 137.7, 132.0, 131.8, 129.7, 129.6, 127.1, 110.0, 88.7, 76.6, 22.4, 9.7.

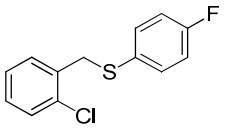
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3510 (m), 2987 (m), 2970 (m), 2925 (m), 1648 (m), 1562 (m), 1468 (m), 1453 (m), 1434 (m), 1401 (m), 1395 (m), 1370 (m), 1351 (m), 1333 (m), 1295 (m), 1282 (m), 1250 (m), 1202 (m), 1170 (m), 1129 (m), 1086 (m), 1062 (s), 1028 (s), 939 (m), 902 (s), 889 (vs), 854 (m), 833 (s), 821 (m), 745 (vs), 727 (s), 695 (m), 671 (s), 616 (m).

MS (EI, 70 eV): m/z (%) = 286 ($[M+H]^+$, <1), 173 (100), 145 (39), 113 (14), 108 (14), 96 (11), 82 (15), 74 (24), 68 (34), 43 (53).

HRMS ($C_{13}H_{13}Cl_2NO_2$): calc.: 286.0402 ($[M+H]^+$); found: 286.0396 ($[M+H]^+$).

3.7. Preparation of benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of $ZnCl_2$ and LiCl

2-Chlorobenzyl 4-fluorophenyl sulfide (97a)



The zinc reagent **95b** was prepared according to **TP9** from 2-chlorobenzyl chloride (**53b**; 322 mg, 2.00 mmol) in 45 min at 25 °C. The freshly prepared zinc reagent **95b** was added to *S*-(4-fluorophenyl) benzenesulfonothioate (**57c**; 376 mg, 1.4 mmol) in 1 mL THF at 25 °C and the mixture was stirred for 17 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 95:5) furnished the sulfide **97a** (306 mg, 86%) as a yellow liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.37-7.33 (m, 1H), 7.32-7.27 (m, 2H), 7.19-7.15 (m, 1H), 7.14-7.08 (m, 2H), 6.97-6.92 (m, 2H), 4.13 (s, 2H).

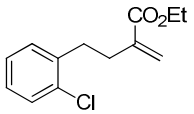
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.3 (d, $^1J_{C\text{-}F}$ = 247.4 Hz), 135.2, 134.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 134.0, 130.7, 130.1 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 129.7, 128.6, 126.6, 115.9 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 38.3 (d, $^6J_{C\text{-}F}$ = 1.1 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1739 (vw), 1589 (m), 1488 (vs), 1472 (m), 1443 (m), 1420 (w), 1396 (w), 1289 (w), 1226 (s), 1155 (m), 1090 (m), 1051 (m), 1037 (m), 1013 (w), 944 (w), 880 (w), 820 (s), 758 (s), 742 (s), 733 (s), 683 (m), 668 (m), 629 (m).

MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 21), 127 (36), 125 (100), 89 (11), 63 (5).

HRMS ($C_{13}H_{10}ClFS$): calc.: 252.0176; found: 252.0176.

Ethyl 2-[2-(2-chlorophenyl)ethyl]acrylate (97b)



The zinc reagent **95b** was prepared according to **TP9** from 2-chlorobenzyl chloride (**53b**; 322 mg, 2.00 mmol) in 45 min at 25 °C. The freshly prepared zinc reagent **95b** was added to ethyl (2-bromomethyl)acrylate (**55b**; 309 mg, 1.60 mmol) in 0.5 mL THF at 25 °C. CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF) was added and the mixture was stirred for 45 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (45 mL) followed by 25% aq. NH_3

solution (5 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 98:2) furnished the acrylate **97b** (295 mg, 77%) as a colourless liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.33 (dd, *J* = 7.6 Hz, 1.3 Hz, 1H), 7.21-7.10 (m, 3H), 6.15 (d, *J* = 1.3 Hz, 1H), 5.49 (d, *J* = 1.3 Hz, 1H), 4.21 (q, *J* = 7.3 Hz, 2H), 2.94-2.89 (m, 2H), 2.64-2.59 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

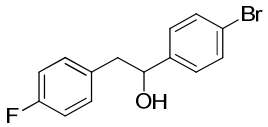
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 167.0, 139.8, 138.9, 134.0, 130.5, 129.4, 127.5, 126.7, 125.4, 60.7, 32.7, 32.1, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 2936 (w), 1713 (vs), 1631 (w), 1475 (m), 1443 (m), 1303 (m), 1182 (s), 1139 (s), 1113 (m), 1052 (m), 1035 (s), 944 (m), 816 (m), 749 (vs), 673 (m).

MS (EI, 70 eV): *m/z* (%) = 238 (M^+, 11), 193 (12), 164 (10), 157 (39), 129 (13), 127 (31), 125 (100), 89 (8).

HRMS ($C_{13}H_{15}O_2Cl$): calc.: 238.0761; found: 238.0762.

1-(4-Bromophenyl)-2-(4-fluorophenyl)ethanol (97c)



The zinc reagent **95c** was prepared according to **TP9** from 4-fluorobenzyl chloride (**53c**; 289 mg, 2.00 mmol) in 45 min at 25 °C. The freshly prepared zinc reagent **95c** was added to 4-bromobenzaldehyde (**61e**; 259 mg, 1.40 mmol) in 1 mL THF at 0 °C. The mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 1:1 + 1 vol-% NEt_3) furnished the alcohol **97c** (209 mg, 51%) as a pale yellow solid.

M.p. (°C): 62-64.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.21-7.21 (m, 2H), 6.79-6.63 (m, 6H), 4.25 (dd, *J* = 7.6 Hz, 5.5 Hz, 1H), 2.65-2.48 (m, 2H), 1.19 (s, 1H).

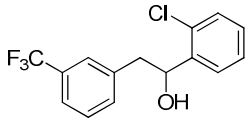
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 162.1 (d, $^1J_{C\text{-}F}$ = 244.3 Hz), 143.3, 133.7 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 131.5, 131.3 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 127.9, 121.4, 115.2 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 74.4, 45.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3603 (w), 2923 (w), 2875 (vw), 2854 (vw), 1601 (w), 1507 (m), 1486 (w), 1402 (w), 1274 (w), 1212 (m), 1157 (m), 1092 (w), 1049 (m), 1009 (m), 873 (w), 821 (vs), 806 (m), 762 (w), 713 (w).

MS (EI, 70 eV): m/z (%) = 294 (M^+, <1), 276, (3), 185 (100), 157 (20), 110 (90), 77 (42), 51 (5).

HRMS ($C_{14}H_{12}BrFO$): calc.: 294.0056; found: 294.0059.

1-(2-Chlorophenyl)-2-[3-(trifluoromethyl)phenyl]ethanol (97d)



The zinc reagent **95g** was prepared according to **TP9** from 3-(trifluoromethyl)benzyl chloride (**53g**; 389 mg, 2.00 mmol) in 30 min at 25 °C. The freshly prepared zinc reagent **95g** was added to 2-chlorobenzaldehyde (**61a**; 197 mg, 1.40 mmol) and the mixture was stirred for 1 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 7:1) furnished the alcohol **97d** (357 mg, 85%) as a colourless solid.

M.p. (°C): 44-45.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.62-7.15 (m, 8H), 5.33 (dd, *J* = 8.8 Hz, 3.3 Hz, 1H), 3.18 (dd, *J* = 13.8 Hz, 3.3 Hz, 1H), 2.89 (dd, *J* = 13.8 Hz, 8.8 Hz, 1H), 1.99 (s, 1H).

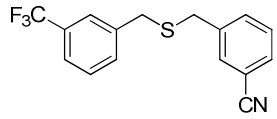
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 140.9, 139.1, 133.0 (q, $^4J_{C\text{-}F}$ = 1.5 Hz), 131.5, 130.7 (q, $^2J_{C\text{-}F}$ = 32.1 Hz), 129.4, 128.8, 128.7, 127.2, 127.0, 126.3 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 124.2 (q, $^1J_{C\text{-}F}$ = 272.3 Hz), 123.5 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 71.5, 43.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3332 (w), 3254 (w), 2932 (w), 1476 (w), 1448 (m), 1332 (s), 1322 (s), 1254 (w), 1198 (m), 1172 (s), 1160 (s), 1114 (vs), 1098 (s), 1072 (s), 1048 (s), 1034 (s), 1004 (m), 910 (m), 854 (m), 794 (s), 758 (s), 722 (m), 708 (s), 698 (s), 660 (m), 650 (m), 622 (m), 586 (s).

MS (EI, 70 eV): *m/z* (%) = 300 (M^+, <1), 283 (4), 281 (10), 159 (15), 143 (100), 141 (32), 139 (12), 113 (22), 77 (46).

HRMS ($C_{15}H_{12}ClF_3O$): calc.: 300.0529; found: 300.0535.

3-({[3-(Trifluoromethyl)benzyl]thio}methyl)benzonitrile (97e)



The zinc reagent **95g** was prepared according to **TP9** from 3-(trifluoromethyl)benzyl chloride (**53g**; 389 mg, 2.00 mmol) in 30 min at 25 °C. The freshly prepared zinc reagent **95g** was added to *S*-(3-cyanobenzyl) benzenesulfonothioate (**57d**; 405 mg, 1.40 mmol) in THF (1 mL) at 25 °C. The mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 9:1) furnished the sulfide **97e** (372 mg, 86%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.56-7.35 (m, 8H), 3.64 (s, 2H), 3.60 (s, 2H).

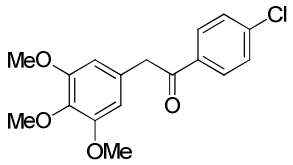
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 139.4, 138.6, 133.3, 132.3, 132.2 (q, $^4J_{C\text{-}F}$ = 1.3 Hz), 131.0 (q, $^2J_{C\text{-}F}$ = 32.3 Hz), 130.9, 129.4, 129.1, 125.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.1 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 123.9 (q, $^1J_{C\text{-}F}$ = 272.4 Hz), 118.5, 112.7, 35.5, 35.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2230 (w), 1598 (vw), 1582 (w), 1482 (w), 1450 (w), 1430 (w), 1328 (vs), 1240 (w), 1226 (w), 1162 (s), 1118 (vs), 1092 (s), 1070 (s), 1002 (w), 900 (m), 800 (m), 738 (m), 700 (s), 684 (s), 658 (s), 606 (w), 558 (w).

MS (EI, 70 eV): *m/z* (%) = 307 (M^+, 33), 191 (10), 159 (100), 148 (13), 116 (25).

HRMS ($C_{16}H_{12}F_2NS$): calc.: 307.0643; found: 307.0638.

1-(4-Chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (97f)



The zinc reagent **95h** was prepared according to **TP9** from 3,4,5-trimethoxybenzyl chloride (**53h**; 433 mg, 2.00 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent **95h** was cooled to -20 °C and CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) was added. After stirring for 15 min 4-chlorobenzoyl chloride (**60d**; 245 mg, 1.40 mmol) was added and the mixture warmed to 25 °C and stirred for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL) followed by 25% aq. NH_3 solution (5 mL) and extracted with Et_2O (3 x 30 mL). The combined

organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 1:1) furnished the ketone **97f** (253 mg, 56%) as a yellow solid.

M.p. (°C): 109-111.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.97-7.90 (m, 2H), 7.45-7.39 (m, 2H), 6.44 (s, 2H), 4.17 (s, 2H), 3.81 (s, 6H), 3.81 (s, 3H).

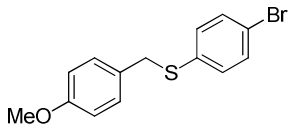
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 196.3, 153.3, 139.7, 136.9, 134.7, 129.9, 129.6, 129.0, 106.3, 60.8, 56.0, 45.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061 (vw), 3011 (vw), 2943 (w), 2842 (w), 2754 (vw), 1681 (m), 1589 (m), 1505 (m), 1458 (m), 1424 (m), 1391 (m), 1322 (s), 1233 (m), 1123 (vs), 1089 (m), 1036 (w), 993 (m), 846 (m), 812 (w), 788 (w), 758 (w), 728 (m).

MS (EI, 70 eV): *m/z* (%) = 320 (M^+, 18), 181 (100), 148 (4), 139 (11), 111 (4).

HRMS ($C_{17}H_{17}ClO_4$): calc.: 320.0815; found: 320.0812.

1-Bromo-4-[(4-methoxybenzyl)thio]benzene (97g)



The zinc reagent **95i** was prepared according to **TP9** from 4-methoxybenzyl chloride (**53i**; 313 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **95i** was added to *S*-(4-bromophenyl) benzenesulfonothioate (**57a**; 461 mg, 1.40 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 17 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 9:1) furnished the sulfide **97g** (379 mg, 88%) as a white solid.

M.p. (°C): 100-102.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.09-7.04 (m, 2H), 7.02-6.97 (m, 2H), 6.86-6.80 (m, 2H), 6.71-6.64 (m, 2H), 3.67 (s, 2H), 3.24 (s, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 159.4, 136.4, 132.0, 131.3, 130.2, 129.1, 120.1, 114.2, 54.7, 38.2.

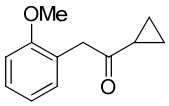
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3015 (w), 2962 (w), 2921 (w), 2837 (w), 1738 (w), 1611 (m), 1583 (w), 1511 (m), 1473 (m), 1454 (m), 1441 (m), 1382 (w), 1302 (m), 1254 (m),

1233 (m), 1176 (m), 1128 (w), 1089 (m), 1027 (s), 1005 (m), 837 (s), 806 (vs), 755 (s), 741 (m), 702 (m), 637 (w)..

MS (EI, 70 eV): *m/z* (%) = 308 (M^+, 4), 241 (3), 189 (5), 121 (100), 108 (18), 91 (12), 77 (18), 51 (7).

HRMS ($C_{14}H_{13}BrOS$): calc.: 307.9870; found: 307.9864.

1-Cyclopropyl-2-(2-methoxyphenyl)ethanone (97h)



The zinc reagent **95j** was prepared according to **TP9** from 2-methoxybenzyl chloride (**53j**; 313 mg, 2.00 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent **95j** was added to CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) at -20 °C. After stirring for 15 min cyclopropanecarbonyl chloride (**60c**; 146 mg, 1.4 mmol) was added and the mixture was slowly warmed to 25 °C within 6.5 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (200 mL) followed by 25% aq. NH_3 solution (50 mL) and extracted with Et_2O (3 x 250 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* Flash chromatography (silica gel, pentane / Et_2O = 8:1) furnished the ketone **97h** (238 mg, 89%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.29-7.21 (m, 1H), 7.18-7.13 (m, 1H), 6.96-6.85 (m, 2H), 3.80 (s, 3H), 3.79 (s, 2H), 2.00-1.90 (m, 1H), 1.06-0.99 (m, 2H), 0.84-0.76 (m, 2H).

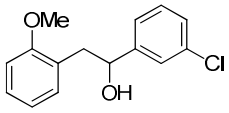
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 208.7, 157.5, 131.1, 128.3, 123.7, 120.6, 110.5, 55.3, 45.0, 19.6, 10.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3008 (w), 2838 (vw), 1694 (s), 1602 (w), 1590 (w), 1494 (s), 1464 (m), 1440 (m), 1378 (s), 1320 (w), 1290 (w), 1244 (vs), 1200 (m), 1112 (m), 1070 (s), 1048 (m), 1024 (s), 930 (w), 898 (m), 818 (w), 750 (vs), 658 (w), 604 (w), 576 (w).

MS (EI, 70 eV): *m/z* (%) = 190 (M^+, 58), 121 (44), 91 (62), 65 (47), 41 (100).

HRMS ($C_{12}H_{14}O_2$): calc.: 190.0994; found: 190.0983.

1-(3-Chlorophenyl)-2-(2-methoxyphenyl)ethanol (97i)



The zinc reagent **95j** was prepared according to **TP9** from 2-methoxybenzyl chloride (**53j**; 313 mg, 2.00 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent **95j** was added to 3-chlorobenzaldehyde (**61c**; 197 mg, 1.40 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 4 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 4:1) furnished the alcohol **97i** (338 mg, 92%) as a colourless solid.

M.p. (°C): 60-61.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.42-7.39 (m, 1H), 7.30-7.21 (m, 4H), 7.10-7.05 (m, 1H), 6.95-6.87 (m, 2H), 4.98-4.91 (m, 1H), 3.87 (s, 3H), 3.13 (dd, *J* = 13.6 Hz, 4.1 Hz, 1H), 2.95 (dd, *J* = 13.6 Hz, 8.8 Hz, 1H), 2.64 (d, *J* = 2.9 Hz, 1H).

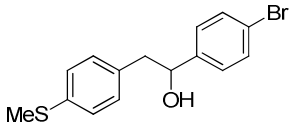
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.5, 146.6, 134.1, 131.5, 129.4, 128.2, 127.3, 126.1, 126.0, 123.9, 120.8, 110.5, 73.7, 55.4, 41.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3322 (w), 3252 (w), 2946 (w), 2922 (w), 2838 (w), 1600 (m), 1492 (s), 1468 (s), 1438 (m), 1420 (m), 1292 (m), 1238 (vs), 1200 (m), 1182 (m), 1114 (s), 1080 (m), 1062 (s), 1050 (s), 1032 (s), 1008 (m), 872 (m), 786 (s), 764 (s), 750 (vs), 728 (m), 708 (s), 692 (s), 642 (m), 604 (s), 558 (s).

MS (EI, 70 eV): *m/z* (%) = 262 (M^+, <1), 165 (2), 122 (100), 91 (25), 77 (13).

HRMS ($C_{15}H_{15}ClO_2$): calc.: 262.0761; found: 262.0747.

1-(4-Bromophenyl)-2-[4-(methylthio)phenyl]ethanol (97j)



The zinc reagent **95l** was prepared according to **TP9** from 4-(methylthio)benzyl chloride (**53l**; 345 mg, 2.00 mmol) in 1.5 h at 25 °C. The freshly prepared zinc reagent **95l** was added to 4-bromobenzaldehyde (**61e**; 259 mg, 1.40 mmol) in 1 mL THF at 25 °C. The mixture was stirred for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated

in vacuo. Flash chromatography (silica gel, pentane / Et_2O = 3:1) furnished the alcohol **97j** (372 mg, 82%) as a colourless solid.

M.p. (°C): 117-119.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.48-7.42 (m, 2H), 7.22-7.16 (m, 4H), 7.09-7.03 (m, 2H), 4.81 (dd, *J* = 7.6 Hz, 5.5 Hz, 1H), 2.98-2.88 (m, 2H), 2.46 (s, 3H), 1.86 (s, 1H).

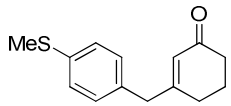
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 142.6, 136.7, 134.3, 131.5, 130.0, 127.6, 126.9, 121.4, 74.6, 45.4, 16.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3310 (w), 2914 (w), 1494 (m), 1488 (m), 1434 (m), 1424 (m), 1404 (m), 1092 (m), 1058 (s), 1008 (m), 1000 (m), 882 (w), 822 (vs), 792 (s), 716 (w).

MS (EI, 70 eV): *m/z* (%) = 322 (M^+, 3), 187 (14), 185 (16), 138 (100), 123 (30), 91 (7), 77 (14).

HRMS ($C_{15}H_{15}BrOS$): calc.: 322.0027; found: 322.0018.

3-[4-(Methylthio)benzyl]cyclohex-2-en-1-one (97k)



The zinc reagent **95l** was prepared according to **TP9** from 4-(methylthio)benzyl chloride (**53l**; 345 mg, 2.00 mmol) in 1.5 h at 25 °C. The freshly prepared zinc reagent **95l** was added to CuCN·2LiCl (2.00 mL, 2.0 mmol, 1.00 M in THF) at -20 °C. After stirring for 15 min, 3-iodocyclohex-2-enone (**58b**; 311 mg, 1.40 mmol) was added at -40 °C and the mixture was slowly warmed to 0 °C within 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (100 mL) followed by 25% aq. NH_3 solution (50 mL) and extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 1:1) furnished the cyclohexenone **97k** (201 mg, 62%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.22-7.16 (m, 2H), 7.09-7.03 (m, 2H), 5.84-5.81 (m, 1H), 3.44 (s, 2H), 2.45 (s, 3H), 2.37-2.30 (m, 2H), 2.26-2.19 (m, 2H), 1.99-1.87 (m, 2H).

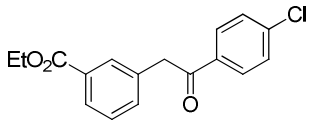
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.8, 164.6, 136.9, 133.7, 129.5, 126.9, 126.8, 43.9, 37.2, 29.1, 22.6, 15.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3675 (w), 2989 (m), 2970 (m), 2920 (m), 1739 (s), 1663 (vs), 1624 (m), 1493 (m), 1425 (m), 1404 (m), 1370 (s), 1349 (m), 1323 (m), 1230 (s), 1217 (s), 1191 (m), 1092 (m), 1066 (m), 1016 (m), 968 (m), 886 (m), 834 (w), 807 (m), 794 (m), 756 (m), 728 (w), 660 (w).

MS (EI, 70 eV): *m/z* (%) = 232 (M^+, 100), 176 (22), 157 (15), 137 (28), 129 (26), 122 (11), 115 (9).

HRMS ($C_{14}H_{16}OS$**):** calc.: 232.0922; found: 232.0922.

Ethyl 3-[2-(4-chlorophenyl)-2-oxoethyl]benzoate (97l)



The zinc reagent **95m** was prepared according to **TP9** from 3-(ethoxycarbonyl)benzyl chloride (**53m**; 397 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **95m** was added to CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) at -20 °C. After stirring for 15 min, 4-chlorobenzoyl chloride (**60d**; 245 mg, 1.40 mmol) was added and the mixture was stirred for 1.5 h at 0 °C followed by 30 min at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (40 mL) followed by 25% aq. NH_3 solution (20 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 9:1) furnished the ketone **97l** (347 mg, 82%) as a colourless solid.

M.p. (°C): 76-78.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.97-7.90 (m, 4H), 7.46-7.35 (m, 4H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.30 (s, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

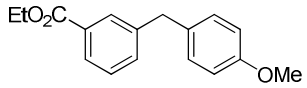
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 195.8, 166.3, 139.8, 134.7, 134.4, 133.9, 130.9, 130.6, 129.9, 129.0, 128.7, 128.3, 61.0, 45.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ **/** cm^{-1} = 2984 (w), 2914 (w), 1694 (vs), 1588 (m), 1394 (m), 1332 (s), 1280 (s), 1208 (vs), 1170 (s), 1108 (s), 1088 (s), 1030 (s), 1000 (s), 990 (s), 944 (m), 832 (s), 814 (vs), 796 (m), 752 (vs), 722 (s), 710 (m), 584 (m), 562 (s).

MS (EI, 70 eV): *m/z* (%) = 302 (M^+, 1), 259 (6), 257 (20), 141 (100), 139 (13), 113 (12), 111 (40).

HRMS ($C_{17}H_{15}ClO_3$): calc.: 302.0710; found: 302.0702.

Ethyl 3-(4-methoxybenzyl)benzoate (97m)



The zinc reagent **95m** was prepared according to **TP9** from 3-(ethoxycarbonyl)benzyl chloride (**53m**; 397 mg, 2.00 mmol) in 2 h at 25 °C. A dry and argon-flushed *Schlenk*-flask was charged with 4-iodoanisole (**4c**; 328 mg, 1.40 mmol) and PEPPSI-IPr (3.4 mg, 0.25 mol%). THF (1.0 mL) was added. The freshly prepared zinc reagent **95m** was added and the reaction mixture was stirred for 21 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 10:1) furnished the diarylmethane **97m** (295 mg, 78%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.92-7.83 (m, 2H), 7.37-7.31 (m, 2H), 7.13-7.06 (m, 2H), 6.86-679 (m, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.96 (s, 2H), 3.77 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H).

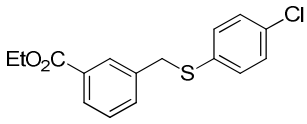
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.7, 158.1, 141.8, 133.3, 132.6, 130.6, 129.9, 129.8, 128.4, 127.3, 114.0, 60.9, 55.2, 40.8, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 2934 (w), 2906 (w), 2836 (w), 1714 (s), 1610 (m), 1586 (w), 1510 (s), 1464 (m), 1442 (m), 1366 (m), 1276 (s), 1244 (vs), 1176 (s), 1102 (s), 1080 (s), 1030 (s), 928 (w), 810 (m), 764 (s), 738 (s), 690 (m), 670 (m), 606 (m).

MS (EI, 70 eV): *m/z* (%) = 270 (M^+, 100), 241 (20), 225 (23), 197 (32), 165 (13), 232 (23).

HRMS ($C_{17}H_{18}O_3$): calc.: 270.1256; found: 270.1252.

Ethyl 3-{[(4-chlorophenyl)thio]methyl}benzoate (97n)



The zinc reagent **95m** was prepared according to **TP9** from 3-(ethoxycarbonyl)benzyl chloride (**53m**; 397 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **95m** was added to *S*-(4-chlorophenyl) benzenesulfonothioate (**57e**; 399 mg, 1.40 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried

over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane to pentane / Et_2O = 98:2) furnished the sulfide **97n** (288 mg, 67%) as a yellow solid.

M.p. (°C): 41-43.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.94-7.88 (m, 2H), 7.45-7.39 (m, 1H), 7.37-7.30 (m, 1H), 7.20 (s, 4H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.09 (s, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

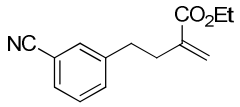
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.2, 137.6, 134.0, 133.1, 132.8, 131.9, 130.8, 129.9, 129.0, 128.5, 128.5, 61.0, 39.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052 (w), 2992 (w), 2934 (w), 1708 (s), 1584 (w), 1470 (s), 1444 (m), 1390 (m), 1282 (s), 1264 (m), 1234 (s), 1194 (s), 1176 (m), 1108 (s), 1090 (s), 1022 (m), 1006 (m), 944 (m), 934 (m), 806 (s), 778 (s), 730 (vs), 688 (s), 674 (m), 586 (m).

MS (EI, 70 eV): *m/z* (%) = 306 (M^+, 23), 163 (100), 135 (12), 119(18) 89 (6).

HRMS ($C_{16}H_{15}ClO_2S$): calc.: 306.0481; found: 306.0481.

Ethyl 2-[2-(3-cyanophenyl)ethyl]acrylate (97o)



The zinc reagent **95o** was prepared according to **TP9** from 3-cyanobenzyl chloride (**53o**; 303 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **95o** was added to ethyl (2-bromomethyl)acrylate (**55b**; 270 mg, 1.40 mmol) in 0.5 mL THF at 25 °C. CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF) was added and the mixture was stirred for 60 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (45 mL) followed by 25% aq. NH_3 solution (5 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 1:1) furnished the acrylate **97o** (255 mg, 79%) as a colourless liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.497.45 (m, 2H), 7.42-7.39 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.15 (d, *J* = 1.3 Hz, 1H), 5.46 (q, *J* = 1.2 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 2.84-2.80 (m, 2H), 2.62-2.57 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H).

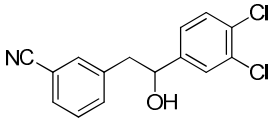
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 166.7, 142.7, 139.3, 133.1, 132.0, 129.8, 129.1, 125.7, 118.9, 112.3, 60.8, 34.4, 33.5, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983 (w), 2935 (w), 2230 (m), 1710 (vs), 1631 (w), 1583 (w), 1483 (w), 1445 (w), 1369 (w), 1300 (m), 1256 (m), 1186 (vs), 1134 (s), 1095 (m), 1028 (m), 945 (m), 917 (w), 797 (s), 690 (s).

MS (EI, 70 eV): *m/z* (%) = 229 (M^+, 10), 183 (71), 155 (34), 116 (100), 89 (14).

HRMS ($C_{14}H_{15}NO_2$): calc.: 229.1103; found: 229.1090.

3-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]benzonitrile (97p)



The zinc reagent **95o** was prepared according to **TP9** from 3-cyanobenzyl chloride (**53o**; 303 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **95o** was added to 3,4-dichlorobenzaldehyde (**61b**; 245 mg, 1.40 mmol) in 1 mL THF at 0 °C. The mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 7:3) furnished the alcohol **97p** (341 mg, 83%) as a white solid.

M.p. (°C): 96-97.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.55-7.47 (m, 2H), 7.44-7.33 (m, 4H), 7.11 (dd, *J* = 8.2 Hz, 2.0 Hz, 1H), 4.86 (t, *J* = 6.4 Hz, 1H), 2.99 (d, *J* = 6.4 Hz, 2H), 2.02-1.89 (s, 1H).

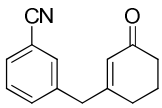
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 143.5, 138.9, 134.1, 133.1, 132.7, 131.8, 130.5, 130.5, 129.2, 127.8, 125.1, 118.7, 112.5, 73.6, 45.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3328 (m), 3260 (m), 2232 (m), 1484 (m), 1470 (s), 1426 (m), 1398 (m), 1202 (m), 1142 (m), 1058 (s), 1028 (s), 1014 (m), 904 (m), 818 (s), 798 (vs), 690 (s), 650 (s), 602 (m).

MS (EI, 70 eV): *m/z* (%) = 291 (M^+, 2), 179 (13), 177 (100), 175 (61), 147 (29), 117 (71), 111 (19), 90 (13), 75 (12).

HRMS ($C_{15}H_{11}Cl_2NO$): calc.: 291.0218; found: 291.0214.

3-[(3-Oxocyclohex-1-en-1-yl)methyl]benzonitrile (97q)



The zinc reagent **95o** was prepared according to **TP9** from 3-cyanobenzyl chloride (**53o**; 303 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **95o** was added to CuCN·2LiCl (2.00 mL, 2.00 mmol 1.00 M in THF) at -20 °C. After stirring for 15 min, 3-iodocyclohex-2-

enone (**58b**; 311 mg, 1.40 mmol) was added at -60 °C and the mixture was slowly warmed to 0°C within 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (100 mL) followed by 25% aq. NH_3 solution (50 mL) and extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 1:2) furnished the cyclohexenone **97q** (227 mg, 77%) as a yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.58-7.52 (m, 1H), 7.47-7.36 (m, 3H), 5.80-5.76 (m, 1H), 3.53 (s, 2H), 2.40-2.32 (m, 2H), 2.27-2.20 (m, 2H), 2.03-1.91 (m, 2H).

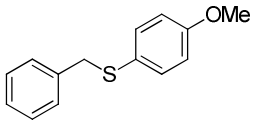
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.3, 162.6, 138.4, 133.6, 132.5, 130.7, 129.5, 127.4, 118.5, 112.9, 43.7, 37.2, 29.3, 22.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926 (w), 2228 (m), 1660 (vs), 1626 (m), 1600 (w), 1582 (w), 1484 (w), 1428 (m), 1372 (m), 1348 (m), 1324 (m), 1250 (m), 1192 (m), 1128 (w), 968 (m), 906 (m), 884 (m), 796 (s), 758 (m), 724 (m), 694 (s), 672 (m), 556 (m).

MS (EI, 70 eV): *m/z* (%) = 211 (M^+, 62), 183 (100), 154 (48), 140 (16), 67 (23).

HRMS ($C_{14}H_{13}NO$): calc.: 211.0997; found: 211.0994.

1-(Benzylthio)-4-methoxybenzene (97r)



The zinc reagent **95a** was prepared according to **TP9** from benzyl chloride (**53a**; 253 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **95a** was added to *S*-(4-methoxyphenyl) benzenesulfonothioate (**57f**; 393 mg, 1.40 mmol) in THF (1 mL) at 25 °C. The mixture was stirred for 13 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 15:1) furnished the sulfide **97r** (252 mg, 78%) as a pale yellow solid.

M.p. (°C): 51-52.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.33-7.19 (m, 7H), 6.86-6.78 (m, 2H), 4.01 (s, 2H), 3.80 (s, 3H).

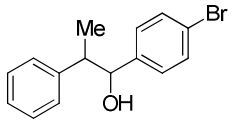
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.1, 138.1, 134.0, 128.8, 128.3, 126.9, 126.0, 114.4, 55.2, 41.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3675 (w), 2989 (m), 2970 (m), 1739 (s), 1595 (m), 1571 (m), 1492 (s), 1465 (m), 1453 (s), 1435 (m), 1365 (m), 1307 (w), 1284 (m), 1232 (s), 1217 (s), 1203 (s), 1180 (s), 1117 (m), 1105 (m), 1095 (m), 1070 (m), 1023 (s), 1004 (m), 914 (m), 808 (vs), 794 (m), 778 (m), 710 (vs), 695 (vs), 637 (s), 626 (m).

MS (EI, 70 eV): m/z (%) = 230 (M^+, 100), 139 (22), 91 (98), 65 (7).

HRMS ($C_{14}H_{14}OS$): calc.: 230.0765; found: 230.0745.

1-(4-Bromophenyl)-2-phenylpropan-1-ol (97s)



The zinc reagent **95u** was prepared according to **TP9** from 1-(chloroethyl)benzene (**54v**; 281 mg, 2.00 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent **54u** was added to 4-bromobenzaldehyde (**61e**; 259 mg, 1.40 mmol) in THF (1 mL) at 25 °C. The mixture was stirred for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 9:1) furnished the alcohol **97s** (285 mg, 70%) as a colourless solid. Two diastereomers were observed with a ratio of 2:1. Analtical data for the main diastereomer is given.

M.p. (°C): 63-65.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.57-7.07 (m, 9H), 4.66 (d, *J* = 8.5 Hz, 1H), 3.06-2.94 (m, 1H), 1.90 (s_{br}, 1H), 1.13 (d, *J* = 7.1 Hz, 3H).

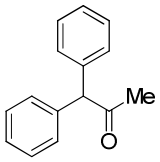
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 142.8, 141.4, 131.3, 128.7, 128.7, 128.0, 127.1, 121.5, 79.0, 48.1, 18.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3378 (w), 3028 (w), 2968 (w), 2896 (w), 2878 (w), 2360 (vw), 1602 (w), 1488 (m), 1450 (m), 1406 (m), 1378 (w), 1198 (w), 1092 (m), 1070 (m), 1036 (m), 1026 (m), 1004 (s), 992 (m), 906 (m), 834 (m), 820 (s), 774 (m), 756 (s), 698 (vs), 658 (m), 628 (m), 620 (m), 608 (m), 580 (s), 568 (m), 556 (m).

MS (EI, 70 eV): *m/z* (%) = 290 (M^+, 2), 211 (8), 185 (22), 91 (100), 78 (66), 51 (20).

HRMS ($C_{15}H_{15}BrO$): calc.: 290.0306; found: 290.0302.

1,1-Diphenylacetone (97t)



The zinc reagent **95v** was prepared according to **TP9** from 1,1'-(chloromethylene)dibenzene (**53v**; 405 mg, 2.00 mmol) in 30 min at 0 °C. The freshly prepared zinc reagent **95v** was added to CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) at -20 °C. After stirring for 15 min, acetyl chloride (**60a**; 110 mg, 1.40 mmol) was added and the mixture was slowly warmed to 10 °C within 24 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (90 mL) followed by 25% aq. NH_3 solution (30 mL) and extracted with Et_2O (3 x 120 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 5:1) furnished the ketone **97t** (199 mg, 68%) as a colourless liquid.

M.p. (°C): 100-102.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.34-7.17 (m, 10H), 5.09 (s, 1H), 2.21 (s, 3H).

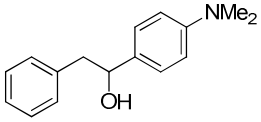
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 206.4, 138.2, 128.9, 128.7, 127.2, 65.0, 30.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3669 (vw), 2989 (m), 2970 (m), 1738 (s), 1714 (s), 1598 (w), 1494 (m), 1451 (m), 1419 (w), 1354 (s), 1228 (m), 1217 (m), 1152 (m), 1080 (m), 1032 (m), 893 (w), 753 (m), 695 (vs), 629 (w).

MS (EI, 70 eV): m/z (%) = 210 (M^+, 1), 167 (100), 152 (15), 139 (4), 43 (11).

HRMS ($C_{15}H_{14}O$): calc.: 210.1045; found: 210.1041.

1-[4-(Dimethylamino)phenyl]-2-phenylethanol (97u)



The zinc reagent **95a** was prepared according to **TP9** from benzyl chloride (**53u**; 253 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **95a** was added to 4-(dimethylamino)benzaldehyde (**61h**; 209 mg, 1.40 mmol) at 25 °C. The mixture was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 1:1) furnished the alcohol **97u** (331 mg, 98 %) as a yellow solid.

M.p. (°C): 57-59.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.34-7.18 (m, 7H), 6.78-6.70 (m, 2H), 4.81 (t, *J* = 6.7 Hz, 1H), 3.02 (d, *J* = 6.7 Hz, 2H), 2.95 (s, 6H), 1.94 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.1, 138.5, 131.9, 129.4, 128.4, 126.9, 126.3, 112.5, 75.1, 45.7, 40.7.

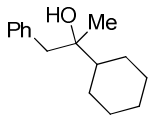
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3312 (m), 3054 (w), 3026 (w), 2922 (m), 2856 (m), 2812 (w), 1618 (s), 1526 (s), 1448 (m), 1358 (s), 1336 (m), 1324 (m), 1232 (m), 1188 (m), 1170 (m), 1068 (m), 1020 (s), 1002 (m), 946 (m), 814 (s), 794 (m), 746 (s), 732 (s), 696 (vs), 638 (m), 620 (m), 608 (s).

HRMS (ESI; $C_{16}H_{20}NO$): calc.: 242.1545 ($[M+H]^+$); found: 242.1540 ($[M+H]^+$).

4. Lewis-Acid Promoted Additions of Functionalized Organomagnesium and Organozinc Reagents to Carbonyl Derivatives

4.1. Addition of Grignard reagents to ketones in the presence of catalytic amounts of $LaCl_3 \cdot 2LiCl$

2-Cyclohexyl-1-phenylpropan-2-ol (98a)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): according to **TP10** cyclohexylmagnesium bromide (**28b**; 5.79 mL, 2.20 mmol, 0.38 M in THF) was added to a solution of phenylacetone (**58c**; 268 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 15 min at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 1 vol-% NEt_3) afforded the alcohol **98a** (406 mg, 93%) as a colourless liquid.

Condition B (30 mol% $LaCl_3 \cdot 2LiCl$): cyclohexylmagnesium bromide (**28b**; 5.79 mL, 2.20 mmol, 0.38 M in THF), phenylacetone (**58c**; 268 mg, 2.00 mmol, in 2.5 mL THF), $LaCl_3 \cdot 2LiCl$ (1.15 mL, 0.60 mmol, 0.52 M in THF), 15 min at 25 °C. The alcohol **98a** (382 mg, 87%) was obtained as a colourless liquid.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): cyclohexylmagnesium bromide (**28b**; 5.79 mL, 2.20 mmol, 0.38 M in THF), phenylacetone (**98a**; 268 mg, 2.00 mmol, in 3.5 mL THF), 1.75 h at 25 °C. The alcohol **58c** was obtained in 33% yield (yield determined by ^{1}H-NMR after purification by flash chromatography).

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.18-7.04 (m, 5H), 2.66 (d, *J* = 13.1 Hz, 1H), 2.50 (d, *J* = 13.3 Hz, 1H), 1.89-1.54 (m, 5H), 1.30-0.87 (m, 7H), 0.87 (s, 3H).

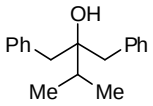
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 138.4, 131.1, 128.3, 126.5, 73.8, 48.0, 45.6, 28.1, 27.3, 27.1 (double), 27.0, 23.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3467 (vw), 3028 (vw), 2923 (m), 2852 (m), 1604 (vw), 1494 (w), 1451 (m), 1377 (w), 1346 (w), 1195 (w), 1138 (w), 1107 (w), 1083 (m), 1060 (w), 1031 (w), 937 (w), 892 (m), 849 (w), 802 (w), 769 (w), 736 (m), 726 (m), 700 (vs).

MS (EI, 70 eV): m/z (%) = 218 (M^+, < 1), 200 (2), 180 (10), 127 (100), 109 (42), 92 (75), 83 (43), 67 (18), 55 (25).

HRMS ($C_{15}H_{22}O$): calc.: 218.1617; found: 218.1649.

2-Benzyl-3-methyl-1-phenylbutan-2-ol (98b)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): according to **TP10** *i*-PrMgCl (**28c**; 1.29 mL, 2.20 mmol, 1.70 M in THF) was added to a solution of 1,3-diphenylacetone (**58d**; 421 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 5 min at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2 + 1 vol-% NEt_3) afforded the alcohol **98b** (436 mg, 86%) as a white solid.

Condition B (30 mol% $LaCl_3 \cdot 2LiCl$): *i*-PrMgCl (**28c**; 1.29 mL, 2.20 mmol, 1.70 M in THF), 1,3-diphenylacetone (**58d**; 421 mg, 2.00 mmol, in 2.5 mL THF), $LaCl_3 \cdot 2LiCl$ (1.15 mL, 0.60 mmol, 0.52 M in THF), 5 min at 25 °C. The alcohol **98b** (333 mg, 65%) was obtained as a white solid.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): *i*-PrMgCl (**28c**; 1.29 mL, 2.20 mmol, 1.70 M in THF), 1,3-diphenylacetone (**58d**; 421 mg, 2.00 mmol, in 3.5 mL THF), 1.75 h at 25 °C. The alcohol **98b** was obtained in < 3% yield (GC).

Condition D (100 mol% $LaCl_3 \cdot 2LiCl$; upscaled reaction): *i*-PrMgCl (**28c**; 14.4 mL, 22.3 mmol, 1.55 M in THF), 1,3-diphenylacetone (**58d**; 4.27 g, 20.3 mmol), $LaCl_3 \cdot 2LiCl$ (39.0 mL, 20.3 mmol, 0.52 M in THF), 1 h at 25 °C. The alcohol **98b** (4.30 g, 83%) was obtained as a white solid.

M.p. (°C): 59-60.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.21-7.08 (m, 10H), 2.78 (d, *J* = 13.7 Hz, 2H), 2.54 (d, *J* = 13.7 Hz, 2H), 1.78-1.67 (m, 1H), 1.09 (s, 1H), 0.90 (d, *J* = 6.7 Hz, 6H).

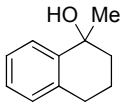
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 138.0, 131.2, 128.3, 126.5, 76.1, 41.8, 34.2, 17.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3560 (w), 3064 (vw), 3024 (vw), 2983 (vw), 2958 (w), 2942 (w), 2930 (w), 2917 (w), 2877 (vw), 2852 (vw), 1602 (w), 1494 (m), 1470 (w), 1454 (w), 1434 (w), 1366 (w), 1350 (w), 1272 (w), 1235 (w), 1195 (w), 1181 (w), 1080 (m), 1049 (w), 1031 (m), 985 (w), 893 (w), 861 (w), 770 (w), 751 (s), 709 (s), 701 (vs).

MS (EI, 70 eV): m/z (%) = 236 ($[M-H_2O]^+$, <1), 163 (53), 145 (11), 119 (11), 91 (100), 71 (11), 43 (12).

HRMS ($C_{18}H_{22}O$): calc.: 236.1551 ($[M-H_2O]^+$); found: 236.1551 ($[M-H_2O]^+$).

1-Methyl-1,2,3,4-tetrahydronaphthalen-1-ol (98c)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): according to **TP10** MeMgCl (**28d**; 0.74 mL, 2.20 mmol, 2.99 M in THF) was added to a solution of α-tetralone (**58e**; 292 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 1 vol-% NEt_3) afforded the alcohol **98c** (307 mg, 95%) as a white solid.

Condition B (30 mol% $LaCl_3 \cdot 2LiCl$): MeMgCl (**28d**; 0.74 mL, 2.20 mmol, 2.99 M in THF,), α-tetralone (**58e**; 292 mg, 2.00 mmol, in 2.5 mL THF), $LaCl_3 \cdot 2LiCl$ (1.15 mL, 0.60 mmol, 0.52 M in THF), 2 h at 25 °C. The alcohol **98c** (306 mg, 94%) was obtained as a white solid.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): MeMgCl (**28d**; 0.74 mL, 2.20 mmol, 2.99 M in THF,), α-tetralone (**58e**; 292 mg, 2.00 mmol, in 3.5 mL THF), 2 h at 25 °C. The alcohol **98c** (224 mg, 69%) was obtained as a white solid.

M. p. (°C): 92-94.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.58-7.52 (m, 1H), 7.11-7.04 (m, 1H), 7.04-6.98 (m, 1H), 6.90-6.84 (m, 1H), 2.60-2.39 (m, 2H), 1.70-1.42 (m, 5H), 1.39 (s, 3H).

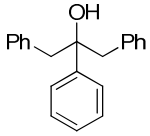
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 143.7, 136.2, 128.8, 127.1, 126.9, 126.5, 70.2, 40.0, 31.1, 30.2, 20.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3313 (m), 2969 (w), 2933 (m), 2865 (w), 1487 (m), 1440 (m), 1366 (m), 1337 (m), 1284 (m), 1230 (w), 1184 (m), 1152 (m), 1103 (s), 1066 (m), 1048 (m), 990 (m), 949 (m), 930 (s), 854 (m), 761 (vs), 728 (s), 686 (s).

MS (EI, 70 eV): *m/z* (%) = 162 (M^+, 1), 147 (100), 129 (56), 119 (17), 91 (32), 84 (34), 44 (6).

HRMS ($C_{11}H_{14}O$): calc.162.1045; found: 162.1040.

1,2,3-Triphenylpropan-2-ol (98d)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): according to **TP10** PhMgCl (**28e**; 1.38 mL, 2.20 mmol, 1.60 M in THF) was added to a solution of 1,3-diphenylacetone (**58d**; 421 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 1 h at

25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2 + 1 vol-% NEt_3) afforded the alcohol **98d** (582 mg, 97%) as a white solid.

Condition B (25 mol% $LaCl_3 \cdot 2LiCl$): PhMgCl (**28e**; 1.38 mL, 2.20 mmol, 1.60 M in THF), 1,3-diphenylacetone (**58d**; 421 mg, 2.00 mmol, in 3.0 mL THF), $LaCl_3 \cdot 2LiCl$ (0.96 mL, 0.50 mmol, 0.52 M in THF), 2.5 h at 25 °C. The alcohol **98d** (538 mg, 93%) was obtained as a white solid.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): PhMgCl (**28e**; 1.38 mL, 2.20 mmol, 1.60 M in THF), 1,3-diphenylacetone (**58d**; 421 mg, 2.00 mmol, in 3.5 mL THF), 2.5 h at 25 °C. The alcohol **98d** was obtained in 67% yield (yield determined by ^{1}H-NMR after purification by flash chromatography).

Condition D (30 mol% $LaCl_3 \cdot 2LiCl$; upscaled reaction): PhMgCl (**28e**; 12.9 mL, 20.7 mmol, 1.60 M in THF), 1,3-diphenylacetone (**58d**; 3.96 g, 18.8 mmol, in 25 mL THF), $LaCl_3 \cdot 2LiCl$ (10.8 mL, 5.64 mmol, 0.52 M in THF), 1 h at 25 °C. The alcohol **98d** (4.75 g, 88%) was obtained as a white solid.

M. p. (°C): 85-86.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.15-7.10 (m, 3H), 7.10-7.04 (m, 2H), 7.04-6.97 (m, 6H), 6.97-6.90 (m, 4H), 3.11 (d, *J* = 13.5 Hz, 2H), 2.99 (d, *J* = 13.5 Hz, 2H), 1.72 (s_{br}, 1H).

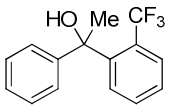
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 146.0, 136.9, 131.1, 128.1, 127.9, 126.7, 126.6, 126.2, 76.9, 49.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3565 (w), 3058 (vw), 3027 (w), 2925 (w), 1598 (w), 1495 (m), 1454 (m), 1444 (w), 1349 (w), 1324 (w), 1273 (w), 1256 (w), 1158 (vw), 1103 (w), 1080 (w), 1064 (w), 1033 (w), 1008 (w), 918 (w), 867 (w), 799 (w), 774 (m), 755 (s), 711 (s), 697 (vs), 647 (s).

MS (EI, 70 eV): m/z (%) = 288 (M^+, <1), 197 (100), 179 (7), 105 (90), 77 (28), 44 (6).

HRMS ($C_{21}H_{20}O$): calc.: 288.1514; found: 288.1503.

1-Phenyl-1-[2-(trifluoromethyl)phenyl]ethanol (98f)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): into a flame dried and argon-flushed flask, 2-(trifluoromethyl)bromobenzene (495 mg, 2.20 mmol) was added followed by *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF). The reaction mixture was stirred for 1.5 h. Then, the resulting aromatic Grignard reagent **28g** was added to acetophenone (**30**; 240 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF) according to **TP10**. The reaction mixture was

stirred for 2 h at 0 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 7:1 + 1 vol-% NEt_3) afforded the alcohol **98f** (384 mg, 72%) as a pale yellow liquid.

Condition B (30 mol% $LaCl_3 \cdot 2LiCl$): 2-(trifluoromethyl)bromobenzene (495 mg, 2.20 mmol), *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), acetophenone (**30**; 240 mg, 2.00 mmol, in 2.5 mL THF), $LaCl_3 \cdot 2LiCl$ (1.15 mL, 0.60 mmol, 0.52 M in THF), 2 h at 0 °C. The alcohol **98f** (381 mg, 72%) was obtained as a pale yellow liquid.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): 2-(trifluoromethyl)bromobenzene (495 mg, 2.20 mmol), *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), acetophenone (**30**; 240 mg, 2.00 mmol, in 3.5 mL THF), 2 h at 0 °C. The alcohol **98f** (67 mg, 13%) was obtained as a pale yellow liquid.

^{1}H-NMR (600 MHz, $C_4D_{10}O$): δ / ppm = 7.80 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 4.31 (s, 1H), 1.93 (s, 3H).

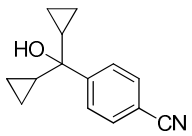
^{13}C-NMR (150 MHz, $C_4D_{10}O$): δ / ppm = 149.9 (q, $^4J_{C\text{-}F}$ = 1.6 Hz), 148.4 (q, $^4J_{C\text{-}F}$ = 1.4 Hz), 131.6 (q, $^5J_{C\text{-}F}$ = 1,1 Hz), 129.9, 129.5 (q, $^2J_{C\text{-}F}$ = 31.6 Hz), 128.8 (q, $^3J_{C\text{-}F}$ = 6.7 Hz), 128.4, 127.7, 127.1, 126.5 (q, $^5J_{C\text{-}F}$ = 0.8 Hz), 125.4 (q, $^1J_{C\text{-}F}$ = 273.4 Hz), 76.7, 33.0 (q, $^4J_{C\text{-}F}$ = 1.7 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3463 (vw), 2983 (vw), 1602 (w), 1494 (w), 1446 (m), 1304 (vs), 1271 (s), 1164 (s), 1122 (vs), 1095 (s), 1032 (vs), 928 (m), 910 (m), 765 (vs), 754 (s), 698 (vs).

MS (EI, 70 eV): *m/z* (%) = 266 (M^+, 2), 251 (100), 231 (61), 211 (29), 183 (6), 169 (5), 121 (5).

HRMS ($C_{15}H_{13}F_3O$): calc.: 266.0918; found: 266.0905.

4-[Dicyclopropyl(hydroxy)methyl]benzonitrile (98g)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): into a flame dried and argon-flushed flask, 4-iodobenzonitrile (504 mg, 2.20 mmol, in 1 mL THF) was added followed by *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol 1.64 M in THF) at 0 °C. The reaction mixture was stirred for 2 h. Then, the resulting aromatic Grignard reagent **28h** was added to dicyclopropylmethanone (**58g**; 220 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF) according to **TP10**. The reaction mixture was stirred for 2.5 h at 25 °C. Purification by flash chromatography (silica gel,

pentane / Et_2O = 3:1 + 1 vol-% NEt_3) afforded the alcohol **98g** (328 mg, 77%) as a pale yellow solid.

Condition B (30 mol% $LaCl_3 \cdot 2LiCl$): 4-iodobenzonitrile (504 mg, 2.20 mmol, in 1 mL THF), *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), dicyclopropylmethanone (**58g**; 220 mg, 2.00 mmol, in 2.5 mL THF), $LaCl_3 \cdot 2LiCl$ (1.15 mL, 0.60 mmol, 0.52 M in THF), 2.5 h at 25 °C. The alcohol **98g** (357 mg, 84%) was obtained as a pale yellow solid.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): 4-iodobenzonitrile (504 mg, 2.20 mmol, in 1 mL THF), *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), dicyclopropylmethanone (**58g**; 220 mg, 2.00 mmol, in 3.5 mL THF), 2.5 h at 25 °C. The alcohol **98g** (371 mg, 87%) was obtained as a pale yellow solid.

M.p. (°C): 78-80.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.29-7.23 (m, 2H), 7.15-7.10 (m, 2H), 1.01 (s_{br}, 1H), 0.75-0.63 (m, 2H), 0.43-0.33 (m, 2H), 0.30-0.17 (m, 4H), 0.10-(-0.01) (m, 2H).

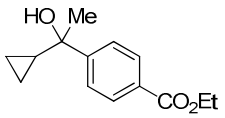
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 153.1, 131.6, 126.4, 119.1, 110.9, 73.0, 20.7, 2.3, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3518 (m), 3089 (vw), 3004 (w), 2226 (m), 1735 (vw), 1605 (m), 1500 (w), 1460 (w), 1400 (m), 1332 (w), 1191 (m), 1161 (m), 1106 (m), 1052 (w), 1028 (s), 1003 (m), 965 (m), 909 (m), 881 (m), 853 (m), 831 (vs), 656 (m).

MS (EI, 70 eV): m/z (%) = 213 (M^+, <1), 185 (100), 170 (37), 154 (7), 143 (20), 130 (80), 127 (8), 102 (19), 69 (13), 41 (6).

HRMS ($C_{14}H_{15}NO$): calc.: 213.1154; found: 213.1145.

Ethyl 4-(1-cyclopropyl-1-hydroxyethyl)benzoate (98h)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): into a flame dried and argon-flushed flask, ethyl 4-iodobenzoate (607 mg, 2.20 mmol, in 1 mL THF) was added followed by *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF) at -20 °C. The reaction mixture was stirred for 30 min at -20 °C. Then, the resulting aromatic Grignard reagent **28i** was added to 1-cyclopropylethanone (**58h**; 220 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF) according to **TP10**. The reaction mixture was stirred for 2.5 h at 25 °C. Purification by flash chromatography

(silica gel, pentane / Et_2O = 3:1 + 1 vol-% NEt_3) afforded the alcohol **98h** (354 mg, 76%) as a yellow oil.

Condition B (30 mol% $LaCl_3 \cdot 2LiCl$): ethyl 4-iodobenzoate (607 mg, 2.20 mmol, in 1 mL THF), *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), 1-cyclopropylethanone (**58h**; 220 mg, 2.00 mmol, in 2.5 mL THF), $LaCl_3 \cdot 2LiCl$ (1.15 mL, 0.60 mmol, 0.52 M in THF), 2.5 h at 25 °C. The alcohol **98h** (389 mg, 83%) was obtained as a yellow oil.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): ethyl 4-iodobenzoate (607 mg, 2.20 mmol, in 1 mL THF), *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), 1-cyclopropylethanone (**58h**; 220 mg, 2.00 mmol, in 3.5 mL THF), 3 h at 25 °C. The alcohol **98h** (378 mg, 81%) was obtained as a yellow oil.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 8.24-8.16 (m, 2H), 7.49-7.42 (m, 2H), 4.15 (d, *J* = 7.0 Hz, 2H), 1.27 (s_{br}, 1H), 1.24 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H), 0.97-0.84 (m, 1H), 0.45-0.22 (m, 3H), 0.20-0.09 (m, 1H).

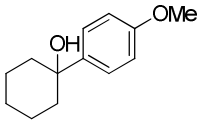
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 166.4, 154.0, 129.7, 129.4, 125.5, 72.3, 60.8, 28.9, 23.1, 14.3, 2.0, 1.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3490 (w), 2980 (w), 1698 (s), 1610 (w), 1574 (vw), 1448 (w), 1406 (m), 1368 (m), 1272 (vs), 1182 (m), 1100 (s), 1046 (m), 1018 (s), 926 (w), 900 (m), 860 (m), 770 (s), 706 (m).

MS (EI, 70 eV): m/z (%) = 234 (M^+, <1), 219 (22), 206 (100), 193 (23), 189 (17), 161 (19), 143 (5), 133 (6), 91 (7), 43 (10).

HRMS ($C_{14}H_{18}O_3$): calc.: 234.1256; found: 234.1238.

1-(4-Methoxyphenyl)cyclohexanol (98i)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): into a flame dried and argon-flushed flask, 4-iodoanisole (515 mg, 2.20 mmol, in 1 mL THF) was added followed by *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF) at 25 °C. The reaction mixture was stirred for 1 h at 25 °C. Then, the resulting aromatic Grignard reagent **28j** was added to cyclohexanone (**58i**; 196 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF) according to **TP10**. The reaction mixture was

stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1 + 1 vol-% NEt_3) afforded the alcohol **98i** (303 mg, 73%) as a colourless liquid.

Condition B (30 mol% $LaCl_3 \cdot 2LiCl$): 4-iodoanisole (515 mg, 2.20 mmol, in 1 mL THF), *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), cyclohexanone (**58i**; 196 mg, 2.00 mmol, in 2.5 mL THF), $LaCl_3 \cdot 2LiCl$ (1.15 mL, 0.60 mmol, 0.52 M in THF), 2 h at 25 °C. The alcohol **98i** (306 mg, 74%) was obtained as a colourless liquid.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): 4-iodoanisole (515 mg, 2.20 mmol, in 1 mL THF), *i*-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), cyclohexanone (**58i**; 196 mg, 2.00 mmol, in 3.5 mL THF), 2 h at 25 °C. The alcohol **98i** (348 mg, 84%) was obtained as a colourless liquid.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.39-7.33 (m, 2H), 6.88-6.81 (m, 2H), 3.36 (s, 3H), 1.88-1.56 (m, 7H), 1.54-1.43 (m, 2H), 1.19 (s, 1H), 1.17-1.04 (m, 1H).

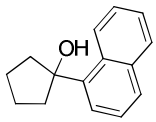
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 158.8, 142.5, 126.1, 113.7, 72.5, 54.8, 39.3, 25.9, 22.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3443 (w), 2930 (m), 2856 (w), 1739 (w), 1608 (m), 1582 (w), 1510 (s), 1447 (m), 1298 (m), 1244 (vs), 1212 (m), 1177 (s), 1132 (w), 1112 (m), 1036 (s), 1021 (m), 966 (m), 904 (w), 849 (m), 824 (vs), 792 (m).

MS (EI, 70 eV): m/z (%) = 206 (M^+, 38), 163 (100), 150 (24), 135 (33), 77 (5), 55 (6).

HRMS ($C_{13}H_{18}O_2$): calc.: 206.1307; found: 206.1300.

1-(1-Naphthyl)cyclopentanol (98k)



Condition A (100 mol% $LaCl_3 \cdot 2LiCl$): according to **TP10** naphthylmagnesium chloride (**28f**; 3.44 mL, 2.20 mmol, 0.64 M in THF) was added to a solution of cyclopentanone (**58j**; 168 mg, 2.00 mmol) in $LaCl_3 \cdot 2LiCl$ (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 1 vol-% NEt_3) afforded the alcohol **98k** (251 mg, 59%) as a yellow solid.

Condition B (30 mol% $LaCl_3 \cdot 2LiCl$): naphthylmagnesium chloride (**28f**; 3.44 mL, 2.20 mmol, 0.64 M in THF), cyclopentanone (**58j**; 168 mg, 2.00 mmol, in 2.5 mL THF), $LaCl_3 \cdot 2LiCl$ (1.15 mL, 0.60 mmol, 0.52 M in THF), 2 h at 25 °C. The alcohol **98k** (277 mg, 65%) was obtained as a yellow solid.

Condition C (no $LaCl_3 \cdot 2LiCl$ present): naphthylmagnesium chloride (**28f**; 3.44 mL, 2.20 mmol, 0.64 M in THF), cyclopentanone (**58j**; 168 mg, 2.00 mmol, in 3.5 mL THF), 2 h at 25 °C. The alcohol **98k** (317 mg, 75%) was obtained as a yellow solid.

M.p. (°C): 74-75.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 8.84 (dd, *J* = 8.6 Hz, 0.8 Hz, 1H), 7.70 (dd, *J* = 8.0 Hz, 1.7 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.41-7.33 (m, 2H), 7.33-7.26 (m, 1H), 7.25-7.18 (m, 1H), 2.16-1.83 (m, 6H), 1.66-1.49 (m, 2H), 1.32 (s_{br}, 1H).

^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 142.6, 135.4, 132.5, 129.1, 128.7, 128.1, 125.5, 125.5, 124.8, 122.8, 83.8, 40.8, 23.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3296 (w), 3043 (vw), 2955 (w), 2871 (w), 1735 (vw), 1598 (w), 1508 (w), 1385 (w), 1317 (w), 1241 (w), 1191 (w), 1109 (w), 1061 (w), 997 (m), 951 (w), 935 (w), 907 (w), 880 (w), 861 (w), 797 (m), 774 (vs), 656 (m), 641 (m).

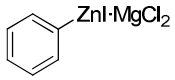
MS (EI, 70 eV): m/z (%) = 212 (M^+, 78), 194 (9), 183 (42), 170 (23), 165 (32), 155 (100), 141 (26), 127 (27).

HRMS ($C_{15}H_{16}O$): calc.: 212.1201; found: 212.1191.

4.2. Addition of functionalized organozinc reagents to aldehydes, ketones and carbon dioxide under mediation of $MgCl_2$

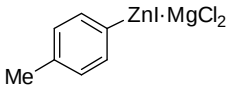
4.2.1. Preparation of the organozinc reagents

Phenylzinc iodid (93b)



According to **TP11** iodobenzene (3.06 g, 15.0 mmol, in 10.0 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) in a THF solution (15 mL) of $ZnCl_2$ (16.5 mmol) and LiCl (22.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **93b** indicated a concentration of 0.68 M.

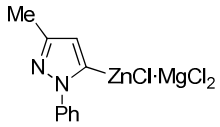
Tolylzinc iodid (93e)



According to **TP11** 4-iodotoluene (2.17 g, 10.0 mmol, in 6.00 mL THF) was reacted with magnesium powder (608 mg, 25.0 mmol) in a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and

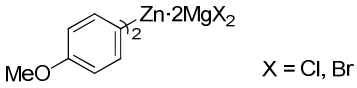
LiCl (15.0 mmol) at 25 °C for 45 min. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **93e** indicated a concentration of 0.52 M.

(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)zinc chlorid (93f)



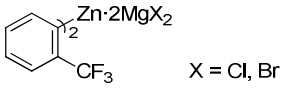
According to **TP11** 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole (963 mg, 5.00 mmol, in 2.5 mL THF) was reacted with magnesium turnings (304 mg, 12.5 mmol) in a THF solution (5 mL) of $ZnCl_2$ (6.5 mmol) and LiCl (7.5 mmol) at 25 °C for 4 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **93f** indicated a concentration of 0.57 M.

Bis(4-methoxyphenyl)zinc (103a)



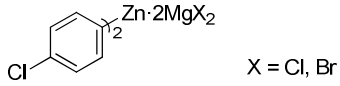
According to **TP11** 4-bromoanisole (2.81 g, 15.0 mmol, in 10.0 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) in a THF solution (7.5 mL) of $ZnCl_2$ (8.25 mmol) and LiCl (11.3 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **103a** indicated a concentration of 0.39 M.

Bis[2-(trifluoromethyl)phenyl]zinc (103b)



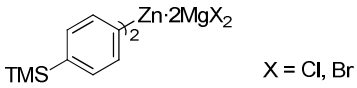
According to **TP11** 1-bromo-2-(trifluoromethyl)benzene (6.75 g, 30.0 mmol, in 15.0 mL THF) was reacted with magnesium turnings (729 mg, 75.0 mmol) in a THF solution (15 mL) of $ZnCl_2$ (16.5 mmol) and LiCl (22.5 mmol) at 25 °C for 3 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **103b** indicated a concentration of 0.42 M.

Bis(4-chlorophenyl)zinc (103c)



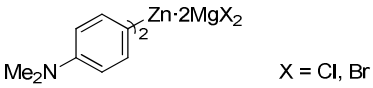
According to **TP11** 1-bromo-4-chlorobenzene (3.83 g, 20.0 mmol, in 4.0 mL THF) was reacted with magnesium turnings (1.22 g, 50.0 mmol) in a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 1.5 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **103c** indicated a concentration of 0.71 M.

Bis(4-trimethylsilylphenyl)zinc (103d)



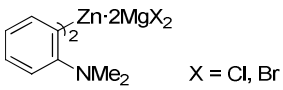
According to **TP11** (4-bromophenyl)trimethylsilane (2.29 g, 10.0 mmol, in 8.0 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (5 mL) of $ZnCl_2$ (6.0 mmol) and LiCl (7.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **103d** indicated a concentration of 0.28 M.

Bis[4-(dimethylamino)phenyl]zinc (103e)



According to **TP11** (4-bromophenyl)dimethylamine (8.00 g, 40.0 mmol, in 16.0 mL THF) was reacted with magnesium turnings (2.43 g, 100 mmol) in a THF solution (20 mL) of $ZnCl_2$ (22.0 mmol) and LiCl (30.0 mmol) at 25 °C for 1 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **103e** indicated a concentration of 0.41 M.

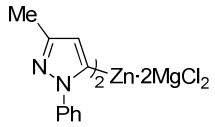
Bis[2-(dimethylamino)phenyl]zinc (103f)



According to **TP11** (2-bromophenyl)dimethylamine (2.00 g, 10.0 mmol, in 6.7 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (5.0 mL) of $ZnCl_2$ (5.5 mmol) and LiCl (7.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another

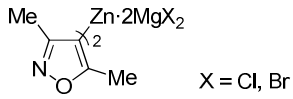
argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **103f** indicated a concentration of 0.29 M.

Bis(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)zinc (103g)



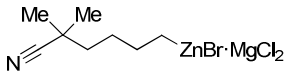
According to **TP11** 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole (2.70 g, 14.0 mmol, in 9.3 mL THF) was reacted with magnesium turnings (851 mg, 34.9 mmol) in a THF solution (7 mL) of $ZnCl_2$ (7.7 mmol) and LiCl (10.5 mmol) at 25 °C for 4 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **103g** indicated a concentration of 0.34 M.

Bis(3,5-dimethylisoxazol-4-yl)zinc (103h)



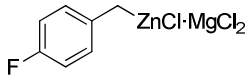
According to **TP11** 4-bromo-3,5-dimethylisoxazole (3.52 g, 20.0 mmol, in 10.0 mL THF) was reacted with magnesium turnings (1.22 mg, 50.0 mmol) in a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 1 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **103h** indicated a concentration of 0.20 M.

(5-Cyano-5-methylhexyl)zinc bromide (107a)



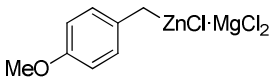
According to **TP11** 6-bromo-2,2-dimethylhexanitrile (2.04 g, 10.0 mmol, in 5.0 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 4 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **107a** indicated a concentration of 0.79 M.

4-Fluorobenzylzinc chloride (95c)



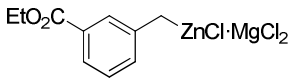
According to **TP11** 4-fluorobenzyl chloride (2.17 g, 15.0 mmol, in 7.5 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) in a THF solution (15 mL) of $ZnCl_2$ (16.5 mmol) and LiCl (22.5 mmol) at 25 °C for 45 min. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **95c** indicated a concentration of 0.39 M.

4-Methoxybenzylzinc chloride (95i)



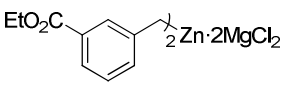
According to **TP11** 4-methoxybenzyl chloride (1.10 g, 7.00 mmol, in 1.0 mL THF) was reacted with magnesium powder (425 mg, 17.5 mmol) in a THF solution (7.0 mL) of $ZnCl_2$ (7.7 mmol) and LiCl (10.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **95i** indicated a concentration of 0.72 M.

3-(Ethoxycarbonyl)benzylzinc chloride (95m)



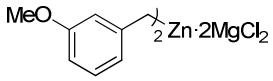
According to **TP11** 3-(ethoxycarbonyl)benzyl chloride (1.39 g, 7.00 mmol, in 3.75 mL THF) was reacted with magnesium turnings (425 mg, 17.5 mmol) in a THF solution (15 mL) of $ZnCl_2$ (7.70 mmol) and LiCl (10.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **95m** indicated a concentration of 0.40 M.

Bis(3-ethoxycarbonyl)benzylzinc (106a)



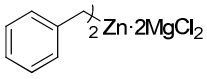
According to **TP11** 3-(ethoxycarbonyl)benzyl chloride (2.71 g, 13.6 mmol, in 12 mL THF) was reacted with magnesium turnings (826 mg, 34.0 mmol) in a THF solution (6.80 mL) of $ZnCl_2$ (7.45 mmol) and LiCl (10.2 mmol) at 25 °C for 1.5 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **106a** (premix of an aliqout with excess $ZnCl_2$ solution (1.00 M in THF)) indicated a concentration of 0.33 M.

Bis(3-methoxybenzyl)zinc (106b)



According to **TP11** 3-methoxybenzyl chlorid (2.35 g, 15.0 mmol, in 8.0 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (7.5 mL) of $ZnCl_2$ (8.25 mmol) and LiCl (11.3 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **106b** (premix of an aliqout with excess $ZnCl_2$ solution (1.00 M in THF)) indicated a concentration of 0.31 M.

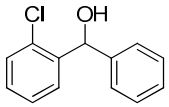
Bis(benzyl)zinc (106c)



According to **TP11** benzyl chlorid (1.27 g, 10.0 mmol, in 2.0 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (5.0 mL) of $ZnCl_2$ (5.5 mmol) and LiCl (7.5 mmol) at 25 °C for 1 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **106c** (premix of an aliqout with excess $ZnCl_2$ solution (1.00 M in THF)) indicated a concentration of 0.42 M.

4.2.2. Preparation of the title compounds

(2-Chlorophenyl)(phenyl)methanol (101)



According to **TP12** phenylzinc iodide·$MgCl_2$ (**93b**; 2.65 mL, 1.80 mmol, 0.68 M in THF) was added to 2-chlorobenzaldehyde (**61a**; 211 mg, 1.50 mmol, in 3.87 mL THF). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 1 vol-% NEt_3) afforded the alcohol **101** (289 mg, 88%) as a pale yellow solid.

M.p. (°C): 71-73.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.59-7.52 (m, 1H), 7.37-7.31 (m, 2H), 7.13-7.06 (m, 3H), 7.05-6.99 (m, 1H), 6.94-6.87 (m, 1H), 6.78-6.71 (m, 1H), 6.04 (s, 1H), 1.66 (s_{br}, 1H).

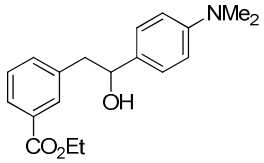
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 143.1, 142.1, 132.7, 129.5, 128.7, 128.5, 128.5, 127.7, 127.2, 127.1, 72.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3174 (w), 1570 (vw), 1465 (w), 1456 (w), 1440 (w), 1315 (w), 1236 (w), 1183 (m), 1122 (w), 1075 (w), 1059 (w), 1024 (m), 953 (w), 916 (vw), 877 (vw), 853 (w), 824 (w), 760 (vs), 725 (m), 696 (s).

MS (EI, 70 eV): m/z (%) = 218 (M^+, 100), 201 (13), 183 (13), 165 (47), 140 (24), 112 (20), 105 (70), 77 (38).

HRMS ($C_{13}H_{11}ClO$): calc.: 218.0498; found: 218.0493.

Ethyl 3-{2-[4-(dimethylamino)phenyl]-2-hydroxyethyl}benzoate (105)



According to **TP12** 3-(ethoxycarbonyl)benzylzinc chloride·$MgCl_2$ (**95m**; 3.90 mL, 1.56 mmol, 0.40 M in THF) was added to 4-(dimethylamino)benzaldehyde (**61h**; 194 mg, 1.30 mmol, in 1.0 mL THF). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1 + 1 vol-% NEt_3) afforded the alcohol **105** (326 mg, 80%) as a yellow oil.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 8.21-8.17 (m, 1H), 8.08-8.02 (m, 1H), 7.19-7.15 (m, 3H), 7.03 (t, *J* = 7.7, 1H), 6.61-6.54 (m, 2H), 4.66 (dd, *J* = 7.9 Hz, 5.5 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.09-2.98 (m, 1H), 2.97-2.88 (m, 1H), 2.51 (s, 6H), 1.70 (s_{br}, 1H) 1.02 (t, *J* = 7.2 Hz, 3H).

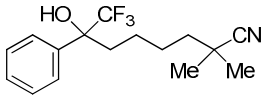
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 166.5, 150.4, 139.8, 134.5, 132.7, 131.2, 131.1, 128.6, 127.7, 127.2, 112.7, 75.1, 60.7, 46.1, 40.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3412 (w), 2980 (w), 2885 (w), 2801 (w), 1713 (s), 1614 (m), 1521 (s), 1444 (m), 1348 (m), 1277 (vs), 1193 (vs), 1163 (s), 1104 (s), 1082 (s), 1022 (s), 946 (m), 817 (s), 751 (s), 691 (m), 672 (w).

MS (EI, 70 eV): m/z (%) = 313 (M^+, <1), 295 (100), 267 (13), 222 (2), 178 (4), 125 (3), 110 (3).

HRMS ($C_{19}H_{23}NO_3$): calc.: 313.1678; found: 313.1669.

8,8,8-Trifluoro-7-hydroxy-2,2-dimethyl-7-phenyloctanenitrile (109)



According to **TP12** (5-cyano-5-methylhexyl)zinc bromide·$MgCl_2$ (**107a**; 1.40 mL, 1.09 mmol, 0.78 M in THF) was added to 2,2,2-trifluoro-1-phenylethanone (**58l**; 146 mg, 0.84 mmol). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the alcohol **109** (192 mg, 76%) as a white solid.

M.p. (°C): 76-78.

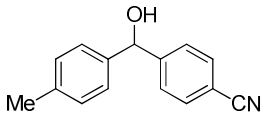
^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.46 (d, *J* = 7.8 Hz, 2H), 7.13-7.07 (m, 2H), 7.05-6.99 (m, 1H), 2.40-2.19 (s_{br}, 1H), 1.96-1.85 (m, 1H), 1.69-1.59 (m, 1H), 1.13-0.92 (m, 3H), 0.78-0.66 (m, 3H), 0.73 (s, 3H), 0.71 (s, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 137.0, 128.5, 128.5, 126.7 (q, $^3J_{C\text{-}F}$ = 1.3 Hz), 126.5 (q, $^1J_{C\text{-}F}$ = 286.1 Hz), 124.7, 77.3 (q, $^2J_{C\text{-}F}$ = 27.8 Hz), 40.6, 35.1, 32.0, 26.4, 26.1, 25.5, 22.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3443 (w), 2978 (vw), 2941 (w), 2858 (vw), 2242 (vw), 1502 (vw), 1470 (w), 1452 (w), 1406 (w), 1372 (w), 1307 (w), 1275 (m), 1243 (m), 1212 (m), 1182 (m), 1151 (vs), 1075 (m), 987 (m), 934 (w), 916 (w), 895 (w), 767 (m), 734 (w), 704 (s), 689 (m).

HRMS (ESI; $C_{16}H_{20}F_3NO$): calc.: 322.1395 ($[M+Na]^+$); found: 322.1390 ($[M+Na]^+$).

4-[Hydroxy(4-methylphenyl)methyl]benzonitrile (110a)



According to **TP12** tolylzinc iodide·$MgCl_2$ (**93e**; 3.46 mL, 1.80 mmol, 0.52 M in THF) was added to 4-formylbenzonitrile (**61i**; 197 mg, 1.50 mmol, in 0.5 mL THF). The reaction mixture was stirred for 13 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the alcohol **110a** (244 mg, 73%) as a pale yellow solid.

M.p. (°C): 44-46.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.03-6.97 (m, 6H), 6.96-6.91 (m, 2H), 5.26 (d, *J* = 2.7 Hz, 1H), 2.07 (s, 3H), 1.80 (d, *J* = 3.3 Hz, 1H).

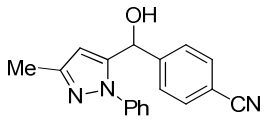
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 149.3, 140.8, 137.7, 132.0, 129.4, 127.0, 126.9, 118.9, 111.3, 75.3, 21.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3448 (m), 2234 (m), 1607 (m), 1503 (w), 1404 (m), 1322 (w), 1265 (w), 1230 (m), 1189 (m), 1173 (m), 1120 (w), 1052 (s), 1018 (m), 871 (m), 812 (vs), 770 (vs), 744 (m).

MS (EI, 70 eV): m/z (%) = 223 (M^+, 26), 208 (30), 189 (13), 130 (40), 121 (17), 118 (33), 104 (29), 93 (100), 76 (35), 65 (25); 51 (14).

HRMS ($C_{15}H_{13}NO$): calc.: 223.0997; found: 223. 0991.

4-[Hydroxy(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)methyl]benzonitrile (110b)



According to **TP12** (3-methyl-1-phenyl-1*H*-pyrazol-5-yl)zinc chloride·$MgCl_2$ (**93f**; 3.16 mL, 1.80 mmol, 0.57 M in THF) was added to 4-formylbenzonitrile (**61i**; 197 mg, 1.50 mmol, in 2.0 mL THF). The reaction mixture was stirred for 10 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1 to Et_2O) afforded the alcohol **110b** (425 mg, 98%) as a white solid.

M.p. (°C): 140-142.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.56-7.50 (m, 2H), 7.36 (s, 5H), 7.34-7.28 (m, 2H), 5.91 (s, 1H), 5.75 (s, 1H), 3.43 (s, 1H), 2.22 (s, 3H).

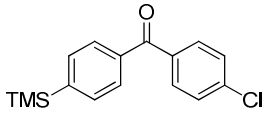
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 149.1, 146.7, 145.1, 139.1, 132.1, 129.2, 128.4, 126.9, 125.5, 118.5, 111.5, 106.6, 67.1, 13.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3265 (w), 2927 (w), 2228 (m), 1598 (w), 1538 (m), 1502 (m), 1440 (m), 1407 (m), 1370 (m), 1323 (w), 1230 (w), 1197 (w), 1055 (s), 1034 (s), 1028 (m), 860 (m), 810 (vs), 797 (s), 770 (s), 748 (m), 698 (s), 685 (m), 660 (w).

MS (EI, 70 eV): m/z (%) = 289 (M^+, 100), 272 (8), 159 (36), 130 (11), 118 (6), 77 (19).

HRMS ($C_{18}H_{15}N_3O$): calc.: 289.1215; found: 289.1204.

(4-Chlorophenyl)[4-(trimethylsilyl)phenyl]methanone (110c)



According to **TP12** 4-(trimethylsilyphenyl)zinc bromide·$2MgCl_2$ (**93g**; 2.40 mL, 1.80 mmol, 0.75 M in THF) was added to 4-chlorobenzoyl chloride (**60d**; 525 mg, 3.00 mmol, in 6.0 mL

THF) and the reaction mixture was stirred for 18 h at 50 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 98:2) afforded the ketone **110c** (423 mg, 81%) as white solid.

M.p. (°C): 67-69.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.70-7.66 (m, 2H), 7.50-7.45 (m, 2H), 7.42-7.38 (m, 2H), 7.03-6.97 (m, 2H), 0.18 (s, 9H).

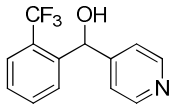
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 194.6, 145.9, 138.6, 138.1, 136.3, 133.5, 131.6, 129.1, 128.7, -1.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 1725 (vw), 1646 (m), 1586 (m), 1543 (w), 1482 (w), 1387 (m), 1300 (m), 1283 (m), 1254 (m), 1173 (w), 1151 (w), 1085 (m), 1012 (w), 967 (w), 958 (w), 929 (m), 836 (vs), 824 (vs), 754 (s), 741 (s), 706 (m), 672 (s).

MS (EI, 70 eV): m/z (%) = 288 (M^+, 29), 275 (100), 139 (10), 73 (7).

HRMS ($C_{16}H_{17}ClOSi$): calc.: 288.0737; found: 288.0736.

Pyridin-4-yl[2-(trifluoromethyl)phenyl]methanol (110d)



According to **TP12** isonicotinaldehyde (**61j**; 161 mg, 1.50 mmol) was added to bis[2-(trifluoromethyl)phenyl]zinc·2MgX_2 (**103b**; X = Cl, Br; 2.20 mL, 0.90 mmol, 0.41 M in THF). The reaction mixture was stirred for 8 h at 25 °C. Purification by flash chromatography (silica gel, Et_2O + 1 vol-% NEt_3) afforded the alcohol **110d** (311 mg, 82%) as a white solid.

M.p. (°C): 159-160.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 8.50 (d, *J* = 1.6 Hz, 1H), 8.49 (d, *J* = 1.6 Hz, 1H), 7.75-7.70 (m, 1H), 7.70-7.64 (m, 1H), 7.63-7.58 (m, 1H), 7.54-7.46 (m, 1H), 7.27-7.22 (m, 2H), 6.48 (d, *J* = 4.7 Hz, 1H), 5.99 (d, *J* = 4.5 Hz, 1H).

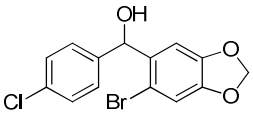
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 152.7, 149.6, 142.2 (q, $^4J_{C\text{-}F}$ = 1.5 Hz), 132.9 (q, $^4J_{C\text{-}F}$ = 1.1 Hz), 129.8, 128.1, 126.0 (q, $^2J_{C\text{-}F}$ = 29.6 Hz), 125.3 (q, $^3J_{C\text{-}F}$ = 5.8 Hz), 124.4 (q, $^1J_{C\text{-}F}$ = 274.0 Hz), 121.3, 68.4 (q, $^4J_{C\text{-}F}$ = 2.3 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3042 (w), 2924 (w), 2850 (w), 1738 (w), 1602 (m), 1583 (w), 1452 (m), 1416 (m), 1310 (s), 1282 (m), 1247 (w), 1152 (s), 1109 (vs), 1063 (s), 1051 (s), 1032 (s), 1006 (s), 791 (s), 766 (s), 752 (s), 669 (m).

MS (EI, 70 eV): m/z (%) = 253 (M^+, 72), 237 (17), 233 (18), 204 (60), 184 (28), 155 (100), 145 (19), 127 (58), 106 (33), 80 (59), 51 (20).

HRMS ($C_{13}H_{10}F_3NO$): calc.: 253.0714; found: 253.0711.

(6-Bromo-1,3-benzodioxol-5-yl)(4-chlorophenyl)methanol (110e)



According to **TP12** bis(4-chlorophenyl)zinc·2MgX$_2$ (**103c**; X = Cl, Br; 6.00 mL, 0.90 mmol, 0.15 M in THF) was added to 6-bromo-1,3-benzodioxole-5-carbaldehyde (**61k**; 344 mg, 1.50 mmol, in 1.0 mL THF). The reaction mixture was stirred for 10 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 6:1 + 1 vol-% NEt_3) afforded the alcohol **110e** (438 mg, 85%) as pale yellow oil.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 7.44-7.38 (m, 2H), 7.35-7.30 (m, 2H), 7.12 (s, 1H), 7.02 (s, 1H), 6.07 (s, 1H), 6.05 (d, *J* = 1.0 Hz, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 2.83 (s_{br}, 1H).

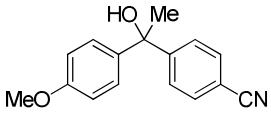
^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 148.8, 148.7, 143.7, 138.0, 133.2, 129.3, 129.0, 112.9, 112.7, 108.8, 103.0, 73.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3316 (w), 2973 (w), 2896 (w), 1596 (vw), 1501 (m), 1471 (vs), 1407 (m), 1388 (m), 1231 (s), 1103 (m), 1090 (m), 1035 (vs), 1013 (s), 966 (m), 931 (s), 845 (s), 780 (m), 728 (w), 672 (w).

MS (EI, 70 eV): m/z (%) = 342 (100), 340 (M^+, 76), 229 (48), 209 (13), 201 (10), 149 (14), 139 (50), 122 (35), 110 (10), 77 (18), 63 (8).

HRMS ($C_{14}H_{10}BrClO_3$): calc.: 339.9502; found: 339.9504.

4-[1-Hydroxy-1-(4-methoxyphenyl)ethyl]benzonitrile (110f)



According to **TP12** bis(4-methoxyphenyl)zinc·2MgX$_2$ (**103a**; X = Cl, Br; 2.31 mL, 0.90 mmol, 0.39 M in THF) was added to 4-acetylbenzonitrile (**58m**; 218 mg, 1.50 mmol, in 0.5 mL THF) and the reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 1 vol-% NEt_3) afforded the alcohol **110f** (236 mg, 62%) as white solid.

M.p. (°C): 77-79.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.13-7.07 (m, 4H), 7.05-7.00 (m, 2H), 6.76-6.70 (m, 2H), 3.30 (s, 3H), 1.70 (s_{br}, 1H), 1.50 (s, 3H).

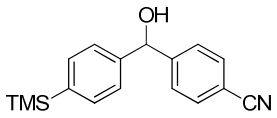
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 159.3, 153.7, 139.5, 131.8, 127.4, 126.6, 118.9, 113.8, 111.0, 75.2, 54.8, 30.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3494 (m), 2967 (w), 2231 (m), 1607 (m), 1504 (s), 1448 (m), 1403 (m), 1367 (m), 1299 (w), 1245 (vs), 1194 (m), 1178 (s), 1134 (m), 1090 (m), 1061 (m), 1028 (vs), 960 (w), 919 (m), 840 (s), 816 (s), 696 (w).

MS (EI, 70 eV): m/z (%) = 253 (M^+, 12), 235 (100), 220 (27), 190 (9), 151 (8), 130 (21), 43 (5).

HRMS ($C_{16}H_{15}NO_2$): calc.: 253.1103; found: 253.1094.

4-{Hydroxy[4-(trimethylsilyl)phenyl]methyl}benzonitrile (110g)



According to **TP2b** bis[4-(trimethylsilyl)phenyl]zinc·2MgX$_2$ (**103d**; X = Cl, Br; 3.21 mL, 0.90 mmol, 0.28 M in THF) was added to 4-formylbenzonitrile (**61i**; 197 mg, 1.50 mmol, in 0.5 mL THF). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 12:1 + 1 vol-% NEt$_3$) afforded the alcohol **110g** (401 mg, 95%) as a pale yellow solid.

M.p. (°C): 73-75.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.45-7.40 (m, 2H), 7.18-7.12 (m, 2H), 7.04-6.96 (m, 4H), 5.27 (s, 1H), 1.82 (s, 1H), 0.20 (s, 9H).

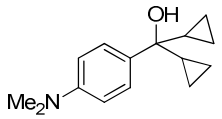
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 149.0, 144.2, 140.2, 133.9, 132.0, 127.0, 126.3, 118.8, 111.5, 75.4, -1.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3243 (w), 2956 (w), 2902 (w), 2231 (w), 1598 (w), 1500 (w), 1404 (w), 1328 (w), 1275 (w), 1250 (m), 1187 (w), 1172 (w), 1108 (w), 1028 (m), 1014 (m), 836 (vs), 808 (vs), 745 (m), 678 (m).

MS (EI, 70 eV): m/z (%) = 281 (M^+, 5), 266 (100), 250 (17), 190 (6), 119 (3), 73 (7).

HRMS ($C_{17}H_{19}NOSi$): calc.: 281.1236; found: 281.1223.

Dicyclopropyl[4-(dimethylamino)phenyl]methanol (110h)



According to **TP12** dicyclopropylmethanone (**58g**; 165 mg, 1.50 mmol) was added to bis[4-(dimethylamino)phenyl]zinc·2MgX$_2$ (**103e**; X = Cl, Br; 2.14 mL, 0.90 mmol, 0.42 M in THF). The reaction mixture was stirred for 24 h at 50 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 8:1 + 1 vol-% NEt$_3$) afforded the alcohol **110h** (257 mg, 74%) as a yellow oil.

^{1}H-NMR (400 MHz, C_6D_6) δ / ppm = 7.61-7.53 (m, 2H), 6.71-6.64 (m, 2H), 2.56 (s, 6H), 1.17-1.08 (m, 2H), 1.05 (s_{br}, 1H), 0.67-0.58 (m, 2H), 0.52-0.44 (m, 2H), 0.41-0.33 (m, 2H), 0.31-0.20 (m, 2H).

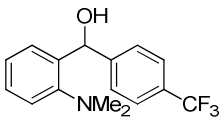
^{13}C-NMR (100 MHz, C_6D_6) δ / ppm = 149.8, 135.7, 127.1, 112.4, 73.1, 40.4, 21.5, 1.9, 0.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3084 (w), 3005 (w), 2882 (w), 2799 (w), 1612 (s), 1563 (w), 1519 (vs), 1480 (m), 1444 (m), 1424 (w), 1346 (m), 1221 (m), 1191 (m), 1157 (s), 1056 (m), 1024 (s), 992 (m), 947 (m), 914 (m), 871 (m), 849 (m), 812 (vs), 751 (w), 732 (w).

MS (EI, 70 eV): m/z (%) = 231 (M$^+$, 32), 213 (100), 198 (24), 190 (27), 185 (19), 172 (38), 141 (14).

HRMS ($C_{15}H_{21}NO$): calc.: 231.1623; found: 231.1616.

[2-(Dimethylamino)phenyl][4-(trifluoromethyl)phenyl]methanol (110i)



According to **TP12** bis[2-(dimethylamino)phenyl]zinc·2MgX$_2$ (**103f**; X = Cl, Br; 3.00 mL, 0.90 mmol, 0.30 M in THF). was added to 4-(trifluoromethyl)benzaldehyde (**61l**; 261 mg, 1.5 mmol) The reaction mixture was stirred for 3 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 8:1 + 1 vol-% NEt$_3$) afforded the alcohol **110i** (413 mg, 93%) as a yellow oil.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.63 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.32-7.26 (m, 1H), 7.24-7.18 (m, 2H), 7.09-7.02 (m, 1H), 6.27 (d, *J* = 4.3 Hz, 1H), 6.01 (d, *J* = 4.9 Hz, 1H), 2.61 (s, 6H).

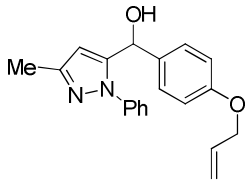
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 151.6, 150.7 (q, $^{4}J_{C-F}$ = 1.5 Hz), 139.7, 128.0, 128.0, 127.0 (q, $^{2}J_{C-F}$ = 31.9 Hz), 126.8, 124.8 (q, $^{3}J_{C-F}$ = 3.8 Hz), 124.4 (q, $^{1}J_{C-F}$ = 271.7 Hz), 124.1, 120.3, 68.3, 45.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3390 (vw), 2945 (w), 2866 (w), 2833 (w), 2790 (w), 1618 (w), 1599 (w), 1489 (m), 1454 (w), 1412 (w), 1322 (vs), 1160 (s), 1110 (s), 1065 (s), 1035 (m), 1016 (s), 936 (m), 859 (m), 805 (m), 768 (m), 744 (m), 664 (m).

MS (EI, 70 eV): m/z (%) = 295 (M^{+}, 94), 280 (100), 276 (20), 262 (65), 242 (69), 173 (16), 145 (12), 106 (9), 91 (10), 77 (11).

HRMS ($C_{16}H_{16}F_3NO$): calc.: 295.1184; found: 295.1178.

[4-(Allyloxy)phenyl](3-methyl-1-phenyl-1*H*-pyrazol-5-yl)methanol (110j)



According to **TP12** 4-(allyoxy)benzaldehyde (**61m**; 243 mg, 1.50 mmol) was added to bis(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)zinc·2MgCl$_2$ (**103g**; 2.65 mL, 0.90 mmol, 0.34 M in THF). The reaction mixture was stirred for 15 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 1:2 + 1 vol-% NEt$_3$) afforded the alcohol **110j** (439 mg, 91%) as a pale yellow oil.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.63-7.58 (m, 2H), 7.14-7.03 (m, 4H), 7.00-6.94 (m, 1H), 6.77-6.71 (m, 2H), 6.05 (s, 1H), 5.86-5.74 (m, 1H), 5.66 (s, 1H), 5.25-5.17 (m, 1H), 5.05-4.99 (m, 1H), 4.14-4.09 (m, 2H), 2.70 (s, 1H), 2.26 (s, 3H).

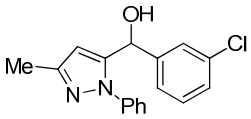
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 158.6, 148.9, 146.9, 140.7, 135.1, 133.7, 129.0, 128.1, 127.4, 125.4, 117.0, 114.7, 107.2, 68.6, 68.0, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3241 (w), 3070 (w), 2923 (w), 2866 (w), 1609 (m), 1598 (m), 1548 (w), 1502 (vs), 1458 (m), 1425 (m), 1366 (m), 1302 (m), 1239 (s), 1222 (s), 1173 (s), 1127 (m), 1020 (vs), 997 (s), 920 (m), 793 (s), 763 (vs), 695 (vs), 673 (s), 659 (s).

MS (EI, 70 eV): m/z (%) = 320 (M^{+}, 100), 303 (35), 279 (96), 261 (34), 233 (13), 185 (24), 169 (9), 159 (17), 77 (17), 41 (17).

HRMS ($C_{20}H_{20}N_2O_2$): calc.: 320.1525; found: 320.1512.

(3-Chlorophenyl)(3-methyl-1-phenyl-1H-pyrazol-5-yl)methanol (110k)



According to **TP12** 3-chlorobenzaldehyde (**61c**; 211 mg, 1.50 mmol) was added to bis(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)zinc·2MgCl$_2$ (**103g**; 2.65 mL, 0.90 mmol, 0.34 M in THF). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1 + 1 vol-% NEt_3) afforded the alcohol **110k** (358 mg, 80%) as a white solid.

M.p. (°C): 100-102.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.53-7.47 (m, 2H), 7.28-7.25 (m, 1H), 7.07-6.94 (m, 4H), 6.87-6.83 (m, 1H), 6.74 (t, *J* = 7.7 Hz, 1H), 5.78 (s, 1H), 5.45 (s, 1H), 2.92 (s, 1H), 2.16 (s, 3H).

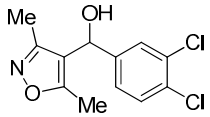
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 149.0, 145.8, 144.9, 140.3, 134.4, 129.6, 129.1, 127.8, 127.7, 126.9, 125.5, 124.8, 107.3, 67.3, 13.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3261 (w), 2926 (vw), 1597 (w), 1575 (w), 1543 (w), 1504 (m), 1481 (w), 1437 (m), 1370 (m), 1338 (w), 1298 (w), 1232 (w), 1194 (m), 1146 (w), 1130 (w), 1098 (w), 1079 (w), 1050 (m), 1032 (s), 1000 (w), 918 (vw), 888 (w), 874 (w), 826 (w), 797 (vs), 772 (vs), 726 (s), 697 (vs), 660 (m).

MS (EI, 70 eV): m/z (%) = 298 (M^+, 100), 221 (5), 204 (7), 185 (12), 159 (48), 139 (9), 116 (4), 77 (11).

HRMS ($C_{17}H_{15}ClN_2O$): calc.: 298.0873; found: 298.0869.

(3,4-Dichlorophenyl)(3,5-dimethylisoxazol-4-yl)methanol (110l)



According to **TP12** bis(3,5-dimethylisoxazol-4-yl)zinc·2MgX$_2$ (**103h**; X = Cl, Br; 3.64 mL, 1.20 mmol, 0.33 M in THF) was added to 3,4-dichlorobenzaldehyde (**61b**; 350 mg, 2.00 mmol, in 1.0 mL THF). The reaction mixture was stirred for 24 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 2:1 + 1 vol-% NEt_3) afforded the alcohol **110l** (451 mg, 83%) as a white solid.

M.p. (°C): 108-110.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.54-7.50 (m, 1H), 7.01 (dd, *J* = 8.1 Hz, 1.4 Hz, 1H), 6.69 (t, *J* = 7.9 Hz, 1H), 5.56 (s, 1H), 2.64 (s, 1H), 1.95 (s, 3H), 1.81 (s, 3H).

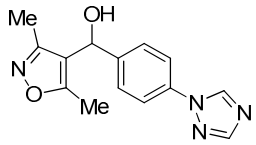
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 166.5, 158.9, 142.1, 133.5, 130.5, 129.5, 127.1, 126.3, 114.5, 64.8, 11.2, 10.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3541 (vw), 3301 (w), 2954 (w), 2923 (m), 2853 (m), 1624 (m), 1446 (m), 1414 (s), 1381 (m), 1323 (w), 1269 (m), 1176 (s), 1153 (m), 1063 (s), 1036 (s), 877 (s), 818 (m), 776 (vs), 748 (s), 680 (s).

MS (EI, 70 eV): m/z (%) = 271 (M^+, 54), 236 (21), 228 (13), 212 (10), 195 (100), 173 (19), 126 (76), 108 (14), 84 (25), 42 (35).

HRMS ($C_{12}H_{11}Cl_2NO_2$): calc.: 271.0167; found: 271.0165.

(3,5-Dimethylisoxazol-4-yl)[4-(1H-1,2,4-triazol-1-yl)phenyl]methanol (110m)



According to **TP12** bis(3,5-dimethylisoxazol-4-yl)zinc·2MgX$_2$ (1**03h**; X = Cl, Br; 3.64 mL, 1.20 mmol, 0.33 M in THF) was added to 4-(1*H*-1,2,4-triazol-1-yl)benzaldehyde (**61n**; 346 mg, 2.00 mmol, in 1.0 mL THF). The reaction mixture was stirred for 14 h at 25 °C. Purification by flash chromatography (silica gel, EtOAc + 1 vol-% NEt$_3$) afforded the alcohol **110m** (413 mg, 76%) as a white solid.

M.p. (°C): 129-130.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 9.01 (s, 1H), 8.08 (s, 1H), 7.89-7.81 (m, 2H), 7.62-7.55 (m, 2H), 5.93 (s, 1H), 2.91 (s$_{br}$, 1H), 2.36 (s, 3H), 2.03 (s, 3H).

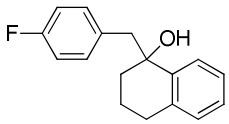
^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 166.4, 159.4, 153.2, 144.0, 142.4, 137.1, 128.0, 120.2, 117.7, 66.2, 11.3, 10.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3560 (vw), 3328 (m), 3124 (w), 3084 (w), 1608 (m), 1522 (vs), 1458 (m), 1438 (m), 1424 (s), 1360 (m), 1320 (w), 1274 (s), 1248 (m), 1226 (m), 1194 (m), 1174 (m), 1154 (s), 1050 (s), 1032 (s), 982 (s), 958 (m), 862 (s), 792 (vs), 674 (vs), 648 (m).

MS (EI, 70 eV): m/z (%) = 270 (M^+, 29), 253 (8), 211 (7), 172 (9), 146 (100), 124 (13), 82 (7), 43 (9).

HRMS ($C_{14}H_{14}N_4O_4$): calc.: 270.1117; found: 270.1115.

1-(4-Fluorobenzyl)-1,2,3,4-tetrahydronaphthalen-1-ol (111a)



According to **TP12** 4-fluorobenzylzinc chloride·$MgCl_2$ (**95c**; 3.12 mL, 2.40 mmol, 0.77 M in THF) was added to α-tetralone (**58e**; 292 mg, 2.00 mmol, in 1 mL THF). The reaction mixture was stirred for 9 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 10:1 + 1 vol-% NEt_3) afforded the alcohol **111a** (378 mg, 74%) as a pale yellow oil.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.52-7.48 (m, 1H), 7.13-7.03 (m, 2H), 7.00-6.93 (m, 2H), 6.93-6.89 (m, 1H), 6.83-6.75 (m, 2H), 2.98 (d, *J* = 13.8 Hz, 1H), 2.70 (d, *J* = 13.8 Hz, 1H), 2.56-2.40 (m, 2H), 1.67-1.59 (m, 1H), 1.52-1.44 (m, 2H), 1.42-1.35 (s, 1H), 1.33-1.24 (m, 1H).

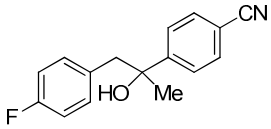
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 162.2 (d, $^1J_{C\text{-}F}$ = 243.7 Hz), 143.1, 136.5, 133.8 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 132.5 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 128.8, 127.2, 127.2, 126.3, 114.8 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 72.4, 47.7, 35.9, 29.9, 20.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3435 (w), 3064 (w), 3020 (w), 2933 (m), 2868 (w), 1603 (m), 1507 (vs), 1488 (m), 1449 (m), 1345 (w), 1219 (vs), 1157 (s), 1095 (m), 1078 (m), 1016 (s), 971 (m), 946 (m), 834 (s), 822 (s), 792 (m), 776 (s), 764 (s), 733 (vs).

MS (EI, 70 eV): m/z (%) = 255 ($[M\text{-}H]^+$, <1), 238 (19), 147 (100), 129 (45), 109 (13), 91 (26).

HRMS ($C_{17}H_{17}FO$): calc.: 255.1185 ($[M\text{-}H]^+$); found: 255.1209 ($[M\text{-}H]^+$).

4-[2-(4-Fluorophenyl)-1-hydroxy-1-methylethyl]benzonitrile (111b)



According to **TP12** 4-fluorobenzylzinc chloride·$MgCl_2$ (**95c**; 4.62 mL, 1.80 mmol, 0.39 M in THF) was added to 4-acetylbenzonitrile (**58m**; 218 mg, 1.50 mmol, in 0.5 mL THF) and the reaction mixture was stirred for 15 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1 + 1 vol-% NEt_3) afforded the alcohol **111b** (305 mg, 80%) as yellowish solid.

M.p. (°C): 93-95.

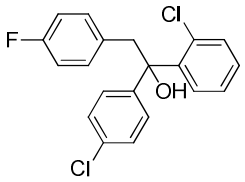
^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.07-7.01 (m, 2H), 6.91-6.85 (m, 2H), 6.73-6.64 (m, 2H), 6.61-6.53 (m, 2H), 2.54 (d, *J* = 13.6 Hz, 1H), 2.49 (d, *J* = 13.6 Hz, 1H), 1.22 (s_{br}, 1H), 1.05 (s, 3H).

^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 162 (d, $^1J_{C\text{-}F}$ = 244.8 Hz), 152.5, 132.2 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 132.2 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 131.7, 125.9, 118.9, 115.0 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 111.0, 73.9 (d, $^5J_{C\text{-}F}$ = 1.4 Hz), 49.3, 28.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3468 (m), 2234 (m), 1739 (w), 1606 (m), 1504 (m), 1404 (m), 1379 (m), 1298 (w), 1220 (s), 1198 (m), 1144 (m), 1098 (m), 1075 (m), 1018 (m), 933 (m), 836 (vs), 821 (s), 770 (m), 734 (m), 709 (m), 679 (m).

HRMS (ESI; $C_{16}H_{14}FNO$): calc.: 273.1403 ([M+NH_4]$^+$); found: 273.1397 ([M+NH_4]$^+$).

1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2-(4-fluorophenyl)ethanol (111c)



According to **TP12** 4-fluorobenzylzinc chloride·$MgCl_2$ (**95c**; 4.62 mL, 1.80 mmol, 0.39 M in THF) was added to (2-chlorophenyl)(4-chlorophenyl)methanone (**58n**; 377 mg, 1.50 mmol, in 0.5 mL THF) and the reaction mixture was stirred for 48 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O / CH_2Cl_2 = 18:1:1) afforded the alcohol **111c** (422 mg, 78%) as yellow solid.

M.p. (°C): 90-92.

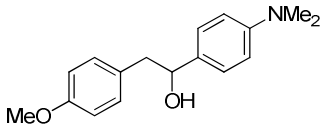
^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.39 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.07-7.00 (m, 3H), 6.88-6.63 (m, 8H), 3.70 (d, *J* = 13.1 Hz, 1H), 3.04 (d, *J* = 13.1 Hz, 1H), 2.31 (s_{br}, 1H).

^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 161.8 (d, $^1J_{C\text{-}F}$ = 244.2 Hz), 144.3, 142.2, 132.9, 132.2 (d, $^3J_{C\text{-}F}$ = 7.8 Hz), 132.0, 132.0 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 130.8, 128.6, 128.5, 128.0, 127.9, 126.1, 114.1 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 77.3 (d, $^1J_{C\text{-}F}$ = 1.4 Hz), 43.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3524 (vw), 3465 (vw), 1606 (w), 1510 (s), 1488 (m), 1433 (m), 1401 (w), 1342 (w), 1269 (w), 1224 (s), 1159 (m), 1129 (w), 1092 (m), 1056 (w), 1035 (m), 1014 (m), 1002 (m), 944 (w), 925 (w), 886 (vw), 822 (vs), 756 (vs), 748 (s), 724 (m), 696 (m).

HRMS (ESI; $C_{20}H_{15}Cl_3FO$): calc.: 405.0466 ([M+HCO_2]$^+$); found: 405.0462 ([M+HCO_2]$^+$).

1-[4-(Dimethylamino)phenyl]-2-(4-methoxyphenyl)ethanol (111d)



According to **TP12** 4-methoxybenzylzinc chloride·$MgCl_2$ (**95i**; 36.1 mL, 13.0 mmol, 0.36 M in THF) was added to 4-(dimethylamino)benzaldehyde (**61h**; 1.49 g, 10.0 mmol, in 5 mL THF) and the reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 2:5) afforded the alcohol **111d** (2.68g, 99%) as yellow solid.

M.p. (°C): 113-115.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.27-7.22 (m, 2H), 7.04-6.99 (m, 2H), 6.76-6.71 (m, 2H), 6.63-6.58 (m, 2H), 4.75-4.70 (m, 1H), 3.30 (s, 3H), 3.06 (dd, *J* = 13.5 Hz, 7.4 Hz, 1H), 2.98 (dd, *J* = 13.5 Hz, 5.7 Hz, 1H), 2.53 (s, 6H), 1.66 (s, 1H).

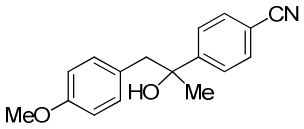
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 158.7, 150.4, 133.0, 131.0, 130.9, 127.3, 114.0, 112.7, 75.6, 54.7, 45.7, 40.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3556 (w), 2961 (w), 2931 (w), 2908 (w), 2856 (w), 2835 (w), 1614 (m), 1522 (s), 1508 (s), 1440 (m), 1386 (w), 1354 (m), 1303 (w), 1243 (s), 1204 (m), 1184 (m), 1175 (m), 1156 (m), 1106 (m), 1045 (m), 1027 (s), 995 (w), 947 (w), 875 (w), 825 (vs), 762 (w), 706 (w), 638 (w).

MS (EI, 70 eV): m/z (%) = 271 (M^+, 2), 253 (58), 238 (27), 165 (6), 150 (100), 122 (7), 120 (6).

HRMS ($C_{17}H_{21}NO$): calc.: 271.1572; found: 271.1570.

4-[1-Hydroxy-2-(4-methoxyphenyl)-1-methylethyl]benzonitrile (111e)



According to **TP12** 4-methoxybenzylzinc chloride·$MgCl_2$ (**95i**; 2.23 mL, 1.61 mmol, 0.72 M in THF) was added to 4-acetylbenzonitrile (**58m**; 195 mg, 1.34 mmol, in 0.5 mL THF). The reaction mixture was stirred for 14 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1 to 1:1 + 1 vol-% NEt_3) afforded the alcohol **111e** (264 mg, 74%) as a pale yellow solid.

M.p. (°C): 120-121.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.10-7.04 (m, 2H), 7.00-6.94 (m, 2H), 6.74-6.63 (m, 4H), 3.29 (s, 3H), 2.69 (d, *J* = 13.4 Hz, 1H), 2.61 (d, *J* = 13.6 Hz, 1H), 1.39 (s, 1H), 1.15 (s, 3H).

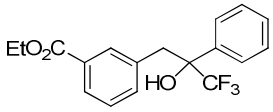
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 159.2, 152.9, 131.7, 131.7, 128.2, 126.1, 119.0, 113.9, 110.9, 74.1, 54.7, 49.4, 29.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3485 (m), 2974 (w), 2936 (w), 2915 (w), 2840 (w), 2229 (m), 1609 (m), 1582 (w), 1512 (s), 1443 (m), 1401 (m), 1370 (w), 1302 (m), 1284 (w), 1249 (vs), 1225 (s), 1174 (m), 1142 (m), 1109 (m), 1074 (m), 1054 (m), 1030 (s), 952 (m), 938 (m), 842 (s), 829 (vs), 763 (m).

MS (EI, 70 eV): m/z (%) = 267 (M^+, 1), 146 (6), 121 (100), 77 (5), 43 (6).

HRMS ($C_{17}H_{17}NO_2$): calc.: 267.1259; found: 267.1250.

Ethyl 3-(3,3,3-trifluoro-2-hydroxy-2-phenylpropyl)benzoate (111f)



According to **TP12** 3-(ethoxycarbonyl)benzylzinc chloride·$MgCl_2$ (**95m**; 3.00 mL, 1.20 mmol, 0.40 M in THF) was added to 2,2,2-trifluoro-1-phenylethanone (**58l**; 174 mg, 1.00 mmol). The reaction mixture was stirred for 16 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 4:1 + 1 vol-% NEt_3) afforded the alcohol **111f** (296 mg, 87%) as a colourless oil.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 7.80-7.78 (m, 1H), 7.76-7.72 (m, 1H), 7.62-7.57 (m, 2H), 7.36-7.26 (m, 4H), 7.22-7.16 (m, 1H), 4.33-4.20 (m, 2H), 3.65 (d, *J* = 14.1 Hz, 1H), 3.49 (d, *J* = 14.3 Hz, 1H), 2.82 (s_{br}, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).

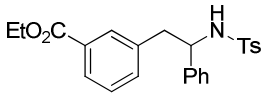
^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 167.2, 138.2, 136.9, 136.7, 133.4, 131.4, 129.6, 129.3, 129.0, 128.9, 128.4 (q, $^3J_{C\text{-}F}$ = 1.6 Hz), 127.8 (q, $^1J_{C\text{-}F}$ = 286.3 Hz), 77.3 (q, $^2J_{C\text{-}F}$ = 28.9 Hz), 61.9, 41.9, 15.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3445 (w), 2984 (vw), 1696 (s), 1608 (w), 1589 (w), 1449 (m), 1370 (m), 1281 (s), 1205 (s), 1150 (vs), 1106 (s), 1084 (m), 1074 (m), 1019 (s), 966 (m), 909 (w), 866 (w), 756 (m), 735 (m), 709 (s), 671 (m).

MS (EI, 70 eV): m/z (%) = 339 ($[M+H]^+$, 5), 293 (19), 175 (16), 164 (100), 136 (33), 118 (15), 105 (19), 91 (14), 77 (6).

HRMS ($C_{18}H_{17}F_3O_3$): calc.: 339.1208 ($[M+H]^+$); found: 339.1196 ($[M+H]^+$).

Ethyl 3-(2-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)benzoate (111g)



According to **TP12** bis(3-(ethoxycarbonyl)benzyl)zinc·2MgCl$_2$ (**106a**; 3.33 mL, 1.1 mmol, 0.33 M in THF) was added to 4-methyl-*N*-[(1E)-phenylmethylene]benzenesulfonamide (**61o**; 519 mg, 2.00 mmol, in 1.0 mL THF). The reaction mixture was stirred for 24 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 3:1 + 1 vol-% NEt$_3$) afforded the amine **111g** (728 mg, 86%) as a white solid.

M.p. (°C): 114-116.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 8.34 (d, *J* = 9.0 Hz, 1H), 7.73-7.68 (m, 1H), 7.67-7.63 (m, 1H), 7.40-7.33 (m, 1H), 7.30-7.21 (m, 5H (incl. N*H*)), 7.21-7.10 (m, 3H), 7.00 (d, *J* = 8.0 Hz, 2H), 4.47-4.38 (m, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.94-2.79 (m, 2H), 2.24 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

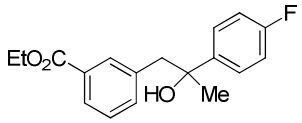
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 165.6, 142.2, 141.6, 138.5, 138.4, 134.1, 130.0, 129.5, 128.9, 128.3, 128.0, 127.0, 126.8, 126.5, 125.9, 60.6, 59.2, 43.0, 20.8, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3269 (m), 2924 (m), 2856 (w), 1696 (vs), 1603 (w), 1589 (w), 1494 (w), 1445 (m), 1426 (m), 1370 (m), 1328 (s), 1284 (vs), 1201 (s), 1158 (vs), 1107 (s), 1092 (s), 1070 (m), 1027 (s), 963 (m), 908 (m), 837 (m), 812 (m), 755 (vs), 699 (m), 692 (m), 664 (s).

MS (EI, 70 eV): m/z (%) = 424 ([M+H]$^+$, <1), 378 (6), 260 (100), 155 (25), 91 (26), 65 (3).

HRMS (C$_{24}$H$_{25}$NO$_4$S): calc.: 424.1583 ([M+H]$^+$); found: 424.1564 ([M+H]$^+$).

Ethyl 3-[2-(4-fluorophenyl)-2-hydroxypropyl]benzoate (111h)



According to **TP12** 1-(4-fluorophenyl)ethanone (**58o**; 276 mg, 2.0 mmol) was added to bis(3-(ethoxycarbonyl)benzyl)zinc·2MgCl$_2$ (**106a**; 6.67 mL, 2.2 mmol, 0.33 M in THF). The reaction mixture was stirred for 24 h at 50 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 4:1 + 1 vol-% NEt$_3$) afforded the alcohol **111h** (444 mg, 68%) as a pale yellow oil.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.07-8.01 (m, 1H), 7.95-7.92 (m, 1H), 7.02-6.95 (m, 3H), 6.95-6.91 (m, 1H), 6.82-6.74 (m, 2H), 4.17-4.08 (m, 2H), 2.76 (d, *J* = 13.3 Hz, 1H), 2.69 (d, *J* = 13.3 Hz, 1H), 1.23 (s, 1H), 1.16 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H).

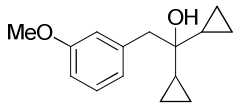
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 166.4, 162.0 (d, $^1J_{C\text{-}F}$ = 244.4 Hz), 143.6 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 137.8, 135.1, 132.2, 130.8, 128.0, 128.0, 127.1 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 114.8 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 73.9, 60.8, 50.5, 29.2, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3480 (w), 2980 (w), 2930 (w), 1699 (s), 1603 (m), 1508 (s), 1444 (m), 1368 (m), 1277 (vs), 1223 (s), 1199 (s), 1160 (m), 1106 (s), 1088 (s), 1015 (m), 952 (w), 932 (w), 863 (m), 836 (s), 815 (m), 755 (s), 720 (s), 700 (m).

MS (EI, 70 eV): m/z (%) = 302 (M^+, <1), 184 (15), 257 (23), 211 (13), 196 (11), 164 (100), 139 (88), 136 (42), 118 (11), 91 (18), 43 (36).

HRMS ($C_{18}H_{19}FO_3$): calc.: 302.1318; found: 302.1306.

1,1-Dicyclopropyl-2-(3-methoxyphenyl)ethanol (111i)



According to **TP12** dicyclopropylmethanone (**58g**; 156 mg, 1.50 mmol) was added to bis(4-methoxybenzyl)zinc·2MgCl$_2$ (**106a**; 2.90 mL, 0.90 mmol, 0.31 M in THF). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 1 vol-% NEt_3) afforded the alcohol **111i** (292 mg, 84%) as a colourless oil.

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.16-7.08 (m, 1H), 7.02-6.98 (m, 1H), 6.94-6.88 (m, 1H), 6.78-6.71 (m, 1H), 3.39 (s, 3H), 2.80 (s, 2H), 0.67-0.55 (m, 3H (incl. O*H*)), 0.44-0.32 (m, 4H), 0.27-0.06 (m, 4H).

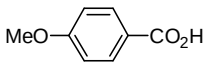
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 159.9, 139.7, 129.0, 123.5, 117.2, 111.8, 70.6, 54.7, 49.4, 19.0, 1.3, -0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3517 (w), 3084 (w), 3006 (w), 2919 (w), 2835 (w), 1601 (m), 1584 (m), 1488 (s), 1453 (m), 1437 (m), 1312 (m), 1260 (vs), 1167 (s), 1153 (s), 1117 (m), 1043 (s), 1022 (s), 994 (s), 913 (m), 875 (m), 865 (m), 826 (m), 778 (s), 749 (m), 738 (m), 703 (s).

MS (EI, 70 eV): m/z (%) = 232 (M^+, <1), 214 (11), 185 (10), 122 (40), 111 (100), 91 (18), 77 (13), 69 (77), 57 (11), 41 (26).

HRMS ($C_{15}H_{20}O_2$): calc.: 232.1463; found: 232.1453.

4-Methoxybenzoic acid (112)



According to **TP13** bis(4-methoxyphenyl)zinc·2MgX$_2$ (**103a**; X = Br, Cl; 2.56 mL, 1.00 mmol, 0.39 M in THF) was reacted with dry $CO_{2(g)}$ at 25 °C for 3 h. After purification, 4-methoxybenzoic acid (**112**; 286 mg, 94%) was obtained as a white solid.

M.p. (°C): 185-186 °C.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 12.59 (s, 1H), 7.91-7.85 (m, 2H), 7.03-6.96 (m, 2H), 3.81 (s, 3H).

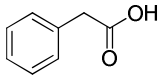
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 166.9, 162.8, 131.3, 122.9, 113.8, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 2940 (w), 2842 (w), 2542 (w), 1924 (w), 1678 (vs), 1602 (s), 1576 (s), 1516 (m), 1426 (m), 1298 (s), 1260 (vs), 1166 (s), 1130 (s), 1106 (s), 1024 (s), 924 (s), 844 (s), 824 (m), 772 (s), 696 (m), 634 (m), 614 (s).

MS (EI, 70 eV): m/z (%) = 152 (M$^+$, 100), 135 (86), 107 (10), 92 (16), 77 (25), 63 (12).

HRMS ($C_8H_8O_3$): calc.: 152.0473; found: 152.0468.

Phenylacetic acid (113)



According to **TP13** bis(benzyl)zinc·2MgCl$_2$ (**106c**; 2.38 mL, 1.00 mmol, 0.42 M in THF) was reacted with dry $CO_{2(g)}$ at 25 °C for 2.5 h. After purification, phenylacetic acid (**113**; 208 mg, 76%) was obtained as a white solid.

M.p. (°C): 80-82.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 12.29 (s_{br}, 1H), 7.33-7.28 (m, 2H), 7.27-7.20 (m, 3H), 3.56 (s, 2H).

^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 172.7, 135.0, 129.3, 128.2, 126.5, 40.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921 (w), 1692 (s), 1498 (w), 1454 (w), 1407 (m), 1336 (m), 1290 (w), 1228 (m), 1186 (m), 1074 (w), 892 (m), 839 (m), 751 (m), 699 (vs), 676 (s).

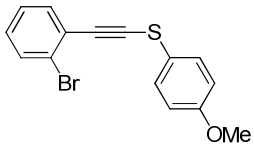
MS (EI, 70 eV): m/z (%) = 136 (M$^+$, 72), 91 (100), 65 (12), 44 (5).

HRMS ($C_8H_8O_2$): calc.: 136.0524; found: 136.0509.

5. Carbocupration of Alkynes With Functionalized Diorganozinc Reagents

5.1. Preparation of the starting materials

1-Bromo-2-{[(4-methoxyphenyl)thio]ethynyl}benzene (118b)



To 1-bromo-2-ethynylbenzene (958 mg, 5.29 mmol) in THF (5 mL) was added MeMgCl (1.77 mL, 5.29 mmol, 2.99 M in THF) at 25 °C and the reaction mixture was stirred for 1 h. Then, *S*-(4-methoxyphenyl) benzenesulfonothioate (**57f**; 1.48 g, 5.29 mmol, in 5 mL THF) was added at -40 °C and the resulting reaction mixture was slowly warmed to 0 °C within 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 95:5) furnished the alkyne **118b** (1.48 g, 86%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.60-7.55 (m, 1H), 7.53-7.44 (m, 3H), 7.28-7.22 (m, 1H), 7.18-7.11 (m, 1H), 6.94-6.88 (m, 2H), 3.80 (s, 3H).

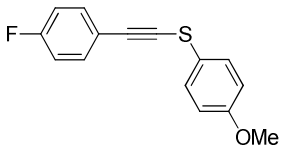
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.1, 133.0, 132.4, 129.2, 129.0, 127.0, 125.3, 125.0, 122.5, 115.1, 95.0, 82.4, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2834 (w), 2169 (w), 1590 (m), 1491 (s), 1290 (m), 1243 (vs), 1174 (s), 1025 (s), 820 (s), 749 (s), 681 (m).

MS (EI, 70 eV): m/z (%) = 318 (M^+, 90), 305 (23), 239 (100), 195 (34), 152 (21), 140 (19), 43 (11).

HRMS ($C_{15}H_{11}BrOS$): calc.: 317.9714; found: 317.9709.

1-Fluoro-4-{[(4-methoxyphenyl)thio]ethynyl}benzene (118d)



To 1-ethynyl-4-fluorobenzene (1.20 g, 10.0 mmol) in THF (10 mL) was added *n*-BuLi (4.20 mL, 10.5 mmol, 2.50 M in THF) at -20 °C and the reaction mixture was stirred for 30 min. Then, freshly prepared $MgCl_2$ (21.0 mL, 10.5 mmol 0.50 M in THF; prepared by the reaction of 1,2-dichloroethane with magnesium turnings in THF) was added and the reaction mixture was stirred

for additional 30 min. Then, *S*-(4-methoxyphenyl) benzenesulfonothioate (**57f**; 3.08 g, 11.0 mmol, in 10 mL THF) was added at -40 °C and the resulting reaction mixture was slowly warmed to 25 °C within 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et_2O = 98:2) furnished the alkyne **118d** (2.08 g, 80%) as a yellow solid.

M.p. (°C): 40-42.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.49-7.39 (m, 4H), 7.05-6.97 (m, 2H), 6.93-6.87 (m, 2H), 3.80 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.6 (d, $^1J_{C\text{-}F}$ = 249.9 Hz), 159.1, 133.7 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 129.0, 122.8, 119.1 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 115.1, 95.0, 76.8, 55.4.

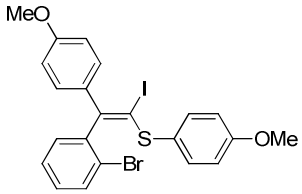
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936 (w), 2836 (w), 1652 (vw), 1596 (m), 1574 (w), 1492 (s), 1456 (m), 1438 (m), 1402 (w), 1294 (m), 1246 (m), 1230 (s), 1214 (s), 1176 (s), 1154 (s), 1106 (m), 1092 (m), 1084 (m), 1024 (s), 1006 (m), 834 (vs), 814 (vs), 796 (s), 634 (w), 622 (w).

MS (EI, 70 eV): m/z (%) = 258 (M^+, 100), 243 (50), 215 (17), 199 (7), 183 (10), 170 (11), 107 (12).

HRMS ($C_{15}H_{11}FOS$): calc.: 258.0515; found: 258.0505.

5.2. Preparation of the title compounds

1-Bromo-2-{(*E*)-2-iodo-1-(4-methoxyphenyl)-2-[(4-methoxyphenyl)thio]vinyl}benzene (120b)



Bis(4-methoxyphenyl)zinc·2MgX_2 (**103a**; X = Br, Cl; 8.11 mL, 3.00 mmol, 0.37 M in THF) was added dropwise to CuCN·2LiCl (3.00 mL, 3.00 mmol, 1.00 M in THF) at -20 °C. The mixture was stirred for 30 min. Then, 1-bromo-2-{[(4-methoxyphenyl)thio]ethynyl}benzene (**118b**; 638 mg, 2.00 mmol, in 1 mL THF) was added and the reaction mixture was stirred for 6 h at 25 °C. The reaction mixture was added dropwise to another flask containing iodine (7.78 g, 7.00 mmol) in THF (7 mL) at -40 °C. After stirring for 10 min, a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 2:1 (100 mL) was added. The phases were separated and the aq.

layer was extracted with Et_2O (3 x 100 mL). The combined extracts were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 3:1 + 1 vol-% NEt_3) afforded the vinylic iodide **120b** (908 mg, 82%, *E*/*Z* = 99:1) as a yellow oil.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 7.63 (dd, *J* = 8.1 Hz, 1.1 Hz, 1H), 7.51 (dd, *J* = 7.6 Hz, 1.8 Hz, 1H), 7.45-7.37 (m, 5H), 7.27-7.21 (m, 1H), 6.99-6.93 (m, 2H), 6.91-6.86 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H).

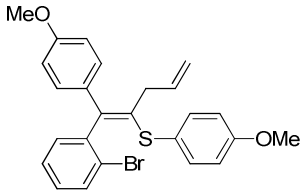
^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 161.1, 160.3, 152.4, 143.2, 136.7, 135.1, 133.7, 131.4, 131.0, 130.1, 128.6, 127.6, 122.9, 115.5, 114.0, 97.7, 55.7, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2932 (w), 2870 (w), 2834 (w), 1590 (m), 1572 (w), 1504 (m), 1492 (s), 1462 (m), 1440 (m), 1288 (m), 1244 (vs), 1172 (s), 1106 (w), 1064 (w), 1028 (s), 952 (w), 910 (w), 826 (s), 770 (m), 742 (s), 708 (w), 656 (w), 640 (w).

MS (EI, 70 eV): m/z (%) = 552 (M^+, 14), 473 (24), 427 (69), 346 (100), 331 (24), 172 (9), 139 (24).

HRMS ($C_{22}H_{18}BrIO_2S$): calc.: 551.9256; found: 551.9249.

1-Bromo-2-{(1*Z*)-1-(4-methoxyphenyl)-2-[(4-methoxyphenyl)thio]penta-1,4-dien-1-yl}-benzene (120c)



Bis(4-methoxyphenyl)zinc·2MgX_2 (**103a**; X = Br, Cl; 4.05 mL, 1.50 mmol, 0.37 M in THF) was added dropwise to CuCN·2LiCl (1.50 mL, 1.50 mmol, 1.00 M in THF) at -20 °C. The mixture was stirred for 30 min. Then, 1-bromo-2-{[(4-methoxyphenyl)thio]ethynyl}benzene (**118b**; 318 mg, 1.00 mmol, in 1 mL THF) was added and the reaction mixture was stirred for 6 h at 25 °C. The reaction mixture was cooled to -50 °C and allyl bromide (436 mg, 3.60 mmol, in 5 mL THF) was added. Then, the mixture was stirred for 30 min at -50 °C followed by 45 min at -30 °C. Then, a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 4:1 (100 mL) was added. The phases were separated and the aq. layer was extracted with Et_2O (3 x 100 mL). The combined extracts were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification by flash

chromatography (silica gel, pentane / Et_2O = 12:1 + 2 vol-% NEt_3) afforded the olefine **120c** (426 mg, 91%, *E*/*Z* = 99:1) as a yellow oil.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 7.63-7.59 (m, 1H), 7.47-7.43 (m, 1H), 7.42-7.36 (m, 3H), 7.34-7.28 (m, 2H), 7.22-7.16 (m, 1H), 6.93-6.84 (m, 4H), 5.89-5.78 (m, 1H), 5.06-4.97 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.01-2.96 (m, 2H).

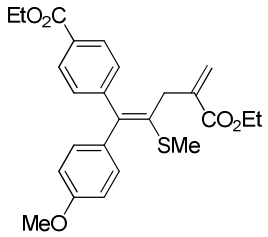
^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 160.7, 159.8, 144.7, 141.6, 136.5, 136.0, 135.7, 133.6, 133.0, 132.1, 131.1, 129.5, 128.4, 124.6, 124.1, 116.6, 115.4, 114.2, 55.6, 55.5, 36.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3002 (w), 2932 (w), 2834 (w), 1592 (m), 1508 (m), 1492 (s), 1462 (m), 1440 (m), 1284 (m), 1242 (vs), 1172 (s), 1104 (m), 1028 (s), 914 (m), 828 (s), 800 (m), 766 (m), 742 (s), 656 (w), 626 (w).

MS (EI, 70 eV): m/z (%) = 466 (M^+, 6), 387 (100), 346 (39), 279 (1), 215 (2), 139 (2).

HRMS ($C_{25}H_{23}BrO_2S$): calc.: 466.0602; found: 466.0600.

Ethyl 4-[(1*Z*)-4-(ethoxycarbonyl)-1-(4-methoxyphenyl)-2-(methylthio)penta-1,4-dien-1-yl]-benzoate (120d)



Into a flame dried and argon-flushed flask, ethyl 4-iodobenzoate (828 mg, 3.00 mmol) was added followed by *i*-PrMgCl·LiCl (1.96 mL, 2.95 mmol, 1.50 M in THF) at -20 °C. The reaction mixture was stirred for 60 min at -20 °C. Then, $ZnCl_2$ (1.50 mL; 1.50 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for 30 min. CuCN·2LiCl (1.50 mL, 1.50 mmol, 1.00 M in THF) was added and the mixture was stirred for additional 30 min at -20 °C. Then, 1-methoxy-4-[(methylthio)ethynyl]benzene (**118c**; 178 mg, 1.00 mmol) was added and the reaction mixture was stirred for 24 h at 25 °C. The reaction mixture was cooled to -40 °C and ethyl (2-bromomethyl)acrylate (695 mg, 3.60 mmol) was added. Then, the mixture was stirred for 30 min at -40 °C followed by 30 min at 0 °C. Then, a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 4:1 (100 mL) was added. The phases were separated and the aq. layer was extracted with Et_2O (3 x 100 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvents

in vacuo and purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 2 vol-% NEt_3) afforded the alkene **120d** (301 mg, 68%, *E*/*Z* = 94:6) as a yellow oil.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 7.95-7.89 (m, 2H), 7.33-7.27 (m, 2H), 7.24-7.18 (m, 2H), 6.92-6.85 (m, 2H), 6.36-6.30 (m, 1H), 5.95-5.91 (m, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.39 (t, *J* = 1.7 Hz, 2H), 2.09 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) .

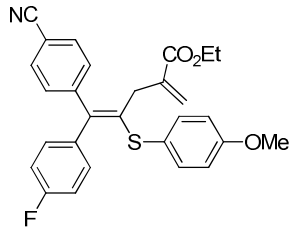
^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 166.8, 166.4, 159.7, 148.2, 140.5, 138.9, 134.8, 134.0, 131.6, 130.0, 129.8, 129.6, 125.8, 114.3, 61.3, 61.3, 55.4, 34.8, 15.0, 14.5, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 1710 (vs), 1604 (m), 1508 (m), 1464 (w), 1444 (w), 1402 (w), 1366 (w), 1268 (vs), 1244 (vs), 1172 (s), 1134 (s), 1098 (s), 1020 (s), 946 (w), 860 (m), 832 (m), 784 (m), 750 (m), 704 (m), 658 (w).

MS (EI, 70 eV): m/z (%) = 440 (M^+, 100), 392 (46), 363 (94), 335 (15), 320 (12), 135 (15).

HRMS ($C_{25}H_{28}O_5S$): calc.: 440.1657; found: 440.1655.

Ethyl (4*Z*)-5-(4-cyanophenyl)-5-(4-fluorophenyl)-4-[(4-methoxyphenyl)thio]-2-methylene-pent-4-enoate (120e)



Into a flame dried and argon-flushed flask, 4-iodobenzonitrile (481 mg, 2.10 mmol, in 1 mL THF) was added followed by *i*-PrMgCl·LiCl (1.42 mL, 2.10 mmol, 1.48 M in THF) at 0 °C. The reaction mixture was stirred for 40 min at 0 °C. Then, $ZnCl_2$ (1.05 mL; 1.05 mmol, 1.00 M in THF) was added at -20 °C and the reaction mixture was stirred for 30 min. CuCN·2LiCl (1.05 mL, 1.05 mmol, 1.00 M in THF) was added at -20 °C and the mixture was stirred for additional 30 min at -20 °C. Then, 1-fluoro-4-{[(4-methoxyphenyl)thio]ethynyl}benzene (**118d**; 181 mg, 0.70 mmol) was added and the reaction mixture was stirred for 16 h at 25 °C. The reaction mixture was cooled to -60 °C and ethyl (2-bromomethyl)acrylate (444 mg, 2.30 mmol) was added. Then, the mixture was stirred for 30 min at -60 °C followed by 90 min at -20 °C. Then, a mixture of sat. aq. NH_4Cl / NH_3 (25% in H_2O) = 4:1 (100 mL) was added. The phases were separated and the aq. layer was extracted with Et_2O (3 x 100 mL). The combined extracts

were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 + 2 vol-% NEt_3) afforded the alkene **120e** (172 mg, 51%, *E*/*Z* = 68:32) as a yellow oil.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 7.75-7.70 (m, 2H), 7.50-7.46 (m, 2H), 7.43-7.37 (m, 2H), 7.33-7.29 (m, 2H), 7.17-7.12 (m, 2H), 6.90-6.86 (m, 2H), 6.26-6.23 (m, 1H), 5.77-5.74 (m, 1H), 4.42(q, *J* = 7.0 Hz, 2H), 3.78 (s, 3H), 3.16 (t, *J* = 1.6 Hz, 2H), 1.15 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 166.4, 162.9 (d, $^1J_{C\text{-}F}$ = 245.2 Hz), 161.0, 147.4, 141.1, 138.5 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 138.3, 136.3, 135.9, 133.0, 132.5 (d, $^3J_{C\text{-}F}$ = 8.2Hz), 130.6, 126.7, 123.7, 119.1, 115.9 (d, $^2J_{C\text{-}F}$ = 21.6Hz), 115.6, 111.7, 61.1, 55.7, 34.9, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2938 (w), 2906 (w), 2838 (w), 2228 (m), 1712 (s), 1630 (w), 1592 (m), 1504 (s), 1492 (vs), 1464 (m), 1442 (w), 1402 (m), 1368 (w), 1286 (m), 1246 (vs), 1222 (s), 1172 (s), 1136 (s), 1102 (m), 1028 (s), 944 (m), 828 (vs), 750 (m), 698 (w), 640 (w).

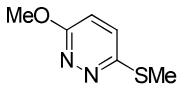
MS (EI, 70 eV): m/z (%) =473 (M^+, 45), 334 (21), 306 (12), 260 (11), 140 (100), 108 (8).

HRMS ($C_{28}H_{24}FNO_3S$): calc.: 473.1461; found: 473.1461.

6. Transition Metal-Catalyzed Cross-Coupling Reactions of Functionalized Organozinc Reagents With Methylthio-Substituted N-Heterocycles

6.1. Preparation of the starting materials

3-Methoxy-6-(methylthio)pyridazine (124a)



3-Chloro-6-methoxypyridazine (**123**; 1.86 g, 12.9 mmol) and sodium thiomethanolate (1.03 g, 14.2 mmol) were dissolved in DMF (6 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (30 mL) followed by extraction using EtOAc (3 x 30 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the pyridazine **124a** (1.38 g, 69%) as a white solid.

M.p. (°C): 93-94.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.21 (d, *J* = 9.3 Hz, 1H), 6.81 (d, *J* = 9.3 Hz, 1H), 4.06 (s, 3H), 2.67 (s, 3H).

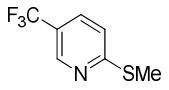
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.3, 156.6, 129.1, 117.7, 54.7, 13.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059 (w), 2982 (w), 2949 (w), 2922 (w), 1596 (w), 1545 (vw), 1456 (m), 1400 (s), 1300 (s), 1196 (m), 1175 (m), 1146 (m), 1006 (vs), 964 (m), 838 (s), 812 (m), 723 (m), 672 (s), 622 (m).

MS (EI, 70 eV): m/z (%) = 156 (M^+, 100), 111 (6), 98 (9), 84 (20), 80 (8), 45 (6).

HRMS ($C_6H_8N_2OS$): calc.: 156.0357; found: 156.0345.

2-(Methylthio)-5-(trifluoromethyl)pyridine (124d)



5-(Trifluoromethyl)pyridine-2-thiol (2.69 g, 15.0 mmol) was dissolved in THF (13.5 mL) and CH_3CN (1.5 mL) at 0 °C. DBU (2.51 g, 16.5 mmol) was added dropwise and the resulting reaction mixture was stirred for 20 min. Then, MeI (2.34 g, 16.5 mmol) was added, the ice-bath was removed and the reaction mixture was stirred for 12.5 h. Addition of H_2O (50 mL) was followed by extraction using EtOAc (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the pyridine **124d** (1.59 g, 55%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.71-8.63 (m, 1H), 7.70-7.60 (m, 1H), 7.30-7.21 (m, 1H), 2.58 (s, 3H).

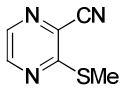
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.9 (q, $^4J_{C-F}$ = 1.5 Hz), 146.2 (q, $^3J_{C-F}$ = 4.4 Hz), 132.3 (q, $^3J_{C-F}$ = 3.4 Hz), 123.8 (q, $^1J_{C-F}$ = 271.6 Hz), 122.0 (q, $^2J_{C-F}$ = 33.0 Hz), 121.0, 13.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932 (vw), 1596 (m), 1556 (w), 1475 (w), 1377 (w), 1321 (vs), 1251 (w), 1166 (m), 1113 (vs), 1073 (s), 1008 (m), 967 (w), 938 (w), 827 (m), 791 (w), 746 (w).

MS (EI, 70 eV): m/z (%) = 193 (M^+, 100), 147 (44), 127 (19), 78 (8).

HRMS ($C_7H_6F_3NS$): calc.: 193.0173; found: 193.0176.

3-(Methylthio)pyrazine-2-carbonitrile (124f)



3-Chloropyrazine-2-carbonitrile (2.61 g, 18.7 mmol) and sodium thiomethanolate (2.10 g, 30.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (20 mL) followed by extraction using EtOAc (3 x 20 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 7:2) afforded the pyrazine **124f** (793 mg, 28%) as a yellow solid.

M.p. (°C): 83-84.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.53 (d, *J* = 2.4 Hz, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 2.62 (s, 3H).

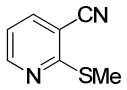
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.8, 145.9, 139.1, 128.1, 114.3, 12.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2230 (w), 1512 (m), 1424 (w), 1354 (s), 1339 (m), 1317 (m), 1196 (m), 1161 (s), 1153 (s), 1142 (m), 1085 (vs), 1074 (s), 1060 (s), 964 (m), 854 (s), 835 (m), 719 (m), 663 (m).

MS (EI, 70 eV): m/z (%) = 151 (M^+, 100), 137 (10), 122 (40), 112 (13), 93 (15), 84 (11), 77 (24), 52 (35).

HRMS ($C_6H_5N_3S$): calc.: 151 .0204; found: 151.0190.

2-(Methylthio)nicotinonitrile (124i)



2-Chloronicotinonitrile (2.77 g, 20.0 mmol) and sodium thiomethanolate (2.31 g, 33.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aq. K_2CO_3 solution (50 mL) followed by extraction using EtOAc (3 x 100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the pyridine **124i** (665 mg, 22%) as a yellow solid.

M.p. (°C): 90-91.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.57 (dd, *J* = 5.0 Hz, *J* = 1.8 Hz, 1H), 7.77 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.05 (dd, *J* = 7.7 Hz, *J* = 5.0 Hz, 1H), 2.60 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.4, 152.0, 140.3, 118.2, 115.5, 107.2, 13.1.

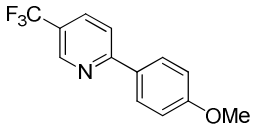
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3046 (w), 2929 (w), 2224 (m), 1574 (m), 1546 (m), 1391 (vs), 1316 (m), 1232 (m), 1184 (m), 1143 (m), 1078 (m), 959 (w), 801 (vs), 736 (m), 721 (m), 667 (m).

MS (EI, 70 eV): m/z (%) = 150 (M^+, 100), 123 (27), 104 (40), 79 (30), 75 (11), 45 (10), 43 (16).

HRMS ($C_7H_6N_3S$): calc.: 150.0252; found: 150.0245.

6.2. Prepartion of the title compounds via Pd-catalyzed cross-couplings

2-(4-Methoxyphenyl)-5-(trifluoromethyl)pyridine (126a)



According to **TP14** 2-(methylthio)-5-(trifluoromethyl)pyridine (**124d**; 193 mg, 1.00 mmol, in 1 mL THF) was reacted with (4-methoxyphenyl)zinc iodide (**5c**; 1.61 mL, 1.50 mmol, 0.93 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 1 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 12:1) afforded the pyridine **126a** (241 mg, 95%) as a white solid.

M.p. (°C): 121-123.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.91-8.86 (m, 1H), 8.05-7.96 (m, 2H), 7.96-7.88 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.05-6.96 (m, 2H), 3.87 (s, 3H).

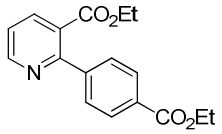
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.4, 160.2, 146.4 (q, $^3J_{C-F}$ = 4.1 Hz), 133.8 (q, $^3J_{C-F}$ = 3.4 Hz), 130.4, 128.7, 124.0 (q, $^2J_{C-F}$ = 32.9 Hz), 123.8 (q, $^1J_{C-F}$ = 271.9 Hz), 119.1, 114.3, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031 (vw), 2970 (vw), 1599 (m), 1580 (m), 1563 (w), 1520 (w), 1483 (w), 1318 (m), 1301 (m), 1282 (m), 1253 (m), 1176 (m), 1166 (m), 1133 (s), 1114 (vs), 1084 (s), 1043 (s), 1024 (s), 1012 (s), 940 (m), 838 (s), 824 (vs), 774 (s), 712 (m).

MS (EI, 70 eV): m/z (%) = 253 (M^+, 100), 238 (25), 211 (73), 177 (61), 169 (28), 141 (24), 135 (21), 95 (23), 69 (31), 55 (35), 41 (26).

HRMS ($C_{13}H_{10}F_3NO$): calc.: 253.0714; found: 253.0706.

Ethyl 2-[4-(ethoxycarbonyl)phenyl]nicotinate (126b)



According to **TP14** ethyl 2-(methylthio)nicotinate (**124e**; 197 mg, 1.00 mmol, in 1 mL THF) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide (**5a**; 2.14 mL, 1.50 mmol, 0.70 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 6 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O / CH_2Cl_2 = 3:2:3) afforded the pyridine **126b** (201 mg, 67%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.80 (dd, *J* = 5.0 Hz, 1.6 Hz, 1H), 8.19 (dd, *J* = 7.9 Hz, 1.9 Hz, 1H), 8.14-8.08 (m, 2H), 7.63-7.57 (m, 2H), 7.42 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 4.15 (q, *J* = 6.9 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.3 Hz, 3H).

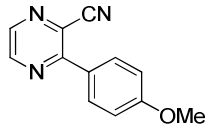
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.2, 166.3, 157.6, 150.8, 143.7, 138.6, 130.7, 129.4, 128.7, 127.7, 122.4, 61.8, 61.1, 14.3, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 1710 (vs), 1612 (w), 1582 (w), 1560 (w), 1432 (m), 1404 (w), 1367 (m), 1268 (vs), 1209 (m), 1175 (m), 1128 (s), 1096 (s), 1054 (s), 1015 (s), 863 (m), 792 (m), 761 (s), 704 (m).

MS (EI, 70 eV): m/z (%) = 299 (M^+, 12), 270 (100), 254 (33), 242 (26), 198 (12), 181 (11), 153 (8), 127 (6).

HRMS ($C_{17}H_{17}NO_4$): calc.: 299.1158; found: 299.1153.

3-(4-Methoxyphenyl)pyrazine-2-carbonitrile (126c)



According to **TP14** 3-(methylthio)pyrazine-2-carbonitrile (**124f**; 151 mg, 1.00 mmol, in 1 mL THF) was reacted with (4-methoxyphenyl)zinc iodide (**5c**; 1.61 mL, 1.50 mmol, 0.93 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 5 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:2 + 5 vol-% NEt_3) afforded the pyrazine **126c** (121 mg, 57%) as a yellow solid.

M.p. (°C): 126-127.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.78 (d, *J* = 2.4 Hz, 1H), 8.57 (d, *J* = 2.4 Hz, 1H), 8.04-7.94 (m, 2H), 7.10-7.02 (m, 2H), 3.89 (s, 3H).

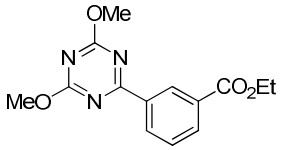
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.1, 156.5, 146.3, 142.2, 130.6, 127.1, 126.6, 116.7, 114.5, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925 (w), 2846 (w), 2232 (w), 1606 (s), 1576 (m), 1525 (w), 1515 (m), 1444 (w), 1435 (m), 1418 (m), 1398 (m), 1386 (m), 1313 (m), 1289 (w), 1254 (vs), 1183 (s), 1170 (s), 1118 (w), 1065 (w), 1033 (m), 1016 (s), 1005 (m), 966 (w), 874 (m), 842 (vs), 822 (m), 798 (m), 792 (m), 667 (w).

MS (EI, 70 eV): m/z (%) = 211 (M^+, 100), 196 (16), 168 (10), 158 (11), 133 (14), 114 (6), 90 (6).

HRMS ($C_{12}H_9N_3O$): calc.: 211.0746; found: 211.0736.

Ethyl 3-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzoate (126d)



According to **TP14** 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**124g**; 187 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (**5d**; 2.21 mL, 1.50 mmol, 0.68 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 21 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by

extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O / EtOAc = 8:1:1) afforded the triazine **126d** (242 mg, 84%) as a yellow solid.

M.p. (°C): 103-105.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.12-9.07 (m, 1H), 8.69-8.60 (m, 1H), 8.25-8-18 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 4.12 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 3H).

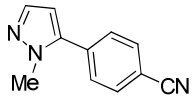
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 174.1, 172.9, 166.0, 135.5, 133.6, 133.1, 131.1, 130.0, 128.6, 61.2, 55.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3310 (vw), 3232 (vw), 1720 (s), 1592 (m), 1566 (s), 1549 (s), 1536 (s), 1504 (s), 1488 (m), 1458 (m), 1368 (s), 1356 (vs), 1298 (s), 1267 (vs), 1191 (m), 1177 (m), 1164 (m), 1118 (m), 1108 (m), 1074 (m), 1039 (s), 1022 (m), 922 (w), 873 (w), 830 (w), 818 (m), 768 (m), 714 (s), 672 (w).

MS (EI, 70 eV): m/z (%) = 289 (M^+, 100), 259 (27), 244 (91), 217 (90), 186 (11), 176 (11), 159 (18), 72 (10).

HRMS ($C_{14}H_{15}N_3O_4$): calc.: 289.1063; found: 289.1064.

4-(1-Methyl-1H-pyrazol-5-yl)benzonitrile (126e)



According to **TP14** 1-methyl-5-(methylthio)-1H-pyrazole (**124h**; 128 mg, 1.00 mmol, in 1 mL THF) was reacted with (4-cyanophenyl)zinc iodide (**5e**; 2.31 mL, 1.50 mmol, 0.65 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 1.5 h at 50 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:4) afforded the pyrazole **126e** (96 mg, 52%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.79-7.69 (m, 2H), 7.58-7.49 (m, 3H), 6.37 (d, *J* = 2.1 Hz, 1H), 3.91 (s, 3H).

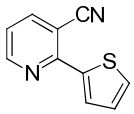
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.7, 138.7, 135.0, 132.5, 129.1, 118.3, 112.2, 107.0, 37.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921 (w), 2224 (m), 1608 (m), 1489 (m), 1468 (w), 1425 (w), 1381 (m), 1279 (m), 1224 (w), 1182 (w), 1113 (w), 1067 (w), 1035 (w), 980 (m), 928 (m), 853 (s), 838 (s), 793 (m), 777 (vs), 708 (m), 664 (w), 649 (m).

MS (EI, 70 eV): m/z (%) = 183 (M^+, 100), 155 (14), 140 (7), 128 (10), 102 (5).

HRMS ($C_{11}H_9N_3$): calc.: 183.0796; found: 183.0792.

2-(2-Thienyl)nicotinonitrile (126f)



According to **TP14** 2-(methylthio)nicotinonitrile (**124i**; 150 mg, 1.00 mmol, in 1 mL THF) was reacted with 2-thienylzinc iodide (**5f**; 1.95 mL, 1.50 mmol, 0.77 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the pyridine **126f** (173 mg, 93%) as a yellow solid.

M.p. (°C): 74-75.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.72 (dd, *J* = 4.8 Hz, *J* = 1.8 Hz, 1H), 8.26 (dd, *J* = 4.0 Hz, *J* = 1.1 Hz, 1H), 8.00 (dd, *J* = 7.9 Hz, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 5.1 Hz, *J* = 0.9 Hz, 1H), 7.23 (dd, *J* = 7.9 Hz, *J* = 4.8 Hz, 1H), 7.17 (dd, *J* = 5.2 Hz, *J* = 3.9 Hz, 1H).

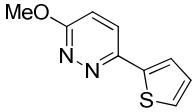
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.5, 152.5, 142.1, 141.6, 130.7, 128.9, 128.7, 120.8, 117.8, 103.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066 (vw), 2921 (w), 2850 (vw), 2225 (w), 1574 (w), 1552 (w), 1528 (w), 1472 (vw), 1439 (s), 1414 (m), 1394 (w), 1358 (w), 1229 (w), 1109 (w), 1067 (w), 976 (w), 860 (w), 844 (w), 806 (w), 798 (w), 762 (s), 716 (vs), 676 (m), 619 (w).

MS (EI, 70 eV): m/z (%) = 186 (M^+, 100), 175 (7), 159 (12), 142 (15), 69 (9), 57 (18), 55 (12), 44 (13).

HRMS ($C_{10}H_6N_2S$): calc.: 186.0252; found: 186.0239.

3-Methoxy-6-(2-thienyl)pyridazine (126g)



According to **TP14** 3-methoxy-6-(methylthio)pyridazine (**124a**; 156 mg, 1.00 mmol, in 1 mL THF) was reacted with 2-thienylzinc iodide (**5f**; 1.94 mL, 1.50 mmol, 0.77 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 5 h at 50 °C, the reaction mixture

was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, EtOAc pure) afforded the pyridazine **126g** (175 mg, 91%) as a white solid.

M.p. (°C): 79-80.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.68 (d, *J* = 9.2 Hz, 1H), 7.49 (dd, *J* = 3.6 Hz, 1.21 Hz, 1H), 7.40-7.37 (m, 1H), 7.89 (dd, *J* = 5.1 Hz, 3.6 Hz, 1H), 6.96 (d, *J* = 9.2 Hz, 1H), 4.13 (s, 3H).

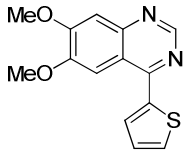
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.9, 151.2, 140.7, 128.1, 127.7, 125.8, 125.0, 117.7, 54.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3104 (w), 3068 (w), 3001 (w), 2958 (w), 1600 (w), 1550 (w), 1528 (w), 1462 (s), 1437 (m), 1409 (m), 1334 (m), 1301 (m), 1279 (m), 1228 (m), 1110 (m), 1025 (s), 852 (m), 830 (s), 812 (m), 707 (vs), 685 (m).

MS (EI, 70 eV): m/z (%) = 192 (M^+, 100), 163 (23), 121 (60), 108 (19), 77 (8), 69 (7), 45 (8).

HRMS ($C_9H_8N_2OS$): calc.: 192.0357; found: 192.0352.

6,7-Dimethoxy-4-(2-thienyl)quinazoline (126h)



According to **TP14** 6,7-dimethoxy-4-(methylthio)quinazoline (**124j**; 236 mg, 1.00 mmol, in 1 mL THF) was reacted with 2-thienylzinc iodide (**5f**; 1.95 mL, 1.50 mmol, 0.77 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 10 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:4 + 2-Vol% NEt_3) afforded the quinazoline **126h** (259 mg, 95%) as a yellow solid.

M.p. (°C): 149-150.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.10 (s, 1H), 7.83 (dd, *J* = 3.7 Hz, 1.2 Hz, 1H), 7.74 (s, 1H), 7.64 (dd, *J* = 5.1 Hz, 1.1 Hz, 1H), 7.38 (s, 1H), 7.27 (dd, *J* = 3.7 Hz, 1.5 Hz, 1H), 4.08 (s, 3H), 4.03 (s, 3H).

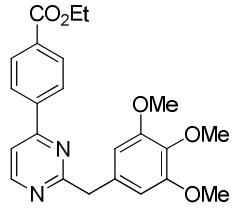
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.4, 155.8, 153.1, 150.9, 149.2, 141.3, 130.0, 130.0, 128.1, 117.5, 107.0, 103.4, 56.4, 56.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3102 (w), 2961 (w), 2920 (w), 2829 (vw), 1615 (w), 1572 (w), 1535 (w), 1499 (s), 1466 (s), 1450 (m), 1427 (s), 1367 (m), 1352 (m), 1296 (m), 1271 (w), 1236 (s), 1217 (s), 1194 (m), 1131 (m), 1101 (m), 1084 (w), 1021 (m), 996 (s), 960 (m), 942 (m), 867 (m), 838 (s), 778 (m), 739 (vs), 702 (m), 662 (m), 642 (m), 618 (m).

MS (EI, 70 eV): m/z (%) = 272 (M^+, 100), 257 (24), 242 (18), 202 (6), 159 (6), 86 (25).

HRMS ($C_{14}H_{12}N_2O_2S$): calc.: 272.0619; found: 272.0615.

Ethyl 4-[2-(4-methoxybenzyl)pyrimidin-4-yl]benzoate (126i)



According to **TP14** ethyl 4-[2-(methylthio)pyrimidin-4-yl]benzoate (**124k**; 261 mg, 0.95 mmol, in 1 mL THF) was reacted with 3,4,5-trimethoxybenzylzinc chloride (**54h**; 1.67 mL, 1.50 mmol, 0.90 M in THF), $Pd(OAc)_2$ (5.3 mg, 2.5 mol%) and S-Phos (19.5 mg, 5.0 mol%). After 1.5 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, EtOAc) afforded the pyrimidine **126i** (343 mg, 88%) as a yellow solid.

M.p. (°C): 121-122.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.75 (d, *J* = 5.5 Hz, 1H), 8.16 (s, 4H), 7.59 (d, *J* = 5.2 Hz, 1H), 6.69 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.29 (s, 2H), 3.84 (s, 6H), 3.80 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

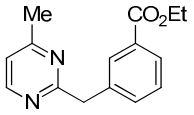
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 169.8, 166.0, 163.3, 157.8, 153.1, 140.6, 136.7, 133.7, 132.6, 130.1, 127.1, 114.7, 106.3, 61.3, 60.8, 56.1, 46.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2939 (w), 2838 (vw), 2826 (vw), 1712 (m), 1591 (m), 1570 (m), 1542 (w), 1506 (m), 1462 (m), 1444 (m), 1422 (m), 1408 (m), 1381 (w), 1369 (w), 1336 (m), 1280 (s), 1246 (m), 1124 (vs), 1009 (m), 845 (m), 829 (m), 784 (w), 754 (m), 700 (m), 658 (w), 650 (w), 636 (w), 619 (m).

MS (EI, 70 eV): m/z (%) = 408 (M^+, 100), 393 (58), 363 (5), 307 (4), 279 (3), 175 (4), 181 (3).

HRMS ($C_{23}H_{24}N_2O_5$): calc.: 408.1685; found: 408.1677.

Ethyl 3-[(4-methylpyrimidin-2-yl)methyl]benzoate (126j)



According to **TP14** 4-methyl-2-(methylthio)pyrimidine (**124c**; 140 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)benzylzinc chloride (**54m**; 1.19 mL, 1.50 mmol, 1.26 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 24 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica, pentane / Et_2O = 1:3) afforded the pyrimidine **126j** (188 mg, 73%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.49 (d, *J* = 5.2 Hz, 1H), 8.03 (s, 1H), 7.94-7.81 (m 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 5.2 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 4.28 (s, 2H), 2.48 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

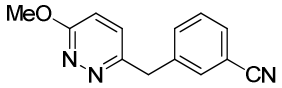
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.8, 167.4, 166.5, 156.8, 138.5, 133.6, 130.6, 130.2, 128.4, 127.7, 118.3, 60.8, 45.5, 24.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981 (w), 1714 (vs), 1578 (s), 1555 (m), 1439 (s), 1387 (m), 1368 (m), 1279 (vs), 1190 (vs), 1105 (s), 1081 (m), 1023 (m), 929 (w), 839 (w), 754 (s), 740 (s), 697 (s), 672 (m), 651 (m).

MS (EI, 70 eV): m/z (%) = 256 (M^+, 97), 255 (100), 227 (54), 182 (62), 168 (21), 116 (13), 89 (19), 43 (39).

HRMS ($C_{15}H_{16}N_2O_2$): calc.: 256.1212; found: 256.1189.

3-[(6-Methoxypyridazin-3-yl)methyl]benzonitrile (126k)



According to **TP14** 3-methoxy-6-(methylthio)pyridazine (**124a**; 156 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-cyanobenzylzinc chloride (**54o**; 1.05 mL, 1.50 mmol, 1.43 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 14 h at 50 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, EtOAc) afforded the pyridazine **126k** (160 mg, 71%) as a yellow solid.

M.p. (°C): 76-78.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.57-7.49 (m, 3H), 7.43-7.39 (m, 1H), 7.18 (d, *J* = 9.2 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 4.26 (s, 2H), 4.10 (s, 3H).

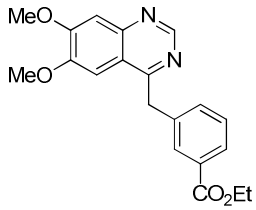
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.2, 156.5, 139.9, 133.5, 132.4, 130.5, 129.5, 129.5, 118.6, 118.2, 112.7, 54.8, 41.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065 (vw), 2961 (w), 2923 (w), 2854 (w), 2227 (w), 1595 (w), 1458 (s), 1438 (m), 1412 (m), 1306 (s), 1260 (m), 1234 (w), 1091 (m), 1010 (vs), 900 (m), 858 (m), 784 (s), 718 (m), 688 (s).

MS (EI, 70 eV): m/z (%) = 225 (M^+, 30), 224 (100), 153 (4), 127 (5), 89 (3).

HRMS ($C_{13}H_{11}N_3O$): calc.: 225.0902; found: 225.0900.

Ethyl 3-[(6,7-dimethoxyquinazolin-4-yl)methyl]benzoate (126l)



According to **TP14** 6,7-dimethoxy-4-(methylthio)quinazoline (**124j**; 236 mg, 1.00 mmol, in 1 mL THF) was reacted with (3-ethoxycarbonyl)benzylzinc chloride (**54m**; 1.74 mL, 1.50 mmol, 0.86 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 12 h at 50 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / EtOAc = 1:6) afforded the quinazoline **126l** (275 mg, 78%) as a pale yellow solid.

M.p. (°C): 119-121.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.06 (s, 1H), 8.03-7.98 (m, 1H), 7.89-7.83 (m, 1H), 7.46-7.40 (m, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.27 (s, 1H), 7.21 (s, 1H), 4.54 (s, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

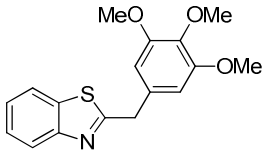
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 165.3, 155.9, 153.1, 150.4, 148.3, 138.0, 133.2, 130.9, 129.9, 128.8, 128.0, 119.4, 107.1, 102.1, 61.0, 56.4, 56.1, 41.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (vw), 1709 (m), 1615 (w), 1552 (w), 1505 (s), 1425 (s), 1365 (s), 1288 (vs), 1270 (s), 1234 (vs), 1193 (s), 1123 (m), 1027 (m), 985 (m), 850 (s), 753 (s), 728 (m), 700 (m).

MS (EI, 70 eV): m/z (%) = 352 (M^+, 32), 323 (18), 321 (100), 307 (14), 291 (19), 277 (5), 263 (6).

HRMS ($C_{20}H_{20}N_2O_4$): calc.: 352.1423; found: 352.1414.

2-(3,4,5-Trimethoxybenzyl)-1,3-benzothiazole (126m)



According to **TP14** 2-(methylthio)-1,3-benzothiazole (**124l**; 181 mg, 1.00 mmol, in 1 mL THF) was reacted with 3,4,5-trimethoxybenzylzinc chloride (**54h**; 1.56 mL, 1.50 mmol, 0.95 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%), S-Phos (20.5 mg, 5.0 mol%) and $Zn(OAc)_2$ (183 mg, 1.00 mmol). After 16 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the benzothiazole **126m** (222 mg, 70%) as a white solid.

M.p. (°C): 105-107.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01-7.96 (m, 1H), 7.82-7.76 (m, 1H), 7.47-7.41 (m, 1H), 7.36-7.29 (m, 1H), 6.57 (s, 2H), 4.35 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H).

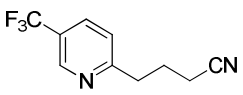
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 171.0, 153.4, 153.0, 137.1, 135.5, 132.6, 125.9, 124.8, 122.7, 121.5, 106.0, 60.8, 56.1, 40.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3051 (vw), 2936 (w), 2839 (w), 2361 (vw), 1590 (m), 1501 (m), 1422 (m), 1334 (m), 1238 (s), 1203 (w), 1154 (w), 1119 (vs), 1063 (m), 996 (s), 977 (m), 856 (m), 834 (m), 764 (vs), 732 (m), 722 (s), 663 (m), 642 (m).

MS (EI, 70 eV): m/z (%) = 315 (M^+, 100), 300 (53), 268 (5), 257 (5), 186 (10).

HRMS ($C_{17}H_{17}NO_3S$): calc.: 315.0929; found: 315.0925.

4-[5-(Trifluoromethyl)pyridin-2-yl]butanenitrile (126n)



According to **TP14** 2-(methylthio)-5-(trifluoromethyl)pyridine (**124d**; 193 mg, 1.0 mmol, in 1 mL THF) was reacted with (3-cyanopropyl)zinc bromide (**127a**; 3.66 mL, 1.5 mmol, 0.41 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 16 h at 25 °C, the reaction mixture was quenched with sat. Na_2CO_3 solution (25 mL) followed by extraction using

EtOAc (3 x 25 mL). Purification by flash chromatography (pentane / Et_2O = 1:1 + 2 vol-% NEt_3) furnished the pyridine **126n** (180 mg, 0.84 mmol, 84%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.83-8.76 (m, 1H), 7.85 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 3.02 (t, *J* = 7.3 Hz, 2H), 2.43 (t, *J* = 7.0 Hz, 2H), 2.23-2.09 (m, 2H).

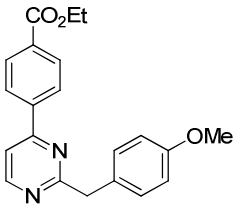
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.5 (q, $^4J_{C\text{-}F}$ = 1.4 Hz), 146.4 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 133.7 (q, $^3J_{C\text{-}F}$ = 3.5 Hz), 124.8 (q, $^2J_{C\text{-}F}$ = 33.1 Hz), 123.5 (q, $^1J_{C\text{-}F}$ = 272.3 Hz), 122.9, 119.2, 36.2, 24.4, 16.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2941 (vw), 2248 (vw), 1609 (m), 1574 (w), 1496 (vw), 1430 (w), 1396 (w), 1325 (vs), 1166 (m), 1121 (vs), 1079 (s), 1017 (s), 940 (w), 854 (w), 738 (w), 654 (w).

MS (EI, 70 eV): m/z (%) = 214 (M^+, <1), 195 (5), 174 (47), 161 (100), 147 (6), 86 (11), .

HRMS ($C_{10}H_9F_3N_2$): calc.: 214.0718; found: 214. 0697.

Ethyl 4-[2-(4-methoxybenzyl)pyrimidin-4-yl]benzoate (126o)



To a solution of 2-bromo-4-(methylthio)pyrimidine (**124b**; 205 mg, 1.00 mmol), $Pd(dba)_2$ (14.4 mg, 2.5 mol%) and tfp (11.6 mg, 5.0 mol%) in THF (1 mL) was added dropwise 4-methoxybenzylzinc chloride (**54i**; 0.82 mL, 1.02 mmol, 1.24 M in THF). After stirring for 3 h at 25 °C $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) were added followed by 4-(ethoxycarbonyl)phenylzinc iodide (**5a**; 2.14 mL, 1.50 mmol, 0.70 M in THF) and the reaction mixture was stirred for additional 24 h. Then, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, CH_2Cl_2 / Et_2O = 1:1) afforded the pyrimidine **126o** (236 mg, 68%) as a yellow solid.

M.p. (°C): 70-71.

^{1}H-NMR (600 MHz, C_6D_6): δ / ppm = 8.28 (d, *J* = 5.3 Hz, 1H), 8.23-8.20 (m, 2H), 8.00-7.92 (m, 2H), 7.48-7.41 (m, 2H), 6.83-6.77 (m, 2H), 6.68 (d, *J* = 5.3 Hz, 1H), 4. 38 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.27 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

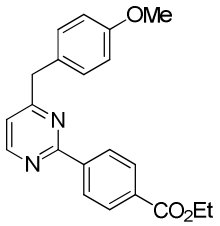
^{13}C-NMR (150 MHz, C_6D_6): δ / ppm = 171.0, 165.8, 162.6, 159.0, 158.1, 141.2, 132.9, 131.1, 130.7, 130.2, 127.4, 114.3, 114.2, 61.1, 54.7, 45.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2934 (w), 2835 (vw), 1712 (s), 1611 (w), 1569 (s), 1547 (m), 1510 (s), 1438 (m), 1409 (m), 1383 (m), 1270 (vs), 1242 (vs), 1176 (s), 1105 (s), 1018 (s), 818 (m), 776 (s), 740 (s), 700 (s).

MS (EI, 70 eV): m/z (%) = 348 (M^+, 100), 333 (26), 305 (15), 160 (4), 121 (10).

HRMS ($C_{23}H_{24}N_2O_5$): calc.: 348.1474; found: 348.1467.

Ethyl 4-[4-(4-methoxybenzyl)pyrimidin-2-yl]benzoate (126p)



To a solution of 4-iodo-2-(methylthio)pyrimidine (**124m**; 252 mg, 1.00 mmol), $Pd(dba)_2$ (14.4 mg, 2.5 mol%) and tfp (11.6 mg, 5.0 mol%) in THF (1 mL) was added dropwise 4-methoxybenzylzinc chloride (**54i**; 1.31 mL, 1.02 mmol, 0.78 M in THF). After stirring for 10 min at 25 °C $Pd(OAc)_2$ (5.6 mg, 2.5 mol%), S-Phos (20.5 mg, 5.0 mol%) and THF (0.5 mL) were added followed by 4-(ethoxycarbonyl)phenylzinc iodide (**5a**; 2.14 mL, 1.50 mmol, 0.70 M in THF) and the reaction mixture was stirred for additional 20 h. Then, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / CH_2Cl_2 / Et_2O = 12:4:1) afforded the pyrimidine **126p** (280 mg, 80%) as a yellow solid.

M.p. (°C): 71-73.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.67 (d, *J* = 5.2 Hz, 1H), 8.59-8.50 (m, 2H), 8.20-8.11 (m, 2H), 7.28-7.18 (m, 2H), 6.99 (d, *J* = 5.1 Hz, 1H), 6.93-6.81 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 3.79 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.4, 166.4, 163.2, 158.6, 157.1, 141.5, 132.2, 130.3, 129.7, 129.5, 128.1, 118.5, 114.2, 61.1, 55.2, 43.5, 14.3.

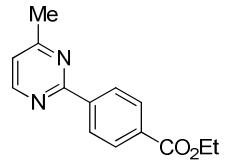
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2992 (w), 2980 (w), 2898 (w), 2836 (w), 1709 (vs), 1611 (w), 1583 (m), 1552 (s), 1512 (s), 1456 (w), 1438 (m), 1401 (s), 1386 (m), 1274 (vs), 1245 (vs),

1178 (s), 1110 (s), 1099 (s), 1018 (s), 921 (w), 884 (w), 875 (w), 845 (m), 820 (m), 763 (m), 755 (s), 699 (m), 614 (w).

MS (EI, 70 eV): m/z (%) = 348 (M^+, 100), 333 (24), 303 (8), 151 (5), 121 (15).

HRMS ($C_{23}H_{24}N_2O_5$): calc.: 348.1474; found: 348.1462.

Ethyl 3-(4-methylpyrimidin-2-yl)benzoate (126q)



According to **TP14** 4-methyl-2-(methylthio)pyrimidine (**124c**; 1.40 g, 10.0 mmol, in 5 mL THF) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide (**5a**; 20.0 mL, 15.0 mmol, 0.75 M in THF), $Pd(OAc)_2$ (56 mg, 2.5 mol%) and S-Phos (205 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (250 mL) followed by extraction using EtOAc (3 x 250 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the pyrimidine **126o** (2.20 g, 91%) as a yellow solid.

M.p. (°C): 46-48.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.66 (d, *J* = 5.1 Hz, 1H), 8.54-8.48 (m, 2H), 8.18-8.08 (m, 2H), 7.08 (dd, *J* = 5.1 Hz, 0.5 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.59 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.6, 166.4, 163.3, 156.7, 141.6, 132.1, 129.7, 128.1, 119.1, 61.1, 24.4, 14.3.

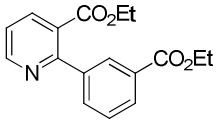
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2986 (w), 2904 (w), 1706 (s), 1586 (m), 1568 (m), 1550 (m), 1510 (w), 1480 (w), 1430 (w), 1400 (m), 1364 (m), 1304 (w), 1266 (vs), 1126 (m), 1106 (s), 1090 (m), 1026 (m), 1018 (m), 880 (m), 850 (m), 838 (m), 760 (s), 698 (m), 610 (w).

MS (EI, 70 eV): m/z (%) = 242 (M^+, 45), 214 (38), 197 (100), 169 (25), 129 (3), 102 (4).

HRMS ($C_{14}H_{14}N_2O_2$): calc.: 242.1055; found: 242.1051.

6.3. Prepartion of the title compounds via Ni-catalyzed cross-couplings

Ethyl 2-[3-(ethoxycarbonyl)phenyl]nicotinate (128a)



According to **TP15** ethyl 2-(methylthio)nicotinate (**124e**; 197 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (**5d**; 2.24 mL, 1.50 mmol, 0.67 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 14 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / EtOAc = 4:1) afforded the pyridine **128a** (273 mg, 91%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.78 (dd, *J* = 4.7 Hz, 1.7 Hz, 1H), 8.22-8.19 (m, 1H), 8.17 (dd, *J* = 7.9 Hz, 1.7 Hz, 1H), 8.13-8.08 (m, 1H), 7.77-7.71 (m, 1H), 7.55-7.47 (m, 1H), 7.38 (dd, *J* = 7.9 Hz, 4.7 Hz, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H).

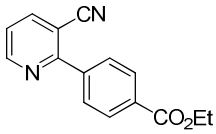
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.4, 166.2, 157.9, 151.1, 140.2, 138.3, 132.9, 130.4, 129.8, 129.8, 128.2, 127.3, 122.0, 61.6, 61.0, 14.3, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 1713 (vs), 1582 (w), 1562 (m), 1439 (m), 1420 (m), 1391 (w), 1367 (m), 1283 (s), 1245 (vs), 1207 (s), 1170 (m), 1111 (s), 1097 (s), 1056 (s), 1015 (m), 855 (w), 822 (w), 787 (m), 753 (vs), 694 (s).

MS (EI, 70 eV): m/z (%) = 299 (M^+, 16), 270 (100), 254 (37), 242 (27), 227 (28), 208 (12), 198 (14), 182 (14), 155 (18), 127 (8), 91 (5).

HRMS ($C_{17}H_{17}NO_4$): calc.: 299.1158; found: 299.1155.

Ethyl 4-(3-cyanopyridin-2-yl)benzoate (128b)



According to **TP15** 2-(methylthio)nicotinonitrile (**124i**; 150 mg, 1.00 mmol, in 1 mL THF) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide (**5a**; 2.14 mL, 1.50 mmol, 0.70 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction

using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1 + 2 vol-% NEt_3) afforded the pyridine **128b** (173 mg, 69%) as white solid.

M.p. (°C): 98-100.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.89 (dd, *J* = 4.9 Hz, 1.7 Hz, 1H), 8.22-8.16 (m, 2H), 8.09 (dd, *J* = 8.0 Hz, 1.9 Hz, 1H), 8.03-7.96 (m, 2H), 7.42 (dd, *J* = 7.8 Hz, 4.9 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

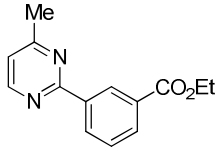
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.0, 160.0, 152.7, 141.8, 141.0, 131.9, 129.8, 128.9, 122.1, 117.2, 107.9, 61.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2977 (vw), 2225 (w), 1714 (m), 1581 (w), 1551 (w), 1432 (m), 1405 (w), 1368 (w), 1319 (vw), 1271 (vs), 1226 (w), 1184 (w), 1175 (w), 1102 (s), 1016 (m), 966 (w), 862 (m), 806 (m), 787 (w), 750 (vs), 719 (w), 698 (m).

MS (EI, 70 eV): m/z (%) = 252 (M^+, 43), 224 (36), 207 (100), 179 (36), 152 (15), 90 (4).

HRMS ($C_{15}H_{12}N_2O_2$): calc.: 252.0899; found: 252.0902.

Ethyl 3-(4-methylpyrimidin-2-yl)benzoate (128c)



According to **TP15** 4-methyl-2-(methylthio)pyrimidine (**124c**; 140 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (**5d**; 2.21 mL, 1.50 mmol, 0.68 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 12 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 20:1) afforded the pyrimidine **128c** (230 mg, 95%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.10-9.06 (m, 1H), 8.68-8.60 (m, 2H), 8.17-8.11 (m, 1H), 7.58-7.51 (m, 1H), 7.07 (d, *J* = 5.1 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.59 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

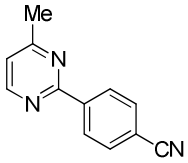
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.6, 166.4, 163.4, 156.7, 138.0, 132.4, 131.5, 131.0, 129.3, 128.6, 119.0, 61.0, 24.4, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976 (w), 2928 (vw), 1712 (s), 1572 (s), 1552 (m), 1422 (m), 1386 (m), 1365 (m), 1280 (s), 1255 (s), 1237 (vs), 1164 (m), 1126 (s), 1103 (s), 1078 (m), 1021 (s), 916 (m), 849 (m), 822 (m), 746 (vs), 685 (s).

MS (EI, 70 eV): m/z (%) = 242 (M^+, 53), 214 (11), 197 (80), 170 (100), 129 (6), 102 (9).

HRMS ($C_{14}H_{14}N_2O_2$): calc.: 242.1055; found: 242.1052.

4-(4-Methylpyrimidin-2-yl)benzonitrile (128d)



According to **TP15** 4-methyl-2-(methylthio)pyrimidine (**124c**; 140 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-cyanophenylzinc iodide (**5e**; 2.31 mL, 1.50 mmol, 0.65 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O / EtOAc = 2:6:1) afforded the pyrimidine **129d** (143 mg, 73%) as a white solid.

M.p. (°C): 191-193.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.66 (d, *J* = 5.2 Hz, 1H), 8.60-8.52 (m, 2H), 7.78-7.71 (m, 2H), 7.11 (d, *J* = 5.6 Hz, 1H), 2.59 (s, 3H).

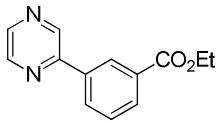
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.7, 162.4, 156.9, 141.8, 132.3, 128.6, 119.5, 118.8, 113.8, 24.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3047 (w), 2224 (w), 1678 (w), 1606 (w), 1583 (s), 1550 (s), 1378 (s), 1288 (m), 1254 (w), 1197 (w), 1108 (w), 1018 (w), 994 (w), 949 (w), 868 (m), 860 (m), 836 (vs), 789 (vs), 706 (w).

MS (EI, 70 eV): m/z (%) = 195 (M^+, 100), 180 (13), 128 (29), 101 (5), 67 (5).

HRMS ($C_{12}H_9N_3$): calc.: 195.0796; found: 195.0796.

Ethyl 3-pyrazin-2-ylbenzoate (128e)



According to **TP15** 2-(methylthio)pyrazine (**124n**; 26 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (**5d**; 2.31 mL, 1.50 mmol, 0.65 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 14 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the pyrazine **128e** (170 mg, 74%) as a white solid.

M.p. (°C): 121-123.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.95 (t, *J* = 1.6 Hz, 1H), 8.76 (d, *J* = 1.6 Hz, 1H), 8.18-8.13 (m, 1H), 8.08-8.06 (m, 1H), 8.03 (d, *J* = 2.5 Hz, 1H), 7.95-7.91 (m, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 1.03 (t, *J* = 7.1 Hz, 3H).

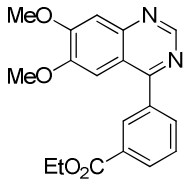
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 165.9, 151.6, 144.2, 143.6, 142.2, 137.1, 131.9, 131.0, 130.9, 129.1, 128.4, 61.0, 14.2

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3090 (vw), 3053 (w), 2983 (w), 2939 (w), 1705 (s), 1606 (w), 1465 (m), 1392 (m), 1367 (m), 1278 (s), 1247 (vs), 1176 (m), 1147 (m), 1123 (m), 1109 (s), 1081 (m), 1024 (s), 1014 (s), 936 (m), 896 (m), 856 (s), 820 (m), 765 (s), 745 (s), 689 (s), 652 (m).

MS (EI, 70 eV): m/z (%) = 228 (M^+, 61), 200 (31), 183 (100), 155 (49), 102 (10), 77 (6).

HRMS ($C_{13}H_{12}N_2O_2$): calc.: 228.0899; found: 228.0883.

Ethyl 3-(6,7-dimethoxyquinazolin-4-yl)benzoate (128f)



According to **TP15** 6,7-dimethoxy-4-(methylthio)quinazoline (**124j**; 236 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (**5d**; 2.31 mL, 1.50 mmol, 0.65 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction

using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / EtOAc / CH_2Cl_2 = 1:1:2) afforded the quinazoline **128f** (270 mg, 80%) as a white solid.

M.p. (°C): 174-175.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.20 (s, 1H), 8.46 (t, *J* = 1.8 Hz, 1H), 8.24-8.21 (m, 1H), 7.99-7.97 (m, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.27 (s, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 4.08 (s, 3H), 3.89 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

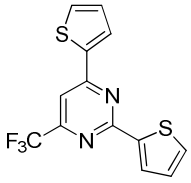
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 165.9, 164.0, 156.1, 153.2, 150.7, 148.9, 137.8, 133.7, 131.1, 130.8, 130.6, 129.0, 118.6, 106.8, 103.5, 61.3, 56.5, 56.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920 (w), 2851 (w), 1730 (s), 1617 (w), 1569 (w), 1540 (m), 1501 (vs), 1464 (m), 1427 (s), 1371 (m), 1321 (m), 1302 (m), 1261 (s), 1230 (vs), 1214 (s), 1143 (m), 1122 (m), 1080 (m), 1030 (m), 1011 (m), 974 (w), 850 (m), 753 (m), 694 (m).

MS (EI, 70 eV): m/z (%) = 338 (M^+, 100), 323 (22), 309 (22), 277 (24), 265 (20), 249 (8), 221 (13), 192 (6), 147 (5), 84 (8).

HRMS ($C_{19}H_{18}N_2O_4$): calc.: 338.1267; found: 338.1265.

2,4-Di-2-thienyl-6-(trifluoromethyl)pyrimidine (128g)



According to **TP15** 2-(methylthio)-4-(2-thienyl)-6-(trifluoromethyl)pyrimidine (**124o**; 276 mg, 1.00 mmol, in 1.5 mL THF) was reacted with 2-thienylzinc iodide (**5f**; 1.95 mL, 1.50 mmol, 0.77 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 16 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 500:1) afforded the pyrimidine **128g** (294 mg, 94%) as a yellow solid.

M.p. (°C): 102-104.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.14 (dd, *J* = 3.7 Hz, 1.3 Hz, 1H), 7.87 (dd, *J* = 3.7 Hz, 1.1 Hz, 1H), 7.60 (dd, *J* = 5.0 Hz, 1.2 Hz, 1H), 7.58 (s, 1H), 7.54 (dd, *J* = 5.0 Hz, 1.2 Hz, 1H), 7.21-7.15 (m, 2H).

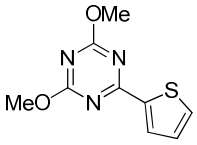
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.1, 161.2, 156.4 (q, $^2J_{C\text{-}F}$ = 35.8 Hz), 141.9, 141.3, 131.6, 131.2, 130.6, 128.9, 128.6, 128.3, 120.6 (q, $^1J_{C\text{-}F}$ = 275.4 Hz), 107.7 (q, $^3J_{C\text{-}F}$ = 2.8 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3101 (vw), 1739 (w), 1586 (m), 1542 (m), 1526 (m), 1427 (s), 1410 (m), 1379 (s), 1334 (w), 1263 (s), 1215 (m), 1182 (s), 1137 (vs), 1102 (m), 1034 (m), 998 (m), 860 (m), 724 (m), 712 (s), 697 (vs).

MS (EI, 70 eV): m/z (%) = 312 (M^+, 100), 134 (47), 109 (18), 90 (6), 45 (10).

HRMS ($C_{13}H_7F_3N_2S_2$): calc.: 312.0003; found: 311.9985.

2,4-Dimethoxy-6-(2-thienyl)-1,3,5-triazine (128h)



According to **TP15** dimethoxy-6-(methylthio)-1,3,5-triazine (**124p**; 187 mg, 1.00 mmol, in 1 mL THF) was reacted with 2-thienylzinc iodide (**5f**; 1.95 mL, 1.50 mmol, 0.77 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 16 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O / CH_2Cl_2 = 8:1:1) afforded the pyrimidine **128h** (194 mg, 87%) as a pale yellow solid.

M.p. (°C): 93-95.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.14 (dd, *J* = 3.8 Hz, 1.3 Hz, 1H), 7.57 (dd, *J* = 5.0 Hz, 1.2 Hz, 1H), 7.14 (dd, *J* = 4.9 Hz, 3.7 Hz, 1H), 4.07 (s, 6H).

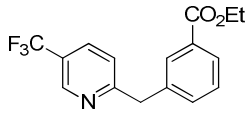
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 172.5, 170.6, 140.6, 132.5, 131.9, 128.3, 55.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079 (w), 2953 (w), 1563 (s), 1544 (s), 1531 (s), 1490 (s), 1452 (s), 1428 (s), 1378 (s), 1350 (vs), 1335 (s), 1231 (m), 1194 (m), 1096 (s), 1085 (m), 1041 (s), 1011 (m), 931 (m), 813 (s), 738 (s), 722 (s).

MS (EI, 70 eV): m/z (%) = 223 (M^+, 100), 193 (33), 178 (21), 152 (31), 110 (30), 109 (19), 69 (18).

HRMS ($C_9H_9N_3O_2S$): calc.: 223.0415; found: 223.0399.

Ethyl 3-{[5-(trifluoromethyl)pyridin-2-yl]methyl}benzoate (128i)



According to **TP15** 2-(methylthio)-5-(trifluoromethyl)pyridine (**124i**; 193 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)benzylzinc chloride (**54m**; 1.19 mL, 1.50 mmol, 1.26 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 24 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the pyridine **128i** (230 mg, 74%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.82-8.79 (m, 1H), 7.97-7.89 (m, 2H), 7.81 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 7.48-7.42 (m, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.26 (s, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

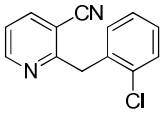
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 164.3 (q, $^4J_{C\text{-}F}$ = 1.4 Hz), 146.3 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 138.6, 133.8 (q, $^3J_{C\text{-}F}$ = 3.4 Hz), 133.6, 131.0, 130.2, 128.8, 128.1, 124.6 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 123.6 (q, $^1J_{C\text{-}F}$ = 272.1 Hz), 122.8, 61.0, 44.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984 (vw), 1715 (s), 1605 (m), 1574 (w), 1490 (w), 1445 (w), 1392 (w), 1368 (w), 1326 (vs), 1277 (s), 1192 (s), 1164 (m), 1123 (vs), 1105 (s), 1077 (vs), 1016 (s), 944 (w), 860 (w), 836 (w), 742 (s), 695 (m), 673 (w), 650 (w).

MS (EI, 70 eV): m/z (%) = 309 (M^+, 41), 308 (100), 290 (11), 280 (93), 264 (44), 235 (86), 208 (16), 167 (32), 132 (13), 118 (11), 44 (21).

HRMS ($C_{16}H_{14}F_3NO_2$): calc.: 309.0977; found: 309.0957.

2-(2-Chlorobenzyl)nicotinonitrile (128j)



According to **TP15** 2-(methylthio)nicotinonitrile (**124i**; 150 mg, 1.00 mmol in 1 mL THF) was reacted with 2-chlorobenzylzinc chloride (**54b**; 2.14 mL, 1.50 mmol, 0.70 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 24 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O / CH_2Cl_2 = 5:1:1 + 2 vol-% NEt_3) afforded the pyridine **128j** (258 mg, 69%) as white solid.

M.p. (°C): 74-76.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.71 (dd, *J* = 5.0 Hz, 1.8 Hz, 1H), 7.96 (dd, *J* = 7.9 Hz, 1.7 Hz, 1H), 7.41-7.34 (m, 1H), 7.29 (dd, *J* = 7.9 Hz, 4.7 Hz, 1H), 7.26-7.18 (m, 3H), 4.53 (s, 2H).

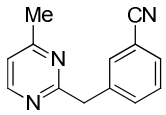
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.1, 152.3, 140.7, 135.2, 134.4, 131.4, 129.6, 128.5, 126.9, 121.4, 116.4, 109.8, 40.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057 (vw), 2923 (vw), 2228 (w), 1579 (m), 1562 (m), 1474 (m), 1434 (s), 1164 (w), 1127 (w), 1090 (m), 1050 (m), 1038 (m), 987 (w), 949 (w), 910 (w), 805 (m), 752 (vs), 717 (m), 704 (m), 678 (m), 623 (m).

MS (EI, 70 eV): m/z (%) = 228 (M^+, <1), 193 (100), 164 (4), 96 (4), 82 (2), 63 (2).

HRMS ($C_{13}H_9ClN_2$): calc.: 227.0376 ($[M-H]^+$); found: 227.0377 ($[M-H]^+$).

3-[(4-Methylpyrimidin-2-yl)methyl]benzonitrile (128k)



According to **TP15** 4-methyl-2-(methylthio)pyrimidine (**124c**; 140 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-cyanobenzylzinc chloride (**54o**; 1.05 mL, 1.50 mmol, 1.43 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 7 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O / EtOAc = 2:6:1) afforded the pyrimidine **128k** (197 mg, 94%) as a white solid.

M.p. (°C): 67-68.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.50 (d, *J* = 5.2 Hz, 1H), 7.65-7.62 (m, 1H), 7.62-7.56 (m, 1H), 7.51-7.46 (m, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 5.2 Hz, 1H), 4.25 (s, 2H), 2.50 (s, 3H).

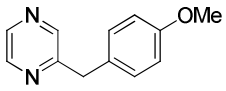
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.1, 167.6, 156.9, 139.7, 133.7, 132.7, 130.2, 129.1, 118.9, 118.6, 112.4, 45.2, 24.2.

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

MS (EI, 70 eV): m/z (%) = 209 (M^+; 46), 208 (100), 193 (5), 116 (8), 104 (4), 89 (7), 44 (8).

HRMS ($C_{13}H_{11}N_3$): calc.: 209.0953; found: 209.0936.

2-(4-Methoxybenzyl)pyrazine (128l)



According to **TP15** 2-(methylthio)pyrazine (**126n**; 1.26 g, 10.0 mmol, in 5 mL THF) was reacted with 4-methoxybenzylzinc chloride (**54i**; 20.8 mL, 15.0 mmol, 0.72 M in THF), $Ni(acac)_2$ (64 mg, 2.5 mol%) and DPE-Phos (268 mg, 5.0 mol%). After 15 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (250 mL) followed by extraction using EtOAc (3 x 250 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:4) afforded the pyrazine **128l** (1.69 g, 84%) as a yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.48 (dd, *J* = 2.5 Hz, 1.6 Hz, 1H), 8.44 (d, *J* = 1.7 Hz, 1H), 8.38 (d, *J* = 2.6 Hz, 1H), 7.21-7.14 (m, 2H), 6.87-6.81 (m, 2H), 4.10 (s, 2H), 3.76 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.4, 156.8, 144.6, 144.0, 142.2, 130.1, 130.0, 114.2, 55.2, 41.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004 (w), 2956 (w), 2932 (w), 2908 (w), 2836 (w), 1610 (m), 1584 (w), 1510 (vs), 1472 (m), 1440 (w), 1400 (m), 1300 (m), 1246 (vs), 1176 (s), 1126 (m), 1104 (w), 1056 (m), 1032 (s), 1018 (s), 808 (s), 772 (m), 648 (w).

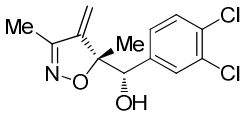
MS (EI, 70 eV): m/z (%) = 200 (M^+; 100), 185 (31), 157 (7), 121 (42), 77 (5).

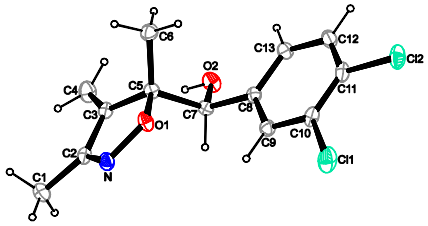
HRMS ($C_{12}H_{12}N_2O$): calc.: 200.0950; found: 200.0940.

D. APPENDIX

1. Data of the X-ray Analysis

3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)(phenyl)methanol (92e)





Crystal Data	
Formula	$C_{13}H_{13}Cl_2NO_2$
Formula weight	286.14
Crystal system	monoclinic
Space group	$P2_1/c$
[*a*/*b*/*c*] (Å)	[10.5555(8), 10.6222(8),11.8958(18)]
[α/β/γ] (deg)	[90.000(9), 92.856(9), 90.000(6)]
V/Å^3	1332.1(2)
Z	4
D_{calc}/(g/cm^3)	1.427
μ ($Mo_{κα}$)/mm^{-1}	0.480
Crystal size/mm	0.41 × 0.38 × 0.15

Data Collection	
Temperature/K	173(2)
Radiation ($Mo_{κα}$) (Å)	0.71073
$θ_{min}$, $θ_{max}$ (deg)	4.29–26.24
Tot., Uniq. Data, R_{int}	5543, 2700, 0.246
Observed data [$I < 2σ(I)$]	1741

Refinement	
$N_{ref,}$ N_{par}	2337, 165
R, wR^2, S	0.0348, 0.0833, 0.893
Max. and av. shift/error	0.001, 0.001
Min. max. resd. dens. (e Å^{-3})	-0.357, 0.389

CCDC 778844 contains the supplementary crystallographic data for this compound. This data has been deposit in the Cambridge Crystallographic Data Centre and can be obtained free of charge via the internet: www.ccdc.cam.ac.uk/data_request/cif

2. Curriculum Vitae

Albrecht Metzger

Personal Informations

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Date of Birth	24.10.1981
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Citizenship	German
Maritial Status	married

Education

06/2006 – 05/2010	Ph.D. thesis in the group of Prof. Dr. Paul Knochel on "Preparation and Applications of Benzylic Zinc Chlorides. Lewis-Acid Promoted Additions of Organomagnesium and Organozinc Reagents to Carbonyl Derivatives. Transition Metal-Catalyzed Cross-Coupling Reactions With Methylthio-Substituted N-Heterocycles."
01/2006	diploma exams (all over diploma average grade: 1.2)
05/2005 – 10/2005	Diploma thesis in the group of Prof. Dr. Armin de Meijere on "New Polymerisable Adhesives for Dental Composites"
10/2003 – 01/2006	Advanced Studies in Chemistry at the Georg-August-Universität Göttingen
10/2001 – 09/2003	Basic Studies in Chemistry at the Martin-Luther-Universität Halle (Saale)
09/1996 – 07/2000	Georg-Cantor-Gymnasium Halle (Saale)
09/1992 – 08/1996	Christian-Thomasius-Gymnasium Halle (Saale)
09/1991 – 08/1992	Grundschule Weidenplan Halle (Saale)
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Languages

German: mother tongue
English: fluently
French: basic proficiency

Awards

12/2008 Römer-Fellowship 2008 of the Dr. Klaus Römer Stiftung

Personal Interests

Playing bass guitar and violoncello
Hiking, Diving
Sports (Cycling)

Publications

1. Sylvie Perrone, Albrecht Metzger, Paul Knochel, "Chiral Allylic Cyanohydrins as Versatile Substrates for Diastereoselective Copper(I)-Mediated S_N2' Allylic Substitutions", *Synlett* **2007**, 1047.

2. Albrecht Metzger, Matthias A. Schade, Paul Knochel, "LiCl-Mediated Preparation of Highly Functionalized Benzylic Zinc Chlorides", *Org. Lett.* **2008**, *10*, 1107-1110.

3. Matthias A. Schade, Albrecht Metzger, Stefan Hug, Paul Knochel, "Nickel-Catalyzed Cross-Coupling Reactions of Benzylic Zinc Reagents With Aromatic Bromides, Chlorides and Tosylates", *Chem. Commun.* **2008**, 3046-3048.

4. Albrecht Metzger, Matthias A. Schade, Georg Manolikakes, Paul Knochel, "A General Preparation of Polyfunctional Benzylic Zinc Organometallic Compounds", *Chem. Asian J.* **2008**, *3*, 1678-1691.
   (*special issue in honor of Professor Ryoji Noyori (Nobel prize 2001) on the occasion of his 70th birthday)*

5. Shohei Sase, Milica Jaric, Albrecht Metzger, Vladimir Malakhov, Paul Knochel, "One-Pot Negishi Cross-Coupling Reactions of In Situ Generated Zinc Reagents With Aryl Chlorides, Bromides and Triflates", *J. Org. Chem.* **2008**, *73*, 7380-7382.

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7. Albrecht Metzger, Fabian M. Piller, Paul Knochel, "Polyfunctional Benzylic Zinc Chlorides by the Direct Insertion of Magnesium Into Benzylic Chlorides in the Presence of LiCl and $ZnCl_2$", *Chem. Commun.* **2008**, 5824-5826.

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Reviews

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Patents

1. Sebastian Bernhardt, Albrecht Metzger, Georg Manolikakes, Paul Knochel "Carbonylierung von organischen Zinkverbindungen" patent pending.

Posters

1. "Preparation of Highly Functionalized Benzylic Zinc Reagents by the Direct Insertion of Zn or Mg Into Benzylic Chlorides in the Presence of LiCl" Synthesefest, 17.3.-18.3.2009, Ludwig-Maximilians-Universität München

2. "Preparation and Application of Polyfunctional Benzylic Zinc Reagents" OMCOS 15th, 26.-30.7.2009, Glasgow, Scotland.