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Cross-Coupling of Benzylic Zinc Reagents, Preparation and Applications of Alkenyl Zinc Reagents, Preparation of Primary Amides and Synthesis of Functionalized Allenes

von

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Communications and Full Papers

1.) Albrecht Metzger, Matthias A. Schade, Paul Knochel: "LiCl-Mediated Preparation of Highly Functionalized Benzylic Zinc Chlorides" *Org. Lett.* **2008**, *10*, 1107-1110.

2.) Matthias A. Schade, Albrecht Metzger, Stephan Hug, Paul Knochel: "Nickel-Catalyzed Cross-Coupling Reactions of Benzylic Zinc Reagents with Aromatic Bromides, Chlorides and Tosylates" *Chem. Commun*. **2008**, 3046-3048.

3.) Georg Manolikakes, Matthias A. Schade, Carmen M. Hernandez, Herbert Mayr, Paul Knochel: "Negishi Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents" *Org. Lett.* **2008**, *10*, 2765-2768.

4.) Albrecht Metzger, Matthias A. Schade, Georg Manolikakes, Carmen M. Hernandez, Paul Knochel: "A General Preparation of Polyfunctional Benzylic Zinc Compounds" *Chem. Asian J.* **2008**, *3*, 1678-1691.

5.) Georg Manolikakes, Carmen M. Hernandez, Matthias A. Schade, Albrecht Metzger, Paul Knochel: "Negishi Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents" *J. Org. Chem.* **2008**, *73*, 8422-8436.

6.) Fabian M. Piller, Albrecht Metzger, Matthias A. Schade, Benjamin A. Haag, Andrei Gavryushin, Paul Knochel: "Preparation of Polyfunctional Arylmagnesium, Arylzinc and Benzylic Zinc Reagents by Using Magnesium in the Presence of LiCl" *Chem. Eur. J.* **2009**, *15*, 7192-7202.

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8.) Matthias A. Schade, Julia E. Fleckenstein, Paul Knochel, Konrad Koszinowski: "Charged Tags as Probes for Analyzing Organometallic Intermediates and Monitoring Cross-Coupling Reactions by Electrospray-Ionization Mass Spectrometry" *J. Org. Chem.* **2010**, *75*, 6848-6857.

9.) Matthias A. Schade, Shigeyuki Yamada, Paul Knochel: "Synthesis of Polyfunctional Allenes via Successive Copper-Mediated Substitutions" *Chem. Eur. J.* **2011,** *17*, 4232-4237.

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Reviews

1.) Paul Knochel, Prasad Appukkuttan, Andrej Gavryushin, Georg Manolikakes, Albrecht Metzger, Marc Mosrin, Fabian M. Piller, Christoph J. Rohbogner, Matthias A. Schade, Stefan H. Wunderlich: "Functionalization of Heterocyclic Compounds using Polyfunctional Magnesium and Zinc Reagents" *Pfizer In-House Journal Synthon* **2008**.

“Nature is relentless and unchangeable, and it is indifferent as to whether its hidden reasons and actions are understandable to man or not.”

Galileo Galilei

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TABLE OF CONTENTS

A Introduction 1

1 Overview 3

2 Organomagnesium Reagents 5

3 Organozinc Reagents 7

4 Objectives 10

B Results and Discussion 13

1 Cross-Coupling Reactions of Benzylic Zinc Reagents 15

1.1 Introduction 15

1.2 Nickel-Catalyzed Cross-Coupling Reactions of Benzylic Zinc Reagents 18

1.3 Palladium-Catalyzed Cross-Coupling Reactions of Benzylic Zinc Reagents 24

2 Preparation and Applications of Alkenyl Zinc Reagents 26

2.1 Introduction 26

2.2 Direct Insertion of Zinc in Activated Alkenyl Bromides 28

2.3 Magnesium Insertion in the Presence of Zinc Chloride in Alkenyl Bromides 33

3 Regioselective Magnesium and Zinc Insertions in Polybrominated Phenol Derivatives 36

3.1 Introduction 36

3.2 Regioselective Ortho Insertion in Polybrominated Benzene Derivatives 37

3.3 Large Scale Insertion Reactions 40

4 Preparation of Primary Amides From Organozinc Halides 44

4.1 Introduction 44

4.2 Preparation of Primary Amides 46

4.3 Reactions of Organozinc Reagents with Substituted Isocyanates 50

5 Preparation of Highly Functionalized Allenes via Successive Copper-Mediated Substitution Reactions 53

5.1 Introduction 53

5.2 Preliminary Experiments 55

5.3 Preparation of Functionalized Chloroallenes 57

5.4 Preparation of Trisubstituted Allenes 61

6 Preparation of Charge-Tagged Organozinc Reagents 64

6.1 Introduction 64

6.2 Preparation of Charge-Tagged Organozinc Reagents 66
6.3 ESI-MS Analysis of Charge-Tagged Organozinc Reagents 67
6.4 Monitoring of Cross-Coupling Reactions 70
7 Summary and Outlook 75
7.1 Cross-Coupling Reactions of Benzylic Zinc Reagents 75
7.2 Preparation and Application of Alkenyl Zinc Reagents 76
7.3 Regioselective Magnesium and Zinc Insertions in Polybrominated Protected Phenols 78
7.4 Preparation of Amides from Functionalized Organozinc Reagents 79
7.5 Preparation of Highly Functionalized Allenes via Successive Copper-Mediated Substitution Reactions 80
7.6 Preparation of Charge-Tagged Organozinc Reagents 81
C Experimental 83
1 General Considerations 85
2 Cross-Coupling Reactions of Benzylic Zinc Reagents 87
2.1 General Procedures 87
2.2 Preparation of the aryl tosylates 88
2.3 Preparation of the Cross-Coupling Products 92
2.4 Nickel-Catalyzed Cross-Couplings with Bromoaniline Derivatives 103
2.5 Palladium-Catalyzed Cross-Couplings with Bromoaniline Derivatives 108
3 Preparation an Applications of Alkenyl Zinc Reagents 113
3.1 General Procedures 113
3.2 Direct Insertion of Zinc in Activated Alkenyl Bromides 114
3.3 Magnesium Insertion in the Presence of Zinc Chloride in Alkenyl Bromides 128
4 Regioselective Magnesium and Zinc Insertions in Polybrominated Phenol Derivatives 136
4.1 General Prodcedures 136
4.2.1 Regioselective Zinc Insertion in Polybrominated Arenes 138
4.2.2 Directed Ortho Insertion in Large Scale 145
4.2.3 Reactions of Ortho-Zincated Polybrominated Arenes with Electrophiles 146
4.2.4 Regioselective Magnesium Insertion in Polybrominated Arenes 152
5 Preparation of Primary Amides From Organozinc Halides 156
5.1 General Procedures 156
5.2 Preparation of Primary Amides 157

5.3 Preparation of Secondary Amides 172
6 Preparation of Highly Functionalized Allens Via Successive Copper-Mediated Substitution Reactions 177
6.1 General Procedures 177
6.2 Preparation of 1,1-dichloro-2-alkynes 177
6.3 Preparation of Substituted Allenes Starting from Bromoallenes 178
6.4 Preparation of Substituted Chloroallenes 185
6.5 Preparation of Polyfunctionalized Allenes Starting from Chloroallenes 193
7 Preparation of Charge-Tagged Organozinc Reagents 200
7.1 General Considerations 200
7.2 Additional Figures 201
D Appendix 209
1 Curriculum Vitae 211

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
aq.	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
calc.	calculated
conc.	concentrated
dba	trans,trans-dibenzylideneacetone
DBE	1,2-dibromoethane
dest.	distilled
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DoI	directed *ortho* insertion
δ	chemical shifts in parts per million
E	electrophile
EI	electron impact ionization
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectrometry
*i*Pr	*iso*-propyl
IR	infra-red
J	coupling constant (NMR)
LDA	lithium diisopropylamide
M	molarity
m	meta
m.p.	melting point
Me	methyl
Met	metal
min	minute
mmol	millimole
MS	mass spectrometry
NEP	N-ethyl-2-pyrrolidine
NMP	N-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	ortho
p	para
PG	protecting group
Ph	phenyl
R	organic substituents
rt	room temperature
sat.	saturated
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBDMS	tertbutyldimethylsilyl
*t*Bu	*tert*-Butyl
Tf	triflate
tfp	tris-(2-furyl)phosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

A Introduction

1 OVERVIEW

All modern civilizations are based on economic growth and technological progress.[1] With a turnover of 145 billion Euro and 416250 employees in 2009, the chemical and pharmaceutical industries are one of the most important branches in the manufacturing sector of Germany, along with automotive industry (266 bn €), engineering (170 bn €) and electronics industry (145 bn €).[2] Chemical and pharmaceutical industry expends a total of 18.6 % of its turnover for research and development therefore investing second most in R&D among all other branches.[3] Providing basic chemicals and processable materials for other industrial branches on the one hand and commodities and pharmaceuticals for consuments on the other, chemical industry is strongly dependent on research. Furthermore, limited fossile resources and the need to reduce environmental pollution require new concepts for the supply of basic chemicals and a change towards sustainable chemistry is inevitable.[4] Particularly, organic chemistry will play an important role in this fundamental task. Ranging from small molecules over sophisticated materials and highly specialized polymers to complex pharmaceuticals and natural products, modern organic synthesis must address more than mere chemical issues namely, the challenge of atom economical syntheses along with minimized waste production.[5] Especially, total syntheses of natural products often suffer from extensive protection group interconversions and long linear sequences resulting in poor atom economy.[6] Great efforts are done to shorten syntheses by avoiding protection group manipulations.[7] To overcome long, yield-reducing linear reaction sequences,[8] a convergent synthesis strategy combining highly functionalized building blocks to form complex target molecules is highly desireable. Nowadays, organometallic chemistry provides versatile tools for modern organic synthesis. Synthetic organic chemists can choose from an ever growing toolbox of organometallic reagents, each possessing a unique reactivity and selectivity depending on the nature of the metal used.[9] Highly reactive organometallics, such as organolithium reagents, react with numerous electrophiles but are incompatible with sensitive functional groups.[10] Organoboron, -indium or –tin reagents show, due to a more covalent carbon-metal bond, a higher functional group tolerance, hence needing either harsh conditions or appropriate catalysts to react with electrophiles. Organomagnesium, -copper and -zinc reagents are settled between those two extremes. Although *Grignard* reagents are highly reactive towards electrophiles, they show an excellent functional group tolerance at an appropriate low temperature.[11] Organocopper reagents possess a well-balanced reactivity allowing reactions with various electrophilic substrates on the one

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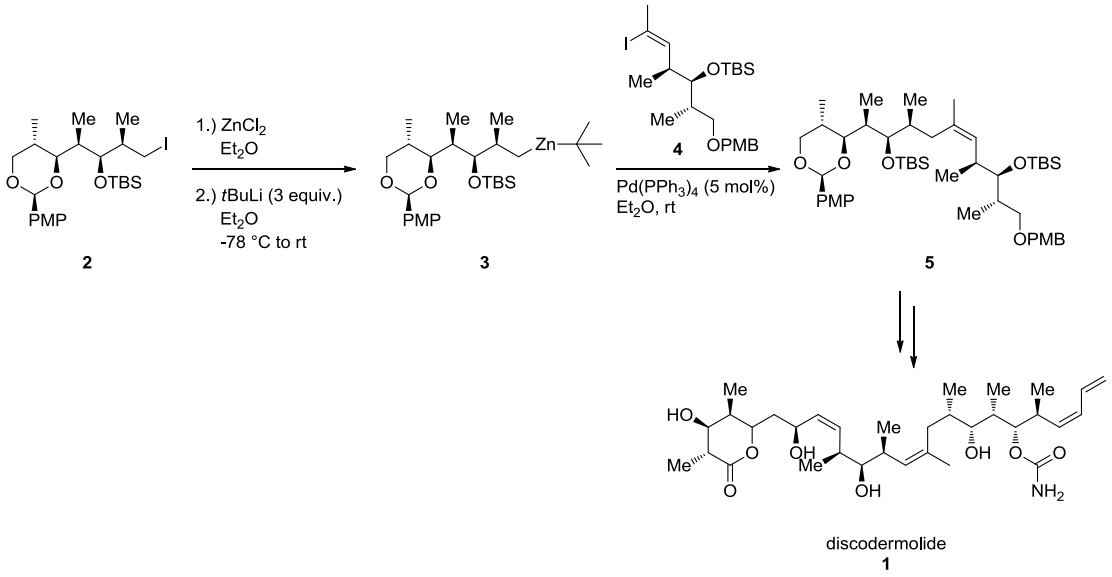
[2] Verband der Chemischen Industrie (VCI), *Chemiewirtschaft in Zahlen*, **2010**, 42.
[3] http://www.vci.de/default2~cmd~shd~docnr~124244~rub~735~tma~875~nd~.htm#_ftnref1 (accessed Mar 25, 2011).
[4] (a) T. Collins, *Science* **2001**, *291*, 48; (b) C. Okkerse, H. van Bekkum, *Green Chemistry* **1999**, *1*, 107.
[5] (a) B. M. Trost, *Science* **1991**, *254*, 1471; (b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259.
[6] (a) *Protective Groups in Organic Synthesis 3rd Ed.*, (Eds.: T.W. Green, P. G. Wuts) Wiley & Sons, Hoboken, **1999**; (b) *Protecting Groups 3rd Ed.* (Ed. P. J. Kocienski) Thieme, New York, **2005**.
[7] (a) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404; (b) R. W. Hoffmann, *Synthesis* **2006**, 3531; (c) V. Sofiyev, G. Navarro, D. Trauner, *Org. Lett.* **2008**, *10*, 149.
[8] *Organic Synthesis* (Eds.: J.-H. Fuhrhop, G. Li) Wiley-VCH, Weinheim, **2003**.
[9] *Handbook of Functionalized Oganometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.
[10] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596.
[11] 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.

hand but still allow the presence of versatile functional groups.[12] A main drawback of organocopper reagents is their thermal instability as well as their preparation from other organometallic species such as organolithium or organomagnesium reagents.[13] In contrast, organozinc reagents generally are stable even at elevated temperature. Thus, they are less reactive and often require suitable transition metal catalysis to undergo reactions with electrophiles.[14] However, this limited reactivity goes in line with an exceptional functional group tolerance.[15] Despite their stability and functional group tolerance, organozinc reagents are rarely used in total syntheses.[16] Their moderate reactivity towards standard organic electrophiles is compensated by their high reactivity in transition metal catalyzed cross-coupling reactions. Due to a relatively fast transmetalation, Pd-catalyzed *Negishi* coupling reactions usually proceed faster and under milder conditions than the corresponding *Stille* or *Suzuki* couplings. The applicability of a *Negishi*-coupling of highly functionalized building blocks was impressively shown by *Smith* in the gram-scale synthesis of discodermolide (**1**, Scheme 1).[17]

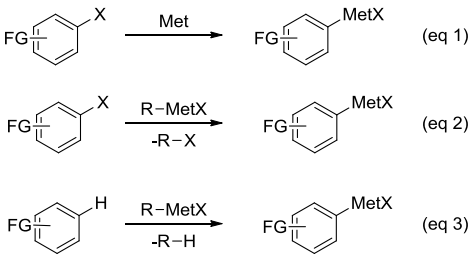


Scheme 1: Total synthesis of discodermolide (**1**) using a *Negishi* cross-coupling.

Iodine-lithium exchange on alkyl iodide **2** using *t*BuLi (3 equiv.) in the presence of $ZnCl_2$ leads to the asymmetric diorganozinc reagent **3** which undergoes a smooth cross-coupling reaction with the alkenyl iodide **4** affording in 66 % yield the highly functionalized product **5**, a precursor of discodermolide (**1**).

[12] (a) P. Knochel, M. J. Rozema, C. E. Tucker, *Preparation of Highly Functionalized Copper Reagents* in *Practical Approach Series in Chemistry - Organocopper Reagents*, (Ed.: R. J. K. Taylor), Oxford University Press, **1993**, 348; (b) *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**.
[13] (a) *Organometallics in Organic Synthesis* (Ed.: E.-i. Negishi), Wiley, New York, **1980**; (b) for halogen-copper exchange reactions see: (i) X. Yang, T. Rotter, C. Piazza, P. Knochel, *Org. Lett.* **2003**, *8*, 1229; (ii) X. Yang, P. Knochel, *Synlett* **2004**, *1*, 81; (iii) M. I. Calaza, X. Yang, D. Soorukram, P. Knochel, *Org. Lett.* **2004**, *8*, 1229; (iv) X. Yang, A. Althammer, P. Knochel, *Org. Lett.* **2004**, *6*, 1665; (c) for a direct insertion of highly reactive copper see: (i) G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1984**, *49*, 5280; (ii) R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 5056; (iii) G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1988**, *53*, 4482.
[14] (a) *Metal-Catalyzed Cross-Coupling Reactions 2nd Ed.* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; (b) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley-Interscience, New York, **2002**; (c) *Transition Metals for Organic Synthesis 2nd Ed.* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2002**.
[15] (a) P. Knochel, N. Millot, A. L. Rodriguez, *Org. React.* **2001**, *58*, 417; (b) *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**.
[16] K. C. Nicolaou, P. Bulger, S. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[17] (a) A. B. Smith III, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. Qiu, H. Arimoto, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8654; (b) A. B. Smith III, M. D. Kaufman, T. J. Beauchamp, M. J. LaMarche, H. Arimoto, *Org. Lett.* **1999**, *1*, 1823.

Besides transmetalation reactions from other organometallics, there are generally three methods for the synthesis of functionalized organometallics (Scheme 2): (i) a direct metal insertion (eq 1); (ii) a halogen-metal exchange reaction (eq 2); (iii) a direct metalation via C-H activation (eq 3).

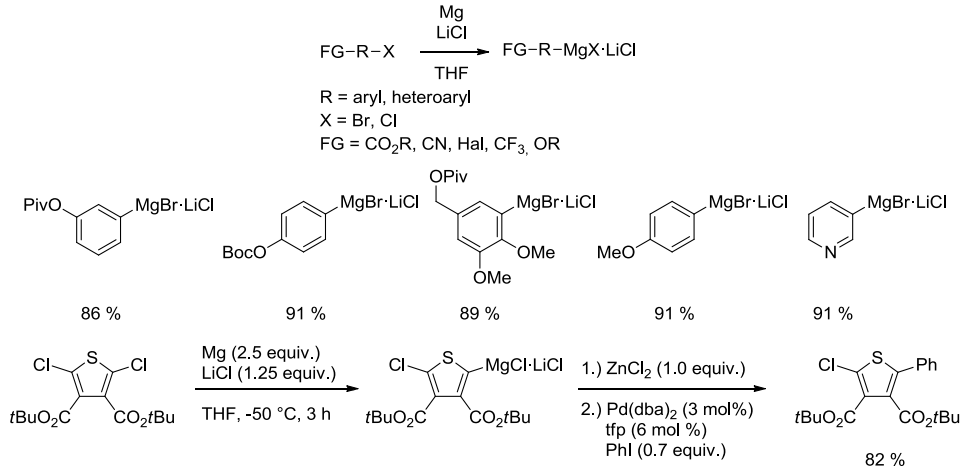


Scheme 2: General methods for the synthesis of organometallics.

2 Organomagnesium Reagents

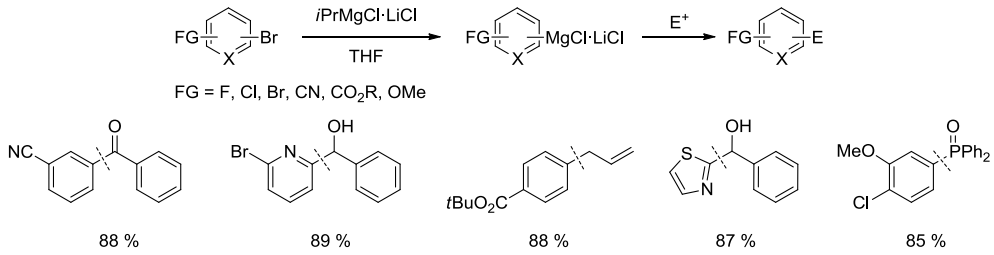
Since the times when *Victor Grignard* in 1900 prepared organomagnesium reagents for the first time more than 100 years have passed. Nowadays, these so called *Grignard* reagents are versatile nucleophiles and widely used in chemical laboratories and have found their way to chemical industry.[18] The direct magnesium insertion into a carbon-halogen bond is still the mostly used protocol for the synthesis of *Grignard* reagents (Scheme 2, eq 1). As the insertion reaction according to the standard protocols is highly exothermic and normaly performed at the boiling point of the solvent (Et_2O or THF), the functional group tolerance is limited and the preparation in plant scale is accompanied with safety risks.[19] Highly reactive magnesium prepared via reduction of magnesium salts using lithium naphthalide allows the synthesis of functionalized organomagnesium reagents even at low temperatures.[20] The drawback of the prior preparation of the highly active magnesium can be avoided by the use of stoichiometric amounts of LiCl (Scheme 3).[21]

[18] (a) V. Grignard, *Compt. Rend.* **1900**, *130*, 1322; (b) *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **2000**; (c) *Grignard Reagents, New Developments* (Ed.: H. G. Richey Jr.), Wiley & Sons, New York, **2000**; (d) J. Wiss, M. Länzlinger, M. Wermuth, *Org. Proc. Res. Dev.* **2005**, *9*, 365.
[19] M. C. Jones, *Plant and Operations Progress* **1989**, *8*, 200.
[20] (a) R. D. Rieke, *Science* **1989**, *246*, 1260; (b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925.
[21] (a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; (b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.



Scheme 3: Synthesis of organomagnesium reagents using Mg in the presence of LiCl.

According to the well established halogen-lithium exchange reaction developed by *Wittig* and *Gilman*,[22] the corresponding halogen-magnesium exchange reaction allows an efficient preparation of *Grignard* reagents (Scheme 2, eq 2).[23] *Knochel et al.* developed a general protocol for an iodine-magnesium exchange on functionalized aromatic iodides using *i*PrMgBr or PhMgCl.[24] With the development of the reagent *i*PrMgCl·LiCl, the halogen-magnesium exchange reaction could be further improved. This reagent allows the general preparation of organomagnesium reagents starting from aromatic and heteroaromatic bromides (Scheme 4).[25]



Scheme 4: *i*PrMgCl·LiCl as reagent for the bromine-magnesium exchange.

Besides these two halogen-metal interconversions, a direct magnesiation using magnesium amide bases is the third major pathway to magnesium organometallics.[26] The recently developed "Turbo-Hauser" bases TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ allow efficient deprotonations of various functionalized aromatics and heteroaromatics (Scheme 5).[27]

[22] (a) G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903; (b) R. G. Jones, H. Gilman, *Org. React.* **1951**, *6*, 339; (c) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106.
[23] (a) C. Prévost, *Bull. Chem. Soc. Fr.* **1931**, *49*, 1372; (b) J. Villéras, *Bull. Chem. Soc. Fr.* **1967**, *5*, 1520; (c) J. Villéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Chem. Soc. Fr.* **1986**, *24*, 470.
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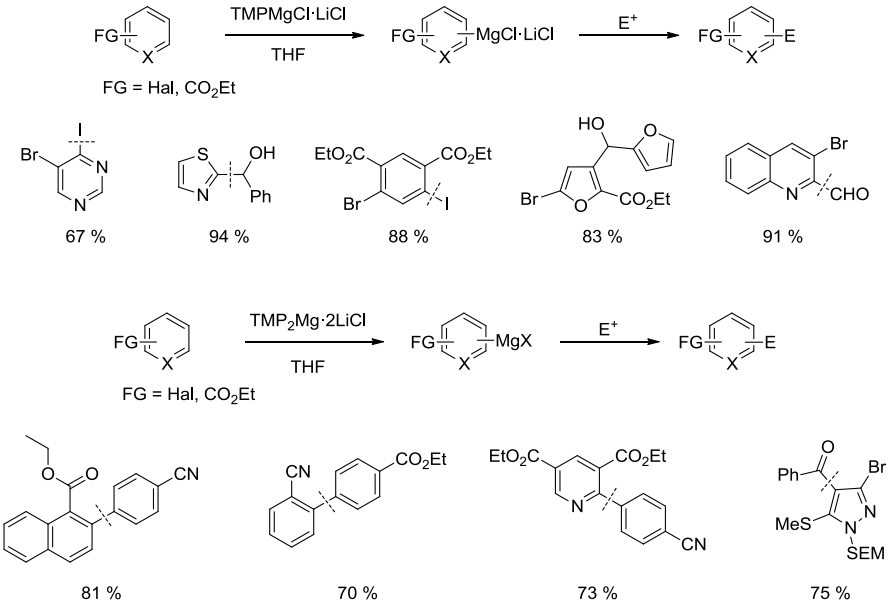
[25] (a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *41*, 1610; (b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159; (c) H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726; (d) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; (e) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.
[26] (a) L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758; (b) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; (c) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350; (d) A. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.
[27] (a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; (b) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525; (c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497; (d) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113; (e) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; (f) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, *86*, 374; (g) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *47*, 1503.

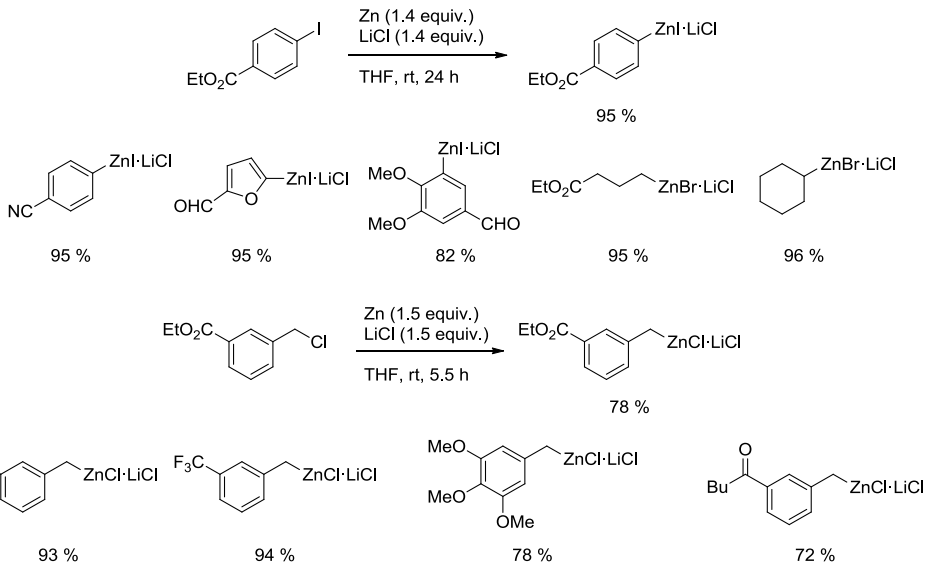


Scheme 5: Direct magnesiation using "Turbo-Hauser" bases TMPMgCl·LiCl and $TMP_2Mg·2LiCl$.

3 Organozinc Reagents

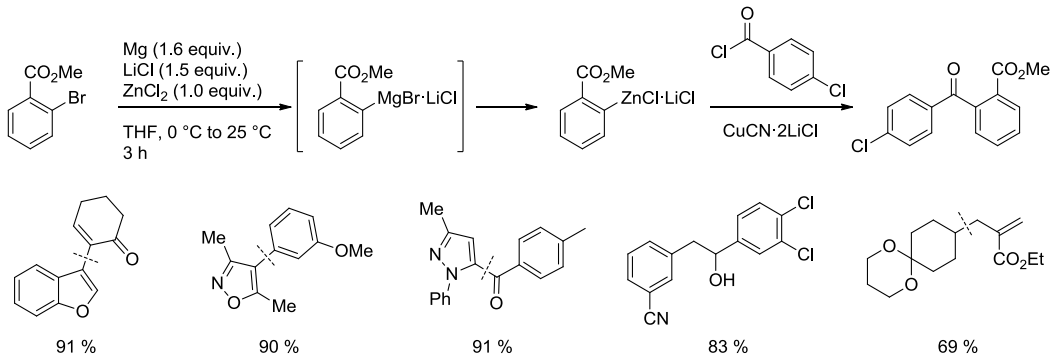
The most common method for the direct synthesis of organozinc reagents is the direct insertion of zinc dust in organic halides (Scheme 2, eq 1).[28, 15] Although organozinc reagents were already discovered in the middle of the 19th century by *Frankland*,[29] their potential in organic synthesis laid idle for over 50 years.[30] Their resurrection began in 1936 with the synthesis of ester substituted alkyl zinc iodides starting from the corresponding alkyl iodides and zinc dust by *Hunsdiecker*.[31] Based on this work, a broad range of organozinc iodides could be prepared often at elevated temperature and in polar solvents such as dimethylacetamide, HMPA, DMF, or DMSO.[32] Alternatively, highly active zinc metal prepared *via* reduction of $ZnCl_2$ with lithium naphthalide, allows a smooth conversion of organic halides to the corresponding organozinc reagents.[33, 20] A simple and efficient method for the preparation of organozinc reagents using commercially available zinc dust in the presence of LiCl was developed by *Knochel et al.*[34] Besides aromatic iodides, also alkyl bromides and benzyl chlorides react in the LiCl-mediated Zn insertion to form the corresponding zinc reagents (Scheme 6).

[28] "Polyfunctional Zinc Organometallics for Organic Synthesis": P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel, *Handbook of Functionalized Organometallics, Vol. 1* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**, p. 251.
[29] E. Frankland, *Liebigs Ann. Chem.* **1848**, *71*, 171.
[30] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.
[31] H. Hunsdiecker, H. Erlbach, E. Vogt, *German Patent 722467*, **1942**.
[32] (a) K. Tagaki, N. Hayama, S. Inokawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691; (b) K. Tagaki, *Chem. Lett.* **1994**, 469; (c) K. Tagaki, Y. Shimoishi, K. Sasaki, *Chem. Lett.* **1994**, 2055; (d) T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413.
[33] (a) M. V. Hanson, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; (b) R. D. Rieke, P. T.-T. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323.
[34] (a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; (b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.



Scheme 6: LiCl-mediated preparation of functionalized organozinc reagents.

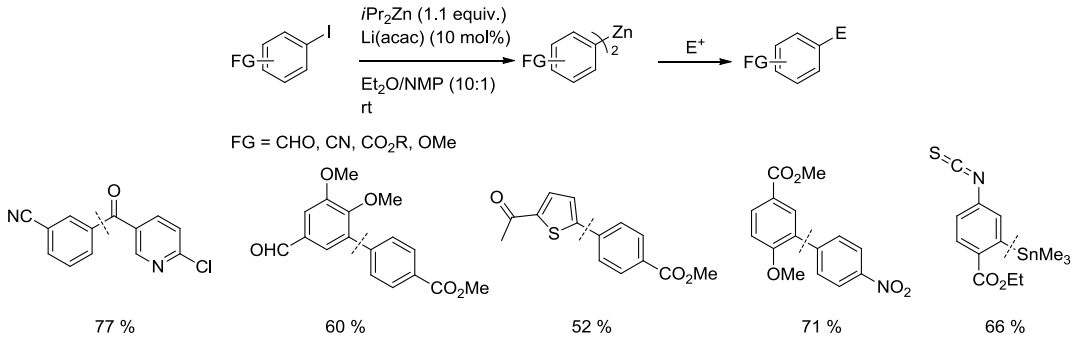
Recently, a second insertion method leading to functionalized organozinc reagents *via* LiCl-mediated magnesium insertion in the presence of $ZnCl_2$ was developed.[21, 35] This method uses the higher reduction potential of Mg to form a highly reactive organomagnesium reagent which is *in situ* trapped with $ZnCl_2$ leading to the more stable zinc organometallic (Scheme 7).



Scheme 7: Preparation of functionalized zinc reagents *via* LiCl-mediated magnesium insertion in the presence of $ZnCl_2$.

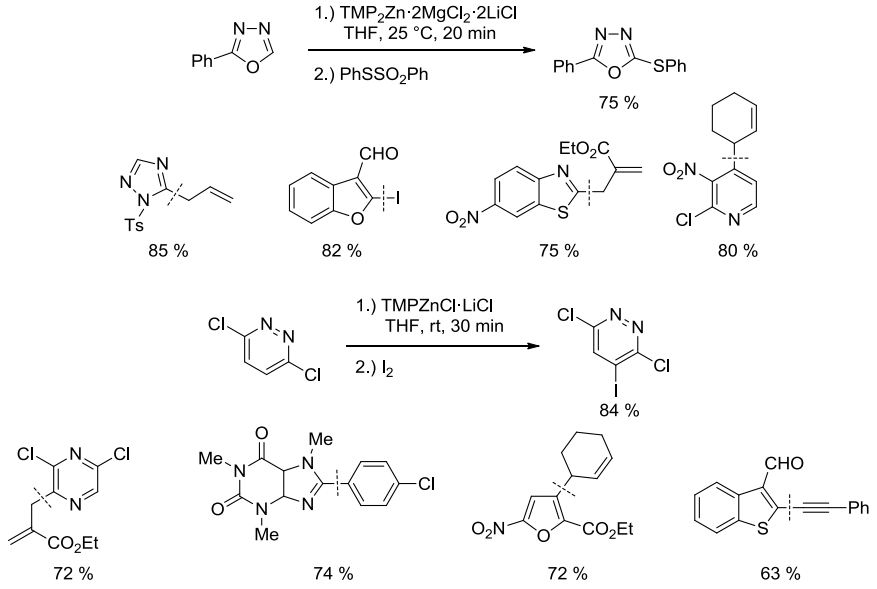
Another way for the synthesis of organozinc reagents with high functional group tolerance is the halogen-zinc exchange reaction (Scheme 2, eq 2).[36] Whereas catalytic amounts of Cu(I)-salts facilitate the iodine-zinc exchange on alkyl iodides,[37] *Knochel et al.* demonstrated that $(i\text{Pr})_2Zn$ in the presence of Li(acac) allows the convenient conversion of aromatic iodides to their diorganozinc derivatives (Scheme 8).[38]

[35] (a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; (b) T. Blümke, F. M. Piller P. Knochel, *Chem. Commun.* **2010**, 4082.
[36] M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956.
[37] M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115.
[38] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.



Scheme 8: Iodine-zinc exchange on aromatic iodides and subsequent reaction with electrophiles.

Inspired by the work on the "Turbo-Hauser" bases, the mild and chemoselective bases $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ and TMPZnCl·LiCl were developed for the hydrogen-metal interconversion on sensitive substrates.[39] A variety of sensitive heterocycles such as 2-phenyl-1,3,4-oxadiazole, *N*-tosyl-1,2,4-triazole or 3,6-dichloropyridazine are smoothly zincated and important functionalities such as nitro groups or aldehydes can be tolerated (Scheme 9).

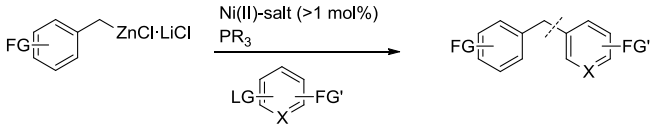


Scheme 9: Zincation of sensitive heterocycles using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ and TMPZnCl·LiCl.

[39] (a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *47*, 7685; (b) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837.

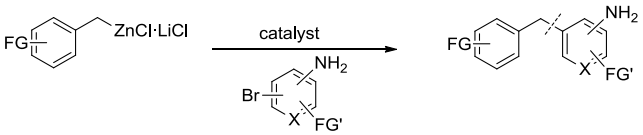
4 OBJECTIVES

The aim of the first topic was the development of a novel Ni-catalyzed cross-coupling reaction of benzylic zinc reagents prepared *via* LiCl-mediated insertion of Zn-dust in benzylic chlorides. The catalyst system should combine a cheap Ni(II)-salt, a simple phosphine ligand and a low catalyst loading with the possibility to use aromatic and heteroaromatic bromides, chlorides and tosylates as electrophiles (Scheme 10).



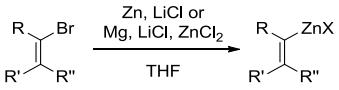
Scheme 10: Nickel-catalyzed cross-coupling of aromatic and heteroaromatic bromides, chlorides and tosylates.

Furthermore, the catalytic system should allow the coupling of bromoanilines bearing relatively acidic NH-protons (Scheme 11).



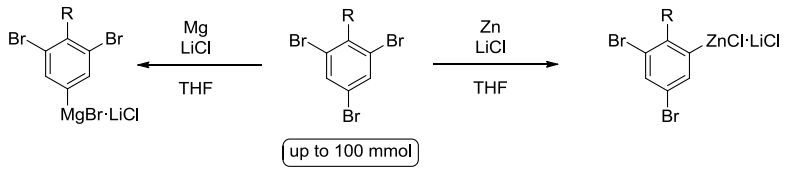
Scheme 11: Negishi-coupling of benzylic zinc reagents with bromoaniline derivatives.

As the addition of LiCl to various insertion reactions allows the simple preparation of alkyl, aryl, and benzylic zinc reagents, a general method for the synthesis of alkenyl zinc reagents starting from the corresponding unsaturated bromides should be developed (Scheme 12).



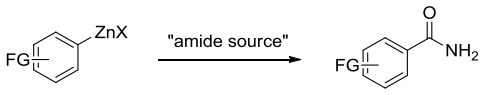
Scheme 12: Preparation of alkenyl zinc reagents.

A further project was the extension of the scope of the directed *ortho* insertion (DoI) of zinc and the orthogonal *para* insertion of magnesium in polybrominated arenes (Scheme 13). The scale-up of these reactions up to 100 mmol should demonstrate the industrial applicability of this method.



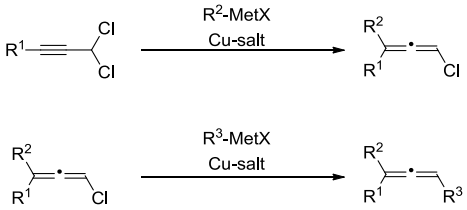
Scheme 13: Directed *ortho* insertion (DoI) of zinc and orthogonal magnesium insertion in polybrominated arenes.

As primary amides are important pharmacophores, a simple method for their preparation from functionalized organozinc reagents would be highly desireable. Therefore, a general one-pot procedure for the conversion of aromatic, heteroaromatic, alkenyl and alkynyl zinc reagents leading to primary amides should be developed (Scheme 14).



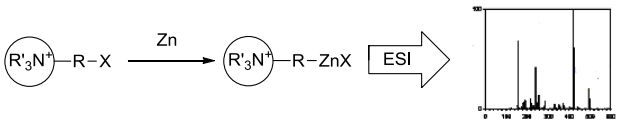
Scheme 14: Synthesis of primary amides from functionalized organozinc reagents.

Allenes have found increasing interest in organic chemistry, as they are either target molecules or intermediates in the synthesis of complex systems. Thus, a synthesis of highly functionalized allenes from readily available starting materials using two successive copper-mediated substitution reactions was envisioned (Scheme 15).



Scheme 15: Strategy towards highly functionalized allenes using successive copper-mediated substitutions.

Finally, the structure of organozinc reagents should by elucidated *via* electrospray ionization mass spectrometry. Therefore, organozinc reagents bearing a quaternary ammonium group as charged tag had to be synthesized and subjected to ESI mass-spectrometry (Scheme 16).



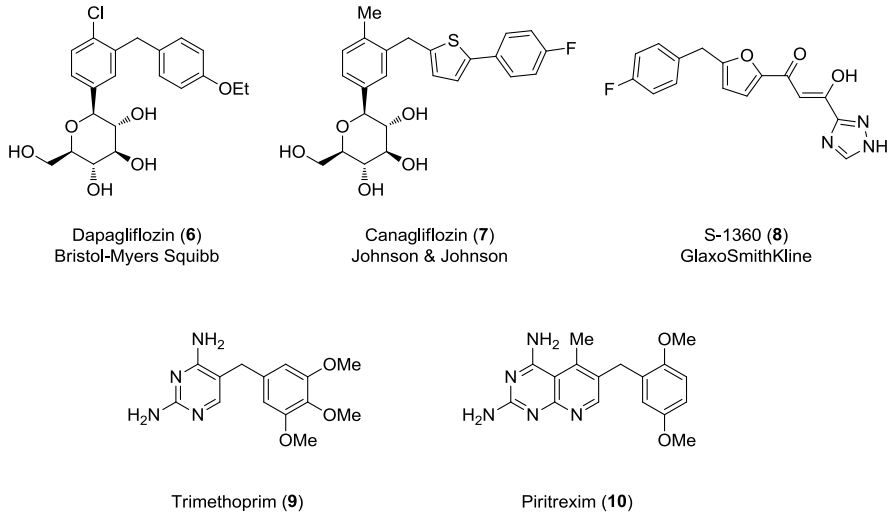
Scheme 16: Synthesis of organozinc reagents bearing a charged tag for structure elucidation *via* ESI mass-spectrometry.

B RESULTS AND DISCUSSION

1 Cross-Coupling Reactions of Benzylic Zinc Reagents

1.1 Introduction

Diarylmethanes are an important class of compounds with biological or pharmacological activity.[40] For example Dapagliflozin (**6**), developed by Bristol-Myers Squibb, or Canagliflozin (**7**), developed by Johnson & Johnson, are selective SGLT2 inhibitors currently in clinical trial against diabetes type 1 and 2 (Scheme 17).[41] Shionogi-GlaxoSmithKline Pharmaceuticals have developed S-1360 (**8**), a HIV integrase inhibitor which is in clinical trial, also bearing a diarylmethane motif.[42]



Scheme 17: Pharmaceutically active diarylmethanes.

Also, more simple diarylmethanes such as Trimethoprim (**9**),[43] a widely used bacteriostatic antibiotic, or Piritrexim (**10**),[44] a folate antagonist which is in clinical trial against cancer, show biological activity and illustrate the importance of an efficient synthesis strategy towards these methylene-linked biaryls.

[40] (a) 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; (b) 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; (c) Y.-Y. Ku, R. R. Patel, D. P. Sawick, *Tetrahedron Lett.* **1996**, *37*, 1949; (d) H. Juteau, Y. Gareau, M. Labelle, C. F. Sturino, N. Sawyer, N. Tremblay, S. Lamontagne, M.-C. Carrière, D. Denis, K. M. Metters, *Bioorg. Med. Chem.* **2001**, *9*, 1977.

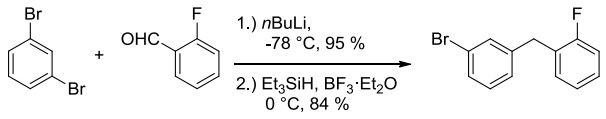
[41] (a) W. Meng, B. A. Ellsworth, A. A. Nirschl, P. J. McCann, M. Patel, R. N. Girotra, G. Wu, P. M. Sher, E. P. Morrison, S. A. Biller, R. Zahler, P. P. Deshpande, A. Pullockaran, D. L. Hagan, N. Morgan, J. R. Taylor, M. T. Obermeier, W. G. Humphreys, A. Khanna, L. Discenza, J. G. Robertson, A. Wang, S. Han, J. R. Wetterau, E. B. Janovitz, O. P. Flint, J. M. Whaley, W. N. Washburn, *J. Med. Chem.* **2008**, *51*, 1145; (b) B. Xu. B. Lv, Y. Feng, G. Xu, J. Du, A. Welihinda, Z. Sheng, B. Seed, Y. Chen, *Bioorg. Med. Chem.* **2009**, *19*, 5632; (c) S. Nomura, S. Sakamaki, M. Hongu, E. Kawanishi, Y. Koga, T. Sakamoto, Y. Yamamoto, K. Ueta, H. Kimata, K. Nakayama, M. Tsuda-Tsukimoto, *J. Med. Chem.* **2010**, *53*, 6355.

[42] (a) S. Shimizu, T. Endo, K. Izumi, H. Mikamiyama, *Org. Proc. Res. Dev.* **2007**, *11*, 1055; (b) Y.-Q. Long, X.-H. Jiang, R. Dayam, T. Sanchez, R. Shoemaker, S. Sei, N. Neamati, *J. Med. Chem.* **2004**, *47*, 2561.

[43] (a) R. N. Brogden, A. A. Carmine, R. C. Heel, T. M. Speight, G. S. Avery, *Drugs* **1982**, *23*, 405; (b) B. Roth, E. A. Falco, G. H. Hitchings, S. R. M. Bushby, *J. Med. Pharm. Chem.* **1962**, *5*, 1103; (c) B. Roth, J. Z. Strelitz, B. S. Rauckman, *J. Med. Chem.* **1980**, *23*, 379.

[44] (a) A. Rosowsky, C. E. Mota, J. E. Wright, S. F. Queener, *J. Med. Chem.* **1994**, *37*, 4522; (b) L. G. Feun, R. Gonzalez, N. Savaraj, J. Hanlon, M. Collier, W. A. Robinson, N. J. Clendeninn, *J. Clin. Oncol.* **1991**, *9*, 464.

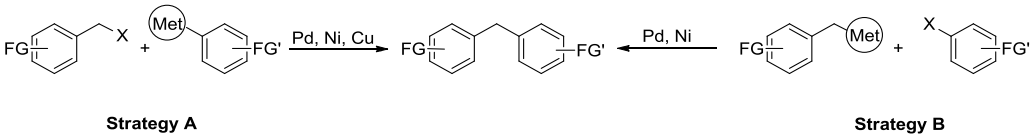
So far, the most popular route to diarylmethanes is the addition of organometallic reagents to benzaldehydes followed by reduction (Scheme 18).[45]



Scheme 18: Synthesis of a diarylmethane *via* addition of an organolithium reagent to 2-fluorobenzaldehyde and subsequent reduction.

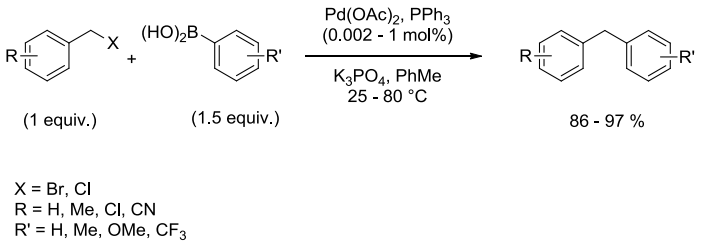
Besides the fact that for the synthesis of the relatively simple diarylmethane a two-step sequence is used, the biggest drawback of this method is the low functional group tolerance towards the nucleophile and the electrophile.

A more concise strategy to substituted diarylmethanes involves the cross-coupling reaction of either an aryl organometallic with a benzylic halide (strategy A) or a benzylic organometallic reagent with an aryl halide (strategy B, Scheme 19).



Scheme 19: Synthesis of diarylmethanes starting from benzylic or aryl organometallics.

Compared to aryl-aryl-cross-coupling reactions, only few examples are known for the reaction of aryl organometallics with benzylic halides.[46] A simple and efficient method for the *Suzuki-Miyaura* coupling of arylboronic acids with benzylic halides using $Pd(OAc)_2$ and PPh_3 as catalyst was developed by *Monteiro* (Scheme 20).[46d]



Scheme 20: Cross-coupling of arylboronic acids with benzylic halides according to *Monteiro*.

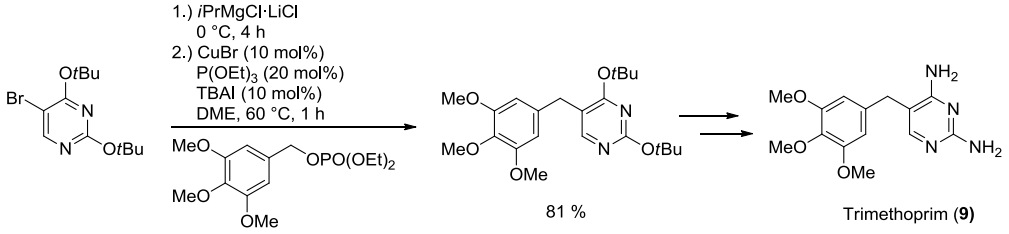
Although this method provides high yields, the scope of the reaction is limited to only a few non-sensitive substituents. Extension of this work, i.e. by *Kuwano* or *McLaughlin* allows the use of benzylic carbonates, acetates and phosphates as electrophiles instead of the corresponding

[45] (a) D.A. Barda, Z.-Q. Wang, T. C. Britton, S. S. Henry, G. E. Jagdmann, D. S. Coleman, M. P. Johnson, S. L. Andis, D. D. Schoepp, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3099; (b) Y.-Q. Long, X.-H. Jiang, R. Dayam, T. Sanchez, R. Shoemaker, S. Sei, N. Neamati, *J. Med. Chem.* **2004**, *47*, 2561; (c) X. Wu, A. K. Mahalingam, M. Alterman, *Tetrahedron Lett.* **2005**, *46*, 1501; (d) P. E. Gordon, A. J. Frey, *Tetrahedron Lett.* **2001**, *42*, 831; (e) N. L'Hermite, A. Giraud, O. Provot, J.-F. Peyrat, M. Alami, J.-D. Brion, *Tetrahedron* **2006**, *62*, 11994.

[46] (a) H. Juteau, Y. Gareau, M. Labelle, S. F. Sturino, N. Sawyer, N. Tremblay, S. Lamontagne, M.-C. Carriere, D. Denis, K. M. Metters, *Bioorg. Med. Chem.* **2001**, *9*, 1977; (b) C. Klaner, A. Greiner, *Macromol. Rapid Commun.* **1998**, *19*, 605; (c) N. Miyaura, T. Yano, A. Suzuki, *Tetrahedron Lett.* **1980**, *21*, 2865; (c) M. J. Sharp, V. Snieckus, *Tetrahedron Lett.* **1985**, *26*, 5997; (d) S. N. Nobre, A. L. Monteiro, *Tetrahedron Lett.* **2004**, *45*, 8225.

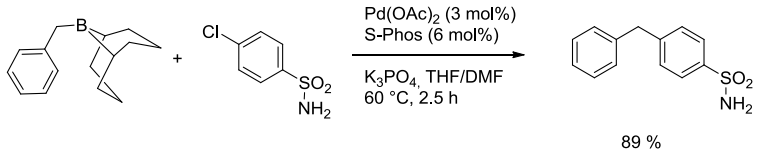
halides.[47, 48] Also the nucleophile is not limited to arylboronic acids. *Molander* showed that the cross-coupling of potassium aryltrifluoroborates with benzylic halides proceeds with only small excess of the nucleophile in excellent yields.[49]

As a manifold of functionalized *Grignard*-reagents has become available by simple and efficient halogen-magnesium exchange or direct metal insertion, a direct synthesis of diarylmethanes starting from magnesium organometallics was developed by *Knochel*.[21, 24, 25, 50] Starting from readily available functionalized *Grignard*-reagents and benzylic phosphates, a Cu(I)-mediated coupling reaction using CuBr (10 mol%) and $P(OEt)_3$ (20 mol%) as catalyst with TBAI (10 mol%) as additive in DME leads to highly functionalized diarylmethanes in excellent yields (Scheme 21).



Scheme 21: Synthesis of Trimethoprim (**9**) *via* copper-mediated coupling of an organomagnesium reagent with a benzylic phosphate.

Strategy B towards functionalized diarylmethanes starts from a benzylic organometallic reagent and an aryl halide (Scheme 19). Although the synthesis of benzylic boronates *via* the borylation of benzyl halides with pinacolborane/diborane is well established, their use in *Suzuki-Miyaura* coupling reactions is only rarely described in the literature.[51] A direct cross-coupling of benzylboranes, such as *B*-benzyl-9-BBN with numerous aryl and heteroaryl halides was reported in 2005 by *Flaherty* (Scheme 22).[52]



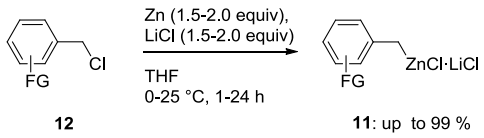
Scheme 22: *Suzuki-Miyaura* coupling of a benzylborane with a chloro-sulfonamide according to *Flaherty*.

Other functionalized benzylic organometallics, such as benzylic lithium or magnesium reagents are, due to their high reactivity, rarely known and have never been used in direct cross-coupling reactions.[53] Less reactive benzylic organometallics such as benzylic organostannanes or benzylic

[47] (a) R. Kuwano, M. Yokogi, *Org. Lett.* **2005**, *7*, 945; (b) R. Kuwano, M. Yokogi, *Chem. Commun.* **2005**, 5899.
[48] M. McLaughlin, *Org. Lett.* **2005**, *7*, 4875.
[49] G. A. Molander, M. D. Elia, *J. Org. Chem.* **2006**, *71*, 9198.
[50] C. C. Kofink, P. Knochel, *Org. Lett.* **2006**, *8*, 4121.
[51] (a) A. Giroux, *Tetrahedron Lett.* **2003**, *44*, 233; (b) M Murata, T. Oyama, S. Watanabe, Y. Masuda, *Synth. Commun.* **2002**, *32*, 2513.
[52] A. Flaherty, A.Trunkfield, W. Barton, *Org. Lett.* **2005**, *7*, 4975.
[53] A. H. Stoll, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *118*, 621.

manganese reagents suffer from either high toxicity or complicated synthesis and are relegated to a niche existence.[54]

Recently, we have developed a general method for the preparation of highly functionalized benzylic zinc reagents **11** derived from benzylic chlorides **12** using zinc dust and LiCl (Scheme 23).

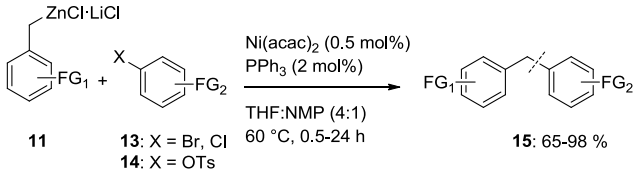


Scheme 23: Synthesis of highly functionalized benzylic zinc reagents.

Remarkably, this method tolerates the presence of important functional groups such as an ester, a ketone and a cyanide.[34b] Although, there are some reports of transition metal-catalyzed cross-coupling reactions of benzylic zinc reagents, this method broadens dramatically the scope of a direct synthesis of diarylmethanes.[55]

1.2 Nickel-Catalyzed Cross-Coupling Reactions of Benzylic Zinc Reagents

Due to the high toxicity and the high price of Pd-catalysts and their highly sophisticated ligands, a catalytic system consisting of a cheap Ni-salt and a simple phosphine ligand is highly desireable. Thus, a Ni-catalyzed cross-coupling reaction[56] of polyfunctionalized benzylic zinc reagents of type **11** with aryl halides (**13**) and tosylates (**14**) was developed (Scheme 24). Although, many ligands have been tested, it was found as a highly efficient, cheap and convenient catalytic system PPh_3 (2 mol%) combined with $Ni(acac)_2$ (0.5 mol%)[57] in a mixture of THF and NMP. Under these conditions, a broad range of aromatic and heteroaromatic halides (bromides and chlorides, Table 1) and tosylates (Table 2) undergo a smooth cross-coupling leading to polyfunctional diarylmethanes of type **15**.

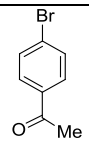
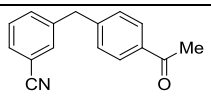
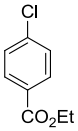
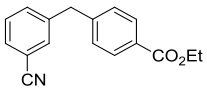
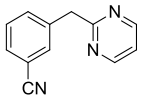
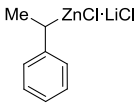
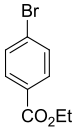
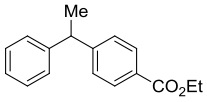
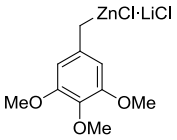
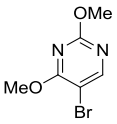
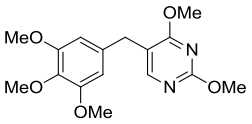
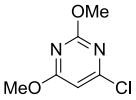
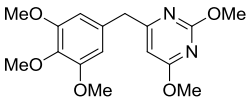
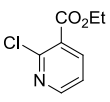
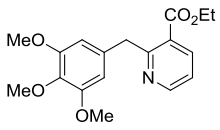


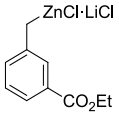
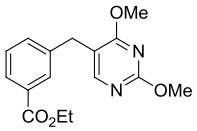
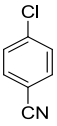
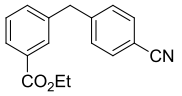
Scheme 24: Ni-catalyzed cross-coupling reaction of benzylic zinc reagents with aromatic halides and tosylates.

[54] (a) L.-L. Gundersen, *Tetrahedron Lett.* **1994**, *35*, 3155; (b) L.-L.Gundersen, A. K. Bakkestuen, A. J. Aasen, H. Øverås, F. Rise, *Tetrahedron* **1994**, *50*, 9743; (c) S. Usse, G. Guillaumet, M.-C. Viaud, *Tetrahedron Lett.* **1997**, *38*, 5501; (d) K. Mori, S. Maki, H. Niwa, H. Ikeda, T. Hirano, *Tetrahedron* **2006**, *62*, 6272; (e) Y.S. Suh, J.-s. Lee, S.-H. Kim, R. D. Rieke, *J. Organomet. Chem.* **2003**, *684*, 20.
[55] E.-i. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821
[56] (a) R. M. Moslin, K. Miller-Moslin, T. F. Jamison, *Chem. Commun.* **2007**, 4441; (b) A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Org. Lett.* **2005**, *7*, 4871; (c) J. W. Han, N. Tokunaga, T. Hayashi, *Synlett* **2002**, *6*, 871; (d) E. Shirakawa, K. Yamasaki, T. Hiyama, *Synthesis* **1998**, *10*, 1544; (e) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222; (f) J. Terao, S. Nii, F. A. Chowdhury, A. Nakamura, N. Kambe, *Adv. Synth. Cat.* **2004**, *346*, 905; (g) V. Percec, J.-Y. Bae, D. H. Hill, *J. Org. Chem.* **1995**, *60*, 6895; (h) S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 2756; (i) C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594; (j) J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 14726.
[57] E.-i. Negishi, H. Matsushita, N. Okukado, *Tetrahedron Lett.* **1981**, *22*, 2715.

Thus, the reaction of 3-cyanobenzylzinc chloride (**11a**, 1.2 equiv.) with 4-bromoacetophenone (**13a**) at 60 °C (0.5 h) using $Ni(acac)_2$ (0.5 mol%) and PPh_3 (2 mol%) in THF:NMP (4:1 mixture) afforded the desired diarylmethane **15a** in 75 % yield (Table 1, entry 1). Also, aromatic chlorides such as **13b** and 2-chloropyrimidine (**13c**) react readily within 30 min to the corresponding diarylmethanes (**15b**: 89 %, **15c**: 69 %, entries 2 and 3).

Table 1: $Ni(acac)_2$ and PPh_3 catalyzed cross-coupling reactions between functionalized benzylic zinc reagents (**11**) and aryl chlorides and bromides (**13**).

Entry	Zinc Reagent[a]	Electrophile	Diarylmethane Reaction Time (h)	Yield [%][b]
1			 (0.5)	
	11a	**13a**	**15a**	75
2			 (0.5)	
	11a	**13b**	**15b**	89
3			 (0.5)	
	11a	**13c**	**15c**	69
4			 (12)	
	11b	**13d**	**15d**	95
5			 (2)	
	11c	**13e**	**15e**	86
6			 (2)	
	11c	**13f**	**15f**	98
7			 (1)	
	11c	**13g**	**15g**	96

8			 (1.5)	
	11d	**13e**	**15h**	84
9			 (0.5)	
	11d	**13h**	**15i**	91

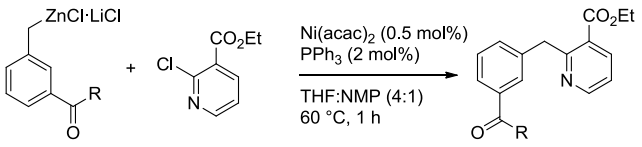
[a]For the cross-coupling reaction, 1.2 equiv. of the zinc reagent is used; [b]Isolated yield of analytically pure product.

The reaction of the secondary benzylic zinc chloride **11b** with ethyl 4-bromobenzoate (**13d**) affords the 1,1-bisarylethane within 12 h at 60 °C (**15d**, 95 %, entry 4).

The cross-coupling of an electron rich benzylic zinc chloride such as 3,4,5-trimethoxybenzylzinc chloride (**11c**) with the protected uracil **13e** affords the uracil derivative **15e**, a precursor of Trimethoprim (**9**),[58] in 86 % yield (entry 5). The isomeric uracil derivative **15f** was also prepared by cross-coupling of **11c** with 4-chloro-2,6-dimethoxypyrimidine (**13f**) in 98 % yield (entry 6). Ethyl 2-chloronicotinate (**13g**) is also a suitable substrate for the cross-coupling of **11c** and leads to the nicotinic acid derivative **15g** in almost quantitative yield (96 %, entry 7).

Moreover, an electron poor benzylic zinc chloride bearing a carbethoxy function in *meta* position (**11d**) undergoes a smooth reaction with the protected uracil **13e** to afford **15h** in 84 % yield (entry 8). Its cross-coupling with 4-chlorobenzonitrile (**13h**) leads to the diarylmethane **15i** (60 °C, 30 min) in 91 % yield (entry 9).

Remarkably, benzylzinc chlorides bearing keto groups in *meta* position react as well. Thus, the reaction of 3-pentanoylbenzylzinc chloride (**11e**) with the chloropyridine **13g** leads to the nicotinic acid derivative **15j** in 90 % yield (Scheme 25). Even the sensitive acetyl-substituted benzylic zinc reagent (**11f**), added over 30 min *via* syringe pump, reacts with the chloropyridine (**13g**) without significant enolization to the nicotinic acid derivative **15k** in 68 % yield.



11e: R = Bu
11f: R = Me

13g

15j: R = Bu: 90 %
15k: R = Me: 68 %

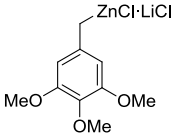
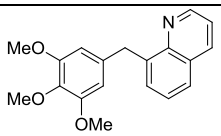
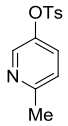
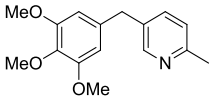
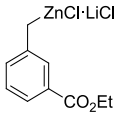
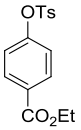
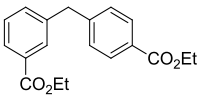
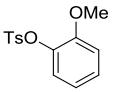
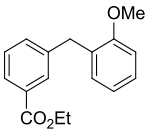
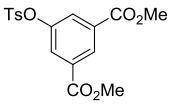
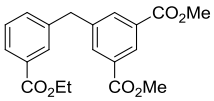
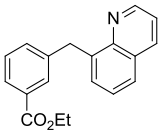
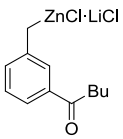
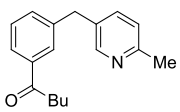
Scheme 25: Ni-catalyzed cross-coupling reaction of keto-substituted benzylic zinc reagents **11e** and **11f** with ethyl 2-chloronicotinate (**13g**).

Various aromatic and heteroaromatic tosylates, which are easily available from the corresponding phenols,[59] are efficient cross-coupling partners. Thus, aryl tosylates **14a** and **14b** react with 3,4,5-trimethoxybenzylzinc chloride **11c** to give the corresponding diarylmethanes

[58] C. C. Kofink, P. Knochel, *Org. Lett.* **2006**, *8*, 18, 4121.
[59] C.-H. Cho, H.-S. Yun, K. Park, *J. Org. Chem.* **2003**, *68*, 3017; Z.-T. Tang, Q.-S. Hu, *J. Am. Chem. Soc.* **2004**, *126*, 3058.

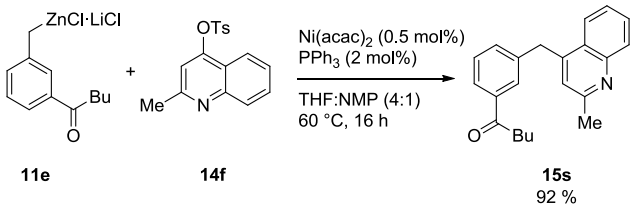
15l and **15m** in yields up to 90 % (Table 2, entries 1 and 2). Also the electron-deficient benzylic zinc reagent **11d** undergoes smooth Ni-catalyzed coupling reactions with the phenol-derived tosylates **14c-e** leading to the diarylmethanes **15n-p** in 61-69 % yield (entries 3-5). Its reaction with the heterocyclic tosylate **14a** affords the quinoline derivative **15q** in 69 % yield (entry 6).

Table 2: Ni-catalyzed cross-coupling of benzylic zinc reagents with aromatic and heteroaromatic tosylates.

Entry	Zinc Reagent[a]	Electrophile	Diarylmethane Reaction Time (h)	Yield [%][b]
1			 (12)	
	11c	**14a**	**15l**	82
2	**11c**		 (12)	
		14b	**15m**	90
3			 (2)	
	11d	**14c**	**15n**	65
4	**11d**		 (24)	
		14d	**15o**	69
5	**11d**		 (5)	
		14e	**15p**	61
6	**11d**	**14a**	 (3)	
			15q	69
7		**14b**	 (16)	
	11e		**15r**	84

[a]For the cross-coupling reaction, 1.2 equiv. of the zinc reagent is used; [b]Isolated yield of analytically pure product.

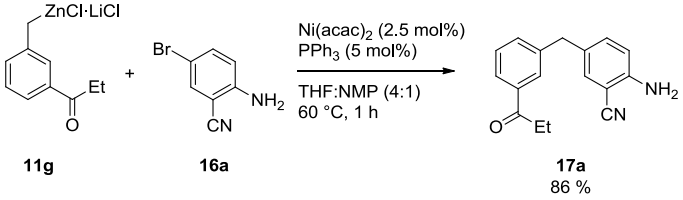
The keto-substituted benzylic zinc reagent **11e** reacts under Ni-catalysis with the heteroaromatic tosylates **14b** and **f** to afford the corresponding diarylmethanes **15r** and **15s** in 84 and 92 % yield, respectively (entry 7 and Scheme 26).



11e **14f** **15s** 92 %

Scheme 26: Cross-coupling of the benzylic zinc reagent **11e** with the heterocyclic tosylate **14f**.

This exceptional reactivity of benzylic zinc reagents in the Ni-catalyzed cross-coupling reaction with various aromatic halides and tosylates and the high reaction rates of the coupling with aromatic bromides (usually 30 min) allows the use of electrophiles bearing relatively acidic protons such as substituted bromoanilines of type **16**. Although organozinc reagents are reactive towards acidic protons, the catalytic system consisting of $Ni(acac)_2$ and PPh_3 in a mixture of THF and NMP allows an efficient cross-coupling reaction of benzylic zinc reagents and bromoaniline derivatives. As the cross-coupling is performed at 60 °C, a certain amount of zinc reagent is quenched by the aniline derivative. Therefore, the catalyst loading is increased to 2.5 mol% of $Ni(acac)_2$ and 5 mol% of PPh_3. Further improvement can be done by addition of the organozinc reagent to a premixed solution of the electrophile and the catalyst in THF/NMP *via* syringe pump. Thus, adding the benzylic zinc reagent **11g** over a period of 1 h to a solution of 4-bromo-2-cyanoaniline (**16a**), $Ni(acac)_2$ (2.5 mol%) and PPh_3 (5 mol%) in THF/NMP affords the amino-functionalized diarylmethane **17a** in 86 % yield (Scheme 27).

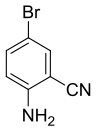
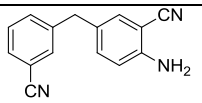
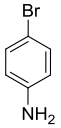
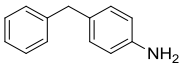
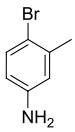
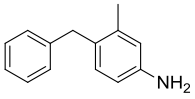
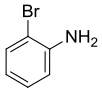
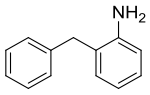
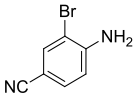
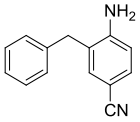
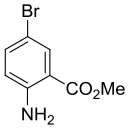
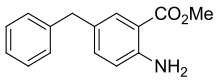
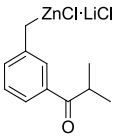
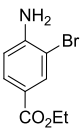
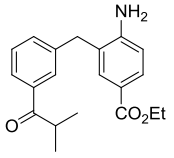


11g **16a** **17a** 86 %

Scheme 27: Ni-catalyzed cross-coupling of keto-substituted benzylic zinc reagent **11g** and bromoaniline derivative **16a**.

In the case of the cyano-substituted benzylic zinc reagent **11a**, the cross-coupling with **16a** occurs satisfactorily to the aniline derivative **17b** in 81 % yield (Table 3, entry 1). Benzylzinc chloride (**11h**) reacts smoothly with the electron-rich bromo-anilines **16b-d** to give the corresponding amino-substituted diarylmethanes **17c-e** in yields up to 90 % (entries 2-4). The cross-coupling of **11h** with cyano or ester substituted bromoanilines **16e** and **16f** to their benzylated derivatives **17f** and **17g** occurs in 77–84 % yield (entries 5 and 6).

Table 3: Ni-catalyzed cross-couplings with aromatic bromides bearing relatively acidic protons.

Entry	Zinc Reagent[a]	Electrophile	Diarylmethane Reaction Time (h)	Yield [%][b]
1			 (1)	
	11a	**16a**	**17b**	81
2			 (1)	
	11h	**16b**	**17c**	90
3			 (0.5)	
	11h	**16c**	**17d**	79
4			 (0.5)	
	11h	**16d**	**17e**	75
5			 (0.5)	
	11h	**16e**	**17f**	84
6			 (2)	
	11h	**16f**	**17g**	77
7			 (1)	
	11i	**16g**	**17h**	60

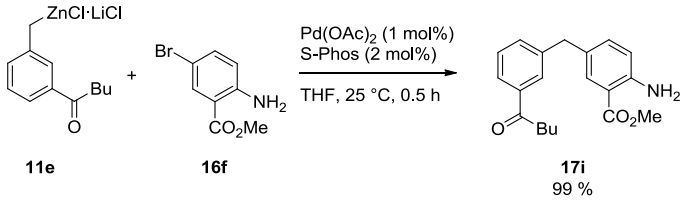
[a]For the cross-coupling reaction, 1.2 equiv. of the zinc reagent is used; [b]Isolated yield of analytically pure product.

Finally, the keto-substituted benzylic zinc reagent **11i** undergoes a smooth cross-coupling with ethyl 4-amino-3-bromobenzoate (**16g**) affording the benzocaine derivative **17h** in 60 % yield (entry 7).

1.3 Palladium-Catalyzed Cross-Coupling Reactions of Benzylic Zinc Reagents

Although the nickel-catalyzed cross-coupling reaction of benzylic zinc reagents with bromoaniline derivatives affords high yields and uses a cheap nickel salt and ligand,[60] the reaction was not reliable. As a result, it was difficult to predict if a chosen combination of benzylic zinc reagent and aryl bromide would afford the desired diarylmethane in a reasonable yield. Therefore, a Pd-catalyzed version of this *Negishi* cross-coupling reaction was developed.[61]

A catalytic system consisiting of $Pd(OAc)_2$ and S-Phos, introduced by *Buchwald*,[62] gave reproducible results for a broad range of substrates. Thus, the keto-substituted benzylic zinc reagent **11e** reacted with the bromoaniline derivative **16f** at room temperature using $Pd(OAc)_2$ (1 mol%) and S-Phos (2 mol%) providing the highly substituted diarylmethane **17i** in almost quantitative yield (99 %, Scheme 28).

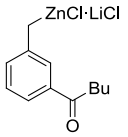
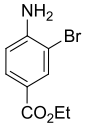
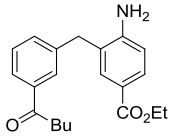


11e **16f** **17i** 99 %

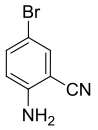
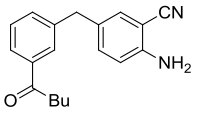
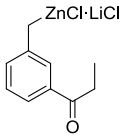
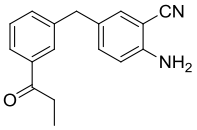
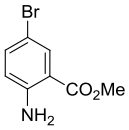
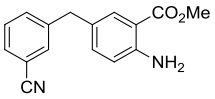
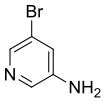
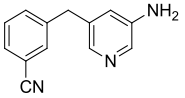
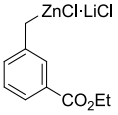
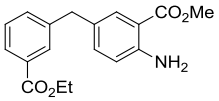
Scheme 28: Pd-catalyzed cross-coupling reaction of keto-substituted benzylic zinc reagent **11e** with **16f**.

Also, **16g** and **16a** were suitable substrates for the Pd-catalyzed coupling reaction with keto substituted benzylic zinc reagents such as **11e** and **11g** and afforded the desired products **17j**, **17k** and **17l** in 73–90 % yield, respectively (Table 4, entries 1-3).

Table 4: Pd-catalyzed cross-coupling with aromatic bromides bearing relatively acidic protons.

Entry	Zinc Reagent[a]	Electrophile	Diarylmethane Reaction Time (h)	Yield [%][b]
1			 (1)	
	11e	**16g**	**17j**	73

[60] $Ni(acac)_2$ (730 €/mol), $Pd(OAc)_2$ (13308 €/mol) and PPh_3 (28 €/mol) were purchased from Acros Organics, S-Phos (29886 €/mol) from Sigma-Aldrich.
[61] Screening and optimization of the Pd-catalyzed version was performed by Dr. Georg Manolikakes. For further information see: (a) G. Manolikakes, C. Munoz Hernandez, M. A. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422; (b) Ph.D. thesis G. Manolikakes, Ludwig-Maximilians-Universität München, **2008**.
[62] (a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871; (b) R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3844; (c) T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 5096; (d) M. R. Biscoe, T. E. Barder, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 7232.

2				
	11e	**16a**	(0.5) **17k**	90
3				
	11g	**16a**	(1) **17l**	88
4				
	11a	**16f**	(1) **17m**	86
5				
	11a	**16h**	(12) **17n**	90
6				
	11d	**16f**	(0.5) **17o**	97

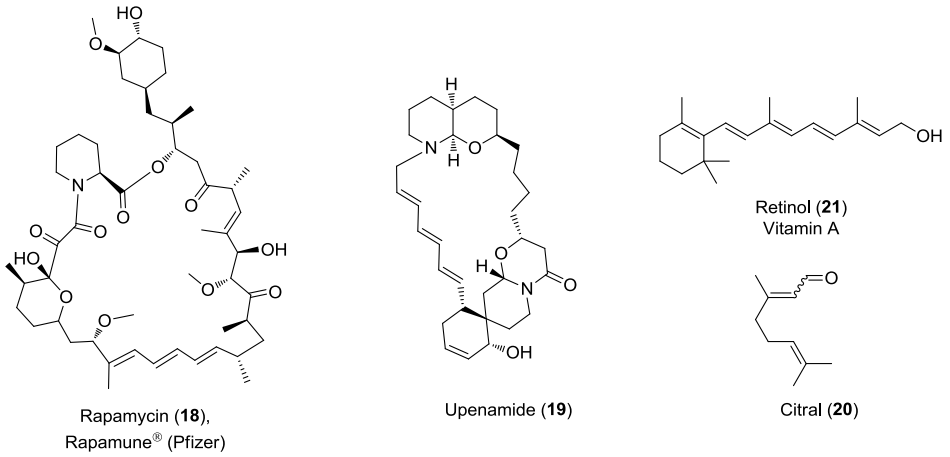
[a]For the cross-coupling reaction, 1.2 equiv. of the zinc reagent is used; [b]Isolated yield of analytically pure product.

Furthermore, the benzylic zinc chloride bearing a cyano function in *meta*-position (**11a**) reacts with the bromoaniline **16f** under Pd-catalysis to afford the substituted benzonitrile **17m** in 86 % yield (entry 4). Additionally, **11a** undergoes a smooth cross-coupling reaction with 3-amino-5-bromopyridine (**16h**) to provide the heterodiarylmethane **17n** in 90 % yield (entry 5). Finally, the electron-deficient benzylic zinc reagent **11d** reacts with **16f** to give the highly functionalized diarylmethane **17o** in 97 % yield (entry 6).

2 Preparation and Applications of Alkenyl Zinc Reagents

2.1 Introduction

Alkenyl substructures can be found in a plethora of naturally occurring products (Scheme 29). For instance, Rapamycin (**18**), found in *Streptomyces hygroscopicus*, [63] is a known immunosuppressant used during organ transplantation and was first synthesized in 1993.[64] The marine alkaloid Upenamide (**19**) was first described in 2000 and contains an extended conjugated system of double bonds.[65]



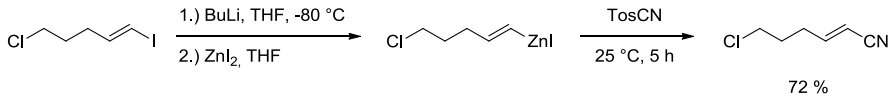
Scheme 29: Selected naturally occurring substances bearing alkenyl substructures.

Besides extended macrocycles and highly sophisticated molecules, terpenes and terpenoids constitute an important class of naturally occurring molecules often containing unsaturated carbon-carbon bonds. For instance, Citral (**20**), a terpenoid present in a variety of plants and having a strong lemon odor, and Retinol (**21**), also known as Vitamin A, a diterpenoid essential for vision, should be mentioned (Scheme 29).

One important and frequently used method for the synthesis of natural products containing unsaturated carbon-carbon bonds is olefin metathesis.[66] A different approach is the cross-coupling reaction of alkenyl organometallics with alkenyl halides.[67] The first synthesis of Rapamycin mentioned above includes as a key step a *Stille*-coupling of two alkenyl iodides with vinylenedistannane to install the three conjugated double bonds.[64] Thus, there is a need for a simple and efficient synthesis of highly functionalized alkenyl organometallics. Especially alkenyl zinc halides are useful organometallics due to their high functional group tolerance and their excellent reactivity using an appropriate catalyst. Their synthesis starting from functionalized iodoalkenes is known. For instance, an iodine-lithium exchange at -90 to -80 °C on

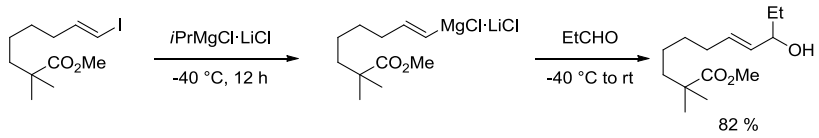
[63] C. Vézina, A. Kudelski, S. N. Sehgal, *J. Antibiot.* **1975**, *28*. 721.
[64] K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, *115*, 4419.
[65] J. I. Jimenez, G. Goetz, C. M. S. Mau, W. Y. Yoshida, P. J. Scheuer, R. T. Williamson, M. Kelly, *J. Org. Chem.* **2000**, *65*, 8465.
[66] (a) *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts* (Eds.: J. Cossy, S. Arseniyadis, C. Meyer), Wiley-VCH, Weinheim, **2010**; (b) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446; (c) D. G. Gillingham, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2007**, *46*, 3860.
[67] K. Kiewel, Z. Luo, G. A. Sulikowski, *Org. Lett.* **2005**, *7*, 5163.

5-chloro-1-iodopent-1-ene and subsequent transmetalation allows the synthesis of the corresponding alkenyl zinc reagent (Scheme 30).[68]



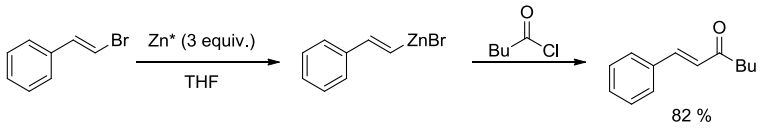
Scheme 30: Synthesis of alkenyl zinc reagents *via* iodine-lithium exchange followed by transmetalation with ZnI_2.

The big drawback of this method is the very low temperature required to achieve an exchange reaction without decomposition of starting materials. The use of *i*PrMgCl·LiCl as exchange reagent allows the formation of an alkenyl magnesium reagent at a higher temperature (Scheme 31).[69]



Scheme 31: Preparation of alkenyl magnesium reagents via iodine-magnesium exchange and subsequent reaction with propanal.

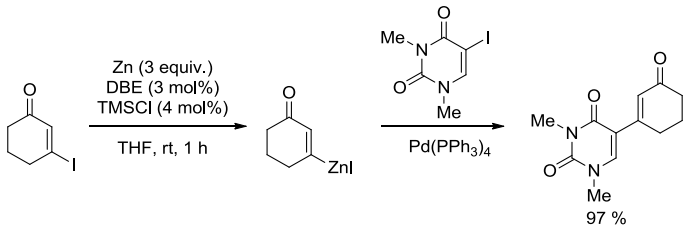
Besides the iodine-metal exchange reaction follows by transmetalation there are only few methods reported for a direct zinc metalation starting from alkenyl halides. The synthesis of alkenyl zinc reagents *via* zinc insertion in alkenyl halides using highly active zinc metal (Zn*) prepared by the reduction of $ZnCl_2$ with lithium naphthalide was reported by *Rieke* and allows a smooth insertion in various bromostyrenes (Scheme 32).[70]



Scheme 32: Insertion of highly active zinc (Zn*) in beta-bromostyrene and subsequent reaction with valeryl chloride.

Furthermore, activated alkenyl iodides such as 3-iodocyclohex-2-en-1-one undergo a smooth zinc insertion using commercially available zinc dust to form the corresponding zinc reagents (Scheme 33).[71]

[68] (a) I. Klement, M. Rottländer, C. E. Tucker, T. N. Majid, P. Knochel, P. Venegas, G. Cahiez, *Tetrahedron* **1996**, *52*, 7201; (b) L. Labaudinière, J.-F. Normant, *Tetrahedron Lett.* **1992**, *33*, 6139.
[69] (a) H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *6*, 4215; (b) H. Ren, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2005**, 543.
[70] (a) L. Zhu, W. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; (b) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4324.
[71] (a) P. Knochel, C. J. Rao, *Tetrahedron* **1993**, *49*, 29; (b) A. S. Bhanu Prasad, P. Knochel, *Tetrahedron* **1997**, *53*, 16711; (c) T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413.

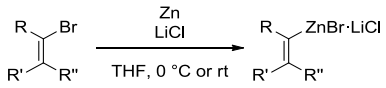


Scheme 33: Insertion of zinc dust in 3-iodocyclohex-2-en-1-one and subsequent cross-coupling reaction.

Although these methods allow the general synthesis of alkenyl zinc reagents, they display several drawbacks. Both approaches start from unstable and expensive alkenyl iodides. Additionally, the exchange reactions mentioned above require very low temperatures to form the organometallic reagents. Therefore, there is a need for a simple and efficient synthesis of alkenyl zinc reagents from easily accessible alkenyl bromides.

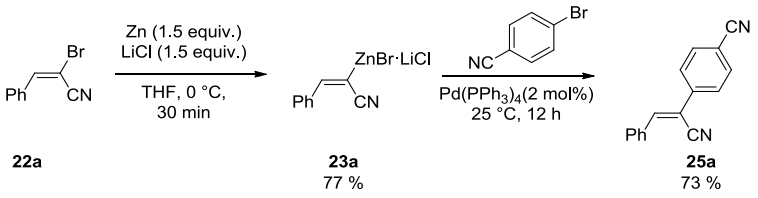
2.2 Direct Insertion of Zinc in Activated Alkenyl Bromides

In the last decade, several variations of the LiCl-mediated metal insertion in oganic halides were reported.[21, 34, 35] Therefore, LiCl allows a smooth zinc insertion into aromatic halides, benzylic chlorides and alkyl bromides. Applying this method to activated alkenyl bromides allows an efficient synthesis of functionalized alkenyl zinc reagents (Scheme 34).



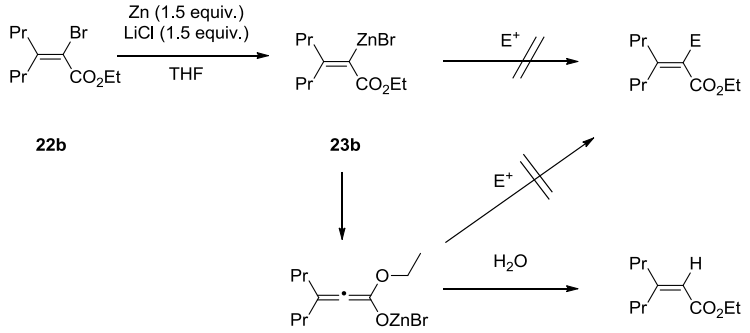
Scheme 34: Synthesis of alkenyl zinc reagents starting from activated alkenyl bromides.

Thus, the LiCl-mediated (1.5 equiv.) reaction of the highly activated alkenyl bromide **22a**, bearing a geminal cyano group, with commercially available zinc dust (1.5 equiv.) in THF (0 °C, 30 min) leads to the organozinc reagent **23a** (Scheme 35). After Pd-catalyzed cross-coupling reaction with 4-bromobenzonitrile (**24a**), the corresponding cinnamonitrile derivative **25a** can be isolated in 73 % yield.



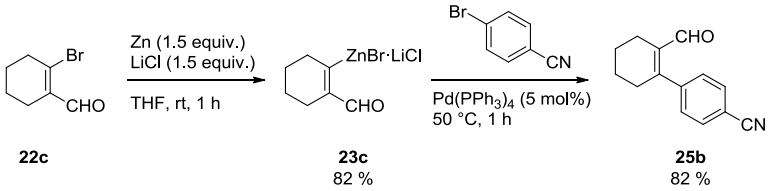
Scheme 35: Synthesis of the highly functionalized styrene derivate **25a**.

However, the related ester substituted alkenyl bromide **22b** does not afford the expected organozinc reagent **23b** but only leads to hydrolysis (Scheme 36). A possible explanation for this behavior is the formation of a Zn-hemiacetal structure which is not reactive against standard electrophiles but prone to hydrolysis.



Scheme 36: Zn insertion in the ester-substituted alkenyl bromide **22b** only leading to hydrolysis.

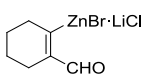
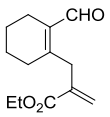
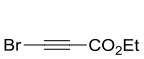
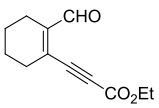
In contrast, a vicinal aldehyde function is perfectly tolerated and allows fast insertion. Hence, 2-bromocyclohex-1-encarbaldehyde (**22c**) undergoes a smooth zinc insertion (1.5 equiv., 1 h, 25 °C) leading to **23c** (82 % yield, Scheme 37). Its cross-coupling reaction with 4-bromobenzonitrile (**24a**) affords the highly functionalized benzonitrile **25b** in 82 % yield.



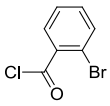
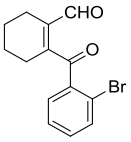
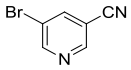
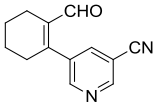
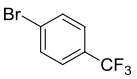
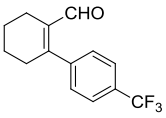
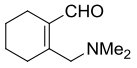
Scheme 37: LiCl-mediated zinc insertion in the alkenyl bromide **22c** and subsequent cross-coupling reaction.

Moreover, a Cu(I)-catalyzed allylation reaction with ethyl 2-bromomethyl acrylate (**24b**) leads to the desired product **25c** in 94 % yield (Table 5, entry 1). The copper-catalyzed reaction of **23c** with the bromoacetylene **24c** affords the highly functionalized acetylene **25d** in 80 % yield (entry 2). Furthermore, the acylation reaction using 2-bromobenzoylchloride (**24d**) affords ketone **25e** in 56 % yield (entry 3). Additionally, Pd-catalyzed cross-coupling reactions with 5-bromo-3-cyanopyridine (**24e**) and 4-bromobenzotrifluoride (**24f**) furnish the highly functionalized tetrahydrobiphenyls **25f** and **25g** in 65% and 73% yield (entries 4 and 5). Finally, the reaction of **23c** with the immonium salt **24g**[72] leads to the dimethylaminomethyl substituted cyclohexene derivative **25h** (68 % yield, entry 6).

Table 5: Reactions the alkenyl zinc reagent **23c** with electrophiles.

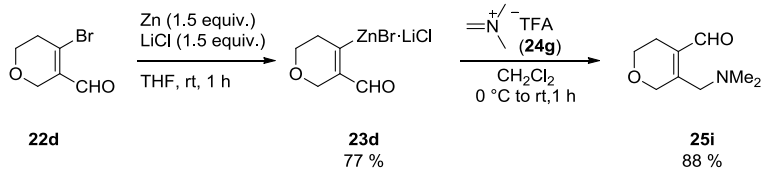
Entry	Zinc Reagent	Electrophile	Product	Yield [%][a]
1				
	23c	**24b**	**25c**	94
2				

[72] (a) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; (b) N. Millot, C. Piazza, S. Avolio, P. Knochel, *Synthesis* **2000**, 941.

	23c	**24c**	**25d**	80
3				
	23c	**24d**	**25e**	56
4				
	23c	**24e**	**25f**	65
5				
	23c	**24f**	**25g**	73
6				
	23c	**24g**	**25h**	68

[a]Isolated yield of analytically pure product.

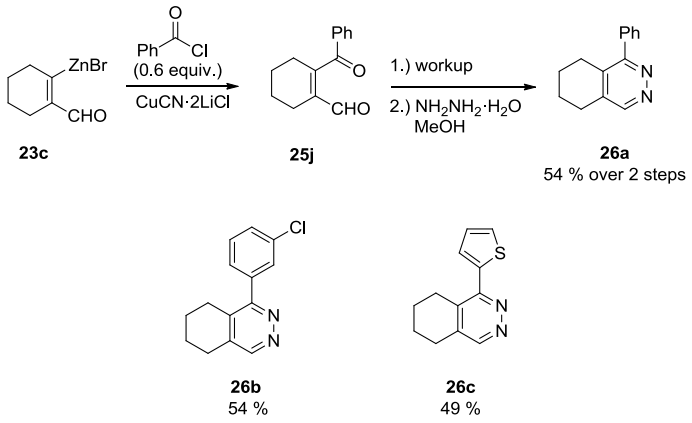
The heterocyclic dihydropyran derivative **22d** can also be converted to its Zn-derivative **23d** in 77 % yield (Scheme 38). After reaction with *N,N*-dimethylimmonium trifluoroacetate (**24g**), the dimethylaminomethyl substituted dihydropyran derivative **25i** can be isolated in 88 % yield.



Scheme 38: Synthesis of the dihydropyran derived Zn-reagent **23d** followed by a reaction with **24g**.

Acylation of unsaturated zinc reagents bearing a vicinal aldehyde lead to unsaturated 1,4-dicarbonyl compounds such as **25e**. These substances are highly reactive and are prone to condensation reactions with hydrazine giving access to tetrahydrophthalazines.[73] Thus, **23c** can be acylated with benzoyl chloride using CuCN·2LiCl as catalyst affording **25j**. After aqueous workup, the crude unsaturated 1,4-dicarbonyl compound undergoes a smooth condensation reaction using hydrazine hydrate ($NH_2NH_2 \cdot H_2O$) in methanol to afford the 1-substituted tetrahydrophthalazine **26a** in 54 % yield (Scheme 39).

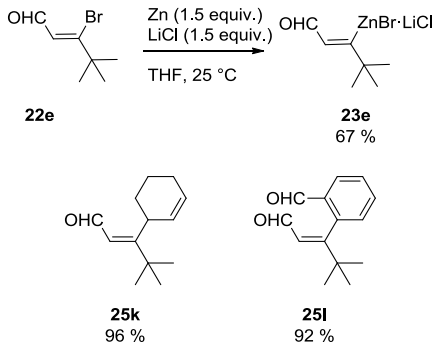
[73] G. Bold, K.-H. Altmann, J. Frei, M. Lang, P. W. Manley, P. Traxler, B. Wietfeld, J. Brüggen, E. Buchdunger, R. Cozens, S. Ferrari, P. Furet, F. Hofmann, G. Martiny-Baron, J. Mestan, J. Rösel, M. Sills, D. Stover, F. Acemoglu, E. Boss, R. Emmenegger, L. Lässer, E. Masso, R. Roth, C. Schlachter, W. Vetterli, D. Wyss, J. M. Wood, *J. Med. Chem.* **2000**, *43*, 2310.



Scheme 39: Synthesis of 1-substituted tetrahydrophthalazines of type **26**.

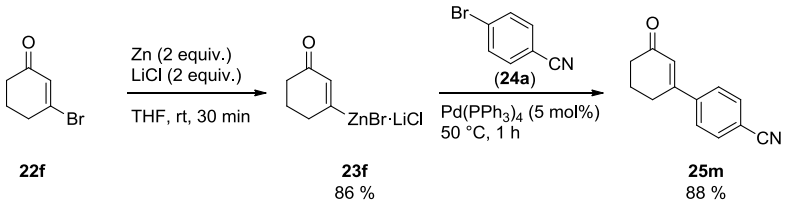
Furthermore, **26b** and **26c** bearing a 3-chlorophenyl or a thiophene substituent have been prepared (54 and 49 % yield, Scheme 39).

Besides cyclic alkenyl derivatives, also acyclic alkenyl zinc reagents bearing a vicinal aldehyde can be prepared. Thus, 3-bromo-4,4-dimethylpent-2-enal (**22e**) reacts with zinc dust (1.5 equiv.) in the presence of LiCl (1.5 equiv.) leading to the alkenyl zinc reagent **23e** (67 %, 25 °C, 1 h, Scheme 40). Standard reactions with electrophiles such as Cu(I)-catalyzed allylation using 3-bromocyclohexene (**24h**) or Pd-catalyzed cross-coupling with 2-bromobenzaldehyde (**24i**) furnish the products **25k** and **25l** in 92-96 % yield (Scheme 40)



Scheme 40: Synthesis of acyclic alkenylzinc reagent **23e**.

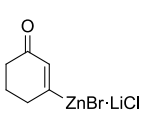
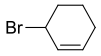
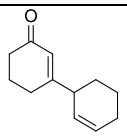
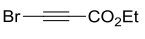
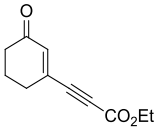
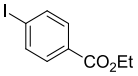
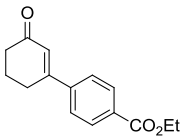
As mentioned before, a direct insertion of zinc dust in 3-iodocyclohex-2-en-1-one and related structures is possible.[71] However, the corresponding iodides are often unstable at room temperature and a synthesis starting from the corresponding bromide would be highly desireable. Hence, applying the method described above to 3-bromo-cyclohex-2-en-1-one (**22f**) a smooth insertion reaction occurs furnishing the 3-zincated cyclohexenone **23f** in 86 % yield (Scheme 41). Pd-catalyzed cross-coupling reaction with 4-bromobenzonitrile (**24a**) affords the 3-substituted cyclohexenone derivative **25m** in 88 % yield.



Scheme 41: Synthesis of **23f** starting from 3-bromocyclohex-2-en-1-one (**22f**) and subsequent cross-coupling.

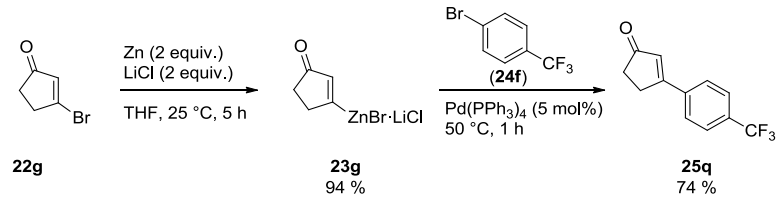
Furthermore, Cu(I)-mediated of reactions **23f** with 3-bromocyclohexene (**24h**) or the bromoacetylene **24c** furnish the unsaturated ketones **25n** and **25o** in 76 and 71 % yield, respectively (Table 6, entries 1 and 2). Moreover, a cross-coupling reaction of **23f** with ethyl 4-iodobenzoate (**24j**) affords the expected product **25p** in 76 % yield (entry 3).

Table 6: Reaction of cyclohexenone derived zinc reagents with electrophiles.

Entry	Zinc Reagent	Electrophile	Product	Yield [%][a]
1				
	23f	**24h**	**25n**	76
2				
	23f	**24c**	**25o**	71
3				
	23f	**24j**	**25p**	76

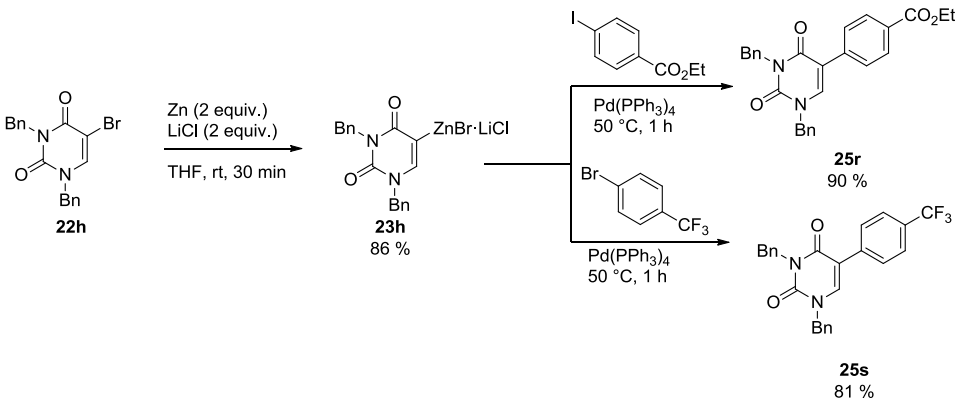
[a]Isolated yield of analytically pure product.

Additionally, the corresponding 3-bromocyclopentenone (**22g**) can be converted to its alkenyl zinc reagent in 94 % yield (25 °C, 5 h). Pd-catalyzed cross-coupling with 4-(trifluoromethyl)-bromobenzene (**24f**) leads to the substituted cyclopentenone **25q** in 74 % yield (Scheme 42).



Scheme 42: LiCl-mediated Zn insertion in 3-bromocyclopentenone (**22g**) and subsequent cross-coupling.

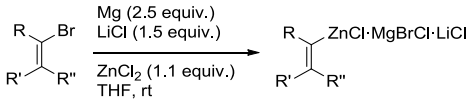
Also, the related benzyl protected uracil derivative **22h** smoothly reacts with zinc dust affording the heterocyclic zinc reagent **23h** in 86 % yield. Its cross-couplings with ethyl 4-iodobenzoate (**24j**) and 4-trifluoromethylbromobenzene (**24f**) furnish the substituted uracil derivatives **25r** and **25s** in 90 and 81 % yield, respectively (Scheme 43).



Scheme 43: Synthesis of substituted uracil derivatives **25r** and **25s**.

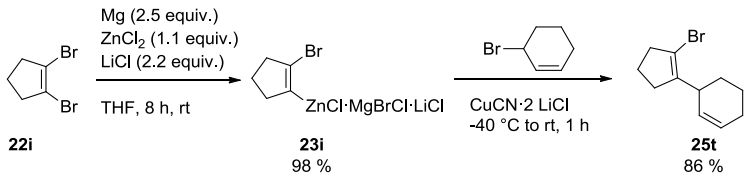
2.3 Magnesium Insertion in the Presence of Zinc Chloride in Alkenyl Bromides

The direct insertion of zinc into alkenyl bromides requires a certain electronic activation via adjacent electron-withdrawing functional groups. Alkenyl bromides without electronic activation either don't undergo an insertion reaction or require elevetated temperature and long reaction times. To avoid these drawbacks it is possible to make use of the stronger reduction potential of Mg. A LiCl mediated Mg insertion in the presence of $ZnCl_2$ allows efficiently the synthesis of alkenyl zinc chlorides starting from electronically less activated alkenyl bromides. (Scheme 44)



Scheme 44: LiCl mediated magnesium insertion in the presence of $ZnCl_2$ in electronically less activated alkenyl bromides.

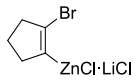
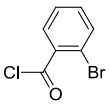
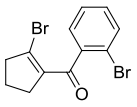
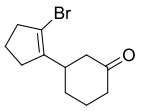
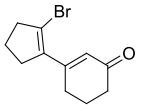
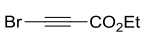
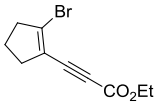
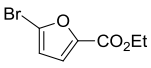
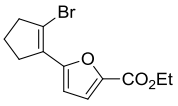
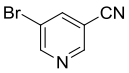
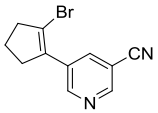
Thus, 1,2-dibromocyclopentene undergoes a selective mono magnesium insertion in the presence of $ZnCl_2$ and LiCl furnishing the alkenyl zinc reagent **23i** in 98 % yield. Its Cu(I)-catalyzed reaction with 3-bromocyclohexene furnishes **25t** (86 %, Scheme 45).



Scheme 45: Selective mono insertion of Mg in the presence of $ZnCl_2$ and LiCl in 1,2-dibromocyclopentene.

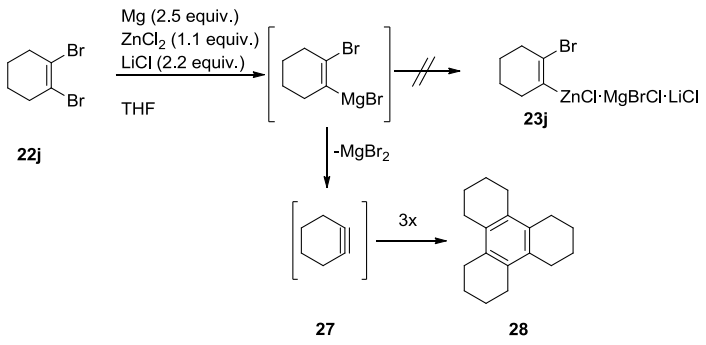
Furthermore, an acylation reaction using 2-bromobenzoyl chloride affords the unsaturated ketone **25u** in 64 % yield (Table 7, entry 1). Additional Cu(I)-mediated reactions with cyclohexenone (**24k**), 3-iodocyclohexenone (**24l**) and bromoacetylene **24c** lead to the expected products **25v–25x** in 65-78 % yield (entries 2-4). Finally, the Pd-catalyzed cross-coupling reactions of **23i** with ethyl 5-bromofuran-2-carboxylate (**24m**) and 3-bromo-5-cyanopyridine (**24e**) furnish the substituted heterocycles **25y** and **25z** in 71 and 54 % yield (entries 5 and 6).

Table 7: Reactions of bromocyclopentene zinc chloride (**23i**) with electrophiles.

Entry	Zinc Reagent	Electrophile	Product	Yield [%][a]
1				
	23i	**24d**	**25u**	64
2				
	23i	**24k**	**25v**	70
3				
	23i	**24l**	**25w**	65
4				
	23i	**24c**	**25x**	78
5				
	23i	**24m**	**25y**	72
6				
	23i	**24e**	**25z**	54

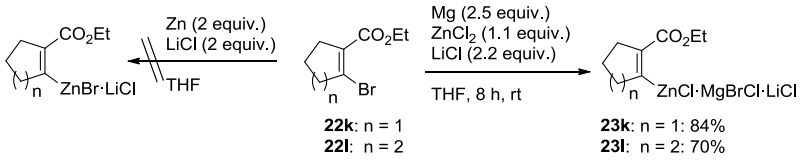
[a] Isolated yield of analytically pure product.

However, a functionalization of the related 1,2-dibromocyclohexene (**22j**) using this method is not possible. As the 6-membered ring has a smaller ring strain, the initially formed organometallic reagent presumably eliminates $MgBr_2$ leading to cyclohexyne **27**. The elimination reaction seems to be faster than the transmetalation with $ZnCl_2$, in spite its presence in the reaction mixture. Therefore, organozinc reagent **23j** could not be observed. Instead, trimerisation of **27** affords the cyclic system **28** along with other sideproducts (Scheme 46).



Scheme 46: Reaction of **22j** with Mg in the presence of $ZnCl_2$ and LiCl leading to trimerisation.

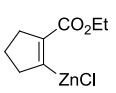
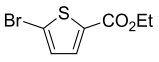
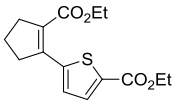
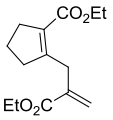
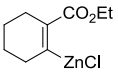
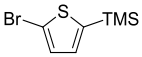
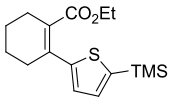
Interestingly, a vicinal ethyl ester functionality does not sufficiently activate the alkenyl bromide for a LiCl-mediated zinc insertion. However, the ester substituted alkenyl bromides **22k** and **22l** can be converted to their corresponding zinc reagents **23k** and **23l** using a magnesium insertion in the presence of $ZnCl_2$ and LiCl (Scheme 47).



Scheme 47: Mg insertion in the presence of $ZnCl_2$ and LiCl in cyclic ethyl acrylate derivatives **22k** and **22l**.

These alkenyl zinc reagents then react with standard electrophiles to afford highly functionalized unsaturated carboxylic acid ester derivatives (Table 8). Therefore, ester substituted cyclopentenezinc chloride **23k** reacts in a Pd-catalyzed cross-coupling with ethyl 5-bromothiophene-2-carboxylate (**24n**) to give the substituted thiophene **25aa** in 79 % yield (Table 8, entry 1). Also a Cu(I)-mediated allylation with **24b** affords the unsaturated product **25ab** in 86 % yield (entry 2). Finally, the corresponding 6-membered zinc reagent (**23l**) undergoes a smooth cross-coupling reaction with the silyl substituted bromothiophene **24o** furnishing the 2,5-difunctionalized thiophene **25ac** in 71 % yield (entry 3).

Table 8: Reactions of cyclic alkenyl zinc reagents bearing an ester functionality in alpha position.

Entry	Zinc Reagent[a]	Electrophile	Product	Yield [%][b]
1				
	23k	**24n**	**25aa**	79
2				
	23k	**24b**	**25ab**	86
3				
	23l	**24o**	**25ac**	71

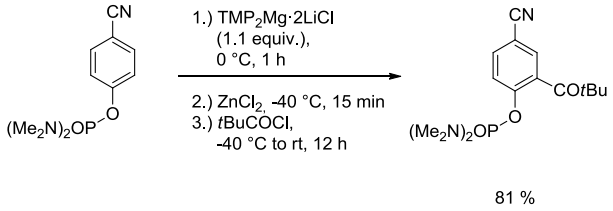
[a] Additional complexed salts are omitted for the sake of clarity; [b] Isolated yield of the analytically pure product.

3 Regioselective Magnesium and Zinc Insertions in Polybrominated Phenol Derivatives

3.1 Introduction

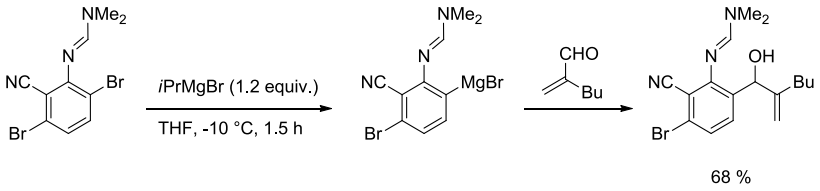
Magnesium and zinc organometallics are versatile nucleophiles in organic synthesis. As shown in the general introduction, there are in general three routes to functionalized organomagnesium or –zinc reagents (Scheme 2).

By using the direct metalation approach, the question of regioselectivity arises. Therefore, so called DMGs (directed metalation groups) are used to direct the metalation in *ortho*-position of the DMG. [74] For instance, a *N,N,N',N'*-tetramethylphosphorodiamidate group is a very strong directing group for selective magnesiations of aromatic systems using $TMP_2Mg{\cdot}2LiCl$ (Scheme 48).[75]



Scheme 48: C-H-activation using $TMP_2Mg{\cdot}2LiCl$ and a phosphorodiamidate as DMG.

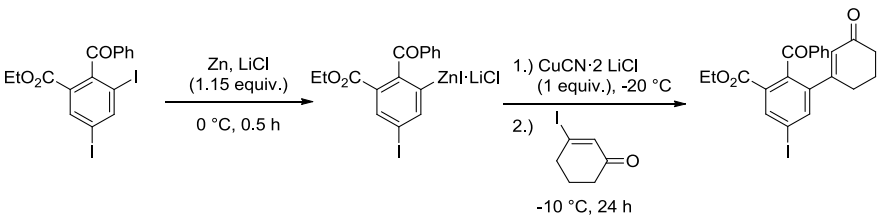
In the case of di- or tri-haloaromatics, the question of regioselectivity arises also for the exchange and the direct metal insertion approaches. For the halogen-metal exchange, DMGs have also been used.[11, 76] Thus, an amidine functionality is a strong directing group for Br-Mg exchange reactions and directs the exchange in its *ortho*-position (Scheme 49).[77]



Scheme 49: Regioselective Br-Mg exchange with an amidine as directing group.

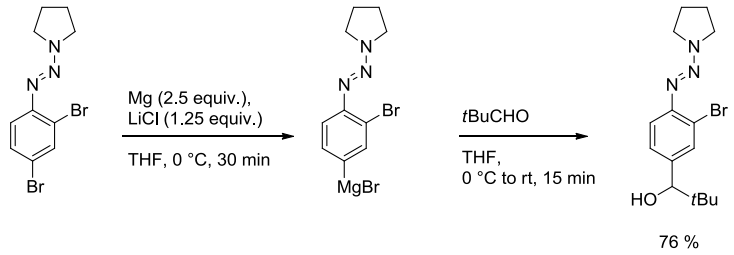
In 2007, *Knochel* reported a method for directed *ortho* insertions (DoI) of Zn in the presence of LiCl in di- or tri-halogenated aromatics and heteroaromatics (Scheme 50).[78]

[74] (a) E. J.-G. Anctil, V. Snieckus, *J. Organomet. Chem.* **2002**, *653*, 150; (b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; (c) F. F. Wagner, D. L. Comins, *Eur. J. Org. Chem.* **2006**, 3562; (d) A. R. Katritzky, Y.-J. Xu, R. Jain, *J. Org. Chem.* **2002**, *67*, 8234.
[75] C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503.
[76] (a) R. D. Rieke, *Science* **1989**, *246*, 1260; (b) X. Wu, R. D. Rieke, *J. Org. Chem.* **1995**, *60*, 6658.
[77] G. Varchi, A. E. Jensen, W. Dohle, A. Ricci, G. Cahiez, P. Knochel, *Synlett* **2001**, 477.
[78] N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.



Scheme 50: Regioslective zinc insertion in polyiodinated aromatics.

This method tolerates a variety of functional groups and allows the efficient functionalization of polyhalogenated aromatics and heteroaromatics. Remarkably, the corresponding Mg insertion in the presence of LiCl reacts selectively in *para*-position and allows an orthogonal reaction strategy (Scheme 51).[21b]

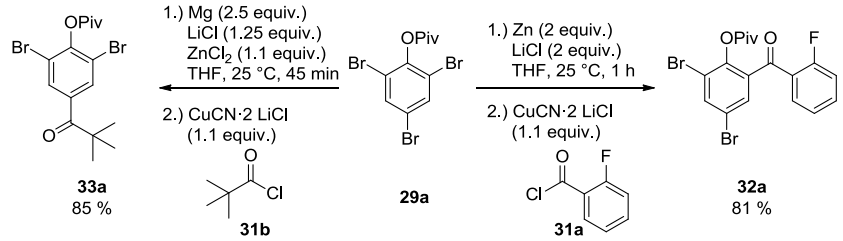


Scheme 51: Regioselective *para* insertion of magnesium in a polybrominated aniline derivative.

3.2 Regioselective Ortho Insertion in Polybrominated Benzene Derivatives

The DoI mentioned above allows an efficient functionalization of mainly di- or triiodinated protected phenols or derivatives thereof. Although some polybrominated phenols can be used, the scope of this directed *ortho* insertion could be broadened by using different directing groups on polybrominated phenols.

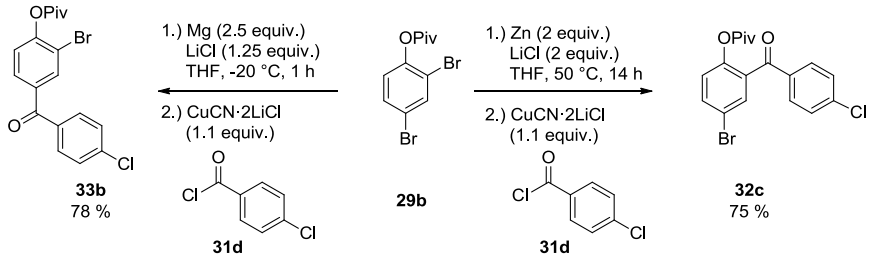
Thus, the pivaloyl protected 2,4,6-tribromophenol **29a** reacts smoothly to its organozinc reagent **30a** (25 °C, 1 h) using zinc dust (2 equiv.) and LiCl (2 equiv.). **30a** then reacts, after a transmetalation with CuCN·2LiCl, with 2-fluorobenzoyl chloride (**31a**) to give the substituted benzophenone **32a** in 81 % yield (Scheme 52).



Scheme 52: Regioselective metal insertion in the polybrominated phenol derivative **29a**.

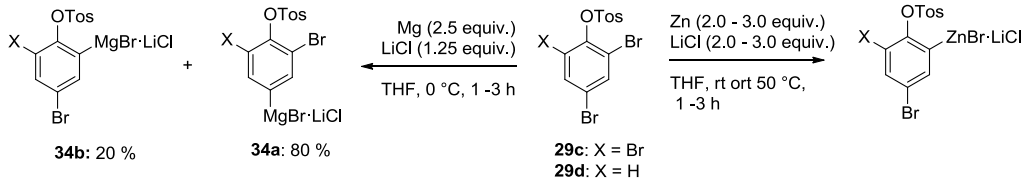
The corresponding magnesium insertion in the presence of LiCl and $ZnCl_2$ leads exclusively to the *para*-organometallic and after a copper-mediated acylation reaction, ketone **33a** can be isolated in 85 % yield.[79] A Pd-catalyzed cross-coupling reaction of **30a** using $Pd(dba)_2$ (2 mol%) and tris-*o*-furylphosphine (tfp, 4 mol%) as catalyst with ethyl 4-iodobenzoate (**31c**) affords the highly functionalized biphenyl **32b** in 78 % isolated yield (Table 9, entry 1).

Similarly, the related pivaloyl protected 2,4-dibromophenol **29b** undergoes a smooth Zn insertion (50 °C, 14 h) to the *ortho* insertion product **30b**. A copper-mediated acylation with 4-chlorobenzoyl chloride (**31d**) leads to the benzophenone derivative **32c** (75 %). Using Mg in the presence of LiCl on **29b**, the orthogonal insertion product is observed and after acylation with **31d** the desired product **33b** is isolated in 78 % yield (Scheme 53).[79]



Scheme 53: Orthogonal insertion pattern in pivaloyl protect 2,4-dibromophenol (**29b**).

Furthermore, a tosyloxy moiety orients the zinc insertion into tribromo- or dibromo-substituted aromatics to the *ortho*-position, thereby providing after quenching with standard electrophiles the expected products **32d-h** in 60-75 % yield (Table 9, entries 2-7, Scheme 54). However, the analogous Mg insertions lead to two regioisomers **34a** and **34b** in 4:1 ratios (Scheme 54).[79]

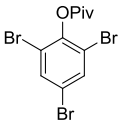
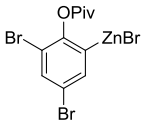
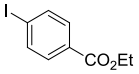
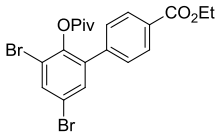
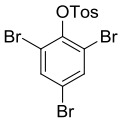
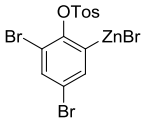
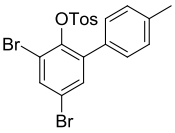
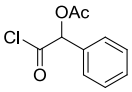
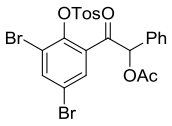
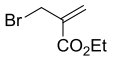
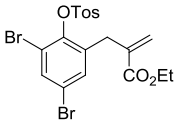
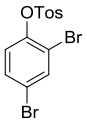
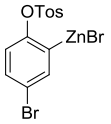
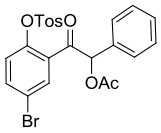
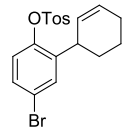
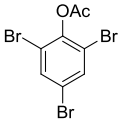
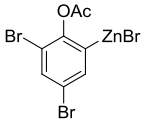
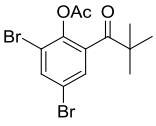
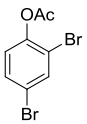
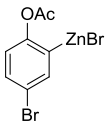
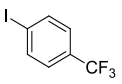
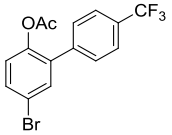


Scheme 54: Regioselectivities for the magnesium and zinc insertion in tosyl-protected di- and tribromophenols.

Similar regioselectivities can be observed when changing the protecting group to an acetyl group. Again, using Zn/LiCl, a regioselective insertion occurs in the tribromophenol derivative (**29e**, 25 °C, 1 h) as well as in the dibromo derivative (**29f**, 50 °C, 6 h). After a copper-mediated acylation or a Pd-catalyzed cross-coupling, the expected products **32i** and **32j** can be isolated in 79-84 % yield (entries 7 and 8).

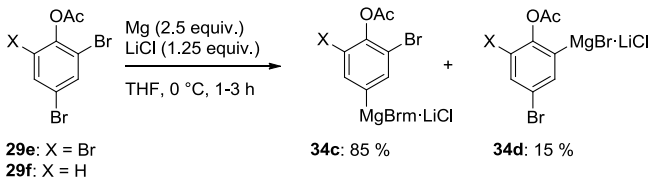
[79] The regioslective magnesium insertions were performed by Dr. F. M. Piller and are given here for the sake of completeness.

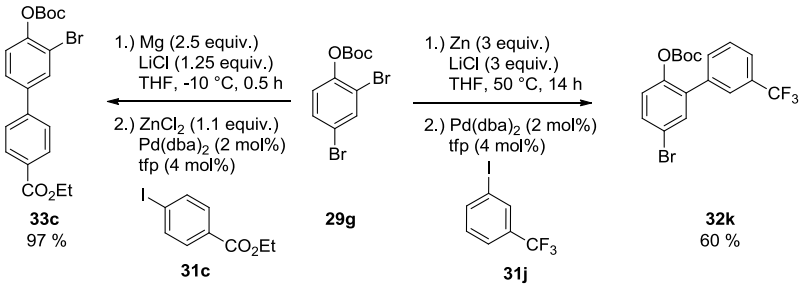
Table 9: Regioselective zinc insertion in polybrominated phenol derivatives.

Entry	Bromide	Zinc Reagent, Conditions[a] [Time]	Electrophile	Product, Yield [%][b]
1				
	29a	**30a**, A [1 h]	**31c**	**32b**, 78 %[c]
2				
	29c	**30c**, A [1 h]	**31e**	**32d**, 73 %[d]
3				
	29c	**30c**	**31f**	**32e**, 74 %[d]
4				
	29c	**30c**	**31g**	**32f**, 75 %[e]
5				
	29d	**30d**, B [14 h]	**31f**	**32g**, 61 %[d]
6				
	29d	**30d**	**31h**	**32h**, 60 %[e]
7				
	29e	**30e**, A [1 h]	**31b**	**32i**, 79 %[d]
8				
	29f	**30f**, B [6 h]	**31i**	**32j**, 84 %[c]

[a] Conditions A: 2 equiv. of Zn and LiCl were used and the reaction was performed at 25 °C; conditions B: 3 equiv. of Zn and LiCl were used and reaction was performed at 50 °C; [b] Isolated yield of analytically pure product; [c] The cross-coupling reaction was performed using $Pd(dba)_2$ (2 mol%) and tris-o-furylphosphine (4 mol%); [d] Prior to the reaction with the acid chloride, the zinc reagent was transmetalated with 1.1 equiv. CuCN·2LiCl; [e] catalytic amounts of CuCN·2LiCl were added.

Again, the respective Mg insertions only lead to mixtures of regioisomers **34c** and **34d** in 85:15 ratios (Scheme 55).[79]



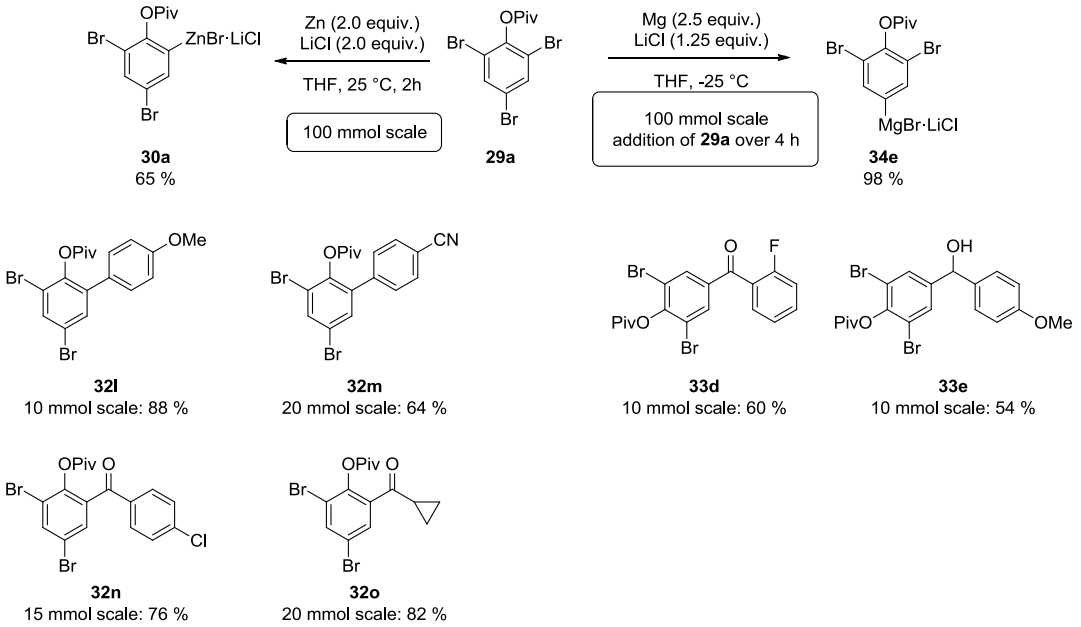


Scheme 55: Regioselective magnesium and zinc insertions in polybrominated phenol derivatives.

Finally, *tert*-butyl 2,4-dibromophenyl carbonate (**29g**) allows both, the *ortho*-functionalization after a directed zinc insertion (50 °C, 14 h) and the selective orthogonal *para*-functionalization using Mg/LiCl (-10 °C, 0.5 h). Pd-catalyzed reaction of the organozinc reagent with 3-trifluoromethyliodobenzene (**31j**) affords the biphenyl **32k** (60 %), whereas the magnesiated organometallic after transmetalation and coupling with ethyl 4-iodobenzoate (**31c**) provides **33c** (97 %, Scheme 55).[79]

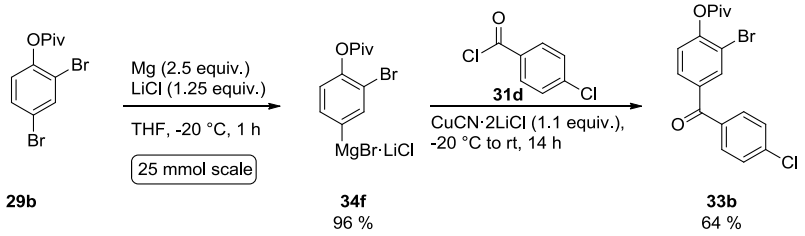
3.3 Large Scale Insertion Reactions

For a potential industrial application, the scale-up of these reactions is of great importance. One great aspect in the scale-up process is the control of the reaction enthalpy. Direct metal insertions are often exothermic and need a certain initiation time. Due to the lower reduction potential of zinc compared to magnesium, zinc insertions are often less exothermic and therefore easier to control. In order to show a possible industrial applicability, the scale up of the regioselective *ortho* and *para* insertion was studied (up to 100 mmol). Thus, the regioselective zinc insertion in 2,4,6-tribromopivaloyloxybenzene (**29a**) can be smoothly performed at ambient temperature with simple watercooling in a 100 mmol scale using zinc dust (2.0 equiv.) and LiCl (2.0 equiv.) in THF (2 h, 65 % yield). In contrast, the orthogonal magnesium insertion in a 100 mmol scale requires extensive cooling (-20 °C) and a slow addition of **29a** over 4 h to form the *Grignard*-reagent **34e** in almost quantitative yield (98 %). Both organometallic reagents then react with standard electrophiles to provide the expected products **32l-o** (64-88 %) and **33d-e** (54-60 %, Scheme 56).



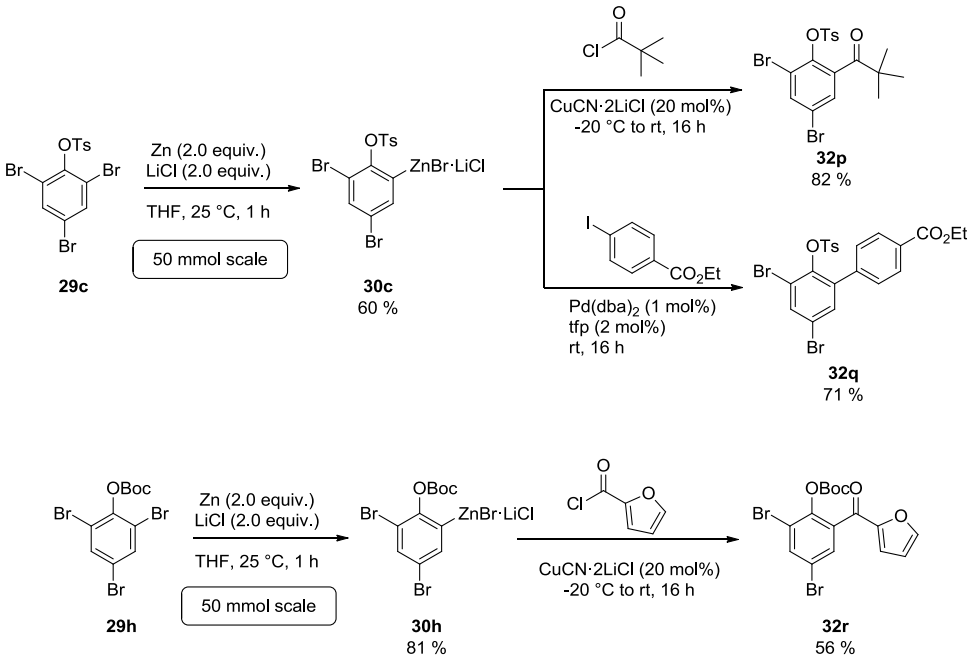
Scheme 56: Large scale preparation of **30a** and **34e** and subsequent reactions with electrophiles.

Additionally, the reaction of 2,4-dibromo-1-pivaloyloxybenzene (**29b**) with Mg (2.5 equiv.)/LiCl (1.25 equiv.) leads selectively to an insertion in *para*-position (-20 °C, addition over 1 h, 96 %) and the resulting organomagnesium reagent (**34f**) can be trapped with 4-chlorobenzoyl chloride (**31d**) affording the highly substituted benzophenone **33b** in 64 % yield (Scheme 57).



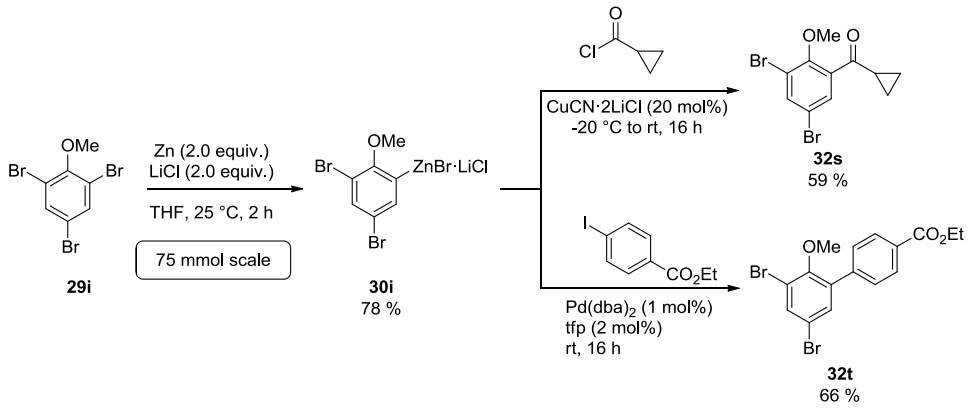
Scheme 57: Selective *para* insertion in **29b** using Mg and LiCl.

The directed *ortho* insertion in larger scale (50 mmol) can also be performed using the tosyl- or *Boc*-protected 2,4,6-tribromophenol derivatives **29c** and **29h**. Both substrates undergo smooth insertion reactions (25 °C, 1 h) to their zinc reagents **30c** and **30h** (60-81 %) and afford ketones **32p** and **32r** (56 and 82 % yield) after acylation reactions or the biphenyl **32q** (71 %, Scheme 58) after a Pd-catalyzed cross-coupling.



Scheme 58: Regioselective Zn-insertion in tribrominated protected phenols **29c** and **29h** in larger scale.

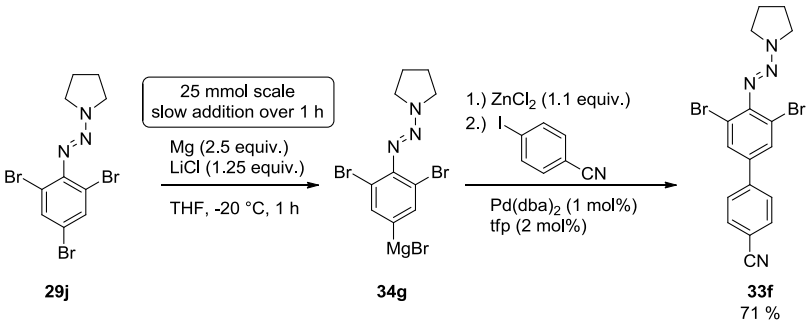
Besides coordinating carbonyl, carbonate or sulfonate groups, a simple methoxy substituent allows an efficient regioselective *ortho* insertion using Zn dust in the presence of LiCl. Thus, **30i** can be readily prepared (2 h, 25 °C, 78 %) from **29i** using Zn dust (2 equiv.) and LiCl (2 equiv.) on a 75 mmol scale and reacts with cylcopropanecarboxylic acid chloride (**31k**) using CuCN·2LiCl to the cyclopropyl ketone **32s** or under Pd-catalysis with ethyl 4-iodobenzoate (**31c**) to the biphenyl **32t** in 59-66 % yield (Scheme 59).



Scheme 59: Directed *ortho* insertion in 2,4,6-tribromoanisole and subsequent reaction with electrophiles.

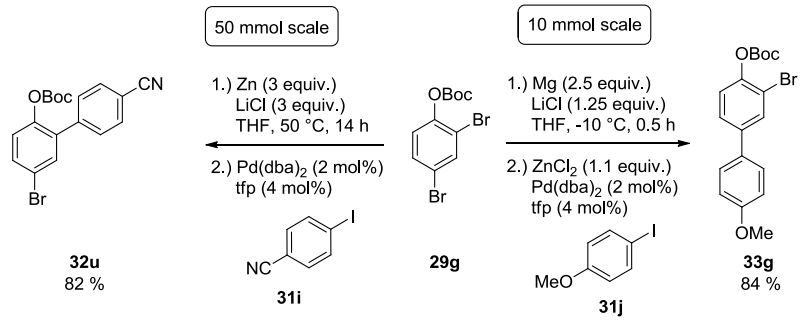
Additionally, a triazene moiety, which is a synthetic equivalent of a diazonium salt,[80] allows the selective *para*-functionalization using Mg/LiCl. Thus, the slow addition of **29j** to Mg/LiCl in THF (-20 °C, 1 h) furnishes the *Grignard* reagent **34g** which, after transmetalation with $ZnCl_2$, reacts in a Pd-catalyzed coupling reaction with 4-iodobenzonitrile (**31i**) to afford the highly functionalized triazene **33f** in 71 % yield (Scheme 60).

[80] (a) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; (b) C.-Y. Liu, P. Knochel, *Synlett* **2007**, 2081; (c) S. Braese, *Acc. Chem. Res.* **2004**, *37*, 805.



Scheme 60: *para*-Functionalization of **29j** using magnesium in the presence of LiCl.

Finally, the previously mentioned regioselective *ortho* and *para* insertion in *tert*-butyl 2,4-dibromophenyl carbonate (**29g**) can be perfomed in larger scale. Thus, biphenyl **32u** can be prepared in 82 % yield after a regioselective Zn insertion in 50 mmol scale and subsequent cross-coupling with 4-iodobenzonitrile (**31i**). The orthogonal *para* insertion using Mg/LiCl can be performed on a 10 mmol scale (-10 °C, 0.5 h) and provides **33g** in 84 % yield after transmetalation with $ZnCl_2$ and Pd-catalyzed reaction with 4-iodoanisole (**31j**) (Scheme 61).

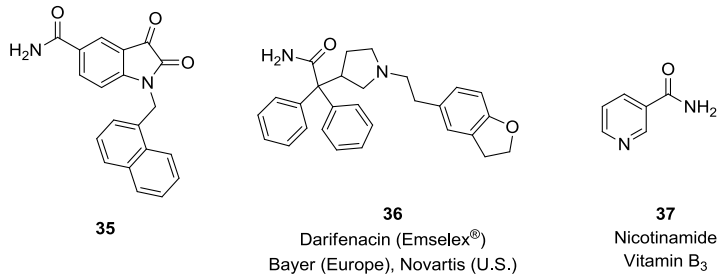


Scheme 61: Regioselective metal insertion in **29g** in large scale.

4 Preparation of Primary Amides From Organozinc Halides

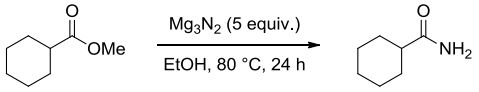
4.1 Introduction

The primary amide functionality ($CONH_2$) is found in a variety of natural products and pharmaceutically active substances.[81] For instance, the isatin derivative **35** was found to be a highly selective, reversible SARS CoV 3C-like protease inhibitor with an IC_{50} value of 0.37 µM.[81b] Darifenacin (**36**), an acetamide derivative, which is a selective M_3 acetylcholine receptor antagonist used to treat urinary incontinence.[82] Nicotinamide (**37**) also called vitamin B_3, is a simple benzamide which is essential for the human body as it is incorporated into nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), two coenzymes involved in redox reactions in all living cells (Scheme 62).[83]



Scheme 62: Biologically active compounds and natural products bearing a primary amide function.

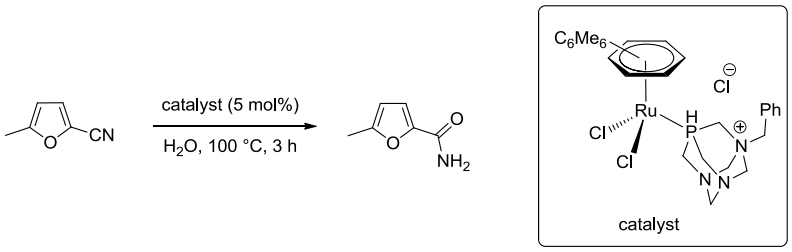
The preparation of functionalized amides from readily available precursors is therefore of great interest. Among others, the reaction of carboxylic acid derivatives with ammonia and the hydration of nitriles are common methods for preparing primary amides.[84, 85] The group of *Ley* developed a general method for the synthesis of primary amides starting from carboxylic esters and magnesium nitride as nitrogen source. Upon reaction with water, magnesium nitride releases ammonia, which then reacts with the ester to form the corresponding carboxamide (Scheme 63).[84a]



Scheme 63: Preparation of primary amides according to *Ley*.

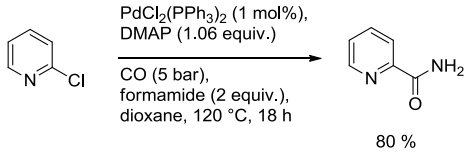
[81] For example: (a) *The Chemistry of Amides* (Ed.: J. Zabicky), Wiley-Interscience, New York, **1970**; (b) L. Zhuo, Y. Liu, W. Zhang, P. Wie, C. Huang, J. Pei, Y. Yuan, L. Lai, *J. Med. Chem.* **2006**, *49*, 3440; (c) A. Bhattcharaya, B. P. Scott, N. Nasser, H. Ao, M. P. Mahre, A. E. Dubin, D. M. Swanson, N. P. Shankley, A. D. Wickenden, S. R. Chaplan, *J. Pharmcol. Exp. Ther.* **2007**, *323*, 665; (d) W. Pringle, J. M. Peterson, L. Xie, P. Ge, Y. Gao, J. W. Ochterski, J. Lan, WO 2006/089076 A2, Aug 24, **2006**.
[82] K. Miyamae, M. Yoshida, S. Murakami, H. Iwashita, M. Ohtani, K. Masunaga, S. Ueda, *Pharmacology* **2003**, *69*, 205.
[83] *Chemistry of Natural Products* (Eds.: S. V. Bhat, B. A. Nagasampagi, N. Sivakumar), Springer, Berlin, **2005**.
[84] (a) For the use of Mg_3N_2 as NH_3 source see: G. E. Veitch, K. L. Bridegwood, S. V. Ley, *Org. Lett.* **2008**, *10*, 3623; (b) For a Ru-catalyzed hydration of nitriles, see: V. Cadierno, J. Francos, J. Gimeno, *Chem. Eur. J.* **2008**, *14*, 6601; (c) V. Y. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta* **2005**, *1*, 1; (d) For a $Bi(OTf)_3$-catalyzed *Ritter* reaction see: E. Callens, A. J. Burton, A. G. M. Barrett, *Tetrahedron Lett.* **2006**, *47*, 8699; (e) For a Pd-catalyzed aminocarbonylation of aryl halides see: A. Schnyder, M. Beller, G. Mehltretter, T. Nsenda, M. Studer, A. F. Indolese, *J. Org. Chem.* **2001**, *66*, 4311.
[85] (a) For related cyanations see: P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 4725; (b) For a *Grignard* addition-acylation route to enamides see: F. F. Fleming, G. Wei, Z. Zhang, O. W. Steward, *Org. Lett.* **2006**, *8*, 4903; (c) For carbonylations of zinc reagents with CO_2, see: K. Kobayashi, Y. Kondo, *Org. Lett.* **2009**, *11*, 2035; (d) A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.

The hydration of nitriles leading to primary amides is conventionally performed in the presence of a strong acid or base as catalyst under harsh conditions.[86] *Gimeno* developed a mild and efficient method for hydration of nitriles using a Ru-catalyst in aqueous medium and under neutral conditions (Scheme 64).[84b]



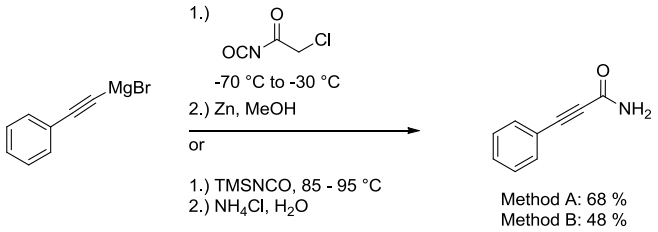
Scheme 64: Ru-catalyzed hydration of nitriles to primary amides.

As these methods are functional group interconversion of already existent carbonyl functions, methods for installing a primary amide with a C-C-bond forming reaction would be highly desireable. *Beller* and *Indolese* recently reported a Pd-catalyzed aminocarbonylation of aryl halides using formamide as an ammonia source (Scheme 65).[84e]



Scheme 65: Pd-catalyzed aminocarbonylation according to *Beller*.

A direct organometallic approach is the addition of *Grignard* reagents to trimethylsilyl isocyanate or chloroacetyl isocyanate (Scheme 66).[87] A major drawback of this protocol is the incompatibility with sensitive functional groups and heterocycles.



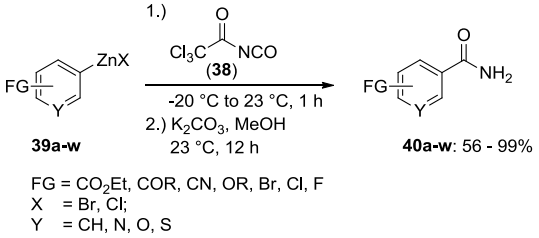
Scheme 66: Preparation of primary amides starting from organomagnesium reagents and substituted isocyanates.

In contrast, the use of organozinc reagents is compatible with a broad range of functional groups and sensitive heterocycles in the starting zinc organometallic and allows a one-carbon homologation establishing a carbamide function.[88]

[86] *Methoden Org. Chem. (Houben Weyl) 4th ed., Vol. E5(2)*, **1985**, 1024-1031.
[87] K. A. Parker, E. G. Gibbons, *Tetrahedron Lett.* **1975**, *12*, 981.
[88] (a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; (b) R. F. W. Jackson, N. Wishart, A. Wood, K. James, M. J. Wythes, *J. Org. Chem.* **1992**, *57*, 3397; (c) F. Crestey, P. Knochel, *Synthesis* **2010**, 1097; (f) M. Mosrin, M. Petrera, P. Knochel, *Synthesis* **2008**, 3697; (g) G. Monzon, P. Knochel, *Synlett* **2010**, 304.

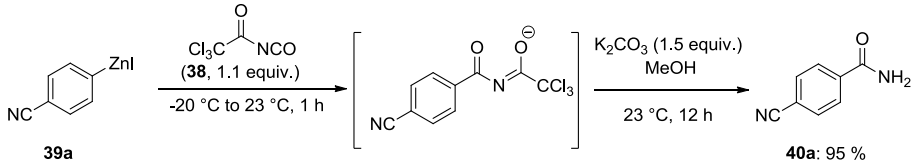
4.2 Preparation of Primary Amides

Initial experiments showed that organozinc reagents do not react with trimethylsilyl isocyanate and chloroacetyl isocyanate to form the desired primary amide. Obviously, organozinc reagents are not nucleophilic enough to attack the carbonyl carbon of these isocyanates. The use of commercially available trichloroacetyl isocyanate (**38**) instead allows a smooth addition of various organozinc halides of type **39**, and the primary amides of type **40** can, after basic hydrolysis, be isolated in yields up to 99 % (Scheme 67).[89,90]



Scheme 67: Reaction of unsaturated zinc reagents with trichloroacetyl isocyanate (**38**) leading to primary amides.

Thus, 4-cyanophenylzinc iodide (**39a**) prepared by the direct insertion of zinc into 4-iodobenzonitrile, reacts with trichloroacetyl isocyanate (**38**, 1.1 equiv., -20 °C to 23 °C) to the corresponding imidate. After basic hydrolysis using K_2CO_3 (1.5 equiv.) and MeOH, 4-cyanobenzamide (**40a**) was isolated in 95% yield (Scheme 68).



Scheme 68: Reaction of 4-cyanophenylzinc iodide (**39a**) with trichloroacetyl isocyanate (**38**).

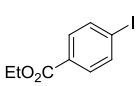
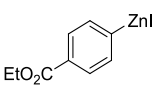
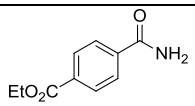
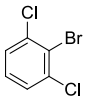
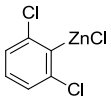
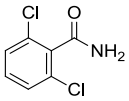
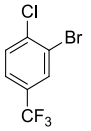
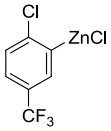
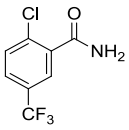
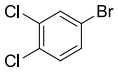
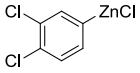
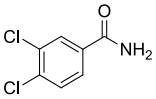
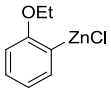
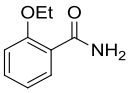
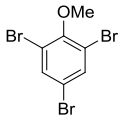
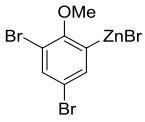
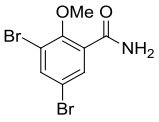
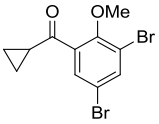
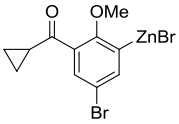
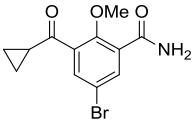
Using this method, other substituted benzamides have been prepared. Thus, 4-(ethoxycarbonyl)phenylzinc iodide (**39b**) reacts smoothly with trichloroacetyl isocyanate to produce the expected primary amide **40b** in 90 % yield (Table 10, entry 1). Furthermore, chloro- or trifluoromethyl- substituted arylzinc reagents such as **39c-e** react with trichloroacetyl isocyanate furnishing the expected primary amides **40c-e** in 60-98 % yield (entries 2-4). Starting from 2-ethoxyphenylzinc chloride (**39f**), ethenzamide[91] (**40f**), an analgesic and anti-inflammatory drug, is obtained in almost quantitative yield (98 %, entry 5).

[89] (a) M.-Z. Deng, P. Caubère, J. P. Senet, S. Lecolier, *Tetrahedron* **1988**, *44*, 6079; (b) G. Manolikakes, Z. Dong, H. Mayr, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1324; (c) For a recent overview on the addition of organozinc reagents to carbonyl compounds, see: L. Salvi, J. G. Kim, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 12483.

[90] Zinc reagents prepared by direct C-H activation using TMPZnCl·LiCl or $TMP_2Zn·2MgCl_2·2LiCl$ do not give the desired products. Also, the use of the corresponding organomagnesium reagents either do not yield in the desired primary amides or only in low yields.

[91] H. Buschmann, T. Christoph, E. Friderichs, *Analgesics: From Chemistry and Pharmacology to Clinical Application*; Wiley-VCH, Weinheim, **2002**.

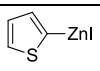
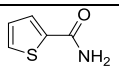
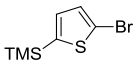
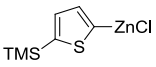
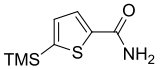
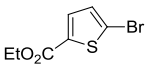
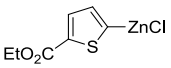
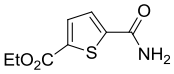
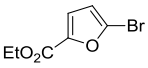
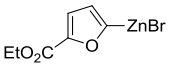
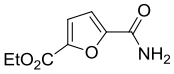
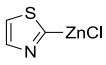
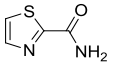
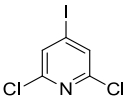
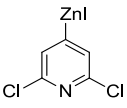
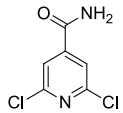
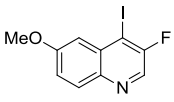
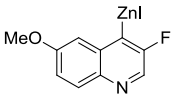
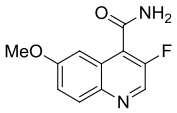
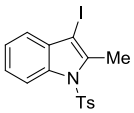
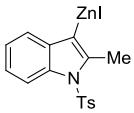
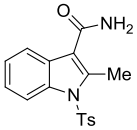
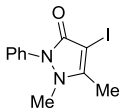
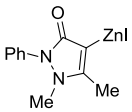
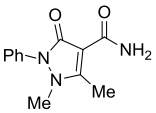
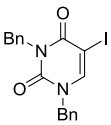
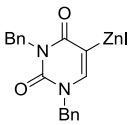
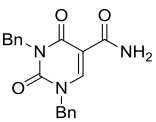
Table 10: Reactions of aromatic organozinc reagents leading to funtionalized benzamides.

Entry	Aryl halide	Zinc Reagent[a]	Primary Amide[b]	Yield [%][c]
1				
		39b[d]	**40b**	90
2				
		39c[e]	**40c**	60
3				
		39d[e]	**40d**	98
4				
5		**39e**[e]	**40e**	71
				
6		**39f**[e]	**40f**	98
				
7		**39g**[d]	**40g**	78
				
		39h[d]	**40h**	66

[a] For the sake of clarity, additional complexed salts are omitted; [b] All reactions were hydrolyzed at 23 °C, 12 h; [c] Isolated yield of analytically pure product; [d] Zinc reagent was prepared *via* LiCl-mediated zinc insertion in the corresponding aryl halide; [e] Zinc reagent was prepared *via* halogen-magnesium exchange using *i*PrMgCl·LiCl from the corresponding aryl halide.

The directed zinc insertion in polybrominated protected phenols[78, 21] gives regioselectively the arylzinc reagents **39g** and **39h** which then react with trichloroacetyl isocyanate affording the corresponding benzamides **40g** and **40h** in 66-78 % yield (entries 6 and 7). Furthermore, heterocyclic zinc reagents such as the thiophenylzinc derivatives **39i-k** provide the expected primary amides **40i-k** in 61-99 % yield (Table 11, entries 1-3). Moreover, ethyl 5-carbamoylfuran-2-carboxylate (**40l**) and thiazole-2-carboxamide (**40m**) have been prepared by this way in 78-82 % yield (entries 4 and 5). Also electron-deficient 6-membered N-heterocyclic zinc reagents have been reacted with trichloroacetyl isocyanate leading to the corresponding primary amides. 2,6-Dichloro-4-pyridylzinc iodide (**39n**) is converted to the isonicotinamide **40n** in 63 % yield (entry 6).

Table 11: Reactions of heterocyclic zinc halides with trichloroacetyl isocyanate providing heterocyclic amides.

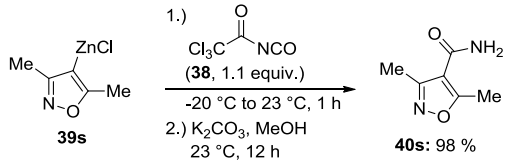
Entry	Arylhalide	Zinc reagent[a]	Primary amide[b]	Yield [%][c]
1				
		39i[d]	**40i**	99
2				
		39j[e]	**40j**	99
3				
		39k[e]	**40k**	61
4				
		39l[e]	**40l**	78
5				
		39m[e]	**40m**	82
6				
		39n[d]	**40n**	63
7				
		39o[d]	**40o**	69
8				
		39p[d]	**40p**	73
9				
		39q[d]	**40q**	70
10				
		39r[d]	**40q**	78

[a] For the sake of clarity, additional complexed salts are omitted; [b] All reactions were hydrolyzed at 23 °C, 12 h; [c] Isolated yield of analytically pure product; [d] Zinc reagent was prepared *via* LiCl-mediated zinc insertion in the corresponding aryl halide; [e] Zinc reagent was prepared *via* halogen-magnesium exchange using *i*PrMgCl·LiCl from the corresponding aryl halide.

Also, the substituted quinoloylzinc iodide **39o** and the the protected indole **39p** have been smoothly converted to the benzamides **40o** and **40p** in 69-73 % yield (entries 7 and 8). Moreover, sensitive 5-membered heterocyclic zinc reagents, such as pyrazolylzinc iodide **39q** or the zinc reagent derived from the benzyl protected bromo-uracil derivative **39r** react with

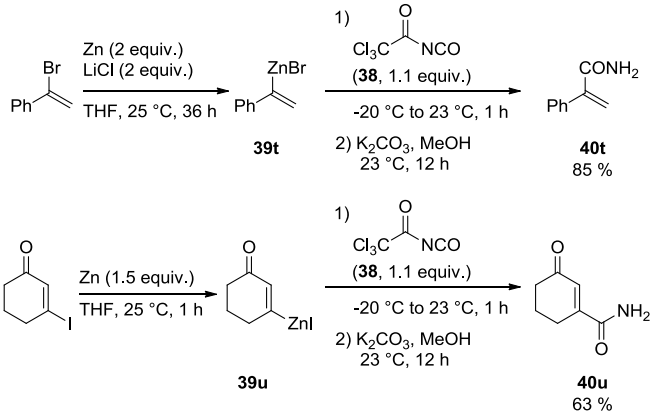
trichloroacetyl isocyanate to provide the corresponding primary amides **40q** and **40r** in 70-78 % yield (entries 9 and 10).

Additionally, 3,5-dimethylisoxazolylzinc chloride **39s** provides the amide **40s** in almost quantitative yield (98 %, Scheme 69).



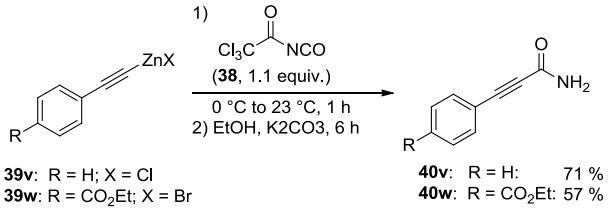
Scheme 69: Addition of 3,5-dimethylisoxazolylzinc chloride (**39s**) to trichloroacetyl isocyanate leadin to **40s**.

Also α,β-unsaturated amides can be prepared from the corresponding zinc reagents. Thus, the unsaturated zinc reagents derived from α-bromostyrene[34a] (**39t**) and 3-iodocyclohex-2-enone (**39u**)[71] react with trichloroacetyl isocyanate to give **40t** and **40u** in 63-85 % yield (Scheme 70).



Scheme 70: Preparation of the unsaturated primary amides **40t** and **40u**.

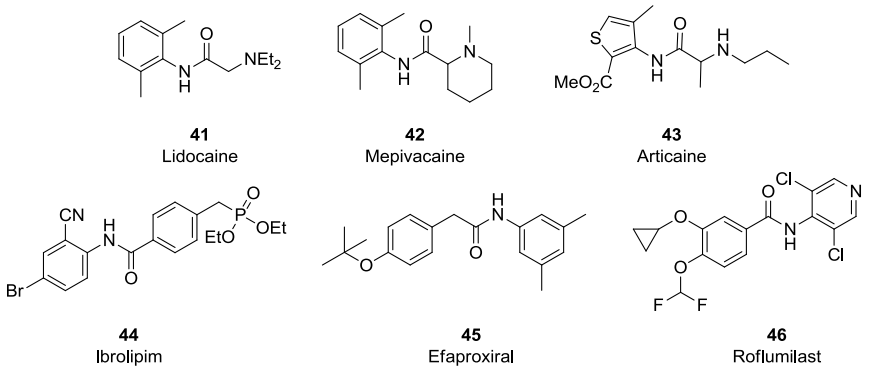
Finally, acetylenic amides can also be prepared by this method. Phenylacetylenezinc chloride (**39v**) reacts with trichloroacetyl isocyanate at room temperature and the acetylenic amide **40v** was isolated in 71 % yield (Scheme 71). The ester substituted phenylacetylene derived zinc reagent **39w** can be converted to the primary amide **40w** in 57 % yield (Scheme 71).



Scheme 71: Reaction of alkynylzinc halides with trichloroacetyl isocyanate affording **40v** and **40w**.

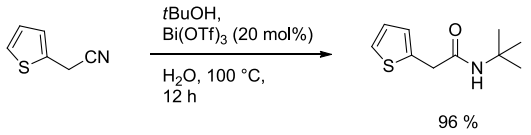
4.3 Reactions of Organozinc Reagents with Substituted Isocyanates

The extension of the methodology described before to substituted isocyanates would give access to *N*-substituted amides. The secondary amide group is a widespread functionality in natural products as well as in pharmaceutically active substances.[92] A variety of widely used local anesthetics such as Lidocaine (**41**), Mepivacaine (**42**) or Articaine (**43**), possess a secondary amide function (Scheme 72). Ibrolipim (**44**) is a cholesterol lowering drug, which acts as a lipoprotein lipase activator.[93] Efaproxiral (**45**) is supportingly used in chemotherapy against certain hypoxic tumors.[94]



Scheme 72: Various parmaceuticals bearing a secondary amide function.

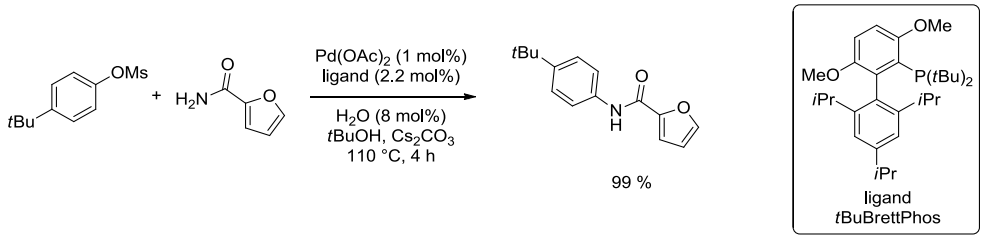
Furthermore, Roflumilast (**46**) is a selective PDE-4 inhibitor and is used as an anti-inflammatory drug in the therapy of asthma and chronic obstructive pulmonary disease.[95] Standard procedures for the synthesis of secondary amides often use harsh conditions and are not compatible with a variety of functional groups. A $Bi(OTf)_3$-catalyzed *Ritter* reaction developed by *Barrett* allows a simple and efficient synthesis of secondary amides (Scheme 73).[84d]



Scheme 73: Synthesis of secondary amides using a $Bi(OTf)_3$-catalyzed *Ritter* reaction.

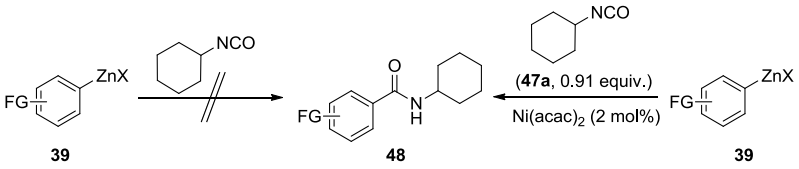
In 2010, *Buchwald* showed a Pd-catalyzed cross-coupling reaction of primary amides with aryl mesylates leading to aryl substituted secondary amides.[96] The use of *t*BuBrettPhos allows the efficient coupling of a variety of functionalized aryl and heteroaryl mesylates with various aryl and alkyl carboxamides (Scheme 74).

[92] *The Organic Chemistry of Drug Synthesis Vol.7* (Ed.: D. Lednicer), Wiley-Interscience, Hoboken, New Jersey, **2008**.
[93] S. Kano, M. Doi, *Metabolism* **2006**, *55* 151.
[94] C. Scott, J. Suh, B. Stea, A. Nabid, J. Hackman, *Am. J. Clin. Oncol.* **2007**, *30*, 580
[95] (a) C. Herbert, A. Hettiaratchi, D. C. Webb, P. S. Thomas, P. S. Foster, R. K. Kumar, *Clin. Exp. Allergy* **2008**, *38*, 847; (b) V. Boswell-Smith, D. Spina, *Int. J. Chron. Obst. Pulmon. Dis.* **2010**, *5*, 11.
[96] K. Dooleweedt, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2010**, *12*, 2350.



Scheme 74: Pd-catalyzed cross-coupling of primary amides with aryl mesylates according to *Buchwald*.

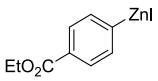
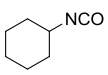
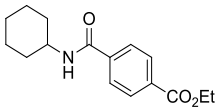
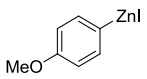
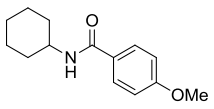
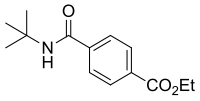
In contrast to trichloroacetyl isocyanate, other substituted isocyanates, such as cyclohexyl isocyanate or *tert*-butyl isocyanate, do not react directly with organozinc reagents. A short catalyst screening showed that by adding catalytic amounts of $Ni(acac)_2$ (2 mol%), a smooth addition reaction occurs (Scheme 75)

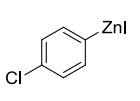
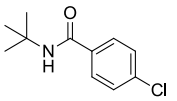
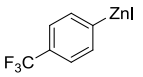
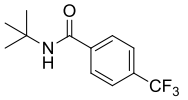
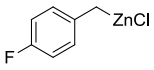
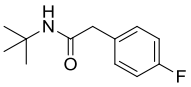


Scheme 75: Ni-catalyzed reaction of organozinc reagents with cyclohexyl isocyanate.

To show the scope of this novel Ni-catalyzed addition reaction, a variety of aryl and benzylic zinc reagents were coupled with substituted isocyanates. Thus, 4-(ethoxycarbonyl)phenylzinc iodide (**39b**) reacts with cyclohexyl isocyanate (**47a**, 0.91 equiv) and catalytic amounts of $Ni(acac)_2$ (2 mol%) to give the corresponding secondary amide **48a** in 60 % yield (Table 12, entry 1). The reaction of 4-methoxyphenylzinc iodide (**39x**) with cyclohexyl isocyanate (**47a**) affords the substituted amide **48b** in 53 % yield (entry 2). Aryl zinc reagents bearing electron-withdrawing groups such as **39b**, 4-chlorophenylzinc iodide (**39y**) or 4-(trifluoromethyl)phenylzinc iodide (**39z**) react with *tert*-butyl isocyanate (**47b**) affording the desired amides **48c-e** in 63-79 % yield (entries 3-5).

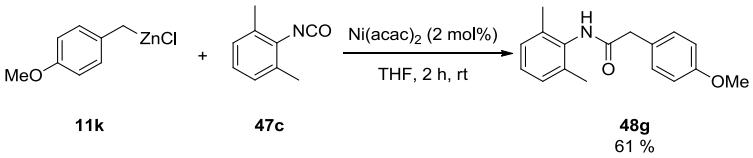
Table 12: Ni-catalyzed reaction of organozinc reagents with substituted isocyanates affording secondary amides of type **48**.

Entry	Organozinc reagent[a]	Isocyanate	Amide of Type **48**	Yield [%][b]
1				
	39b	**47a**	**48a**	60
2		**47a**		
	39x		**48b**	53
3	**39b**			
		47b	**48c**	79

4				
	39y	**47b**	**48d**	63
5				
	39z	**47b**	**48e**	75
6				
	11j	**47b**	**48f**	61

[a] For the sake of clarity, additional complexed salts are omitted; [b] Isolated yield of analytically pure product.

Also, the benzylic zinc reagent **11j** reacts with *tert*-butyl isocyanate (**47b**) providing the secondary amide (**48f**) in 61 % yield (entry 6).



11k **47c** **48g** 61 %

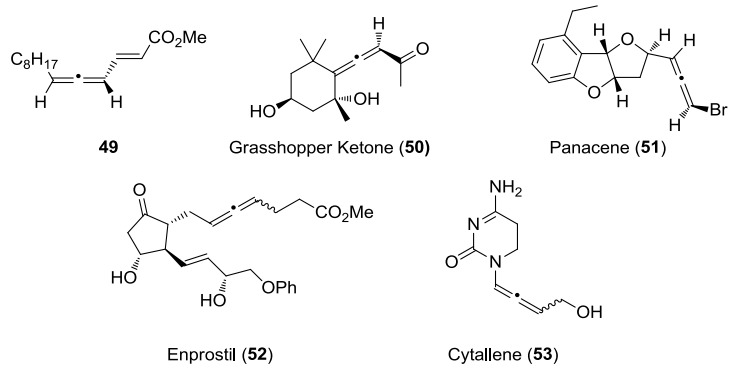
Scheme 76: Reaction of 4-(methoxy)benzylzinc chloride (**11k**) with 2,6-dimethylphenyl isocyanate (**47c**).

Finally, the electron-rich benzylic zinc reagent **11k** reacts with 2,6-dimethylphenyl isocyanate (**47c**) in the presence of catalytic amounts of $Ni(acac)_2$ to give the highly substituted amide **48g** in 61 % yield (Scheme 76).

5 Preparation of Highly Functionalized Allenes via Successive Copper-Mediated Substitution Reactions

5.1 Introduction

Allenes have found increasing synthethic applications over the years.[97] They are either target molecules (Scheme 77) or versatile intermediates for the preparation of various cyclic or heterocyclic compounds.[98] Thus, **49** is a pheromone extracted from the insect *Acanthoscelides obtectus*, in which it was found in rather large amounts (0.5 % of its total mass).[99] The allenic terpenoid **50**, has a repellent effect on ants and was isolated from the defence secrete of the grasshopper *Romalea microptera*, and is therefore called grasshopper ketone.[100] Compound **50** can also be found as a subunit in various glycoside derivatives.[101] The most recently discovered group of naturally occurring allenes is the group of bromoallenes.[97] Panacene (**51**), found in the sea hare *Aplysia brasiliana* in which it acts as antifeedant against fishes, is mentioned exemplarily.[102]



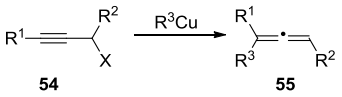
Scheme 77: Natural occurring and pharmaceutically active allenes.

Enprostil (**52**), a PGE2-analog, has an in inhibitory effect on gastric acid secretion and is used in the treatment of gastroduodenal ulcers.[103] Also, the allenic nucleoside analog Cytallene (**53**) shows interesting pharmaceutical activity as it acts as an inhibitor of the replication of retroviruses, for instance HIV or hepatitis B virus. [104]

[97] (a) *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; (b) *The Chemistry of Ketenes, Allenes and Related Compounds* (Ed.: S. Patai), Wiley, New York, **1980**; (c) *The Chemistry of the Allenes* (Ed.: S. R. Landor), Academic, London, **1982**; (d) *Allenes in Organic Synthesis* (Eds.: H. F. Schuster, G. M. Coppola), Wiley, New York, **1984**.
[98] (a) A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed.* **2004**, *43*, 1196; (b) N. Krause, A. Hoffmann-Röder, *Tetrahedron* **2004**, *60*, 11671; (c) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; d) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; (e) S. Ma, E.-i. Negishi, *J. Am. Chem. Soc.* **1995**, *117*, 6345; (f) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2000**, *20*, 3590.
[99] D. F. Hofer, *J. Chem. Soc. C* **1970**, 859.
[100] (a) J. Meinwald, K. Erickson, M. Hartshorn, Y. C. Meinwald, T. Eisner, *Tetrahedron Lett.* **1968**, *9*, 2959; (b) J. Meinwald, L. Hendry, *Tetrahedron Lett.* **1969**, *10*, 1657.
[101] (a) Y. Shiraga, K. Okano, T. Akira, C. Fukaya, K. Yokoyama, S. Tanaka, H. Fukui, M. Tabata, *Tetrahedron* **1988**, *44*, 4703; (b) T. Miyase, A. Ueno, N. Takizawa, H. Kobayashi, H. Oguchi, *Phytochemistry* **1989**, *28*, 3483.
[102] (a) R. Kinnel, A. J. Duggan, T. Eisner, J. Meinwald, *Tetrahedron Lett.* **1977**, *18*, 3913; (b) K. S. Feldman, C. C. Mechem, L. Nader, *J. Am. Chem. Soc.* **1982**, *104*, 4011.
[103] (a) P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533; (b) N. Omura, H. Kashiwagi, T. Aoki, K. Omura, Y. Fukuchi, *J. Gastroenterol.* **1997**, *32*, 740.
[104] (a) J. Zemlicka, *Pharmacol. Ther.* **2000**, *85*, 251; (b) Y. L. Zhu, S. B. Pai, S. H. Liu, K. L. Grove, B. C. Jones, C. Simons, J. Zemlicka, Y. C. Cheng, *Antimicrob. Agents Chemother.* **1997**, *41*, 1755.

Therefore, the preparation of polyfunctionalized allenes is especially important [105] and there is a need for synthetic methods allowing to build up allenes bearing various functional groups.[106]

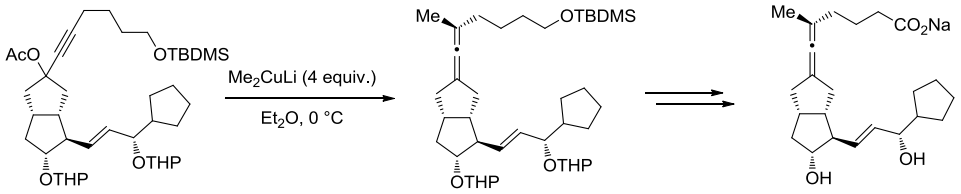
The preparation of allenes from propargylic halides, sulfonates or acetates *via* substitution reactions with copper organometallics is well known.[107] Generally, a S_N2'-substitution is observed with high regio- and stereo-selectivity. Thus, propargylic derivatives of type **54** react with organocopper reagents (R^3Cu) providing allenes of type **55** (Scheme 78).



X = Hal, OSO_2R, OAc, OMe

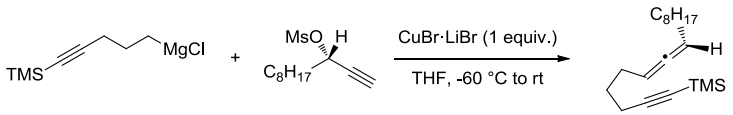
Scheme 78: Reactivity pattern of organocopper reagents on propargylic systems.

The stereoselective synthesis of "allene-carbacyclin" (**56**), a prostacyclin analog, includes a S_N2'-substitution to form allene **57**.[108] The reaction of 4 equivalents of Me_2CuLi with the propargylic acetate **54a** affords the corresponding allene in excellent yield (Scheme 79).



Scheme 79: Reaction of Me_2CuLi with propargylic acetate **54a** affording the allene **57**.

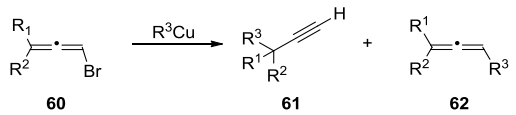
In addition to this high regioselectivity, the S_N2'-substitution on propargylic substrates is highly stereoselective. [109] Therefore, alkylmagnesium reagent **58** reacts in the presence of CuBr·LiBr (1 equiv.) in a stereoselective manner with the propargylic mesylate **54b** to provide the corresponding allene **59** without loss of stereoinformation (Scheme 80).



Scheme 80: Stereoselective synthesis of **59**.

[105] (a) A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed.* **2002**, *41*, 2933; (b) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067; (c) C. Deutsch, B. H. Lipshutz, N. Krause, *Org. Lett.* **2009**, *11*, 5010; (d) K. M. Brummond, J. E. DeForest, *Synthesis* **2007**, 795; (e) A. H. Stoll, S. B. Blakey, *J. Am. Chem. Soc.* **2010**, *132*, 2108.
[106] (a) K. M. Brummond, D. Chen, M. M. Davis, *J. Org. Chem.* **2008**, *73*, 5064; (b) J. P. Varghese, P. Knochel, I. Marek, *Org. Lett.* **2000**, *2*, 1849; (c) M. Ogasawara, H. Ikeda, T. Hayashi, *Angew. Chem. Int. Ed.* **2000**, *39*, 1042.
[107] (a) P. Rona, P. J. Crabbé, *J. Am. Chem. Soc.* **1968**, *90*, 4733; (b) P. Rona, P. J. Crabbé, *J. Am. Chem. Soc.* **1969**, *91*, 3289; (c) N. Krause, A. Hoffmann-Röder in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 145-166.
[108] S. W. Djuric, M. Miyano, M. Clare, R. M. Rydzewski, *Tett. Lett.* **1987**, *38*, 299.
[109] K. M. Brummond, A. D. Kerekes, H. Wan, *J. Org. Chem.* **2002**, *67*, 5156.

In contrast, the substitution reaction of allenyl bromides of type **60** provides usually a mixture of alkyne **61** (S_N2'-substitution) and allene **62** (S_N2-substitution, Scheme 81).[110]



Scheme 81: Reactivity pattern of organocopper reagents with allenyl bromides.

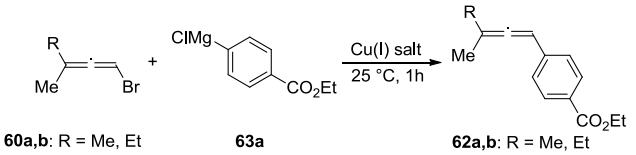
In all of these substitution reactions on bromoallenes of type **60**, the copper organometallics were prepared from organo-magnesium or -lithium reagents.[111]

Since arylmagnesium reagents of type **63** (ArMgX) tolerating various functional groups can be readily prepared and have proven to be versatile organometallic intermediates for the preparation of various polyfunctional molecules,[21, 24] their reactivity with bromo- or chloro-allenes in the presence of copper salts was investigated and a complete S_N2-selectivity providing only allenes was found. Furthermore, a new reaction sequence allowing the preparation of various polyfunctional allenes **62** starting from commercially available terminal alkynes was developed.

5.2 Preliminary Experiments

In preliminary studies, the copper-catalyzed substitution of two unfunctionalized bromoallenes[112] **60a** (R = Me) and **60b** (R = Et) with 4-(carbethoxy) phenylmagnesium chloride (**63a**) using catalytic amounts of various copper salts (Table 13) was examined. In all cases, the reaction produces only the S_N2-substitution product.[113]

Table 13: Influence of the nature of the copper-catalyst.



60a,b: R = Me, Et **63a** **62a,b**: R = Me, Et

Entry	Cu(I)-salt (10 mol%)	R	Yield [%][a]
1	CuBr	Et	85
2	CuCN·2LiCl	Et	89

[110] (a) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1984**, *25*, 3059; (b) A. M. Caporusso, C. Polizzi, L. Lardicci, *J. Org. Chem.* **1987**, *52*, 3920; (d) C. Polizzi, C. Consoloni, L. Lardicci, A. M. Caporusso, *J. Organomet. Chem.* **1991**, *417*, 289; (e) A. M. Caporusso, S. Filippi, F. Barontini, P. Salvadori, *Tetrahedron Lett.* **2000**, *41*, 1227; (f) A. M. Caporusso, C. Polizzi, L. Lardicci, *Tetrahedron Lett.* **1987**, *28*, 6073; (g) A. M. Caporusso, A. Zampieri, L. A. Aronica, D. Banti, *J. Org. Chem.* **2006**, *71*, 1902.

[111] (a) M. Kalli, P. D. Landor, S. R. Landor, *J. Chem. Soc., Perkin Trans. 1* **1973**, 1347; (b) R. K. Dieter, N. Chen, V. K. Gore, *J. Org. Chem.* **2006**, *71*, 8755; (c) For the use of organozinc reagents, see: K. Kobayashi, H. Naka, A. E. Wheatley, Y. Kondo, *Org. Lett.* **2008**, *10*, 3375; (d) For the use of organoindium reagents, see: i) R. Riveiros, D. Rodríguez, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **2006**, *8*, 1403; ii) K. Lee, P. H. Lee, *Org. Lett.* **2008**, *10*, 2441; (e) For an allene synthesis via sulfoxide-metal exchange, see: T. Satoh, N. Hanaki, Y. Kuramochi, Y. Inoue, K. Hosoya, K. Sakai, *Tetrahedron* **2002**, *58*, 2533.

[112] (a) S. R. Landor, A. N. Patel, P. F. Whiter, P. M. Greaves, *J. Chem Soc.* **1966**, 1223; (b) M. Montury, J. Goré, *Synth. Commun.* **1980**, *10*, 873.

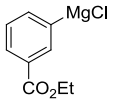
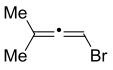
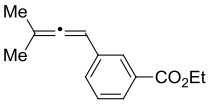
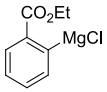
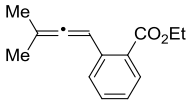
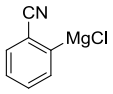
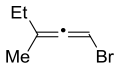
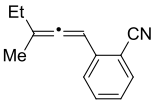
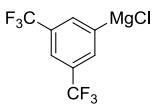
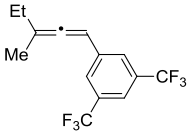
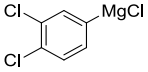
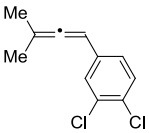
[113] The formation of the isomeric alkyne of type **61** is only observed if stoichiometric amounts of CuBr were used.

3	CuBr	Me	73
4	CuCl·2LiCl	Me	79
5	CuI	Me	75
6	CuCN·2LiCl	Me	80

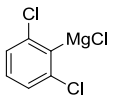
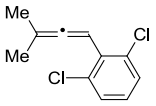
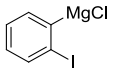
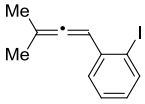
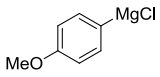
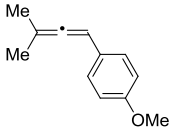
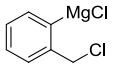
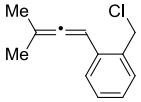
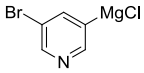
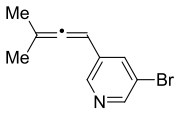
[a] Isolated yield of analytically pure product.

CuCN·2LiCl[114] provides the highest yields and the reaction scope varying the nature of the arylmagnesium reagents **63** was examined (Table 14). Thus, the ester-substituted aromatic organomagnesium reagents **63b-c** (1.0 equiv) reacted with 1-bromo-3-methylbuta-1,2-diene (**60a**, 1.2 equiv, 25 °C, 1 h) to the corresponding trisubstituted allenes **62c-d** in 76-85 % yield (Table 14, entries 1 and 2). Similarly, the reaction of 2-cyanophenylmagnesium chloride (**63d**, 1.0 equiv) and 3,5-bis(trifluoromethyl)phenylmagnesium chloride (**63e**, 1.0 equiv) with 1-bromo-3-methylpenta-1,2-diene (**60b**, 1.2 equiv) at 25 °C provided the allenes **62e-f** in 92-89 % yield within 1 h reaction time (entries 3 and 4). Aromatic *Grignard* reagents bearing halogen substituents, such as **63f-h** react smoothly with the bromoallene **60a** leading to the polyfunctional allenes **62g-i** (64-84 %, entries 5-7).

Table 14: Preparation of functionalized allenes starting from bromallenes **60a** and **60b**.

Entry	Organomagnesium Reagent[a]	Bromoallene	Product of Type **62**	Yield [%][b]
1	 **63b**	 **60a**	 **62c**	76
2	 **63c**		 **62d**	85
3	 **63d**	 **60b**	 **62e**	92
4	 **63e**		 **62f**	89
5	 **63f**		 **62g**	67

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

6				
	63g	**60a**	**62h**	64
7				
	63h	**60a**	**62i**	84
8				
	63i	**60a**	**62j**	69
9				
	63j	**60a**	**62k**	82
10				
	63k	**60a**	**62l**	87

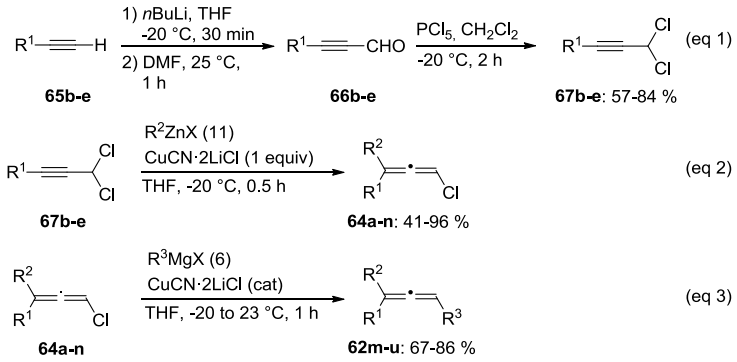
[a] For the sake of clarity, additional complexed salts are omitted; [b] Isolated yield of analytically pure product.

Furthermore, the reaction of the electron-rich 4-methoxyphenylmagnesium chloride (**63i**) with the bromoallene **60a** afforded the desired allene **62j** in 69 % yield (entry 8). The functionalized 2-chloromethylphenylmagnesium chloride (**63j**), prepared via iodine-magnesium exchange from 2-iodobenzyl chloride (*i*PrMgCl·LiCl, -20 °C, 30 min),[115] reacts with the bromoallene **60a** to the expected allene **62k** in 82 % yield (entry 9). Finally, the pyridylmagnesium derivative **63k** undergoes a copper-catalyzed substitution with **60a** furnishing the 3-allenylpyridine **62l** (87 %, entry 10).

5.3 Preparation of Functionalized Chloroallenes

In order to expand the reaction scope of our method, we also developed a general preparation method of functionalized chloroallenes of type **64** starting from commercially available alkynes of type **65** (Scheme 82).

[115] (a) T. Delacroix, L. Bérillon, G. Cahiez, P. Knochel, *J. Org. Chem.* **2000**, *65*, 8108; (b) C. B. Rauhut, C. Cervino, P. Knochel, *Synlett* **2009**, 67.



Scheme 82: Reaction sequence allowing the preparation of polyfunctionalzed allenes of type **62**.

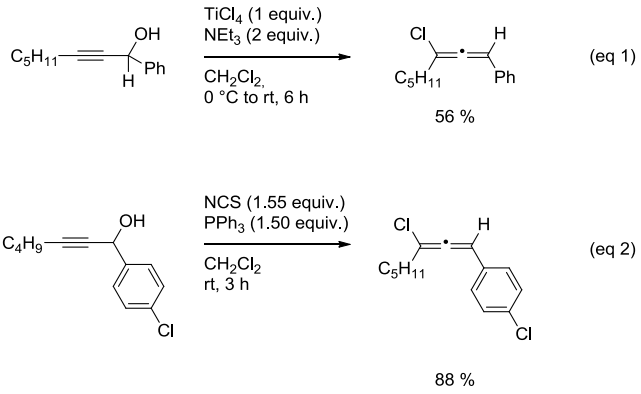
Thus, the alkynes **65b-e** were treated with *n*BuLi (1.1 equiv, -20 °C, 30 min) in THF followed by a reaction with DMF (2 equiv, -20 °C to 25 °C, 1 h) leading to the acetylenic aldehydes **66b-e**.[116] After work-up, the crude unsaturated aldehydes of type **66** were dissolved in CH_2Cl_2 and treated with PCl_5 providing the 1,1-dichloromethyl alkynes **67a-e** in 57-84 % yield (Scheme 82, eq 1).[117] The 1,1-dichloro propargylic reagents of type **67** prove to be versatile starting materials for the preparation of various polyfunctional allenes. Thus, we have developed a two step reaction sequence leading to functionalized allenes of type **62**:

(i) a highly regioselective copper-mediated S_N2'-substitution of alkyl and benzylic zinc reagents[34, 35, 118] with the dichloropropargyl derivatives **67a-e** leading to the chloroallenes **64a-m** in 41-96 % yield (Scheme 82, eq 2);

(ii) a highly regioselective copper-catalyzed S_N2-substitution of chloroallenes of type **64** with functionalized arylmagnesium reagents (**63**) providing the polyfunctionalized allenes **62m-u** in 67-86 % yield (Scheme 82, eq 3).

The preparation of chloroallenes from propargylic alcohols using $SOCl_2$, HCl or halocuprates is well known.[119] Due to the often strongly acidic conditions the tolerance towards functional groups is limited and often isomeric alkynes are observed. Other approaches involve the use of $TiCl_4$ and a tertiary amine (Scheme 83, eq 1)[120] or a modified Appel-reaction using *N*-chlorosuccinimide and PPh_3 (Scheme 83, eq 2).[121]

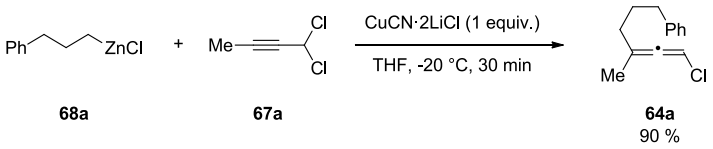
[116] M. Journet, D. Cai, L. M. DiMichele, R. D. Larsen, *Tetrahedron Lett.* **1998**, *39*, 6427.
[117] K. N. Shavrin, I. V. Krylova, I. B. Shvedova, G. P. Okonnishnikova, I. E. Dolgy, O. M. Nefedov, *J. Chem. Soc., Perkin Trans. 2* **1991**, 1875.
[118] A. Metzger, C. Argyo, P. Knochel, *Synthesis* **2010**, 882.
[119] (a) H. Mayr, I. K. Halberstad-Kausch, *Chem. Ber.* **1982**, *115*, 3479; (b) T. L. Jacobs, W. L. Petty, E. G. Teach, *J. Am. Chem. Soc.* **1960**, *82*, 4094.
[120] G. V. Karunakar, M. Periasamy, *J. Org. Chem.* **2006**, *71*, 7463.
[121] X. Du, Y. Dai, R. He, S. Lu, M. Bao, *Synthetic Commun.* **2009**, *39*, 3940.



Scheme 83: Synthesis of chloroallenes using either $TiCl_4/NEt_3$ (eq 1) or NCS/PPh_3 (eq 2).

Nevertheless, these approaches have certain drawbacks, such as poor yields or low atom economy combined with several byproducts.

Starting from 1,1-dichloromethyl alkynes, a copper-catalyzed S_N2'-substitution using organozinc reagents of type **68** allows a simple preparation of functionalized 1-chloroallenes. Thus, the alkylzinc reagent **68a** (1.0 equiv.) reacts with 1,1-dichlorobut-2-yne (**67a**, 1.1 equiv., -20 °C, 30 min) using CuCN·2LiCl (1.0 equiv.) leading to the chloroallene **64a** in 90 % yield (Scheme 84).

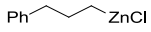
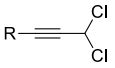
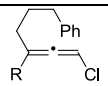
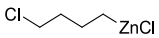
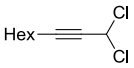
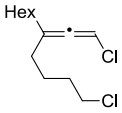
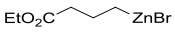
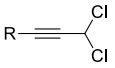
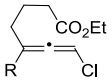
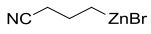
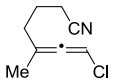
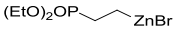
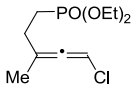
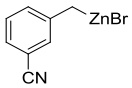
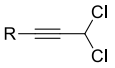
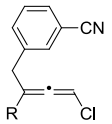
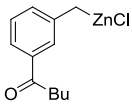
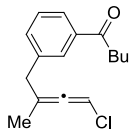
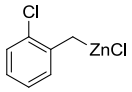
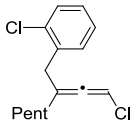
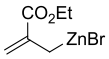
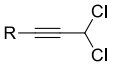
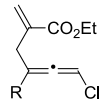


Scheme 84: Synthesis of chloroallene **64a** via a Cu(I)-mediated reaction of alkyl zinc reagent **68a** with the geminal dichloride **67a**.

The reaction of **68a** with 1,1,7-trichlorohept-2-yne (**67b**) affords exclusively the allene **64b** in 66 % yield (Table 15, entry 1). Similarly, 4-chlorobutylzinc chloride (**68b**) undergoes a smooth substitution reaction with 1,1-dichlorononon-2-yne (**67c**) to the desired chloroallene **64c** in 91 % yield (entry 2). The ester-substituted alkylzinc reagent **68c** reacts with the propargylic dichlorides **67a** and **67d** furnishing the corresponding chloroallenes **64d** and **64e** in 76 and 96 % yield (entries 3 and 4). Furthermore, 4-cyanobutylzinc chloride (**68d**) affords after a copper-catalyzed substitution reaction the cyanobutyl functionalized chloroallene **64f** (76 %, entry 5). The highly functionalized alkylzinc reagent **68e** bearing a diethylphosphate group[122] reacts with **67a** to provide the allene **64g** in 79 % yield (entry 6).

[122] C. Retherford, T.-S. Chou, R. M. Schelkun, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 1833.

Table 15: Cu(I)-mediated substitution on geminal progargylic dichlorides of type **67** leading to substituted chloroallenes.

Entry	Organozinc Reagent[a]	Propargylic Dichloride	Product of Type **64**	Yield [%][b]
1				
	68a	R = $Cl(CH_2)_4$: **67b**	R = $Cl(CH_2)_4$: **64b**	66
2				
	68b	**67c**	**64c**	91
3				
	68c	R = Me: **67a**	R = Me: **64d**	76
4	**68c**	R = Pent: **67d**	R = Pent: **64e**	96
5				
	68d	**67a**	**64f**	76
6				
	68e	**67a**	**64g**	79
7				
	68f	R = Me: **67a**	R = Me: **64h**	76
8	**68f**	R = $Cl(CH_2)_4$: **67b**	R = $Cl(CH_2)_4$: **64i**	87
9				
	68g	**67a**	**64j**	41
10				
	68h	**67d**	**64k**	89
11				
	68i	R = Pent: **67d**	R = Pent: **64l**	70[c]
12	**68i**	R = $CN(CH_2)_4$: **67e**	R = $CN(CH_2)_4$: **64m**	50[c]

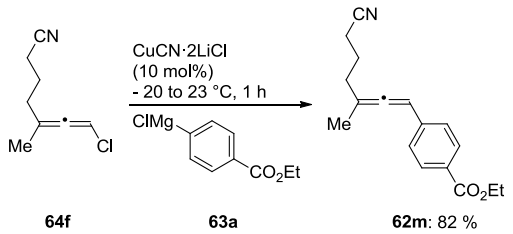
[a] Additional salts generated during the organometallic synthesis are omitted for the sake of clarity; [b] Isolated yield of analytically pure product; [c] The reaction was performed at -50 °C.

Also, benzylic zinc reagents, such as 3-cyanobenzylzinc chloride (**68f**), the keto-substituted benzylic zinc reagent **68g** and 2-chlorobenzylzinc chloride (**68h**) react under copper-catalysis with **67a**, **67b** or **67d** to the benzyl substituted chloroallenes **64h-k** in 41-89 % yield (entries 7-

10). Finally, the ester-substituted allylic zinc reagent **68i**[123] provided by a reaction with **67d** and **67e** the highly functionalized chloroallenes **64l** and **m** in 70 and 50 % yield, respectively (entries 11 and 12).

5.4 Preparation of Trisubstituted Allenes

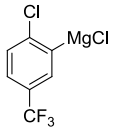
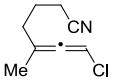
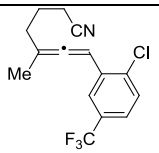
Encouraged by the good results found in the copper-catalyzed substitution of bromoallenes, we applied the method to chloroallenes of type **64**. To our delight, this novel substitution reaction occurred with S_N2-selectivity leading to highly functionalized trisubstituted allenes. Hence, the chloroallene **64f** (1.2 equiv.) bearing a remote nitrile function smoothly reacts with 4-carbethoxyphenylmagnesium chloride (**63a**, 1.0 equiv., -20 to 25 °C, 1 h) using CuCN·2LiCl as catalyst (10 mol%) to give the polyfunctionalized allene **62m** in 82 % yield (Scheme 85).



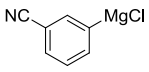
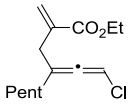
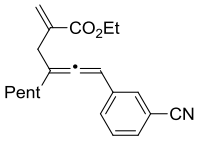
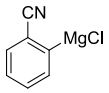
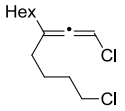
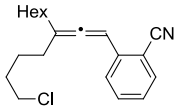
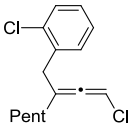
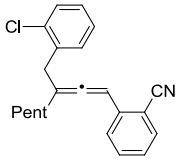
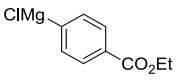
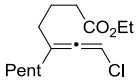
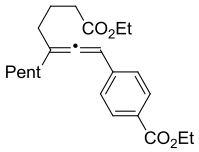
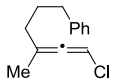
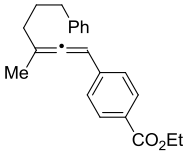
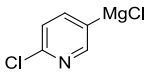
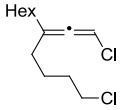
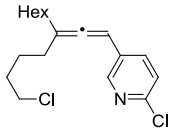
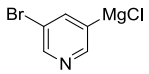
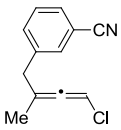
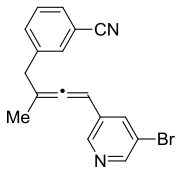
Scheme 85: Preparation of the trisubstituted allene **62m** via Cu(I)-mediated coupling of arylmagnesium reagent **63a** with chloroallene **64f**.

In order to show the scope of this novel S_N2-substitution on functionalized chloroallenes, we examined the reaction of diverse substituted chloroallenes with various arylmagnesium reagents (Table 16). Thus, 2-chloro-5-trifluoromethylphenylmagnesium chloride (**63l**, 1.0 equiv.) reacts with chloroallene **64f** (1.2 equiv.) to provide the trisubstituted allene **62n** in 86 % yield (Table 16, entry 1). Organomagnesium reagents bearing electron-withdrawing groups, such as 3-cyanophenylmagnesium chloride (**63m**) react smoothly with the allenyl chloride **64l** affording the functionalized trisubstituted allene **62o** in 67 % yield (entry 2).

Table 16: Cu(I)-mediated substitutions on allenyl chlorides leading to polyfunctional allenes of type **62**.

Entry	*Grignard* Reagent[a]	Chloroallene	Product of Type **62**	Yield [%][b]
1				
	63l	**64f**	**62n**	86

[123] N. El Alami, B. Belaud, J. Villiéras, *J. Organomet. Chem.* **1988**, *348*, 1.

2				
	63m	**64l**	**62o**	67
3				
	63d	**64c**	**62p**	76
4	**63d**			
		64k	**62q**	71
5				
	63a	**64e**	**62r**	83
6				
		64a	**62s**	67
7				
	63o	**64c**	**62t**	76
8				
	63k	**64h**	**62u**	71

[a] Additional salts generated during the organometallic synthesis are omitted for the sake of clarity; [b] Isolated yield of analytically pure product.

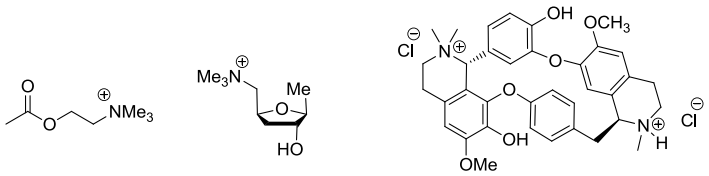
Furthermore, remote halogen substituents are well tolerated and the reaction of the arylmagnesium reagent **63d** with the chloroallene **64c** gives the expected trisubstituted allene **62p** in 76 % yield (entry 3). The copper-catalyzed reaction of the *Grignard*-reagent **63d** with the 2-chlorobenzyl substituted chloroallene **64k** furnishes the highly substituted allene **62q** in 71 % yield (entry 4). 4-Ethoxycarbonylphenylmagnesium chloride (**63a**), prepared from ethyl 4-iodobenzoate (*i*PrMgCl·LiCl, -20 °C, 30 min), reacts smoothly with the substituted chloroallenes **64e** and **64a** to the highly functionalized allenes **62r** and **62s** (83 and 67 % yield, entries 5 and 6). Moreover, functionalized heterocyclic *Grignard*-reagents, such as the pyridylmagnesium derivatives **63o** and **63k**, undergo clean substitution reactions with the

chloroallenes **64c** and **64h** furnishing the polyfunctionalized trisubstituted allenes **62t** and **62u** in 71 and 79 % yield (entries 7 and 8).

6 PREPARATION OF CHARGE-TAGGED ORGANOZINC REAGENTS

6.1 INTRODUCTION

The quaternary ammonium group is a common motif in biologically active molecules. Acetylcholine (**69**) is an important neurotransmitter bearing a trimethylammonium group.[124] Also Muscarine (**70**), the poison of *Amanita muscaria*, better known as fly agaric, contains a quaternary nitrogen.[125] Finally Tubocurarine hydrochloride (**71**) is an alkaloid form the bark of *Chondrodendron tomentosum* and is a component of various arrow poisons. [126]



69 Acetylcholine | **70** Muscarine | **71** Tubocurarine hydrochloride

Scheme 86: Biologically active molecules bearing cationic quaternary nitrogens.

Moreover, quaternary ammonium groups are present in a variety of commodities[127] and industrial chemicals[128] and have found increasing interest in material science.[129] Besides this extrodinary importance in living systems, quaternary ammonium groups allow a direct probing of molecules using electrospray-ionization (ESI) mass spectrometry.

As was shown before, there is a plethora of syntheses for organometallic reagents with an enormous diversity of electronic properties, coordination geometries, and aggregation states. This diversity in turn leads to various reactivity patterns and offers tremendous opportunities for synthesis and catalysis. However, elucidating the mechanism of many synthetically or catalytically useful reactions involving organometallics is rather difficult. In particular, the ability of metal centers to switch between different oxidation or coordination states and to engage in dynamic equilibria can dramatically complicate the situation. Several analytical techniques have been used to address this problem. Highly detailed and valuable structural information is given by X-ray crystallography. However, this method does not provide direct insight into the behavior of reactive intermediates in solution. In contrast, spectroscopic techniques can directly probe dissolved organometallic species. While NMR, IR, UV/Vis, and X-ray spectroscopy are suitable for the identification of reactive organometallic intermediates, the information obtained by these methods is not always sufficient for a full characterization of the system under investigation. Particularly, the distinction between different coordination and aggregation states can be challenging.

[124] (a) C. Gotti, M. Zoli, F. Clementi, *Trends Pharmacol. Sci.* **2006**, *27*, 482; (b) C. P. Hansen, A. A. Jensen, J. K. Christensen, T. Balle, T. Liljefors, B. Frølund, *J. Med. Chem.* **2008**, *51*, 7380.
[125] H. Corrodi, E. Hardegger, F. Kögl, *Helv. Chim. Acta* **1957**, *40*, 2454.
[126] (a) H. King, *J. Chem. Soc.* **1948**, 265; (b) A. J. Everett, L. A. Lowe, S. Wilkinson, *J. Chem. Soc. D* **1970**, 1020; (c) A. M. Betcher, *Anesth. Analg.* **1977**, *57*, 305.
[127] (a) L. Taub, H. Hahl, F. Leuchs (Alba-Pharmaceutical Company, Inc., New York), US 2087131, **1937**; (b) *Handbook of Topical Antimicrobials, Industrial Application in Consumer Products and Pharmaceuticals* (Ed.: D. S. Paulson), Marcel Dekker, New York, **2003**.
[128] L. Gulajski, M. Mauduit, K. Grela, *Pure Appl. Chem.* **2009**, *81*, 2001.
[129] (a) D. Izuhara, T. M. Swager, *J. Am. Chem. Soc.* **2009**, *131*, 17724; (b) T. L. Andre, T. M. Swager, *J. Am. Chem. Soc.* **2007**, *129*, 7254.

An alternative approach, which may help to overcome these problems by providing unambiguous stoichiometric information, relies on electrospray-ionization (ESI) mass spectrometry.[130] This method permits the transfer of ions from solution into the gas phase, thus allowing the sampling of dissolved charged organometallics *in situ*. It is therefore not surprising that ESI mass spectrometry has been applied to the analysis of numerous different organometallic systems.[131] The successful detection of various charged organometallics, including rather labile ones,[131,132] is consistent with the commonly accepted view that ESI constitutes a relatively "soft" ionization technique, which transfers only limited amounts of energy into the probed ions and does not significantly change their nature.[133] This assumption forms the basis on which properties of the solution-phase system are deduced from gas-phase measurements.

Unlike spectroscopic techniques, ESI mass spectrometry exclusively detects charged species. This feature can be advantageous if ionic systems shall be probed selectively. In most cases, however, the restriction to charged species forms a substantial drawback because neutral organometallics usually prevail over their ionized counterparts. While the fraction of ionized species may be increased by additives that lead to protonation, deprotonation, or complexation,[131a] these reactions can possibly change the nature of the organometallic system under investigation. For instance, protonation will obviously adversely affect organometallics sensitive to hydrolysis. In other cases, the use of additives may have more subtle effects and can thus lead to less conspicuous artifacts.

A potentially better approach pioneered by *Colton* and *Traeger*[134] and the groups of *Dyson*[135] and *Chen*[131c,136] uses covalently attached charged tags to make neutral organometallics amenable to ESI mass spectrometry. Provided that the charged tags have only low tendencies to form ion pairs with the counterions in the chosen solvent, almost the complete population of neutral organometallics can thus be ionized. Commonly employed tags are quaternary ammonium cations[131,134,136-138] and sulfonate anions.[135,139] In these ions, the charge is spread over several atoms, which does not only reduce their propensity to ion pairing, but also minimizes possible interactions with the metal center and unwanted changes in reactivity. Most of the examples reported so far bear a charged tag linked to coordinating ligands,[140] such as phosphines[135,136a,c,138,139] or carbenes.[136d] Obviously, this strategy is particularly suited for

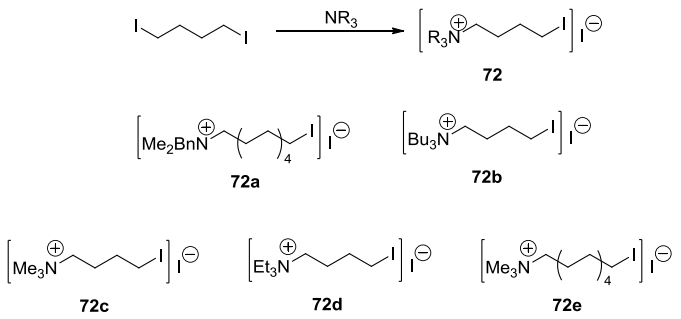
[130] M. Yamashita, J. B. Fenn, *J. Phys. Chem*. **1984**, *88*, 4451.
[131] For selected reviews, see: (a) J. C. Traeger, *Int. J. Mass Spectrom*. **2000**, *200*, 387; (b) D. A. Plattner, *Int. J. Mass Spectrom*. **2001**, *207*, 125; (c) P. Chen, *Angew. Chem. Int. Ed*. **2003**, *42*, 2832; (d) L. S. Santos, L. Knaack, J. O. Metzger, *Int. J. Mass Spectrom*. **2005**, *246*, 84; (e) W. Henderson, J. S. McIndoe, *Mass Spectrometry of Inorganic, Coordination and Organometallic Compounds: Tools, Techniques, Tips*, Wiley, Chichester, **2005**, pp. 175-219; (f) C. A. Müller, C. Markert, A. M. Teichert, A. Pfaltz, *Chem. Commun*. **2009**, 1607; (g) A. Roglans, A. Pla-Quintana in *Reactive Intermediates: MS investigations in solution*, (Ed.: L. S. Santos), Wiley-VCH, Weinheim, **2009**, pp. 229-276.
[132] (a) L. A. Hammad, D. Gerdes, P. Chen, *Organometallics* **2005**, *24*, 1907; (b) M.-E. Moret, P. Chen, *Organometallics* **2007**, *26*, 1523.
[133] R. B. Cole, *J. Mass Spectrom*. **2000**, *35*, 763.
[134] (a) R. Colton, J. C. Traeger, *Inorg. Chim. Acta* **1992**, *201*, 153; (b) I. Ahmed, A. M. Bond, R. Colton, M. Jurcevic, J. C. Traeger, J. N. Walter, *J. Organomet. Chem*. **1993**, *447*, 59.
[135] D. J. F. Bryce, P. J. Dyson, B. K. Nicholson, D. G. Parker, *Polyhedron* **1998**, *17*, 2899.
[136] (a) C. Hinderling, C. Adlhart, P. Chen, *Angew. Chem. Int. Ed*. **1998**, *37*, 2685 (b) C. Adlhart, P. Chen, *Helv. Chim. Acta* **2000**, *83*, 2192; (c) C. Adlhart, C. Hinderling, H. Baumann, P. Chen, *J. Am. Chem. Soc*. **2000**, *122*, 8204.
[137] C. Adlhart, P. Chen, *Helv. Chim. Acta* **2003**, *86*, 941.
[138] A. Dorcier, P. J. Dyson, C. Gossens, U. Rothlisberger, R. Scopelliti, I. Tavernelli, *Organometallics* **2005**, *24*, 2114.
[139] J. M. Basset, D. Bouchu, G. Godard, I. Karamé, E. Kuntz, F. Lefebre, N. Legagneux, C. Lucas, D. Michelet, J. B. Tommasino, *Organometallics* **2008**, *27*, 4300.
[140] For a recent review, see: D. M. Chisholm, J. S. McIndoe, *Dalton Trans*. **2008**, 3933.

probing transition metal complexes, whereas it cannot be applied to the detection of main-group organometallics that do not bear coordinating ligands.

Alternatively, the charged tag can be directly incorporated into an organyl moiety covalently bound to the metal center.[141, 142] This tagging scheme not only enables the analysis of systems lacking coordinating ligands but also lends itself to the analysis of coupling reactions that transfer the organyl moiety with the charged tag and thus ensure straightforward product identification.

6.2 Preparation of Charge-Tagged Organozinc Reagents

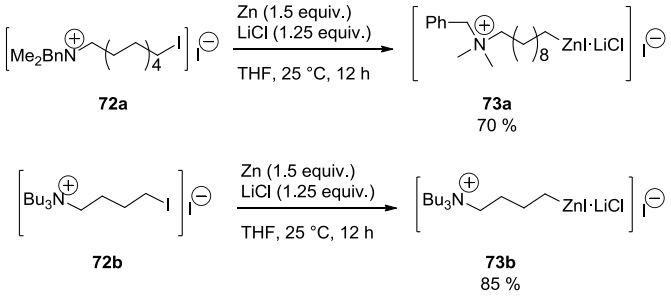
Among the commonly used organometallic reagents, organozinc reagents have an extraordinary functional group tolerance and unique reactivity. Although, *Frankland*'s synthesis of diethylzinc is known for more than 150 years, only little is known about their aggregates and stoichiometry in solution. Therefore, a synthesis of charge-tagged organozinc reagents was envisioned. Starting from α,ω-diiodoalkanes, a substitution reaction using a tertiary amine leads to the corresponding charge tagged alkyl iodide of type **72** (Scheme 87). [143]



Scheme 87: Synthesis of charge-tagged alkyliodides.

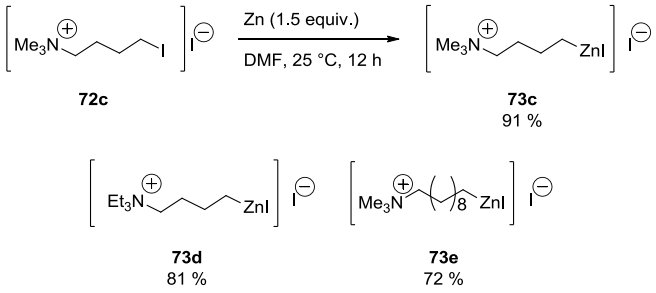
Using this method, a variety of charge tagged alkyl iodides have been prepared (**72a**-**e**). Due to the polarity of the ammonium group, only **72a** and **72b** are soluble in THF. Therefore, **72a** undergoes a smooth LiCl-mediated zinc insertion in THF affording the charge-tagged zinc reagent **73a** in 70 % yield (Scheme 88).

[141] E. Crawford, T. Lohr, E. M. Leitao, S. Kwok, J. S. McIndoe, *Dalton Trans*. **2009**, 9110.
[142] (a) R. A. J. O'Hair, T. Waters, B. Cao, *Angew. Chem. Int. Ed*. **2007**, *46*, 7048; (b) G. N. Khairallah, E. J. H. Yoo, R. A. J. O'Hair, *Organometallics* **2010**, *29*, 1238.
[143] J. Pliml, M. Borovička, M. Protiva, *Collect. Czech. Chem. Commun.*, **1958**, *23*, 704.



Scheme 88: Synthesis of charge-tagged organozinc reagents **73a** and **73b** in THF.

Also **72b** can be converted to its zinc reagent **73b** in 85 % yield. As mentioned before, the quaternary ammonium salts **72a-c** are not soluble in THF. Therfore, a LiCl mediated Zn insertion can not be performed in this solvent. The use of DMF instead of THF turned out to be suitable as it dissolves the quaternary ammonium salts and allows an efficient insertion reaction. Thus, the reaction of **72c** with zinc dust (1.5 equiv.) in DMF affords the charge-tagged organozinc reagent **73c** in 91 % (Scheme 89).

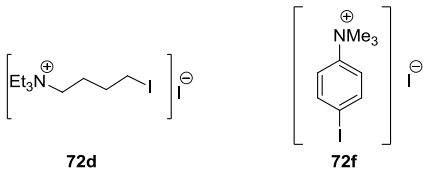


Scheme 89: Synthesis of charge-tagged organozinc reagents **73c-e** in DMF.

Moreover, the triethylammonium substituted butyl iodide **72d** reacts with Zn dust to form **73d** in 81 % yield. Finally, **73e** was prepared in 72 % yield from the corresponding charge-tagged alkyl iodide **72e**.

6.3 ESI-MS Analysis of Charge-Tagged Organozinc Reagents

As test system for the ESI-analysis of organozinc reagents the charge-tagged butyl iodide **72d** ($[RI]^+I^-$) and 4-iodo trimethylanilinium iodide (**72f**, $[ArI]^+I^-$)[144] were chosen.



Scheme 90: Charge-tagged substrates for ESI-analysis of organozinc reagents.

[144] H. Kobayashi, T. Sonada, K. Takuma, N. Honda, T. Nakata, *J. Flourine Chem.* **1985**, *27*, 1.

The reaction of zinc dust with the charge-tagged organic iodides $[ArI]^+I^-$ (**72f**) and $[RI]^+I^-$ (**72d**) in THF and ESI-mass spectrometric analysis of the resulting solutions afforded $[ArH]^+$ (m/z 136, Figure 8 in the experimental section) and $[RH]^+$ (m/z 158, Figure 9 in the experimental section), thus indicating conversion of both $[ArI]^+$ (m/z 262, and $[RI]^+$ (m/z 284), but also complete hydrolysis of the charge-tagged organozinc intermediates.[145] A comparison of the two reactions shows complete consumption of the alkyl iodide $[RI]^+$ at room temperature overnight whereas its aryl counterpart $[ArI]^+$ did not react to completion even at 50 °C. This lower reactivity of the aryl iodide toward Zn fully agrees with reports in the literature.

The extreme hydrolysis sensitivity of the charge-tagged organozinc intermediates is surprising because previous studies observed related intact zinc species with simple neutral alkyl substituents, such as $ZnR(THF)^{n+}$ and $ZnRHal_2^-$ (R = benzyl and butyl, Hal = Br and I, n = 1-3), under very similar experimental conditions. The stability of these ions was further enhanced in DMF.[146] We therefore also tested this solvent for the reaction of Zn with $[RI]^+I^-$ and now indeed could detect the charge-tagged organozinc species $[RZnI(DMF)_n]^+$, n = 1 and 2 (m/z 421 and 494, respectively), along with some hydrolysis product $[RH]^+$ (m/z 158) and a small amount of remaining reactant $[RI]^+$ (m/z 284, Figure 1).

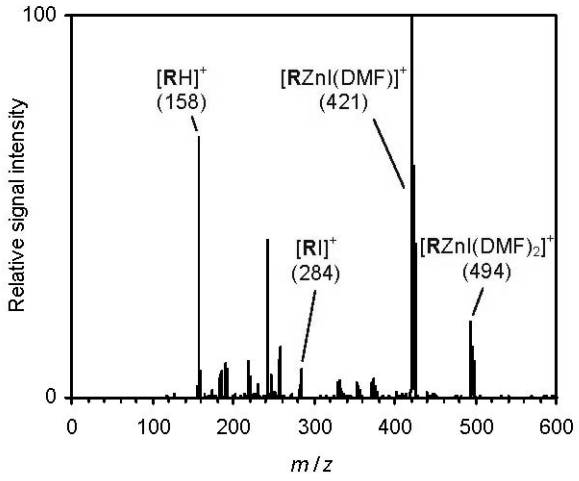


Figure 1: Positive ion mode ESI mass spectrum of an approx. 1 mM solution of the products (m/z ratios the most abundant isotopologues in brackets) formed upon reaction of Zn dust with triethyl-(4-iodobutyl)-ammonium iodide (**72d**,$[RI]^+I^-$) in DMF measured with the TSQ 7000 instrument. The ion at m/z = 242 corresponds to $Na(DMF)_3^+$, which presumably originates from a contamination of the ESI source.

The organozinc species observed display the stoichiometry expected for Zn(II) compounds and moreover provide insight into their solvation behavior. The fact that abundant DMF adducts are only found for Zn-containing species but not for $[RH]^+$ or $[RI]^+$ strongly suggests coordination of the solvent molecules to the Zn center and not to the quaternary ammonium group. The inferred coordination numbers of 3 and 4 agree with results obtained for microsolvated alkylzinc cations $ZnR(solv)_n^+$ (solv = THF, CH_3CN, and DMF), for which coordination numbers ≤4 were

[145] All ESI-experiments in this chapter were performed by Dr. K. Koszinowski or J. E. Fleckenstein.
[146] (a) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771; (b) J. E. Fleckenstein, K. Koszinowski, *Chem. Eur. J.* **2009**, *15*, 12745.

observed.[146b] Presumably, these organozinc species adopt tetrahedral coordination geometries in solution[147b] but are prone to lose one solvent molecule during the ESI process. In line with this conjecture, we found mass-selected $[RZnI(DMF)_2]^+$ (m/z 494) to lose the attached solvent molecules quite easily when subjected to gas-phase fragmentation (Figure 2).

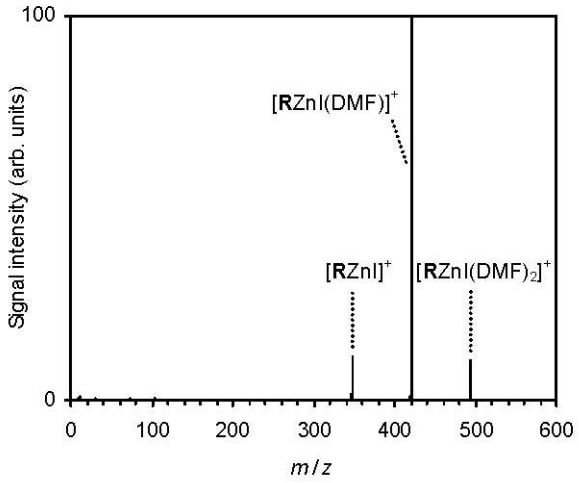


Figure 2: Mass spectrum of mass-selected $[R^{64}ZnI(DMF)_2]^+$ (m/z = 494, R = 4-triethylammonium-butyl) and its fragment ions produced upon collision-induced dissociation (E_{LAB} = 2 eV).

The cationic charged tags employed were obviously designed for the detection of organometallic intermediates by positive-ion mode ESI mass spectrometry. Therefore, we were surprised that analysis of the products formed upon reaction of Zn with $[RI]^+I^-$ in DMF by negative ion mode ESI mass spectrometry (Figure 3) not only resulted in the detection of $I(DMF)_n^-$, n = 0 (m/z 127) and 1 (m/z 200), I_3^- (m/z 381), and ZnI_3^- (m/z 445), but also of small quantities of $[RZnI_3]^-$ (m/z 602).

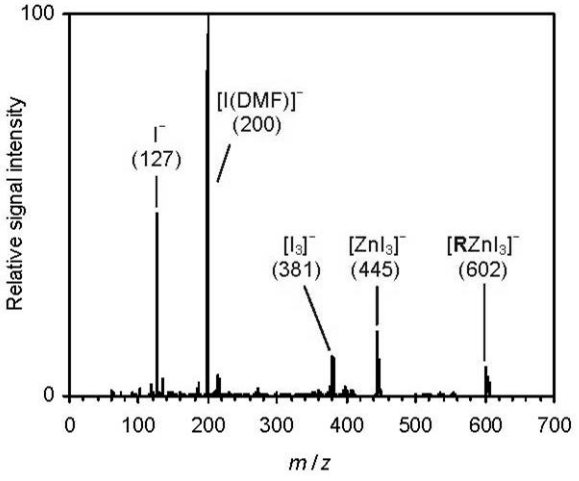
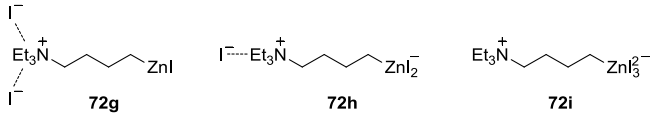


Figure 3: Negative ion mode ESI mass spectrum of an approx. 1 mM solution of the products (m/z ratios of the most abundant isotopologues in brackets) formed upon reaction of Zn with triethyl-(4-iodobutyl)-ammonium iodide (**72d**, [RI]+I−) in DMF measured with the TSQ 7000 instrument.

[147] (a) L. Caggiano, R. F. W. Jackson, A. J. H. M. Meijer, B. T. Pickup, K. A. Wilkinson, *Chem. Eur. J.* **2008**, *14*, 8798; (b) F. Dreiocker, J. Oomens, A. J. H. M. Meijer, B. T. Pickup, R. F. W. Jackson, M. Schäfer, *J. Org. Chem*. **2010**, *75*, 1203.

For the latter, three different structures seem conceivable (Scheme 91).



Scheme 91: Conceivable structures for the observed anion $[RZnI_3]^-$ (m/z 602).

In structure **72g**, two I^- anions are bound electrostatically to the ammonium group. This type of complex is considered less likely because the absence of the analogous ions $[(RH)I_2]^-$ (m/z 412) and $[(RI)I_2]^-$ (m/z 538) in the mass spectrum indicates a low stability of this binding motif under the ESI conditions applied. Structure **72h** contains an organozincate moiety, which closely resembles previously observed alkylzincates $RZnHal_2^-$.[146] In structure **72i**, coordination of all three I^- anions to the Zn atom builds up a twofold negative charge at the metal center, which would be prohibitively demanding in energy for a linear conformation. However, adoption of a cyclic conformation could permit a stabilizing electrostatic interaction between the dianionic ZnI_3 moiety and the cationic ammonium group. Fragmentation of mass-selected $[RZnI_3]^-$ (m/z 602) yields I^- and ZnI_3^- as ionic products (Figure 4), which is of limited significance only because the involvement of rearrangement reactions seems quite likely. Hence, the experimental results do not suffice for an unambiguous structural assignment.

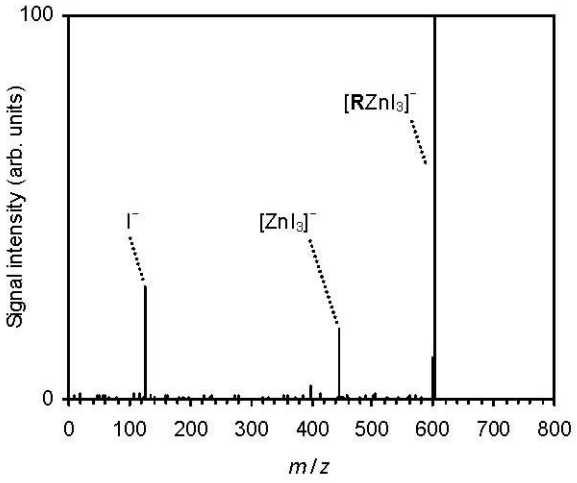
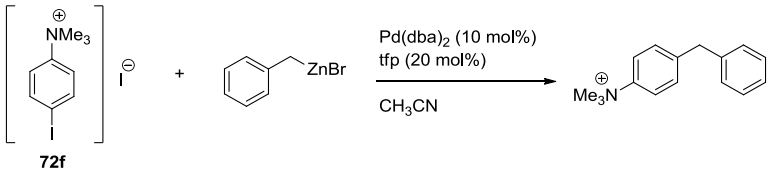


Figure 4: Mass spectrum of mass-selected $[R^{64}ZnI_3]^-$ (m/z = 602, R = 4-triethylammonium-butyl) and its fragment ions produced upon collision-induced dissociation (E_{LAB} = 17 eV).

6.4 Monitoring of Cross-Coupling Reactions

As shown above, ESI mass spectrometry has permitted us to track the degradation and hydrolysis of organometallics bearing organic substituents with charged tags. Obviously, it would be even more interesting to use this approach for analyzing synthetically valuable reactions of these species. We have done so and demonstrated the potential of this analytical

method by studying the Pd-catalyzed cross-coupling of $[ArI]^+$ with benzylzinc bromide (*Negishi* cross-coupling, Scheme 92).[148]



Scheme 92: Test system for the Pd-catalyzed cross-coupling of **72f** with benzylzinc bromide.

Negishi cross-couplings constitute one of the most versatile tools in modern organic synthesis.[149] The mechanisms of these reactions therefore have attracted a great deal of attention. It is commonly assumed that these reactions start by the oxidative addition of the organic halide to the zero-valent Pd (or Ni) catalyst. The resulting insertion product then undergoes transmetallation by the organozinc reagent and finally yields the coupling product by reductive elimination.[149c]

For our experiments, we employed $Pd(dba)_2$/tfp (L) in CH_3CN as catalytic system, which efficiently adds $[ArI]^+$.[150] In the presence of BnZnBr, the expected coupling product $[ArBn]^+$ (m/z 226) could indeed be detected by ESI mass spectrometry (Figure 5). The identity of this species was confirmed by analysis of its fragmentation pattern (Figure 10 in the experimental section) and by a control experiment in which BnZnBr was substituted by *m*-methylbenzylzinc bromide. This resulted in a coupling product of an m/z ratio shifted by 14 amu relative to $[ArBn]^+$.

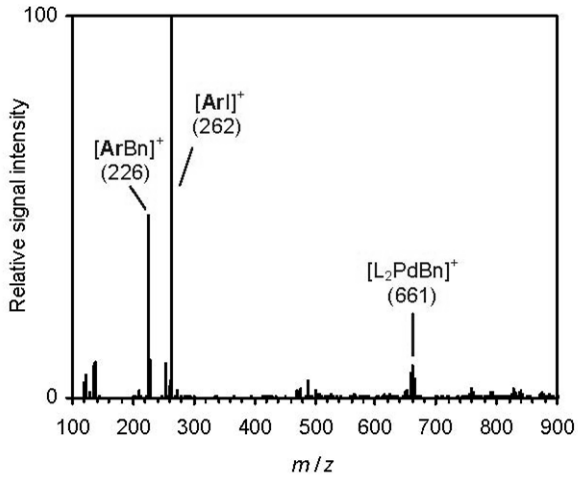
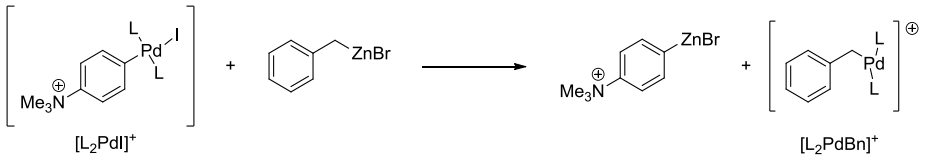


Figure 5: Positive ion mode ESI mass spectrum of an approx. 2 mM solution of (*p*-iodophenyl)-trimethylammonium iodide ($[ArI]^+I^-$), BnZnBr (1.2 equiv), $Pd(dba)_2$ (10 mol%), and tri-(2-furyl)phosphine (L, 20 mol%) in CH_3CN approx. 15 min after mixing measured with the HCT ion trap (m/z ratios of the most abundant isotopologues of the ions observed given in brackets).

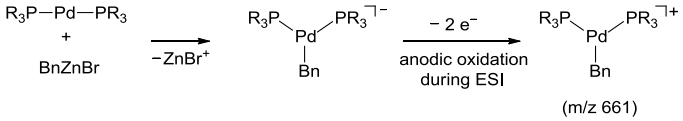
[148] All ESI-experiments were done by Dr. K. Koszinowski.
[149] (a) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal*. **2004**, *346*, 1525; (b) A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed*. **2005**, *44*, 674; (c) E.-i. Negishi, Q. Hu, Z. Huang, G. Wang, N. Yin, in *The Chemistry of Organozinc Compounds*; (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2006**, pp 457-553; (d) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; (e) V. B. Phapale, D. J. Cárdenas, *Chem. Soc. Rev*. **2009**, *38*, 1598; (f) S. Calimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem. Int. Ed*. **2010**, *49*, 2014.
[150] M. A. Schade, J. E. Fleckenstrein, P. Knochel, K. Koszinowski, *J. Org. Chem.* **2010**, *75*, 6848.

In addition, smaller amounts of $[L_2PdBn]^+$ (m/z 661) were produced. Again, this assignment is based on the recorded isotope pattern (Figure 11 in the experimental section), fragmentation experiments (Figure 12 and Figure 13 in the experimental section) and on an observed mass shift of 14 amu when BnZnBr was replaced by *m*-methylbenzylzinc bromide. The $[L_2PdBn]^+$ (m/z 661) complex accumulated with time and increased in signal intensity as a function of catalyst loading (Figure 14 in the experimental section). Surprisingly, it even formed to some extent in the reaction of the Pd catalyst with BnZnBr in the absence of aryl iodide $[ArI]^+$ (Figure 15 in the experimental section). However, in this case the abundance of $[L_2PdBn]^+$ (m/z 661) was considerably decreased as indicated by the relatively poor signal/noise ratio. As a consequence, additional ions of similarly low absolute signal intensity, such as $[CuL_n]^+$ and $[(LO)_nZnBn]^+$ also became visible; the assignments of these species, which may have originated from contaminations, are based on the observed isotope patterns and fragmentation experiments (Figure 16–Figure 27 in the experimental section). The genesis of the complex $[L_2PdBn]^+$ (m/z 661) itself is not obvious. The higher absolute signal intensities observed in the presence of added $[ArI]^+$ might suggest that it forms in a metathesis reaction between the primary insertion product $[L_2ArPdI]^+$ and BnZnBr (Scheme 93).



Scheme 93: Possible reaction to form $[L_2PdBn]^+$.

In this case, however, one would also expect to observe $[ArZnX]^+$, X = Br and/or I (m/z 278/280 and 326, respectively, or degradation products thereof), which was not detected. Alternatively, one may speculate that $[L_2PdBn]^+$ (m/z 661) could result from the transmetallation of a Pd(0) species. For related Ni(0) phosphine complexes in the presence of organomagnesium and –zinc reagents, *Terao* and *Kambe* have suggested the occurrence of transmetallation reactions and formation of nickelate anions.[151] In analogy, the current experiments might potentially produce a palladate species (Scheme 94). This extremely electron-rich species could then possibly afford the observed $[L_2PdBn]^+$ cation by anodic oxidation during the ESI process.[152] Negative ion mode ESI mass-spectrometric experiments did not detect any palladate species, however, and instead only showed the presence of various zincate complexes (Figure 28 in the experimental section).



Scheme 94: Possible genesis of the observed $[L_2PdBn]^+$ complex (R = 2-furyl) by anodic oxidation during ESI.

Returning to the actual *Negishi* coupling between $[ArI]^+I^-$ and BnZnBr itself, we wondered whether ESI mass spectrometry could also be used to monitor the temporal evolution of

[151] J. Terao, N. Kambe, *Bull. Chem. Soc. Jpn*. **2006**, *79*, 663.
[152] G. J. Van Berkel, *J. Mass Spectrom*. **2000**, *35*, 773.

reactants and products and to derive the rate constant(s) of this reaction. To test for this possibility, we prepared a mixture of the reactants and the catalyst and continuously administered it into the ESI source of the mass spectrometer while recording the positive ion mode ESI mass spectrum. Averaging every 50–100 scans then gave a time resolution of approx. 10 s. The resulting averaged signal intensities still show rather high noise levels (Figure 8), which directly reflect the relatively poor absolute signal stability typical of the ESI process. Nevertheless, the obtained time profiles clearly exhibit the opposing trends expected for reactants and products. While varying the concentration of the benzylzinc reagent (1.2–2.0 equiv relative to $[ArI]^+I^-$) did not have a discernible effect, an increase in the catalyst loading strongly accelerated the decay of reactant $[ArI]^+$ (m/z 262, Figure 6). This finding points to a rate-determining oxidative addition, which is followed by fast transmetallation and reductive elimination steps. The same conclusion can also be derived from the fact that the mass spectra show the simultaneous presence of reactant $[ArI]^+$ (m/z 262) and product $[ArBn]^+$ (m/z 226) but far less of intermediate $[L_2ArPdI]^+$ (m/z 832), because it is almost completely consumed by the fast consecutive reaction with BnZnBr (compare Figure 5, although in this case the lower concentration of the catalyst helps to suppress the relative signal intensity of $[L_2ArPdI]^+$). Note that an alternative tagging mode that attached the charged tag to the phosphine ligand would neither permit the detection of the reactant aryl iodide nor the cross-coupling product and thus would be less useful than the present approach.

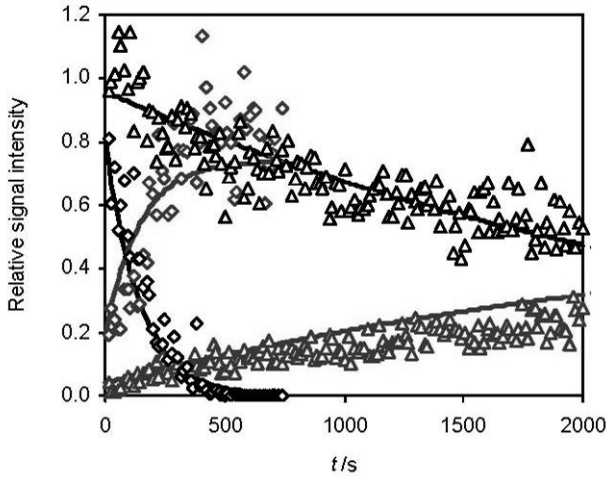


Figure 6: Time dependence of the normalized signal intensities of reactant $[ArI]^+$ (m/z 262, black) and product $[ArBn]^+$ (m/z 226, grey) formed in the Pd-catalyzed cross-coupling reaction with BnZnBr in CH_3CN at room temperature as determined by ESI mass spectrometry. Results of two experiments with different catalyst loadings are shown (diamonds: 100 mol%, triangles: 5 mol% relative to $[ArI]^+$). The solid lines represent simulated time profiles based on a second-order rate constant of k_2 = 3.5 L mol^{-1} s^{-1} (see text for details). Time zero corresponds to the start of the ESI mass-spectrometric experiments, which was approx. 2 min after the mixing of the reaction partners.

For a quantitative analysis, we focused on the decline of reactant $[ArI]^+$ (m/z 262), which according to our model should proceed under pseudo first-order conditions (virtually constant concentration of free Pd catalyst). Indeed, the individual time profiles of the $[ArI]^+$ (m/z 262) signal intensity could be satisfactorily fitted with mono-exponential functions. Correlating the corresponding pseudo first-order rate constants with the concentrations of the Pd catalyst in the individual experiments ($c(Pd(dba)_2)$ = 10^{-4}–2×10^{-3} mol L^{-1}) then gave a second-order rate

constant of k_2 = 4 ± 2 L mol^{-1} s^{-1} for the oxidative addition at room temperature. Based on this value, the decline of the [ArI]$^+$ (m/z 262) signal intensities in Figure 6 could be reproduced quite well. The derived k_2 rate constant was also used to predict the increase of the [ArBn]$^+$ (m/z 226) signal intensities. Here, it was furthermore necessary to introduce a constant scaling factor to account for apparently slightly deviating ESI response factors[153] of reactant and product ions and/or mass-dependent ion transmission and detection efficiencies. The agreement between observed and simulated signal intensities of the [ArBn]$^+$ (m/z 226) coupling product does not equal that observed for the [ArI]$^+$ (m/z 262) reactant but still is reasonably good.

The oxidative addition of [ArI]$^+$ to PdL_2 (L = tfp) in CH_3CN can be compared to the analogous addition of simple PhI to PdL_2 in THF and DMF. The latter reactions are somewhat faster (k_2(THF) = 500 ± 200 and k_2(DMF) = 99 ± 2 L mol^{-1} s^{-1}),[154] although the presence of the electron-withdrawing ammonium group in [ArI]$^+$ should activate this substrate for the oxidative addition.[155] This comparison suggests that CH_3CN significantly slows down the addition of aryl iodides to zero-valent Pd complexes, presumably by binding to the metal center and blocking of a coordination site. In line with this assessment, CH_3CN is not commonly used as solvent in *Negishi* cross-coupling reactions[149c] although its high polarity and volatility make it ideally suitable for the present model studies.

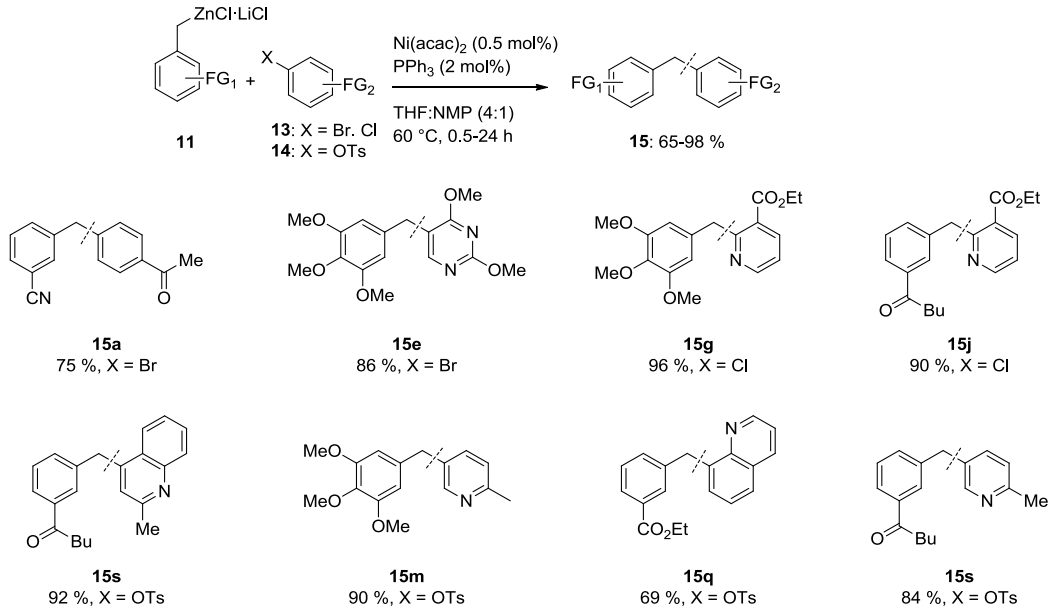
[153] (a) L. Tang, P. Kebarle, *Anal. Chem*. **1993**, *65*, 3654; (b) C. G. Enke, *Anal. Chem*. **1997**, *69*, 4885.
[154] C. Amatore, A. Jutand, F. Khalil, *Arkivoc* **2006**, 38.
[155] (a) J. F. Fauvarque, F. Pflüger, M. Troupel, *J. Organomet. Chem*. **1981**, *208*, 419; (b) A. Jutand, A. Mosleh, *Organometallics* **1995**, *14*, 1810.

7 SUMMARY AND OUTLOOK

This work focused on the synthesis and application of organozinc reagents. A cheap and efficient Ni-catalyzed cross-coupling reaction of benzylic zinc chlorides has been developed and extended to a more general Pd-catalyzed coupling reaction. Furthermore, a general synthesis of functionalized alkenyl zinc reagents starting from alkenylbromides has been developed. Also, the scope of the directed *ortho* insertion of zinc dust in polybrominated arenes and the orthogonal *para* insertion using magnesium in the presence of LiCl was broadend and the industrial applicability of this method by a scale-up to 100 mmol reactions was shown. Moreover, it was demonstrated, that primary amides can easily prepared starting from functionalized organozinc halides *via* an addition reaction to trichloroacetyl isocyanate. A Ni-catalyzed version of this reaction also allows the synthesis of secondary amides. Additionally, the synthesis of highly functionalized allenes via two successive Cu(I)-mediated substitution reaction was studied. Finally, a synthesis of organozinc reagents bearing a cationic moiety was developed and successfully used in monitoring a *Negishi*-type cross-coupling reaction.

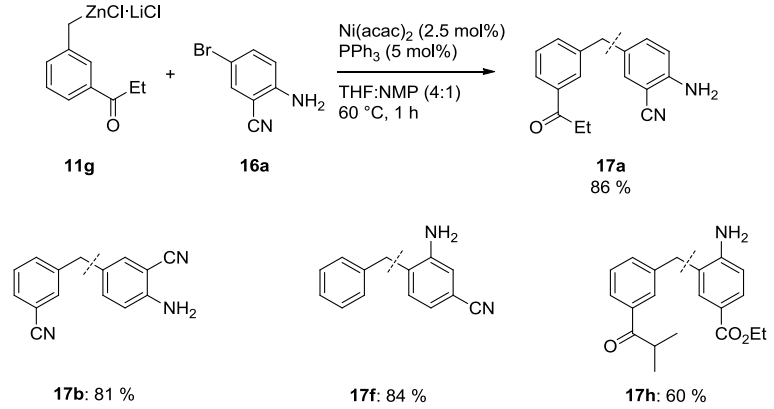
7.1 CROSS-COUPLING REACTIONS OF BENZYLIC ZINC REAGENTS

A new and highly efficient Ni-catalyzed cross-coupling reaction of benzylic zinc reagents with aromatic and heteroaromatic halides and tosylates was developed. With 0.5 mol% catalyst loading and cheap and readily available PPh_3 as ligand, the reaction tolerates various functional groups in the electrophile as well as in the used benzylic zinc reagent and affords a manifold of valuable diarylmethanes (Scheme 95).



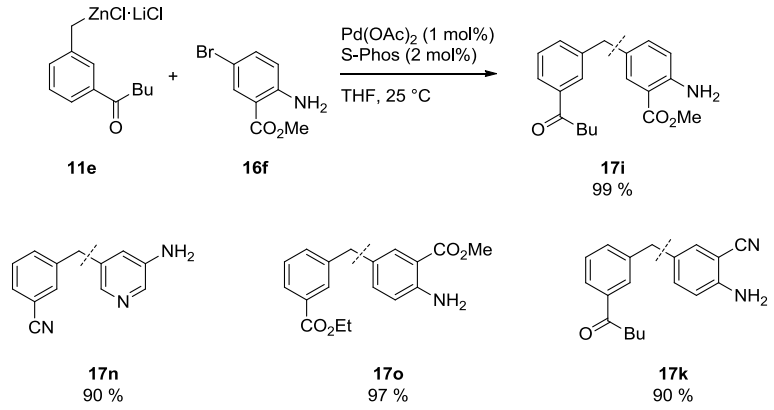
Scheme 95: Ni-catalyzed cross-coupling reaction of aromatic and heteroaromatic bromides, chlorides, and tosylates.

Using a higher catalyst loading (2.5 mol%) and a slow addition of the organozinc reagent to the electrophile, also bromoaniline derivatives can be used as electrophiles in the cross-coupling reaction without prior deprotonation of the acidic protons (Scheme 96).



Scheme 96: Ni-catalyzed cross-coupling of benzylic zinc reagents with bromoaniline derivatives bearing relatively acidic protons.

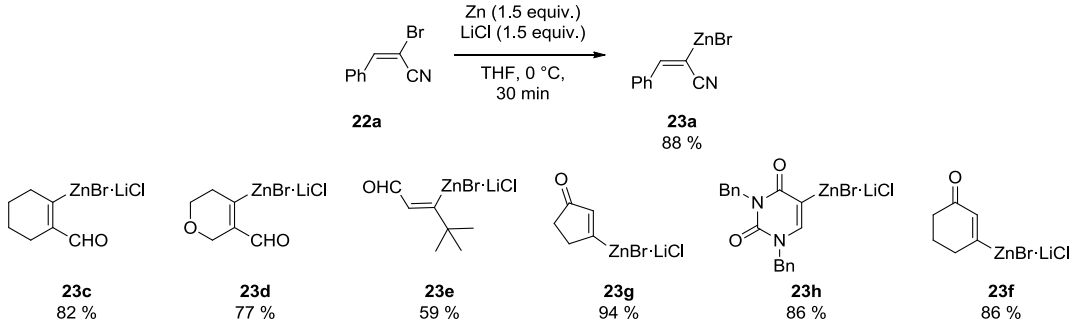
To extend the scope of this cross-coupling reaction with bromoaniline derivatives, $Pd(OAc)_2$ and S-Phos was found to be a reliable catalytic system (Scheme 97).



Scheme 97: Pd-catalyzed cross-coupling reactions of benzylic zinc reagents with bromoaniline derivatives bearing relatively acidic protons.

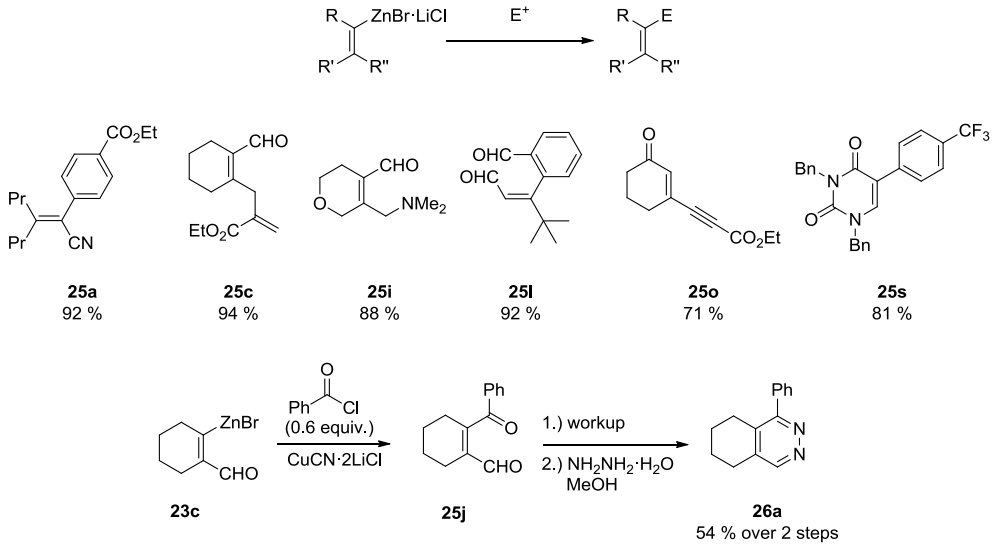
7.2 Preparation and Application of Alkenyl Zinc Reagents

In summary, the LiCl-mediated preparation of alkenyl zinc reagents *via* direct metal insertion was examined. Electronically activated alkenyl bromides, for instance by a geminal cyano group or a vicinal aldehyde, undergo a smooth insertion of commercially available Zn dust in the presence of LiCl (Scheme 98).



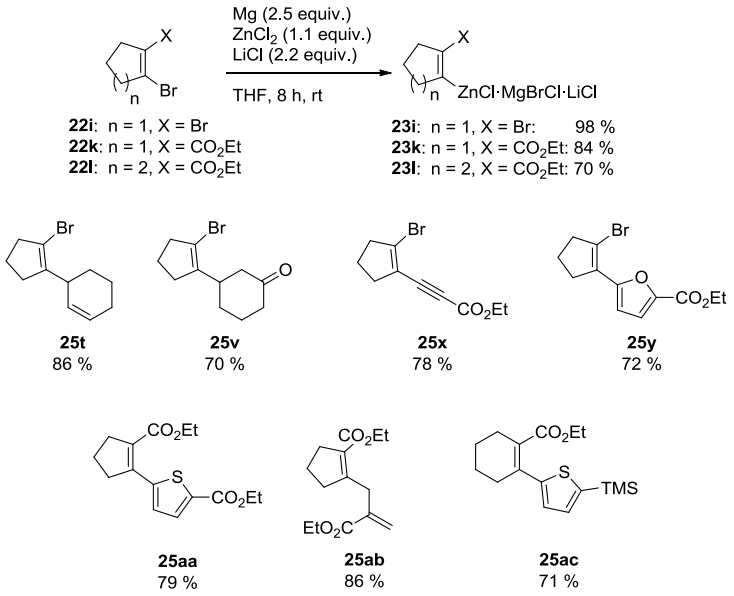
Scheme 98: Synthesis of alkenyl zinc reagents via LiCl-mediated zinc insertion.

These alkenyl zinc reagents undergo smooth reaction with a variety of electrophiles leading to highly functionalized unsaturated systems (Scheme 99).



Scheme 99: Reaction of alkenyl zinc reagents with various electrophiles leading to highly functionalized unsaturated systems.

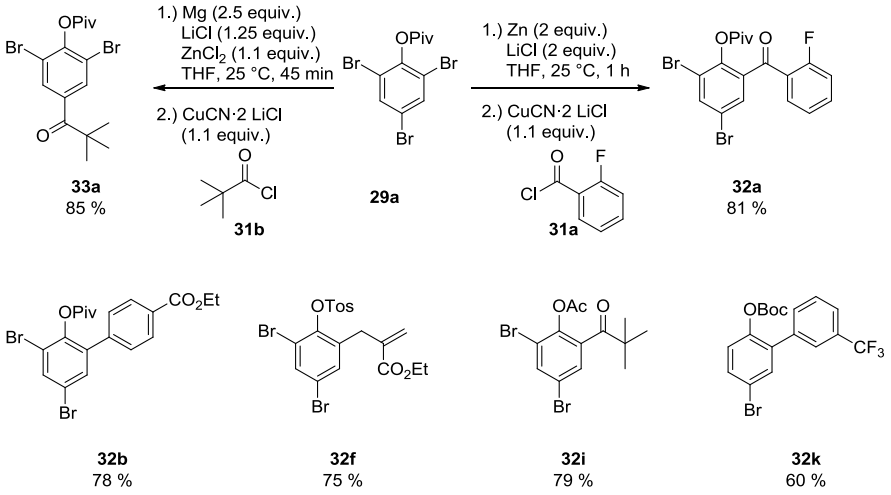
Electronically less activated alkenyl bromides, such as 1,2-dibromocyclopentene (**22i**) or the ester substituted alkenyl bromides **22k** and **22l**, can be converted to their zinc reagents *via* a LiCl-mediated Mg insertion in the presence of $ZnCl_2$. The corresponding zinc reagents then react with a variety of electrophiles furnishing the substituted alkenyl derivatives (Scheme 100).



Scheme 100: LiCl-mediated magnesium insertion in the presence of $ZnCl_2$ in electronically less activated alkenyl bromides.

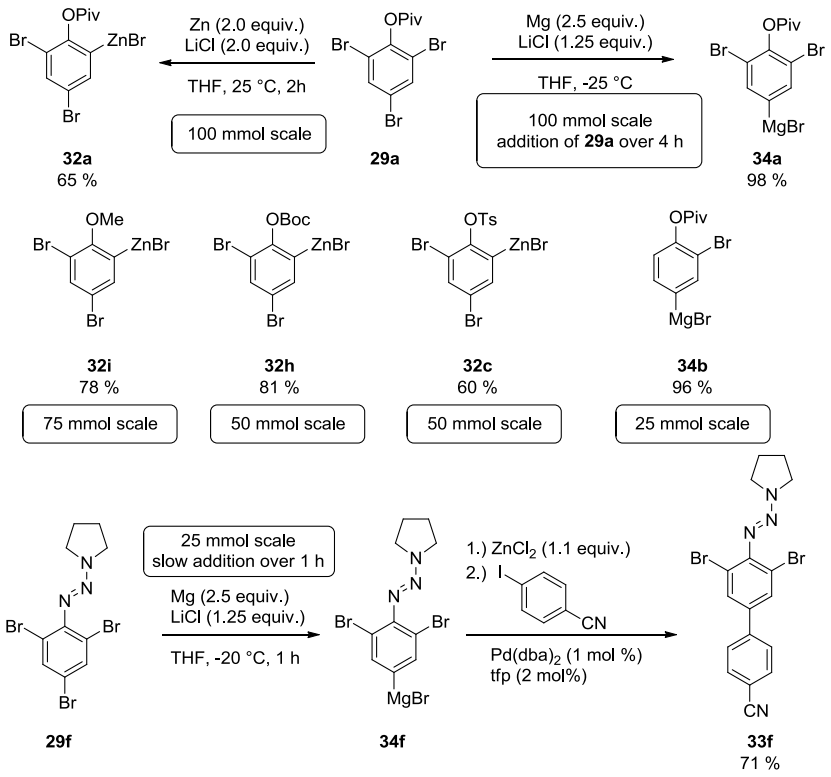
7.3 Regioselective Magnesium and Zinc Insertions in Polybrominated Protected Phenols

The scope of the directed *ortho*-insertion using Zn/LiCl and the orthogonal magnesium insertion using Mg/LiCl was examined. High regioselectivities were obtained in all Zn insertions whereas the corresponding Mg insertion is limited to certain protecting groups (Scheme 101).



Scheme 101: Regioselective Zn insertions in polybrominated phenol derivatives.

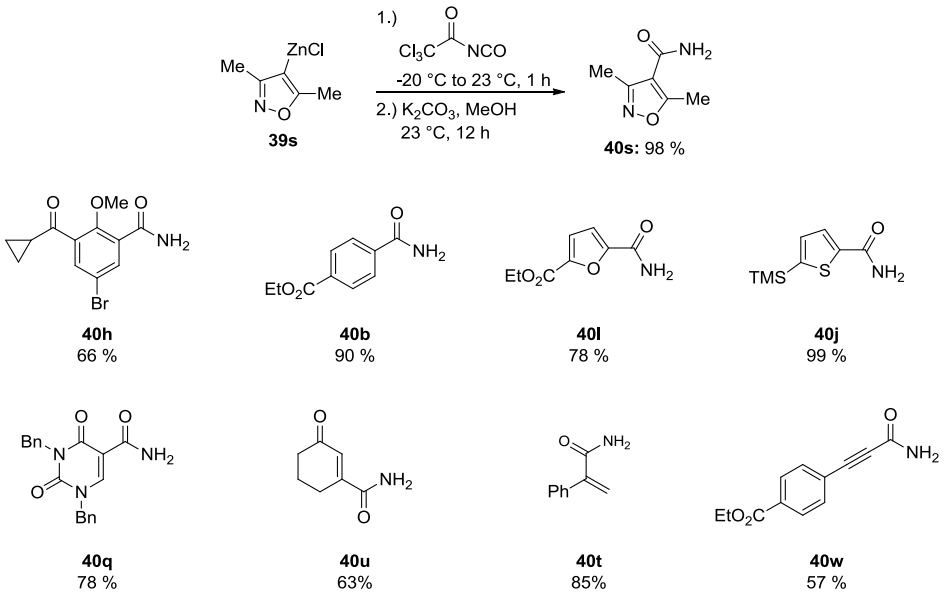
With regard to industrial application, the scale up of these reactions was studied. It was shown, that both, the directed *ortho*-insertion and the orthogonal *para*-insertion can be performed up to 100 mmol without loss of regioselectivity (Scheme 102).



Scheme 102: Regioselective metal insertions in larger scale.

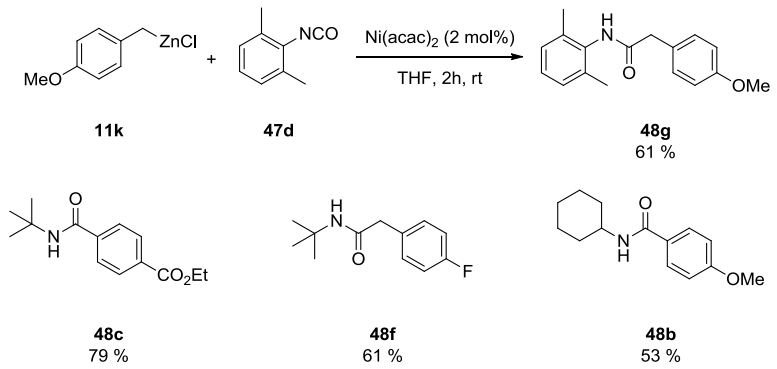
7.4 Preparation of Amides from Functionalized Organozinc Reagents

A new synthetic route to highly functionalized primary amides ($CONH_2$) using commercially available trichloroacetyl isocyanates and organozinc halides was developed. Mild reaction conditions, high efficiency and a broad scope of substrates gives an easy access to a great variety of substituted primary amides (Scheme 103).



Scheme 103: Synthesis of primary amides starting from functionalized organozinc halides.

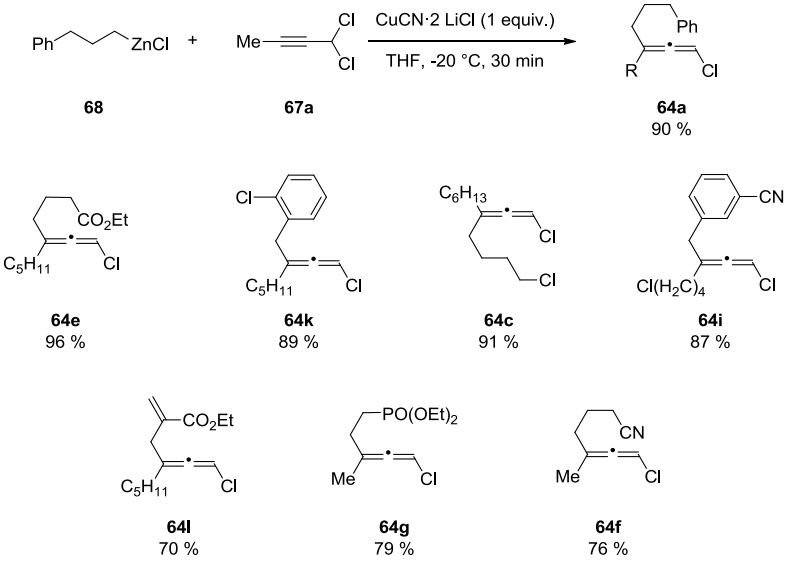
Using this method, aromatic, heterocyclic, alkenylic and alkynylic primary carboxamides have been prepared. Extension of this work to substituted isocyanates is limited and a Ni-catalyst is needed to afford the desired secondary amides (Scheme 104).



Scheme 104: Ni-catalyzed synthesis of secondary amides using substituted isocyanates and functionalized organozinc halides.

7.5 Preparation of Highly Functionalized Allenes via Successive Copper-Mediated Substitution Reactions

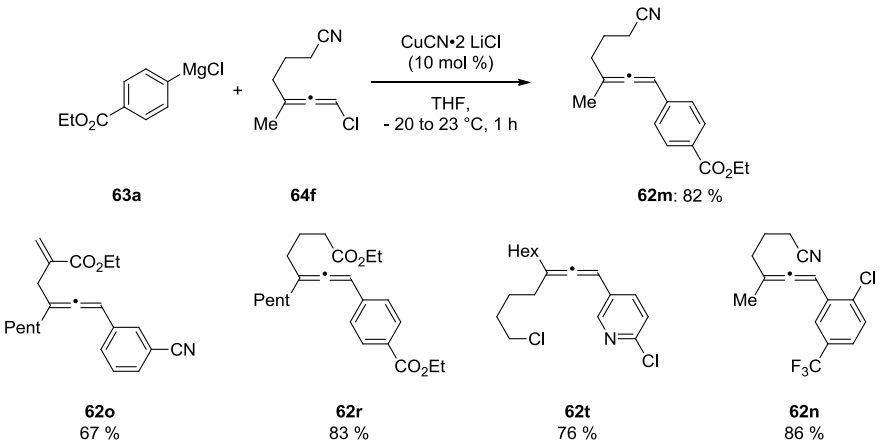
By using readily available 1,1-dichloromethyl alkynes of type **67** (prepared in two steps from commercially available alkynes), a convenient synthesis of polyfunctional allenes using two successive copper-catalyzed substitution reactions was developed. The first substitution of alkyl and benzylic zinc halides on the 1,1-dichloromethyl alkynes **67** proceeds with complete S_N2' selectivity leading to 1-chloroallenes of type **64** (Scheme 105).



Scheme 105: Cu(I)-mediated synthesis of 1-chloroallenes of type **64**.

The second copper-catalyzed substitution on chloroallenes **64** using aromatic and heteroaromatic *Grignard* reagents proceeds with complete S_N2 selectivity leading to polyfunctional trisubstituted allenes of type **62**. The functional group compatibility is excellent

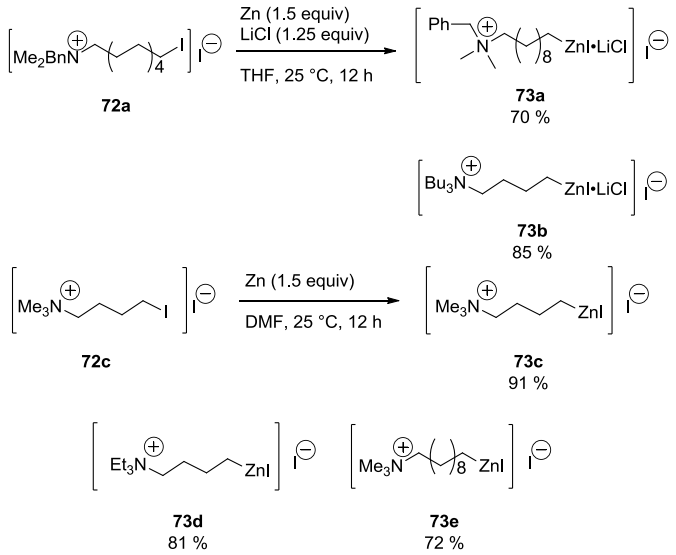
and functionalities such as ester, cyano, keto, trifluoromethyl and halogens are readily tolerated (Scheme 106).



Scheme 106: Cu(I)-catalyzed reaction of arylmagnesium reagents **63** with chloroallenes **64** to polyfunctionalized allenes.

7.6 Preparation of Charge-Tagged Organozinc Reagents

Alkyl iodides bearing a trialkylammonium group can be readily converted to the corresponding organozinc reagents. Depending on the solubility of the ammonium salts, either a LiCl-mediated Zn insertion in THF or a direct insertion of Zn in DMF is possible (Scheme 107).



Scheme 107: Synthesis of charge-tagged organozinc reagents.

ESI mass spectrometric analysis of **73d** reveals that the organozinc species is monomeric and the zinc cation is coordinated by 2 solvent molecules (DMF) to adapt presumably a tetrahedral geomentry (Figure 7).

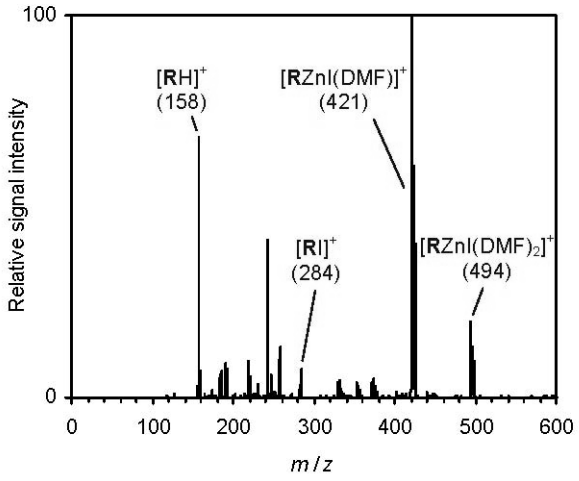
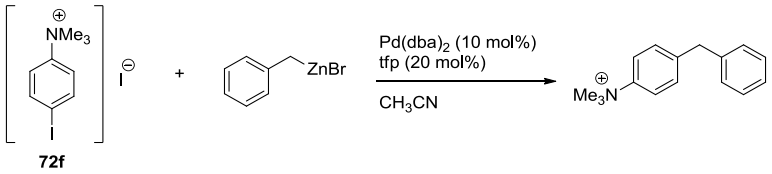


Figure 7: Positive ion mode ESI mass spectrum of **73d**.

Furthermore, it was shown that this approach is suitable for monitoring cross-coupling reactions (Scheme 108).



Scheme 108: Reaction of **72f** with benzylzinc bromide as test system for monitoring cross-coupling reaction using ESI-mass spectrometry.

Although, intermediates of the coupling reaction are not detectable, probably due to a very fast reductive elimination, it is possible to monitor the reaction via decrease of the starting iodide and the increase of the resulting charge-tagged diarylmethane.

C EXPERIMENTAL

1 General Considerations

If not otherwise stated, all reactions have been carried out using standard *Schlenk*-techniques in flame-dried glassware under nitrogen or argon. Prior to use, syringes and needles have been purged with the respective inert gas.

Solvents

Solvents needed for moisture sensitive reactions were dried according to the following standard procedures via distillation over drying agents and stored under an inert gas atmosphere:

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

DME (1,2-dimethoxyethane) was predried over $CaCl_2$ and destilled from Na/benzophenone ketyl under argon.

DMF was refluxed over CaH_2 (14 h) and distilled from CaH_2.

DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinon) was predried over CaH_2 (4 h) and distillied off.

Et_2O was predried over $CaCl_2$ and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.

NEP (*N*-ethylpyrrolidinone) was refluxed over CaH_2 and distilled from CaH_2.

NMP (*N*-methylpyrrolidinone) was refluxed over CaH_2 and distilled from CaH_2.

Pyridine was dried over KOH and distilled.

THF (tetrahydrofuran) was continuously refluxed and freshly distilled from Na/benzophenon ketyl under nitrogen.

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

Triethylamine was dried over KOH and distilled.

Solvents for reaction workup and for column chromatography were distilled prior to use.

Analytical data

Gas chromatography was performed with machines of type *Hewlett-Packard* 6890 or 5890 series II, using a column of type HP 5 (*Hewlett-Packard*, 5% phenylmethylpolysiloxane; length: 15 m, diameter: 0.25 mm; film thickness: 0.25 µm). The detection was accomplished by using a

flame ionization detector. The carrier gas was nitrogen. Alkanes like decane or tetradecane were used as internal standards.

Infrared spectra were recorded from 4000-400 cm^{-1} on a Perkin 281 IR spectrometer. Samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm^{-1}).

Mass spectra were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument for electron impact ionization (EI). High resolution mass spectra (HRMS) were recorded on the same instrument.

Melting points are uncorrected and were measured on a *Büchi* B.540 apparatus.

NMR spectra were recorded on *Varian* Mercury 200, *Bruker* AC 300, WH 400, or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak. For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), m (multiplet), q (quartet), quint (quintet), sxt (sextet), as well as br (broad).

Chromatography

Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The spots were visiualized by UV-light or by staining of the TLC plate with the solution below followed by heating if necessary:

- Phosphormolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12.0 mL) in water (230 mL).
- Iodine absorbed on silica gel.
- $KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g) in water (300 mL).
- Ninhydrin (0.3 g) and AcOH (3.0 mL) in butanol (100 mL).

Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm, 230-400 mesh) from Merck.

Reagents

Commercially available reagents were used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use.

Preparation of organometallic reagents:

CuCN·2LiCl solution was prepared by drying CuCN (8.96 g, 100 mmol) and LiCl (8.48 g, 200 mmol) in a *Schlenk*-flask under high vaccum fo 5 h at 140 °C. After cooling to 25 °C dry THF (100 mL) was added and the mixture was stirred for 24 h.

$ZnCl_2$ solution was prepared by drying $ZnCl_2$ (68.2 g, 500 mmol) in a *Schlenk*-flask under high vacuum for 6 h at 140 °C. After cooling to 25 °C dry THF (500 mL) was added and the mixture was stirred until all salts were dissolved.

***i*PrMgCl·LiCl** was purchased as a solution in THF from Chemetall GmbH (Frankfurt, Germany).

PhMgCl was purchased as a solution in THF from Chemetall GmbH (Frankfurt, Germany).

***i*PrMgCl** was purchased as a solution in THF from Chemetall GmbH (Frankfurt, Germany).

***n*BuLi** was purchased as a solution in hexane from Chemetall GmbH (Frankfurt, Germany).

The content of organometallic reagents was determined either by the method of *Paquette* (organolithium or -magnesium reagents)[156] or the method of *Knochel* (organomagnesium or -zinc reagents)[157] prior to use.

2 Cross-Coupling Reactions of Benzylic Zinc Reagents

2.1 General Procedures

Benzylic zinc reagents used for the cross-coupling reaction were prepared *via* LiCl-mediated zinc insertion in the corresponding benzylic chlorides as described in the literature.[34b]

General procedure 1 (GP1): Preparation of the aromatic tosylates:

In a round bottom flask equipped with a magnetic stirring bar, the aromatic alcohol was dissolved in THF, then NEt_3 (1.1 equiv.) and DMAP (2 mol%) were added at 25 °C. After that, tosyl chloride (1.1 equiv.) was added at 0 °C and the reaction mixture was allowed to warm up to 25 °C and stirred for the given time. Then, CH_2Cl_2 was added and the reaction mixture was washed 3 times with saturated aqueous NH_4Cl-solution. The combined aqueous layers were extracted 3 times with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* and recrystallization afforded the analytically pure product.

General procedure 2 (GP2): Nickel-catalyzed cross-coupling reactions:

In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the aromatic bromide, chloride or tosylate (2.00 mmol) was dissolved in NMP (0.4 mL) and PPh_3 (0.1 mL, 0.4 M in THF, 0.40 mmol, 2 mol%) was added. Then, $Ni(acac)_2$ (0.1 mL, 0.1 M in THF,

[156] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[157] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.

0.1 mmol, 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 saturated aqueous NH_4Cl-solution and extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The product was purified by flash column chromatography.

General procedure 3 (GP3): Nickel-catalyzed cross-coupling reactions using a syringe pump:

In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the bromoaniline derivative (2.00 mmol) was dissolved in NMP (0.4 mL) and PPh_3 (2.5 mL, 0.4 M in THF, 1.00 mmol, 5 mol%) was added. Then, $Ni(acac)_2$ (2.5 mL, 0.1 M in THF, 2.50 mmol, 2.5 mol%) was added. The reaction mixture was heated to 60 °C and the corresponding benzylic zinc reagent (2.40 mmol, 1.2 equiv.) was added slowly over 30 min and stirred for the given time until GC-analysis showed full conversion of the electrophile. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution and extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The product was purified by flash column chromatography.

General procedure 4 (GP4): Palladium-catalyzed cross-coupling reactions with bromoanilines:

In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the bromoaniline derivative (2.00 mmol) was dissolved in THF (2.0 mL) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 1 mol%) and S-Phos (16.5 mg, 0.04 mmol, 2 mol%) were added. Then, the corresponding benzylic zinc reagent (2.40 mmol, 1.2 equiv.) is added and the reaction mixture is stirred for the given time until GC-analysis showed full conversion of the electrophile. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution and extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The product was purified by flash column chromatography.

2.2 Preparation of the Aryl Tosylates

Preparation of toluene-4-sulfonic acid quinolin-8-yl ester (14a):

According to **GP1** quinolin-8-ol (3.63 g, 25.0 mmol) was reacted with NEt_3 (2.78 g, 27.5 mmol), DMAP (61 mg, 2 mol%) and tosyl chloride (5.24 g, 27.5 mmol) in THF (40 mL) for 20 h. Recrystallization from heptane/EtOAc afforded **14a** as a colorless crystalline solid (6.00 g, 20.0 mmol, 80 %).

m.p.: 116.9-119.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.85 (dd, *J* = 4.4 and 1.7 Hz, 1 H), 8.16 (dd, *J* = 8.3 and 1.7 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 2 H), 7.76 (dd, *J* = 8.3 and 1.5 Hz, 1 H), 7.62 (dd, *J* = 7.5 and 1.2 Hz, 1 H), 7.64–7.60 (m, 1 H), 7.41 (dd, *J* = 8.3 and 4.1 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 2.42 (s, 3 H).

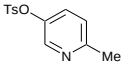
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 150.6, 145.4, 145.0, 141.3, 135.9, 133.1, 129.6, 129.4, 128.8, 126.9, 126.0, 122.5, 121.8, 21.6.

MS (70 eV, EI): *m/z* (%): 299 (M^+, 1), 236 (79), 234 (29), 218 (33), 155 (34), 145 (100), 117 (87), 91 (87).

HRMS *m/z* : calc. for $C_{16}H_{13}NO_3S$ 299.0616, found 299.0594**.**

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3064 (vw), 1941 (vw), 1596 (m), 1493 (m), 1470 (m), 1422 (w), 1369 (s), 1355 (m), 1309 (m), 1229 (m), 1188 (m), 1177 (s), 1161 (s), 1079 (s), 1073 (m), 1048 (s), 1029 (m), 1021 (m), 907 (m), 886 (s), 828 (s), 811 (s), 799 (s), 771 (s), 762 (vs), 710 (s), 706 (s), 662 (s), 643 (s), 632 (m), 607 (m).

Preparation of toluene-4-sulfonic acid 6-methyl-pyridin-3-yl ester (14b):



According to **GP1** 6-methyl-pyridin-3-ol (2.70 g, 24.7 mmol) was reacted with NEt_3 (2.78 g, 27.5 mmol), DMAP (61 mg, 2 mol%) and tosyl chloride (5.24 g, 27.5 mmol) in THF (40 mL) for 20 h. Recrystallization from heptane/EtOAc afforded **14b** as colorless crystalline solid (4.20 g, 16.0 mmol, 65 %).

m.p.: 104.7-107.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.97 (d, *J* = 2.7 Hz, 1 H), 7.67 (d, *J* = 8.3 Hz, 2 H), 7.38-7.34 (m, 1 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 1 H), 2.52 (s, 3 H), 2.43 (s, 3 H).

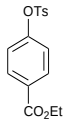
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 157.2, 145.9, 144.5, 142.7, 131.7, 130.6, 130.0, 128.5, 123.9, 23.8, 21.7.

MS (70 eV, EI): *m/z* (%): 263 (M^+, 38), 155 (54), 91 (100), 65 (7), 53 (6).

HRMS *m/z*: calc. for $C_{13}H_{13}NO_3S$ 263.0616, found 263.0622.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3351 (vw), 3259 (vw), 1596 (m), 1478 (m), 1374 (m), 1365 (s), 1349 (m), 1299 (m), 1284 (m), 1199 (m), 1169 (vs), 1120 (m), 1089 (s), 1021 (s), 923 (m), 860 (s), 845 (s), 840 (s), 815 (s), 801 (s), 793 (vs), 731 (s), 715 (vs), 701 (s), 655 (vs), 638 (s).

Preparation of 4-(toluene-4-sulfonyloxy)-benzoic acid ethyl ester (14c):



4-Hydroxy-benzoic acid ethyl ester (3.34 g, 20.1 mmol) was dissolved in pyridine (20 mL), tosyl chloride (5.00 g, 26.2 mmol) was added portionwise and the reaction mixture was stirred at 25 °C for 20 h. Then, the reaction mixture was poured on ice, EtOAc and 2 M HCl were added. The aqueous layer was extracted 3 times with EtOAc, and the combined organic layers were washed with 2 M HCl, saturated aqueous $NaHCO_3$-solution, brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and flash column chromatographical purification (silica; pentane:Et_2O, 6:1) afforded **14c** as a colorless oil (6.65 g, 20.8 mmol, 99 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.96 (d, *J* = 8.9 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.04 (d, *J* = 8.9 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 2.43 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.4, 152.9, 145.7, 132.1, 131.2, 129.8, 129.2, 128.5, 122.2, 61.2, 21.7, 14.2.

MS (70 eV, EI): *m/z* (%): 320 (M^+, 30), 275 (13), 156 (8), 155 (100), 121 (7), 62 (6), 91 (69), 65 (9).

HRMS *m/z*: calc. for $C_{16}H_{16}O_5S$ 320.0718, found 320.0726.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2980 (w), 2358 (w), 2116 (vw), 1714 (s), 1598 (m), 1498 (m), 1446 (m), 1372 (s), 1272 (vs), 1198 (s), 1174 (vs), 1152 (vs), 1092 (vs), 1016 (s), 864 (vs), 846 (s), 814 (s), 800 (s), 778 (s), 734 (vs), 696 (s), 668 (s).

Preparation of toluene-4-sulfonic acid 2-methoxy-phenyl ester (14d):

According to **GP1** 2-methoxy-phenol (3.05 g, 25.0 mmol) was reacted with NEt_3 (2.78 g, 27.5 mmol), DMAP (61 mg, 2 mol%) and tosyl chloride (5.24 g, 27.5 mmol) in THF (40 mL) for 20 h. Recrystallization from heptane/EtOAc afforded **14d** as a colorless crystalline solid (5.91 g, 21.2 mmol, 85 %).

m.p.: 77.1-79.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.74 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 9.2 Hz, 2 H), 7.22-7.17 (m, 1 H), 7.16-7.11 (m, 1 H), 6.88 (dd, *J* = 7.9 and 1.8 Hz, 1 H), 6.85-6.80 (m, 1 H), 3.54 (s, 3 H), 2.43 (s, 3 H).

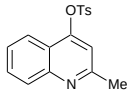
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 151.8, 144.9, 138.4, 133.3, 129.3, 128.6, 128.0, 124.0, 120.6, 112.7, 55.5, 21.6.

MS (70 eV, EI): *m/z* (%): 278 (M^+, 39), 207 (25), 124 (28), 123 (100), 109 (17), 95 (46), 91 (52), 77 (28), 65 (19), 52 (12).

HRMS *m/z*: calc. for $C_{14}H_{14}O_4S$ 278.0613, found 278.0615.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3065 (vw), 2946 (vw), 2845 (vw), 1596 (w), 1498 (m), 1455 (m), 1362 (s), 1287 (m), 1257 (s), 1188 (s), 1166 (s), 1158 (s), 1106 (s), 1086 (s), 1041 (m), 1023 (s), 925 (m), 863 (s), 814 (s), 779 (s), 754 (vs), 713 (s), 700 (s), 659 (s), 611 (m).

Preparation of toluene-4-sulfonic acid 2-methyl-quinolin-4-yl ester (14f):



According to **GP1** 2-methyl-quinolin-4-ol (2.39 g, 15.0 mmol) was reacted with NEt_3 (1.67 g, 16.5 mmol), DMAP (37 mg, 2 mol%) and tosyl chloride (3.15 g, 16.5 mmol) in THF (40 mL) for 20 h. Recrystallization from heptane afforded **3l** as colorless crystalline solid (3.85 g, 12.3 mmol, 82 %).

m.p.: 113.5-115.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.97 (d, *J* = 8.5 Hz, 1 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 7.76 (dd, *J* = 8.8 and 1.7 Hz, 1 H), 7.65 (dt, *J* = 8.4, 6.9 and 1.5 Hz, 1 H), 7.38 (dt, *J* = 8.3, 7.0 and 1.0 Hz, 1 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 7.20 (s, 1 H), 2.71 (s, 3 H), 2.41 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.8, 153.2, 149.5, 146.0, 132.3, 130.3, 130.0, 128.3, 126.3, 121.3, 120.5, 112.9, 76.4, 25.5, 21.7.

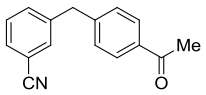
MS (70 eV, EI): *m/z* (%): 313 (M^+, 100), 159 (13), 155 (87), 130 (20), 91 (33), 65 (14).

HRMS *m/z*: calc. for $C_{17}H_{15}NO_3S$ 313.0773, found 313.0773.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3069 (vw), 3049 (vw), 2917 (vw), 1600 (m), 1557 (m), 1498 (m), 1406 (w), 1376 (s), 1332 (m), 1304 (m), 1230 (m), 1188 (s), 1173 (s), 1151 (m), 1091 (m), 1048 (s), 1018 (m), 993 (m), 965 (s), 870 (s), 814 (s), 804 (s), 786 (m), 765 (vs), 746 (vs), 664 (vs).

2.3 Preparation of the Cross-Coupling Products

Preparation of 3-(4-acetyl-benzyl)-benzonitrile (15a):



According to **GP2** the benzylic zinc reagent **11a** (1.75 mL, 1.37 M in THF, 2.40 mmol) was reacted with 1-(4-bromo-phenyl)-ethanone (**13a**) (398 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et_2O, 2:1) afforded **15a** as a colorless solid (352 mg, 1.50 mmol, 75 %).

m.p.: 71.6–73.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.90 (d, *J* = 8.2 Hz, 2 H),7.53-7.50 (m, 1 H), 7.45 (s, 1 H), 7.42-7.40 (m, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 4.06 (s, 2 H), 2.58 (s, 3 H).

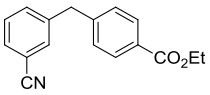
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 197.6, 144.8, 141.5, 135.7, 133.4, 132.3, 130.2, 129.4, 129.1, 128.9, 126.8, 112.7, 41.3, 26.6.

MS (70 eV, EI): *m/z* (%): 235 (M^+, 33), 220 (100), 201 (83), 199 (90), 116 (24), 89 (43).

HRMS *m/z*: calc. for $C_{16}H_{13}NO$ 235.0997, found 235.1009.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3516 (m), 2228 (m), 1672 (vs), 1600 (m), 1584 (m), 1568 (w), 1484 (w), 1456 (w), 1412 (m), 1356 (m), 1268 (m), 1200 (w), 1184 (w), 1140 (w), 1112 (w), 1076 (w), 1012 (w), 960 (w), 904 (w), 888 (w), 848 (w), 824 (m), 808 (w), 792 (m), 748 (m), 716 (w), 692 (m), 624 (m), 592 (w), 576 (w), 560 (w).

Preparation of 4-(3-cyano-benzyl)-benzoic acid ethyl ester (15b):



According to **GP2** the benzylic zinc reagent **11a** (1.75 mL, 1.37 M in THF, 2.40 mmol) was reacted with 4-chloro-benzoic acid ethyl ester (**13b**) (370 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et_2O, 6:1) afforded **15b** as a colorless solid (473 mg, 1.78 mmol, 89 %).

m.p.: 60.5–62.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.98 (d, *J* = 8.4 Hz, 2 H), 7.53–7.38 (m, 4 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.05 (s, 2 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

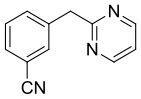
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.5, 144.7, 141.9, 133.6, 132.6, 130.4, 130.3, 129.6, 129.3, 129.1, 118.9, 112.9, 61.2, 41.5, 14.6.

MS (70 eV, EI): *m/z* (%): 265 (M^+, 37), 237 (20), 220 (100), 192 (30), 190 (28), 165 (24).

HRMS *m/z*: calc. for $C_{17}H_{15}NO_2$ 265.1103, found 265.1077.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3076 (w), 3052 (w), 3000 (w), 2976 (w), 2956 (w), 2900 (w), 2228 (m), 1708 (vs), 1608 (m), 1576 (w), 1476 (w), 1448 (w), 1436 (w), 1416 (w), 1392 (w), 1364 (m), 1324 (w), 1308 (w), 1276 (vs), 1192 (w), 1176 (m), 1128 (m), 1108 (s), 1020 (m), 980 (w), 940 (w), 908 (w), 876 (w), 856 (w), 788 (m), 764 (m), 728 (m), 700 (w), 688 (m), 652 (w), 560 (w).

Preparation of 3-pyrimidin-2-ylmethyl-benzonitrile (15c):



According to **GP2** the benzylic zinc reagent **11a** (1.75 mL, 1.37 M in THF, 2.40 mmol) was reacted with 2-chloro-pyrimidine (**13c**) (230 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; Et_2O) afforded **15c** as a yellow oil (269 mg, 1.38 mmol, 69 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.67 (d, *J* = 5.1 Hz, 2 H), 7.64 (s, 1 H), 7.60–7.57 (m, 1 H), 7.52–7.48 (m, 1 H), 7.41–7.36 (m, 1 H), 7.16 (t, *J* = 4.9 Hz, 1 H), 4.30 (s, 2 H).

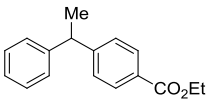
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 168.7, 157.4, 139.5, 133.7, 132.7, 130.3, 129.2, 119.0, 118.8, 112.5, 45.3.

MS (70 eV, EI): *m/z* (%): 196 (6), 195 (M^+, 53), 194 (100), 193 (5), 167 (2). 142 (3), 116 (4), 115 (5), 114 (3).

HRMS *m/z*: calc. for $C_{12}H_9N_3$ 195.0796, found 195.0803.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3040 (w), 2972 (vw), 2924 (vw), 2228 (m), 1604 (vw), 1560 (vs), 1484 (w), 1416 (vs), 1320 (vw), 1296 (vw), 1280 (vw), 1232 (w), 1180 (w), 1152 (vw), 1096 (w), 996 (w), 944 (vw), 912 (w), 856 (vw), 792 (m), 716 (w), 688 (m), 636 (w), 584 (w), 564 (w).

Preparation of 4-(1-phenyl-ethyl)-benzoic acid ethyl ester (15d):



According to **GP2** the benzylic zinc reagent **11b** (1.78 mL, 1.35 M in THF, 2.40 mmol) was reacted with 4-bromo benzoic acid ethyl ester (**13d**) (458 mg, 2.00 mmol). The reaction time was 12 h. Flash column chromatographical purification (silica; pentane:Et_2O, 98:2) afforded **15d** as a colorless oil (485 mg, 1.91 mmol, 95 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.97 (d, *J* = 8.3 Hz, 2 H), 7.33-7.25 (m, 4 H), 7.23-7.16 (m, 3 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.20 (q, *J* = 7.1 Hz, 1 H), 1.66 (d, *J* = 7.3 Hz, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

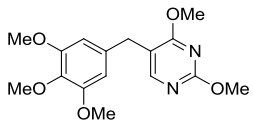
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.5, 151.5, 145.4, 129.7, 128.5, 128.4, 127.6, 127.5, 126.3, 60.7, 44.8, 21.6, 14.3.

MS (70 eV, EI): *m/z* (%): 254 (M^+, 100), 239 (45), 209 (40), 181 (41), 165 (57).

HRMS *m/z*: calc. for $C_{17}H_{18}O_2$ 254.1307, found 254.1305.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3028 (vw), 2973 (w), 2934 (vw), 1712 (s), 1610 (m), 1494 (w), 1451 (w), 1415 (w), 1367 (m), 1310 (w), 1271 (vs), 1178 (m), 1102 (s), 1019 (s), 857 (m), 758 (m), 738 (m), 698 (vs), 646 (w), 595 (w).

Preparation of 2,4-dimethoxy-5-(3,4,5-trimethoxy-benzyl)-pyrimidine (15e):



According to **GP2** the benzylic zinc reagent **11c** (2.00 mL, 1.21 M in THF, 2.40 mmol) was reacted with 5-bromo-2,4-dimethoxy-pyrimidine (**13e**) (438 mg, 2.00 mmol). The reaction time was 2 h. Flash column chromatographical purification (silica; pentane:Et_2O, 1:2) afforded **15e** as a colorless solid (551 mg, 1.72 mmol, 86 %).

m.p.: 74.1-76.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.94 (s, 1 H), 6.39 (s, 2 H), 3.98 (s, 3 H), 3.96 (s, 3 H), 3.80 (s, 9 H), 3.72 (s, 2 H).

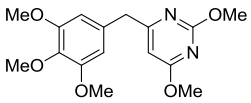
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 169.2, 164.2, 157.1, 153.2, 136.6, 134.6, 114.5, 105.7, 60.8, 56.1, 54.7, 53.9, 32.7.

MS (70 eV, EI): *m/z* (%): 320 (M^+, 100), 305 (45), 289 (9), 230 (14), 181 (62).

HRMS *m/z*: calc. for $C_{16}H_{20}N_2O_5$ 320.1372, found 320.1348.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2947 (w), 2909 (w), 2842 (w), 2828 (w), 1593 (s), 1573 (s), 1510 (m), 1456 (s), 1403 (s), 1373 (s), 1331 (s), 1286 (s), 1249 (s), 1232 (s), 1193 (s), 1121 (vs), 1076 (vs), 1005 (vs), 976 (s), 935 (m), 859 (s), 833 (s), 784 (vs), 749 (s), 699 (m), 636 (m), 602 (s).

Preparation of 2,4-dimethoxy-6-(3,4,5-trimethoxy-benzyl)-pyrimidine (15f):



According to **GP2** the benzylic zinc reagent **11c** (2.00 mL, 1.21 M in THF, 2.40 mmol) was reacted with 4-chloro-2,6-dimethoxy-pyrimidine (**13f**) (349 mg, 2.00 mmol). The reaction time was 2 h. Flash column chromatographical purification (silica; pentane:Et_2O, 1:2) afforded **15f** as a colorless solid (628 mg, 1.96 mmol, 98 %).

m.p.: 60.8-62.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.49 (s, 2 H), 6.12 (s, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.84 (s, 2 H), 3.82 (s, 6 H), 3.81 (s, 3 H).

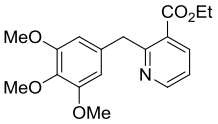
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 172.0, 171.4, 165.2, 153.2, 136.8, 133.2, 106.3, 99.9, 60.8, 56.1, 54.6, 53.7, 44.0.

MS (70 eV, EI): *m/z* (%): 320 (M^+, 74), 305 (60), 181 (13), 69 (13), 57 (11), 44 (100).

HRMS *m/z*: calc. for $C_{16}H_{20}N_2O_5$ 320.1372, found 320.1360.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3083 (w), 2945 (w), 2932 (w), 2831 (w), 1588 (s), 1564 (vs), 1505 (s), 1451 (s), 1433 (m), 1419 (s), 1375 (m), 1350 (vs), 1331 (s), 1299 (s), 1244 (s), 1233 (s), 1204 (s), 1193 (m), 1186 (m), 1149 (s), 1121 (vs), 1092 (vs), 1036 (s), 1003 (s), 980 (s), 922 (m), 862 (m), 835 (s), 826 (s), 816 (m), 792 (m), 742 (m), 729 (s), 717 (m), 686 (m), 612 (m), 602 (s).

Preparation of ethyl 2-(3,4,5-trimethoxybenzyl)nicotinate (15g):



According to **GP2** the benzylic zinc reagent **11c** (2.00 mL, 1.21 M in THF, 2.40 mmol) was reacted with ethyl 2-chloronicotinate (**13g**) (371 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et_2O, 1:1) afforded **15g** as a yellow oil (639 mg, 1.93 mmol, 96%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.68 (dd, *J* = 4.9 Hz and 1.9 Hz, 1 H), 8.15 (dd, *J* = 7.9 Hz and 1.8 Hz, 1 H), 7.23 (dd, *J* = 7.9 Hz and 4.7 Hz, 1 H), 6.52 (s, 2 H), 4.51 (s, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H) 3.78 (s, 9 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

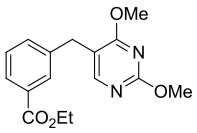
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.5, 161.0, 152.9, 151.8, 138.6, 136.4, 135.2, 126.1, 121.3, 106.2, 61.4, 60.7, 56.0, 42.3, 14.2.

MS (70 eV, EI): *m/z* (%): (19), 331 (M^+, 100), 330 (16), 317 (13), 316 (64), 286 (10), 270 (15), 227 (22), 44 (21).

HRMS *m/z*: calc. for $C_{18}H_{21}NO_5$ 331.1420, found 331.1395.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2937 (w), 2836 (w), 1718 (s), 1587 (m), 1567 (m), 1505 (m), 1456 (m), 1420 (s), 1366 (w), 1330 (m), 1258 (s), 1235 (s), 1182 (m), 1119 (vs), 1079 (s), 1057 (s), 1006 (s), 968 (m), 809 (m), 789 (m), 739 (m), 680 (m), 656 (m)

Preparation of 3-(2,4-dimethoxy-pyrimidin-5-ylmethyl)-benzoic acid ethyl ester (15h):



According to **GP2** the benzylic zinc reagent **11d** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with 5-bromo-2,4-dimethoxy-pyrimidine (**13e**) (438 mg, 2.00 mmol). The reaction time was 1.5 h. Flash column chromatographical purification (silica; pentane:Et_2O, 1:1) afforded **15h** as a colorless oil (505 mg, 1.67 mmol, 84 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.96 (s, 1 H), 7.89–7.86 (m, 2 H), 7.34–7.32 (m, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 3.95 (s, 3 H), 3.95 (s, 3 H), 3.82 (s, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

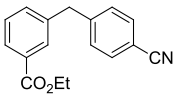
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 169.2, 166.5, 164.3, 157.1, 139.4, 133.0, 130.7, 129.7, 128.4, 127.6, 114.1, 60.9, 54.7, 53.9, 32.3, 14.3.

MS (70 eV, EI): *m/z* (%): 302 (M^+, 100), 301 (53), 287 (27), 273 (33), 257 (33), 241 (21), 200 (25).

HRMS *m/z*: calc. for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1269.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2985 (w), 2957 (w), 2902 (w), 1715 (s), 1600 (s), 1567 (s), 1466 (s), 1398 (s), 1379 (vs), 1350 (m), 1273 (vs), 1239 (m), 1190 (s), 1153 (w), 1104 (m), 1070 (s), 1052 (m), 1015 (s), 788 (w), 763 (w), 744 (m), 694 (w).

Preparation of 3-(4-cyano-benzyl)-benzoic acid ethyl ester (15i):



According to **GP2** the benzylic zinc reagent **11d** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with 4-chloro-benzonitrile (**13h**) (276 mg, 2.00 mmol). The reaction time was 0.5 h.

Flash column chromatographical purification (silica; pentane:Et_2O, 2:1) afforded **15i** as a colorless solid (482 mg, 1.82 mmol, 91 %).

m.p.: 51.0-53.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.93–7.89 (m, 1 H), 7.87–7.85 (m, 1 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 7.40–7.30 (m, 2 H), 7.27 (d, *J* = 8.5 Hz, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.07 (s, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

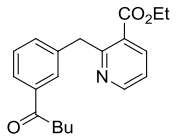
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.3, 146.0, 139.6, 133.3, 132.4, 131.0, 130.0, 129.6, 128.8, 127.9, 118.8, 110.3, 61.0, 41.7, 14.3.

MS (70 eV, EI): *m/z* (%): 265 (M^+, 56), 237 (49), 221 (20), 220 (100), 207 (29), 193 (16), 192 (30), 191 (21), 190 (26), 165 (17).

HRMS *m/z*: calc. for $C_{17}H_{15}NO_2$ 265.1103, found 265.1089.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3054 (vw), 2991 (w), 2983 (w), 2937 (w), 2912 (w), 2874 (vw), 2228 (m), 1707 (vs), 1669 (w), 1604 (m), 1586 (w), 1477 (w), 1446 (m), 1362 (m), 1279 (s), 1188 (s), 1105 (m), 1024 (m), 939 (m), 854 (m), 796 (w), 762 (m), 734 (m), 696 (m), 602 (m).

Preparation of 2-(3-pentanoyl-benzyl)-nicotinic acid ethyl ester (15j):



According to **GP2** the benzylic zinc reagent **11e** (2.30 mL, 1.06 M in THF, 2.40 mmol) was reacted with 2-chloro-nicotinic acid ethyl ester (**13g**) (371 mg, 2.00 mmol). The reaction time was 1 h. Flash column chromatographical purification (silica; pentane:Et_2O, 6:1 then 1:1) afforded **15j** as a pale yellow liquid (583 mg, 1.79 mmol, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.67 (dd, *J* = 4.9 and 1.9 Hz, 1 H), 8.12 (dd, *J* = 7.9 and 1.8 Hz, 1 H), 7.86 (m, 1 H), 7.75 (m, 1 H), 7.44 (m, 1 H), 7.32 (t, *J* = 7.7 Hz, 1 H), 7.24 (dd, *J* = 8.0 and 4.9 Hz, 1 H), 4.63 (s, 2 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 2.90 (t, *J* = 7.3 Hz, 2 H), 1.67 (quint, *J* = 7.4 Hz, 2 H), 1.37 (sext, *J* = 7.5 Hz, 2 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 0.92 (t, *J* = 7.3 Hz,3 H).

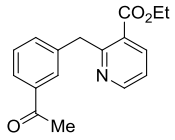
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.6, 166.3, 160.6, 151.9, 140.1, 138.8, 137.1, 133.6, 128.7, 128.4, 126.1, 125.9, 121.4, 61.5, 42.1, 38.3, 26.5, 22.4, 14.1, 13.9.

MS (70 eV, EI): *m/z* (%): 325 (M^+, 79), 283 (12), 282 (12), 269 (16), 268 (100), 212 (10), 211 (13), 167 (27), 166 (24).

HRMS *m/z* : calc. for $C_{20}H_{23}NO_3$ 325.1678, found 325.1666.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958 (m), 2933 (m), 2872 (w), 1719 (vs), 1681 (s), 1582 (m), 1568 (m), 1436 (m), 1366 (m), 1274 (s), 1256 (vs), 1173 (m), 1158 (m), 1130 (s), 1111 (m), 1079 (s), 1057 (m), 1018 (m), 862 (w), 776 (m), 752 (m), 741 (m), 694 (m), 629 (w), 576 (w).

Preparation of 2-(3-acetyl-benzyl)-nicotinic acid ethyl ester (15k):



In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, 2-chloro-nicotinic acid ethyl ester (**13g**) (371 mg, 2.00 mmol) was dissolved in NMP (0.4 mL), PPh_3 (0.1 mL, 0.4 M in THF, 0.40 mmol, 2 mol%) and $Ni(acac)_2$ (0.1 mL, 0.1 M in THF, 0.1 mmol, 0.5 mol%) were added. Then, the benzylic zinc reagent **11f** (2.24 mL, 1.07 M in THF, 2.40 mmol) was added over 30 min via a syringe pump. The reaction time was 2 h. Flash column chromatographical purification (silica; pentane:Et_2O, 1:1 then 1:3) afforded **15k** as a yellow oil (385 mg, 1.36 mmol, 68 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.67 (dd, *J* = 4.7 and 1.8 Hz, 1 H), 8.19 (dd, *J* = 7.9 and 1.8 Hz, 1 H), 7.88–7.85 (m, 1 H), 7.75 (d, *J* = 7.5 Hz, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H), 7.32 (t, *J* = 7.7 Hz, 1 H), 7.24 (dd, *J* = 7.9 and 4.7 Hz, 1 H), 4.63 (s, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 2.54 (s, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H).

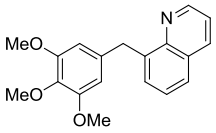
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 198.2, 166.3, 160.5, 151.9, 140.1, 138.8, 137.1, 133.8, 129.0, 128.4, 126.2, 126.0, 121.5, 61.5, 42.1, 26.6, 14.1.

MS (70 eV, EI): *m/z* (%): 283 (100), 267 (37), 210 (39), 195 (13), 167 (29), 135 (12), 43 (58).

HRMS *m/z*: calc. for $C_{17}H_{17}NO_3$ 283.1208, found 283.1187.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3049 (vw), 2982 (w), 2936 (w), 1718 (s), 1681 (vs), 1601 (w), 1582 (m), 1568 (m), 1484 (w), 1436 (m), 1357 (m), 1296 (m), 1258 (vs), 1173 (m), 1130 (m), 1079 (s), 1057 (m), 1018 (w), 976 (w), 956 (w), 863 (w), 777 (m), 741 (m), 693 (m), 589 (w), 577 (w).

Preparation of 8-(3,4,5-trimethoxybenzyl)quinoline (15l):



According to **GP2** the benzylic zinc reagent **11c** (2.20 mL, 1.09 M in THF, 2.40 mmol) was reacted with quinoline-8-yl-4-methylbenzenesulfonate (**14a**) (599 mg, 2.00 mmol). The reaction time

was 2 h. Flash column chromatographical purification (silica; pentane:Et_2O, 1:1) afforded **15l** as a colorless oil (510 mg, 1.65 mmol, 82 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.98 (dd, *J* = 4.1 Hz and 1.7 Hz, 1 H), 8.17 (dd, *J* = 8.3 Hz and 1.7 Hz, 1 H), 7.70 (m, 1 H), 7.45 (m, 2 H), 7.43 (dd, *J* = 8.3 Hz and 4.1 Hz, 1 H), 6.58 (s, 2 H), 4.62 (s, 2 H), 3.81 (s, 3 H), 3.78 (s, 6 H).

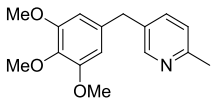
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 153.1, 149.3, 146.4, 139.9, 136.8, 136.6, 136.2, 129.4, 128.4, 126.5, 126.4, 121.0, 106.4, 60.8, 56.0, 37.1.

MS (70 eV, EI): *m/z* (%): 310 (15), 309 (M^+, 72), 295 (17), 294 (100), 278 (10), 263 (8), 208 (9), 181 (8), 180 (9).

HRMS *m/z*: calc. for $C_{19}H_{19}NO_3$ 309.1365, found 309.1363.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2994 (w), 2944 (w), 2832 (w), 1586 (s), 1496 (m), 1450 (m), 1420 (m), 1327 (m), 1232 (s), 1181 (m), 1121 (vs), 1050 (m), 1027 (m), 997 (s), 967 (m), 907 (m), 875 (w), 833 (m), 796 (vs), 768 (s), 738 (m), 672 (m), 613 (m).

Preparation of 2-methyl-5-(3,4,5-trimethoxybenzyl)pyridine (15m):



According to **GP2** the benzylic zinc reagent **11c** (1.90 mL, 1.27 M in THF, 2.40 mmol) was reacted with 6-methylpyridin-3-yl-4-methylbenzenesulfonate (**14b**) (527 mg, 2.00 mmol). The reaction time was 1 h. Flash column chromatographical purification (silica; Et_2O) afforded **15m** as a colorless oil (493 mg, 1.80 mmol, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.37 (m, 1 H), 7.35 (dd, *J* = 7.9 Hz and 2.3 Hz, 1 H), 7.06 (d, *J* = 7.8 Hz, 1 H), 6.35 (s, 2 H), 3.85 (s, 2 H), 3.80 (s, 3 H), 3.79 (s, 6 H), 2.51 (s, 3 H).

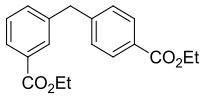
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 156.2, 153.3, 149.1, 136.6, 136.6, 135.7, 133.1, 123.0, 105.8, 60.8, 56.1, 38.9, 23.9.

MS (70 eV, EI): *m/z* (%): 274 (15), 273 (M^+, 100), 259 (7), 258 (37), 230 (14), 215 (11), 214 (8), 106 (7).

HRMS *m/z*: calc. for $C_{16}H_{19}NO_3$ 273.1365, found 273.1364.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2936 (w), 2837 (w), 1588 (s), 1505 (m), 1489 (m), 1455 (m), 1419 (s), 1391 (m), 1331 (m), 1234 (s), 1182 (w), 1121 (vs), 1029 (m), 1005 (s), 969 (m), 816 (m), 781 (m), 759 (m), 727 (m), 672 (m), 645 (m).

Preparation of ethyl-3-[4-(ethoxycarbonyl)-benzyl]-benzoate (15n):



According to **GP2** the benzylic zinc reagent **11d** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with 4-(toluene-4-sulfonyloxy)-benzoic acid ethyl ester (**14c**) (641 mg, 2.00 mmol). The reaction time was 2 h. Flash column chromatographical purification (silica; pentane:Et_2O, 9:1) afforded **15n** as a yellow oil (385 mg, 1.29 mmol, 65 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.99 (d, *J* = 8.4 Hz, 2 H), 7.94–7.91 (m, 2 H), 7.41–7.34 (m, 2 H), 7.27 (d, *J* = 8.6 Hz, 2 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 4.09 (s, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

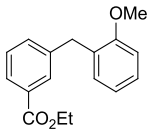
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.5, 166.5, 145.7, 140.4, 140.4, 133.3, 130.8, 130.0, 129.9, 128.8, 128.7, 128.6, 127.6, 61.0, 60.8, 41.6, 14.3.

MS (70 eV, EI): *m/z* (%): 312 (M^+, 40), 268 (17), 267 (100), 240 (14), 239 (37), 167 (15), 166 (16), 165 (36), 111 (11).

HRMS *m/z*: calc. for $C_{19}H_{20}O_4$ 312.1362, found 312.1354.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982 (w), 2937 (vw), 2906 (vw), 1711 (vs), 1609 (w), 1588 (w), 1444 (w), 1415 (w), 1366 (w), 1270 (vs), 1187 (m), 1177 (m), 1100 (s), 1082 (m), 1020 (m), 940 (w), 855 (w), 746 (m), 710 (m), 689 (w), 637 (vw), 590 (w).

Preparation of 3-(2-methoxy-benzyl)-benzoic acid ethyl ester (15o):



According to **GP2** the benzylic zinc reagent **11d** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with toluene-4-sulfonic acid 2-methoxy-phenyl ester (**14d**) (557 mg, 2.00 mmol). The reaction time was 24 h. Flash column chromatographical purification (silica; pentane:Et_2O, 19:1) afforded **15o** as a colorless liquid (370 mg, 1.37 mmol, 69 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.95-7.92 (m, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.40-7.35 (m, 1 H), 7.31 (t, *J* = 7.4 Hz, 1 H), 7.20 (td, *J* = 7.8 and 1.9 Hz, 1 H), 7.07 (dd, *J* = 7.9 and 1.8 Hz, 1 H), 6.91-6.84 (m, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.01 (s, 2 H), 3.81 (s, 3 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

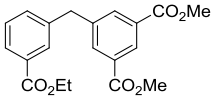
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.8, 157.3, 141.4, 133.4, 130.4, 130.2, 130.1, 129.1, 128.2, 127.6, 127.1, 120.5, 110.5, 60.8, 55.3, 35.8, 14.3.

MS (70 eV, EI): *m/z* (%): 270 (M^+, 87), 225 (66), 224 (96), 196 (100), 165 (49), 135 (89), 91 (53).

HRMS *m/z*: calc. for $C_{17}H_{18}O_3$ 270.1256, found 270.1259.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2978 (w), 2936 (w), 2835 (vw), 1713 (s), 1586 (m), 1492 (m), 1463 (m), 1438 (m), 1366 (m), 1275 (s), 1241 (vs), 1193 (m), 1182 (s), 1102 (s), 1079 (m), 1049 (m), 1026 (s), 1002 (m), 929 (w), 741 (vs), 714 (m), 691 (m), 670 (m), 619 (m).

Preparation of 3-(2-methoxy-benzyl)-benzoic acid ethyl ester (15p):



According to **GP2** the benzylic zinc reagent **11d** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with dimethyl 5-{[(4-methylphenyl)sulfonyl]oxy}benzene-1,3-dicarboxylate (**14e**) (729 mg, 2.00 mmol). The reaction time was 5 h. Flash column chromatographical purification (silica; pentane:Et_2O, 4:1) afforded **15p** as a colorless oil (432 mg, 1.21 mmol, 61 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.52 (s, 1 H), 8.05 (s, 2 H), 7.88 (m, 2 H), 7.35 (m, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 4.10 (s, 2 H), 3.91 (s, 6 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

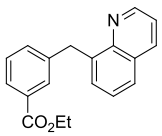
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.5, 166.2, 141.5, 140.1, 134.2, 133.3, 131.0, 130.9, 129.9, 128.9, 128.8, 127.8, 61.0, 52.3, 41.3, 14.3.

MS (70 eV, EI): *m/z* (%): 356 (M^+, 61), 325 (35), 312 (18), 311 (100), 284 (15), 252 (13), 165 (32), 140 (20).

HRMS *m/z* : calc. for $C_{20}H_{20}O$ 356.1260, found 356.1257.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952 (w), 1713 (vs), 1602 (w), 1432 (m), 1334 (m), 1276 (s), 1236 (vs), 1192 (s), 1104 (s), 1081 (m), 1001 (s), 920 (w), 868 (w), 789 (w), 749 (s), 706 (s), 632 (m).

Preparation of 3-quinolin-8-ylmethyl-benzoic acid ethyl ester (15q):



According to **GP2** the benzylic zinc reagent **11d** (1.74 mL, 1.38 M, 2.40 mmol) was reacted with toluene-4-sulfonic acid quinolin-8-yl ester (**14a**) (599 mg, 2.00 mmol). The reaction time was 3 h. Flash column chromatographical purification (silica; pentane:Et_2O, 6:1) afforded **15q** as a colorless oil (491 mg, 1.69 mmol, 85 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.96 (dd, *J* = 4.3 and 1.8 Hz, 1 H), 8.15 (dd, *J* = 8.3 and 1.7 Hz, 1 H), 8.05-8.02 (m, 1 H), 7.89-7.84 (m, 1 H), 7.72-7.66 (m, 1 H), 7.52-7.47 (m, 1 H), 7.46-7.38 (m, 3 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 4.73 (s, 2 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

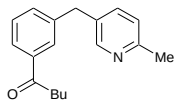
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.8, 149.4, 146.4, 141.6, 139.5, 136.4, 133.9, 130.5, 130.4, 129.6, 128.4, 128.3, 127.2, 126.5, 126.4, 121.1, 60.8, 36.6, 14.3.

MS (70 eV, EI): *m/z* (%): 291 (M^+, 100), 262 (63), 246 (12), 218 (28), 217 (55), 108 (34).

HRMS *m/z*: calc. for $C_{19}H_{17}NO_2$ 291.1259, found 291.1261.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3033 (vw), 2979 (w), 2928 (w), 2902 (w), 1710 (vs), 1594 (w), 1497 (m), 1442 (m), 1366 (m), 1272 (vs), 1188 (s), 1103 (s), 1081 (s), 1024 (m), 928 (w), 870 (w), 818 (m), 809 (m), 789 (s), 751 (s), 713 (s), 689 (m), 672 (m), 612 (m).

Preparation of 1-[3-(6-methyl-pyridin-3-ylmethyl)-phenyl]-pentan-1-one (15r):



According to **GP2** the benzylic zinc reagent **11e** (2.30 mL, 1.06 M, 2.40 mmol) was reacted with toluene-4-sulfonic acid-6-methyl-pyridin-3-yl ester (**14b**) (527 mg, 2.00 mmol). The reaction time was 16 h. Flash column chromatographical purification (silica; pentane:Et_2O, 1:1 then Et_2O) afforded **15r** as a pale yellow liquid (448 mg, 1.68 mmol, 84 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.36 (s, 1 H), 7.78 (m, 2 H), 7.35 (m, 3 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 3.97 (s, 2 H), 2.90 (t, *J* = 7.4 Hz, 2 H), 2.5 (s, 3 H), 1.67 (quint, *J* = 7.4 Hz, 2 H), 1.37 (sext, *J* = 7.4 Hz, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

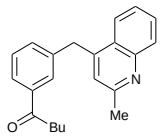
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.4, 156.4, 149.2, 140.7, 137.4, 136.7, 133.2, 132.7, 128.8, 128.2, 126.2, 123.1, 38.5, 38.3, 26.4, 23.9, 22.4, 13.9.

MS (70 eV, EI): *m/z* (%): 268 ($[M+H]^+$, 100), 225 (26), 224 (10), 211 (12), 210 (72), 183 (10), 182 (13), 181 (15).

HRMS *m/z*: calc. for $C_{18}H_{22}NO$ 268.1701[M+H] , found 268.1697.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2957 (s), 2930 (m), 2871 (m), 1681 (vs), 1601 (m), 1585 (w), 1568 (w), 1488 (m), 1465 (m), 1438 (m), 1409 (w), 1392 (m), 1378 (w), 1346 (w), 1320 (w), 1297 (m), 1266 (m), 1256 (m), 1228 (m), 1176 (m), 1159 (m), 1109 (w), 1096 (w), 1029 (m), 913 (w), 812 (w), 792 (w), 754 (m), 728 (m), 693 (m), 646 (w).

Preparation of 1-[3-(2-methyl-quinolin-4-ylmethyl)-phenyl]-pentan-1-one (15s):



According to **GP2** the benzylic zinc reagent **11e** (2.30 mL, 1.06 M in THF, 2.40 mmol) was reacted with toluene-4-sulfonic acid 2-methyl-quinolin-4-yl ester (**14f**) (627 mg, 2.00 mmol). The reaction time was 16 h. Flash column chromatographical purification (silica; pentane:Et_2O, 1:1 then Et_2O) afforded **15s** as a colorless, high viscous oil (585 mg, 1.85 mmol, 92 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.04 (d, *J* = 8.5 Hz, 1 H), 7.92 (d, *J* = 9.2 Hz, 1 H), 7.81 (m, 2 H), 7.64 (t, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 1 H), 7.35 (m, 2 H), 7.00 (s, 1 H), 4.43 (s, 2 H), 2.89 (t, *J* = 7.4 Hz, 2 H), 2.68 (s, 3 H), 1.67 (quint, *J* = 7.5 Hz, 2 H), 1.39 (sext, *J* = 7.5 Hz, 2 H), 0.91 (t, *J* = 7.3 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.4, 158.8, 148.0, 145.8, 139.3, 137.5, 133.2, 129.3, 129.2, 128.9, 128.3, 126.5, 125.8, 125.6, 123.4, 122.7, 38.4, 38.0, 26.4, 25.3, 22.4, 13.9.

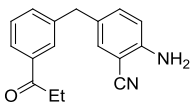
MS (70 eV, EI): *m/z* (%): 317 (M^+, 25), 275 (100), 261 (44), 260 (38), 247 (15), 231 (63), 216 (15), 189 (18), 115 (12).

HRMS *m/z*: calc. for $C_{22}H_{23}NO$ 317.1780, found 317.1756.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3063 (w), 2954 (s), 2930 (m), 2871 (m), 1674 (vs), 1601 (s), 1585 (m), 1562 (w), 1511 (m), 1466 (w), 1437 (m), 1415 (m), 1376 (m), 1336 (m), 1274 (m), 1227 (m), 1158 (m), 1024 (w), 964 (w), 910 (w), 869 (w), 763 (s), 756 (s), 733 (m), 700 (m), 637 (w), 570 (w).

2.4 Nickel-Catalyzed Cross-Couplings with Bromoaniline Derivatives

Preparation of 2-amino-5-(3-propionylbenzyl)benzonitrile (17a):



According to **GP3** the benzylic zinc reagent **11g** (2.2 mL, 1.07 M in THF, 2.4 mmol) was reacted with 2-amino-5-bromo-benzonitrile (**16a**, 394 mg, 2 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et_2O, 3:1 then 2:1) afforded **17a** as a yellow oil (452 mg, 1.71 mmol, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.81-7.74 (m, 2 H), 7.37 (t, *J* = 7.8 Hz, 1 H), 7.31 (d, *J* = 7.7 Hz, 1 H), 7.16-7.11(m, 2 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 3.89 (s, 2 H), 3.86 (s, 2H), 2.96 (q, *J* = 7.2 Hz, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

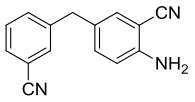
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.8, 148.1, 141.0, 137.3, 134.8, 133.2, 132.0, 130.3, 128.8, 128.1, 126.2, 117.5, 115.6, 96.1, 40.3, 31.8, 8.2.

MS (EI, 70 eV), *m/z* (%): 264 (M^+, 100), 235 (43), 207 (20), 205 (14), 190 (13), 131 (46).

HRMS *m/z* : calc. for $C_{17}H_{16}N_2O$ 264.1263, found 264.1259.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3460 (m), 3362 (s), 3236 (w), 2972 (m), 2938 (m), 2360 (w), 2212 (s), 1738 (m), 1680 (s), 1630 (s), 1504 (vs), 1424 (m), 1352 (m), 1314 (m), 1240 (s), 1160 (m), 778 (m), 690 (m).

Preparation of 2-amino-5-(3-cyanobenzyl)benzonitrile (17b):



According to **GP3** the benzylic zinc reagent **11a** (1.7 mL, 1.4 M in THF, 2.4 mmol) was reacted with 2-amino-5-bromo-benzonitrile (**16a**, 394 mg, 2 mmol). The reaction time was 1 h. Flash column chromatographical purification (silica; pentane:Et_2O, 3:1) afforded **17b** as a colorless oil (376 mg, 1.61 mmol, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.50-7.47 (m, 1 H), 7.41-7.36 (m, 3 H), 7.14-7.08 (m, 2 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 4.35 (s, 2H), 3.86 (s, 2 H).

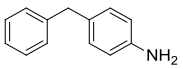
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.4, 142.0, 134.7, 133.2, 132.1, 132.0, 130.1, 129.3, 129.0, 118.7, 117.3, 115.7, 112.5, 96.0, 39.8.

MS (EI, 70 eV), *m/z* (%): 233 (M^+, 100), 232 (37), 215 (6), 205 (8), 131 (41), 103 (6).

HRMS *m/z* : calc. for $C_{15}H_{11}N_3$ 233.0953, found 233.0949.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3438 (s), 3320 (s), 3220 (m), 2224 (s), 2208 (s), 1738 (w), 1632 (s), 1504 (vs), 1478 (m), 1424 (m), 1320 (m), 1264 (m), 1170 (m), 890 (w), 802 (w), 740 (m), 686 (m).

Preparation of 4-benzyl-phenylamine (17c):



According to **GP3** the benzylic zinc reagent **11h** (1.4 mL, 1.7 M in THF, 2.4 mmol) was reacted with 4-bromo-phenylamine (**16b**, 344 mg, 2.00 mmol). The reaction time was 1 h. Flash column chromatographical purification (silica; pentane:Et_2O, 6:1) afforded **17c** as a brown oil (330 mg, 1.80 mmol, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.42-7.14 (m, 5 H), 7.04 (d, *J* = 8.04 Hz, 2 H), 6.67 (d, *J* = 8.4 Hz, 2 H), 3.94 (s, 2 H), 3.46 (s, 2 H).

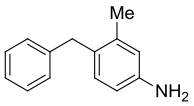
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 144.4, 141.9, 131.2, 129.7, 128.7, 128.3, 125.8, 115.3, 41.0.

MS (EI, 70 eV), *m/z* (%): 183 (M^+, 100), 180 (8), 165 (13), 106 (33), 91 (14), 77 (9).

HRMS *m/z* : calc. for $C_{13}H_{13}N$ 183.1048, found 183.1045.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3448 (w), 3354 (m), 3214 (w), 3024 (m), 3002 (m), 2904 (w), 2838 (w), 1738 (m), 1620 (s), 1514 (vs), 1492 (m), 1452 (m), 1436 (m), 1366 (w), 1272 (m), 1178 (m), 1124 (w), 1074 (w), 1028 (w), 836 (m), 726 (m), 696 (m).

Preparation of 4-benzyl-3-methyl-phenylamine (17d):



According to **GP3** the benzylic zinc reagent **11h** (1.4 mL, 1.7 M in THF, 2.4 mmol) was reacted with 4-bromo-3-methyl-phenylamine (**16c**, 372 mg, 2.00 mmol). The reaction time was 1 h. Flash column chromatographical purification (silica; pentane:Et_2O, 9:1) afforded **17d** as a brown oil (312 mg, 1.58 mmol, 79 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.31-7.25 (m, 2 H), 7.22-7.18 (m, 1 H), 7.18–7.12 (m, 2 H), 6.93 (d, *J* =7.9 Hz, 1 H), 6.56-6.50 (m, 2 H), 3.92 (s, 2 H), 3.45 (s, 2 H), 2.18 (s, 3 H).

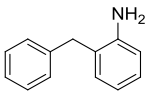
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 144.6, 141.2, 137.5, 130.8, 129.1, 128.5, 128.2, 125.6, 117.3, 112.7, 38.6, 19.7.

MS (EI, 70 eV), *m/z* (%): 197 (M^+, 80), 182 (55), 180 (11), 120 (100), 99 (10), 91 (21), 77 (13).

HRMS *m/z* : calc. for $C_{14}H_{15}N$ 197.1204, found 197.1185.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3448 (m), 3352 (m), 3214 (w), 3024 (m), 2914 (m), 1738 (m), 1622 (s), 1504 (vs), 1450 (s), 1378 (m), 1308 (m), 1278 (m), 1208 (m), 1072 (w), 1028 (m), 858 (m), 828 (m), 790 (m), 726 (vs), 696 (s).

Preparation of 2-benzyl-phenylamine (17e):



According to **GP3** the benzylic zinc reagent **11h** (1.4 mL, 1.7 M in THF, 2.4 mmol) was reacted with 2-bromo-phenylamine (**16d**, 344 mg, 2.00 mmol). The reaction time was 0.5 h. Flash

column chromatographical purification (silica; pentane:Et_2O, 6:1) afforded **17e** as a brown oil (274 mg, 1.50 mmol, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.35-7.28 (m, 2 H), 7.26-7.18 (m, 3 H), 7.17-7.05 (m, 2 H), 6.80 (dt, *J* = 7.3, 1.1 Hz, 1 H), 6.70 (d, *J* = 7.9 Hz, 1 H), 3.93 (s, 2 H), 3.43 (s, 2 H).

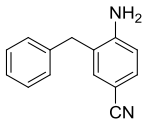
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 144.6, 139.3, 130.8, 128.6, 128.5, 127.6, 126.3, 125.1, 118.7, 115.9, 38.0.

MS (EI, 70 eV), *m/z* (%): 183 (M^+, 100), 180 (16), 167 (11), 165 (27), 106 (27), 77 (9).

HRMS *m/z* : calc. for $C_{13}H_{13}N$ 183.1048, found 183.1039.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3452 (m), 3370 (m), 3060 (m), 3024 (m), 2904 (w), 2838 (w), 1738 (m), 1620 (s), 1492 (vs), 1452 (s), 1366 (m), 1278 (m), 1074 (w), 1028 (w), 932 (w), 852 (w), 748 (s), 728 (s), 696 (s).

Preparation of 4-amino-3-benzyl-benzonitrile (17f):



According to **GP3** the benzylic zinc reagent **11h** (1.40 mL, 1.70 M in THF, 2.40 mmol) was reacted with 4-amino-3-bromo-benzonitrile (**16e**, 394 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et_2O, 6:1 then 3:1) afforded **17f** as a brown oil (350 mg, 1.68 mmol, 84 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.40-7.13 (m, 7H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.34 (s, 2H), 3.88 (s, 2H).

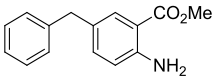
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.9, 140.4, 134.8, 131.9, 130.9, 128.7, 128.5, 126.3, 117.6, 115.5, 95.9, 40.4.

MS (EI, 70 eV), *m/z* (%): 208 (M^+, 100), 207 (60), 205 (8), 190 (8), 180 (6), 131 (25), 103 (5).

HRMS *m/z* : calc. for $C_{14}H_{12}N_2$ 208.1000, found 208.0986.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3460 (vs), 3366 (vs), 3238 (m), 3022 (m), 2218 (s), 1738 (w), 1634 (s), 1504 (s), 1492 (m), 1454 (m), 1422 (m), 1300 (m), 1262 (m), 1164 (m), 1072 (w), 1030 (w), 942 (w), 798 (m), 706 (m), 694 (m).

Preparation of 2-amino-5-benzyl-benzoic acid methyl ester (17g):



According to **GP3** the benzylic zinc reagent **11h** (0.75 mL, 1.60 M in THF, 1.20 mmol) was reacted with 2-amino-5-bromo-benzoic acid methyl ester (**2b**, 230 mg, 1.00 mmol). The reaction time was 2 h. Flash column chromatographical purification (silica; pentane:Et_2O, 6:1) afforded **17g** as a colorless oil (185 mg, 0.77 mmol, 77 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.71 (d, *J* = 2.21 Hz, 1 H), 7.30-7.24 (m, 2 H), 7.22-7.13 (m, 3 H), 7.08 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.60 (d, *J* = 8.6 Hz, 1 H), 5.59 (s, 2 H), 3.86 (s, 2 H), 3.85 (s, 3 H).

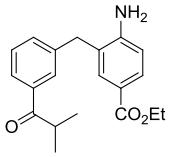
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 168.5, 148.8, 141.5, 135.0, 131.0, 128.8, 128.7, 128.4, 126.0, 117.1, 110.7, 51.5, 40.9.

MS (EI, 70 eV), *m/z* (%): 241 (M^+, 100), 209 (36), 182 (22), 180 (21).

HRMS *m/z* : calc. for $C_{15}H_{13}NO_2$ 241.1103, found 241.1080.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3476 (vs), 3376 (vs), 3024 (w), 2948 (w), 2920 (w), 1680 (s), 1624 (m), 1588 (m), 1560 (m), 1492 (m), 1436 (s), 1296 (s), 1244 (s), 1204 (s), 1160 (s), 1096 (m), 1072 (m), 840 (m), 796 (m), 696 (m), 608 (m).

Preparation of ethyl 4-amino-3-(3-isobutyrylbenzyl)benzoate (17h):



According to **GP3** the benzylic zinc reagent **11i** (3.5 mL, 0.69 M in THF, 2.4 mmol) was reacted with 4-amino-3-bromo-benzoic acid ethyl ester (**16g**, 394 mg, 2.00 mmol). The reaction time was 15 h. Flash column chromatographical purification (silica; pentane:Et_2O 2:1) afforded **17h** as a pale yellow oil (389 mg, 1.20 mmol, 60 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.82-7.77 (m, 4 H), 7.39-7.31 (m, 2 H), 6.64 (d, *J* = 8.8 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 3.96 (s, 2 H), 3.55-3.41 (m, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.18 (s, 3 H), 1.16 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.4, 166.7, 149.0, 139.3, 136.6, 132.8, 132.6, 130.1, 129.0, 128.1, 126.7, 122.9, 120.3, 114.8, 60.3, 37.7, 35.4, 19.1, 14.4.

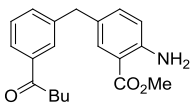
MS (EI, 70 eV), *m/z* (%): 325 (M^+, 64), 282 (25), 280 (100), 180 (23), 118 (11).

HRMS *m/z* : calc. for $C_{20}H_{23}NO_3$ 325.1678, found 325.1664.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3450 (m), 3352 (s), 2970 (s), 2930 (m), 1738 (m), 1694 (vs), 1668 (s), 1632 (s), 1604 (s), 1434 (m), 1364 (s), 1268 (vs), 1234 (vs), 1190 (s), 1026 (m), 996 (m), 814 (m), 768 (m), 738 (m).

2.5 Palladium-Catalyzed Cross-Couplings with Bromoaniline Derivatives

Preparation of 2-Amino-5-(3-pentanoyl-benzyl)-benzoic acid methyl ester (17i):



According to **GP4** the benzylic zinc reagent **11e** (3.8 mL, 0.63 M in THF, 2.4 mmol) was reacted with 2-amino-5-bromo-benzoic acid methyl ester (**16f**, 460 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et_2O 3:1) afforded **17i** as a colorless solid (638 mg, 1.96 mmol, 98 %).

m.p.: 76.8–79.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.78–7.74 (m, 2 H), 7.70 (dd, *J* = 2.2, 0.4 Hz, 1 H), 7.35–7.33 (m, 2 H), 7.07 (dd, *J* = 8.4 and 2.2 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 5.63 (s, 2 H), 3.90 (s, 2 H), 3.84 (s, 3 H), 2.92 (t, *J* = 7.5 Hz, 2 H), 1.69 (ddd, *J* = 14.7 and 7.6 and 7.4 Hz, 2 H), 1.39 (td, *J* = 14.9 and 7.3 Hz, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

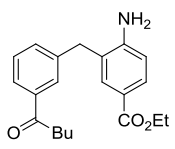
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.9, 168.7, 149.2, 142.3, 137.6, 135.1, 133.5, 131.3, 128.9, 128.5, 128.3, 126.2, 117.4, 110.9, 51.7, 41.0, 38.6, 26.8, 22.7, 14.2.

MS (EI, 70 eV), *m/z* (%):326 (18), 325 (M^+, 100), 294 (6), 269 (9), 268 (67), 266 (4), 180 (8), 164 (25), 132 (14).

HRMS *m/z* : calc. for $C_{20}H_{22}NO_3$ 325.1678, found 325.1681.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3444 (s), 3340 (s), 2956 (m), 2932 (m), 2872 (m), 1684 (s), 1668 (vs), 1624 (s), 1584 (s), 1564 (m), 1496 (m), 1432 (s), 1404 (m), 1364 (m), 1296 (s), 1248 (vs), 1228 (m), 1204 (s), 1180 (m), 1156 (s), 1100 (m), 1084 (m), 1024 (m), 980 (m), 832 (m), 792 (m), 760 (m), 688 (m), 580 (m).

4-Amino-3-(3-pentanoyl-benzyl)-benzoic acid ethyl ester (17j):



According to **GP4** the benzylic zinc reagent **11e** (3.8 mL, 0.63 M in THF, 2.4 mmol) was reacted with 4-amino-3-bromo-benzoic acid ethyl ester (**16g**, 488 mg, 2.00 mmol). The reaction time was 3 h. Flash column chromatographical purification (silica; pentane:Et_2O 1:1) afforded **17j** as a colorless solid (498 mg, 1.47 mmol, 73 %).

m.p.: 137.8–139.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.83–7.75 (m, 4 H), 7.39–7.29 (m, 2 H), 6.64 (d, *J* = 8.8 Hz, 1 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 3.96 (s, 2 H), 3.90 (bs, 2 H), 2.90 (t, *J* = 7.3 Hz, 2 H), 1.67 (quint, *J* = 7.4 Hz, 2 H), 1.38 (sext, *J* = 7.5 Hz, 2 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

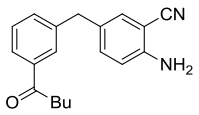
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.5, 165.7, 148.0, 138.2, 136.5, 131.9, 131.7, 129.1, 128.0, 126.8, 125.5, 121.9, 119.3, 113.8, 59.3, 37.4, 36.8, 25.5, 21.4, 13.4, 12.9.

MS (EI, 70 eV), *m/z* (%): 339 (M^+, 61), 295 (16), 294 (100), 293 (45), 292 (47), 181 (10), 180 (24).

HRMS *m/z* : calc. for $C_{21}H_{25}NO_3$ 339.1834, found 339.1837.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3468 (m), 3368 (s), 2960 (m), 2936 (m), 2900 (m), 2872 (w), 1680 (vs), 1628 (s), 1596 (m), 1512 (m), 1436 (m), 1364 (m), 1316 (m), 1268 (s), 1228 (m), 1192 (s), 1152 (m), 1120 (m), 1108 (m), 1024 (m), 956 (m), 932 (w), 840 (w), 768 (m), 740 (w), 688 (w), 568 (w).

Preparation of 2-amino-5-(3-pentanoyl-benzyl)-benzonitrile (17k):



According to **GP4** the benzylic zinc reagent **11e** (3.8 mL, 0.63 M in THF, 2.4 mmol) was reacted with 2-amino-5-bromo-benzonitrile (**16a**, 394 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et_2O 2:1) afforded **17k** as a colorless solid (529 mg, 1.81 mmol, 90 %).

m.p.: 98.6–100.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.85–7.75 (m, 2 H), 7.43–7.31 (m, 2 H), 7.21–7.14 (m, 2 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 4.18 (br, 2 H), 3.89 (s, 2 H), 2.93 (t, *J* = 7.7 Hz, 2 H), 1.69 (dt, *J* = 14.7 and 7.6 Hz, 2 H), 1.46-1.31 (m, 2 H), 0.93 (t, *J* = 7.3 H, 3 H).

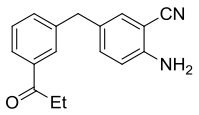
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.8, 148.4, 141.3, 137.7, 135.1, 133.5, 132.2, 130.5, 129.1, 128.5, 126.5, 117.8, 115.9, 96.4, 40.6, 38.7, 26.7, 22.7, 14.2.

MS (EI, 70 eV), *m/z* (%): 292 (M^+, 100), 250 (21), 236 (46), 235 (35), 207 (22), 205 (30), 190 (23), 131 (32).

HRMS *m/z* : calc. for $C_{19}H_{20}N_2O$ 292.1576, found 292.1560.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3452 (s), 3360 (vs), 3240 (s), 2956 (m), 2216 (vs), 1664 (s), 1640 (s), 1504 (vs), 1464 (m), 1420 (m), 1408 (s), 1372 (s), 1348 (s), 1312 (s), 1272 (s), 1216 (m), 1172 (m), 924 (m), 840 (m), 776 (m), 756 (m), 728 (s), 684 (m).

Preparation of 2-Amino-5-(3-propionyl-benzyl)-benzonitrile (17l):



According to **GP4** the benzylic zinc reagent **11g** (2.25 mL, 1.07 M in THF, 2.4 mmol) was reacted with 2-amino-5-bromo-benzonitrile (**16a**, 394 mg, 2.00 mmol). The reaction time was 1 h. Flash column chromatographical purification (silica; pentane:Et_2O 3:1) afforded **17l** as a colorless solid (466 mg, 1.76 mmol, 88 %).

m.p.: 80.5-83.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.81–7.74 (m, 2 H), 7.40–7.29 (m, 2 H), 7.16–7.11 (m, 2 H), 6.67 (dd, *J* = 8.4, 0.7 Hz, 1 H), 4.35 (bs, 2 H), 3.88 (s, 2 H), 2.96 (q, *J* = 7.3 Hz, 2 H), 1.20 (t, *J* = 7.3 Hz, 3 H).

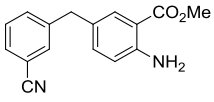
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.8, 148.2, 141.0, 137.3, 134.8, 133.2, 131.9, 130.2, 128.8, 128.1, 126.1, 117.5, 115.6, 96.1, 40.3, 31.8, 8.2.

MS (EI, 70 eV), *m/z* (%): 264 (M^+, 65), 235 (100), 207 (13), 205 (9), 190 (9), 180 (5), 131 (27), 117 (8).

HRMS *m/z* : calc. for $C_{17}H_{16}N_2O$ 264.1263, found 264.1254.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3364 (vs), 2980 (m), 2212 (vs), 1676 (s), 1644 (s), 1612 (m), 1508 (s), 1424 (m), 1412 (m), 1376 (m), 1340 (m), 1316 (s), 1268 (m), 1232 (s), 1172 (m), 1160 (m), 972 (m), 904 (m), 868 (m), 828 (m), 804 (m), 776 (s), 740 (m), 688 (m), 648 (m).

Preparation of 2-amino-5-(3-cyano-benzyl)-benzoic acid methyl ester (17m):



According to **GP4** the benzylic zinc reagent **11a** (1.55 mL, 1.55 M in THF, 2.4 mmol) was reacted with 2-amino-5-bromo-benzoic acid methyl ester (**16f**, 460 mg, 2.00 mmol). The reaction time was 1 h. Flash column chromatographical purification (silica; pentane:Et_2O 3:1) afforded **17m** as a colorless oil (459 mg, 1.72 mmol, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.67 (dd, *J* = 2.2 and 0.4 Hz, 1 H), 7.48–7.32 (m, 4 H), 7.04 (dd, *J* = 8.4 and 2.2 Hz, 1 H), 6.63 (d, *J* = 8.6 Hz, 1 H), 5.49 (s, 2 H), 3.87 (s, 2 H), 3.85 (s, 3 H).

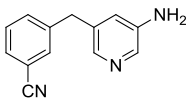
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 168.2, 149.0, 143.0, 134.8, 133.1, 132.1, 131.2, 129.8, 129.2, 127.0, 118.9, 117.4, 112.4, 110.8, 51.5, 40.3.

MS (EI, 70 eV), *m/z* (%): 266 (M^+, 100), 235 (23), 234 (80), 207 (23), 205 (19), 132 (12), 116 (12).

HRMS *m/z* : calc. for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1044.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3476 (s), 3372 (s), 2228 (s), 1692 (vs), 1628 (s), 1588 (s), 1560 (s), 1500 (s), 1480 (m), 1440 (s), 1312 (m), 1292 (s), 1248 (s), 1196 (s), 1164 (s), 1092 (s), 800 (m), 788 (m), 732 (m), 684 (s).

Preparation of 3-(5-Amino-pyridin-3-ylmethyl)-benzonitrile (17n):



According to **GP4** the benzylic zinc reagent **11a** (1.55 mL, 1.55 M in THF, 2.4 mmol) was reacted with 5-bromo-pyridin-3-ylamine (**16h**, 346 mg, 2.00 mmol). The reaction time was 12 h. Flash column chromatographical purification (silica; Et_2O) afforded **17n** as a brown solid (376 mg, 1.80 mmol, 90 %).

m.p.: 120.9–123.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.01 (s, 1 H), 7.47–7.43 (m, 3 H), 7.36–7.31 (m, 1 H), 6.93–6.86 (m, 2 H), 4.02 (s, 2 H), 3.62 (bs, 2 H).

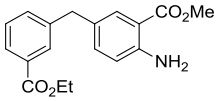
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 149.1, 142.2, 141.2, 137.4, 133.7, 132.6, 130.1, 129.4, 123.5, 122.8, 119.2, 112.6, 43.2.

MS (EI, 70 eV), *m/z* (%): 210 (4), 209 (M^+, 35), 208 (100), 207 (8), 206 (2), 192 (2), 181 (3), 179 (2), 154 (2), 127 (2). 91 (2).

HRMS *m/z* :calc. for $C_{13}H_{11}N_3$ 209.0953, found 209.0936.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3420 (vs), 3312 (s), 3168 (vs), 3080 (s), 3052 (s), 3016 (s), 2928 (s), 2852 (s), 2228 (vs), 1644 (s), 1600 (s), 1572 (s), 1488 (vs), 1416 (s), 1312 (s), 1268 (s), 780 (s), 708 (s), 692 (s), 648 (s).

Preparation of methyl 2-amino-5-[3-(ethoxycarbonyl)benzyl]benzoat (17o):



According to **GP4** the benzylic zinc reagent **11d** (1.80 mL, 1.34 M in THF, 2.4 mmol) was reacted with 2-amino-5-bromo-benzoic acid methyl ester (**16f**, 460 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et_2O 3:1 then 2:1) afforded **17o** as a colorless oil (606 mg, 1.93 mmol, 97 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.88-7.84 (m, 2 H), 7.69 (d, *J* = 2.4, 1 H), 7.33–7.31 (m, 2 H), 7.07 (dd, *J* = 8.5, 2.1 Hz, 1 H), 6.61 (d, *J* = 8.2 Hz, 1 H), 5.18 (s, 2 H), 4.35 (q, *J* = 7.0 Hz, 2 H), 3.89 (s, 2 H), 3.84 (s, 3 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 168.4, 166.7, 148.7, 141.8, 134.9, 133.2, 131.0, 130.6, 129.7, 128.4, 128.3, 127.3, 117.3, 110.8, 60.9, 51.5, 40.7, 14.3.

MS (EI, 70 eV), *m/z* (%): 314 (20), 313 (M^+, 100), 282 (14), 281 (38), 268 (14), 254 (21), 209 (10), 180 (13), 164 (14), 132 (14), 118 (14).

HRMS *m/z* : calc. for $C_{18}H_{19}NO_4$ 313.1314, found 313.1311.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3431 (m), 3322 (m), 3051 (w), 3027 (w), 2981 (m), 1711 (s), 1687 (vs), 1621 (m), 1583 (m), 1493 (m), 1438 (s), 1364 (w), 1274 (vs), 1245 (vs), 1190 (vs), 1102 (s), 1029 (m), 835 (m), 792 (m), 746 (m), 693 (m).

3 Preparation an Applications of Alkenyl Zinc Reagents

Starting materials of type **22** were prepared according to known literature procedures.[158]

3.1 General Procedures

General procedure 1 (GP1): LiCl-mediated zinc insertion in alkenyl bromides:

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.5–2 equiv.) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, zinc dust (1.5–2 equiv.) was added, followed by THF (1 mL/mmol). The zinc powder then was activated using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then, the substrate (1 equiv.) was added neat at 25 °C. In the case of very exothermic reactions, the reaction mixture was kept at 25 °C using a water bath and stirred for the given time until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, the remaining zinc dust was allowed to settle down or centrifuged (10 min, 2000 rpm). The yield of the insertion rection was determined by iodometric titration and the supernatant solution was then used in the reaction with electrophiles.

General procedure 2 (GP2): Allylation of alkenyl zinc reagents:

The freshly prepared zinc reagent was cooled to -40 °C and the corresponding allyl bromide (0.8–0.9 equiv.) was added, followed by 3 drops of CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF). The reaction mixture was allowed to warm to 0 °C. After stirring for the given time, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

General procedure 3 (GP3): Cross-coupling reactions of alkenyl zinc reagents:

The desired arylbromide or -iodide (0.8 equiv.) was added to the freshly prepared zinc reagent followed by $Pd(PPh_3)_4$ (5 mol%) and the mixture was stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

[158] (a) J. Thibonnet, V. A. Vu, L. Berillont, P. Knochel, *Tetrahedron* **2002**, *58*, 4787; (b) J.-J. Lian, A. Odedra, C.-J. Wu, R.-S. Liu, *J. Am. Chem. Soc.* **2005**, *127*, 4186; (c) C. Shih, J. S. Swenton, *J. Org. Chem.* **1982**, *60*, 210; (d) A. E. Nikolaev, V. E. Semenov, D. R. Sharafutdinova, Y. Y. Efremov, V. S. Reznik, *Tetrahedron Lett.* **2008**, *49*, 5994; (e) R. D. McCullough, D. O. Cowan, *J. Org. Chem.* **1985**, *50*, 4646, (f) Ph.D. thesis H. Ren, Ludwig-Maximilians-Universität München, **2006**.

General procedure 4 (GP4): LiCl-mediated magnesium insertion in the presence of zinc chloride in alkenyl bromides:

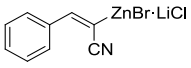
A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.5 equiv.) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, magnesium turnings (2.5 equiv.) were added, followed by THF (1 mL/mmol). The magnesium was activated using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then, $ZnCl_2$-solution (1.1 equiv., 1 M in THF) was added followed by the substrate (1 equiv.). The reaction mixture was stirred at 25 °C until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, solids were allowed to settle down or the reation mixture was centrifuged (10 min, 2000 rpm). The yield of the insertion rection was determined by iodometric titration of the supernatant solution. This clear solution was then used in the reaction with electrophiles.

General procedure 5 (GP5): Synthesis of tetrahydrophthalates of type 26:

The freshly prepared zinc reagent was cooled to -40 °C and CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) was added followed by the corresponding acid chloride (0.6 equiv.). After stirring for the given time at -40 °C, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 2x10 mL) and extracted with Et_2O (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was dissolved in MeOH (20 mL) and hydrazine hydrate (3 equiv.) was added at room temperature. After stirring for the given time, the reaction mixture was concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

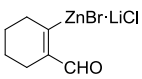
3.2 Direct Insertion of Zinc in Activated Alkenyl Bromides

Preparation of (1-cyano-2-phenylvinyl)zinc bromide (23a):



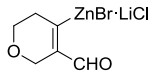
According to **GP1**, the zinc reagent **23a** was prepared from (*E*)-2-bromo-3-phenylacrylonitrile (**22a**, 2.08 g, 10.0 mmol) using Zn dust (980 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration against iodine indicates a concentration of 0.80 M (90%).

Preparation of (2-formylcyclohex-1-en-1-yl)zinc bromide (23c):



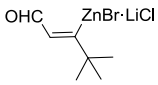
According to **GP1**, the zinc reagent **23c** was prepared from 2-bromocyclohex-1-ene-1-carbaldehyde (**22c**, 1.89 g, 10.0 mmol) using Zn dust (1.31 g, 20.0 mmol) and LiCl (848 mg, 20.0 mmol) in 1 h at 25 °C. Titration against iodine indicates a concentration of 0.77 M (86%).

Preparation of (5-formyl-3,6-dihydro-*2H*-pyran-4-yl)zinc bromide (23d):



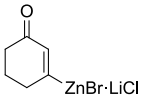
According to **GP1**, the zinc reagent **23d** was prepared from 4-bromo-5,6-dihydro-2H-pyran-3-carbaldehyde (**22d**, 955 mg, 5.00 mmol) using Zn dust (490 mg, 7.50 mmol) and LiCl (318 mg, 7.5 mmol) in 1 h at 25 °C. Titration against iodine indicates a concentration of 0.72 M (77%).

Preparation of (4,4-dimethyl-1-oxopent-2-en-3-yl)zinc bromide (23e):



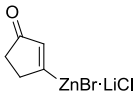
According to **GP1**, the zinc reagent **23e** was prepared from 3-bromo-4,4-dimethylpent-2-enal (**22e**, 1.91 g, 10.0 mmol) using Zn dust (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration against iodine indicates a concentration of 0.61 M (67%).

Preparation of (3-oxocyclohex-1-en-1-yl)zinc bromide (23f):



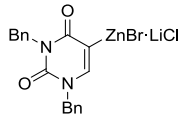
According to **GP1**, the zinc reagent **23f** was prepared from 3-bromocyclohex-2-enon (**22f**, 1.75 g, 10.0 mmol) using Zn dust (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration against iodine indicates a concentration of 0.77 M (86%).

Preparation of (3-oxocyclohex-1-en-1-yl)zinc bromide (23g):



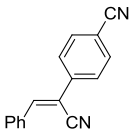
According to **GP1**, the zinc reagent **23g** was prepared from 3-bromocyclopent-2-enon (**22g**, 1.50 g, 10.0 mmol) using Zn dust (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration against iodine indicates a concentration of 0.99 M (94%).

Preparation of (1,3-dibenzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)zinc bromide (23h):



According to **GP1**, the zinc reagent **23h** was prepared from 1,3-dibenzyl-5-bromopyrimidine-2,4(*1H*,*3H*)-dione (**22h**, 5.58 g, 15.0 mmol) using Zn dust (1.47 g, 22.5 mmol) and LiCl (954 mg, 22.5 mmol) in 8 h at 25 °C. Titration against iodine indicates a concentration of 0.72 M (86%).

Preparation of ethyl 4-(1-cyano-2-propylpent-1-en-1-yl)benzoate (25a):



The cross-coupling reaction of **23a** (3.35 mL, 2.45 mmol, 0.71 M in THF) with 4-bromobenzonitrile (400 mg, 2.20 mmol) was performed according to **GP3** in 12 h. Flash column chromatography (silica, pentane:Et_2O 7:3) furnished **25a** as a yellow solid (276 mg, 73 %).

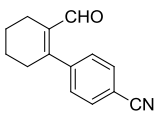
m.p.: 137.6–139.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.93 (dd, *J* = 6.7 and 3.0 Hz, 2 H), 7.81 (d, *J* = 8.8 Hz, 2 H), 7.74 (d, *J* = 8.8 Hz, 2 H), 7.65 (s, 1 H), 7.48–7.54 (m, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 144.9, 138.7, 132.9, 132.8, 131.5, 129.6, 129.1, 126.5, 118.1, 117.1, 112.6, 109.8.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3055 (w), 2229 (m), 2215 (m), 1588 (w), 1569 (w), 1510 (w), 1448 (w), 1418 (w), 1374 (w), 1324 (w), 1182 (w), 933 (m), 834 (vs), 753 (m), 680 (vs).

Preparation of 4-(2-formylcyclohex-1-en-1-yl)benzonitrile (25b):



The cross-coupling reaction of **23c** (2.60 mL, 2.00 mmol, 0.77 M in THF) with 4-bromobenzonitrile (291 mg, 1.60 mmol) was performed according to **GP3** in 1.5 h. Flash column chromatography (silica, pentane:Et_2O 8.5:1.5) furnished **25b** as a yellow solid (276 mg, 82 %).

m.p.: 78.0–79.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.42 (s, 1 H), 7.68 (d, *J* = 8.6 Hz, 2 H), 7.35 (d, *J* = 8.6 Hz, 2 H), 2.57–2.47 (m, 2 H), 2.43–2.11 (m, 2 H), 1.89–1.65 (m, 4 H).

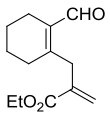
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 192.2, 156.7, 144.3, 136.9, 132.0, 129.3, 118.3, 112.1, 33.6, 22.2, 22.2, 21.2.

MS (EI, 70 eV), *m/z* (%): 211 (M^+, 100), 210 (84), 182 (28), 154 (29), 140 (24), 116 (32).

HRMS *m/z* : calc. for $C_{14}H_{13}NO$ 211.0997, found 211.0992.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2928 (w), 2856 (w), 2227 (m), 1709 (w), 1663 (vs), 1621 (m), 1604 (m), 1500 (w), 1408 (m), 1361 (w), 1275 (w), 1211 (m), 1193 (w), 1171 (m), 984 (w), 856 (m), 826 (s), 711 (m).

Preparation of ethyl 2-[(2-formylcyclohex-1-en-1-yl)methyl]prop-2-enoate (25c):



The allylation reaction of **23c** (2.60 mL, 2.00 mmol, 0.77 M in THF) with ethyl (2-bromomethyl)acrylate (347 mg, 1.80 mmol) was performed according to **GP2** in 1 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **25c** as a colorless oil (377 mg, 94 %).

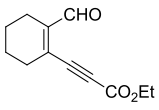
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.07 (s, 1 H), 6.27 (d, *J* = 1.1, 1 H), 5.51 (d, *J* = 1.1, 1 H), 4.21 (d, *J* = 7.1 Hz, 2 H), 3.54 (s, 2 H), 2.28-2.14 (m, 4 H), 1.16 (dt, *J* = 6.4 and 3.2 Hz, 4 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.2, 166.5, 154.8, 138.0, 135.5, 126.2, 61.0, 33.7, 31.6, 22.4, 22.0, 21.6, 14.1.

MS (EI, 70 eV), *m/z* (%): 222 (M^+, 3), 149 (100), 148 (49), 147 (28), 119 (25), 91 (37), 79 (25).

HRMS *m/z* : calc. for $C_{13}H_{18}O_3$ 222.1256, found 222.1258.

Preparation of ethyl 3-(2-formylcyclohex-1-en-1-yl)prop-2-ynoate (25d):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with the alkenyl zinc reagent **23c** (2.80 mL, 2.40 mmol, 0.85 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.24 mL, 0.24 mmol, 1.0 M in THF) was added, followed by ethyl 3-bromoprop-2-ynoate (354 mg, 2.00 mmol) and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 4:1) to give **25d** as a colorless oil (331 mg, 80 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.15 (s, 1H), 4.28 (q, *J* = 6.0 Hz, 2H), 2.50-2.40 (m, 2H), 2.35-2.25 (m, 2H), 1.75-1.60 (m, 4H), 1.33 (t, *J* = 6.0 Hz, 3H).

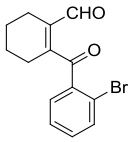
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.5, 153.3, 147.6, 135.8, 88.32, 81.8, 62.4, 31.2, 22.3, 21.5, 20.6, 14.0.

MS (EI, 70 eV), *m/z* (%): 296 (M^+, 9), 162 (75), 105 (36), 91 (40), 77 (49), 43 (100).

HRMS *m/z* : calc. for $C_{12}H_{14}O_3$ 206.0943, found 206.0946.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2939 (m), 2210 (m), 1708 (vs), 1678 (vs), 1366 (m), 1255 (vs), 1217 (vs), 1140 (s), 1017 (s), 747 (m).

Preparation of 2-[(2-bromophenyl)carbonyl]cyclohex-1-ene-1-carbaldehyde (25e):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with the alkenyl zinc reagent **23c** (2.80 mL, 2.40 mmol, 0.85 M in THF) and cooled to -50 °C. CuCN·2LiCl (2.40 mL, 2.40 mmol, 1.0 M in THF) was added, followed by 2-bromobenzoyl chloride (439 mg, 2.00 mmol) and the reaction mixture was stirred for 4 h at -50 °C. The reaction was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 10:1 then 4:1) to give **25e** as a colorless oil (297 mg, 51 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.74 (s, 1 H). 7.70-7.55 (m, 2 H), 7.45-7.35 (m, 2 H), 2.50-2.35 (m, 4 H), 1.80-1.70 (m, 4 H),

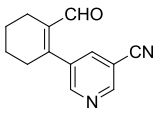
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 197.3, 191.2, 154.6, 141.7, 139.0, 134.3, 133.2, 131.2, 127.9, 120.7, 28.7, 22.5, 21.8, 20.8.

MS (EI, 70 eV), *m/z* (%):213 (M^+, 100), 185 (77), 183 (77), 109 (72), 43 (80).

HRMS *m/z* : calc. for $C_{14}H_{13}BrO_2$ 292.0099, found 292.0092.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2937 (w), 1751 (vs), 1434 (m), 1172 (m), 1065 (m), 1026 (vs), 1008 (vs), 911 (s), 755 (vs), 734 (s).

Preparation of 5-(2-formylcyclohex-1-en-1-yl)pyridine-3-carbonitrile (25f):



The cross-coupling reaction of **23c** (2.80 mL, 2.40 mmol, 0.85 M in THF) with 5-bromopyridine-3-carbonitrile (366 mg, 2.00 mmol) was performed according to **GP3** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 1:1) furnished **25f** as a yellow oil (276 mg, 65 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.42 (s, 1 H). 8.88-8.87 (m, 1 H), 8.69-8.68 (m, 1 H), 7.88-7.87(m, 1 H), 2.55-2.45 (m, 2 H), 2.43-2.35 (m, 2 H), 1.85-1.70 (m, 4 H),

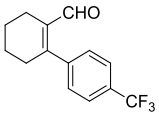
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.0, 152.2, 151.9, 151.7, 138.8, 138.6, 135.5, 115.9, 109.9, 33.8, 22.3, 22.1, 21.0.

MS (EI, 70 eV), *m/z* (%): 212 (M^+, 73), 211 (73), 183 (100), 169 (29), 155 (63).

HRMS *m/z* : calc. for $C_{13}H_{12}N_2O$ 212.0950, found 212.0939.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2934 (m), 2860 (w), 2234 (w), 1667 (vs), 1625 (m), 1418 (m), 1223 (m), 1024 (w), 905 (m), 707 (s), 652 (w).

Preparation of 2-[4-(trifluoromethyl)phenyl]cyclohex-1-ene-1-carbaldehyde (25g):



The cross-coupling reaction of **23c** (2.80 mL, 2.40 mmol, 0.85 M in THF) with 4-bromobenzotrifluoride (450 mg, 2.00 mmol) was performed according to **GP3** in 4 h. Flash column chromatography (silica, hexanes:Et_2O 10:1 then 4:1) furnished **25g** as a yellow oil (369 mg, 73 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.45 (s, 1 H). 7.66 (q, *J* = 9.0 Hz, 2 H), 7.37 (q, *J* = 9.0 Hz, 2 H), 2.60-2.50 (m, 2 H), 2.40-2.30 (m, 2 H), 1.85-1.60 (m, 4 H).

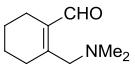
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 192.1, 157.4, 143.2, 136.7, 130.4 (q, *J* = 33 Hz), 128.9, 125.3 (q, *J* = 4 Hz), 123.9 (q, *J* = 272 Hz), 33.9, 22.3, 22.2, 21.3.

MS (EI, 70 eV), *m/z* (%): 254 (M^+, 25), 253 (22), 185 (50), 159 (19), 43 (100).

HRMS *m/z* : calc. for $C_{14}H_{13}F_3O$ 254.0918, found 254.0907.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2937 (w), 1671 (s), 1614 (w), 1322 (vs), 1211 (w), 1163 (s), 1121 (vs), 1109 (vs), 1067 (vs), 1017 (m), 840 (m).

Preparation of 2-[(dimethylamino)methyl]cyclohex-1-ene-1-carbaldehyde (25h):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with CH_2Cl_2 (2 mL) and *N*, *N*, *N*', *N*'-tetramethyldiaminomethane (204 mg, 2.00 mmol) and was cooled to 0 °C. Then, trifluoroacetic anhydride (420 mg, 2 mmol) was added dropwise at 0 °C and the resulting clear solution was stirred for 15 min. Then, the alkenyl zinc reagent **23c** (2.82 mL, 2.00 mmol, 0.71 M in THF) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with sat. NaCl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was dissolved in EtOAc (30 mL) and washed with HCl (2x20 mL, 2 M). The aqueous solution was neutralized with $NaHCO_3$, NaOH (2 M, 10 mL) was added and subsequently extracted with EtOAc (3x10 mL). After drying over Na_2SO_4 and evaporation of solvents **25h** was isolated as a yellow liquid (226 mg, 68 %).

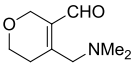
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.13 (s, 1 H), 3.27 (s, 2 H), 2.36–2.27 (m, 2 H), 2.24 (s, 6 H), 2.24–2.19 (m, 2 H), 1.68–1.54 (m, 4 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 188.4, 155.1, 136.5, 59.7, 45.4, 30.8, 22.4, 22.0, 21.6.

MS (EI, 70 eV), *m/z* (%): 167 (M^+, 20), 138 (100), 122 (22), 110 (22), 79 (23), 58 (34), 42 (57).

HRMS *m/z* : calc. for $C_{10}H_{17}NO$ 167.1310, found 167.1307.

Preparation of 4-[(dimethylamino)methyl]-5,6-dihydro-*2H*-pyran-3-carbaldehyde (25i):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar ans septum was charged with CH_2Cl_2 (2 mL) and *N*, *N*, *N*', *N*'-tetramethyldiaminomethane (163 mg, 1.6 mmol) and was cooled to 0 °C. Then, trifluoroacetic anhydride (336 mg, 1.6 mmol) was added dropwise at 0 °C and the resulting clear solution was stirred for 15 min. Then, the alkenyl zinc reagent **23d**

(3.1 mL, 2.00 mmol, 0.65 M in THF) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with sat. NaCl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was dissolved in EtOAc (30 mL) and washed with HCl (2x 20 mL, 2 M). The aqueous solution was neutralized with $NaHCO_3$, NaOH (2 M, 10 mL) was added and subsequently extracted with EtOAc (3x10 mL). After drying over Na_2SO_4 and evaporation of solvents **25i** was isolated as a yellow liquid (237 mg, 88 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.08 (s, 1 H), 4.49–4.45 (m, 2 H), 3.39 (t, *J* = 5.5 Hz, 2 H), 2.67 (s, 2 H), 2.01–1.95 (m, 2 H), 1.83 (s, 6 H).

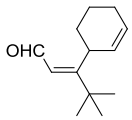
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 188.1, 152.7, 136.1, 64.3, 64.0, 58.9, 45.4, 29.7.

MS (EI, 70 eV), *m/z* (%): 169 (M^+, 19), 124 (100), 123 (16), 94 (25), 58 (87), 44 (15), 42 (16).

HRMS *m/z* : calc. for $C_9H_{15}NO_2$ 169.1103, found 161.1108.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2944 (w), 2822 (m), 2768 (w), 1663 (vs), 1461 (m), 1387 (m), 1290 (m), 1252 (s), 1165 (m), 1115 (m), 1041 (m), 1016 (m), 1002 (m), 950 (m), 855 (m), 839 (m), 758 (m), 694 (m), 675 (m).

Preparation of ethyl 2-[(2-formylcyclohex-1-en-1-yl)methyl]prop-2-enoate (25k):



The allylation reaction of **23e** (3.85 mL, 2.00 mmol, 0.52 M in THF) with 3-bromocyclohexene (258 mg, 1.60 mmol) was performed according to **GP2** in 30 min. Flash column chromatography (silica, pentane:Et_2O 95:5) furnished **25k** as a colorless oil (294 mg, 96 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.36 (d, *J* = 8.3 Hz, 1 H), 5.84 (dd, *J* = 8.2 and 1.2 Hz, 1 H), 5.77–5.58 (m, 2 H), 3.35–3.14 (m, 1 H), 2.23–2.09 (m, 3 H), 2.00–1.81 (m, 1 H), 1.79–1.51 (m, 2 H), 1.14 (s, 9 H).

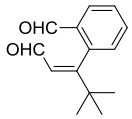
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.2, 188.1, 152.7, 145.9, 136.1, 64.3, 64.0, 58.9, 45.4, 29.7, 26.5.

MS (EI, 70 eV), *m/z* (%): 192 (M^+, 23), 163 (85), 135 (100), 108 (75), 79 (86), 57 (81), 41 (89).

HRMS *m/z* : calc. for $C_{13}H_{20}O$ 192.1514, found 192.1508.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2938 (m), 2868 (w), 1668 (vs), 1614 (m), 1449 (w), 1394 (w), 1366 (w), 1208 (w), 1152 (s), 1134 (m), 1030 (w), 890 (m), 855 (m), 722 (m), 664 (s).

Preparation of 2-[1-tert-butyl-3-oxoprop-1-en-1-yl]benzaldehyde (25l):



The cross-coupling reaction of **23e** (3.80 mL, 2.00 mmol, 0.53 M in THF) with 2-bromobenzaldehyde (296 mg, 1.60 mmol) was performed according to **GP3** in 2 h. Flash column chromatography (silica, hexanes:Et_2O 1:1) furnished **25l** as a yellow wax (319 mg, 92 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.04 (s, 1 H). 9.10 (d, *J* = 8.0 Hz, 1 H), 8.02 (dd, *J* = 8.0 and 1.4 Hz, 1 H), 7.65 (td, *J* = 7.5 and 1.7 Hz, 1 H), 7.56 (td, *J* = 7.5 and 1.4 Hz, 1 H), 7.22 (dd, *J* = 7.6 and 1.0 Hz, 1 H), 6.39 (d, *J* = 8.0 Hz, 1 H), 1.18 (s, 9 H).

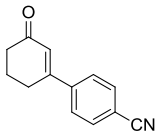
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 193.0, 190.9, 171.3, 139.3, 134.6, 133.3, 130.2, 129.3, 128.7, 128.7, 38.0, 29.3.

MS (EI, 70 eV), *m/z* (%): 216 (M^+, >1), 187 (100), 160 (17), 131 (23), 103 (11), 77 (13), 57 (17), 41 (11).

HRMS *m/z* : calc. for $C_{14}H_{16}O_2$ 216.1150, found 216.1158.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2970 (m), 2850 (w), 2758 (vw), 1684 (vs), 1671 (vs), 1591 (m), 1480 (m), 1396 (m), 1366 (w), 1264 (m), 1198 (s), 1176 (m), 1132 (s), 878 (m), 826 (s), 803 (m), 781 (m), 754 (s), 713 (m), 702 (m).

Preparation of 3-(4-Cyanophenyl)-2-cyclohexen-1-one (25m):



The cross-coupling reaction of **23f** (4.80 mL, 2.40 mmol, 0.50 M in THF) with 4-iodobenzonitrile (458 mg, 2.00 mmol) was performed according to **GP3** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 1:1 then 1:2) furnished **25m** as a colorless solid (349 mg, 88 %).

m.p.: 95.8–97.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.70 (d, *J* = 8.3 Hz, 2 H). 7.61 (d, *J* = 8.5 Hz, 2 H), 6.41 (s, 1 H), 2.75 (td, *J* = 6.0 and 1.2 Hz, 2 H), 2.50 (d, *J* = 7.1 Hz, 2 H), 2.18 (quint, *J* = 6.4 Hz, 2 H),

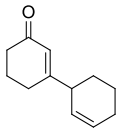
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.1, 157.2, 143.3, 132.5, 127.3, 126.6, 118.2, 113.2, 37.1, 27.9, 22.6,

MS (EI, 70 eV), *m/z* (%): 197 (M^+, 44), 169 (100), 141 (69), 140 (90), 113 (24).

HRMS *m/z* : calc. for $C_{13}H_{11}NO$ 197.0841, found 197.0838.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2951 (w), 2223 (w), 1662 (vs), 1603 (m), 1343 (m), 1259 (m), 1183 (m), 1130 (m), 889 (m), 830 (m), 816 (vs).

Preparation of ethyl 1,1'-bi(cyclohexane)-1,2'-dien-3-one (25n):



The allylation reaction of **23f** (4.80 mL, 2.40 mmol, 0.50 M in THF) with 3-bromocyclohexene (322 mg, 2.00 mmol) was performed according to **GP2** in 1 h. Flash column chromatography (silica, pentane:Et_2O 4:5) furnished **25n** as a colorless oil (269 mg, 76 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.90-5.80 (m, 2 H), 5.55-5.48 (m, 1 H), 2.95-2.85 (m, 1 H), 2.40-2.20 (m, 4 H), 2.15-1.80 (m, 5 H), 1.75-1.40 (m, 3 H).

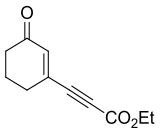
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.1, 169.4, 129.7, 126.9, 125.8, 43.22, 37.5, 28.3, 27.6, 24.9, 23.0, 20.6.

MS (EI, 70 eV), *m/z* (%): 176 (M^+, 45), 120 (100), 105 (72), 92 (74), 91 (92).

HRMS *m/z* : calc. for $C_{12}H_{16}O$ 176.1201, found 176.1201.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2930 (m), 1662 (vs), 1619 (m), 1257 (m), 1241 (m), 1187 (m), 1133 (w), 965 (w), 884 (m), 725 (m).

Preparation of 3-[2-(Ethoxycarbonyl)ethynyl]-2-cyclohexen-1-one (25o):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with the alkenyl zinc reagent **23f** (4.80 mL, 2.40 mmol, 0.50 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.24 mL, 0.24 mmol, 1.0 M in THF) was added, followed by ethyl 3-bromoprop-2-ynoate (354 mg, 2.00 mmol) and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 2:1) to give **25o** as a colorless oil (273 mg, 71 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.35 (t, *J* = 1.9 Hz, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 2.50-2.40 (m, 4 H), 2.11–2.01 (m, 2 H), 1.33 (t, *J* = 7.2 Hz, 3H),

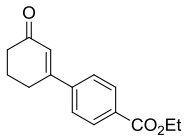
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 197.6, 153.1, 139.4, 135.7, 88.2, 83.1, 62.5, 37.2, 29.3, 22.34, 13.9.

MS (EI, 70 eV), *m/z* (%): 192 (M^+, 41), 164 (85), 147 (85), 120 (99), 92 (100).

HRMS *m/z* : calc. for $C_{11}H_{12}O_3$ 192.0786, found 192.0780.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942 (w), 2218 (m), 1707 (vs), 1676 (vs), 1261 (vs), 1245 (vs), 1187 (s), 1145 (vs), 1135 (vs), 1015 (m), 747 (m).

Preparation of 3-[4-(ethoxycarbonyl)phenyl]-2-cyclohexen-1-one (25p):



The cross-coupling reaction of **23f** (4.80 mL, 2.40 mmol, 0.50 M in THF) with ethyl 4-iodobenzoate (552 mg, 2.00 mmol) was performed according to **GP3** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 2:1 then 1:1) furnished **25p** as a colorless solid (373 mg, 76 %).

m.p.: 62.2–64.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 6.44 (t, *J* = 1.5 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.78 (td, *J* = 6.1 and 1.5 Hz, 2 H), 2.53–2.47 (m, 2 H), 2.17 (quint, *J* = 6.4 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

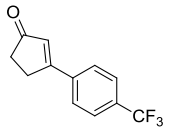
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.5, 165.9, 158.4, 143.0, 131.5, 129.8, 126.7, 125.9, 61.2, 37.2, 28.0, 22.7, 14.3.

MS (EI, 70 eV), *m/z* (%): 244 (M^+, 100), 216 (41), 199 (48), 171 (99), 144 (94).

HRMS *m/z* : calc. for $C_{15}H_{16}O_3$ 244.1099, found 244.1099.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2944 (w), 1704 (vs), 1665 (vs), 1602 (s), 1287 (s), 1269 (vs), 1184 (s), 1110 (vs), 1021 (m), 766 (vs), 698 (s).

Preparation of 3-[4-(trifluoromethyl)phenyl]-2-cyclopenten-1-one (25q):



The cross-coupling reaction of **23g** (3.43 mL, 2.40 mmol, 0.70 M in THF) with 4-iodobenzotrifluoride (544 mg, 2.00 mmol) was performed according to **GP3** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 1:1 then 1:2) furnished **25q** as a colorless solid (333 mg, 74 %).

m.p.: 106.5–108.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 6.44 (t, *J* = 1.5 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.78 (td, *J* = 6.1 and 1.5 Hz, 2 H), 2.53–2.47 (m, 2 H), 2.17 (quint, *J* = 6.4 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

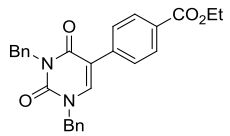
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 208.7, 171.7, 137.4, 132.6 (q, *J* = 32 Hz), 129.4, 127.0, 125.9 (q, *J* = 4 Hz), 123.7 (q, *J* = 272 Hz), 35.3, 28.7,

MS (EI, 70 eV), *m/z* (%):226 (M^+, 95), 225 (33), 170 (28), 157 (100), 129 (38).

HRMS *m/z* : calc. for $C_{12}H_9F_3O$ 226.0605, found 226.0597.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2925 (w), 1689 (s), 1677 (s), 1601 (m), 1319 (vs), 1163 (vs), 1132 (vs), 1110 (vs), 1064 (vs), 1014 (m), 829 (vs).

Preparation of ethyl 4-(1,3-dibenzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)benzoate (25r):



The cross-coupling reaction of **23g** (4.17 mL, 3.00 mmol, 0.72 M in THF) with ethyl 4-iodobenzoate (745 mg, 2.70 mmol) was performed according to **GP3** in 2 h. Flash column chromatography (silica, pentane:Et_2O 3:2) furnished **25r** as a colorless solid (1.19 g, 90 %).

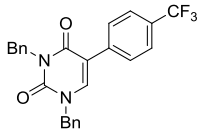
m.p.: 108.9–110.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.04 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 7.45–7.24 (m, 11 H), 5.26 (s, 2 H), 5.04 (s, 2 H), 4.39 (q, *J* = 7.2 HZ, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.2, 161.5, 151.2, 140.0, 137.3, 136.7, 135.1, 129.7, 129.6, 129.2, 129.2, 128.6, 128.4, 128.0, 127.7, 114.0, 61.0, 52.5, 45.0, 14.3.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1696 (s), 1654 (vs), 1605 (m), 1447 (s), 1408 (m), 1380 (m), 1363 (m), 1270 (s), 1105 (s), 1020 (m), 943 (m), 859 (m), 784 (s), 753 (m), 731 (s), 697 (vs).

Preparation of 1,3-dibenzyl-5-(4-(trifluoromethyl)phenyl)pyrimidine-2,4(*1H*,*3H*)-dione (25s):



The cross-coupling reaction of **23g** (4.17 mL, 3.00 mmol, 0.72 M in THF) with 4-trifluoromethylbromobenzene (608 mg, 2.70 mmol) was performed according to **GP3** in 2 h. Flash column chromatography (silica, hexanes:Et_2O 1:1) furnished **25s** as a colorless solid (1.07 g, 81 %).

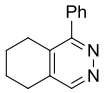
m.p.: 160.2–161.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.67–7.52 (m, 6 H), 7.46–7.24 (m, 9 H), 5.26 (s, 2 H), 5.04 (s, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 161.5, 151.2, 140.0, 136.6, 136.4 (q, *J* = 1.4 Hz), 135.0, 129.8 (q, *J* = 33 Hz), 129.3, 129.2, 128.7, 128.5, 128.4, 128.1, 127.7, 125.3 (q, *J* = 4 Hz), 124.0 (q, *J* = 272 Hz), 113.7, 52.6, 45.1.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3064 (vw), 1704 (m), 1651 (vs), 1451 (m), 1409 (m), 1356 (m), 1325 (s), 1237 (m), 1110 (s), 1063 (m), 1018 (w), 941 (m), 832 (w), 729 (s), 695 (s), 609 (m).

Preparation of 1-phenyl-5,6,7,8-tetrahydrophthalazine (26a):



The acylation reaction of **23c** (3.10 mL, 2.00 mmol, 0.65 M in THF) with benzoyl chloride (225 mg, 1.60 mmol) was performed in 14 h followed by the reaction hydrazine hydrate (300 mg, 6.00 mmol) according to **GP5**. Flash column chromatography (silica, CH_2Cl_2:EtOAc 9:1) furnished **26c** as a colorless solid (166 mg, 49 %).

m.p.: 80.0–84.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.83 (s, 1 H), 7.57–7.33 (m, 5 H), 2.80 (t, *J* = 6.4 Hz, 2 H), 2.64 (t, *J* = 6.2 Hz, 2 H), 1.94–1.66 (m, 4 H).

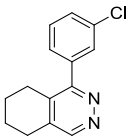
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 161.4, 151.3, 137.2, 137.0, 135.5, 129.0, 128.7, 128.2, 26.4, 26.0, 22.1, 21.4.

MS (EI, 70 eV), *m/z* (%): 210 (M^+, 67), 209 (100), 195 (11), 165 (11), 152 (11), 77 (14).

HRMS *m/z* : calc. for $C_{14}H_{14}N_2$ 209.1073 [M^+-H], found 209.1079.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922 (m), 2859 (w), 1663 (m), 1565 (m), 1444 (m), 1427 (m), 1407 (m), 1339 (m), 1234 (w), 1070 (w), 1027 (w), 1017 (w), 1001 (w), 951 (m), 928 (m), 777 (s), 756 (s), 708 (vs).

Preparation of 1-(3-chlorophenyl)-5,6,7,8-tetrahydrophthalazine (26b):



The acylation reaction of **23c** (3.77 mL, 2.00 mmol, 0.53 M in THF) with 3-chlorobenzoyl chloride (210 mg, 1.20 mmol) was performed in 14 h followed by the reaction hydrazine hydrate (300 mg, 6.00 mmol) according to **GP5**. Flash column chromatography (silica, CH_2Cl_2:EtOAc 1:1) furnished **26c** as a brown solid (160 mg, 54 %).

m.p.: 110.3–112.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.85 (s, 1 H), 7.56–7.51 (m, 1 H), 7.46-7.36 (m, 3 H), 2.81 (t, *J* = 6.3 Hz, 2 H), 2.64 (t, *J* = 6.2 Hz, 2 H), 1.93-1.72 (m, 4 H)

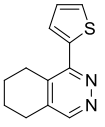
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.1, 151.5, 138.7, 137.6, 135.7, 134.3, 129.6, 129.2, 128.9, 127.2, 26.4, 26.0, 22.0, 21.3.

MS (EI, 70 eV), *m/z* (%): 244 (M^+, 61), 243 (100), 229 (14), 109 (7), 165 (8), 153 (8), 152 (16).

HRMS *m/z* : calc. for $C_{14}H_{13}ClN_2$ 245.0846 [M^++H], found 245.0839.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2944 (w), 2855 (w), 1562 (m), 1425 (m), 1398 (m), 1331 (m), 1231 (m), 1076 (m), 1022 (m), 1006 (m), 956 (m), 885 (m), 860 (m), 828 (m), 800 (vs), 768 (m), 728 (s), 700 (vs).

Preparation of 1-thiophen-2-yl-5,6,7,8-tetrahydrophthalazine (26c):



The acylation reaction of **23c** (4.00 mL, 3.00 mmol, 0.75 M in THF) with 2-thiophenecarbonyl chloride (264 mg, 1.80 mmol) was performed in 14 h followed by the reaction hydrazine hydrate (450 mg, 9.00 mmol) according to **GP5**. Flash column chromatography (silica, CH_2Cl_2:EtOAc 9:1) furnished **26c** as a yellow solid (164 mg, 42 %).

m.p.: 120.6–123.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.72 (s, 1 H), 7.52 (dd, *J* = 3.7 and 1.1 Hz, 1 H), 7.49 (dd, *J* = 5.0 and 1.1 Hz, 1 H), 7.15 (dd, *J* = 5.2 and 3.7 Hz, 1 H), 2.99-2.86 (m, 2 H), 2.84-2.71 (m, 2 H), 1.96-1.76 (m, 4 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 154.8, 150.6, 140.5, 137.2, 134.1, 128.6, 128.5, 127.4, 26.9, 26.3, 22.2, 21.1.

MS (EI, 70 eV), *m/z* (%): 216 (M^+, 100), 215 (68), 160 (50), 91 (49), 77 (54), 44 (67), 41 (66).

HRMS *m/z* : calc. for $C_{12}H_{12}N_2S$ 216.0721, found 216.0719.

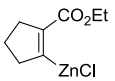
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2940 (w), 2860 (w), 1559 (w), 1542 (w), 1437 (m), 1414 (w), 1365 (m), 1300 (m), 1114 (w), 1053 (m), 940 (w), 928 (w), 858 (m), 836 (m), 798 (m), 708 (vs).

3.3 Magnesium Insertion in the Presence of Zinc Chloride in Alkenyl Bromides

Preparation of 2-bromocyclopentenzinc chloride (23i):

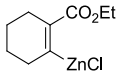
According to **GP4**, the zinc reagent **23i** was prepared from 1,2-dibromocyclopenetene (**22i**, 2.26 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and $ZnCl_2$ (11.0 mL, 1 M in THF) in 8 h at 25 °C. Titration against iodine indicates a concentration of 0.51 M (98 %).

Preparation of (2-(ethoxycarbonyl)cyclopent-1-en-1-yl)zinc chloride (23k):



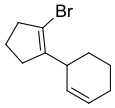
According to **GP4**, the zinc reagent **23k** was prepared from ethyl 2-bromocyclopent-1-ene-1-carboxylate (**22k**, 438 mg, 2.00 mmol) using Mg turnings (122 mg, 5.00 mmol), LiCl (127 mg, 3.00 mmol) and $ZnCl_2$ (2.2 mL, 1 M in THF) in 14 h at 25 °C. Titration against iodine indicates a concentration of 0.42 M (84 %).

Preparation of (2-(ethoxycarbonyl)cyclohex-1-en-1-yl)zinc chloride (23l):



According to **GP4**, the zinc reagent **23l** was prepared from ethyl 2-bromocyclohex-1-ene-1-carboxylate (**22l**, 2.33 g, 10.0 mmol) using Mg turnings (608 mg, 25.00 mmol), LiCl (636 mg, 15.0 mmol) and $ZnCl_2$ (11.0 mL, 1 M in THF) in 14 h at 25 °C. Titration against iodine indicates a concentration of 0.33 M (70 %).

Preparation of 1-bromo-2-(3-cyclohexen-1-yl)cyclopentene (25t):



The allylation reaction of **23i** (4.30 mL, 2.40 mmol, 0.56 M in THF) with 3-bromocyclohexene (322 mg, 2.00 mmol) was performed according to **GP2** in 1 h. Flash column chromatography (silica, hexanes) furnished **25t** as a colorless oil (392 mg, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.85–5.70 (m, 1 H), 5.45–5.35 (m, 1 H), 3.40–3.30 (m, 1 H), 2.70–2.55 (m, 2 H), 2.35–2.20 (m, 2 H), 2.20–1.40 (m, 8 H).

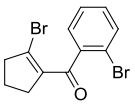
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 143.9, 128.8, 128.2, 115.2, 39.8, 36.7, 31.1, 26.7, 24.7, 21.8, 21.7.

MS (EI, 70 eV), *m/z* (%): 226 (M^+, 7), 147 (100), 119 (37), 91 (57), 91 (57).

HRMS *m/z* : calc. for $C_{11}H_{15}Br$ 226.0357, found 226.0335.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2930 (vs), 2855 (s), 1708 (m), 1652 (m), 1445 (m), 1316 (m), 1044 (m), 917 (m), 881 (s), 722 (vs).

Preparation of (2-bromocyclopent-1-en-1-yl)(2-bromophenyl)methanone (25u):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with the alkenyl zinc reagent **23i** (3.51 mL, 2.00 mmol, 0.57 M in THF) and cooled to -20 °C. CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.0 M in THF) was added, followed by 2-bromobenzoyl chloride (527 mg, 2.40 mmol) and the reaction mixture was stirred for 4 h at -20 °C. The reaction was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10

mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:CH_2Cl_2 4:1) to give **25u** as a colorless oil (421 mg, 64 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.67–7.52 (m, 1 H), 7.49–7.19 (m, 3 H), 2.90 (tt, *J* = 7.8 and 2.3 Hz, 2 H), 2.84–2.74 (m, 2 H), 2.04 (quint, *J* = 7.7 Hz, 2 H).

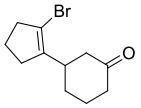
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 193.4, 141.2, 139.5, 133.1, 133.0, 131.3, 128.9, 127.5, 119.5, 43.94, 33.4, 21.5.

MS (EI, 70 eV), *m/z* (%): 330 (M^+, 14), 250 (96), 249 (100), 185 (51), 183 (51), 170 (50).

HRMS *m/z* : calc. for $C_{12}H_{12}Br_2O$ 329.9255, found 329.9074.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2925 (w), 1647 (vs), 1588 (vs), 1431 (s), 1330 (vs), 1298 (s), 1250 (m), 1025 (m), 744 (vs), 683 (s).

Preparation of 3-(2-bromocyclopent-1-en-1-yl)cyclohexanone (25v):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with the alkenyl zinc reagent **23i** (4.3 mL, 2.40 mmol, 0.56 M in THF) and cooled to -40 °C. CuCN·2LiCl (2.40 mL, 2.40 mmol, 1.0 M in THF) was added, followed by a solution of cyclohexenone (192 mg, 2.00 mmol) and chlorotrimethylsilane (0.8 mL, 5 mmol) in THF (1 mL) and the reaction mixture was stirred for 0.5 h at -40 °C and then 2 h at room temperature. The reaction was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 9:1) to give **25v** as a colorless oil (338 mg, 70 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 3.04–2.91 (m, 1 H), 2.68–2.58 (m, 2 H), 2.47-2.20 (m, 5 H), 2.19–2.05 (m, 1 H), 2.01–1.88 (m, 2 H), 1.85–1.53 (m, 4H).

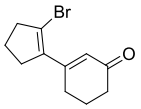
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 210.5, 141.6, 116.0, 45.1, 41.1, 39.8, 39.5, 30.3, 29.0, 25.4, 21.5.

MS (EI, 70 eV), *m/z* (%): 242 (M^+, >1), 163 (35), 91 (16), 70 (16), 61 (16), 43 (100).

HRMS *m/z* : calc. for $C_{11}H_{15}BrO$ 242.0306, found 242.0288.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2935 (m), 1699 (vs), 1652 (w), 1446 (w), 1319 (m), 1261 (m), 1221 (m), 1061 (w), 926 (w), 755 (w).

Preparation of 3-(2-bromocyclopent-1-en-1-yl)cyclohex-3-enone (25w):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with the alkenyl zinc reagent **23i** (4.3 mL, 2.40 mmol, 0.56 M in THF) and cooled to -40 °C. CuCN·2LiCl (2.40 mL, 2.40 mmol, 1.0 M in THF) was added, followed by 3-iodocyclohexenone (444 mg, 2.00 mmol) and the reaction mixture was stirred for 0.5 h at -40 °C and then 2 h at 0 °C. The reaction was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 9:1) to give **25w** as a colorless oil (314 mg, 65 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.10 (s, 1 H). 2.85–2.70 (m, 4 H), 2.65–2.50 (m, 2 H), 2.45–2.35 (m, 2 H), 2.20–1.90 (m, 4 H),

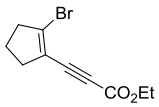
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.1, 155.9, 137.9, 127.2, 123.7, 43.66, 37.4, 34.9, 28.3, 22.9, 21.7.

MS (EI, 70 eV), *m/z* (%): 242 (31), 240 (M^+, 32), 161 (38), 133 (100), 105 (44).

HRMS *m/z* : calc. for $C_{11}H_{13}BrO$ 240.0150, found 240.0146.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2945 (m), 1658 (vs), 1589 (s), 1325 (m), 1254 (s), 1188 (s), 1133 (m), 956 (m), 884 (s), 732 (m).

Preparation of 1-bromo-2-(2-ethoxycarbonylethynyl)cyclopentene (25x):



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with the alkenyl zinc reagent **23i** (3.80 mL, 2.00 mmol, 0.53 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.0 M in THF) was added, followed by a solution of ethyl 3-bromoprop-2-ynoate (425 mg, 2.40 mmol) in THF (2 mL) and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 10:1) to give **25x** as a colorless oil (377 mg, 78 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 4.27 (q, *J* = 7.1 Hz, 2 H), 2.78 (tt, *J* = 7.7 and 2.6Hz, 2 H), 2.61–2.51 (m, 2 H), 2.11–1.97 (m, 2 H), 1.33 (t, *J* = 7.1 Hz, 3H),

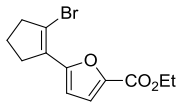
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 153.9, 134.8, 121.9, 85.9, 81.4, 62.1, 40.9, 35.5, 22.6, 14.1.

MS (EI, 70 eV), *m/z* (%): 242 (M^+, 4), 91 (100), 90 (53), 89 (57), 63 (62), 62 (53).

HRMS *m/z* : calc. for $C_{10}H_{11}BrO_2$ 241.9942, found 241.9936.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2981 (w), 2204 (m), 1704 (vs), 1366 (w), 1268 (s), 1207 (s), 1162 (vs), 1092 (s), 1020 (m), 746 (m).

Preparation of ethyl 5-(2-bromocyclopent-1-en-1-yl)furan-2-carboxylate (25y):



The cross-coupling reaction of **23i** (3.40 mL, 2.00 mmol, 0.59 M in THF) with ethyl 5-bromofuran-2-carboxylat (350 mg, 1.60 mmol) was performed according to **GP3** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 9:1) furnished **25y** as a yellow liquid (333 mg, 74 %).

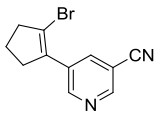
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.20 (d, *J* = 3.6 Hz, 1 H), 7.07 (d, *J* = 3.6 Hz, 1 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 2.87 (t, *J* = 7.6 Hz, 4 H), 2.05 (dt, *J* = 15.2 and 7.6 Hz, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.8, 153.7, 143.0, 129.4, 119.6, 119.2, 110.5, 60.8, 42.3, 33.2, 21.8, 14.3.

MS (EI, 70 eV), *m/z* (%): 284 (M^+, 100), 241 (24), 177 (59), 131 (32), 103 (34), 77 (28).

HRMS *m/z* : calc. for $C_{12}H_3BrO_3$ 284.0048, found 284.0061.

Preparation of 5-(2-bromocyclopent-1-en-1-yl)pyridine-3-carbonitrile (25z):



The cross-coupling reaction of **23i** (3.92 mL, 2.00 mmol, 0.51 M in THF) with 5-bromo-3-cyanopyridine (403 mg, 2.20 mmol) was performed according to **GP3** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 3:1) furnished **25z** as a brown solid (271 mg, 54 %).

m.p.: 74.8–76.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.01 (d, *J* = 2.2 Hz, 1 H), 8.77 (d, *J* = 1.9 Hz, 1 H), 8.25 (t, *J* = 2.1 Hz, 1 H), 2.97-2.86 (m, 2 H), 2.86-2.75 (m, 2 H), 2.18-2.04 (m, 2 H)

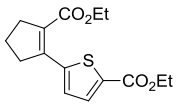
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 151.5, 150.4, 137.5, 133.3, 132.2, 122.2, 116.4, 109.5, 42.5, 35.4, 21.8.

MS (EI, 70 eV), *m/z* (%): 248 (M^+, 34), 169 (100), 168 (23), 142 (12), 115 (12), 63 (11).

HRMS *m/z* : calc. for $C_{11}H_9BrN_2$ 247.9949, found 247.9930.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2943 (w), 2844 (w), 2231 (m), 1620 (w), 1559 (w), 1431 (m), 1423 (m), 1308 (w), 1289 (w), 1186 (w), 1158 (w), 1092 (m), 1026 (m), 932 (m), 904 (s), 787 (m), 701 (vs), 666 (m).

Preparation of ethyl 5-[2-(ethoxycarbonyl)cyclopent-1-en-1-yl]thiophene-2-carboxylate (25aa):



The cross-coupling reaction of **23k** (6.25 mL, 2.00 mmol, 0.32 M in THF) with ethyl 5-bromothiophene-2-carboxylate (376 mg, 1.60 mmol) was performed according to **GP3** in 1.5 h. Flash column chromatography (silica, hexanes:Et_2O 9:1) furnished **25aa** as a colorless solid (373 mg, 79 %).

m.p.: 64.2–65.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.70 (d, *J* = 3.9 Hz, 1 H), 7.46 (d, *J* = 3.9 Hz, 1 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 3.00 (tt, *J* = 7.7 and 2.3 Hz, 2 H), 2.91–2.83 (m, 2 H), 1. 98 (quint, *J* = 7.7 Hz, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H).

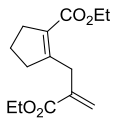
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.9, 162.4, 143.8, 143.0, 134.7, 132.6, 129.9, 129.7, 61.1, 60.5, 39.7, 35.9, 21.5, 14.3, 14.2.

MS (EI, 70 eV), *m/z* (%):294 (M^+, 100), 265 (30), 251 (45), 223 (16), 222 (58), 221 (36), 193 (11), 147 (12).

HRMS *m/z* : calc. for $C_{15}H_{18}O_4S$ 294.0926, found 294.0920.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982 (w), 2961 (w), 1695 (s), 1599 (m), 1519 (m), 1474 (m), 1440 (m), 1366 (m), 1328 (m), 1216 (vs), 1098 (s), 1040 (s), 1022 (s), 824 (s), 752 (vs).

Preparation of ethyl 2-[2-(ethoxycarbonyl)prop-2-en-1-yl]cyclopent-1-ene-1-carboxylate (25ab):



The allylation reaction of **23k** (6.25 mL, 2.00 mmol, 0.32 M in THF) with ethyl (2-bromomethyl)acrylate (309 mg, 1.60 mmol) was performed according to **GP2** in 1.5 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **25ab** as a colorless oil (348 mg, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) =6.23–6.18 (m, 1 H), 5.54–5.49 (m, 1 H), 4.26–4.12 (m, 4 H), 3.66-3.61 (n, 2 H), 2.69–2.60 (m, 2 H), 2.49–2.39 (m, 2 H), 1.81 (quint, *J* = 7.7 Hz, 2 H), 1.33–1.21 (m, 6 H).

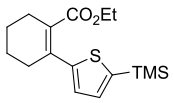
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 167.0, 165.9, 155.1, 137.8, 129.4, 125.5, 60.7, 59.7, 37.9, 33.6, 31.9, 21.5, 14.3, 14.1.

MS (EI, 70 eV), *m/z* (%): 252 (M^+, 2), 206 (100), 149 (56), 134 (35), 133 (75), 105 (68), 79 (31).

HRMS *m/z* : calc. for $C_{14}H_{20}O_4$ 252.1362, found 252.1353.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2980 (w), 1706 (vs), 1631 (m), 1446 (w), 1368 (m), 1255 (s), 1174 (s), 1144 (s), 1107 (vs), 1026 (s), 946 (m), 818 (m), 771 (m).

Preparation of ethyl 5-[2-(ethoxycarbonyl)cyclopent-1-en-1-yl]thiophene-2-carboxylate (25ac):



The cross-coupling reaction of **23k** (4.00 mL, 2.00 mmol, 0.50 M in THF) with 2-bromo-5-trimethylsilylthiophene (470 mg, 2.00 mmol) was performed according to **GP3** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 1:1 then 9:1) furnished **25ac** as a colorless solid (436 mg, 71 %).

m.p.: 106.5–108.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 6.44 (t, *J* = 1.5 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.78 (td, *J* = 6.1 and 1.5 Hz, 2 H), 2.53–2.47 (m, 2 H), 2.17 (quint, *J* = 6.4 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 170.8, 149.3, 139.7, 134.9, 133.6, 129.7, 126.0, 60.5, 32.4, 27.2, 22.4, 21.6, 13.6, -0.1.

MS (EI, 70 eV), *m/z* (%):308 (M^+, 100), 293 (41), 262 (18), 235 (43), 234 (30), 103 (20).

HRMS *m/z* : calc. for $C_{16}H_{24}O_2SSi$ 308.1266, found 308.1246.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2936 (w), 1709 (s), 1277 (m), 1247 (s), 1218 (m), 1046 (m), 990 (m), 836 (vs), 804 (m), 755 (m).

4 Regioselective Magnesium and Zinc Insertions in Polybrominated Phenol Derivatives

4.1 General Prodcedures

General procedure 1 (GP1): Regioselective zinc insertion:

A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (tribromoarenes: 254 mg, 6 mmol, 2 equiv.; dibromoarenes: 382 mg, 9 mmol, 3 equiv.) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, zinc dust (tribromoarenes: 392 mg, 6 mmol, 2 equiv.; dibromoarenes: 589 mg, 9 mmol, 3 equiv.) was added, followed by THF (3 mL). The zinc powder then was activated using 1,2-dibromoethane (5 mol%) and TMSCl (2 mol%). Then, the substrate (3 mmol) was added neat at 25 °C. For tribromoarenes, the reaction mixture was kept at 25 °C using a water bath and stirred for the given time. For dibromoarenes, the mixture was heated to 50 °C and stirred for the given time. After completion, the remaining zinc dust was allowed to settle down and the supernatant solution was carefully transferred to a second dry and argon-flushed *Schlenk*-flask. The resulting clear solution was then used in the reaction with electrophiles.

General procedure 2 (GP2): Acylation of aryl zinc reagents prepared by direct zinc insertion:

The freshly prepared zinc reagent was cooled to -20 °C, CuCN·2LiCl (3 mL, 3 mmol, 1 M in THF) was added and the reaction mixture was stirred for 15 min. After the addition of the acid chloride, the reaction mixture was allowed to warm to 25 °C and stirred for the given time. The reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

General procedure 3 (GP3): Cross-coupling of aryl zinc reagents prepared by direct zinc insertion:

$Pd(dba)_2$ (32 mg, 2 mol%), P(o-furyl)$_3$ (26 mg, 4 mol%) were added to the freshly prepared zinc reagent followed by the aryliodide (2.7 mmol) and the mixture was stirred for the given time at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

General procedure 4 (GP4): Allylation of aryl zinc reagent prepared by direct zinc insertion

The freshly prepared zinc reagent was cooled to 20 °C, the corresponding allylic bromide (3.3 mmol) was added, followed by 3 drops of CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and the reaction mixture was allowed to warm to 25 °C. After stirring for the given time, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

General procedure 5 (GP5): Directed zinc insertion in large scale:

A dry, argon flushed 250 mL *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (tribromoarenes: 2 equiv.; dibromoarenes: 3 equiv.) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, zinc dust (tribromoarenes: 2 equiv.; dibromoarenes: 3 equiv.) was added, followed by THF (1 mL/mmol). The zinc powder then was activated using 1,2-dibromoethane (5 mol%) and TMSCl (2 mol%). Prior to the addition of the substrate, the reaction mixture was cooled with a water bath. Then, the desired polybrominated arene was added neat. For tribromoarenes, the reaction mixture was kept at 25 °C using a water bath and stirred for the given time. For dibromoarenes, the mixture was heated to 50 °C and stirred for the given time. After completion, the remaining zinc dust was allowed to settle down and the supernatant solution was carefully transferred to a second dry and argon-flushed *Schlenk*-flask. The yield of the zinc reagent was determined via titration against iodine.

General procedure 6 (GP6): Cross-coupling of aryl zinc reagents prepared by direct zinc insertion:

A dry, argon flushed 100 mL *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the freshly titrated aryl zinc bromide (1.0 equiv.). The corresponding aryl iodide (0.8 equiv.) is added followed by $Pd(dba)_2$ (1 mol%), $P(o\text{-furyl})_3$ (2 mol%) and the mixture was stirred for the given time at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (50 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with sat. NaCl solution (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography or recrystallization to give the analytically pure product.

General procedure 7 (GP7): Large scale acylation of aryl zinc or magnesium reagents:

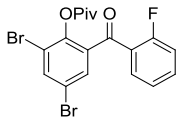
A dry, argon flushed 100 mL *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the freshly titrated organometallic reagent (1.0 equiv.), cooled to -20 °C, CuCN·2LiCl (0.2 equiv., 1 M in THF) was added and the reaction mixture was stirred for 15 min. After the addition of the acid chloride (0.8 equiv.), the reaction mixture was allowed to warm to 25 °C and stirred for the given time. The reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (100 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 3x100 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with sat. NaCl solution (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography or recrystallization to give the analytically pure product.

General Procedure 8 (GP8): Regioselective magnesium insertion in large scale

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (1.25 equiv.) and heated under high vacuum using a heat gun (5 min). After cooling to room temperature, magnesium turnings (2.5 equiv.) were added followed by THF. The magnesium was activated with DIBAL-H (1 mol%). After 5 min of stirring the aryl bromide (1 equiv.) was added neat or as a solution in THF over the specified time at the given temperature. The reaction mixture was stirred for the indicated time and then cannulated to a new *Schlenk*-flask for the reaction with an electrophile. The yield of the organomagnesium reagent was determined via titration against iodine.

4.2.1 Regioselective Zinc Insertion in Polybrominated Arenes

Preparation of 2,4-dibromo-6-(2-fluorobenzoyl)phenyl pivalate (**32a**):



According to **GP1**, the zinc reagent **30a** was prepared from 2,4,6-tribromophenyl pivalate (**29a**, 1.25 g, 3.00 mmol) in 1 h at 25 °C. The acylation reaction with 2-fluoro-benzoyl chloride (**31a**, 444 mg, 2.8 mmol) was performed according to **GP2** in 14 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **32a** as a colorless solid (1.04 g, 81 %).

m.p.: 79.8-81.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.89 (d, *J* = 2.4 Hz, 1 H), 7.67 (dt, *J* = 5.6 Hz and 1.9 Hz, 1 H), 7.60–7.53 (m, 1 H), 7.57 (d, *J* = 2.4 Hz, 1 H), 7.26 (t, *J* = 7.3 Hz, 1 H), 7.16–7.10 (m, 1 H), 1.16 (s, 9 H).

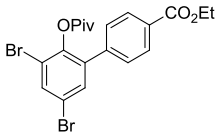
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 188.4, 175.0, 161.3 (d, *J* = 258.0 Hz), 145.7, 145.7, 138.4, 135.9 (d, *J* = 1.0 Hz), 135.1 (d, *J* = 8.7 Hz), 131.9 (d, *J* = 1.6 Hz), 131.5 (d, *J* = 1.6 Hz), 125.5 (d, *J* = 11.1 Hz), 124.5 (d, *J* = 3.6 Hz), 118.9 (d, *J* = 19.1 Hz), 116.8 (d, *J* = 21.7 Hz), 39.3, 26.8.

HRMS *m/z* : calc. for $C_{18}H_{15}Br_2FO_3$ 455.9372, found 455.9352.

MS (EI, 70 eV): *m/z* (%) = 456 (M^+, 2), 374 (100), 278 (36), 157 (10), 123 (34), 95 (18), 41 (10).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2975, 1760, 1666, 1610, 1481, 1452, 1440, 1294, 1241, 1209, 1090, 1028, 968, 886, 830, 760, 639.

Preparation of ethyl 3',5'-dibromo-2'-[(2,2-dimethylpropanoyl) oxy]biphenyl-4-carboxylate (32b):



According to **GP1**, the zinc reagent **30a** was prepared from 2,4,6-tribromophenyl pivalate (**29a**, 1.25 g, 3.00 mmol) in 1 h at 25 °C. The cross-coupling reaction with ethyl 4-iodobenzoate (**31c**, 773 mg, 2.8 mmol) was performed according to **GP3** in 1.5 h at 25 °C. Flash column chromatography (silica, pentane:Et_2O 19:1 to 9:1) furnished **32b** as a colorless oil (825 mg, 78 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.06 (d, *J* = 8.1 Hz, 2 H), 7.76 (d, *J* = 2.2 Hz, 1 H), 7.43 (d, *J* = 2.2 Hz, 1 H), 7.39 (d, *J* = 8.6 Hz, 2 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.12 (s, 9 H).

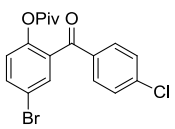
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 175.0, 166.1, 145.1, 140.2, 138.0, 135.1, 132.5, 130.3, 129.4, 129.0, 119.3, 118.5, 61.2, 39.1, 27.0, 14.3.

MS (EI, 70 eV): *m/z* (%) = 482 (M^+, 1), 399 (91), 372 (18), 355 (19), 138 (10), 57 (100).

HRMS *m/z* : calc. for $C_{20}H_{20}Br_2O_4$ 481.9728; found: 481.9723.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2977, 1758, 1716, 1440, 1367, 1269, 1209, 1182, 1085, 1044, 1022, 885, 859, 774, 711.

Preparation of 4-bromo-2-(4-chlorobenzoyl)phenyl pivalate (32c):



According to **GP1**, the zinc reagent **30b** was prepared from 2,4-dibromophenyl pivalate (**29b**, 1.01 g, 3.01 mmol) in 14 h at 50 °C. The acylation reaction with 4-chlorobenzoyl chloride (**31d**, 420 mg, 2.4 mmol) was performed according to **GP2** in 6 h. Flash column chromatography (silica, pentane:Et_2O 29:1) furnished **32c** as a pale yellow oil (708 mg, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.75 (d, *J* = 8.6 Hz, 2 H), 7.67 (dd, *J* = 8.6 and 2.4 Hz, 1 H), 7.61 (d, *J* = 2.1 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 7.07 (d, *J* = 8.6 Hz, 1 H), 1.06 (s, 9 H).

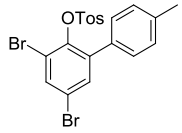
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.8, 175.9, 147.5, 140.1, 135.0, 134.8, 133.3, 132.3, 131.2, 128.9, 124.7, 118.7, 38.9, 26.5.

MS (EI, 70 eV): *m/z* (%) = 394 (M^+, 3), 312 (100), 275 (17), 198 (18), 149 (27), 139 (30), 111 (17), 85 (40), 57 (95).

HRMS *m/z* : calc. for $C_{18}H_{16}BrClO_3$ 393.9971, found 393.9965.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2974, 1754, 1671, 1588, 1471, 1400, 1266, 1201, 1175, 1091, 1077, 1028, 1014, 939, 889, 842, 818, 766.

Preparation of 3,5-dibromo-4'-methylbiphenyl-2-yl 4-methylbenzenesulfonate (32d):



According to **GP1**, the zinc reagent **30c** was prepared from 2,4,6-tribromophenyl 4-methylbenzenesulfonate (**29c**, 1.46 g, 3.00 mmol) in 1 h at 25 °C. The cross-coupling reaction with 4-iodotoluoene (**31e**,610 mg, 2.8 mmol) was performed according to **GP3** in 6 h at 25 °C. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **32d** as a colorless solid (1.016 g, 73 %).

m.p.: 119.5-121.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.72 (d, *J* = 2.5 Hz, 1 H), 7.38 (d, *J* = 2.5 Hz, 1 H), 7.36 (d, *J* = 9.2 Hz, 2 H), 7.07 (d, *J* = 7.8 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 6.94 (d, *J* = 8.2 Hz, 2 H), 2.37 (s, 3 H), 2.30 (s, 3 H).

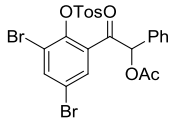
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 144.6, 144.3, 139.4, 138.1, 134.8, 133.8, 133.3, 132.8, 129.2, 128.9, 128.9, 127.9, 120.6, 120.1, 21.6, 21.2.

MS (EI, 70 eV): *m/z* (%) = 494 (M^+, 15), 341 (34), 260 (100), 152 (17), 91 (19).

HRMS *m/z* : calc. for $C_{20}H_{16}Br_2O_3S$ 493.9187, found 493.9185.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1544, 1428, 1368, 1167, 1091, 1043, 864, 822, 752, 717, 669, 631.

Preparation of 2-(3,5-dibromo-2-{[(4-methylphenyl)sulfonyl]oxy}phenyl)-2-oxo-1-phenylethyl acetate (32e):



According to **GP1**, the zinc reagent **30c** was prepared from 2,4,6-tribromophenyl 4-methylbenzenesulfonate (**29c**, 1.46 g, 3.00 mmol) in 1 h at 25 °C. The acylation reaction with *O*-acetylmandelic acid chloride (**31f**, 510 mg, 2.4 mmol) was performed according to **GP2** in 14 h. Flash column chromatography (silica, pentane:Et_2O 7:1 to 4:1) furnished **32e** as a colorless solid (1.03 g, 74 %).

m.p.: 122.4-124.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.84 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 2.5 Hz, 1 H), 7.50 (d, *J* = 2.5 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.28 (s, 5 H), 6.90 (s, 1 H), 2.48 (s, 3 H), 2.14 (s, 3 H).

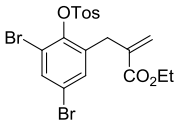
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 193.3, 169.3, 146.5, 142.5, 139.1, 135.5, 133.8, 132.4, 131.9, 130.0, 129.2, 129.1, 128.9, 128.3, 121.0, 119.7, 78.7, 21.9, 20.8.

MS (EI, 70 eV): *m/z* (%) = 580 (M^+, 1), 433 (100), 155 (74), 149 (11), 105 (56), 91 (40), 77 (13), 43 (31).

HRMS *m/z* : calc. for $C_{23}H_{18}Br_2O_6S$ 579.9191, found 579.9172.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1749, 1711, 1595, 1552, 1428, 1383, 1222, 1165, 1086, 1056, 1016, 983, 831, 816, 735, 696, 674.

Preparation of ethyl 2-(3,5-dibromo-2-{[(4-methylphenyl)sulfonyl]oxy}benzyl)acrylate (32f):



According to **GP1**, the zinc reagent **30c** was prepared from 2,4,6-tribromophenyl 4-methylbenzenesulfonate (**29c**, 1.46 g, 3.00 mmol) in 1 h at 25 °C. The allylation reaction with ethyl (2-bromomethyl)acrylate (638 mg, 3.3 mmol) was performed according to **GP4** in 5 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **32f** as a colorless oil (1.17 g, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.88 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 2.4 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 2.4 Hz, 1 H), 6.32 (s, 1 H), 5.60 (s, 1 H), 4.13 (1, *J* = 7.1 Hz, 2 H), 3.74 (s, 2 H), 2.46 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H).

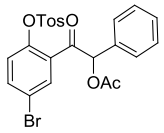
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.0, 145.8, 145.3, 137.7, 137.5, 134.5, 133.8, 132.8, 129.8, 128.5, 128.1, 120.5, 118.5, 60.9, 33.5, 21.8, 14.0.

MS (EI, 70 eV): *m/z* (%) = 516 (M^+, 4), 363 (41), 317 (41), 284 (70), 211 (17), 155 (100), 91 (97).

HRMS *m/z* : calc. for $C_{19}H_{18}Br_2O_5S$ 515.9242, found 515.5138.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2981, 1713, 1632, 1597, 1554, 1436, 1367, 1299, 1177, 1136, 1086, 1024, 952, 843, 813, 744, 704, 668, 646.

Preparation of 2-(5-bromo-2-{[(4-methylphenyl)sulfonyl]oxy}phenyl)-2-oxo-1-phenylethyl acetate (32g):



According to **GP1**, the zinc reagent **30d** was prepared from 2,4-dibromophenyl 4-methylbenzenesulfonate (**29d**, 1.22 g, 3.00 mmol) in 14 h at 50 °C. The acylation reaction with *O*-acetylmandelic acid chloride (**31f**, 510 mg, 2.4 mmol) was performed according to **GP2** in 14 h. Flash column chromatography (silica, pentane:Et_2O 6:1 to 4:1) furnished **32g** as a yellow oil (865 mg, 61 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.73 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 2.6 Hz, 1 H), 7.46 (dd, *J* = 8.7 and 2.5 Hz, 1 H), 7.31–7.28 (m, 7 H), 7.19 (d, *J* = 8.6 Hz, 1 H), 6.73 (s, 1 H), 2.43 (s, 3 H), 2.17 (s, 3 H).

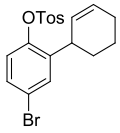
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 192.8, 169.8, 146.2, 145.7, 135.8, 133.2, 132.5, 132.1, 131.2, 130.0, 129.3, 128.9, 128.8, 128.7, 123.8, 120.2, 79.7, 21.7, 20.7.

MS (EI, 70 eV): *m/z* (%) = 502 (M^+, 0.3), 355 (100), 155 (63), 105 (44), 91 (42), 43 (29).

HRMS *m/z* : calc. for $C_{23}H_{19}BrO_6S$ 502.0086, found 502.0096.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3068, 2959, 1742, 1713, 1595, 1469, 1371, 1225, 1198, 1171, 1118, 1089, 1056, 976, 934, 836, 815, 735, 676.

Preparation of 4-bromo-2-cyclohex-2-en-1-ylphenyl 4-methylbenzenesulfonate (32h):



According to **GP1**, the zinc reagent **30d** was prepared from 2,4-dibromophenyl 4-methylbenzenesulfonate (**29d**, 1.22 g, 3.00 mmol) in 14 h at 50 °C. The allylation reaction with 3-bromocyclohexene (**31h**, 531 mg, 3.3 mmol) was performed according to **GP4** in 14 h. Flash column chromatography (silica, pentane:Et_2O 19:1) furnished **32h** as a colorless solid (739 mg, 60 %).

m.p.: 89.4-91.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.74 (d, *J* = 8.3 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 2.6 Hz, 1 H), 7.26 (dd, *J* = 8.1 and 3.1 Hz, 1 H), 6.98 (d, *J* = 8.6 Hz, 1 H), 5.87–5.82 (m, 1 H), 5.22 (dd, *J* = 10.1 and 2.0 Hz, 1 H), 3.49–3.42 (m, 1 H), 2.45 (s, 3 H), 2.08–1.98 (m, 2 H), 1.83–1.74 (m, 1 H), 1.68–1.58 (m, 1 H), 1.56–1.44 (m, 1 H), 1.40–1.27 (m, 1 H).

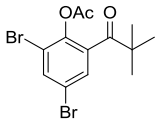
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 146.4, 145.6, 141.7, 132.6, 132.4, 130.0, 129.9, 129.4, 128.3, 128.3, 123.8, 120.5, 34.9, 30.7, 24.7, 21.7, 20.9.

MS (EI, 70 eV): *m/z* (%) = 406 (M^+, 4), 251 (64), 187 (16), 172 (100), 144 (18), 91 (35).

HRMS *m/z* : calc. for $C_{19}H_{19}BrO_3S$ 406.0238, found 406.0235.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2928, 1595, 1476, 1370, 1182, 1151, 1089, 865, 842, 816, 755, 734, 716, 678, 660.

Preparation of 2,4-dibromo-6-(2,2-dimethylpropanoyl)phenyl acetate (32i):



According to **GP1**, the zinc reagent **30e** was prepared from 2,4,6-tribromophenyl acetate (**29e**, 1.19 g, 3.00 mmol) in 1 h at 25 °C. The acylation reaction with pivaloyl chloride (**31b**, 289 mg, 2.4 mmol) was performed according to **GP2** in 14 h. Flash column chromatography (silica, pentane:Et_2O 29:1) furnished **32i** as a yellow solid (714 mg, 79 %).

m.p.: 101.7-105.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.76 (d, *J* = 2.1 Hz, 1 H), 7.31 (d, *J* = 2.2 Hz, 1 H), 2.24 (s, 3 H), 1.22 (s, 9 H).

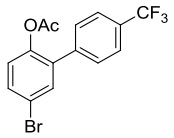
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 207.6, 167.1, 143.7, 136.9, 136.0, 128.2, 119.0, 119.0, 45.1, 26.9, 20.4.

MS (EI, 70 eV): *m/z* (%) = 376 (M^+, 0.5), 336 (11), 323 (15), 319 (15), 279 (100), 57 (23).

HRMS *m/z* : calc. for $C_{13}H_{14}Br_2O_3$ 375.9310, found 375.9301.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2973, 1781, 1695, 1551, 1478, 1434, 1363, 1279, 1180, 1150, 1041, 1012, 985, 899, 861, 768, 727, 682.

Preparation of 5-bromo-4'-(trifluoromethyl)biphenyl-2-yl acetate (32j):



According to **GP1**, the zinc reagent **30f** was prepared from 2,4-dibromophenyl acetate (**29f**, 1.06 g, 3.00 mmol) in 14 h at 50 °C. The cross-coupling reaction with 1-iodo-4-(trifluoromethyl)benzene (**31i**, 653 mg, 2.4 mmol) was performed according to **GP3** in 12 h at 25 °C. Flash column chromatography (silica, pentane:Et_2O 99:1) furnished **32j** as a colorless oil (701 mg, 81 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.71 (d, *J* = 8.8 Hz, 2H), 7.58-7.50 (m, 4H), 7.08 (d, *J* = 9.9 Hz, 1H), 2.11 (s, 3H).

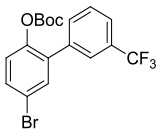
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 168.9, 146.8, 139.9, 135.5, 133.4, 132.2, 130.3 (q, $^5J_{CF}$ = 32.7 Hz), 129.2, 125.4 (q, $^3J_{CF}$ = 3.8 Hz), 124.8, 124.0 (q, $^1J_{CF}$ = 272.1 Hz), 119.6, 20.8.

MS (EI, 70 eV): *m/z* (%) = 358 (M^+, 1), 316 (100), 236 (17), 217 (9), 168 (9), 139 (13), 43 (46).

HRMS *m/z* : calc. for $C_{15}H_{10}BrF_3O_2$ 357.9816, found 357.9811.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1764, 1620, 1475, 1414, 1375, 1325, 1156, 1109, 1082, 1068, 1048, 1025, 1014, 897, 891, 853, 842, 804, 736, 678.

Preparation of 5-bromo-3'-(trifluoromethyl)biphenyl-2-yl tert-butyl carbonate (32k):



According to **GP1**, the zinc reagent **30g** was prepared from *tert*-butyl 2,4-dibromophenyl carbonate (**29g**, 1.06 g, 3.00 mmol) in 14 h at 50 °C. The cross-coupling reaction with 1-iodo-3-(trifluoromethyl)benzene (**31j**, 653 mg, 2.4 mmol) was performed according to **GP6** in 12 h at 25 °C. Flash column chromatography (silica, pentane:Et_2O 19:1) furnished **32k** as a colorless oil (816 mg, inseperable mixture of product and hydrolyzed zinc reagent. Yield determined by 1H-NMR: 60 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.77 (d, *J* = 2.2 Hz, 1 H), 7.67–7.56 (m, 4 H), 7.46 (dd, *J* = 8.6 and 2.2 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 1.32 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm):27.2, 84.0, 117.5, 119.6, 122.2, 123.1, 124.4, 124.8, 125.7, 125.7, 125.8, 129.1, 130.7, 131.1, 131.6, 132.2, 132.3, 132.3, 133.3, 135.5, 135.7, 136.8, 147.2, 147.7, 150.4, 150.9 (observed complexicity due to C-F splitting, definitive assignments have not been made).

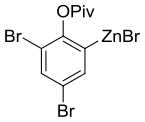
MS (EI, 70 eV): *m/z* (%) = 417 (M^+ +H, <1), 343 (11), 316 (100), 236 (37), 220 (28), 57 (49).

HRMS *m/z* : calc. for $C_{18}H_{17}BrF_3O_3$ 417.0313, found 417.0314.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2984, 1757, 1330, 1278, 1244, 1210, 1165, 1142, 1122, 1096, 1075, 1036, 892, 803, 702.

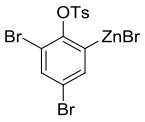
4.2.2 Directed Ortho Insertion in Large Scale

Preparation of 3,5-dibromo-2-(pivaloyloxy)phenylzinc bromide (30a):



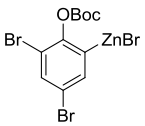
According to **GP5**, the zinc reagent **30a** was prepared from 2,4,6-tribromophenyl pivalate (**29a**, 41.5 g, 100 mmol) using zinc dust (13.1 g, 200 mmol) and LiCl (8.48 g, 200 mmol) in 2 h at 25 °C. Titration against iodine indicates a concentration of 0.56 M (65%).

Preparation of 3,5-dibromo-2-(tosyloxy)phenylzinc bromide (30c):



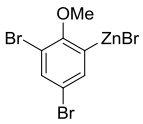
According to **GP5**, the zinc reagent **30c** was prepared from 2,4,6-tribromophenyl 4-methylbenzenesulfonate (**29c**, 24.3 g, 50.0 mmol) using zinc dust (6.54 g, 100 mmol) and LiCl (4.24 g, 100 mmol) in 1 h at 25 °C. Titration against iodine indicates a concentration of 0.52 M (60%).

Preparation of 3,5-dibromo-2-(*tert*-butoxycarbonyloxy)phenylzinc bromide (30h):



According to **GP5**, the zinc reagent **30h** was prepared from *tert*-butyl-2,4,6-tribromophenyl carbonate (**29h**, 21.5 g, 50.0 mmol) using zinc dust (6.54 g, 100 mmol) and LiCl (4.24 g, 100 mmol) in 3 h at 25 °C. Titration against iodine indicates a concentration of 0.68 M (81%).

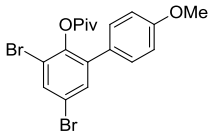
Preparation of 3,5-dibromo-2-methoxyphenylzinc bromide (30i):



According to **GP5**, the zinc reagent **30i** was prepared from 2,4,6-tribromoanisole (**29i**, 26.1 g, 75.0 mmol) using zinc dust (9.81 g, 150 mmol) and LiCl (6.36 g, 150 mmol) in 2 h at 25 °C. Titration against iodine indicates a concentration of 0.71 M (78%).

4.2.3 Reactions of Ortho-Zincated Polybrominated Arenes with Electrophiles

Preparation of 3,5-dibromo-4'-methoxybiphenyl-2-yl 2,2-dimethylpropanoate (32l):



The cross-coupling reaction of the zinc reagent **30a** (17.9 mL, 0.56 M in THF, 10 mmol) with 4-iodoanisole (**31i**, 2.13 g, 9.1 mmol) was performed according to **GP6** in 1 h at 25 °C. Flash column chromatography (silica, pentane:Et_2O 29:1) furnished **32l** as a colorless oil (3.54 g, 88 %).

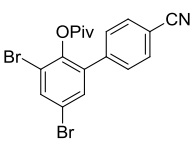
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.72 (d, *J* = 2.4 Hz, 1 H), 7.44 (d, *J* = 2.4 Hz, 1 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 3.84 (s, 3 H), 1.18 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 175.1, 159.6, 145.3, 138.7, 134.1, 132.8, 130.1, 128.1, 119.1, 118.2, 113.6, 55.3, 39.1, 27.0.

MS (EI, 70 eV): *m/z* (%) = 440 (M^+, 8), 358 (100), 356 (51), 58 (38), 57 (68), 44 (54), 43 (80).

HRMS *m/z* : calc. for $C_{18}H_{18}Br_2O_3$ 439.9623, found 439.9617.

Preparation of 3,5-dibromo-4'-cyanobiphenyl-2-yl 2,2-dimethylpropanoate (32m):



The cross-coupling reaction of the zinc reagent **30a** (35.7 mL, 0.56 M in THF, 20 mmol) with 4-iodobenzonitrile (**31i**, 3.69 g, 16.0 mmol) was performed according to **GP6** in 16 h at 25 °C. Flash column chromatography (silica, pentane:CH_2Cl_2 2:1) furnished **32m** as a colorless solid (4.51 g, 64 %).

m.p.: 127.8–129.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.79 (d, *J* = 2.2 Hz, 1 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.41 (d, *J* = 2.2 Hz, 1 H), 1.12 (s, 9 H).

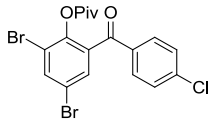
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 175.4, 145.4, 140.8, 137.5, 136.1, 132.6, 132.4, 130.2, 119.9, 119.1, 118.7, 112.7, 39.5, 27.3.

MS (EI, 70 eV): *m/z* (%) = 435 (M^+, 1), 355 (37), 353 (82), 351 (35), 164 (27), 85 (45), 57 (100).

HRMS *m/z* : calc. for $C_{18}H_{15}Br_2NO_2$ 434.9370, found 434.9464.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3066 (vw), 2987 (vw), 2936 (vw), 2225 (vw), 1754 (m), 1606 (vw), 1582 (vw), 1545 (vw), 1506 (vw), 1480 (vw), 1464 (vw), 1440 (w), 1398 (vw), 1384 (w), 1269 (vw), 1229 (vw), 1211 (w), 1189 (w), 1180 (vw), 1107 (w), 1084 (vs), 1044 (m), 1027 (m), 944 (vw), 904 (vw), 884 (w), 856 (m), 834 (w), 799 (w), 751 (w), 741 (w), 731 (w), 700 (w).

Preparation of 2,4-dibromo-6-[(4-chlorophenyl)carbonyl]phenyl 2,2-dimethylpropanoate (32n):



The acylation reaction of the zinc reagent **30a** (26.8 mL, 0.56 M in THF, 15 mmol) with 2-chlorobenzoyl chloride (**31d**, 2.10 g, 12.0 mmol) was performed according to **GP7** in 6 h. Flash column chromatography (silica, pentane:Et2O 99:1) furnished **32n** as a colorless oil (4.32 g, 76 %).

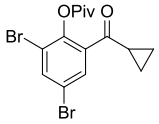
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.92 (d, *J* = 2.2 Hz, 1 H), 7.74 (d, *J* = 8.5 Hz, 2 H), 7.50 (d, *J* = 2.4 Hz, 1 H), 7.46 (d, *J* = 8.5 Hz, 2 H), 1.14 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 190.6, 174.8, 145.3, 140.5, 137.9, 135.0, 134.3, 131.5, 131.4, 129.0, 119.1, 119.0, 39.1, 26.7.

MS (EI, 70 eV): *m/z* (%) = 472 (M^+, >1), 392 (36), 390 (55), 3188 (22), 278 (20), 85 (25), 57 (100).

HRMS *m/z* : calc. for $C_{18}H_{15}Br_2ClO_3$ 471.9076, found 471.9079.

Preparation of 2,4-dibromo-6-(cyclopropylcarbonyl)phenyl 2,2-dimethylpropanoate (32o):



The acylation reaction of the zinc reagent **30a** (35.7 mL, 0.56 M in THF, 20 mmol) with cyclopropanoylacid chloride (1.45 mL, 16.0 mmol) was performed according to **GP7** in 16 h. Flash column chromatography (silica, pentane:Et_2O 19:1) furnished **32o** as a colorless solid (5.33 g, 82 %).

m.p.: 80.5–82.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.84 (d, *J* = 2.2 Hz, 1 H), 7.76 (d, *J* = 2.5 Hz, 1 H), 2.38–2.29 (m, 1 H) 1.37 (s, 9 H), 1.22 (m, 2 H), 1.06 (m, 2 H).

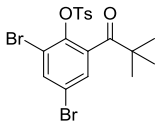
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.4, 175.7, 145.5, 138.3, 136.9, 131.4, 119.6, 119.5, 39.8, 27.6, 20.9, 13.5.

MS (EI, 70 eV): *m/z* (%) = 402 (M^+, 3), 322 (35), 320 (75), 318 (34), 85 (36), 57 (100).

HRMS *m/z* : calc. for $C_{15}H_{16}Br_2O_3$ 401.9466, found 401.9469.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3067 (vw), 3015 (vw), 2974 (w), 2934 (vw), 2908 (vw), 2872 (vw), 1751 (s), 1664 (m), 1577 (vw), 1553 (w), 1479 (w), 1427 (m), 1396 (m), 1363 (m), 1270 (w), 1224 (m), 1213 (m), 1162 (m), 1081 (vs), 1042 (m), 1027 (m), 1006 (m), 871 (s), 773 (w), 761 (w), 751 (w), 699 (w), 664 (m).

Preparation of 2,4-dibromo-6-(2,2-dimethylpropanoyl)phenyl 4-methylbenzenesulfonate (32p):



The acylation reaction of the zinc reagent **30c** (28.8 mL, 0.52 M in THF, 15 mmol) with cyclopropanoylacid chloride (1.45 g, 12.0 mmol) was performed according to **GP7** in 8 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **32p** as a colorless oil (4.79 g, 82 %).

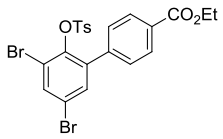
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.83 (d, *J* = 8.5 Hz, 2 H), 7.77 (d, *J* = 2.4 Hz, 1 H), 7.36 (d, *J* = 8.5 HZ, 2 H), 7.30 (d, *J* = 2.4 Hz, 1 H), 2.47 (s, 3 H), 1.17 (s, 9 H) .

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 207.2, 145.9, 142.0, 138.3, 136.9, 132.8, 129.7, 129.5, 128.8, 120.3, 119.8, 45.2, 27.1, 21.8.

MS (EI, 70 eV): *m/z* (%) = 488 (M^+, 1), 435 (39), 433 (83), 156 (100), 91 (89), 57 (37).

HRMS *m/z* : calc. for $C_{18}H_{18}Br_2O_4S$ 487.9293, found 487.9287.

Preparation of ethyl 3',5'-dibromo-2'-{[(4-methylphenyl)sulfonyl]oxy}biphenyl-4-carboxylate (32q):



The cross-coupling reaction of the zinc reagent **30c** (45.6 mL, 0.44 M in THF, 20 mmol) with ethyl 4-iodobenzoate (**31c**, 4.41 g, 16.0 mmol) was performed according to **GP6** in 16 h at 25 °C. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **32q** as a colorless solid (6.30 g, 71 %).

m.p.: 136.6–138.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.84–7.76 (m, 3 H), 7.39 (d, *J* = 2.5 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.28–7.22 (m, 2 H), 6.99 (d, *J* = 8.7 Hz, 2 H), 6.99 (d, *J* = 0.7 Hz, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.32 (s, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H).

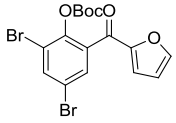
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.3, 145.5, 144.6, 140.4, 138.6, 136.2, 133.9, 133.5, 130.3, 129.8, 129.7, 129.4, 128.1, 121.1, 120.8, 61.5, 21.8, 14.7.

MS (EI, 70 eV): *m/z* (%) = 554 (M^+, 10), 356 (46), 354 (100), 352 (46), 248 (42), 246 (44), 155 (66), 91 (67).

HRMS *m/z* : calc. for $C_{24}H_{22}Br_2O_2S$ 553.9221, found 553.9166.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060 (vw), 2986 (vw), 1709 (m), 1610 (vw), 1594 (vw), 1577 (vw), 1545 (vw), 1494 (vw), 1476 (vw), 1439 (vw), 1380 (m), 1318 (vw), 1289 (w), 1277 (m), 1204 (vw), 1191 (w), 1182 (w), 1168 (m), 1130 (w), 1110 (m), 1090 (w), 1042 (w), 1019 (w), 912 (vw), 856 (m), 816 (w), 788 (w), 780(w), 759 (m), 742 (vs), 700 (w), 677 (m), 663 (m).

Preparation of *tert*-butyl 2,4-dibromo-6-(furan-2-ylcarbonyl)phenyl carbonate (32r):



The acylation reaction of the zinc reagent **30h** (29.4 mL, 0.68 M in THF, 20 mmol) with furan-2-carboxylicacid chloride (1.58 g, 16.0 mmol) was performed according to **GP7** in 16 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **32r** as a brown oil (4.03 g, 56 %).

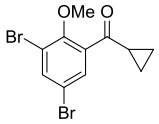
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.88 (d, *J* = 2.3 Hz, 1 H), 7.69–7.67 (m, 1 H), 7.65 (d, *J* = 2.3 Hz, 1 H), 7.13 (d, *J* = 3.6 Hz, 1 H), 6.56 (dd, *J* = 3.6 und 1.7 Hz, 2 H), 1.46 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 178.0, 151.4, 149.7, 148.5, 145.8, 138.2, 134.1, 131.6, 122.1, 119.5, 119.3, 112.8, 85.0, 27.6.

MS (EI, 70 eV): *m/z* (%) = 373 (21), 348 (31), 346 (M^+-Boc, 64), 344 (32), 280 (46), 278 (100), 276 (47), 95 (29), 57 (97), 41 (13).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982 (vw), 1763 (m), 1656 (m), 1561 (w), 1461 (m), 1442 (w), 1395 (w), 1370 (w), 1275 (m), 1258 (m), 1225 (s), 1129 (vs), 1080 (w), 1026 (m), 974 (w), 925 (vw), 883 (m), 828 (w), 765 (m), 732 (m), 694 (m), 669 (m).

Preparation of cyclopropyl(3,5-dibromo-2-methoxyphenyl)methanone (32s):



The acylation reaction of the zinc reagent **30i** (17.0 mL, 0.71 M in THF, 12 mmol) with cyclopropanoylacid chloride (1.01 g, 9.60 mmol) was performed according to **GP7** in 16 h. Flash column chromatography (silica, pentane:Et_2O 99:1 then 9:1) furnished **32s** as a yellow liquid (1.90 g, 59 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.80 (d, *J* = 2.9 Hz, 1 H), 7.59 (d, *J* = 2.9 Hz, 1 H), 3.84 (s, 3 H), 2.72–2.60 (m, 1 H), 1.24–1.31 (m, 2 H), 1.12–1.03 (m, 2 H).

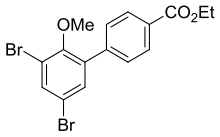
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 201.3, 155.0, 138.4, 136.6, 131.6, 119.2, 117.3, 62.8, 21.2, 13.0.

MS (EI, 70 eV): *m/z* (%) = 332 (M^+, 23), 308 (40), 306 (81), 305 (39), 304 (41), 295 (53), 293 (100).

HRMS *m/z* : calc. for $C_{11}H_{10}Br_2O_2$ 331.9048, found 331.9037.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3067 (vw), 3007 (vw), 2939 (vw), 1669 (s), 1572 (w), 1548 (w), 1458 (s), 1410 (vs), 1398 (s), 1368 (s), 1241 (s), 1222 (s), 1156 (s), 1092 (w), 1062 (w), 1041 (m), 992 (vs), 868 (s), 818 (w), 804 (w), 763 (m), 680 (m).

Preparation of ethyl 3',5'-dibromo-2'-methoxybiphenyl-4-carboxylate (32t):



The cross-coupling reaction of the zinc reagent **30i** (28.1 mL, 0.71 M in THF, 20 mmol) with ethyl 4-iodobenzoate (**31c**, 4.41 g, 16.0 mmol) was performed according to **GP6** in 16 h at 25 °C. Flash column chromatography (silica, pentane:Et_2O 99:1) furnished **32t** as a colorless solid (4.40 g, 66 %).

m.p.: 78.9-80.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10 (d, *J* = 8.6 Hz, 2 H), 7.70 (d, *J* = 2.3 Hz, 1 H), 7.60 (d, *J* = 8.6 Hz, 2 H), 7.43 (d, *J* = 2.3 Hz, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H).

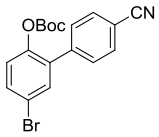
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.6, 154.1, 141.1, 137.4, 135.5, 133.1, 130.4, 130.0, 129.2, 119.5, 117.6, 61.5, 61.0, 14.7.

MS (EI, 70 eV): *m/z* (%) = 414 (100), 412 (M^+, 53), 371 (32), 369 (70), 248 (36), 246 (36).

HRMS *m/z* : calc. for $C_{18}H_{18}Br_2O_3$ 411.9310, found 411.9302.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2981 (vw), 2956 (vw), 2907 (vw), 1720 (s), 1609 (w), 1460 (w), 1385 (w), 1366 (w), 1274 (vs), 1181 (w), 1121 (m), 1103 (m), 988 (s), 852 (m), 772 (m), 708 (vs).

Preparation of 5-bromo-4'-cyanobiphenyl-2-yl *tert*-butyl carbonate (32u):



The cross-coupling reaction of the zinc reagent **30g** (29.0 mL, 0.69 M in THF, 20 mmol) with ethyl 4-iodobenzonitrile (**31i**, 3.66 g, 16.0 mmol) was performed according to **GP6** in 16 h at 25 °C. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **32u** as a colorless solid (4.90 g, 82 %).

m.p.: 116.2-117.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.71 (d, *J* = 8.6 Hz, 2 H), 7.58–7.49 (m, 4 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 1.31 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 151.0, 147.3, 141.1, 135.4, 133.4, 132.9, 132.5, 129.9, 124.8, 119.9, 118.8, 112.1, 84.4, 27.6.

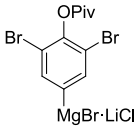
MS (EI, 70 eV): *m/z* (%) = 375 (M^+, < 1), 275 (46), 273 (47), 193 (17), 164 (11), 57 (100).

HRMS *m/z* : calc. for $C_{18}H_{16}BrNO_3$ 373.0392 (M^++H), found 374.0396 (M^++H).

IR (ATR):): $\tilde{\nu}$ (cm^{-1}) = 3098 (vw), 3068 (vw), 2999 (vw), 2985 (vw), 2974 (vw), 2932 (vw), 2230 (vw), 1751 (m), 1708 (vw), 1659 (vw), 1548 (vw), 1506 (vw), 1469 (w), 1453 (vw), 1411 (vw), 1388 (vw), 1371 (w), 1307 (vw), 1281 (m), 1260 (w), 1240 (m), 1212 (w), 1143 (vs), 1114 (m), 1078 (w), 1047 (vw), 1027 (w), 1012 (w), 982 (w), 894 (m), 884 (w), 853 (w), 845 (w), 795 (w), 779 (m), 756 (w), 734 (vw), 692 (w).

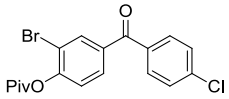
4.2.4 Regioselective Magnesium Insertion in Polybrominated Arenes

Preparation of 2,5-dibromo-4-(pivaloyloxy)phenylmagnesium bromide (34a):



According to **GP8**, 2,4,6-tribromophenyl pivalate (**29a**, 41.5 g, 100 mmol) was added as a solution in THF (50 mL) over 4 h to a suspension of Mg turnings (6.08 g, 250 mmol) and LiCl (5.30 g, 125 mmol) in THF (210 mL) so that the temperature remains below -20 °C. After the addition the reaction mixture was stirred for additional 30 min at -20 °C, unreacted magnesium turnings were allowed to settle down and the supernatant solution was transferred to a second *Schlenk*-flask at -20 °C. Titration against iodine indicates a concentration of 0.27 M (98%).

Preparation of 2-bromo-4-[(4-chlorophenyl)carbonyl]phenyl 2,2-dimethylpropanoate (33b):



According to **GP8** 2,4-dibromophenyl pivalate (8.40 g, 25 mmol) was added as a solution in THF (12.5 mL) over 1 h to a suspension of LiCl (1.32 g, 31.3 mmol) and Mg turnings (1.52 mg, 62.5 mmol) in THF (50 mL) so that the temperature of the reaction mixture remains below -20 °C. After the addition, the reaction mixture was stirred for additional 30 min at -20 °C and then cannulated to a new *Schlenk*-flask. The acylation reaction with 4-chlorobenzoyl chloride (**31d**, 3.50 g, 20.0 mmol) was performed according to **GP7** in 2 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **33b** as a colorless oil (5.1 g, 64 %).

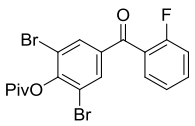
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.02 (d, *J* = 2.1 Hz, 1 H), 7.76-7.69 (m, 3 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 1 H), 1.41 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 193.0, 175.6, 151.9, 139.3, 136.0, 135.1, 134.9, 131.3, 130.1, 128.8, 123.7, 116.6, 39.4, 27.1.

MS (EI, 70 eV): *m/z* (%) = 394 (M^+, <1), 310 (14), 201 (14), 139 (24), 85 (39), 57 (100), 41 (10).

HRMS *m/z* : calc. for $C_{18}H_{16}BrClO_3$ 393.9971, found 393.9947.

Preparation of 2,6-dibromo-4-[(2-fluorophenyl)carbonyl]phenyl 2,2-dimethylpropanoate (33d):



The acylation reaction of the organomagnesium reagent **34a** (27.8 mL, 0.28 M in THF, 10 mmol) with 2-fluorobenzoyl chloride (**31a**, 1.11 g, 7.0 mmol) was performed according to **GP7** in 2 h. Flash column chromatography (silica, pentane:Et_2O 98:2 then 95:5) furnished **33d** as a colorless oil (4.17 g, 60 %).

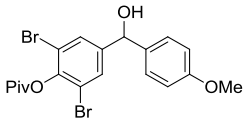
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.00 (s, 2 H), 7.64-7.52 (m, 2 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.20 (t, *J* = 9.1 Hz, 2 H), 1.46 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 189.8, 174.0, 160.0 (d, *J* = 253 Hz), 150.3, 136.9 (d, *J* = 1 Hz), 140.0 (d, *J* = 9 Hz), 133.5 (d, *J* = 2 Hz), 130.7 (d, *J* = 3 Hz), 125.5 (d, *J* = 14 Hz), 124.6 (d, *J* = 4 Hz), 118.3, 116.7 (d, *J* = 21 Hz), 39.6, 27.1.

MS (EI, 70 eV): *m/z* (%) = 457 (M^+, 1), 376 (30), 374 (65), 372 (29), 279 (19), 123 (31), 85 (37), 57 (100).

HRMS *m/z* : calc. for $C_{18}H_{16}Br_2FO_3$ 456.9450 (M^++H), found 456.9437.

Preparation of 2,6-dibromo-4-[hydroxy(4-methoxyphenyl)methyl]phenyl 2,2-dimethylpropanoate (33e):



A dry, argon-flushed *Schlenk*-flask was charged with the organomagnesium reagent **34a** (27.8 mL, 0.28 M in THF, 10 mmol) at -20 °C and anisaldehyde (0.95 g, 7.0 mmol) was added. The reaction was stirred at -20 °C for 1 h and then quenched with a sat. NH_4Cl solution (20 mL). After extraction with EtOAc (3x50 mL), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (silica, pentane:Et_2O 3:1) furnished **33e** as a colorless oil (1.77 g, 54 %).

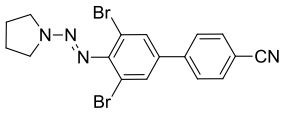
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.57 (s, 1 h), 7.52 (s, 1 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 5.67 (s, 1 H), 3.80 (s, 3 H), 2.57 (br s, 1 H), 1.44 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 174.7, 159.4, 145.0, 144.3, 134.7, 130.2, 128.1, 117.5, 114.1, 74.1, 55.3, 39.4, 27.2.

MS (EI, 70 eV): *m/z* (%) = 470 (M^++H, 8), 389 (22), 388 (49), 135 (74), 109 (95), 57 (100).

HRMS *m/z* : calc. for $C_{19}H_{21}Br_2O_4$ 469.9728 (M^++H), found 469.9722

Preparation of 3',5'-dibromo-4'-(pyrrolidin-1-ylazo)-biphenyl-4-carbonitrile (33f):



According to **GP8** pyrrolidin-1-yl-(2,4,6-tribromo-phenyl)-diazene (**29f**, 10.3 g, 25 mmol) was added as a solution in THF (22.5 mL) over 1 h to a suspension of LiCl (1.32 g, 31.3 mmol) and Mg turnings (1.52 g, 62.5 mmol) in THF (40 mL) so that the temperature of the reaction mixture remains below -20 °C. After the addition, the reaction mixture was stirred for additional 30 min at -20 °C and then cannulated to a new *Schlenk*-flask containing $ZnCl_2$ (27.5 mL, 27.5 mmol, 1 M in THF) at -20 °C. After stirring for 15 min at this temperature, 4-iodobenzonitrile (**31i**, 4.6 g, 20.0 mmol) followed by $Pd(dba)_2$ (143 mg, 0.25 mmol) and tris(*o*-furyl)phosphine (116 mg, 0.5 mmol) were added and the reaction was allowed to warm to 25 °C. The reaction was quenched after 12 h with a sat. NH_4Cl solution (20 mL). After extraction with EtOAc (3x 50 mL), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. After flash column chromatography (silica, pentane:Et_2O 4:1) and recrystallization (heptane/CH_2Cl_2) **33f** was obtained as light yellow solid (6.17 g, 71 %).

m.p.: 144-146°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.73 (s, 2 H), 7.69 (d, *J* = 8.6 Hz. 2 H), 7.59 (d, *J* = 8.8 Hz, 2 H), 3.96 (br s, 2 H), 3.73 (br s, 2 H), 2.08 (br s, 4 H).

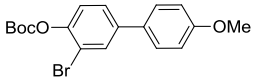
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.1, 142.5, 137.3, 132.6, 130.9, 127.4, 118.6, 118.4, 111.4, 51.2, 46.6, 24.0, 23.5.

MS (EI, 70 eV): *m/z* (%) = 432 (M^+, 7), 364 (61), 337 (97), 257 (100), 177 (67), 149 (14), 89 (11).

HRMS *m/z* : calc. for $C_{17}H_{14}Br_2N_4$ 431.9585, found 431.9574.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2227, 1608, 1519, 1402, 1340, 1308, 1274, 1104, 885, 828, 744, 723.

Preparation of 3-bromo-4'-methoxybiphenyl-4-yl *tert*-butyl carbonate (33h):



According to **GP8** *tert*-butyl 2,4-dibromophenyl carbonate (**29g**, 3.52 g, 10 mmol) was added as a solution in THF (10.0 mL) over 1 h to a suspension of LiCl (530 mg, 12.5 mmol) and Mg turnings (607 mg, 25.0 mmol) in THF (10 mL) so that the temperature of the reaction mixture remains below -20 °C. After the addition, the reaction mixture was stirred for additional 30 min at -20 °C and then cannulated to a new *Schlenk*-flask containing $ZnCl_2$ (11.0 mL, 11.0 mmol, 1 M in THF) at -20 °C. After stirring for 15 min at this temperature, 4-iodoanisole (**31j**, 1.64 g, 7.0 mmol) followed by $Pd(dba)_2$ (114 mg, 0.2 mmol) and tris(*o*-furyl)phosphine (93 mg, 0.4 mmol) were added and the reaction was allowed to warm to 25 °C. The reaction was quenched after 2 h with a sat. NH_4Cl solution (20 mL). After extraction with EtOAc (3x 50 mL), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. After flash column chromatography (silica, pentane:Et_2O 9:1) **33h** was obtained as light yellow oil (2.24 g, 84 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.76 (d, *J* = 2.2 Hz, 1 H), 7.46 (dd, *J* = 8.4 and 2.2 Hz. 1 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 3.84 (s, 3 H), 1.58 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.5, 151.0, 147.1, 140.5, 131.5, 131.4, 128.2, 126.7, 123.5, 116.6, 114.3, 84.2, 55.3, 27.6.

MS (EI, 70 eV): *m/z* (%) = 378 (M^+, 1), 280 (99), 278 (100), 265 (20), 263 (25), 57 (30).

HRMS *m/z* : calc. for $C_{18}H_{19}BrO_4$ 378.0467, found 378.0457.

5 Preparation of Primary Amides From Organozinc Halides

5.1 General Procedures

General procedure 1 (GP1): Typical Procedure for the direct insertion of zinc.

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 (5 mol%) and trimethylsilyl chloride (1 mol%) was added and the reaction mixture was heated until ebullition occurs. After cooling to 25 °C, the substrate (1.0 equiv) was added at the required temperature (usually 25 °C). When capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of >98%, the reaction mixture was allowed to settle down for some hours. The yield of the resulting organozinc reagent was determined by iodiometric titration.[159]

General procedure 2 (GP2): Typical Procedure for the magnesium insertion in the presence of $ZnCl_2$.

A *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.25-1.5 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). Mg turrnings (2.5 equiv) were added followed by $ZnCl_2$ (1.1 equiv., 1 M in THF) and the magnesium turnings were activated with *i*Bu_2AlH (1 mol%).[160] After 5 min stirring at 25 °C the aryl halide (1.0 equiv) was added at the required temperature (usually 25 °C). When capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of > 98%, the Mg turnings were allowed to settle down and the supernatant solution was transferred to a second Schlenk-tube. The yield of the resulting arylzinc reagent was determined by iodometric titration.[159]

General procedure 3 (GP3): Typical Procedure for the preparation of organozinc reagents via halogen-magnesium-exchange and subsequent transmetallation.

A *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the desired aryl halide (1.0 equiv) and THF (1 M). Then *i*PrMgCl·LiCl (1.1 equiv.) was added at the given temperature. When capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of >98%, $ZnCl_2$-solution (1.15 equiv., 1 M in THF) was added. After 5 min of stirring at the required temperature, the organozinc reagent was used for the reaction with the trichloroacetyl isocyanate.

[159] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.
[160] Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 906.

General procedure 4 (GP4): Typical Procedure for the reaction of organozinc reagents with trichloroacetyl isocyanate.

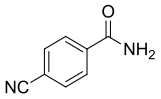
A dry, Ar-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a rubber septum was charged with the organozinc reagent as a solution in THF. After cooling to -20 °C, trichloroacetyl isocyanate (1.1 equiv.) was added at once and the reaction mixture was stirred for 5 min at -20 °C. Then, the cooling bath was removed and the reaction was allowed to warm to 25 °C. After 2 h, K_2CO_3 (1.5 equiv.) and MeOH (2 mL) were added and the reaction mixture was stirred for 12 h. Then, a sat. aqueous NH_4Cl-solution was added and the aqueous layer was extracted with EtOAc (3x100 mL) and $CHCl_3$ (3x100 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. Purification by flash-chromatography afforded the analytically pure product.

General procedure 5 (GP5): Typcial Procedure for the Ni-catalyzed reaction of organozinc reagents with substituted isocyanates.

A dry, Ar-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a rubber septum was charged with the corresponding isocyanate and THF (1 mL/3 mmol). Then, $Ni(acac)_2$ (2 mol%) was added, followed by the desired organozinc reagent (1.1 equiv.). The reaction mixture was stirred at the given temperature until the GC-analysis of a hydrolyzed reaction aliquot showed complete consumption of the isocyanate. Then, a sat. aqueous NH_4Cl-solution was added and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. Purification by flash-chromatography afforded the analytically pure product.

5.2 Preparation of Primary Amides

Preparation of 4-cyanobenzamide (40a):



According to **GP4**, trichloroacetyl isocyanate (622 mg, 3.3 mmol) was added to 4-cyanophenylzinc iodide[161] (**39a**) (4.4 mL, 3.0 mmol, 0.68 M in THF) at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, pentane:EtOAc 1:1) afforded the amide **40a** (416 mg, 95 %) as a colourless solid.

m.p.: 222.1–223.3 °C.

[161] Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; P. Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 8.19 (br s, 1 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 7.93 (d, *J* = 8.6 Hz, 2 H), 7.65 (br s, 1 H).

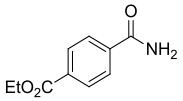
^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 166.4, 138.3, 132.3, 128.2, 118.3, 113.6.

MS (EI, 70 eV): *m/z* (%) = 146 (M^+, 50), 130 (100), 128 (8), 102 (50), 75 (10).

HRMS *m/z* : calc. for $C_8H_6N_2O$ 146.0480, found 146.0475(M^+).

Data are consistent with literature values.[162]

Preparation of ethyl 4-(aminocarbonyl)benzoate (40b):



According to **GP4**, trichloroacetyl isocyanate (622 mg, 3.3 mmol) was added to 4-ethoxycarbonylphenylzinc iodide[161] (**39b**) (4.1 mL, 3.0 mmol, 0.73 M in THF) at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and EtOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, pentane:EtOAc 1:1) afforded the amide **40b** (521 mg, 90 %) as a colourless solid.

m.p.: 170.0–174.2 °C.

^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 8.12 (br s, 1 H), 8.01–7.96 (m, 4 H), 7.54 (br s, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.0 Hz, 3 H).

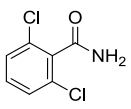
^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 167.0, 165.2, 138.3, 132.0, 129.0, 127.8, 61.0, 14.1.

MS (EI, 70 eV): *m/z* (%) = 193 (M^+, 26), 177 (41), 165 (45), 148 (100), 103 (22).

HRMS *m/z* : calc. for $C_{10}H_{11}NO_3$ 193.0739, found 193.0735.[163]

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3404 (m), 3156 (m), 2994 (w), 2975 (w), 2930 (w), 1697 (s), 1649 (s), 1547 (m), 1444 (m), 1414 (m), 1390 (m), 1370 (m), 1286 (vs), 1182 (m), 1109 (s), 1014 (s), 869 (m), 812 (w), 775 (m), 719 (s).

Preparation of 2,6-dichlorobenzamide (40c):



[162] Crisóstomo, C.; Crestani, M. G.; García, J. J. *J. Mol. Cat. A: Chem.* **2007**, *266*, 139.
[163] Yamazaki, K; Kondo, Y. *J. Comb. Chem.* **2004**, *6*, 121.

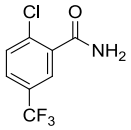
According to **GP3**, *i*PrMgCl·LiCl (2.61 mL, 3.3 mmol, 1.26 M in THF) was added to a solution of 1-bromo-2,3-dichlorobenzene (678 mg, 3 mmol) in THF (3 mL) at 25 °C. After stirring for 1 h at 25 °C, $ZnCl_2$-solution (3.3 mL, 3.3 mmol, 1 M in THF) was added. After 5 min at 25 °C, the reaction mixture was cooled to -20 °C. According to **TP4** trichloroacetyl isocyanate (622 mg, 3.3 mmol) was added at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and EtOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, pentane:EtOAc 9:1) afforded the amide **40c** (340 mg, 60 %) as a colourless solid.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 8.07 (br. s, 1 H), 7.79 (br. s,1 H), 7.49-7.38 (m, 3 H).

^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 165.3, 137.0, 130.7, 130.6, 128.0.

Data are consistent with literature values.[164]

Preparation of 2-chloro-5-(trifluoromethyl)benzamide (40d):



According to **GP4**, trichloroacetyl isocyanate (311 mg, 1.7 mmol) was added to 2-chloro-4-(trifluoromethyl)phenylzinc chloride[165] (**39d**) (3.1 mL, 1.5 mmol, 0.48 M in THF) at -20 °C. After quenching with K_2CO_3 (311 mg, 2.3 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, pentane:EtOAc 1:1 then EtOAC) afforded the amide **40d** (328 mg, 98 %) as a colourless solid.

m.p.: 142.9–144.4 °C.

^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 8.07 (br s, 1 H), 7.84–7.77 (m, 3 H), 7.73 (d, *J* = 9.2 Hz, 1 H).

^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 166.8, 138.0, 134.2 (q, *J* = 1.5 Hz), 130.9, 127.7 (q, *J* = 32.6 Hz), 127.2 (q, *J* = 3.8 Hz), 125.4 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 272.6 Hz).

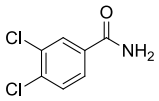
MS (EI, 70 eV): *m/z* (%) = 223 (M^+, 39), 209 (30), 207 (100), 181 (11), 179 (32).

HRMS *m/z* : calc. for $C_8H_5ClF_3NO$ 223.0012, found 223.0007.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3371 (w), 3186 (w), 1651 (vs), 1430 (w), 1387 (m), 1320 (s), 1266 (w), 1169 (m), 1121 (vs), 1080 (s), 1049 (m), 904 (w), 832 (m), 805 (w), 746 (w), 722 (w), 663 (w).

[164] G. van Baelen, U. W. Maes, *Tetrahedron* **2008**, *64*, 5604-5619.
[165] Prepared from via LiCl mediated direct Mg insertion in 2-bromo-1-chloro-4-(trifluoromethyl)benzene and subsequent transmetalation with $ZnCl_2$ (1 equiv.); see: S. Yamada, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 2215.

Preparation of 3,4-dichlorobenzamide (40e):



According to **GP3**, *i*PrMgCl·LiCl (2.54 mL, 3.3 mmol, 1.3 M in THF) was added to a solution of 1-bromo-3,4-dichlorobenzene (678 mg, 3 mmol) in THF (3 mL) at 25 °C. After stirring for 1 h at 25 °C, $ZnCl_2$-solution (3.3 mL, 3.3 mmol, 1 M in THF) was added. After 5 min at 25 °C, the reaction mixture was cooled to -20 °C. According to **TP4** trichloroacetyl isocyanate (622 mg, 3.3 mmol) was added at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and EtOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 1:1) afforded the amide **40e** (404 mg, 71 %) as a colourless solid.

m.p.: 145.4-147.3 °C.

^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 8.14 (br s, 1 H), 8.08 (d, *J* = 1.9 Hz, 1 H), 7.83 (dd, *J* = 8.4 and 1.9 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 1 H), 7.61 (br s, 1 H).

^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 165.5, 134.6, 134.1, 131.2, 130.6, 129.5, 127.7.

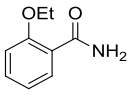
MS (EI, 70 eV): *m/z* (%) =189 (M^+, 61), 175 (64), 173 (100), 145 (30), 109 (14), 74 (13).

HRMS *m/z* : calc. for $C_7H_5Cl_2NO$ 188.9748, found 188.9739(M^+).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 634 (m), 695 (m), 748 (s), 788 (s), 826 (m), 859 (m), 895 (s), 1032 (s), 1118 (s), 1242 (m), 1277 (m), 1367 (s), 1408 (s), 1557 (m), 1587 (m), 1619 (vs), 1654 (s), 3162 (m), 3350 (s).

Data are consistent with literature values.[166]

Preparation of 2-ethoxybenzamide (40f):



A *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (318 mg, 7.5 mmol). The flask was heated with a heat gun (650 °C) for 10 min under high vacuum. After cooling to 25 °C, the flask was flushed with argon (3 times). Mg turrnings (2.5 equiv) were added followed by THF and the magnesium turnings were activated with *i*Bu_2AlH (1 mol%). After 5 min stirring at 25 °C, 1-bromo-2-ethoxybenzene (1.01 g, 5 mmol) was added at 0°C. After 1 h at 0 °C, capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of >98%, the Mg turnings were allowed to settle down.

[166] K. L. Reed, J. T. Gupton, T. L. Solarz, *Synth. Commun.* **1990**, *20*, 563-571.

The yield of the resulting aryl magnesium reagent was determined by iodiometric titration (0.79 M, 79 %). To the corresponding organomagnesium reagent (3.8 mL, 3 mmol, 0.79 M in THF) was added $ZnCl_2$-solution (3.15 mL, 3.15 mmol, 1 M in THF) and the reaction mixture was cooled to -20 °C. According to **TP4**, trichloroacetyl isocyanate (622 mg, 3.3 mmol) was added at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 9:1) afforded the amide **40f** (488 mg, 98 %) as a colourless solid.

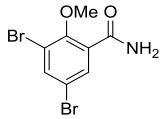
m.p.: 132.4–133.9 °C.[167]

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 7.83 (dd, *J* = 7.6 and 1.8 Hz, 1 H), 7.59 (br s, 1 H), 7.54 (br s, 1 H), 7.47–7.40 (m, 1 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 7.00 (td, *J* = 7.5 Hz and 1.0 Hz, 1 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 1.37 (t, *J* = 6.9 Hz, 3 H) .

^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 166.3, 156.5, 132.4, 130.8, 122.6, 120.4, 112.9, 64.2, 14.5.

Data are consistent with literature values.[168]

Preparation of 3,5-dibromo-2-methoxybenzamide (40g):



According to **GP4**, trichloroacetyl isocyanate (622 mg, 3.3 mmol) was added to 3,5-dibromo-2-methoxyphenylzinc bromide (**39g**) (4.2 mL, 3.0 mmol, 0.71 M in THF) at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 3:1) afforded the amide **40g** (721 mg, 78 %) as a colourless solid.

m.p.: 173.8–175.7 °C.[169]

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 7.97 (d, *J* = 2.5 Hz, 1 H), 7.90 (br s, 1 H), 7.73 (br s, 1 H), 7.64 (d, *J* = 2.5 Hz, 1 H), 3.80 (s, 3 H).

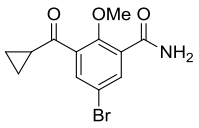
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 165.6, 153.4, 136.4, 133.7, 131.3, 118.5, 116.3, 61.8.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3439 (m), 3151 (m), 1667 (vs), 1596 (m), 1573 (s), 1545 (m), 1451 (s), 1405 (vs), 1355 (s), 1237 (s), 1119 (m), 1088 (m), 973 (vs), 872 (s), 807 (m), 775 (m), 682 (m).

Data are consistent with literature values.[169]

[167] S. L. Shapiro, *J. Am. Chem. Soc.* **1959**, *81*, 3728.
[168] D. G. de Kowalewski, V. J. Kowalewski, E. Botek, R. H. Contreras, J. C. Facelli, *Magn. Reson. Chem.* **1997**, *35*, 351.
[169] T. Nozoe, *Proc. Jpn. Acad.* **1952**, *28*, 192.

Preparation of 5-bromo-3-(cyclopropanecarbonyl)-2-methoxybenzamide (40h):



According to **GP4**, trichloroacetyl isocyanate (311 mg, 1.7 mmol) was added to 5-bromo-3-(cyclopropanecarbonyl)-2-methoxyphenylzinc bromide (**39h**) (2.0 mL, 1.5mmol, 0.75 M in THF) at -20 °C. After quenching with K_2CO_3 (311 mg, 2.3 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 9:1) afforded the amide **40h** (295 mg, 66 %) as a colourless solid.

m.p.: 131.8–133.5 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 7.89 (br s, 1 H), 7.79 (d, *J* = 2.5 Hz, 1 H), 7.71 (br s, 1 H), 7,67 (d, *J* = 2.7 Hz, 1 H), 3.80 (s, 3 H), 2.63 (quint, *J* = 6.2 Hz, 1 H), 1.11 (d, *J* = 6.3 Hz, 4 H).

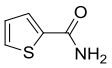
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 201.2, 165.9, 155.0, 136.1, 134.4, 133.2, 132.5, 115.4, 63.2, 21.2, 12.4.

MS (EI, 70 eV): *m/z* (%) = 298 (100), 297 (55) [M$^+$], 227 (95), 201 (60), 69 (56), 43 (49), 41 (52).

HRMS *m/z* : calc. for $C_{12}H_{12}BrNO_3$ 297.0001, found 297.006.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3442 (w), 1670 (m), 1633 (vs), 1574 (m), 1458 (m), 1416 (s), 1407 (vs), 1387 (s), 1359 (m), 1217 (s), 1103 (m), 1048 (m), 1015 (m), 985 (s), 907 (m), 876 (m), 843 (w), 800 (w).

Preparation of thiophene-2-carboxamide (40i):



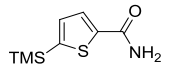
According to **GP4**, trichloroacetyl isocyanate (622 mg, 3.3 mmol) was added to 2-thienyl zinc iodide (**39i**) (3.9 mL, 3.0 mmol, 0.77 M in THF) at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, pentane:EtOAc 3:1) afforded the amide **40i** (380 mg, 99%) as a colourless solid.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 7.97 (br s, 1 H), 7.74 (dd, *J* = 3.8 and 1.3 Hz, 1 H), 7.72 (dd, *J* = 5.1 and 1.2 Hz, 1 H) 7.39 (br s, 1 H), 7.11 (dd, *J* = 4.9 and 3.7 Hz, 1 H).

^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 162.9, 140.3, 131.0, 128.7, 127.9.

Data are consistent with literature values.[170]

Preparation of 5-(trimethylsilyl)thiophene-2-carboxamide (40j):



According to **GP3**, *i*PrMgCl·LiCl (1.60 mL, 2.1 mmol, 1.31 M in THF) was added to a solution of (5-bromothiophen-2-yl)trimethylsilane (470 mg, 2 mmol) in THF (2 mL) at 25 °C. After stirring for 1 h at 25 °C, $ZnCl_2$-solution (3.4 mL, 2.2 mmol, 0.65 M in THF) was added. After 5 min at 25 °C, the reaction mixture was cooled to -20 °C. According to **TP4** trichloroacetyl isocyanate (452 mg, 2.4 mmol) was added at -20 °C. After quenching with K_2CO_3 (414 mg, 3 mmol) and EtOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 1:1) afforded the amide **40j** (397 mg, 99 %) as a colourless solid.

m.p.: 144.8–146.6 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 7.91 (br s, 1 H), 7.76 (d, *J* = 3.5 Hz, 1 H), 7.33 (br s,1 H), 7.28 (d, *J* = 3.5 Hz, 1 H), 0.29 (s, 9 H).

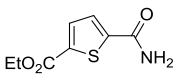
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 162.6, 145.1, 145.0, 134.8, 129.6, -0.4.

MS (EI, 70 eV): *m/z* (%) = 199 (M^+, 22), 184 (100), 127 (6), 74 (6), 69 (7), 43 (14).

HRMS *m/z* : calc. for $C_8H_{13}NOSSi$ 199.0487, found 199.0477.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3392 (w), 3220 (w), 1663 (m), 1633 (m), 1601 (s), 1514 (m), 1435 (m), 1389 (m), 1250 (m), 1214 (m), 1108 (w), 1094 (w), 1058 (m), 989 (s), 839 (vs), 818 (s), 754 (s), 691 (m).

Preparation of ethyl 5-carbamoylthiophene-2-carboxylate (40k):



According to **GP3**, *i*PrMgCl·LiCl (1.60 mL, 2.1 mmol, 1.31 M in THF) was added to a solution of ethyl 5-bromothiophene-2-carboxylate (470 mg, 2 mmol) in THF (2 mL) at -20 °C. After stirring for 2 h at -20 °C, $ZnCl_2$-solution (3.4 mL, 2.2 mmol, 0.65 M in THF) was added. According to **TP4** trichloroacetyl isocyanate (452 mg, 2.4 mmol) was added at -20 °C. After quenching with K_2CO_3 (414 mg, 3 mmol) and EtOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-

[170] M. Kashiwagi, K. Fuhshuku, T. Sugai, *J. Mol. Cat. B: Enzym.* **2004**, *29*, 249.

chromatographical purification (silica, CH_2Cl_2:EtOAc 9:1) afforded the amide **40k** (245 mg, 61%) as a colourless solid.

m.p.: 195.9–198.3 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 8.20 (br s, 1 H), 7.76, (s, 2 H), 7.67 (br s, 1 H), 4.29 (q, 2 H), 1.29 (t, 3 H).

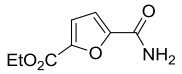
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 162.0, 161.2, 146.2, 136.2, 133.7, 128.9, 61.3, 14.1.

MS (EI, 70 eV): *m/z* (%) = 199 (M^+, 61), 183 (34), 171 (36), 155 (47), 154 (100), 111 (31).

HRMS *m/z* : calc. for $C_8H_9NO_3S$ 199.0303, found 199.0296.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3397 (m), 3159 (m), 1678 (vs), 1621 (s), 1529 (m), 1389 (s), 1363 (s), 1289 (vs), 1232 (m), 1119 (s), 1103 (s), 1039 (m), 1010 (m), 829 (m), 748 (vs), 720 (m), 667 (m).

Preparation of ethyl 5-carbamoylfuran-2-carboxylate (40l):



According to **GP3**, *i*PrMgCl·LiCl (1.60 mL, 2.1 mmol, 1.31 M in THF) was added to a solution of ethyl 5-bromofuran-2-carboxylate (438 mg, 2 mmol) in THF (2 mL) at -20 °C. After stirring for 1 h at -20 °C, $ZnCl_2$-solution (3.4 mL, 2.2 mmol, 0.65 M in THF) was added. According to **TP4** trichloroacetyl isocyanate (452 mg, 2.4 mmol) was added at -20 °C. After quenching with K_2CO_3 (414 mg, 3 mmol) and EtOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 9:1) afforded the amide **40l** (284 mg, 78 %) as a colourless solid.

m.p.: 184.1–185.9 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 8.02 (br s, 1 H), 7.64 (br s, 1 H), 7.35 (d, *J* = 3.5 Hz, 1 H), 7.24 (d, *J* = 3.5 Hz, 1 H), 4.31 (q, *J* = 7.0 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

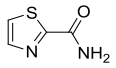
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 158.6, 157.7, 150.4, 144.6, 119.0, 114.7, 61.0, 14.1.

MS (EI, 70 eV): *m/z* (%) = 183 (M^+, 67), 167 (15), 155 (60), 139 (77), 138 (100), 111 (21), 95 (38).

HRMS *m/z* : calc. for $C_8H_9NO_4$ 183.0532, found 183.0527.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3376 (w), 3115 (w), 1723 (s), 1685 (s), 1655 (s), 1623 (m), 1585 (m), 1380 (s), 1295 (vs), 1222 (s), 1177 (s), 1154 (s), 1116 (m), 1079 (m), 1017 (s), 964 (w), 946 (m), 866 (w), 838 (m), 826 (w), 763 (s), 688 (w).

Preparation of 1,3-thiazole-2-carboxamide (40m):



According to **GP3**, *i*PrMgCl·LiCl (2.50 mL, 3.3 mmol, 1.33 M in THF) was added to a solution of 2-bromothiazole (489 mg, 3 mmol) at 25 °C. After stirring for 1.5 h at 25 °C, $ZnCl_2$-solution (3.5 mL, 3.5 mmol, 1 M in THF) was added. After 5 min at 25 °C, the reaction mixture was cooled to -20 °C. According to **TP4** trichloroacetyl isocyanate (678 mg, 3.6 mmol) was added at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 4:1) afforded the amide **40m** (317 mg, 82 %) as a colourless solid.

m.p.: 119.2–120.8 °C.

^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 8.17 (br s, 1 H), 7.99 (d, *J* = 2.9 Hz, 1 H), 7.97 (d, *J* = 3.1 Hz, 1 H), 7.85 (br s, 1 H).

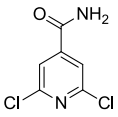
^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 164.2, 161.0, 143.9, 125.9.

MS (EI, 70 eV): *m/z* (%) = 128 (M^+, 22), 85 (100), 58 (85), 57 (25), 44 (21).

HRMS *m/z* : calc. for $C_4H_4N_2OS$ 128.0044, found 128.0032(M^+).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3331 (m), 3146 (m), 1689 (vs), 1619 (s), 1494 (m), 1430 (s), 1379 (s), 1321 (m), 1123 (m), 1088 (s), 757 (m), 732 (s), 710 (s).

Preparation of 2,6-dichloroisonicotinamide (40n):



According to **TP1**, 4-iodo-2,6-dichloropyridine (1.37 g, 5.0 mmol) was converted to the corresponding organozinc reagent **39n** using Zn dust (653 mg, 10 mmol) and LiCl (318 mg, 7.5 mmol) in THF within 1 h at 18 °C (cooling with a water bath). After unreacted Zn dust settled down, the supernatant solution was titrated to be 0.55 M. The organozinc reagent (3.6 mL, 2 mmol, 0.55 M) was transferred to a new *Schlenk*-flask and cooled to -20 °C. According to **TP4** trichloroacetyl isocyanate (415 mg, 2.2 mmol) was added at -20 °C. After quenching with K_2CO_3 (415 mg, 4.5 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 9:1) afforded the amide **40n** (240 mg, 63%) as a colourless solid.

m.p.: 212.8–214.5 °C.

^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 8.35 (br s, 1 H), 7.97 (br s, 1 H), 7.88 (s, 2 H).

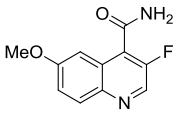
^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 163.5, 149.8, 147.7, 121.6.

MS (EI, 70 eV): *m/z* (%) = 190 (M^+, 100), 176 (55), 174 (96), 147 (31), 85 (28), 44 (40).

HRMS *m/z* : calc. for $C_6H_6Cl_2N_2O$ 189.9701, found 189.9688.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3436 (w), 3167 (m), 1698 (vs), 1613 (m), 1580 (m), 1534 (vs), 1428 (m), 1350 (s), 1197 (m), 1169 (s), 1103 (s), 986 (w), 894 (m), 880 (m), 818 (s), 773 (vs), 707 (m).

Preparation of 6-fluoro-3-methoxyquinoline-4-carboxamide (40o):



According to **GP1**, 3-fluoro-4-iodo-6-methoxyquinoline (1.52 g, 5mmol) was added to a suspension of LiCl (424 mg, 10 mmol) and Zn dust (654 mg, 10 mmol) in THF (5 mL) at 0 °C. After 5 min, the ice bath was removed, and the reaction was stirred 12 h at 25 °C. According to **TP4** trichloroacetyl isocyanate (226 mg, 1.2 mmol) was added at -20 °C. After quenching with K_2CO_3 (207 mg, 1.5 mmol) and MeOH (1 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 9:1) afforded the amide **40o** (239 mg, 73 %) as a colourless solid.

m.p.: 199.3–201.4 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 8.81 (s, 1 H), 8.36 (br s, 1 H), 8.12 (br s, 1 H), 8.00 (d, *J* = 9.2 Hz, 1 H), 7.43 (dd, *J* = 9.2 and 2.7 Hz, 1 H), 7.19 (d, *J* = 2.7 Hz, 1 H), 3.88 (s, 3 H).

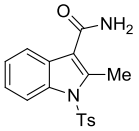
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 163.7 (d, *J* = 1.2 Hz), 158.6, 151.6 (d, *J* = 254.7 Hz), 141.0 (d, *J* = 2.3 Hz), 138.5 (d, *J* = 28.0 Hz), 130.9, 126.2 (d, *J* = 16.4 Hz), 126.1 (d, *J* = 3.5 Hz), 121.3 (d, *J* = 2.7 Hz), 102.9 (d, *J* = 5.1 Hz), 55.5.

MS (EI, 70 eV): *m/z* (%) = 220 (M^+, 100), 204 (31), 189 (10), 176 (16), 174 (8), 149 (8).

HRMS *m/z* : calc. for $C_{11}H_9FN_2O_2$ 220.0648, found 220.0646(M^+).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3311 (w), 2959 (w), 1673 (s), 1619 (s), 1507 (s), 1462 (s), 1429 (m), 1395 (m), 1350 (s), 1311 (m), 1270 (m), 1226 (vs), 1198 (s), 1174 (m), 1134 (m), 1066 (w), 1022 (m), 906 (m), 828 (s), 806 (m).

Preparation of 2-methyl-1-[(4-methylphenyl)sulfonyl]-1H-indole-3-carboxamide (40p):



According to **GP3**, *i*PrMgCl·LiCl (0.83 mL, 1.1 mmol, 1.33 M in THF) was added to a solution of 3-iodo-2-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indole (411 mg, 1 mmol) in THF (1 mL) at -20 °C. After stirring for 4 h at -20 °C, $ZnCl_2$-solution (1.15 mL, 1.15 mmol, 1 M in THF) was added at -20 °C and the reaction was stirred for another 5 min. According to **TP4**, trichloroacetyl isocyanate (226 mg, 1.2 mmol) was added at -20 °C. After quenching with K_2CO_3 (207 mg, 1.5 mmol) and MeOH (1 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 9:1) afforded the amide **40p** (239 mg, 73 %) as a colourless solid.

m.p.: 225.9–227.6 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 8.08 (d, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.67 (br s, 1 H), 7.62 (d, *J* = 7.0 Hz, 1 H), 7.53 (br s, 1 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.32 (td, *J* = 7.7 Hz and 1.4 Hz, 1 H), 7.27 (t, *J* = 6.9 Hz, 1 H), 2.73 (s, 3 H), 2.31 (s, 3 H).

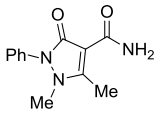
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 165.3, 145.7, 137.2, 134.8, 134.7, 130.4, 127.2, 126.4, 124.4, 123.7, 120.2, 117.8, 113.8, 21.0, 13.7.

MS (EI, 70 eV): *m/z* (%) = 328 (M^+, 63), 247 (15), 173 (100), 155 (13), 145 (49), 91 (55).

HRMS *m/z* : calc. for $C_{17}H_{16}N_2O_3S$ 328.0882, found 328.0867.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1678 (m), 1650 (m), 1616 (m), 1403 (m), 1365 (m), 1239 (m), 1188 (m), 1173 (s), 1159 (m), 1116 (m), 1086 (m), 1022 (m), 965 (m), 788 (m), 749 (vs), 684 (m), 666 (m).

Preparation of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (40q):



According to **GP4**, trichloroacetyl isocyanate (622 mg, 3.3 mmol) was added to 1,5-dimethyl-2-phenyl-1*H*-4-pyrazol-3-(2*H*)-on zinc iodide[171] (**39q**) (3.9 mL, 3.0 mmol, 0.76 M in THF) at -20 °C. After quenching with K_2CO_3 (622 mg, 4.5 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$, flash-chromatographical purification (silica gel, EtOAc) and subsequent recyrstallization from EtOAc afforded the amide **40q** (484 mg, 70 %) as a colourless solid.

[171] P. Knochel, C: J. Rao, C. J. *Tetrahedron Lett.* **1993**, *49*, 29.

m.p.: 253.3–255.5 °C.[172]

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 7.89 (br s, 1 H), 7.54 (t, *J* = 7.6 Hz, 2 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.35 (dd, *J* = 8.4 Hz and 1.2 Hz, 2H), 7.01 (br s, 1 H), 3.26 (s, 3 H), 2.62 (s, 3 H).

^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 164.4, 163.4, 154.7, 133.6, 129.3, 128.2, 126.5, 97.9, 33.3, 11.3.

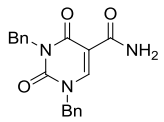
MS (EI, 70 eV): *m/z* (%) = 231 (M^+, 48), 215 (18), 214 (100), 199 (44), 77 (14), 67 (14), 56 (10).

HRMS *m/z* : calc. for $C_{12}H_{13}N_3O_2$ 231.1008, found 231.1003(M^+).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3321 (m), 3158 (w), 1649 (vs), 1604 (s), 1587 (s), 1535 (s), 1499 (s), 1486 (s), 1420 (s), 1290 (s), 1243 (m), 1129 (m), 1071 (w), 1053 (w), 1022 (w), 822 (w), 787 (m), 758 (m), 704 (vs).

Data consistent with literature values.[172]

Preparation of 1,3-dibenzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (40r):



According to **GP4**, trichloroacetyl isocyanate (415 mg, 2.2 mmol) was added to *N*,*N*-dibenzyl-5-uracilzinc iodide[71b] (**39r**) (2.8 mL, 2.0 mmol, 0.71 M in THF) at -20 °C. After quenching with K_2CO_3 (415 mg, 3 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and recrystallization from EtOAc afforded the amide **40r** (522 mg, 78 %) as a colourless solid.

m.p.: 195.1–196.8 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 8.72 (s, 1 H), 8.18 (br s, 1 H), 7.63 (br s, 1 H), 7.38–7.24 (m, 10 H), 5.14 (s, 2 H), 5.05 (s, 2 H).

^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 162.9, 162.1, 150.6, 149.7, 136.5, 136.0, 128.7, 128.3, 127.9, 127.7, 127.5, 127.2, 104.9, 52.3, 44.2.

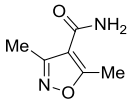
MS (EI, 70 eV): *m/z* (%) = 335 (M^+, 100), 318 (28), 227 (32), 199 (20), 132 (33), 91 (88).

HRMS *m/z* : calc. for $C_{19}H_{13}N_3O_5$ 335.1270, found 335.1262.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3369 (w), 1709 (s), 1693 (vs), 1647 (m), 1581 (m), 1495 (m), 1451 (vs), 1407 (s), 1330 (s), 1230 (m), 1212 (m), 1116 (w), 1071 (w), 1029 (w), 989 (w), 826 (w), 792 (m), 757 (s), 738 (s), 700 (s).

[172] K. Bodendorf, G. Jancke, *Arch. Pharm.* **1960**, *293*, 693.

Preparation of 3,5-dimethylisoxazole-4-carboxamide (40s):



According to **TP2**, 5-bromo-3,5-dimethylisoxazol (220 mg, 1.25 mmol) was converted to the corresponding organozinc reagent **39s** using Mg turnings (97 mg, 4 mmol), LiCl (159 mg, 3.8 mmol) and $ZnCl_2$ (2.75 mL, 2.75 mL, 1 M in THF) within 1.5 h at 23 °C. After the magnesium turnings settled down, the supernatant solution was transferred to a new *Schlenk*-flask and cooled to -20 °C. According to **TP4** trichloroacetyl isocyanate (264 mg, 1.4 mmol) was added at -20 °C. After quenching with K_2CO_3 (276 mg, 2.5 mmol) and MeOH (1 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 1:1) afforded the amide **40s** (173 mg, 98 %) as a colourless solid.

m.p.: 125.6–127.7 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 7.40 (br s, 1 H), 7.31 (br s, 1 H), 2.47 (s, 3 H), 2.26 (s, 3 H).

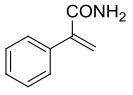
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 169.8, 163.2, 158.3, 112.6, 12.2, 10.7.

MS (EI, 70 eV): *m/z* (%) = 140 (M^+, 100), 124 (22), 123 (41), 82 (80), 81 (26), 43 (61).

HRMS *m/z* : calc. for $C_6H_8N_2O_2$ 140.0586, found 140.0576.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3359 (m), 3195 (m), 1705 (m), 1647 (vs), 1621 (vs), 1604 (vs), 1462 (m), 1431 (s), 1392 (s), 1262 (m), 1152 (s), 1133 (m), 1038 (w), 981 (w), 961 (w), 880 (w), 831 (m), 806 (m), 750 (m), 720 (m), 676 (w).

Preparation of 2-phenylprop-2-enamide (40t):



According to **GP4**, trichloroacetyl isocyanate (415 mg, 2.2 mmol) was added to 1-phenyl-1-ethenylzinc bromide[34] (**39t**) (3.6 mL, 2.0 mmol, 0.56 M in THF) at -20 °C. After quenching with K_2CO_3 (415 mg, 3 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, EtOAc) afforded the amide **40t** (251 mg, 85 %) as a colourless solid.

m.p.: 125.1–126.8 °C.[173]

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 7.61 (br s, 1 H), 7.44–7.29 (m, 6 H), 5.73 (s, 1H), 5.69 (s, 1 H).

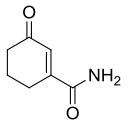
^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 170.0, 145.1, 136.9, 128.2, 127.9, 127.2, 117.8.

MS (EI, 70 eV): *m/z* (%) = 147 (M^+, 74), 146 (24), 118 (17), 104 (25), 103 (100), 77 (35).

HRMS *m/z* : calc. for C_9H_9NO 147.0684, found 147.0679.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3329 (m), 3159 (m), 1656 (s), 1632 (s), 1597 (s), 1495 (m), 1426 (s), 1257 (m), 1117 (m), 933 (s), 776 (m), 693 (vs).

Preparation of 3-oxocyclohex-1-ene-1-carboxamide (40u):



According to **GP4**, trichloroacetyl isocyanate (415 mg, 2.2 mmol) was added to 3-oxo-1-cyclohexen-1-ylzinc iodide[71] (**39u**) (2.7 mL, 2.0 mmol, 0.73 M in THF) at -20 °C. After quenching with K_2CO_3 (415 mg, 3 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica gel, EtOAc) afforded the amide **40u** (176 mg, 63 %) as a colourless solid.

m.p.: 138.8–140.8 °C.

^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 7.82 (br s, 1 H), 7.47 (br s, 1 H), 6.34 (t, *J* = 1.8 Hz, 1 H), 2.47 (td, *J* = 6.0 and 1.75 Hz, 2 H), 2.35–2.32 (m, 2 H), 1.95–1.89 (m, 2 H).

^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 200.0, 168.3, 154.2, 127.9, 37.2, 24.8, 22.0.

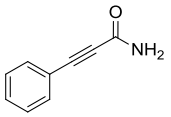
MS (EI, 70 eV): *m/z* (%) = 139 (M^+, 100), 111 (31), 95 (22), 83 (79), 67 (16), 44 (23).

HRMS *m/z* : calc. for $C_7H_9NO_2$ 139.0633, found 139.0627.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3421 (m), 3172 (w), 2922 (w), 1654 (vs), 1600 (s), 1410 (m), 1347 (m), 1325 (m), 1301 (w), 1259 (m), 1237 (w), 1187 (m), 1133 (m), 1115 (m), 962 (m), 930 (m), 786 (m), 679 (w).

[173] H. Staudinger, L. Ružička, *Liebigs Ann. Chem.* **1911**, *380*, 278.

Preparation of 3-phenylpropiolamide (40v):



Phenylacetylene (204 mg, 2 mmol) was dissolved in dry THF (2 mL), cooled to -20 °C and *n*BuLi (0.93 mL, 2.1 mmol 2.27 M in hexane) was added. After 30 min, $ZnCl_2$-solution (3.4 mL, 2.2 mmol, 0.65 M in THF) was added and the reaction mixture was stirred for 5 min at this temperature. According to **GP4**, trichloroacetyl isocyanate (415 mg, 2.2 mmol) was added at -20 °C. After quenching with K_2CO_3 (415 mg, 3 mmol) and MeOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, EtOAc) afforded the amide **40v** (207 mg, 71 %) as a colourless solid.

m.p.: 113.0–140.8 °C.

^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 8.14 (br s, 1 H), 7.67 (br s, 1 H), 7.49 (m, 5 H).

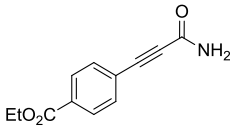
^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 153.9, 132.0, 130.1, 128.9, 119.9, 84.2, 82.9.

MS (EI, 70 eV): *m/z* (%) =145 (M^+, 45), 129 (100), 117 (4), 102 (4), 75 (10), 74 (5).

HRMS *m/z* : calc. for C_9H_7NO 145.0528, found 145.0520.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3377 (m), 3167 (m), 2220 (m), 1649 (vs), 1607 (vs), 1489 (s), 1441 (w), 1387 (vs), 1229 (m), 1181 (w), 1119 (m), 1071 (w), 1027 (w), 908 (m), 752 (vs), 689 (m).

Preparation of ethyl 4-(3-amino-3-oxoprop-1-yn-1-yl)benzoate (40w):



A dry and Ar flushed *Schlenk*-flask equipped with a magnetic stirring bar was charged with Zn-powder (262 mg, 4 mmol). After the addition of THF (2 mL) 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%) were added and the suspension was heated with a heat gun until ebullition occurred. After cooling to room temperature, ethyl 4-(bromoethynyl)benzoate (506 mg, 2 mmol) was added and the reaction mixture was stirred for 16 h at 23 °C. Then, unreacted Zn was allowed to settle down and the supernatant solution was transferred to a second flask. According to **GP4**, trichloroacetyl isocyanate (415 mg, 2.2 mmol) was added at -20 °C. After quenching with K_2CO_3 (415 mg, 3 mmol) and EtOH (2 mL), standard workup with EtOAc and $CHCl_3$ and flash-chromatographical purification (silica, CH_2Cl_2:EtOAc 9:1) afforded the amide **40w** (248 mg, 57 %) as a colourless solid.

m.p.: 139.8–141.7 °C.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm) = 8.23 (br s, 1 H), 7.99 (d, *J* = 8.6 Hz, 2 H), 7.75 (br s, 1 H), 7.69 (d, *J* = 8.6 Hz, 2 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm) = 164.9, 153.5, 132.3, 130.8, 129.4, 124.5, 86.4, 81.7, 61.1, 14.1.

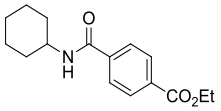
MS (EI, 70 eV): *m/z* (%) = 217 (M^+, 53), 201 (29), 173 (40), 172 (100), 129 (12), 101 (11).

HRMS *m/z* : calc. for $C_{12}H_{11}NO_3$ 217.0739, found 217.0736.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3385 (m), 3153 (w), 2216 (w), 1697 (s), 1666 (vs), 1605 (m), 1563 (w), 1405 (m), 1372 (s), 1292 (s), 1280 (vs), 1177 (m), 1130 (s), 1110 (s), 1021 (m), 900 (w), 863 (m), 767 (vs), 726 (m), 695 (s).

5.3 Preparation of Secondary Amides

Preparation of ethyl 4-(cyclohexylcarbamoyl)benzoate (48a):



According to **GP5**, 4-(ethoxycarbonyl)phenylzinc iodide[161] (**39b**,4.54 mL, 3.30 mmol, 0.73 M in THF) was added to a solution of cyclohexyl isocyanate (**47b**, 376 mg, 3.00 mmol) and $Ni(acac)_2$ (15.6 mg, 0.06 mmol) in THF (1 mL) and stirred for 24 h at ambient temperature. After usual workup and flash-chromatographical purification (silica, pentane:EtOAc 4:1) the amide **48a** (495 mg, 60 %) was isolated as a colourless solid.

m.p.: 167.6-169.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.05 (d, *J* = 8.6 Hz, 2 H), 7.78 (d, *J* = 8.6 Hz, 2 H), 6.13 (d, *J* = 7.6 Hz, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 3.95 (m, 1 H), 2.02 (m, 2 H), 1.74 (m, 2 H), 1.62 (m, 1 H), 1.38 (m, 5 H), 1.21 (m, 3 H).

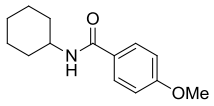
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.8, 165.7, 138.9, 132.8, 129.7, 126.9, 61.3, 48.9, 33.1, 25.5, 24.9, 14.3.

MS (EI, 70 eV): *m/z* (%) = 275 (M^+, 26), 230 (10), 194 (100), 177 (60), 149 (13), 104 (6).

HRMS *m/z* : calc. for $C_{16}H_{21}NO_3$ 275.1521, found 275.1516.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3324 (w), 2931 (m), 2854 (w), 1739 (m), 1712 (vs), 1628 (s), 1532 (s), 1454 (m), 1446 (m), 1367 (m), 1329 (m), 1271 (vs), 1150 (m), 1109 (s), 1080 (m), 1021 (m), 892 (w), 868 (s), 843 (m), 793 (w), 736 (s), 693 (s), 656 (m), 627 (m).

Preparation of *N*-cyclohexyl-4-methoxybenzamide (48b):



According to **GP5**, 4-methoxyphenylzinc iodide[161] (**39x**, 3.10 mL, 3.30 mmol, 1.09 M in THF) was added to a solution of cyclohexyl isocyanate (**47b**, 376 mg, 3.00 mmol) and $Ni(acac)_2$ (15.6 mg, 0.06 mmol) in THF (1 mL) and stirred for 48 h at ambient temperature. After usual workup and flash-chromatographical purification (silica, pentane:EtOAc 1:1) the amide **48b** (372 mg, 53 %) was isolated as a gray solid.

m.p.: 156.2-157.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.70 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 5.98 (br, 1 H), 3.93 (m, 1 H), 3.81 (s, 3 H), 1.99 (m, 2 H), 1.67 (m, 3 H), 1.39 (m, 2 H), 1.20 (m, 3 H).

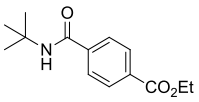
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.1, 161.9, 128.6, 127.3, 113.6, 55.4, 48.6, 33.3, 25.6.

MS (EI, 70 eV): *m/z* (%) = 233 (M^+, 22), 151 (41), 135 (100), 107 (7), 92 (13), 77 (11).

HRMS *m/z* : calc. for $C_{14}H_{19}NO_2$ 233.1416, found 233.1407.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3299 (m), 2928 (m), 2853 (m), 1739 (m), 1624 (s), 1605 (s), 1535 (s), 1506 (s), 1449 (m), 1332 (s), 1251 (vs), 1239 (s), 1175 (s), 1114 (m), 1085 (m), 1027 (s), 893 (m), 838 (vs), 768 (m), 716 (m), 677 (s), 631 (s).

Preparation of ethyl 4-(*tert*-butylcarbamoyl)benzoate (48c):



According to **GP5**, 4-(ethoxycarbonyl)phenylzinc iodide[161] (**39b**, 4.54 mL, 3.30 mmol, 0.72 M in THF) was added to a solution of *tert*-butyl isocyanate (**47c**, 297 mg, 3.00 mmol) and $Ni(acac)_2$ (15.6 mg, 0.06 mmol) in THF (1 mL) and stirred for 2 h at ambient temperature. After usual workup and flash-chromatographical purification (silica, pentane:EtOAc 4:1) the amide **48c** (587 mg, 79 %) was isolated as a colourless solid.

m.p.: 109.8-111.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.03 (d, *J* = 8.8 Hz, 2 H), 7.74 (d, *J* = 8.6 Hz, 2 H), 6.04 (br, 1 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 1.46 (s, 9 H), 1.38 (t, *J* = 7.1 Hz, 2 H).

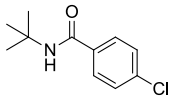
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.0, 165.9, 139.7, 132.6, 129.7, 126.7, 61.3, 51.9, 28.8, 14.3.

MS (EI, 70 eV): *m/z* (%) = 249 (M^+, 14), 234 (16), 194 (25), 177 (100), 149 (13).

HRMS *m/z* : calc. for $C_{14}H_{19}NO_3$ 249.1365, found 249.11352.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3300 (w), 2980 (w), 2965 (w), 1716 (s), 1652 (m), 1634 (s), 1545 (s), 1455 (m), 1391 (m), 1365 (s), 1361 (m), 1321 (m), 1267 (vs), 1232 (s), 1224 (s), 1218 (s), 1173 (m), 1105 (vs), 1020 (s), 870 (m), 848 (m), 730 (s), 701 (m), 689 (m), 665 (m), 641 (m), 623 (m), 615 (m).

Preparation of *N-tert*-butyl-4-chlorobenzamide (48d):



According to **GP5**, 4-chlorophenylzinc iodide[161] (**39y**, 4.23 mL, 3.30 mmol, 0.78 M in THF) was added to a solution of *tert*-butyl isocyanate (**47c**, 297 mg, 3.00 mmol) and $Ni(acac)_2$ (15.6 mg, 0.06 mmol) in THF (1 mL) and stirred for 2 h at ambient temperature. After usual workup and flash-chromatographical purification (silica, pentane:EtOAc 9:1) the amide **48d** (401 mg, 63 %) was isolated as a colourless solid.

m.p.: 134.7-136.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.66 (d, *J* = 8.6 Hz, 2 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 5.95 (br, 1 H), 1.47 (s, 9 H).

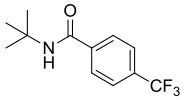
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.8, 137.2, 134.3, 128.7, 128.2, 51.8, 28.8.

MS (EI, 70 eV): *m/z* (%) = 211 (M^+, 17), 196 (24), 156 (15), 139 (100), 111 (18).

HRMS *m/z* : calc. for $C_{11}H_{1a}ClNO$ 211.0764, found 211.0757.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3459 (vw), 3319 (w), 2970 (m), 2929 (w), 2362 (vw), 1739 (s), 1633 (s), 1592 (m), 1536 (s), 1486 (s), 1449 (s), 1360 (s), 1317 (s), 1304 (m), 1229 (s), 1217 (vs), 1113 (m), 1090 (s), 1013 (m), 876 (m), 848 (s), 760 (s), 635 (m).

Preparation of *N-tert*-butyl-4-(trifluoromethyl)benzamide (48e):



According to **GP5**, 4-(trifluoromethyl)phenylzinc iodide[161] (**39z**, 4.64 mL, 3.30 mmol, 0.71 M in THF) was added to a solution of *tert*-butyl isocyanate (**47c**, 297 mg, 3.00 mmol) and $Ni(acac)_2$ (15.6 mg, 0.06 mmol) in THF (1 mL) and stirred for 1 h at ambient temperature. After usual workup and flash-chromatographical purification (silica, pentane:EtOAc 9:1) the amide **48e** (553 mg, 75 %) was isolated as a colourless solid.

m.p.: 152.1-153.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.82 (d, *J* = 8.8 Hz, 2 H), 7.66 (d, *J* = 8.8 Hz, 2 H), 6.04 (br, 1 H), 1.49 (s, 9 H).

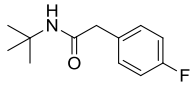
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.7, 139.2 (q, *J* = 1.3 Hz), 132.8 (q, *J* = 32 Hz), 127.2, 125.5 (q, *J* = 3.6 Hz), 123.7 (q, *J* = 272 Hz), 52.0, 28.8.

MS (EI, 70 eV): *m/z* (%) = 245 (M^+, 14), 230 (22), 190 (26), 173 (100), 145 (34).

HRMS *m/z* : calc. for $C_{11}H_{1a}ClNO$ 245.1027, found 245.1024.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3265 (w), 3080 (vw), 2970 (w), 1739 (w), 1641 (m), 1548 (s), 1455 (w), 1365 (m), 1324 (s), 1296 (m), 1218 (m), 1159 (s), 1123 (vs), 1109 (s), 1068 (s), 1017 (s), 881 (m), 876 (m), 855 (s), 775 (m), 678 (m), 632 (m).

Preparation of *N*-*tert*-butyl-4-(trifluoromethyl)benzamide (48f):



According to **GP5**, 4-fluorobenzylzinc chloride[161] (**11j**, 4.64 mL, 3.30 mmol, 0.71 M in THF) was added to a solution of *tert*-butyl isocyanate (**47c**, 297 mg, 3.00 mmol) and $Ni(acac)_2$ (15.6 mg, 0.06 mmol) in THF (1 mL) and stirred for 2 h at ambient temperature. After usual workup and flash-chromatographical purification (silica, pentane:EtOAc 4:1 to 1:1) the amide **48f** (388 mg, 61 %) was isolated as a colourless solid.

m.p.: 117.7-119.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.22 (m, 2 H), 7.03 (m, 2 H), 5.29 (br, 1 H), 3.45 (s, 2 H), 1.30 (s, 9 H).

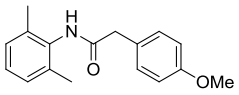
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 170.0, 162.0 (d, *J* = 246 Hz), 131.2 (d, *J* = 3.4 Hz), 130.8 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 21 Hz), 51.4, 43.8, 28.7.

MS (EI, 70 eV): *m/z* (%) = 209 (M^+, 2), 110 (77), 100 (5), 57 (100), 44 (12), 40 (15).

HRMS *m/z* : calc. for $C_{11}H_{1a}ClNO$ 209.1216, found 209.1211.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3285 (m), 3071 (w), 2991 (w), 2970 (m), 2926 (w), 1739 (m), 1640 (s), 1602 (m), 1550 (s), 1506 (vs), 1447 (m), 1356 (vs), 1270 (m), 1226 (s), 1217 (vs), 1202 (s), 1153 (m), 1090 (w), 1017 (w), 947 (m), 913 (w), 860 (w), 837 (m), 824 (m), 790 (s), 720 (m), 706 (m), 681 (m).

Preparation of *N*-(2,6-dimethylphenyl)-2-(4-methoxyphenyl)acetamide (48g):



According to **GP5**, 4-methoxybenzylzinc chloride[161] (**11k**, 2.66 mL, 3.30 mmol, 1.24 M in THF) was added to a solution of 2,6-dimethylphenyl isocyanate (**47d**, 441 mg, 3.00 mmol) and $Ni(acac)_2$ (15.6 mg, 0.06 mmol) in THF (1 mL) and stirred for 2 h at ambient temperature. After usual workup and flash-chromatographical purification (silica, pentane:EtOAc 3:1 to 2:1) the amide **48g** (494 mg, 61 %) was isolated as a colourless solid.

m.p.: 151.8-153.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.32 (d, *J* = 8.8 Hz, 2 H), 7.05 (m, 3 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.73 (br, 1 H), 3.84 (s, 3 H), 3.73 (s, 2 H), 2.13 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 169.9, 159.1, 135.3, 133.7, 130.7, 128.2, 127.4, 127.0, 114.6, 55.4, 43.1, 18.3.

MS (EI, 70 eV): *m/z* (%) = 269 (M^+, 49), 241 (4), 148 (21), 121 (100), 107 (11), 77 (13).

HRMS *m/z* : calc. for $C_{17}H_{19}NO_2$ 269.1416, found 269.1408.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3253 (m), 3030 (w), 3007 (w), 2954 (w), 2929 (w), 2836 (w), 1644 (vs), 1613 (m), 1521 (s), 1509 (vs), 1464 (s), 1439 (s), 1342 (m), 1301 (m), 1253 (s), 1238 (s), 1175 (s), 1159 (s), 1036 (s), 980 (m), 812 (m), 790 (s), 766 (vs), 754 (s), 715 (s), 676 (m), 606 (s).

5 Preparation of Highly Functionalized Allenes via Successive Copper-Mediated Substitution Reactions6 Preparation of Highly Functionalized Allens Via Successive Copper-Mediated Substitution Reactions

6.1 General Procedures

General Procedure 2 (GP1): Cu(I)-catalyzed coupling of arylmagnesium reagents with allenyl halides:

A dry, argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the desired aryl halide (1 equiv) in THF (2 M). *i*PrMgCl·LiCl (1.2 equiv.) in THF was added at the given temperature and the mixture was stirred until the conversion was complete (checked by GC-analysis of a hydrolyzed reaction aliquot). To the freshly prepared *Grignard* reagent was added CuCN·2LiCl solution (1.0 M, 10 mol%) and allenyl halide (1.2 equiv.) at -20 °C, and the reaction mixture was stirred at room temperature. After stirring for 1 h, the reaction mixture was poured into an ice-cooled saturated aqueous NH_4Cl solution (25 mL). After extraction with Et_2O (3x25 mL), the organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica).

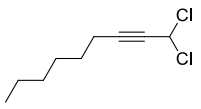
General procedure 2 (GP2): Reaction of organozinc reagents with propargylic dichlorides:

A dry, argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged corresponding organozinc reagent (1 equiv.) and cooled to -20 °C. Then CuCN·2LiCl (1 equiv. or 10 mol%, 1.0 M in THF) was added, followed by the desired propargylic dichloride (1.2 equiv.). After stirring for the given time at -20 °C, the reaction mixture was quenched with sat. NH_4Cl-solution, extracted with Et_2O (3x20 mL), washed with brine (1x20 mL) and dried over Na_2SO_4. After evaporation of solvents, the crude compound was purified via flash-chromatography (silica).

6.2 Preparation of 1,1-dichloro-2-alkynes

1,1-Dichloro-2-alkynes **10a-e** were prepared from the corresponding aldehydes according to a known literature procedure.[174] The following procedure for the preparation of 1,1-dichlorononon-2-yne (**10c**) is representative.

Preparation of 1,1-dichlorononon-2-yne (67c):



[174] K. N. Shavrin, I. V. Krylova, I. B. Shvedova, G. P. Okonnishnikova, I. E. Dolgy, O. M. Nefedov, *J. Chem. Soc., Perkin Trans. 2* **1991**, 1875-1881.

A dry, argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and septum was charged with THF (40 mL) and 1-octyne (5.04 g, 45.7 mmol). The solution was cooled to -20 °C and *n*BuLi (21.1 mL, 48.0 mmol, 2.27 M in hexane) was added dropwise. The reaction mixture was stirred for 1 h at -20 °C followed by the addition of DMF (6.58 g, 90.0 mmol). Then, the reaction mixture was allowed to warm to room temperature overnight. After an aqueous workup using a saturated NH_4Cl-solution (30 mL), the aqueous phase was extracted with Et_2O (3x50 mL), washed with brine (30 mL) and dried over Na_2SO_4. The crude product obtained was dissolved in dry CH_2Cl_2 (100 mL) and cooled to -20 °C. Then, PCl_5 (9.40 g, 45.0 mmol) was added portion wise and the reaction mixture was stirred for 3.5 h at this temperature. It was quenched by the addition of solid $NaHCO_3$ (19.3 g, 230 mmol) at -20 °C and was allowed to warm to 25 °C within 12 h. After filtration and evaporation of solvents, careful distillation afforded **10c** as a colorless liquid (5.33 g, 60 %, 3.30 mbar, 82 °C).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.27 (t, *J* = 2.0 Hz, 1 H), 2.32 (td, *J* = 7.2 and 2.0 Hz, 2 H), 1.61–1.49 (m, 2 H), 1.48–1.21 (m, 6 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 92.5, 76.3, 56.0, 31.2, 28.4, 27.8, 22.5, 18.9, 14.0.

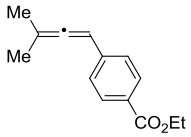
MS (EI, 70 eV): *m/z* (%) = 163 (M^+-C_2H_5, 2), 122 (45), 91 (48), 79 (61), 69 (65), 55 (54), 43 (89), 41 (100).

HRMS *m/z*: calc. for $C_7H_9Cl_2$ 163.0081[M^+-C_2H_5], found 163.0084.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2956 (m), 2930 (s), 2860 (m), 2322 (vw), 2238 (m), 1752 (vw), 1690 (vw), 1466 (w), 1458 (w), 1428 (w), 1380 (w), 1328 (w), 1252 (m), 1198 (w), 1158 (w), 1030 (vw), 958 (vw), 814 (w), 780 (w), 718 (vs), 684 (m).

6.3 Preparation of Substituted Allenes Starting from Bromoallenes

Preparation of 1-[4-(ethoxycarbonyl)phenyl]-3-methyl-1,2-butadiene (62a):



According to **GP1** the *Grignard* reagent was prepared by mixing ethyl 4-iodobenzoate (552 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at -30 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane:Et_2O 10:1) yielded **62a** (346 mg, 80 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.96 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 6.03 (spt, *J* = 2.9 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 1.84 (d, *J* = 3.0 Hz, 6 H), 1.40 (t, *J* = 7.11 Hz, 3 H).

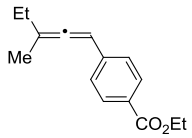
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.4, 166.5, 141.0, 129.8, 128.2, 126.4, 99.6, 92.4, 60.7, 20.0, 14.3.

MS (EI, 70 eV): *m/z* (%) = 216 (M^+, 77), 171 (36), 143 (100), 129 (25), 128 (87).

HRMS *m/z*: calc. for $C_{14}H_{16}O_2$ 216.1150, found 216.1131.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2981 (w), 1712 (s), 1606 (m), 1366 (m), 1268 (vs), 1172 (s), 1097 (vs), 1019 (m), 864 (m).

Preparation of 1-[4-(ethoxycarbonyl)phenyl]-3-methyl-1,2-pentadiene (62b):



According to **GP1** the *Grignard* reagent was prepared by mixing ethyl 4-iodobenzoate (552 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at -30 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-pentadiene (**60b**, 386 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane:Et_2O 10:1) yielded **62b** (410 mg, 89 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.97 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 6.13 (sxt, *J* = 3.0 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 2.19–2.05 (m, 2 H), 1.84 (d, *J* = 2.7 Hz, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.07 (t, *J* = 7.5 Hz, 3 H).

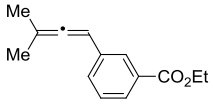
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 203.7, 166.5, 141.1, 129.8, 128.2, 126.2, 106.0, 94.1, 60.7, 27.1, 18.5, 14.3, 12.2.

MS (EI, 70 eV): *m/z* (%) = 230 (M^+, 71), 157 (100), 142 (96), 129 (59), 128 (70).

HRMS *m/z*: calc. for $C_{15}H_{18}O_2$ 230.1307, found 230.1303.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2968 (w), 1712 (s), 1606 (m), 1366 (w), 1268 (vs), 1172 (m), 1097 (s), 1018 (m), 864 (m), 760 (m), 696 (m).

Preparation of 1-[3-(ethoxycarbonyl)phenyl]-3-methyl-1,2-butadiene (62c):



According to **GP1** the *Grignard* reagent was prepared by mixing ethyl 3-iodobenzoate (552 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at -30 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane:Et_2O 10:1) yielded **62c** (328 mg, 76 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.92 (t, *J* = 1.8 Hz, 1 H), 7.85 (dt, *J* = 7.6 and 1.6 Hz, 1 H), 7.49-7.42 (m, 1 H), 7.35 (t, *J* = 7.7 Hz, 1 H), 6.04 (spt, *J* = 2.9 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 1.84 (d, *J* = 2.9 Hz, 6 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

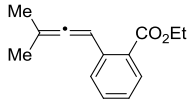
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 203.4, 166.6, 136.5, 132.7, 130.8, 128.4, 127.7, 127.4, 99.7, 91.9, 60.9, 20.2, 14.3.

MS (EI, 70 eV): *m/z* (%) = 216 (M^+, 76), 171 (45), 143 (86), 129 (36), 128 (100).

HRMS *m/z*: calc. for $C_{14}H_{16}O_2$ 216.1150, found 216.1140.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982 (w), 1715 (vs), 1444 (w), 1367 (m), 1277 (vs), 1188 (vs), 1104 (s), 1080 (s), 1022 (s), 749 (s).

Preparation of 1-[2-(ethoxycarbonyl)phenyl]-3-methyl-1,2-butadiene (62d):



According to **GP1** the *Grignard* reagent was prepared by mixing ethyl 2-iodobenzoate (552 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at -30 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane:Et_2O 20:1) yielded **62d** (366 mg, 85 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.84-7.81 (m, 1 H), 7.52-7.50 (m, 1 H), 7.41-7.36 (m, 1 H), 7.21-7.16 (m, 1 H), 6.97 (spt, *J* = 2.9 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 1.84 (d, *J* = 2.9 Hz, 6 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

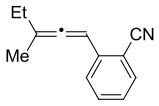
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.6, 167.6, 137.0, 131.5, 130.4, 128.4, 128.1, 125.9, 98.6, 90.3, 60.9, 20.1, 14.3.

MS (EI, 70 eV): *m/z* (%) = 216 (M^+, 37), 188 (31), 187 (100), 169 (27), 115 (23).

HRMS *m/z*: calc. for $C_{14}H_{16}O_2$ 216.1150, found 216.1134.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2981 (w), 1907 (w), 1712 (vs), 1445 (w), 1292 (m), 1250 (vs), 1128 (s), 1074 (vs), 1005 (m), 744 (s).

Preparation of 1-[2-cyanophenyl]-3-methyl-1,2-pentadiene (62e):



According to **GP1** the *Grignard* reagent was prepared by mixing 2-iodobenzonitrile (1.15 g, 5.00 mmol) in THF (2.00 mL) and *i*PrMgCl·LiCl (5.10 mL, 6.00 mmol) at 0 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.50 mL, 0.50 mmol) and 1-bromo-3-methyl-1,2-pentadiene (**60b**, 966 mg, 6.00 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane:CH_2Cl_2 2:1) yielded **62e**(839 mg, 92 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.58 (d, *J* = 7.9 Hz, 1 H), 7.50-7.45 (m, 2 H), 7.27-7.17 (m, 1 H), 6.45 (sxt, *J* = 3.0 Hz, 1 H), 2.20-2.05 (m, 2 H), 1.85 (d, *J* = 3.0 Hz, 3 H), 1.07 (t, *J* = 7.4 Hz, 3 H),

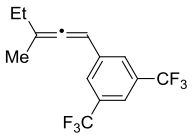
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.2, 140.0, 133.0, 132.4, 127.0, 126.4, 117.9, 109.7, 107.1, 91.6, 27.0, 18.5, 12.1.

MS (EI, 70 eV): *m/z* (%) = 183 (M^+, 67), 182 (57), 168 (100), 167 (38), 154 (42).

HRMS *m/z*: calc. for $C_{13}H_{13}N$ 183.1048, found 183.1035.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2967 (m), 2222 (m), 1949 (m), 1598 (w), 1487 (m), 1447 (m), 1291 (m), 1150 (w), 819 (s), 756 (vs).

Preparation of 1-[3,5-bis(trifluoromethyl)phenyl]-3-methyl-1,2-pentadiene (62f):



According to **GP1** the *Grignard* reagent was prepared by mixing 1-bromo-3,5-bis(trifluoromethyl)benzene (1.46 g, 5.00 mmol) in THF (2.00 mL) and *i*PrMgCl·LiCl (5.10 mL, 6.00 mmol) at 0 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.50 mL, 0.50 mmol) and 1-bromo-3-methyl-1,2-pentadiene (**60b**, 966 mg, 6.00 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane) yielded **62f** (1.307 g, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.66 (s, 3 H), 6.16 (sxt, *J* = 3.0 Hz, 1 H), 2.20-2.05 (m, 2 H), 1.87 (d, *J* = 3.0 Hz, 3 H), 1.07 (t, *J* = 7.4 Hz, 3 H).

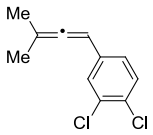
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 203.5, 138.9, 131.7 (q, *J* = 32.2 Hz), 126.1-125.9 (m), 123.4 (q, *J* = 272.6 Hz), 119.8 (q, *J* = 3.0 Hz), 107.6, 92.9, 27.0, 18.5, 12.2.

MS (EI, 70 eV): *m/z* (%) = 294 (M^+, 75), 279 (100),57 (71), 43 (56), 40 (56).

HRMS *m/z*: calc. for $C_{14}H_{12}F_6$ 294.0843, found 294.0833.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2972 (w), 1406 (w), 1360 (m), 1274 (vs), 1168 (s), 1125 (vs), 1106 (s), 892 (m), 846 (m), 681 (m).

Preparation of 1-(3,4-dichlorophenyl)-3-methyl-1,2-butadiene (62g):



According to **GP1** the *Grignard* reagent was prepared by mixing 1-bromo-3,4-dichlorobenzene (452 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at 25 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane) yielded **62g** (287 mg, 67 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.34 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 2.4 Hz, 1 H), 7.07 (dd, *J* = 8.3 and 1.9 Hz, 1 H), 5.90 (spt, *J* = 2.9 Hz, 1 H), 1.84 (d, *J* = 2.9 Hz, 6 H),

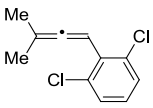
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 203.6, 136.4, 132.5, 130.3, 128.8, 128.1, 125.8, 100.2, 91.0, 20.1.

MS (EI, 70 eV): *m/z* (%) = 212 (M^+, 73), 177 (67), 162 (100), 142 (97), 141 (52).

HRMS *m/z*: calc. for $C_{11}H_{10}C_{l2}$ 212.0160, found 212.0155.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2908 (w), 1955 (w), 1588 (w), 1473 (s), 1457 (m), 1217 (m), 1130 (s), 1028 (s), 881 (s), 827 (vs), 694 (m).

Preparation of 1-(2,6-dichlorophenyl)-3-methyl-1,2-butadiene (62h):



According to **GP1** the *Grignard* reagent was prepared by mixing 1-bromo-2,6-dichlorobenzene (452 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at 25 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and

1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.4 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane) yielded **62h** (273 mg, 64 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.30 (d, *J* = 8.0 Hz, 2 H), 7.04 (dd, *J* = 8.1 and 7.7 Hz, 1 H), 6.30 (spt, *J* = 3.2 Hz, 1 H), 1.80 (d, *J* = 3.2 Hz, 6 H).

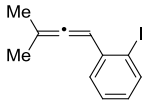
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 205.8, 134.3, 131.7, 128.5, 127.2, 97.5, 86.3, 20.1.

MS (EI, 70 eV): *m/z* (%) = 212 (M^+, 44), 162 (46), 142 (100), 141 (70), 44 (64).

HRMS *m/z*: calc. for $C_{11}H_{10}Cl_2$ 212.0160, found 212.0154.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2910 (w), 1962 (w), 1556 (m), 1434 (s), 1182 (m), 1089 (w), 803 (s), 769 (vs), 750 (s).

Preparation of 1-(2-iodophenyl)-3-methyl-1,2-butadiene (62i):



According to **GP1** the *Grignard* reagent was prepared by mixing 1,2-diiodobenzene (660 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at -78 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane) yielded **62i** (452 mg, 84 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.80 (dd, *J* = 8.0 and 1.2 Hz, 1 H), 7.39 (dd, *J* = 7.8 and 1.9 Hz, 1 H), 7.30–7.24 (m, 1 H), 6.90–6.84 (m, 1 H), 6.33 (spt, *J* = 2.9 Hz, 1 H), 1.83 (s, *J* = 2.9 Hz, 6 H).

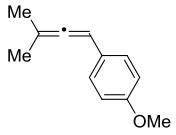
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.3, 139.5, 138.3, 128.1, 127.9, 127.9, 99.4, 99.4, 98.2, 96.7, 20.2.

MS (EI, 70 eV): *m/z* (%) = 269 (M^+, 70), 128 (100), 71 (38), 57 (59), 44 (80).

HRMS *m/z*: calc. for $C_{11}H_{11}I$ 269.9905, found 269.9884.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2904 (w), 1952 (w), 1470 (m), 1433 (m), 1273 (w), 1007 (s), 807 (m), 742 (vs), 655 (m).

Preparation of 1-(4-methoxyphenyl)-3-methyl-1,2-butadiene (62j):



According to **GP1** the *Grignard* reagent was prepared by mixing 4-iodoanisole (468 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at 25 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane:CH_2Cl_2 4:1) yielded **62j** (236 mg, 69 %).

^{1}H-NMR (300 MHz, DMSO-d6) δ (ppm) = 7.16 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.04 (quint, *J* = 2.9 Hz, 1 H), 3.72 (s, 3H), 1.77 (d, *J* = 2.9 Hz, 6 H),

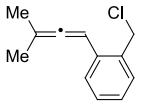
^{13}C-NMR (75 MHz, DMSO-d6) δ (ppm) = 201.7, 158.1, 127.49, 127.47, 114.1, 98.5, 91.9, 55.0, 20.2.

MS (EI, 70 eV): *m/z* (%) = 174 (M^+, 100), 159 (93), 144 (35), 128 (21), 115 (22).

HRMS *m/z*: calc. for $C_{12}H_{14}O$ 174.1045, found 174.1043

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2908 (w), 1714 (w), 1608 (m), 1509 (vs), 1295 (m), 1246 (vs), 1170 (s), 1033 (s), 839 (vs).

Preparation of 1-[2-(chloromethyl)phenyl]-3-methyl-1,2-butadiene (62k):



According to **GP1** the *Grignard* reagent was prepared by mixing 2-iodobenzyl chloride (505 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at -30 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (pentane) yielded **62k** (316 mg, 82 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.40 (dd, *J* = 7.8 and 1.2 Hz, 1 H), 7.32-7.28(m, 2 H), 7.21-7.16 (m, 1 H), 6.31 (sept, *J* = 2.92 Hz, 1 H), 4.69 (s, 2 H), 1.84 (d, *J* = 3.2 Hz, 6 H),

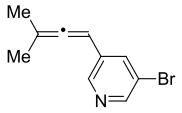
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.6, 134.7, 133.8, 130.3, 128.9, 128.3, 126.7, 98.7, 89.0, 44.5, 20.2.

MS (EI, 70 eV): *m/z* (%) = 192 (M^+, 2), 143 (100), 141 (47), 128 (43), 115 (31).

HRMS *m/z*: calc. for $C_{12}H_{13}Cl$ 192.0706, found 192.0686.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2908 (w), 1954 (w), 1490 (m), 1449 (m), 1262 (m), 813 (m), 763 (s), 736 (s), 668 (vs).

Preparation of 1-(3-bromopyridin-5-yl)-3-methyl-1,2-butadiene (62l):



According to **GP1** the *Grignard* reagent was prepared by mixing 3,5-dibromopyridine (474 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at 0 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl solution in THF (0.20 mL, 0.20 mmol) and 1-bromo-3-methyl-1,2-butadiene (**60a**, 353 mg, 2.40 mmol). Purification of the crude residue obtained after evaporation of the solvents by flash-chromatography (silica, pentane:Et2O 4:1) yielded **62l** (389 mg, 87 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.45 (d, *J* = 2.2 Hz, 1 H), 8.38 (d, *J* = 1.9 Hz, 1 H), 7.69 (t, *J* = 2.1 Hz, 1 H), 5.92 (sept, *J* = 2.9 Hz, 1 H), 1.84 (d, *J* = 2.8 Hz, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.2, 148.2, 146.1, 135.7, 133.8, 120.8, 100.7, 88.3, 20.0.

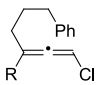
MS (EI, 70 eV): *m/z* (%) = 225 (74), 222 (M^+, 76), 144 (100), 143 (77), 129 (93).

HRMS *m/z*: calc. for $C_{10}H_{10}NBr$ 222.9997, found 222.9981.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2910 (w), 1955 (w), 1575 (m), 1430 (s), 1372 (m), 1093 (s), 1016 (s), 879 (vs), 697 (vs), 681 (vs).

6.4 Preparation of Substituted Chloroallenes

Preparation of (6-chloro-4-methylhexa-4,5-dien-1-yl)benzene (64a):



According to **GP2**, zinc reagent **68a,** prepared via transmetalation of 3-phenylpropylmagnesium bromide (1.37 mL, 1.00 mmol, 0.73 M in THF) with $ZnCl_2$ (1.00 mL, 1.00 mmol, 1.00 M in THF), was mixed with CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorobut-2-yne (**67a**) (148 mg, 1.20 mmol) was added. After 1 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane) furnished **64a** as a colorless liquid (186 mg, 0.90 mmol, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37–7.11 (m, 5 H), 6.02 (s, 1 H), 2.80–2.56 (m, 2 H), 2.19–2.06 (m, 2 H), 1.94-1.61 (m, 5 H).

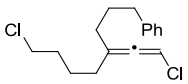
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.0, 142.0, 128.5, 128.3, 125.8, 112.1, 87.5, 35.1, 33.6, 28.8, 19.6.

MS (EI, 70 eV): *m/z* (%) = 206 (M^+, >1), 171 (9), 129 (6), 105 (11), 104 (100), 91 (26), 77 (9).

HRMS *m/z*: calc. for $C_{13}H_{15}Cl$ 206.0862, found 206.0841.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3086 (w), 3062 (w), 3026 (w), 2986 (w), 2932 (m), 2858 (m), 1960 (m), 1604 (w), 1496 (m), 1452 (m), 1368 (w), 1202 (m), 1080 (w), 1030 (w), 908 (vw), 864 (vw), 738 (s), 716 (m), 696 (vs).

Preparation of ([8-chloro-4-(2-chloroethenylidene)octyl] benzene (64b):



According to **GP2**, zinc reagent **68a** prepared via transmetalation of 3-phenylpropylmagnesium bromide (6.90 mL, 5.40 mmol, 0.78 M in THF) with $ZnCl_2$ (5.90 mL, 5.90 mmol, 1.00 M in THF), was mixed with CuCN·2LiCl (1.10 mL, 1.10 mmol, 1.00 M in THF) at -20 °C and 1,1,7-trichlorohept-2-yne (**67b**) (1.18 g, 5.90 mmol) was added. After 0.5 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane) furnished **64b** as a colorless liquid (1.12 g, 3.96 mmol, 66 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.36–7.25 (m, 2 H), 7.25–7.19 (m, 3 H), 6.10 (quint, *J* = 2.2 Hz, 1 H), 3.56 (t, *J* = 6.6 Hz, 2 H), 2.67 (td, *J* = 7.7 and 3.0 Hz, 2 H), 2.12 (td, *J* = 7.3 and 2.1 Hz, 4 H), 1.92–1.73 (m, 4 H), 1.70–1.53 (m, 2 H).

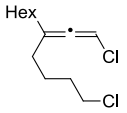
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 198.6, 142.0, 128.5, 128.3, 125.8, 116.3, 89.5, 44.7, 35.2, 32.4, 32.3, 31.9, 28.8, 24.4.

MS (EI, 70 eV): *m/z* (%) = 282 (M^+, >1), 247 (6), 192 (3), 143 (3), 105 (8), 104 (100), 102 (5), 91 (10).

HRMS *m/z*: calc. for $C_{16}H_{20}Cl_2$ 282.0942, found 282.0949.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3084 (vw), 3062 (w), 3026 (w), 3000 (w), 2936 (s), 2860 (m), 1956 (m), 1604 (w), 1496 (m), 1454 (m), 1310 (w), 1300 (w), 1206 (w), 1078 (vw), 1030 (w), 790 (w), 742 (s), 698 (vs), 650 (w).

Preparation of 1-chloro-5-(2-chloroethenylidene)undecane (64c):



According to **GP2**, zinc reagent **68b** (21.4 mL, 18.0 mmol, 0.84 M in THF) was mixed with CuCN·2LiCl (18.0 mL, 18.0 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorononon-2-yne (**67c**) (3.86 g, 20.0 mmol) was added. After 0.5 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane) furnished **64c** as a colorless liquid (4.09 g, 16.4 mmol, 91 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.04 (quint, *J* = 2.2 Hz, 1 H), 3.56 (t, *J* = 6.6 Hz, 2 H), 2.16–2.00 (m, 4 H), 1.92-1.73 (m, 2 H), 1.71–1.54 (m, 2 H), 1.54–1.17 (m, 8 H), 0.98–0.78 (m, 3 H).

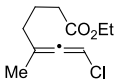
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 198.6, 116.7, 89.1, 44.8, 33.1, 32.2, 31.9, 31.6, 28.8, 27.1, 24.4, 22.6, 14.0.

MS (EI, 70 eV): *m/z* (%) = 248 (M^+, >1), 143 (25), 104 (30), 102 (100), 79 (19), 67 (19), 41 (23).

HRMS *m/z*: calc. for $C_{13}H_{22}Cl_2$ 248.1099, found 248.1077.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3056 (vw), 2954 (s), 2928 (vs), 2858 (s), 1958 (w), 1720 (vw), 1456 (w), 1378 (w), 1310 (w), 1206 (w), 722 (m), 652 (w).

Preparation of ethyl 7-chloro-5-methylhepta-5,6-dienoate (64d):



According to **GP2**, zinc reagent **68c** (1.40 mL, 1.50 mmol, 1.07 M in THF) was mixed with CuCN·2LiCl (0.30 mL, 0.30 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorobut-2-yne (**67a**) (209 mg, 1.70 mmol) was added. After 0.5 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 49:1) furnished **64d** as a colorless liquid (232 mg, 1.14 mmol, 76 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.01–5.94 (m, 1 H), 4.13 (t, *J* = 7.1 Hz, 2 H), 2.40–2.28 (m, 2 H), 2.14–2.06 (m, 2 H), 1.84–1.76 (m, 5 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

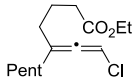
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.0, 173.3, 111.4, 87.6, 60.3, 33.5, 33.4, 22.3, 19.4, 14.2.

MS (EI, 70 eV): *m/z* (%) = 202 (M^+, 1), 167 (17), 157 (17), 128 (33), 121 (31), 93 (100), 91 (28), 79 (36), 77 (32), 65 (18), 51 (18).

HRMS *m/z*: calc. for $C_{10}H_{15}ClO_2$ 202.0761, found 202.0765.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982 (w), 2940 (w), 2362 (vw), 2338 (vw), 1962 (w), 1730 (vs), 1448 (w), 1372 (w), 1180 (m), 1028 (w), 744 (w), 716 (w).

Preparation of ethyl 5-(2-chloroethenylidene)decanoate (64e):



According to **GP2**, zinc reagent **68c** (24.4 mL, 10.0 mmol, 0.41 M in THF) was mixed with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorooct-2-yne (**67d**) (1.97 g, 11.0 mmol) was added. After 1.5 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 99:1) furnished **64e** as a colorless liquid (2.47 g, 9.58 mmol, 96 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.08–5.97 (m , 1 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 2.30 (t, *J* = 7.5 Hz, 2 H), 2.11–1.97 (m, 4 H), 1.73–1.57 (m, 2 H), 1.57–1.30 (m, 6 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

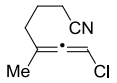
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 198.6, 173.7, 117.0, 88.8, 60.2, 35.2, 34.3, 32.8, 28.6, 26.8, 24.8, 20.5, 14.2, 13.7.

MS (EI, 70 eV): *m/z* (%) = 258 (M^+, 1), 169 (41), 135 (37), 128 (39), 93 (100), 91 (44), 79 (60).

HRMS *m/z*: calc. for $C_{14}H_{23}ClO_2$ 258.1387, found 258.1376.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958 (m), 2934 (m), 2862 (m), 1956 (w), 1732 (vs), 1462 (w), 1374 (w), 1250 (w), 1230 (w), 1178 (m), 1096 (w), 1034 (w), 858 (vw), 800 (vw), 732 (w), 716 (w).

Preparation of 7-chloro-5-methylhepta-5,6-dienenitrile (64f):



According to **GP2**, zinc reagent **68d** (1.76 mL, 1.50 mmol, 0.85 M in THF) was mixed with CuCN·2LiCl (0.30 mL, 0.30 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorobut-2-yne (**67a**) (209 mg, 1.70 mmol) was added. After 1.5 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 9:1) furnished **64f** as a light yellow liquid (178 mg, 1.14 mmol, 76 %).

^{1}H-NMR(600 MHz, $CDCl_3$) δ (ppm) = 6.05–6.01 (m, 1 H), 2.41 (td, *J* = 7.1 and 1.7 Hz, 2 H) 2.25–2.20 (m, 2 H), 1.87–1.80 (m, 5 H).

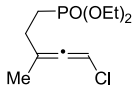
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm) = 198.8, 119.3, 110.3, 88.5, 32.6, 22.8, 19.5, 16.3.

MS (EI, 70 eV): *m/z* (%) = 155 (M^+, 6), 127 (39), 120 (82), 102 (97), 79 (100), 67 (45), 51 (44).

HRMS *m/z*: calc. for $C_8H_{10}ClN$ 155.0502, found 155.0487.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3058 (w), 2988 (w), 2944 (m), 2360 (vw), 2340 (vw), 2246 (m), 1962 (s), 1450 (m), 1426 (m), 1370 (w), 1348 (w), 1204 (m), 1150 (w), 976 (w), 960 (w), 788 (m), 738 (vs), 716 (vs).

Preparation of diethyl (5-chloro-3-methylpenta-3,4-dien-1-yl)phosphonate (64g):



According to **GP2**, zinc reagent **68e** (16.1 mL, 9.00 mmol, 0.56 M in THF) was mixed with CuCN·2LiCl (1.80 mL, 1.80 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorobut-2-yne (**67a**) (1.22 g, 9.90 mmol) was added. After 0.5 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, Et_2O) furnished **64g** as a yellow oil (1.79 g, 7.10 mmol, 79 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.09–5.96 (m, 1 H), 4.23–3.94 (m, 4 H), 2.44–2.20 (m, 2 H), 1.98–1.63 (m, 5 H), 1.38–1.21 (m, 6 H).

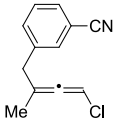
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 198.6, 112.0, 111.7, 88.9, 61.5, 27.0, 24.5, 22.7, 19.4, 16.4.

MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 12), 224 (15), 217 (32), 196 (20), 189 (23), 161 (100), 79 (45), 77 (14).

HRMS *m/z*: calc. for $C_{10}H_{18}ClO_3P$ 252.0682, found 252.0678.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3474 (vs), 3006 (m), 2350 (m), 2010 (m), 1974 (m), 1636 (s), 1398 (m), 1314 (m), 1216 (vs), 1012 (s), 974 (s), 874 (m), 812 (m), 754 (m), 724 (m).

Preparation of 3-(4-chloro-2-methylbuta-2,3-dien-1-yl) benzonitrile (64h):



According to **GP2**, zinc reagent **68f** (10.0 mL, 8.10 mmol, 0.81 M in THF) was mixed with CuCN·2LiCl (8.10 mL, 8.10 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorobut-2-yne (**67a**) (1.09 g, 8.90 mmol) was added. After 1 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 9:1) furnished **64h** as a colorless liquid (1.09 g, 5.34 mmol, 66 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.63–7.34 (m, 4 H), 5.93 (sxt, *J* = 2.1 Hz, 1 H), 3.41 (s, 2 H), 1.81 (d, *J* = 2.1 Hz, 3 H).

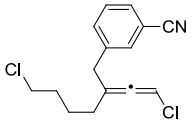
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.4, 139.4, 133.5, 132.4, 130.4, 129.2, 118.7, 112.4, 110.3, 88.1, 40.6, 18.9.

MS (EI, 70 eV): *m/z* (%) = 203 (M^+, 5), 168 (100), 167 (34), 153 (52), 141 (25), 117 (9), 116 (43), 89 (22), 51 (22).

HRMS *m/z*: calc. for $C_{12}H_{10}ClN$ 203.0502, found 203.0495.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3052 (m), 2994 (m), 2950 (m), 2918 (m), 2226 (vs), 1960 (s), 1582 (w), 1484 (m), 1438 (m), 1372 (m), 1304 (w), 1238 (m), 1192 (m), 1178 (m), 1142 (m), 1096 (w), 982 (w), 896 (m), 808 (m), 780 (m), 764 (m), 714 (s), 686 (vs).

Preparation of 3-[6-chloro-2-(2-chloroethenylidene)hexyl] benzonitrile (64i):



According to **GP2**, zinc reagent **68f** (17.0 mL, 12.7 mmol, 0.75 M in THF) was mixed with CuCN·2LiCl (13.0 mL, 13.0 mmol, 1.00 M in THF) at -20 °C and 1,1,7-trichlorohept-2-yne (**67b**) (2.79 g, 14.0 mmol) was added. After 1 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 9:1) furnished **64i** as a colorless liquid (3.10 g, 11.1 mmol, 87 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.62–7.35 (m, 4 H), 6.02 (t, *J* = 2.0 Hz, 1 H), 3.53 (t, *J* = 6.5 Hz, 2 H), 3.43 (s, 2 H), 2.10 (t, *J* = 7.3 and 2.1 Hz, 2 H), 1.79 (m, 2 H), 1.63 (m, 2 H).

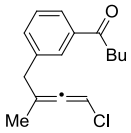
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.1, 139.4, 133.5, 132.4, 130.5, 129.2, 118.7, 114.7, 112.5, 90.2, 44.6, 39.5, 31.7, 31.6, 24.3.

MS (EI, 70 eV): *m/z* (%) = 279 (M^+, 2), 203 (41), 189 (18), 188 (100), 168 (59), 154 (39), 116 (41).

HRMS *m/z*: calc. for $C_{15}H_{15}Cl_2N$ 279.0582, found 279.0577.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3058 (w), 2942 (m), 2866 (w), 2362 (vw), 2230 (s), 1960 (m), 1736 (vw), 1602 (w), 1582 (w), 1482 (m), 1434 (m), 1374 (w), 1300 (w), 1212 (w), 1094 (w), 982 (vw), 896 (w), 810 (m), 790 (m), 744 (m), 718 (vs), 688 (s).

Preparation of 1-[3-(4-chloro-2-methylbuta-2,3-dien-1-yl) phenyl]pentan-1-one (64j):



According to **GP2**, zinc reagent **68g** (17.9 mL, 10.0 mmol, 0.56 M in THF) was mixed with CuCN·2LiCl (10.0 mL, 10.0 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorobut-2-yne (**67a**) (1.33 g, 11.0 mmol) was added. After 0.5 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 95:5) furnished **64j** as a yellow oil (1.07 g, 4.10 mmol, 41 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.89–7.74 (m, 2 H), 7.44–7.35 (m, 2 H), 5.93 (sxt, *J* = 2.0 Hz, 1 H), 3.44 (s, 2 H), 3.03–2.90 (m, 2 H), 1.81 (d, *J* = 2.2 Hz, 3 H), 1.78–1.66 (m, 2 H), 1.549-1.35 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

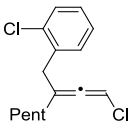
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.5, 200.2, 138.4, 137.3, 133.4, 128.6, 128.5, 126.5, 111.0, 87.6, 41.1, 38.4, 26.4, 22.4, 18.9, 13.9.

MS (EI, 70 eV): *m/z* (%) = 262 (M^+, 5), 227 (100), 205 (29), 142 (29), 85 (61), 57 (57).

HRMS *m/z*: calc. for $C_{16}H_{19}ClO$ 262.1124, found 262.1119.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958 (m), 2932 (m), 2872 (m), 1964 (vw), 1720 (m), 1682 (vs), 1602 (m), 1584 (w), 1440 (m), 1408 (w), 1378 (m), 1262 (m), 1164 (m), 1108 (m), 1036 (w), 940 (w), 914 (w), 788 (w), 752 (w), 696 (m).

Preparation of 1-chloro-3-[2-(2-chloroethenylidene)hexyl] benzene (64k):



According to **GP2**, zinc reagent **68h** (26.0 mL, 20.0 mmol, 0.76 M in THF) was mixed with CuCN·2LiCl (6.00 mL, 6.00 mmol, 1.00 M in THF) at -20 °C and 1,1-dichlorooct-2-yne (**67d**) (3.94 g, 22.0 mmol) was added. After 1 h at -20 °C, standard workup and purification of the crude product via flash-chromatography (pentane) furnished **64k** as a colorless liquid (4.78 g, 17.8 mmol, 89 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.49–7.31 (m, 1 H), 7.30–7.13 (m, 3 H), 5.93 (quint, *J* = 2.1 Hz, 1 H), 3.54 (d, *J* = 1.5 Hz, 2 H), 2.11 (td, *J* = 7.4 and 2.1 Hz, 2 H), 1.62–1.42 (m, 2 H), 1.42–1.21 (m, 4 H), 0.98–0.73 (m, 3 H).

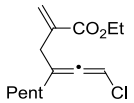
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.8, 136.0, 134.3, 131.0, 129.4, 128.0, 126.7, 115.4, 89.3, 37.3, 32.5, 31.2, 26.8, 22.4, 14.0.

MS (EI, 70 eV): *m/z* (%) = 268 (M^+, 2), 179 (36), 177 (95), 163 (34), 142 (38), 127 (34), 125 (100).

HRMS *m/z*: calc. for $C_{15}H_{18}Cl_2$ 268.0786, found 268.0780.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060 (w), 2956 (s), 2928 (vs), 2872 (m), 2858 (m), 1962 (w), 1474 (m), 1444 (m), 1378 (w), 1208 (w), 1126 (w), 1052 (m), 1038 (m), 802 (w), 748 (s), 728 (vs), 682 (m).

Preparation of ethyl 4-(2-chloroethenylidene)-2-methylidenenonanoate (64l):



According to **GP2**, zinc reagent **68i** (12.0 mL, 10.0 mmol, 0.83 M in THF) was mixed with CuCN·2LiCl (10.0 mL, 10.0 mmol, 1.00 M in THF) at -50 °C and 1,1-dichlorooct-2-yne (**67d**) (1.97 g, 11.0 mmol) was added. After 12 h at -50 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 95:5) furnished **64l** as a yellow liquid (1.80 g, 7.03 mmol, 70 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.25 (d, *J* = 1.2 Hz, 1 H), 6.01 (quint, *J* = 2.2 Hz, 1 H), 5.60 (q, *J* = 1.2 Hz, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 3.15-3.02 (m, 2 H), 2.09 (td, *J* = 7.4 and 2.2 Hz, 2 H), 1.55-1.41 (m, 2 H), 1.40–1.24 (m, 7 H), 0.90 (t, *J* = 6.9 Hz, 3 H).

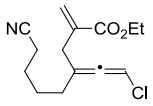
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.4, 166.6, 137.4, 126.6, 115.2, 89.5, 60.8, 35.8, 32.7, 31.2, 26.8, 22.4, 14.2, 14.0.

MS (EI, 70 eV): *m/z* (%) = 256 (M^+, 23), 185 (36), 183 (100), 147 (12), 127 (14), 91 (13).

HRMS *m/z*: calc. for $C_{14}H_{21}ClO_2$ 256.1230, found 256.1220.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3058 (vw), 2958 (m), 2930 (m), 2860 (m), 1960 (w), 1716 (vs), 1634 (w), 1466 (w), 1368 (w), 1326 (w), 1300 (w), 1182 (m), 1144 (m), 1026 (w), 948 (w), 858 (vw), 808 (w), 726 (m).

Preparation of methyl 4-(2-chloroethenylidene)-8-cyano-2-methylideneoctanoate (64m):



According to **GP2**, zinc reagent **68i** (7.70 mL, 6.40 mmol, 0.83 M in THF) was mixed with CuCN·2LiCl (6.40 mL, 6.40 mmol, 1.00 M in THF) at -50 °C and 8,8-dichlorooct-6-ynenitrile (**67e**) (1.25 g, 7.10 mmol) was added. After 12 h at -50 °C, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 3:1) furnished **64m** as a yellow liquid (982 mg, 3.53 mmol, 50 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.26 (d, *J* = 1.5 Hz, 1 H), 6.05 (quint, *J* = 2.2 Hz, 1 H), 5.61 (d, *J*= 1 .0 Hz, 1 H), 4.22 (q, *J* = 7.3 Hz, 2 H), 3.18–3.00 (m, 2 H), 2.37 (t, *J* = 6.7 Hz, 2 H), 2.15 (td, *J* = 6.4 and 2.2 Hz, 2 H), 1.80–1.58 (m, 4 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.4, 166.4, 137.1, 126.9, 119.5, 114.0, 90.3, 60.9, 35.8, 31.7, 26.0, 24.6, 17.0, 14.2.

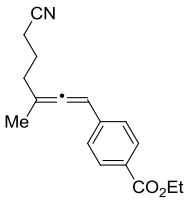
MS (EI, 70 eV): *m/z* (%) = 267 (M^+, 2), 232 (59), 204 (34), 186 (100), 158 (67), 117 (58), 91 (52).

HRMS *m/z*: calc. for $C_{14}H_{18}ClNO_2$ 267.1026, found 267.1017.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3058 (vw), 2982 (w), 2938 (w), 2246 (vw), 1960 (w), 1712 (vs), 1634 (w), 1428 (w), 1368 (w), 1300 (m), 1178 (m), 1142 (m), 1026 (w), 952 (w), 858 (vw), 810 (w), 724 (m).

6.5 Preparation of Polyfunctionalized Allenes Starting from Chloroallenes

Preparation of ethyl 4-(6-cyano-3-methylhexa-1,2-dien-1-yl)benzoate (62m):



According to **GP1** the *Grignard* reagent was prepared by mixing ethyl 4-iodobenzoate (552 g, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (1.60 mL, 2.10 mmol, 1.30 M in THF) at -20 °C for 30 min. The coupling reaction was performed after adding CuCN·2LiCl (0.20 mL, 0.20 mmol, 1 M in THF) at -20 °C followed by 7-chloro-5-methylhepta-5,6-dienenitrile (**64f**, 373 mg, 2.40 mmol). After 1 h at room temperature, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 7:3) furnished **62m** as a light yellow oil (444 mg, 1.65 mmol, 82 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.94 (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 6.14 (d, *J* = 2.8 Hz, 1 H), 4.34 (q, *J* = 7.11 Hz, 2 H), 2.41–2.29 (m, 2 H), 2.29–2.16 (m, 2 H), 1.89–1.74 (m, 5 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

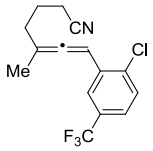
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 203.5, 166.4, 140.1, 129.9, 128.7, 126.3, 119.3, 102.6, 94.8, 60.8, 32.4, 23.2, 18.8, 16.6, 14.3.

MS (EI, 70 eV): *m/z* (%) = 269 (M^+, 15), 224 (30), 216 (27), 196 (81), 155 (27), 143 (100), 128 (42).

HRMS *m/z*: calc. for $C_{17}H_{19}NO_2$ 269.1416, found 269.1407.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982 (w), 2940 (w), 2906 (w), 2246 (vw), 1950 (vw), 1710 (vs), 1606 (m), 1446 (w), 1426 (w), 1392 (w), 1368 (w), 1272 (vs), 1174 (m), 1100 (s), 1018 (m), 868 (w), 762 (w), 698 (w).

Preparation of 7-[2-chloro-5-(trifluoromethyl)phenyl]-5-methylhepta-5,6-dienenitrile (62n):



According to **GP1** 2-chloro-4-(trifluoromethyl)phenylmagnesium bromide (2.60 mL, 2.00 mmol, 0.78 M in THF)[175] was mixed with CuCN·2LiCl (0.20 mL, 0.20 mmol, 1 M in THF) at -20 °C followed by 7-chloro-5-methylhepta-5,6-dienenitrile (**64g**, 373 mg, 2.40 mmol). After 1 h at room temperature, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 4:1) furnished **62n** as a light yellow oil (513 mg, 1.71 mmol, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.59 (d, *J* = 2.24 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.37 (dd, *J* = 8.2 and 2.1 Hz, 1 H), 6.58 (sxt, *J* = 3.0 Hz, 1 H), 2.41 (t, *J* = 7.11 Hz, 2 H), 2.38–2.22 (m, 2 H), 1.93–1.80 (m, 5 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 203.8, 135.4 (q, *J* = 2 Hz), 133.9, 130.4, 129.4 (q, *J* = 32 Hz), 124.7 (q, *J* = 4 Hz), 124.2 (q, *J* = 4 Hz), 123.7 (q, *J* = 272 Hz), 119.2, 103.4, 90.9, 32.4, 23.2, 18.6, 16.7.

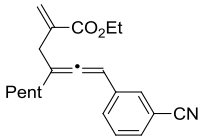
MS (EI, 70 eV): *m/z* (%) = 299 (M^+, 20), 264 (100), 246 (58), 231 (65), 211 (55), 193 (51).

[175] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192-7202.

HRMS *m/z*: calc. for $C_{15}H_{13}ClF_3N$ 299.0689, found 299.0689.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942 (w), 2922 (w), 1954 (vw), 1720 (w), 1610 (w), 1576 (vw), 1486 (w), 1414 (w), 1324 (vs), 1262 (m), 1230 (w), 1166 (m), 1122 (vs), 1080 (vs), 1044 (m), 904 (w), 822 (w), 752 (w), 720 (w), 704 (vw).

Preparation of ethyl 4-[2-(3-cyanophenyl)ethenylidene]-2-methylidenenonanoate (62o):



According to **GP1** the *Grignard* reagent was prepared by mixing 3-iodobenzonitrile (229 mg, 1.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (0.80 mL, 1.10 mmol, 1.28 M in THF) at -20 °C for 45 min. The coupling reaction was performed after adding CuCN·2LiCl (0.10 mL, 0.10 mmol, 1 M in THF) at -20 °C followed by ethyl 4-(2-chloroethenylidene)-2-methylidenenonanoate (**64l**, 229 mg, 1.10 mmol). After 1 h at room temperature, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 9:1) furnished **62o** as a yellow oil (215 mg, 0.67 mmol, 67 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.49 (t, *J* = 1.7 Hz, 1 H), 7.45–7.40 (m, 2 H), 7.38–7.31 (m, 1 H), 6.17 (d, *J* = 1.5 Hz, 1 H), 6.09 (quint, *J* = 2.9 Hz, 1 H), 5.59 (d, *J* = 1.2 Hz, 1H), 4.16–4.01 (m, 2 H), 3.11 (dd, *J* = 10.9 and 2.4 Hz, 2 H), 2.18–2.07 (m, 2 H), 1.55–1.39 (m, 2 H), 1.36–1.24 (m, 4 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 0.85 (t, *J* = 7.1 Hz, 3 H).

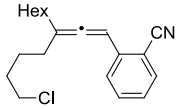
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 203.6, 166.5, 137.9, 137.1, 130.6, 129.7, 129.7, 129.1, 126.2, 118.8, 112.5, 108.4, 94.7, 60.6, 35.4, 32.3, 31.4, 27.1, 22.3, 14.0, 13.9.

MS (EI, 70 eV): *m/z* (%) = 323 (M^+, 25), 250 (100), 210 (41), 194 (80), 180 (77), 154 (75), 116 (47).

HRMS *m/z*: calc. for $C_{21}H_{25}NO_2$ 323.1885, found 323.1878.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958 (s), 2932 (s), 2872 (m), 2232 (w), 1956 (vw), 1726 (vs), 1602 (w), 1584 (w), 1466 (w), 1444 (w), 1434 (w), 1370 (m), 1296 (m), 1244 (m), 1180 (s), 1096 (m), 1020 (m), 924 (w), 860 (w), 802 (m), 754 (m), 688 (w).

Preparation of 2-[3-(4-chlorobutyl)nona-1,2-dien-1-yl]benzonitrile (62p):



According to **GP1** the *Grignard* reagent was prepared by mixing 2-iodobenzonitrile (1.60 g, 7.00 mmol) in THF (5.00 mL) and *i*PrMgCl·LiCl (5.60 mL, 7.40 mmol, 1.31 M in THF) at 0 °C for 30 min. The coupling reaction was performed after adding CuCN·2LiCl (0.70 mL, 0.70 mmol, 1.00 M in THF) at -20 °C followed by 1-chloro-5-(2-chloroethenylidene)undecane (**64c**, 1.91 g, 7.70 mmol). After 1 h at room temperature, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 99:1) furnished **62p** as a yellow liquid (1.68 g, 5.31 mmol, 76 %).

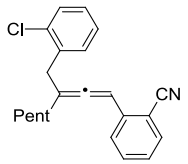
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.65 (d, *J* = 7.48, 1 H), 7.53 (s, 2 H), 7.37–7.21 (m, 1 H), 6.59 (d, *J* = 2.2 Hz, 1 H), 3.58 (t, *J* = 6.6 Hz, 2 H), 2.35–2.07 (m, 4 H), 1.98–1.81 (m, 2 H), 1.81–1.63 (m, 2 H), 1.63–1.47 (m, 2 H), 1.47–1.23 (m, 6 H), 0.92 (t, *J* = 6.0 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.0, 139.7, 133.0, 132.5, 126.8, 126.5, 117.9, 109.7, 109.7, 92.8, 44.7, 32.5, 32.2, 31.7, 31.6, 29.0, 27.4, 24.7, 22.6, 14.0.

MS (EI, 70 eV): *m/z* (%) = 315 (M^+, 24), 258 (57), 252 (53), 182 (42), 169 (100), 154 (85).

HRMS *m/z*: calc. for $C_{20}H_{26}ClN$ 315.1754, found 315.1756.

Preparation of 2-[3-(2-chlorobenzyl)octa-1,2-dien-1-yl]benzonitrile (62q):



According to **GP1** the *Grignard* reagent was prepared by mixing 2-iodobenzonitrile (2.29 g, 10.0 mmol) in THF (5.00 mL) and *i*PrMgCl·LiCl (8.02 mL, 10.5 mmol, 1.31 M in THF) at 0 °C for 1 h. The coupling reaction was performed after adding CuCN·2LiCl (1.00 mL, 1.00 mmol, 1.00 M in THF) at -20 °C followed by 1-chloro-3-[2-(2-chloroethenylidene)hexyl] benzene (**64k**, 3.23 g, 12.0 mmol). After 1 h at room temperature, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 95:5) furnished **62q** as a colorless liquid (2.37 g, 7.05 mmol, 71 %).

^{1}H-NMR (400 MHz, C_6D_6) δ (ppm) = 7.27 (dd, *J* = 8.1 and 0.6 Hz, 1 H), 7.13 (dd, *J* = 8.0 and 1.3 Hz, 1 H), 7.05 (dd, *J* = 7.6 and 1.6 Hz, 1 H), 6.99 (dd, *J* = 7.8 and 0.9 Hz, 1 H), 6.91 (td, *J* = 7.7 and 1.4 Hz, 1 H), 6.84 (td, *J* = 7.6 and 1.3 Hz, 1 H), 6.71 (td, *J* = 7.7 and 1.6 Hz, 1 H), 6.58 (quint, *J* = 2.97 Hz, 1 H), 6.53 (td, 7.6 and 1.2 Hz, 1 H), 3.50–3.35 (m, 2 H), 2.14–1.92 (m, 2 H), 1.52–1.31 (m, 2 H), 1.30–1.11 (m, 4 H), 0.99–0.71 (m, 3 H).

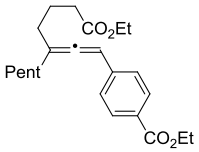
^{13}C-NMR (100 MHz, C_6D_6) δ (ppm) = 205.9, 139.6, 137.4, 134.9, 133.4, 132.4, 131.8, 130.0, 128.6, 127.6, 127.3, 127.0, 118.2, 111.0, 109.6, 93.9, 37.4, 32.8, 32.2, 27.8, 23.1, 14.6.

MS (EI, 70 eV): *m/z* (%) = 335 (M^+, 5), 278 (29), 266 (27), 265 (20), 264 (100), 210 (36).

HRMS *m/z*: calc. for $C_{22}H_{22}ClN$ 335.1441, found 335.1444.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3066 (w), 2956 (s), 2928 (s), 2858 (m), 1950 (w), 1724 (vw), 1596 (w), 1570 (w), 1488 (m), 1474 (m), 1444 (s), 1292 (w), 1210 (w), 1162 (w), 1124 (w), 1052 (m), 1038 (m), 952 (w), 912 (vw), 876 (vw), 812 (w), 750 (vs), 682 (m), 616 (w).

Preparation of ethyl 4-[3-(4-ethoxy-4-oxobutyl)octa-1,2-dien-1-yl]benzoate (62r):



According to **GP1** the *Grignard* reagent was prepared by mixing ethyl 4-iodobenzoate (552 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (1.60 mL, 2.10 mmol, 1.31 M in THF) at -20 °C for 30 min. The coupling reaction was performed after adding CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.00 M in THF) at -20 °C followed by ethyl 5-(2-chloroethenylidene)decanoate (**64e**, 620 mg, 2.40 mmol). After 1 h at room temperature, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 9:1) furnished **62r** as a colorless oil (622 mg, 1.67 mmol, 83 %).

^{1}H-NMR (400 MHz, C_6D_6) δ (ppm) = 8.16 (d, *J* = 8.5 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 6.08 (quint, *J* = 3.0 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 3.93 (q, *J* = 7.1 Hz, 2 H), 2.18 (t, *J* = 7.3 Hz, 2 H), 2.00–1.88 (m, 4 H), 1.83–1.73 (m, 2 H), 1.48–1.34 (m, 2 H), 1.24–1.17 (m, 4 H), 1.02 (t, *J* = 7.1 Hz, 3 H), 0.94 (t, *J* = 7.1 Hz, 3 H), 0.87–0.78 (m, 3 H).

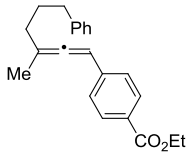
^{13}C-NMR (100 MHz, C_6D_6) δ (ppm) = 204.1, 173.0, 166.5, 141.4, 130.7, 129.7, 127.0, 109.1, 96.4, 61.0, 60.4, 34.2, 33.2, 32.5, 32.2, 28.0, 23.6, 23.2, 14.7, 14.6, 14.6.

MS (EI, 70 eV): *m/z* (%) = 372 (M^+, 5), 270 (65), 241 (100), 155 (52), 141 (63), 129 (61).

HRMS *m/z*: calc. for $C_{23}H_{32}O_4$ 372.2301, found 372.2292.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2980 (w), 2956 (m), 2930 (m), 2858 (w), 1946 (vw), 1732 (s), 1714 (vs), 1606 (m), 1446 (w), 1394 (w), 1368 (w), 1270 (vs), 1172 (m), 1098 (s), 1020 (m), 866 (w), 762 (w), 698 (w).

Preparation of ethyl 4-(3-methyl-6-phenylhexa-1,2-dien-1-yl)benzoate (62s):



According to **GP2**, the *Grignard* reagent was prepared by mixing ethyl 4-iodobenzoate (0.552 g, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (2.00 mL, 2.40 mmol) at -30 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.00 M in THF) and 1-chloro-3-methyl-6-phenyl-1,2-hexadiene (**64a**, 496 mg, 2.40 mmol). After 1 h at room temperature standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 10:1) furnished **62s** as a colorless liquid (427 mg, 1.33 mmol, 67 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.99 (d, *J* = 8.5 Hz, 2 H), 7.34 (d, *J* = 8.3 Hz, 2 H) 7.31–7.24 (m, 2 H) 7.23–7.12 (m, 3 H), 6.14 (sxt, *J* = 2. 9 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 2.67 (t, *J* = 7.8 Hz, 2 H), 2.21–2.12 (m, 2 H), 1.89–1.75 (m, 5 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

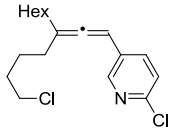
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 203.9, 166.5, 142.2, 140.9, 129.8, 128.4, 128.3, 128.3, 126.3, 125.7, 103.9, 93.9, 60.7, 35.5, 33.4, 29.2, 18.7, 14.3.

MS (EI, 70 eV): *m/z* (%) = 320 (M^+, 1), 216 (36), 143 (100), 129 (12), 128 (25), 91 (14).

HRMS *m/z*: calc. for $C_{22}H_{24}O_2$ 320.1776, found 320.1780.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2934 (w), 1712 (s), 1605 (m), 1269 (vs), 1172 (m), 1097 (s), 1018 (m), 865 (m), 746 (m), 696 (s).

Preparation of 2-chloro-5-(3-(4-chlorobutyl)nona-1,2-dien-1-yl)pyridine (62t):



According to **GP1** the *Grignard* reagent was prepared by mixing 5-bromo-2-chloropyridine (385 mg, 2.00 mmol) in THF (2.00 mL) and *i*PrMgCl·LiCl (1.70 mL, 2.10 mmol, 1.27 M in THF) at 0 °C for 1 h. The coupling reaction was performed after adding CuCN·2LiCl (0.20 mL, 0.20 mmol, 1 M in THF) at -20 °C followed by 1-chloro-5-(2-chloroethenylidene)undecane (**64c**, 598 mg, 2.40 mmol). After 1 h at room temperature, standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 9:1) furnished **62t** as a light yellow oil (498 mg, 1.53 mmol, 76 %).

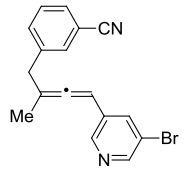
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.25 (d, *J* = 2.4 Hz, 1 H), 7.52 (dd, *J* = 8.3 and 2.5 Hz, 1 H), 7.24 (d, *J* = 8.2 Hz, 1 H), 6.10 (quint, *J* = 3.0 Hz, 1 H), 3.51 (t, *J* = 6.6 Hz, 2 H), 2.17–2.03 (m, 4 H), 1.87–1.75 (m, 2 H), 1.68–1.53 (m, 2 H), 1.52–1.17 (m, 8 H), 0.91–0.78 (m, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 203.0, 148.8, 147.3, 135.9, 131.0, 124.1, 109.6, 91.4, 44.7, 32.5, 32.2, 31.7, 31.6, 29.0, 27.5, 24.8, 22.6, 14.0.

MS (EI, 70 eV): *m/z* (%) = 325 (M^+, 3), 255 (36), 179 (62), 178 (40), 166 (30), 164 (100).

HRMS *m/z*: calc. for $C_{18}H_{25}Cl_2N$ 325.1364, found 325.1369.

Preparation of 3-[4-(5-bromopyridin-3-yl)-2-methylbuta-2,3-dien-1-yl]benzonitrile (62u):



According to **GP2**, the *Grignard* reagent was prepared by mixing 3,5-dibromopyridine (474 mg, 2.00 mmol) in THF (1.00 mL) and *i*PrMgCl·LiCl (1.62 mL, 2.10 mmol, 1.3 M in THF) at 0 °C for 1 h. The coupling reaction was done by using CuCN·2LiCl (0.20 mL, 0.20 mmol, 1 M in THF) and 3-(4-chloro-2-methylbuta-2,3-dien-1-yl) benzonitrile (**64h**, 369 mg, 1.80 mmol). After 1 h at room temperature standard workup and purification of the crude product via flash-chromatography (silica, pentane:Et_2O 1:1) furnished **62u** as a brown oil (413 mg, 1.27 mmol, 71 %).

^{1}H-NMR(200 MHz, $CDCl_3$) δ (ppm) = 8.47 (d, *J* = 2.0 Hz, 1 H), 8.34 (d, *J* = 1.8 Hz, 1 H), 7.63 (t, *J* = 2.0 Hz, 1 H), 7.56–7.34 (m, 4 H), 6.00 (sxt, 2.7 Hz, 1 H), 3.45 (t, *J* = 2.1 Hz, 2 H), 3.3 (d, *J* = 2.9 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 204.7, 148.4, 145.7, 140.0, 135.9, 133.3, 132.9, 132.3, 130.4, 129.2, 120.9, 118.7, 112.5, 104.2, 90.3, 40.2, 18.2.

MS (EI, 70 eV): *m/z* (%) = 324 (M^+, 18), 309 (100), 245 (36), 230 (33), 208 (41), 129 (55).

HRMS *m/z*: calc. for $C_{17}H_{13}BrN_2$ 324.0262, found 324.0629.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3036 (w), 2982 (w), 2914 (m), 2852 (w), 2228 (s), 1954 (w), 1708 (w), 1600 (w), 1576 (m), 1550 (w), 1482 (m), 1430 (s), 1378 (m), 1300 (w), 1224 (m), 1094 (s), 1016 (s), 880 (s), 862 (m), 800 (m), 770 (m), 682 (vs).

7 Preparation of Charge-Tagged Organozinc Reagents

7.1 General Considerations

Synthesis of starting materials. (*p*-iodophenyl)-trimethylammonium iodide (**72f**) and ammonium substituted alkyl iodides **72a-e** were prepared according to known literature procedures.[143]

ESI mass spectrometric experiments. Sample solutions were transferred into a gas-tight syringe and administered into the ESI source of a mass spectrometer at flow rates of approx. 5–30 μL min^{-1}. Most of the experiments were performed with a TSQ 7000 multistage mass spectrometer (Thermo MAT), which has been described in more detail before.[176] Nitrogen was used as sheath gas and ESI voltages ranging from 3.0 to 4.5 kV were applied. Relatively gentle ESI conditions were chosen, the heated capillary being held at 60–100 °C. The m/z ratios of the ions were then determined by scanning the first quadrupole mass filter. For the gas-phase fragmentation experiments, the first quadrupole mass filter was used to mass-select the ions of interest, which then passed an 18 cm long octopole ion guide filled with argon (Linde, 99.998% purity, p(Ar) = 0.6–0.9 mtorr as measured with a Convectron). The collision energy E_{LAB} was controlled by adjusting the voltage offset of the octopole. The m/z ratios of the fragment ions were then determined by scanning the second quadrupole mass filter before the ions reached the detector.

The experiments probing the cross-coupling reaction of [**Ar**I]$^+$ with benzylzinc bromide were performed with a HCT quadrupole ion trap (Bruker Daltonik). Nitrogen was used as sheath gas and an ESI voltage of 3.5 kV was applied. Standard ESI conditions were chosen with nitrogen heated to 60 °C employed as drying gas (5.0 L min^{-1}). The ions were then transferred into the instrument's three-dimensional quadrupole ion trap filled with helium (Air Liquide, 99.999% purity, estimated pressure p(He) ≈ 2 mtorr). The Compass 1.3 software package was used to eject the ions from the trap for their detection. Similar settings were also used for probing the charge-tagged intermediates formed in the reactions of [**Ar**I]$^+$ with $Pd(dba)_2$/tfp. In this case, fragmentation was achieved by subjecting the mass-selected ions to excitation voltages of amplitudes V_{exc} and allowing them to collide with He gas.

Synthesis of charge-tagged organozinc species and sample preparation. A flask was flame-dried under high vacuum and allowed to cool down under argon atmosphere. The procedure was repeated twice and Zn dust (1.4 mmol) and 1 mL of solvent (THF, freshly distilled from sodium benzophenone ketyl, or DMF, stored over molecular sieves) were added. The Zn metal was activated by the addition of 1,2-dibromoethane (4 μL) and TMSCl (4 μL) followed by a short boiling-up of the suspension. 0.7 equiv of **72f** or **72d**, respectively, was added and the resulting suspension was stirred for 14 h at room temperature or at 50 °C. Solid material remaining was allowed to settle down before an aliquot of the supernatant solution was diluted with the respective solvent.

[176] K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 100-110.

Sample preparation for *Negishi* cross-coupling experiments. A flame-dried flask was charged with [**Ar**I]$^{+}$I^{-} and CH_3CN (dried over molecular sieves) under argon atmosphere. To the resulting 2-mM solution were added BnZnBr or *m*-methylbenzylzinc bromide (1.2 or 2.0 equiv),[177] respectively, and $Pd(dba)_2$/2 tfp (0.05, 0.10, or 1.0 equiv) at −20 °C. After mixing, an aliquot of the undiluted solution was taken, warmed up to room temperature, and immediately analyzed by ESI mass spectrometry.

7.2 Additional Figures

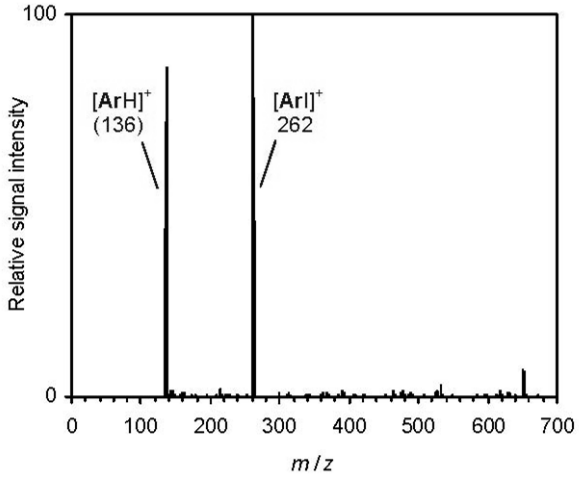


Figure 8: Positive ion mode ESI mass spectrum of an approx. 2 mM solution of the products (*m*/*z* ratios in brackets) formed upon reaction of Zn with (*p*-iodophenyl)-trimethylammonium iodide ([ArI]$^{+}$I^{-}) in THF at 50 °C measured with the TSQ 7000 instrument.

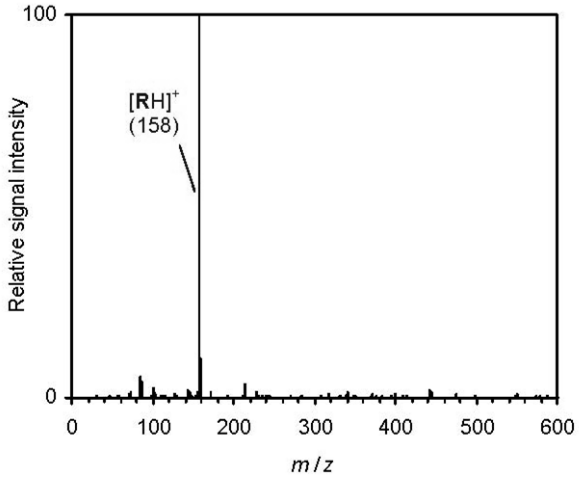


Figure 9: Positive ion mode ESI mass spectrum of an approx. 1 mM solution of the products (*m*/*z* ratios in brackets) formed upon reaction of Zn with triethyl-(4-iodobutyl)-ammonium iodide ([RI]$^{+}$I^{-}) in THF measured with the TSQ 7000 instrument.

[177]The organozinc reagents were prepared according to a procedure reported in the literature: S. C. Berk, M. C. P. Yeh, N. Jeong, P. Knochel, *Organometallics* **1990**, *9*, 3053.

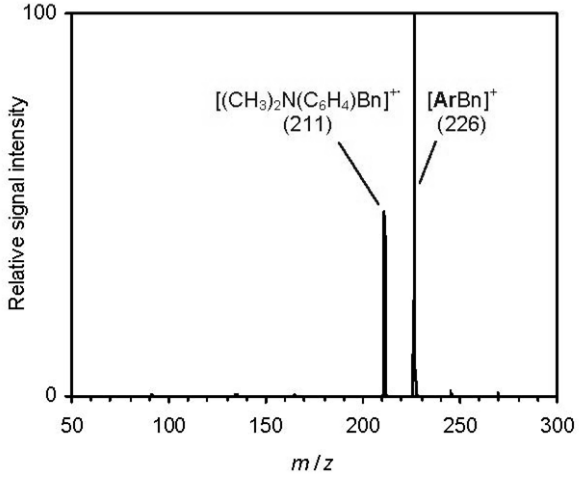


Figure 10: Mass spectrum of mass-selected $[ArBn]^+$ and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.40 V, HCT ion trap).

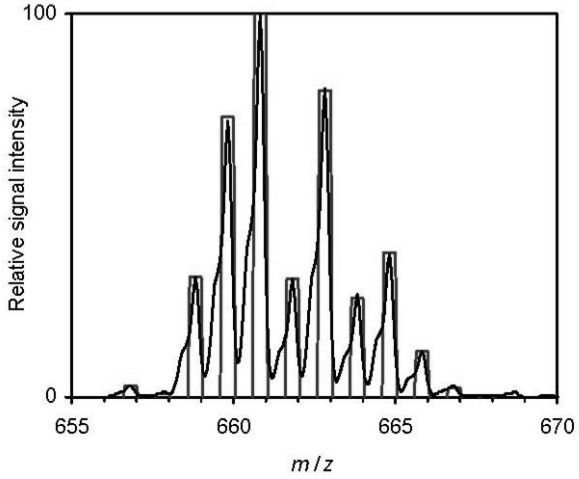


Figure 11: Isotope pattern of the complex $[L_2PdBn]^+$ with the elemental composition $C_{31}H_{25}O_6P_2Pd$ measured with the HCT ion trap (line) and simulated (bars, L = tri-(2-furyl)phosphine).

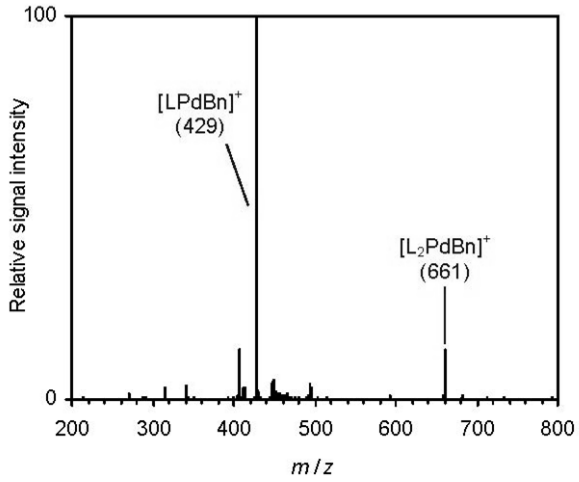


Figure 12: Mass spectrum of mass-selected $[L_2{}^{106}PdBn]^+$ (L = tri-(2-furyl)phosphine) and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.24 V, HCT ion trap).

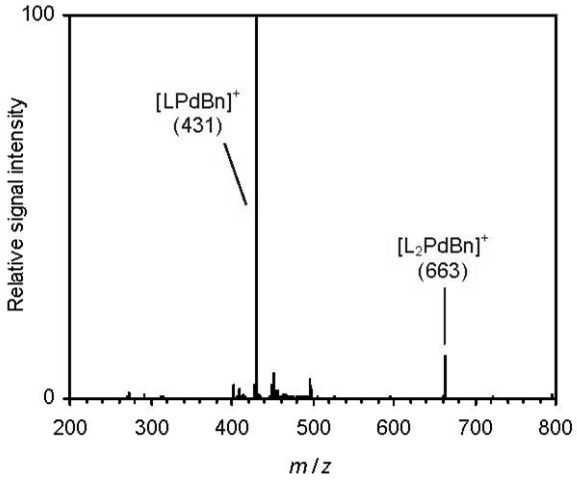


Figure 13: Mass spectrum of mass-selected $[L_2{}^{108}PdBn]^+$ (L = tri-(2-furyl)phosphine) and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.24 V, HCT ion trap).

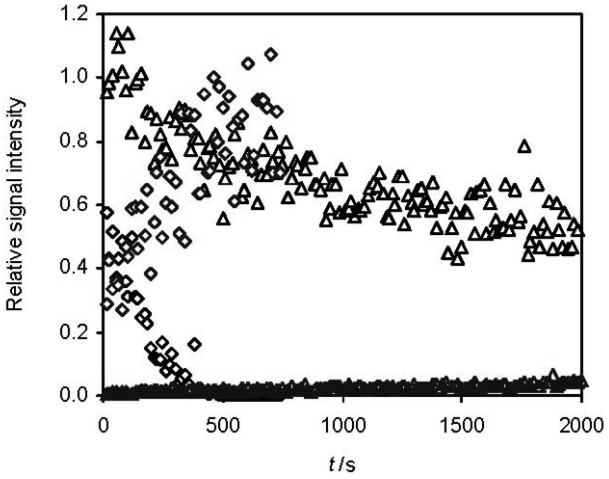


Figure 14: Time dependence of the relative signal intensities of reactant $[ArI]^+$ (m/z 262, increasing) and $[L_2{}^{106}PdBn]^+$ (m/z 661, descending) during the Pd-catalyzed cross-coupling reaction of $[ArI]^+I^-$ with BnZnBr in CH_3CN at room temperature as determined by ESI mass spectrometry. Results of two experiments with different catalyst loadings are shown (diamonds: 100 mol%, triangles: 5 mol% relative to $[ArI]^+$).

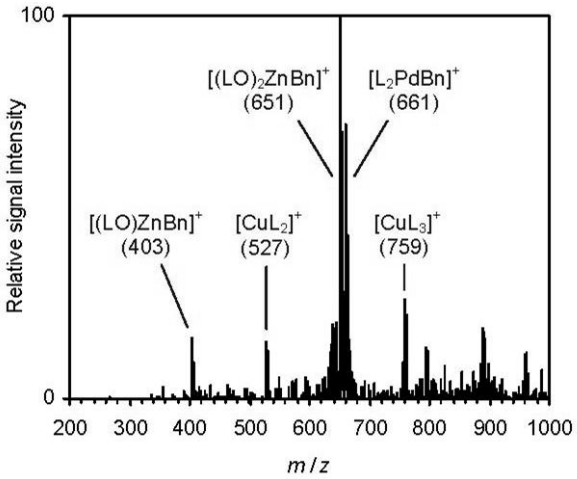


Figure 15: Positive ion mode ESI mass spectrum of an approx. 2 mM solution of $Pd(dba)_2$, tri-(2-furyl)phosphine (L, 2 equiv), and BnZnBr (2 equiv) in CH_3CN measured with the HCT ion trap (LO = tri-(2-furyl)phosphine oxide, m/z ratios of the most abundant isotopologues of the ions observed given in brackets).

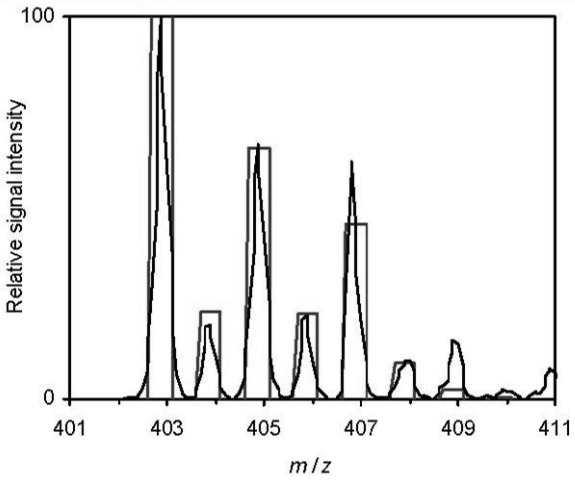


Figure 16: Isotope pattern of the complex $[(LO)ZnBn]^+$ with the elemental composition $C_{19}H_{16}O_4PZn$ measured with the HCT ion trap (line) and simulated (bars, LO = tri-(2-furyl)phosphine oxide). Apparently, small amounts of an additional, unknown cation are also present.

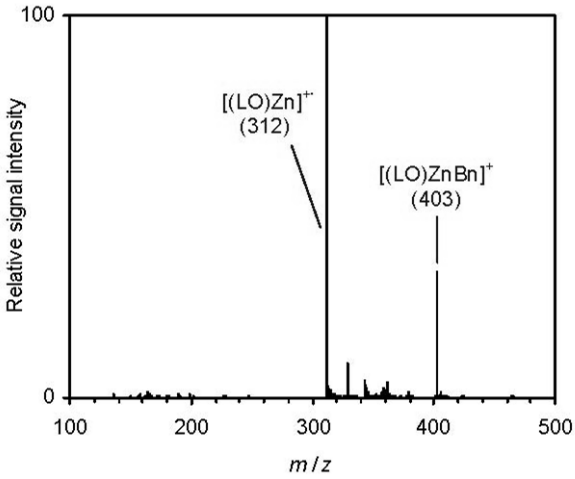


Figure 17: Mass spectrum of mass-selected $[(LO)^{64}ZnBn]^+$ (LO = tri-(2-furyl)phosphine oxide) and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.35 V, HCT ion trap).

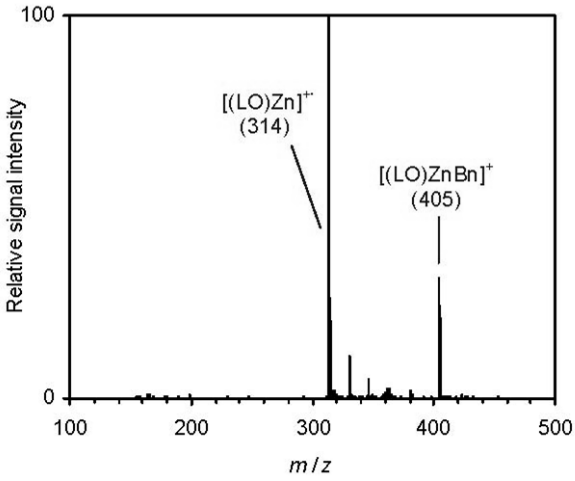


Figure 18: Mass spectrum of mass-selected $[(LO)^{66}ZnBn]^+$ (LO = tri-(2-furyl)phosphine oxide) and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.35 V, HCT ion trap).

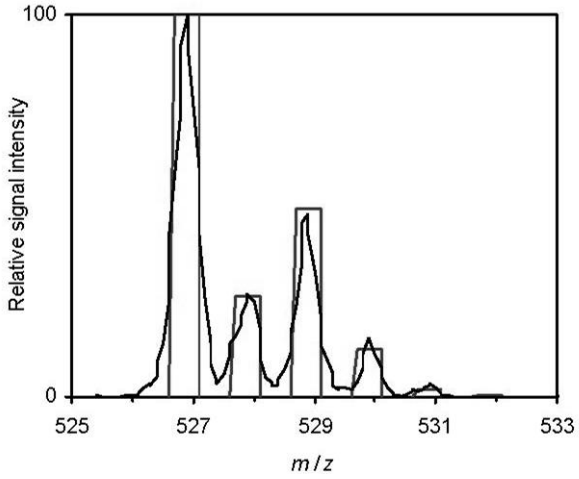


Figure 19: Isotope pattern of the complex $[L_2Cu]^+$ with the elemental composition $C_{24}CuH_{18}O_6P_2$ measured with the HCT ion trap (line) and simulated (bars, L = tri-(2-furyl)phosphine).

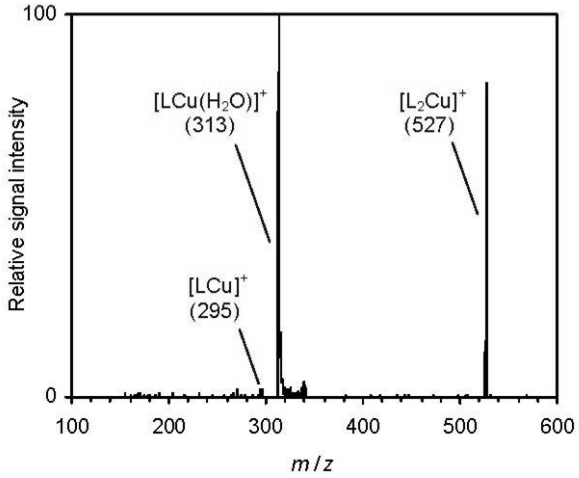


Figure 20: Mass spectrum of mass-selected $[L_2{}^{63}Cu]^+$ (L = tri-(2-furyl)phosphine) and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.30 V, HCT ion trap). $[LCu(H_2O)]^+$ apparently results from the primary fragment $[LCu]^+$ in an ion-molecule reaction with background water present in the ion trap.

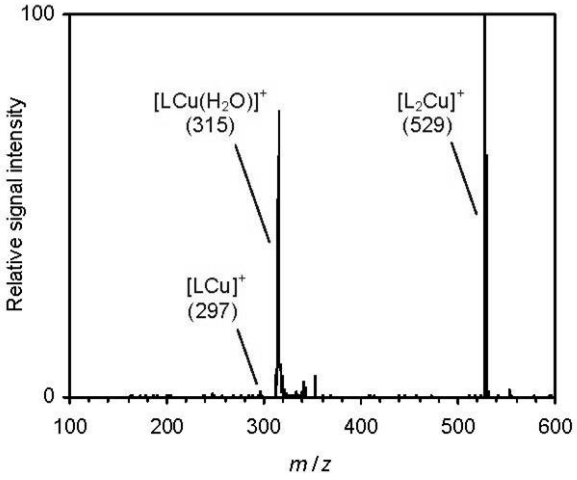


Figure 21: Mass spectrum of mass-selected $[L_2{}^{65}Cu]^+$ (L = tri-(2-furyl)phosphine) and its fragment ions (*m/z* ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.30 V, HCT ion trap). $[LCu(H_2O)]^+$ apparently results from the primary fragment $[LCu]^+$ in an ion-molecule reaction with background water present in the ion trap.

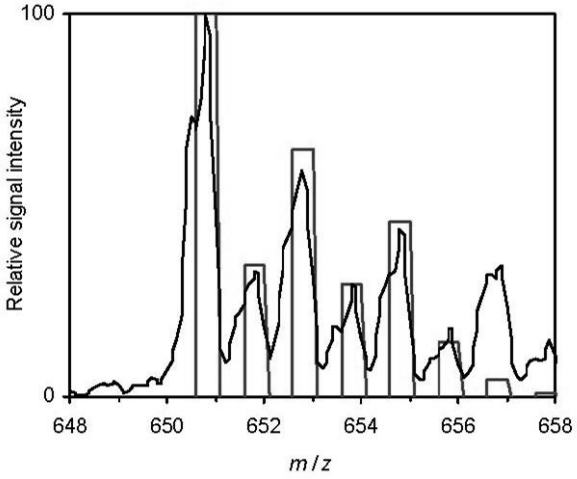


Figure 22: Isotope pattern of the complex $[(LO)_2ZnBn]^+$ with the elemental composition $C_{31}H_{25}O_8P_2Zn$ measured with the HCT ion trap (line) and simulated (bars, LO = tri-(2-furyl)phosphine oxide). Apparently, small amounts of an additional, unknown cation are also present.

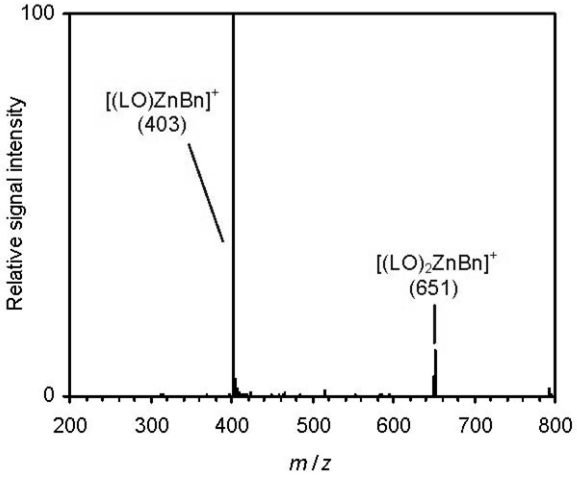


Figure 23: Mass spectrum of mass-selected $[(LO)_2{}^{64}ZnBn]^+$ (LO = tri-(2-furyl)phosphine oxide) and its fragment ions (*m/z* ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.24 V, HCT ion trap).

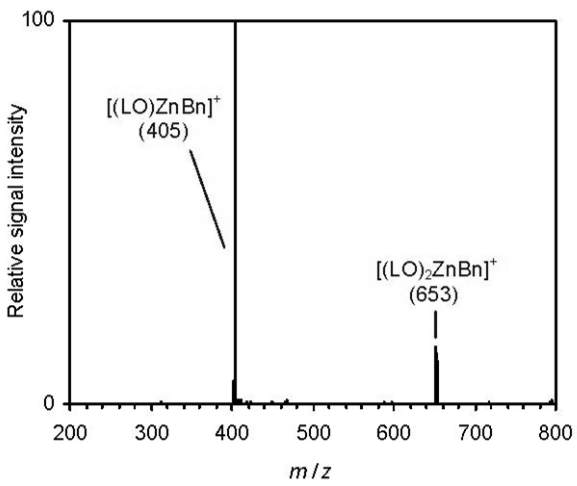


Figure 24: Mass spectrum of mass-selected $[(LO)_2{}^{66}ZnBn]^+$ (LO = tri-(2-furyl)phosphine oxide) and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.24 V, HCT ion trap).

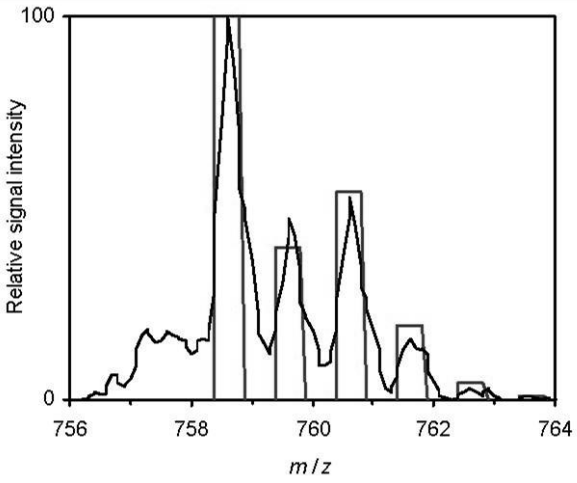


Figure 25: Isotope pattern of the complex $[L_3Cu]^+$ with the elemental composition $C_{36}CuH_{27}O_9P_3$ measured with the HCT ion trap (line) and simulated (bars, L = tri-(2-furyl)phosphine). Apparently, small amounts of an additional, unknown cation are also present.

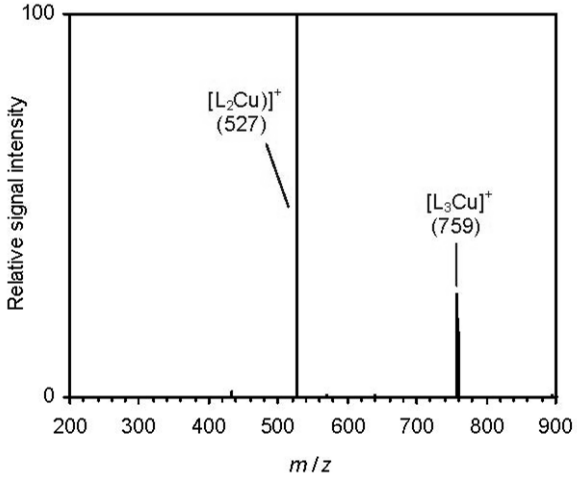


Figure 26: Mass spectrum of mass-selected $[L_3{}^{63}Cu]^+$ (L = tri-(2-furyl)phosphine) and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.20 V, HCT ion trap).

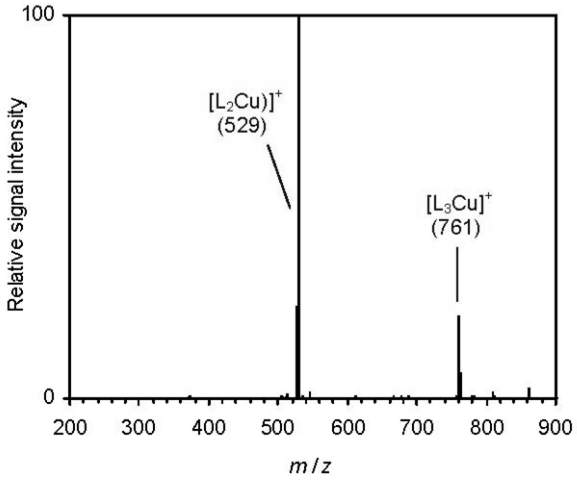


Figure 27: Mass spectrum of mass-selected $[L_3{}^{66}Cu]^+$ (L = tri-(2-furyl)phosphine) and its fragment ions (m/z ratios in brackets) produced upon collision-induced dissociation (V_{exc} = 0.20 V, HCT ion trap).

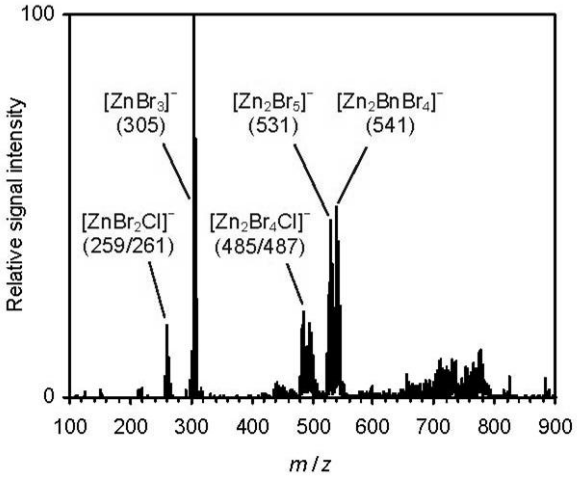


Figure 28: Negative ion mode ESI mass spectrum of an approx. 2 mM solution of $Pd(dba)_2$, tri-(2-furyl)phosphine (2 equiv), and BnZnBr (2 equiv) in CH_3CN measured with the HCT ion trap (m/z ratios of the most abundant isotopologues of the ions observed given in brackets). The ions centred around m/z 497 correspond to $[ZnBnBr_3Cl]^-$.

D Appendix

1 CURRICULUM VITAE

Matthias A. Schade

PERSONAL

Date of Birth	September 22nd 1981
Place of Birth	Ulm
Nationality	German

EDUCATION

since May 2007	PhD student in the group of Prof. Dr. P. Knochel: "Preparation and cross-coupling reactions of benzylic and arylic zinc reagents, preparation of primary amides and formation and substitutions on allenylic systems"
May 2005 – February 2007	Master of Science (MSc) program in chemistry at the Ludwig-Maximilians-Universität (LMU) in Munich; grade: 1.56 (good); Master's thesis under the supervision of Prof. Dr. Paul Knochel: "Transition Metal Catalyzed Cross-Coupling Reactions using Functionalized Benzylic Zinc Reagents" (grade: 1.0).
October 2001 – April 2005	Bachelor of Science (BSc) program in chemistry and biochemistry at the Ludwig-Maximilians-Universität (LMU) in Munich; grade: 2.75; Bachelor's thesis under the supervision of Prof. Dr. Matthias Westerhausen: "Triisopropylsilylcyclopentadiene as Novel Ligand in Organometallic Chemistry"; (grade: 1.0).
1991 - 2001	Abitur Schubart Gymnasium Ulm

AWARDS

December 2008	Recipient of the "Römer-Stipendium"

ORAL AND POSTER PRESENTATIONS

Matthias A. Schade, Julia E. Fleckenstein, P. Knochel and K. Koszinowski: „In Situ Probing of Charge-Tagged Organometallic Intermediates by Electrospray Ionization (ESI) Mass Spectrometry" Poster presentation at the annual *SFB 749* meeting, March 22nd 2010, Kloster Irsee, Germany.

Matthias A. Schade and Paul Knochel: "Preparation of Primary Amides from Functionalized Organozinc Halides" Poster presentation at the *16th European Symposium on Organic Chemistry*, July 12th to 16th 2009, Prague, Czech Republic.

„Mg- and Zn-Functionalized Organometallics for Organic Synthesis", Oral presentation at the annual *SFB 749* meeting, March 27th 2008, Wildbad Kreuth, Germany.

LANGUAGES

German	native speaker
English	fluent, written and spoken
French	basic skills

PUBLICATIONS

1.) Tobias J. Korn, Matthias A. Schade, Stefan Wirth, Paul Knochel: „Cobalt(II)-Catalyzed Cross-Coupling Reactions between Polyfunctional Arylcopper Reagents and Aryl Fluorides or Tosylates" *Org. Lett.* **2006**, *8*, 4, 725-728

2.) Tobias J. Korn, Matthias A. Schade, Murthy N. Cheemala, Stefan Wirth, Simon A. Guevara, Gérard Cahiez, Paul Knochel: „Cobalt-Catalyzed Cross-Coupling Reactions of Heterocyclic Chlorides with Arylmagnesium Halides and Polyfunctionalized Arylcopper Reagents with Aryl Bromides, Chlorides, Fluorides and Tosylates" *Synthesis* **2006**, *21*, 3547-3574

3.) Albrecht Metzger, Matthias A. Schade, Paul Knochel: „LiCl-Mediated Preparation of Highly Functionalized Benzylic Zinc Chlorides" *Org. Lett.* **2008**, *10*, 6, 1107-1110

4.) Matthias A. Schade, Albrecht Metzger, Stephan Hug and Paul Knochel: „Nickel-Catalyzed Cross-Coupling Reactions of Benzylic Zinc Reagents with Aromatic Bromides, Chlorides and Tosylates" *Chem. Commun*. **2008**, 3046-3048

5.) Georg Manolikakes, Matthias A. Schade, Carmen M. Hernandez, Herbert Mayr, Paul Knochel: „Negishi Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents" *Org. Lett.* **2008**, *10*, 2765-2768

6.) Albrecht Metzger, Matthias A. Schade, Georg Manolikakes, Carmen M. Hernandez and Paul Knochel: „A General Preparation of Polyfunctional Benzylic Zinc Compounds" *Chem. Asian. J.* **2008**, *3*, 8, 1678-1691

7.) Georg Manolikakes, Carmen M. Hernandez, Matthias A. Schade, Albrecht Metzger and Paul Knochel: „Negishi Cross-Couplings of Unsaturated Halides bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents" *J. Org. Chem.* **2008**, *73*, 8422-8436

8.) Fabian M. Piller, Albrecht Metzger, Matthias A. Schade, Benjamin A. Haag, Andrei Gavryushin and Paul Knochel: „Preparation of Polyfunctional Arylmagnesium,

Arylzinc and Benzylic Zinc Reagents by Using Magnesium in the Presence of LiCl" *Chem. Eur. J.* **2009**, *15*, 7192-7202.

9.) Matthias A. Schade, Julia Fleckenstein, Paul Knochel and Konrad Koszinowski: „Charged Tags as Probes for Analyzing Organometallic Intermediates and Monitoring Cross-Coupling Reactions by Electrospray-Ionization Mass Spectrometry" *J. Org. Chem.* **2010**, 75, 6848-6857.

10.) Matthias A. Schade, Georg Manolikakes and Paul Knochel: „Preparation of Primary Amides from Functionalized Organozinc Halides" *Org. Lett.* **2010**, *12*, 3648-3650.

11.) Matthias A. Schade, Shigeyuki Yamada and Paul Knochel: „Synthesis of Polyfunctional Allenes via Successive Copper-Mediated Substitutions" *Chem. Eur. J.* **2011**, DOI: 10.1002/chem.201003273

12.) Matthias A. Schade, Shigeyuki Yamada and Paul Knochel: „Preparation of Alkenylzinc Reagents via LiCl mediated Metal Insertion" *manuscript in preparation (2011)*

REVIEWS

Paul Knochel, Prasad Appukkuttan, Andrei Gavryushin, Georg Manolikakes, Albrecht Metzger, Marc Mosrin, Fabian M. Piller, Chrostoph J. Rohbogner, Matthias A. Schade, Stefa7 H. Wunderlich: „Functionalization of Heterocyclic Compounds using Polyfunctional Magnesium and Zinc Reagents" *Pfizer In-House Journal Synthon*, **2008**