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

Magnesium Halide-Mediated Addition of Functionalized Organozinc Reagents to Aldehydes, Ketones and Carbon Dioxide. Preparation of Solid Salt-Stabilized Organozinc Reagents. Preparation of Functionalized Organoindium Reagents *via* Magnesium Insertion in the Presence of $InCl_3$.

Sebastian Daniel Gerhard Bernhardt

aus

Eschenbach in der Oberpfalz, Deutschland

2012

Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Paul Knochel betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, am 2. Juli 2012

……

Sebastian Daniel Gerhard Bernhardt

Dissertation eingereicht am:

1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Manfred Heuschmann
Mündliche Prüfung am:	25.07.2012

This work was carried out from February 2009 to June 2012 under the guidance of Prof. Dr. Paul Knochel at the Fakultät für Chemie und Pharmazie of the Ludwig-Maximilians-Universität, München.

First of all, I would like to thank Prof. Dr. Paul Knochel for giving me the opportunity to prepare my Ph.D. thesis in his group and for giving me the chance to work on the stimulating research field of solid functionalized organozinc reagents. I am very grateful for his invaluable support, guidance and mentorship throughout this time.

I would like to express my appreciation to Prof. Dr. Manfred Heuschmann for agreeing to be the second reviewer of this thesis and I thank all members of my defense committee - Prof. Dr. Herbert Mayr, Prof. Dr. Heinz Langhals, Prof. Dr. Konstantin Karaghiosoff, Prof. Dr. Anja Hoffmann-Röder - for their interest shown in this manuscript and their agreement to take part in the examination.

I thank Klaus Groll, Veronika Werner and Christoph Sämann for the careful correction of this manuscript.

I would like to thank all of the past and present members of the Knochel group for the great time I had in and outside of this laboratory.

My special thanks go to Dr. Albrecht Metzger for being a great mentor throughout my Ph.D. thesis and far beyond. Thank you for everything you've done for me and for bringing punk back to my life. I sincerely thank Dr. Thomas Kunz for our great scientific cooperation and much more for being the best fellow climber where- and whenever one can imagine. I thank Tobias Blümke for his illustrious companionship and constant support throughout our Master and Ph.D. theses. I salute Dr. Andreas J. Wagner, Andreas Unsinn, Klaus Groll, Dr. Christoph J. Rohbogner and Christoph Sämann for the great times at lunch, Pilsdoktor and other Nachsitzungen.

I thank Dr. Fabian Piller, Dr. Sylvia Zimdars, Dr. Thomas Kunz, Dr. Xavier Mollat du Jourdin, Dr. Christos Stathakis and Pauline Quinio for being the greatest labmates one could imagine and for tolerating my music and bad singing. I am deeply indepted to my charming bench-neighbour Veronika Werner for creating an excellent working atmosphere and for cheering me up at any time. I thank Gabriel Monzon for the great time we had together in the office writing this thesis. *Muchas Gracias*!

I would like to express my gratitude to my fantastic collaborators in terms of scientific work. Thank you, Dr. Albrecht Metzger, Zhi-Liang Shen, Dr. Thomas Kunz, Dr. Christos Stathakis, James Colombe and Dr. Georg Manolikakes. Moreover, I thank my fomer students Petra Goldmann, Manuel Boehm, Matthias Trunk, Paul Stockmann and Valentin Quint for their excellent contributions in the course of their internships in the Knochel group.

I would also like to thank Vladimir Malakhov, Simon Matthe, Renate Schröder and Yulia Tsvik for their help in organizing everyday life in the lab and in the office, as well as the analytical team of the LMU for their invaluable help.

I salute my old comrades Dr. Roland Appel and Dr. Garwin Pichler for the great friendship and their support.

Finally, I thank my mother, my brother and my grandparents for their continuous moral, emotional, and financial support! Thank you, for your patience and your trust in me! Without you, nothing of this would have been possible!

"Tonight I hear the neighborhood drummer sound. I can feel my heart begin to pound. You say you're tired and you just want to close your eyes and follow your dreams down. Well, we made a promise we swore we'd always remember. No retreat, baby, no surrender."

Bruce Springsteen-No Surrender, 1984

Parts of this Ph.D. Thesis have been published

A) Communications

$MgCl_2$-Accelerated Addition of Functionalized Organozinc Reagents to Aldehydes, Ketones, and Carbon Dioxide
[$MgCl_2$-beschleunigte Additionen von funktionalisierten Organozinkreagentien an Aldehyde, Ketone und Kohlendioxid]
A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem.* **2010**, *122*, 4769; *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.

Direct Addition of Functionalized Organozinc Reagents to Carbon Dioxide, Ketones, and Aldehydes
S. Bernhardt, A. Metzger, P. Knochel, *Synthesis* **2010**, 3802.
(Highlighted in *Org. Process. Res. Dev.* **2011**, *15*, 5.)

Preparation of Solid Salt-Stabilized Functionalized Organozinc Compounds and their Application to Cross-Coupling and Carbonyl Addition Reactions
[Herstellung von festen salzstabilisierten Organozinkreagentien und deren Anwendung in Kreuzkupplungen und Carbonyladditionen]
S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem.* **2011**, *123*, 9372; *Angew. Chem. Int. Ed.* **2011**, *50*, 9205.
(The publication was rated as VIP (Very Important Paper))

Improved Air-Stable Solid Aromatic and Heterocyclic Zinc Reagents *via* Highly Selective Metalations for Negishi Cross-Couplings
C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *manuscript submitted*.

Preparation of Functionalized Organoindium Reagents *via* Magnesium Insertion in the Presence of $InCl_3$
S. Bernhardt, Z.-L. Shen, P. Knochel, *manuscript in preparation*.

Solid Air-Stable 2-Pyridylzinc Reagents for Negishi Cross-Couplings Under Mild Conditions

S. Bernhardt, C. I. Stathakis, J. Colombe, S. L. Buchwald, P. Knochel, *manuscript in preparation.*

B) Review Articles

Auf den Spuren zweier Chemie-Nobelpreisträger - Verbesserte Metallorganische Intermediate für Kreuzkupplungsreaktionen

P. Knochel, C. Sämann, S. Bernhardt, T. Kunz, *GIT Laborfachzeitschrift* **2011**, *11*, 799.

Functionalization of Heterocyclic Compounds Using Polyfunctional Magnesium and Zinc Reagents

P. Knochel, M. A. Schade, S. Bernhardt, G. Manolikakes, A. Metzger, F. M. Piller, C. J. Rohbogner, M. Mosrin, *Beilstein J. Org. Chem.* **2011**, *7*, 1261.
(Highlighted in *Org. Process. Res. Dev.* **2012**, *16*, 174.)

C) Patents

Carbonylierung von organischen Zinkverbindungen - Eine neue effiziente Darstellungsvariante von Ibuprofen

S. Bernhardt, A. Metzger, P. Knochel, WO 2011/113925 A2.

Organozinc Complexes and Processes for Making and Using the Same

S. Bernhardt, G. Manolikakes, P. Knochel, *an international patent application has been filed.*

Für meinen geliebten Opa Werner Gradl
23.10.1939-16.05.2011

„Du warst koa Übermensch, host a nia so tan,
grad desweg'n war da irgendwia a Kraft.
Und durch die Art, wia Du dei Leben glebt hast,
hob i a Ahnung 'kriagt, wia ma's vielleicht schafft."

STS-Großvater, 1986

List of Abbreviations

aq.	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
br	broad (NMR)
Bu	butyl
conc.	concentrated
Cy	cyclohexyl
d	doublet (NMR)
dba	dibenzylideneacetone
dist.	distilled
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMSO	dimethylsulfoxide
equiv	equivalent
E	eletrophile
EI	electron impact
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
Hex	hexyl
HRMS	high resolution mass spectroscopy
*i*Bu	*iso*-butyl
*i*Pr	*iso*-propyl
IR	infrared spectroscopy
J	coupling constant (NMR)
M	mol/L
Me	methyl
Met	metal
min	minute
MIDA	*N*-methyl-iminodiacetic acid
mmol	millimole

M.P.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
OPiv	pivalate
PEPPSI-*i*Pr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] (3-chloropyridyl)palladium(II)dichloride
Ph	phenyl
ppm	parts per million
q	quartet
R	organic subsituent
s	singulet
sat.	saturated
S-Phos	2-dicylohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
t	reaction time
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

A. INTRODUCTION

1. Overview

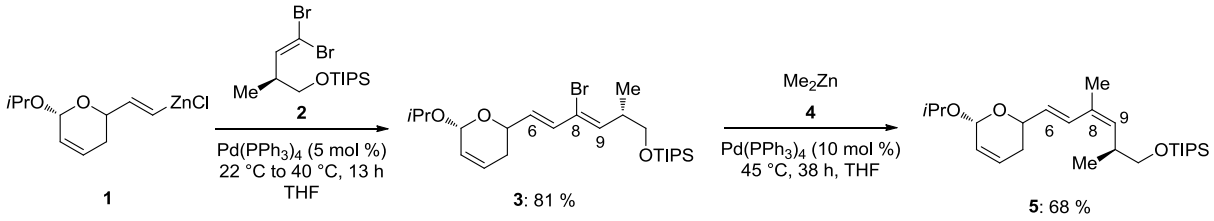
„*The ideology of Green Chemistry calls for the development of new chemical reactivities and reaction conditions that can potentially provide benefits for chemical syntheses in terms of resource and energy efficiency, product selectivity, operational simplicity and health and environmental safety*."[1]

With this statement, Barry Trost precisely summarizes the challenges, which the chemical and pharmaceutical industry has to face nowadays. The continuously growing world population enforces a sustainable handling of the limited fossil resources and a paradigm shift towards the use of renewable raw materials.[2] As chemical industries product line ranges from small molecules to highly complex materials and pharmaceuticals a broad spectrum of efficient synthetic methodologies that can be applied in production processes with a minimum formation of unwanted waste are highly desirable.[3] In this context, organic chemistry and especially organometallic chemistry have come up with a plethora of very useful reagents and synthetic transformations.

As the reactivity of organometallic reagents is determined by the polarity of the incorporated carbon-metal bond, an appropriate selection of the metal atom and the organic moiety creates versatile tools for specific synthetic applications.[4] Due to their strongly polarized carbon-metal bond organolithium reagents represent a highly reactive class of organometallics but show only little tolerance towards sensitive functionalities.[5] In contrast to that, organoboron reagents have been established as air- and moisture-stable building blocks with a comparable high functional group tolerance. However, their almost covalent carbon-boron bond enforces harsh conditions and highly developed catalysts for the reaction with electrophiles.[6] Organomagnesium and –zinc reagents are further important representatives of synthetically useful organometallics and can be ranked in between in terms of reactivity and stability. Whereas, *Grignard*-reagents show excellent reactivity and functional group tolerance at appropriate low temperatures,[7] highly functionalized organozincs are even stable at elevated temperatures. The availability of empty low-energy p-orbitals enables organozinc compounds

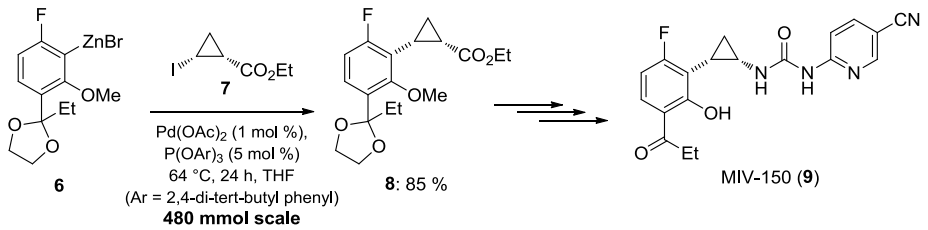
[1] C. J. Li, B. M Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197.
[2] a) C. Okkerse, H. van Beekum, *Green Chem.* **1999**, *1*, 107; b) R. Noyori, *Chem. Commun.* **2005**, 1807.
[3] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259.
[4] a) *Handbook of Functionalized Organometallics*, (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**; b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**. c) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.
[5] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596.
[6] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
[7] 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.

to interact with d-orbitals of transition metals and thus smoothly undergo transmetalation reactions.[4a, 8] The most prominent applications of this behaviour are the Pd-catalyzed *Negishi*-cross-coupling reactions, which proceed under milder reaction conditions and much faster than the corresponding *Suzuki*-cross-couplings of boronic acids.[4b, 9] A powerful application of a sequence of *Negishi*-couplings is demonstrated by *Gademann* in the synthesis of the highly selective tumor-growth inhibitor Anguinomycin C.[10] The coupling of the vinylic zinc reagent **1** with the dibromoolefin **2** afforded selectively the (6*E*, 8*Z*)-diene **3** in 81 % yield. The subsequent cross-coupling with Me_2Zn (**4**) installs a methyl group at position 8 and simultaneously inverts the stereochemistry at position 9 affording exclusively the *cis*-product **5** in 68 % yield (Scheme 1).



Scheme 1: *Negishi* cross-coupling sequence in the total synthesis of Anguinomycin C by *Gademann*.

An impressive industrial application of a *Negishi* cross-coupling is implemented in the synthesis of the HIV-reverse transcriptase inhibitor MIV-150 (**9**) by the *Chiron* Corporation.[11] The reaction of the aryl zinc reagent **6** with the enantiopure cyclopropyl iodide **7** affords stereoselectively the key intermediate **8** in 85 % yield (Scheme 2).



Scheme 2: *Negishi* cross-coupling in the synthesis of HIV reverse trancriptase inhibitor MIV-150 (**9**) by the *Chiron Corporation*.

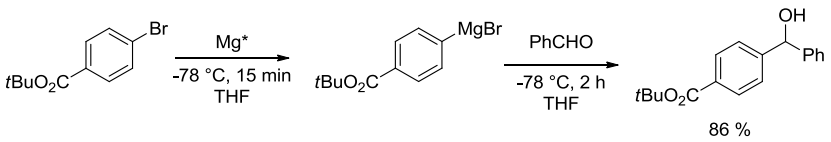
[8] P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React*. **2001**, *58*, 417.
[9] a) E. Negishi, *Angew. Chem Int. Ed.* **2011**, *50*, 673; b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem Int. Ed.* **2012**, *51*, 5062; c) V. F. Slagt, A. H. M. de Vries, J. G. de Vries, R. M. Kellog, *Org. Process Res. Dev.* **2010**, *14*, 30.
[10] S. Bonazzi, O. Eidam, S. Güttinger, J.-Y. Wach, I. Zemp, U. Kutay, K. Gademann, *J. Am. Chem. Soc.* **2010**, *132*, 1432.
[11] S. Cai, M. Dimitroff, T. McKennon, M. Reider, L. Robarge, D. Ryckman, X. Shang, J. Therrien, *Org. Process Res. Dev.* **2004**, *8*, 353.

2. Preparation of Organomagnesium Reagents

2.1. Oxidative Addition of Magnesium to Carbon-Halogen Bonds

Ever since the discovery of organomagnesium reagents by *Victor Grignard* in the year 1900,[12] the direct insertion of magnesium metal into carbon-halogen bonds has been the most straightforward approach to their preparation.[13] While the exact mechanism of this reaction is still not entirely elucidated, radical pathways are generally accepted.[14] However, despite the efficiency of the magnesium insertion in terms of atom economy,[3] the applicability especially in large scales is hampered by its critical initiation stage. A reactive metal surface has to be generated in the reaction media and thus, suitable activation reagents (e.g. dibromoethane, I_2) have to be added to remove the hindering oxide layers. Moreover, this part of the reaction is usually exothermic and requires suitable cooling.[14c, 15] In order to make the formation of the *Grignard*-reagent go to completion the reaction has often to be carried out at elevated temperatures and therefore the scope of suitable functional groups is strongly limited.

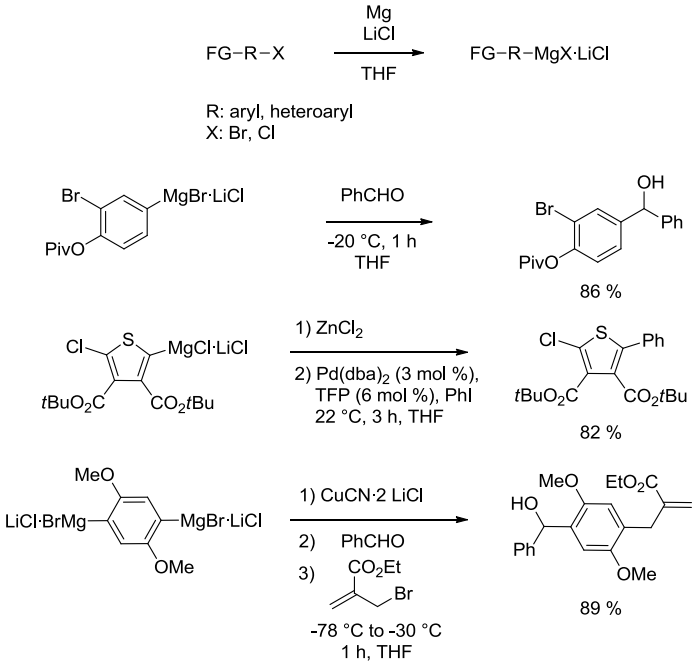
These drawbacks could be elegantly bypassed by *Rieke* and coworkers using highly reactive magnesium powder (Mg*), prepared by the reduction of magnesium salts with lithium naphthalide. This methodology allowed the preparation of the organomagnesium reagents at very low temperatures and enabled the tolerance of very sensitive groups like nitriles and esters (Scheme 3).[16]



Scheme 3: Preparation and reactivity of a functionalized *Grignard*-reagent using highly reactive *Rieke*-Mg (Mg*).

[12] V. Grignard, *Compt. Rend. Acad. Sci. Paris*, **1900**, *130*, 1322.
[13] a) *Handbook of Grignard Reagents*, (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**; b) *Grignard Reagents, New Developments* (Ed.: H. G. Richey jr.), Wiley & Sons, New York, **2000**.
[14] a) H. M. Walborksy, *Acc. Chem. Res.* **1990**, *23*, 286; b) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95; c) J. F. Garst, M. P. Soriaga, *Coord. Chem. Rev.* **2004**, *248*, 623.
[15] a) D. J. am Ende, P. J. Clifford, D. M. DeAntonis, C. SantaMaria, S. J. Brenek, *Org. Process Res. Dev.* **1999**, *3*, 319; b) U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.
[16] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, M.V. Hanson, *Tetrahedron* **1997**, *53*, 1925; b) J. Lee, R. Verlade-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428; d) R. D. Rieke, *Aldrichchim. Acta* **2000**, *33*, 52.

Recently, *Knochel* and coworkers could show that carrying out the insertion reaction in the presence of stoichiometric amounts of LiCl gives access to a range of new functionalized aryl and heteroaryl magnesium species from the corresponding chlorides and bromides under mild reaction conditions (Scheme 4).[17]



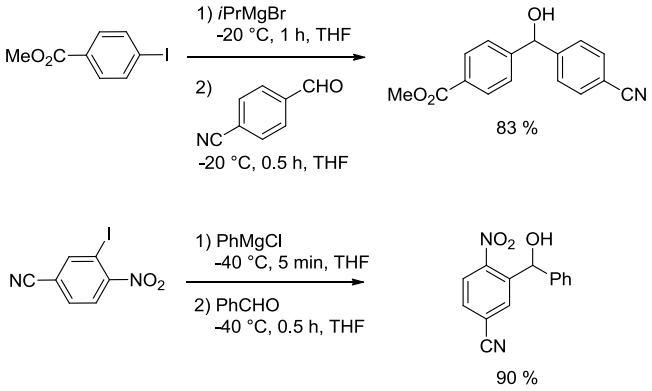
Scheme 4: Preparation of functionalized *Grignard*-reagents using Mg in the presence of LiCl and subsequent reactions with different electrophiles.

2.2. The Halogen-Magnesium Exchange Reaction

Since its discovery by *Prévost* in 1931,[18] the halogen-magnesium reaction has been established has very useful methodology for the preparation of highly functionalized *Grignard*-reagents.[4a, 7] The driving force of this reaction is the formation of an organomagnesium reagent that is more stable than the exchange reagent.[19] *Knochel* and coworkers could impressively demonstrate the potential of *i*PrMgBr and PhMgCl in the I-Mg-

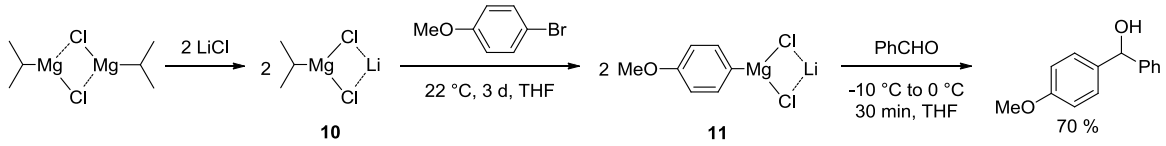
[17] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
[18] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[19] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.

exchange reaction.[4a, 20] The possibility to conduct the reactions at very low temperatures enables the tolerance of very sensitive functionalities like an ester- or a nitro-group (Scheme 5).



Scheme 5: Preparation of functionalized *Grignard*-reagents by iodine-magnesium exchange using *i*PrMgBr or PhMgCl and subsequent reactions with different aldehydes.

Furthermore, *Knochel* and coworkers could show that the so called Turbo-*Grignard* reagents, bearing complexed LiCl, enable smooth exchange reactions with different aryl- and heteroaryl bromides. The reactivity-boosting role of LiCl may be explained by the formation of magnesium-lithium ate complexes of type **10** and **11** (Scheme 6).[19, 21]



Scheme 6: LiCl-enhanced bromine-magnesium exchange reaction with *i*PrMgCl.

2.3. Directed Deprotonation Using Magnesium Amide Bases

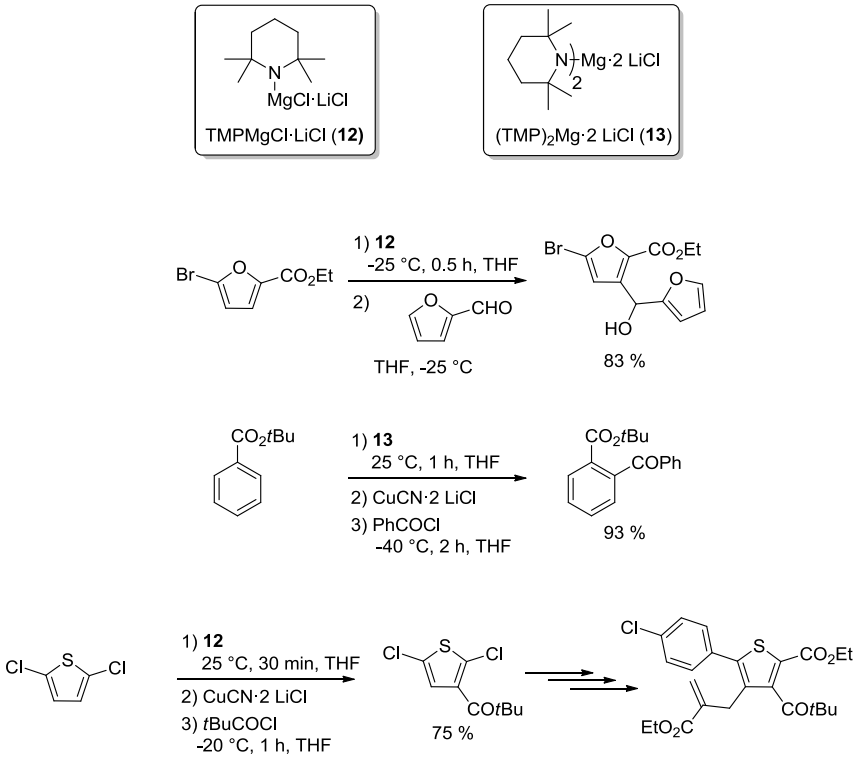
The directed metalation using magnesium amide bases is a further very versatile approach for the preparation of functionalized organomagnesium reagents.[22] The recently developed mixed lithium and magnesium amide bases TMPMgCl·LiCl (**12**) and $TMP_2Mg·2\,LiCl$ (**13**) give

[20] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) I. Sapountzis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; c) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565.

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

[22] a) C. R. Hauser, H. W. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) F. C. Frostick, C. R. Hauser, *J. Am. Chem. Soc.* **1949**, *71*, 1350; c) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.

access to a large number of functionalized aromatic, heteroaromatic and vinylic organomagnesium reagents (Scheme 7).[23, 24]



Scheme 7: Application of hindered magnesium amide bases **12** and **13** for the directed metalation and functionalization of aromatic and heteroaromatic scaffolds.

[23] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; c) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525; d) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; e) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113; f) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497; g) F. M. Piller, P. Knochel, **2009**, *11*, 445; h) C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326; i) S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 339.

[24] For a recent review article about metalation reactions using hindered amide bases see: B. Haag, M. Mosrin, H. Ila, V. Malakhov, P Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

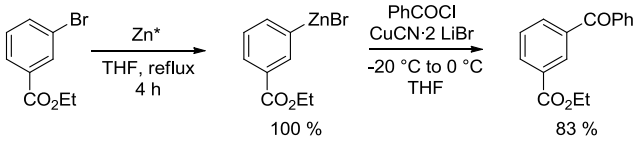
3. Preparation of Organozinc Reagents

3.1. Introduction

Since the initial preparation of diethylzinc by *Frankland* in 1849,[25] a number of very useful direct synthetic applications of organozinc reagents like the *Reformatsky*-reaction[26] or the *Simmons-Smith* cylopropanation[27] have been developed. Furthermore, the strong potential of organozincs to undergo transmetalation reactions with transition metals gives access to highly reactive organocopper reagents[28, 29] and the well established palladium-catalyzed *Negishi* cross-coupling reactions.[4b, 9]

3.2. Oxidative Addition of Zinc Metal to Carbon-Halogen Bonds

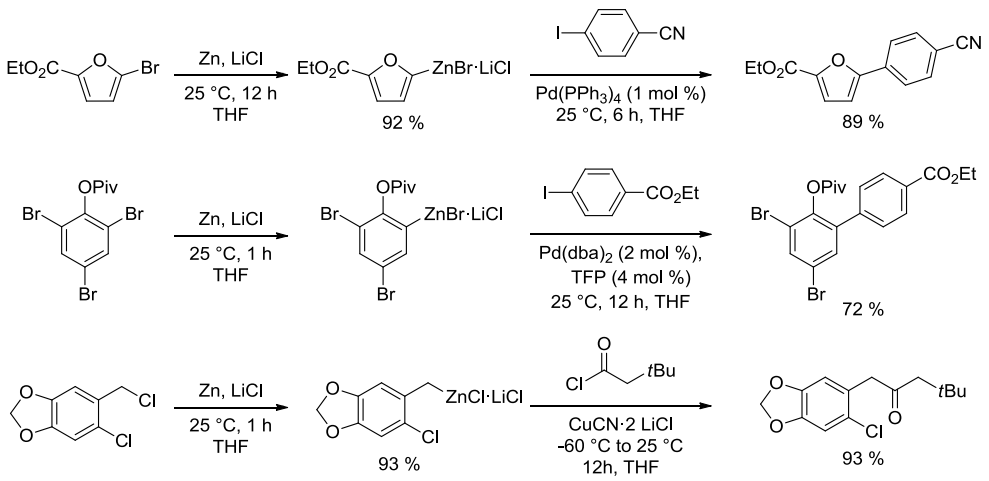
Similarly to organomagnesium compounds, the most common method for the preparation of organozincs is the insertion of elemental zinc into organic halides. A broad range of sensitive functionalities, like esters, nitriles and ketones is well tolerated. However, the use of expensive organic iodides, elevated reaction temperatures and polar solvents is often required. Furthermore, the zinc metal has to be treated with activation reagents like dibromoethane and TMSCl to create a reactive metal surface.[28b] *Rieke* could show that the use of highly active zinc powder (Zn*), produced by a reduction of $ZnCl_2$ with lithium naphthalenide, gives access to functionalized organozincs starting even from the less reactive arylbromides (Scheme 8).[16b-d, 30]



Scheme 8: Preparation and reactivity of a functionalized organozinc reagent using highly reactive *Rieke*-Zn (Zn*).

[25] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171 and 213.
[26] a) S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210; **1895**, *28*, 2842; b) R. Ocampo, *Tetrahedron* **2004**, *60*, 9325.
[27] a) H. E. Simmons, R. D. Smith, *J. Am. Chem Soc.* **1958**, *80*, 5323; b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 5323; c) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.
[28] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117; b) *Organozinc Reagents. A Practical Approach*, (Eds.: P. Knochel, P. Jones), Oxford University Press, **1999**; c) P. Knochel, J. J. A. Perea, P. Jones, *Tetrahedron* **1998**, *54*, 8275.
[29] P. Knochel, M. C. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[30] a) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4324; b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

Knochel and coworkers could demonstrate that the presence of LiCl enables the synthesis of functionalized organozinc reagents from the corresponding aromatic and heteroaromatic bromides and iodides as well as benzyl chlorides using commercially available zinc dust. The reactions proceed in THF under comparable mild conditions (25 °C to 50 °C; Scheme 9).[31]

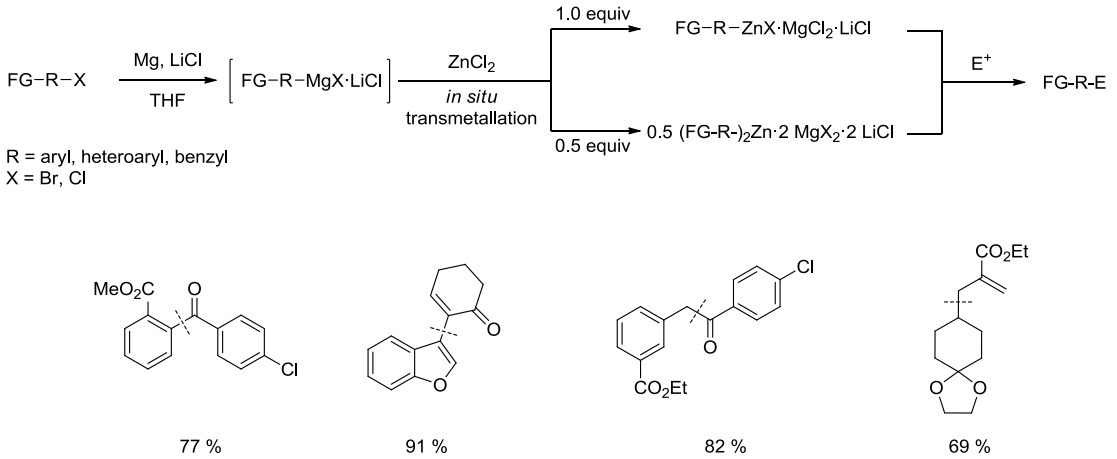


Scheme 9: Preparation of functionalized organozinc reagents using zinc dust in the presence of LiCl.

3.3. Magnesium Insertion in the Presence of $ZnCl_2$

Recently, *Knochel* showed that a broad range of functionalized aryl-, heteroaryl-, benzyl- and alkylzinc reagents are accessible *via* LiCl mediated magnesium insertion in the presence of $ZnCl_2$.[17, 32] Due to the higher reduction potential of magnesium, aryl bromides as well as heteroaryl bromides and chlorides can be used as cheaper starting materials. Furthermore, by reducing the amount of used $ZnCl_2$ to 0.5 equiv the method gives a convenient access to more reactive diorganozinc reagents (Scheme 10).

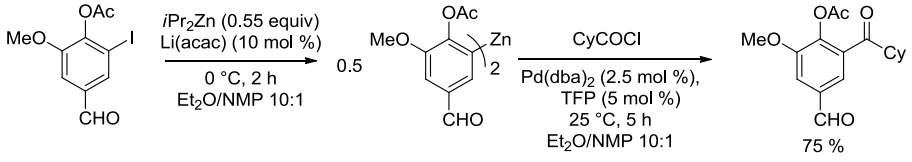
[31] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.
[32] a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; b) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082.



Scheme 10: Preparation of functionalized organozinc reagents by Mg-insertion and *in situ* trapping with $ZnCl_2$.

3.4. The Iodine-Zinc Exchange Reaction

Another convenient approach for the preparation of diorganozincs is the iodine-zinc exchange reaction. A range of alkyl iodides reacted with diethylzinc in the presence of Cu(I) salts to the corresponding dialkylzinc reagents.[33] Furthermore, this methodology could be extended to the preparation of diaryl- and diheteroarylzinc reagents. Therefore, the corresponding aryl- and heteroaryliodides were reacted with diisopropylzinc in the presence of catalytic amounts of Li(acac) (Scheme 11).[34]

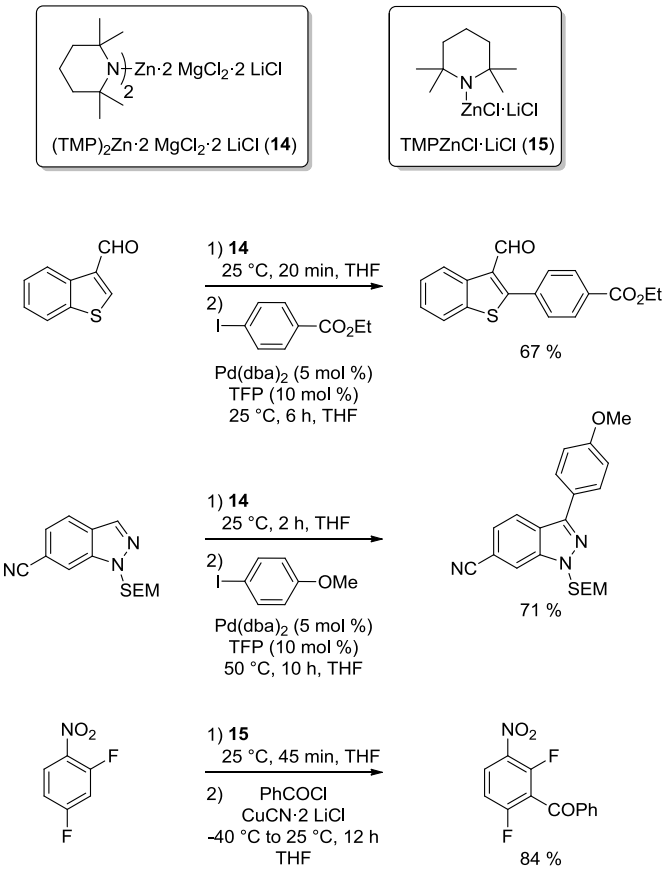


Scheme 11: Preparation of diorganozincs by an Li(acac)-catalyzed iodine-zinc exchange reaction.

[33] a) M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956; b) M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115.
[34] F. F. Kneisel, M. Dochnahl, P. Knochel *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

3.5. Metalation Reactions Using Hindered Zinc-Amide Bases

Kondo and coworkers pioneered the field of highly active zincate bases for the directed ortho metalation.[35] *Knochel* refined this methodology and developed highly chemoselective and sensitive TMP-derived zinc bases of type **14** and **15** for the direct metalation of sensitive aromatics and heterocycles under mild conditions (Scheme 12).[24, 36]



Scheme 12: Application of hindered zinc amide bases **14** and **15** for the directed metalation and functionalization of aromatic and heteroaromatic scaffolds.

[35] a) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; b) T. Imahori, M. Uchiyama, T. Sakamoto, Y. Kondo, *Chem. Commun.* **2001**, 2450; c) P. F. H: Schwab, F. Fleischer, J. Michl, *J. Org. Chem.* **2002**, *67*, 443; d) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514.

[36] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; c) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; d) A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680.

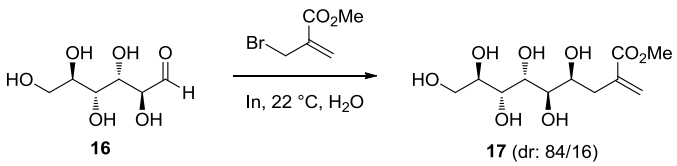
4. Preparation of Organoindium Reagents

4.1. Introduction

Since the initial studies on the reactivity of organoindium reagents by *Gilman* in 1940,[37] the manifold potential of this class of organometallics in organic synthesis has started to be explored only recently.[38] Especially, the fact that organoindium compounds are tolerant towards water as reaction media, makes them very interesting in terms of *Green chemistry*. Furthermore, their tolerance towards many acidic-hydrogen containing functional groups may avoid tedious protection-deprotection strategies.[1, 2, 39]

4.2. Oxidative Addition of Indium Metal to Carbon-Halogen Bonds

The direct insertion of indium metal is known for allylic, propargylic, benzyl and very electron deficient aromatic halides.[38b, 40] The low first ionization potential of indium metal as well as its low propensity to form oxides enable smooth reaction conditions. The reaction proceeds over an initially formed organoindium species in the oxidation state +1, which reacts with a further organic halide molecule leading to the more stable oxidation state +3. The oxidative addition of indium metal can also be performed in a *Barbier*-type manner as exemplified in Scheme 13 where the *in situ* formed allylic organoindium reagent reacts with the aldehyde **16** to give the polyol **17** in good diastereoselectivity.[41]

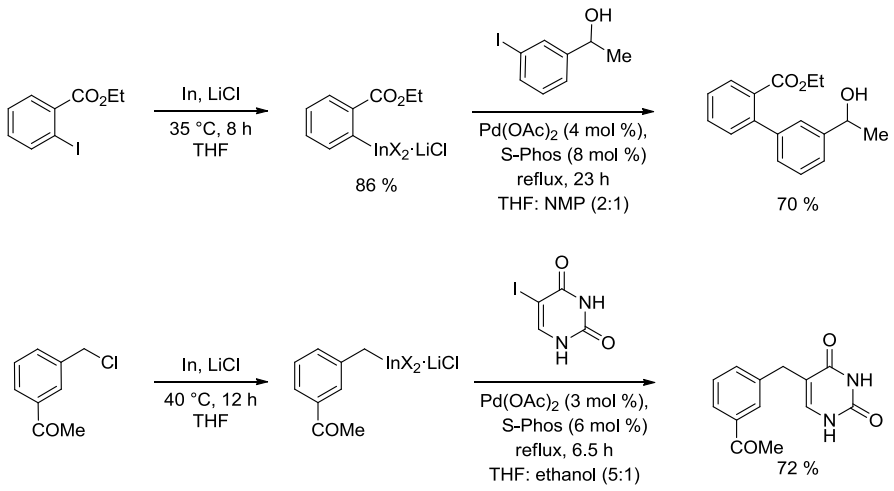


16 **17** (dr: 84/16)

Scheme 13: Indium mediated *Barbier*-type addition.

[37] H. Gilman, R. G. Jones, *J. Am. Chem. Soc.* **1940**, *62*, 2353.
[38] a) P. Cintas, *Synlett* **1995**, 1087; b) C.-J. Li, T.-H. Chan, *Tetrahedron* **1999**, *55*, 11149, c) B. C. Ranu, *Eur. J. Org. Chem.* **2000**, 2347; d) J. Augé, N. Luben-Germain, J. Uziel, *Synthesis* **2007**, 1739.
[39] T.-P. Loh, G.-L. Chua, *Chem. Commun.* **2006**, 2739.
[40] a) K. Koszinowski, *J. Am. Chem. Soc.* **2010**, *132*, 6032; b) N. W. E. Tyrra, *J. Fluorine Chem.* **2001**, *112*, 149; c) N. Fujiwara, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 4095.
[41] T.-H. Chan, C.-J. Li, *J. Chem. Soc., Chem. Commun.* **1992**, 747.

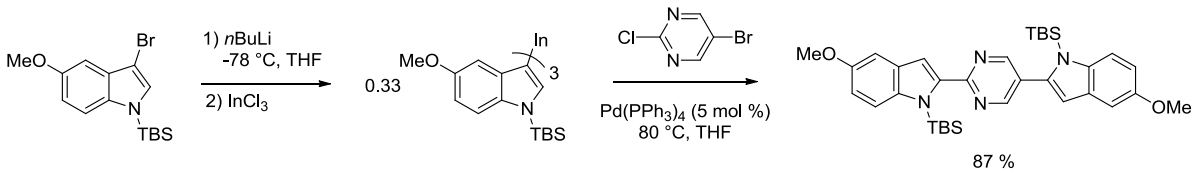
Knochel and *Minehan* could show that in the presence of LiCl commercially available indium powder reacts even with less activated aromatic iodides.[42] This methodology could be further extended to the preparation of highly functionalized benzylindium reagents (Scheme 14).[43]



Scheme 14: Preparation of functionalized organoindium reagents using indium powder in the presence of LiCl.

4.3. Transmetalation From Organolithium or *Grignard*-Reagents with $InCl_3$

The transmetalation of organolithium and *Grignard*-reagents with indium(III) salts provides another convenient access to functionalized organoindium reagents. Moreover, by adopting the stoichiometry of the organomagnesium reagents and the indium salt, tris-, bis- and monoorganoindium reagents are accessible. However, the functional group tolerance is limited by the corresponding organomagnesium or –lithium reagent.[38d] Nevertheless, this methodology gives access to synthetically very useful building blocks like it is shown in the key-step of the synthesis of the *bis*-indole alkaloide Hyrtinadine A by *Sarandeses* (Scheme 15).[44]

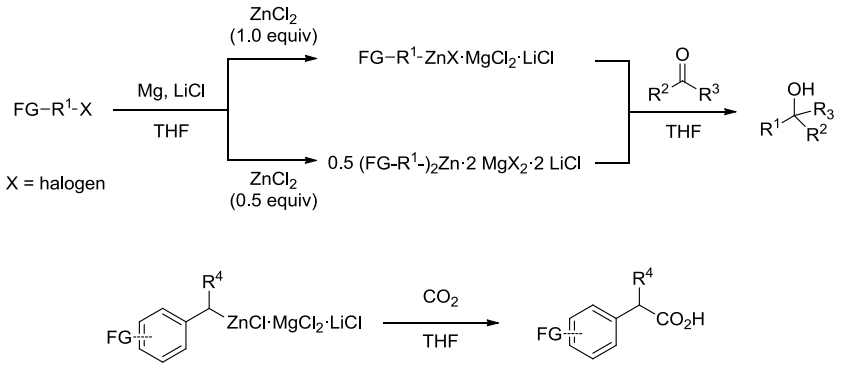


Scheme 15: Preparation of trisorganoindium reagents by halogen-lithium exchange and subsequent transmetalation with $InCl_3$ as well as sequential cross-coupling.

[42] a) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; b) V. Papoian, T. Minehan, *J. Org. Chem.* **2008**, *73*, 7376.
[43] Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236.
[44] A. Mosquera, R. Riveiros, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **2008**, *10*, 3745.

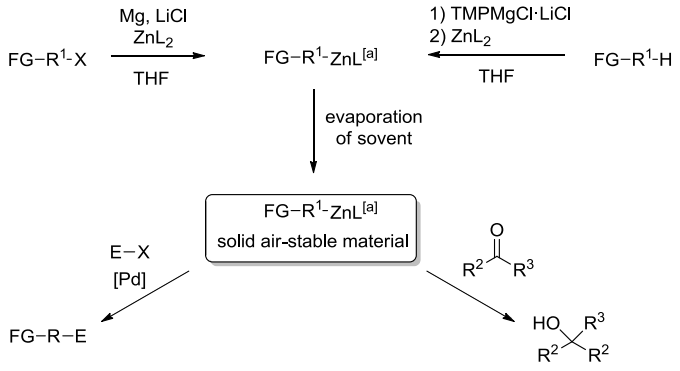
5. Objectives

The aim of the first project was to investigate the direct magnesium halide mediated addition of functionalized organozinc reagents to aldehydes, ketones and carbon dioxide. Furthermore, the applicability of this methodology to the preparation of pharmacologically active phenylacetic acid derivatives should be tested (Scheme 16). As magnesium salts are cheap Lewis acids the addition reactions and the preparation of the organozincs should also be studied on larger scales for potential industrial applications.



Scheme 16: Mg-salt promoted addition of functionalized organozinc reagents to aldehydes, ketones and carbon dioxide.

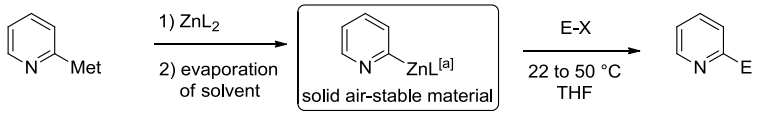
As the application of organozinc reagents is hampered by their limited stability towards air and moisture the preparation of more stable salt-stabilized organozinc derivatives which should be available as easy to handle solid materials was envisioned. Furthermore, the reactivity of these new solid organozinc reagents in Pd-catalyzed cross-coupling reactions and addition to carbonyl derivatives should be tested (Scheme 17).



L = stabilizing ligand; R^1 = aryl, heteroaryl; R^2 = aryl; R^3 = H, aryl; X = halogen
[a] complexed magnesium salts and LiCl are omitted for clarity

Scheme 17: Preparation of solid salt-stabilized organozinc reagents and their application to *Negishi* cross-coupling reactions and additions to carbonyls.

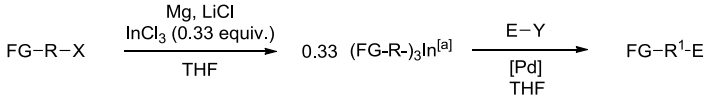
The 2-pyridyl subunit is an important structural motif in natural products, pharmaceuticals, materials and metal-complexing ligands. Thus, the use of 2-pyridyl nucleophiles in metal-catalyzed cross-coupling reactions is an important research field nowadays. Therefore, the preparation of solid 2-pyridylzinc reagents that can be handled on air for a certain amount of time without significant loss of acticity should be investigated. Furthermore, an efficient procedure for *Negishi* cross-couplings of these reagents under mild conditions should be developed (Scheme 18).



L = stabilizing ligand; X = Br, Cl
[a] complexed magnesium or lithium salts are omitted for clarity

Scheme 18: Preparation of solid 2-pyridylzinc reagents and their application to *Negishi* cross-coupling reactions.

The preparation of functionalized trisorganoindium reagents from organic halides *via* magnesium insertion in the presence of $InCl_3$ (0.33 equiv) should be investigated. The *in situ* formed *Grignard*-reagents should be directly transmetalated to the corresponding organoindium reagents. Thus, the method should display a high functional group tolerance at elevated temperatures. Moreover, the application of these reagents in Pd-catalyzed cross-coupling reactions should be studied (Scheme 19).



R = aryl, heteroaryl, benzyl; X = Br, Cl; Y = Br, I
[a] complexed magnesium salts and LiCl are omitted for clarity

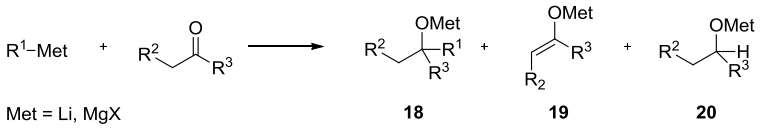
Scheme 19: Preparation of functionalized trisorganoindium reagents from organic halides *via* magnesium insertion in the presence of $InCl_3$ (0.33 equiv).

B. RESULTS AND DISCUSSION

1. Magnesium Halide-Mediated Addition of Functionalized Organozinc Reagents to Aldehydes, Ketones and Carbon Dioxide

1.1. Introduction

The addition of organometallic reagents to aldehydes, ketones and carbon dioxide is a very versatile way for the synthesis of secondary and tertiary alcohols as well as carboxylic acids.[4, 45] However, the direct addition product of organolithiums and *Grignard*-reagents (product **18** in Scheme 20) is often accompanied by byproducts arising from side reactions like the enolization of the carbonyl derivative (leading to **19**) or a *β*-hydride transfer from the organometallic reagent (leading to **20**).[46]



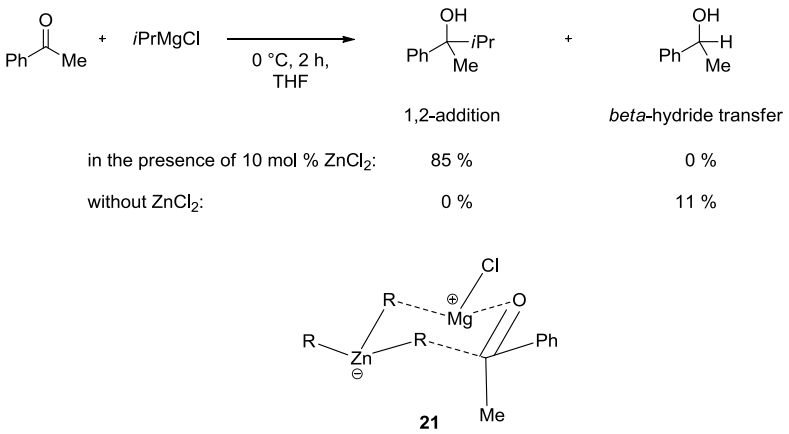
Scheme 20: 1,2-Addition of organolithium and -magnesium reagents to carbonyl compounds and potential side products.

When the addition reactions are carried out in the presence of Lewis acids like $CeCl_3$,[47] $LaCl_3 \cdot 2\ LiCl$[48] or $ZnCl_2$[49] the formation of the side-products can be significantly suppressed. The enhanced reactivity towards the 1,2-addition reaction can be attributed to an activation of the carbonyl function by complexation of the Lewis acid. Moreover, transmetalation reactions with the Lewis-acid may lead to organometallics with increased nucleophilicity and a lowered basicity.[47c, 49a, 50]

Ishihara and coworkers could efficiently demonstrate this principle in a $ZnCl_2$-catalyzed alkylation of ketones with *Grignard*-reagents.[49a] The *in situ* formed trialkylzincate complexes

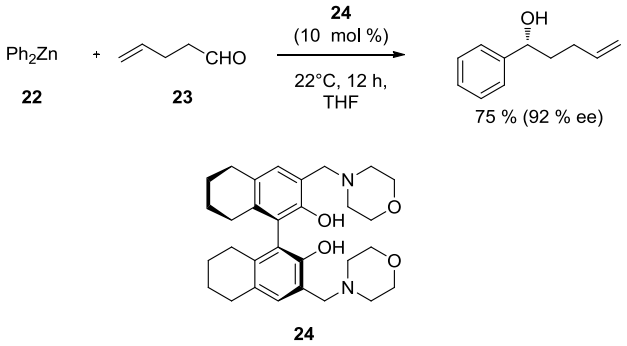
[45] M. Hatano, T. Miyamoto, K. Ishihara, *Curr. Org. Chem.* **2007**, *11*, 127.
[46] a) *The Chemistry of Organolithium Compounds*, (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**; b) *The Chemistry of Organomagnesium Compounds*, (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2007**.
[47] a) T. Imamoto, N. Takiyama, K. Nakamura, *Tetrahedron Lett.* **1985**, *26*, 4763; b) T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, *J. Am. Chem. Soc.* **1989**, *111*, 4392; c) G. Bartoli, E. Marcantoni, M. Marcolini, L. Sambri, *Chem. Rev.* **2010**, *110*, 6104.
[48] a) A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497; b) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227.
[49] a) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998; b) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647; c) M. Hatano, S. Suzuki, K. Ishihara, *Synlett* **2010**, 321.
[50] *Acid Catalysis in Modern Organic Synthesis*, *Vol. 1&2*, (Eds.: H. Yamamoto, K. Ishihara), Wiley-VCH, Weinheim, **2008**.

of the composition $R_3ZnMgCl$ show an optimal compromise in terms of nucleophilicity and basicity and undergo smooth addition reactions *via* a six-membered ring chair conformation of type **21** (Scheme 21).



Scheme 21: Addition of alkylmagnesium reagents to ketones in the presence of catalytic amounts of $ZnCl_2$.

Organozincs show only a low reactivity towards the direct addition to carbonyl derivatives and thus usually highly reactive dialkylzinc reagents have to be used in excess. However, in the presence of suitable chiral catalysts excellent enantioselectivities can be obtained.[51] In Scheme 22 this is exemplified for the addition of diphenylzinc (**22**) to the aliphatic aldehyde **23** in the presence of the H_8-binol **24** as the chiral catalyst.[52]

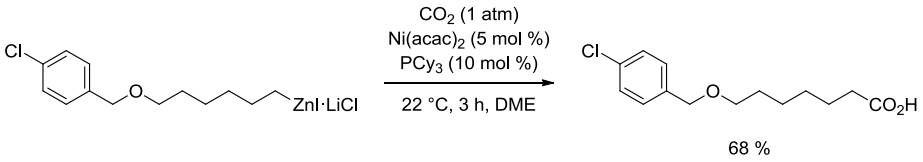


Scheme 22: Enantioselective addition of diphenylzinc (**22**) to the aliphatic aldehyde **23**.

[51] a) K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833; b) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757; c) J. M. Betancort, C. García, P. J. Walsh, *Synlett* **2004**, 749; d) G. Huelgas, L. K. LaRochelle, L. Rivas, Y. Luchinina, R. A. Toscano, P. J. Carroll, P. J. Walsh, C. A. de Parrodi, *Tetrahedron* **2011**, *67*, 4467; e) A. Lemire, A. Côté, M. K. Janes, A. B. Charette, *Aldrichim. Acta* **2009**, *42*, 71; f) M. Hatano, R. Gouzo, T. Mizuno, H. Abe, T. Yamada, K. Ishihara, *Catal. Sci. Technol.* **2011**, *1*, 1149.

[52] Y.-C. Quin, L. Pu, *Angew. Chem. Int. Ed.* **2006**, *45*, 273.

Recently, it was shown that the addition of functionalized organozinc reagents to CO_2 can be carried out *via* Pd-[53] or Ni-catalysis[54] in THF or DME as solvent (Scheme 23).[55]



Scheme 23: Ni-catalyzed addition of organozinc reagents to carbon dioxide.

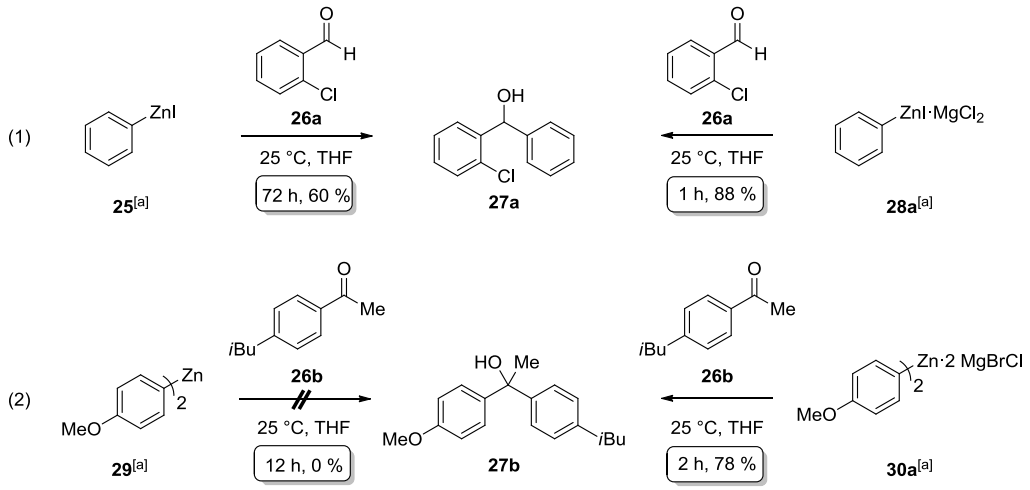
Moreover, *Kondo* and coworkers could show that organozinc reagents bearing complexed LiCl can be directly reacted with carbon dioxide, if DMF is used as solvent.[56]
Knochel and coworkers could demonstrate that benzylzinc chlorides, prepared by the direct insertion of magnesium into benzyl chlorides (compare Scheme 11), show a significantly higher rate of addition to carbonyl derivatives as the ones prepared by direct oxidative addition of zinc powder and thus bearing no complexed magnesium salts.[32a] Based on these result we investigated the reactivity of functionalized organozinc reagents prepared by the Mg/$ZnCl_2$/LiCl-method towards different carbonyl compounds and CO_2-gas.

1.2. Addition of Functionalized Organozinc Reagents to Carbonyl Derivatives

To be able to evaluate the effect of magnesium halides on the addition rates of functionalized organozincs to carbonyl compounds, comparative studies using organozinc reagents with and without complexed magnesium salts were carried out. Thus, the addition of PhZnI (**25**), prepared from iodobenzene by the insertion of zinc dust in the presence of LiCl,[31a] to 2-chlorobenzaldehyde (**26a**) required 72 h at 25 °C to reach completion and afforded (2-chlorophenyl)(phenyl)methanol (**27a**) in 60 % yield. In contrast, by using PhZnI·$MgCl_2$ (**28a**), prepared by the reaction of iodobenzene with magnesium turnings in the presence of $ZnCl_2$ and LiCl,[17] a complete conversion was obtained within 1 h at 25 °C. It led to the desired alcohol **27a** in 88 % yield (equation 1, Scheme 24).[57, 58] This study demonstrates

[53] C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 7826.
[54] H. Ochiai, M. Jang, K. Hirano, H. Yorimitsu, K. Ochima, *Org. Lett.* **2008**, *10*, 2681.
[55] L. Ackermann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3842.
[56] K. Kobayashi, Y. Kondo, *Org. Lett.* **2009**, *11*, 2037.
[57] The addition of $MgCl_2$ (1.0 equiv, prepared from Mg and $ClCH_2CH_2Cl$ in THF) to PhZnI·LiCl (**25**) leads to a similar rate acceleration and full conversion is obtained after 2 h at 25 °C (compared to 72 h in the absence of $MgCl_2$). Using PhZnBr·$MgCl_2$·LiCl (30 min reaction time at 25 °C) leads to the alcohol **27a** in 93 %. Furthermore, using PhZnCl·$MgCl_2$·LiCl (1 h reaction time at 25 °C) **27a** was obtained in 86 % yield.

impressively the dramatic addition rate acceleration triggered by the presence of $MgCl_2$ (1.0 equiv). Diorganozincs are more reactive than organozinc halides[28, 51e] and these reagents were found particularly well suited for addition reactions to ketones. The reaction of bis(4-methoxyphenyl)zinc (**29**) prepared from 4-bromoanisole (**31**; *n*BuLi, –78 °C, 2 h; then $ZnCl_2$ (0.5 equiv)) with 4-*iso*butylacetophenone (**26b**) did not proceed (25 °C, 12 h). However, the corresponding diarylzinc reagent **30a** which was prepared by direct insertion of magnesium into 4-bromoanisole (**31**) in the presence of LiCl and 0.5 equivalents of $ZnCl_2$ underwent a smooth addition to the ketone **26b** within 2 h at 25 °C and the tertiary alcohol **27b** was obtained in 78 %. Remarkably, both Ar-groups (0.60 equiv of **30a** were used) were transferred to the ketone (1.00 equiv of **26b** was used in the addition reactions; equation 2, Scheme 24).

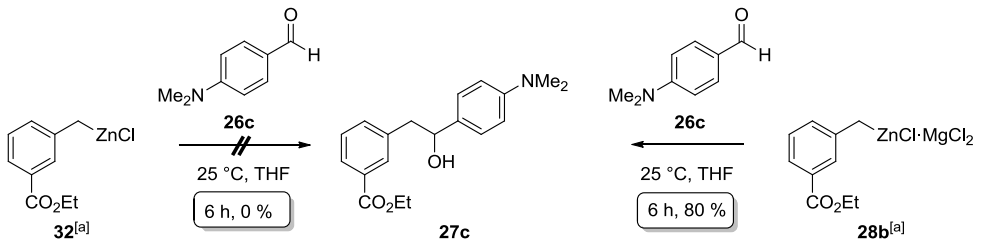


Scheme 24: Comparison of the reactivity of aryl- and diarylzinc reagents towards carbonyl compounds in the presence and absence of magnesium halide salts.

Functionalized benzylzincs showed the same behaviour and the addition of the ester-substituted benzylzinc reagent **32** prepared by the insertion of zinc dust in the presence of LiCl[31c] to the aldehyde **26c** did not proceed at 25 °C. Heating of the reaction mixture at 50 °C for 14 h only led to a conversion of 60 %. In strong contrast, by using the same zinc reagent complexed with $MgCl_2$ **28b** and prepared by the reaction of (3-ethoxycarbonyl)benzyl chloride with magnesium turnings in the presence of $ZnCl_2$ and LiCl,[32a] a full conversion was

[58] These experiments were performed by Albrecht Metzger and are given here for the sake of completeness. For further information, see: A. Metzger, *PhD Thesis*, Ludwig-Maximilians-Universität, Munich, **2010**.

achieved within 6 h at 25 °C and the secondary alcohol **27c** was isolated in 80 % yield (Scheme 25).[58]



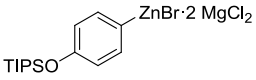
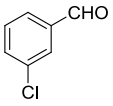
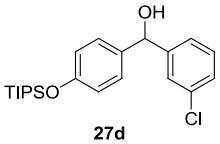
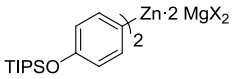
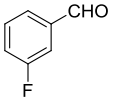
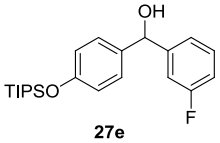
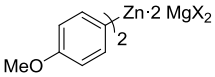
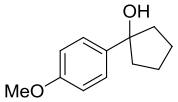
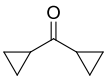
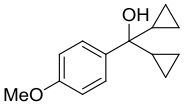
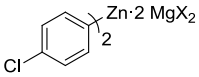
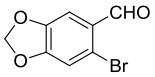
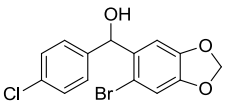
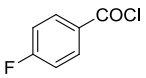
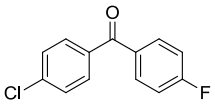
[a] complexed LiCl has been omitted for the sake of clarity

Scheme 25: Comparison of the reactivity of a benzylzinc reagent towards aldehyde **26c** in the presence and absence of magnesium chloride.

These magnesium halide-mediated addition reactions have an excellent reaction scope (Tables 1 and 2). Thus, the electron-rich arylzinc reagent 4-TIPSO-phenylzinc bromide·$MgCl_2$ (**28c**) added to the benzaldehyde **26d** at 25 °C and furnished the secondary alcohol **27d** in 85 % yield (entry 1, Table 1). The reaction of the corresponding bisarylzinc reagent **30b** with 3-fluorobenzaldehyde (**26e**) afforded the addition product **27e** in a comparable yield of 89 % on an 8.0 mmol scale (entry 2). Moreover, the addition of bis (4-methoxyphenyl)zinc·2 MgX_2 (**30a**) to cyclopentanone (**26f**) proceeded in 2 h at 25 °C and the corresponding tertiary alcohol **27f** was obtained in 84 % (entry 3). For the addition of **30a** to dicyclopropyl ketone (**26g**) the reaction temperature had to be raised to 50 °C and after 12 h the corresponding alcohol **27g** was afforded in 87 % yield (entry 4).[59] Furthermore, bis(4-chlorophenyl)zinc·2 MgX_2 (**30c**) smoothly added to the bromopiperonal **26h** in 95 % yield on a 10 mmol scale (entry 5). Interestingly, bis (4-chlorophenyl)zinc·2 MgX_2 (**30c**) could also be reacted with 4-fluorobenzoyl chloride (**26i**) without the need for additional copper(I)-salts. After 12 h reaction time at 25 °C the benzophenone **27i** was obtained in 81 % yield (entry 6).

[59] Using 4-MeO(C_6H_4)ZnBr·$MgCl_2$·LiCl (1.2 equiv) instead of the bis-arylzinc reagent **30a** (0.6 equiv) leads only to 30 % conversion of the ketone **26g** under similar reaction conditions.

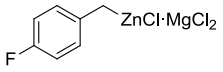
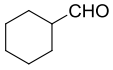
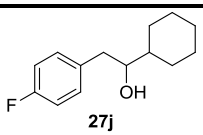
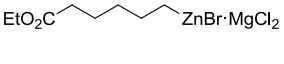
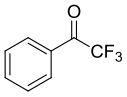
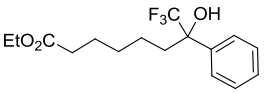
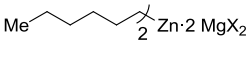
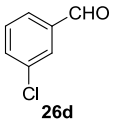
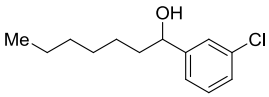
Table 1: Addition of arylzinc reagents of type **28** and diarylzinc reagents of type **30** to various carbonyl derivatives.

Entry	Zinc reagent[a], [b]	Carbonyl derivative	Time (h)[c]	Product	Yield (%)[d]
1	 **28c**	 **26d**	3	 **27d**	85
2	 **30b**	 **26e**	6	 **27e**	89[e]
3	 **30a**	 **26f**	3	 **27f**	84
4	**30a**	 **26g**	12[f]	 **27g**	87
5	 **30c**	 **26h**	10	 **27h**	95[g]
6	**30c**	 **26i**	12	 **27i**	81

[a] Complexed LiCl has been omitted for the sake of clarity. [b] X = Br, Cl. [c] All reactions are carried out at 25 °C unless otherwise indicated. [d] Isolated yield of analytically pure product. [e] Reaction performed on a 8 mmol scale. [f] Reaction performed at 50 °C. [g] Reaction performed on a 10 mmol scale.

Moreover, 4-fluorobenzylzinc chloride·$MgCl_2$ (**28d**) was added to cyclohexylcarbaldehyde (**26j**) at 25 °C in 6 h and afforded the alcohol **27j** in 97 % yield (entry 1, Table 2). In the same manner 5-ethoxycarbonylpentylzinc bromide·$MgCl_2$ (**28e**) added to 2,2,2-trifluoromethylacetophenone **26k** and after 24 h the tertiary alcohol **27k** was obtained in 60 % yield (entry 2). The bisalkylzinc reagent **30d** also reacted smoothly with 3-chlorobenzaldehyde (**26l**) leading to the addition product **27l** in 87 % yield (entry 3).

Table 2: Addition of benzylzinc reagent **28d** and alkylzinc reagents **28e** and **30d** to carbonyl derivatives.

Entry	Zinc reagent[a], [b]	Carbonyl derivative	Time (h)[c]	Product	Yield (%)[d]
1	 **28d**	 **26j**	6	 **27j**	97
2	 **28e**	 **26k**	24	 **27k**	60
3	 **30d**	 **26d**	14	 **27l**	87

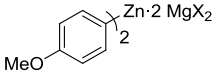
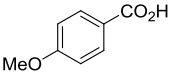
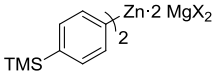
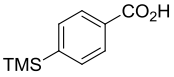
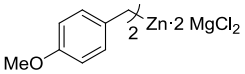
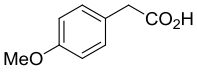
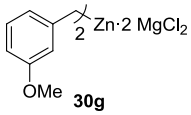
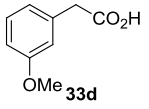
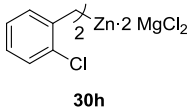
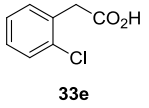
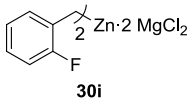
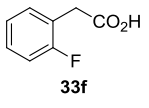
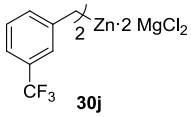
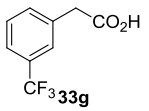
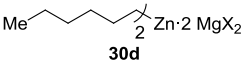
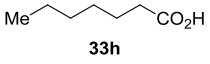
[a] Complexed LiCl has been omitted for the sake of clarity. [b] X = Br, Cl. [c] All reactions are carried out at 25 °C. [d] Isolated yield of analytically pure product.

1.3. Addition of Functionalized Organozinc Reagents to Carbon Dioxide

Remarkably, the presence of $MgCl_2$ allows the addition of aryl-, benzyl- and alkylzinc reagents to CO_2 (1 bar) at 25-50 °C in THF without the need of a polar solvent or transition metal catalysis.[53, 54, 56] In terms of atom economy[1, 3] it is advantageous to use diorganozinc reagents as with these reagents, both organic groups can be transferred to CO_2. Thus, bis(4-methoxyphenyl)zinc·2 MgX_2 (**30a**) added in THF to CO_2 (1 bar, 25 °C, 3 h) providing 4-methoxybenzoic acid (**33a**) in 94 % yield on a 10 mmol scale (entry 1 of Table 3).[60] Similarly, bis(4-trimethylsilylphenyl)zinc·2 MgX_2 (**30e**) was carboxylated within 6 h at 25 °C leading to the benzoic acid **33b** in 73 % yield (entry 2). Bisbenzyl zinc reagents of type **30f** reacted especially well and smoothly provided the corresponding phenylacetic acids **33c-g** in 80-98 % yield (entries 3-7). Furthermore, bis(*n*hexyl)zinc·2 MgX_2 (**30k**) could be converted at 50 °C to heptanoic acid (**33h**) in 86 % yield.

[60] Using 4-MeO(C_6H_4)ZnBr·$MgCl_2$·LiCl instead of the bisarylzinc reagent **30c** leads to full conversion within 6 h reaction time under similar reaction conditions.

Table 3: Addition of diaryl-, dibenzyl and dialkylzinc reagents to CO_2.

Entry	Zinc reagent[a, b]	Time (h)	Temperature (°C)	Product	Yield (%)[c]
1	 **30a**	3	25	 **33a**	94[d]
2	 **30e**	6	25	 **33b**	73
3	 **30f**	2	25	 **33c**	98
4	 **30g**	2	25	 **33d**	98
5	 **30h**	12	50	 **33e**	80[d]
6	 **30i**	12	25	 **33f**	98
7	 **30j**	12	50	 **33g**	86
8	 **30d**	12	50	 **33h**	86

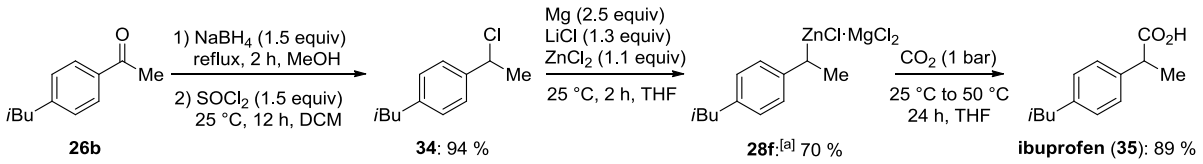
[a] Complexed LiCl has been omitted for the sake of clarity. [b] X = Br, Cl. [c] Isolated yield of analytically pure product. [d] Reaction performed on a 10 mmol scale.

Substituted phenylacetic acids often have useful pharmaceutical properties.[61] Thus, a short synthesis of the blockbuster drug ibuprofen (**35**)[62] based on the direct carboxylation of organozinc reagents in the presence of magnesium halide salts was developed. The synthesis is conducted in four steps which involve no transition metal catalysis and any elaborate purification step (Scheme 26). Thus, the reduction of the commercially available 4-*iso*-butylacetophenone (**26b**) with $NaBH_4$ (1.5 equiv, MeOH, reflux, 2 h) followed by

[61] a) A. Garcia Martínez, A. Herrera Fernández, D. Molero Vilchez, M. L. Laorden Gutiérrez, L. R. Subramanian, *Synlett* **1993**, 229; b) D. Rakowitz, A. Gmeiner, N. Schröder, B. Matuszcak, *Eur. J. Pharm. Sci*. **2006**, *27*, 188.

[62] a) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem. Int. Ed.* **2009**, *48*, 8547; b) Y. Chikusa, T. Fujimoto, M. Ikunaka, T. Inoue, S. Kamiyama, K. Maruo, J. Matsumoto, K. Matsuyama, M. Mariwaki, H. Nohira, S. Saijo, M. Yamanishi, K. Yoshida, *Org. Process Res. Dev.* **2002**, *6*, 291; c) C. R. Smith, T. V. RajanBabu, *J. Org. Chem.* **2009**, *74*, 3066.

chlorination using thionyl chloride (1.0 equiv, 25 °C, 12 h) provides the benzyl chloride **34** in 94 % yield over two steps. The corresponding benzyl zinc reagent **28f** is readily obtained (Mg turnings (2.5 equiv), LiCl (1.25 equiv), $ZnCl_2$ (1.1 equiv), THF, 25 °C, 2 h) in 70 % yield (10 mmol scale).[63] This secondary benzylzinc halide of type **28f** is sufficiently reactive to undergo an addition to CO_2 (1 bar for 12 h at 25 °C and then 12 h at 50 °C) to produce ibuprofen (**35**) in 89 % yield.



26b **34**: 94 % **28f**:[a] 70 % **ibuprofen** (**35**): 89 %

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

Scheme 26: Synthesis of ibuprofen (**35**) by carboxylation of the benzylic zinc reagent **28f**.

1.4. Mechanistic Considerations

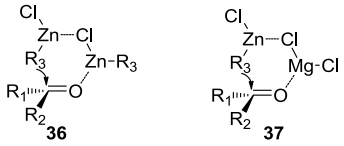
The acceleration effect of $MgCl_2$ may be rationalized by assuming that the usual 6-membered transition state (**36**) is modified by the presence of $MgCl_2$.[49a 64] Thus, R^3ZnCl which complexes the carbonyl group, is replaced by $MgCl_2$ (see the transition state **37**; Scheme 27). Since $MgCl_2$ is a stronger Lewis acid than R^3ZnCl, a more effective activation of the carbonyl group towards the addition of the zinc reagent is expected. Our results show that the addition of an organometallic reagent to a carbonyl group depends not only on the reactivity of the carbon-metal bond, but also on a Lewis acid activation of this carbonyl group. Both of these effects should be considered for predicting the addition rates of organometallics. Similar synergetic effects have been reported.[65, 66]

[63] The yield of the organozinc reagent was determined via titration with I_2: A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890; since LiCl is complexed to the organozinc reagents, neat THF instead of a 0.5 M solution of LiCl in THF can be used as the titration medium.

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

[65] E. Negishi, *Chem. Eur. J.* **1999**, *5*, 411.

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



Scheme 27: Tentative $MgCl_2$-modified six-membered transition state for the addition of R^3ZnCl to a carbonyl reagent (R^1R^2CO).

In a recent study based on this work *Hevia* and coworkers could show that in fact both $MgCl_2$ and LiCl are responsible for the increased intrinsic reactivity of the organozinc reagents by boosting their nucleophilicity as well as the electrophilicity of the carbonyl compound (Lewis acid activation).[67] In the presence of LiCl the formation of highly reactive mixed trimetallic Li-/Mg-/Zn-reagents is most likely.

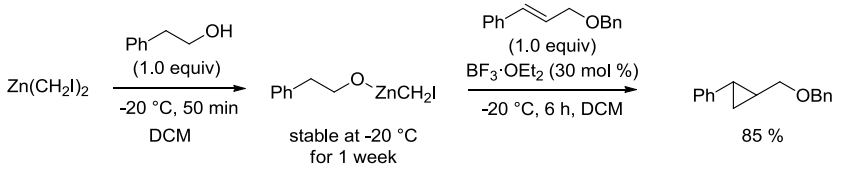
[67] D. R. Armstrong, W. Clegg, P. García-Álvarez, A. R. Kennedy, M. D. McCall, L. Russo, E. Hevia, *Chem. Eur. J.* **2011**, *17*, 8333.

2. Preparation of Solid Salt-Stabilized Organozinc Reagents

2.1. Preparation of Solid Salt-Stabilized Organozinc Reagents by Magnesium-Insertion in the Presence of $Zn(OPiv)_2$

2.1.1. Introduction

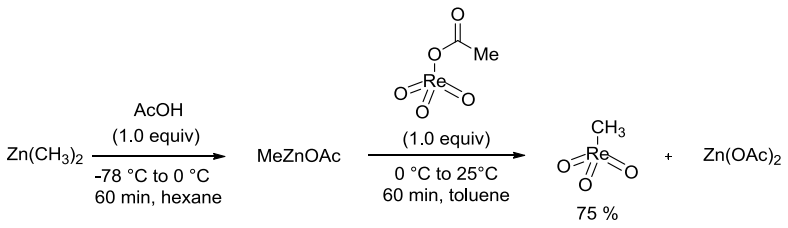
Organozinc reagents have found numerous synthetic applications, especially in the *Negishi* cross-coupling reaction.[4b, 68, 69] Various methods for the preparation of zinc organometallics have been reported.[4a, 8, 51e] However, polyfunctional zinc reagents of type RZnX (X = halide)[28, 31a] or R_2Zn are highly sensitive to moisture and air. These properties represent a serious drawback for their practical use at the laboratory and the industrial scale. Thus, the availability of more easy to handle organozincs is highly desirable. Since the reactivity of organozinc reagents is strongly influenced by the presence of salts,[49a, 50, 70, 71] it was anticipated that the presence of appropriate metallic salts may lead to an improved stability towards air and water. *Charette* has already demonstrated that alkoxides greatly stabilize zinc carbenoids for enantioselective cyclopropanations (Scheme 28).[72]



Scheme 28: Alkoxide-stabilzed iodomethylzinc reagent by *Charette*.

Furthermore, *Herrmann* reported that methylzinc acetate can be efficiently used for the synthesis of methyltrioxorhenium (MTO) even on larger scales (Scheme 29).[73]

[68] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17*, 4118.
[69] a) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028; b) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532; c) S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem. Int. Ed*. **2010**, *49*, 2014; d) N. Hadei, G. T. Achonduh, C. Valente, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed*. **2011**, *50*, 3896.
[70] a) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *Chem. Commun.* **2010**, 2674; b) L. Jin, C. Liu, J. Liu, F. Hu, Y. Lan, A. S. Batsanov, J. A. K. Howard, T. D. Marder, A. Lei, *J. Am. Chem. Soc.* **2009**, *131*, 16656; c) H. Duan, L. Meng, D. Bao, H. Zhang, Y. Li, A. Lei, *Angew. Chem. Int. Ed.* **2010**, *49*, 6387; d) K. Murakami, H. Yorimitsu, K. Oshima, *J. Org. Chem.* **2009**, *74*, 1415.
[71] See chapter **1** of Results and Discussion.
[72] A. B. Charette, C. Molinaro, C. Brochu, *J. Am. Chem. Soc.* **2001**, *123*, 12160.
[73] W. A. Herrmann, A. M. J. Rost, J. K. M. Mitterpleininger, N. Szesni, S. Sturm, R. W. Fischer, F. E. Kühn, *Angew. Chem. Int. Ed*. **2007**, *46*, 7301.



Scheme 29: Methylzinc acetate as efficient alkylation reagent in the synthesis of methyltrioxorhenium (MTO) by *Herrmann*.

2.1.2. Preparation of Solid Salt-Stabilized Arylzinc Reagents by Magnesium-Insertion in the Presence of $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**) and Their Application in *Negishi* Cross-Coupling Reactions

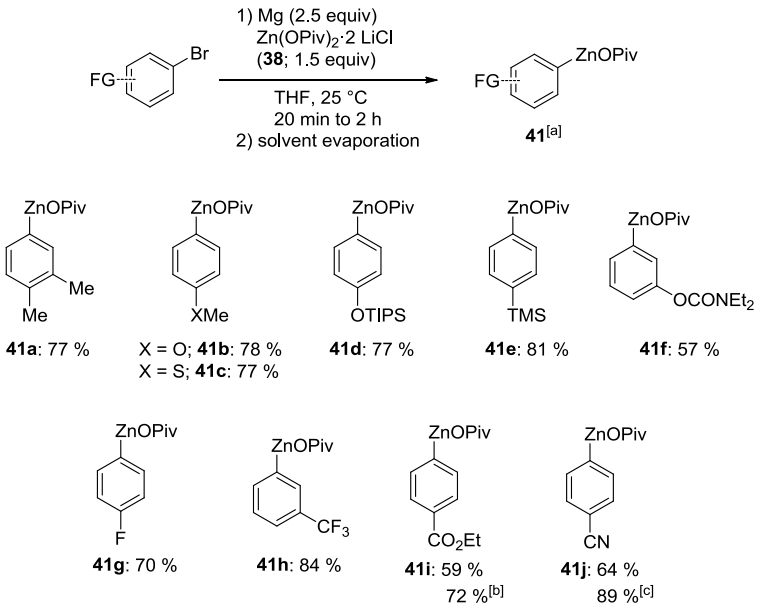
Preliminary studies showed that the presence of mixed magnesium-carboxylate-halide-salts of the composition PivOMgCl·LiCl (OPiv = pivalate) enable the synthesis of highly functionalized organomagnesium reagents *via* insertion of commercially available magnesium powder at low temperatures.[74] Thus, the insertion of magnesium turnings to aromatic halides in the presence of the THF-soluble salt $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**)[75] was investigated, as a comparable stabilizing effect of the pivalate-ligand to the formed organozinc reagent was expected.

Using 2.5 equiv of magnesium turnings and 1.5 equiv of $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**) led to a fast formation of the zinc reagent at 25 °C within 2 h.[17] The presence of $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**) not only stabilizes the resulting zinc reagent, but also accelerates dramatically its formation. Whereas 4-bromo-1,2-dimethylbenzene (**39**) required 2 h using $Mg/ZnCl_2 \cdot 2\,LiCl$,[17] with the combination $Mg/Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**), the insertion reaction was complete within 20 min, leading after evaporation of the solvent to the corresponding solid organozinc pivalate **41a** in 77 % yield.[63] This rate acceleration is essential for tolerating sensitive functional groups. This preparation method proved to have broad generality. After evaporation of THF, the resulting solid arylzinc reagents were obtained in 57-84 % yield as easy to handle powders (Scheme 30). This is in contrast with regular zinc reagents which produce only highly viscous oils when the solvents are evaporated.

[74] S. Bernhardt, *Master Thesis*, Ludwig-Maximilians-Universität, Munich, **2008**.

[75] $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**) is prepared by reacting pivalic acid with MeLi in THF and subsequent addition of $ZnCl_2$ (0.5 equiv). Although $Zn(OPiv)_2$ (**40**) is only moderately soluble in THF, the presence of LiCl allows the preparation of 0.5 to 1.0 M solutions in THF.

Using this method, a range of arylzinc reagents bearing electron-donating substituents (**41a-f**; FG = Me, OMe, SMe, OTIPS, TMS, $OCONEt_2$; 57-81 %) or electron-deficient substituents (**41g-j**; FG = F, CF_3, CO_2Et, CN; 59-84 %; Scheme 30) were prepared. Although the ester and nitrile substituted zinc reagents **41i** and **41j** could be prepared in satisfactory yields (59-64 %) by direct insertion, an improvement has been achieved using an I/Mg- or Br/Mg-exchange with *i*PrMgCl·LiCl followed by a transmetalation with $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; 72-89 %).[21]



[a] complexed Mg(OPiv)X (X = Br, Cl) and LiCl are omitted for clarity
[b] prepared by I/Mg-exchange with *i*PrMgCl·LiCl from ethyl-4-iodobenzoate (**42**) and transmetalation with $Zn(OPiv)_2 \cdot 2$ LiCl (**38**)
[c] prepared by Br/Mg-exchange with *i*PrMgCl·LiCl from 4-bromobenzonitrile (**43**) and transmetalation with $Zn(OPiv)_2 \cdot 2$ LiCl (**38**)

Scheme 30: Preparation of solid functionalized arylzinc pivalates of type **41** from the corresponding aromatic bromides using Mg and $Zn(OPiv)_2 \cdot 2$ LiCl (**38**).

Moreover, the solid zinc reagents of type **41** are stable under argon at room temperature for several weeks without significant loss of activity. Importantly, these zinc compounds can now be weighted in air (95 % of active zinc species **41h** was titrated after 5 min in air; entry 1, Table 4). Some decomposition was observed after longer exposure to air (still 58 % of active zinc species **41h** remained after 15 min, entry 3). After 60 min exposure to air no active zinc reagent could be detected anymore (entry 6). Analysis of the reaction samples after exposure to air and iodometric titration revealed that hydrolysis of the organozinc reagent *via* air moisture leads to trifluoromethylbenzene as the only detectable decomposition product. No side products derived from oxidation reactions, such as for example the corresponding phenol or the homocoupling product, were observed.

Table 4: Stability study of 3-(trifluoromethyl)phenylzinc pivalate (**41h**) towards the exposure to air.

Entry	Treatment	Active zinc species **41h** (%)[a]
1	storage under inert gas (7 d)	100
2	exposure to air (5 min)	95
3	exposure to air (15 min)	58
4	exposure to air (30 min)	43
5	exposure to air (45 min)	40
6	exposure to air (60 min)	0

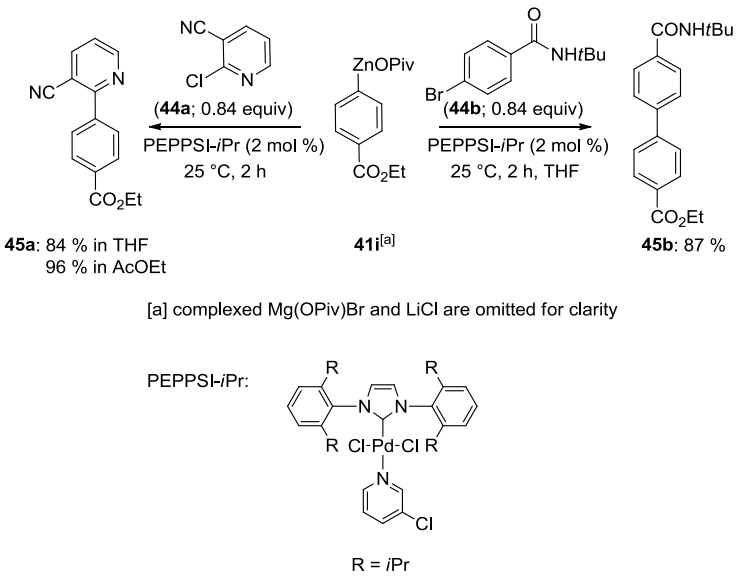
[a] Determined by titration with a stock solution of iodine (1.0 M in THF).

The organozincs of type **41** undergo *Negishi* cross-couplings under comparable mild conditions as the standard zinc reagents RZnX (X = halide) using 2 mol % of PEPPSI-*i*Pr[76] as catalyst. Thus, the reaction of a THF solution of the arylzinc pivalate **41i** with the pyridyl chloride **44a** led to the desired cross-coupling product **45a** at 25 °C within 2 h in 84 % yield. Interestingly, these cross-couplings can be performed in various solvents. Hence, using technical grade ethyl acetate[77] as solvent, the coupling of organozinc pivalate **41i** with the chloropyridine **44a** provided the biphenyl **45a** in 96 % yield. Although aryl bromides bearing relatively acidic protons, like for example an amide function, are suitable for *Negishi* cross-couplings, a slow addition of the zinc reagent over 90 min was usually required.[78] However, using arylzinc pivalates such as **41i** combined with PEPPSI-*i*Pr[76] as catalyst, the bromobenzamide **44b** could be added at once without special precautions leading within 2 h at 25 °C to the biphenyl **45b** in 87 % yield (Scheme 31).

[76] a) C. J. O'Brien, E. Assen B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. Assen B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; c) J. Nasielski, N. Hadei, G. Achonduh, E. Assen B. Kantchev, C. J. O'Brien, A. Lough, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10844; d) H. N. Hunter, N. Hadei, V. Blagojevic, P. Patschinski, G. T. Achonduh, S. Avola, D. K. Bohme, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 7845.

[77] Ethyl acetate was purchased from Sigma-Aldrich with a purity of 99 % and was used without drying or destillation prior to use.

[78] a) G. Manolikakes, Z. Dong, H. Mayr, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1324; b) G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765.

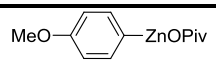
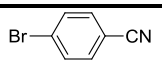
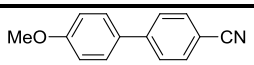
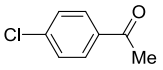
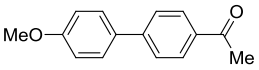
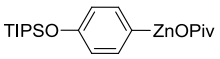
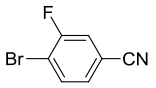
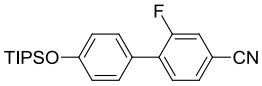
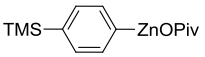
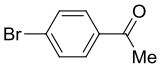
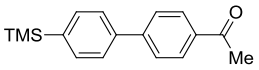
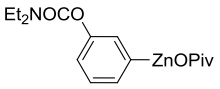
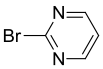
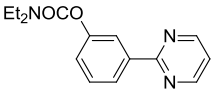
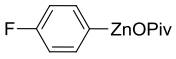
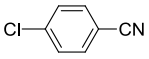
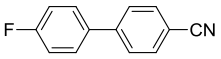
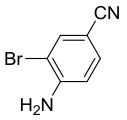
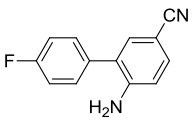
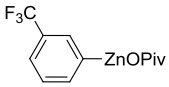
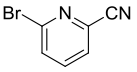
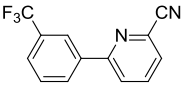
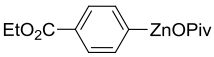
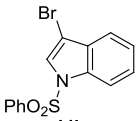
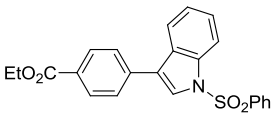
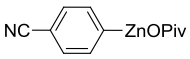
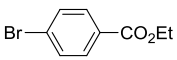
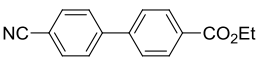
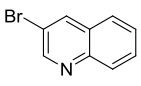
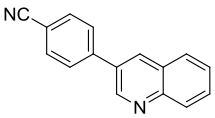


Scheme 31: PEPPSI-*i*Pr catalyzed one-pot cross-couplings of organozinc reagents of type **41** in THF or AcOEt.

The reaction scope of *Negishi* cross-couplings with arylzinc pivalates **41b-j** using functionalized aryl bromides and chlorides as well as heteroaryl bromides is very broad (Table 5). The uniformly fast reactions (2 h) were performed at 25 °C[79] and the expected products were obtained in high yields (67-99 %). The presence of an unprotected amine function in the aryl bromides is well tolerated (entry 7). Also, chloro- or bromo-acetophenones **44d** and **44f** react in satisfactory yields (67-83 %; entries 2 and 4). No appreciable enolization of the acetyl function could be detected and thus no excess of the organozinc reagents is required.

[79] Only the cross-coupling of 4-TIPSO-phenylzinc pivalate **41d** with 4-bromo-3-fluorobenzonitrile (**44e**) had to be performed at 50 °C.

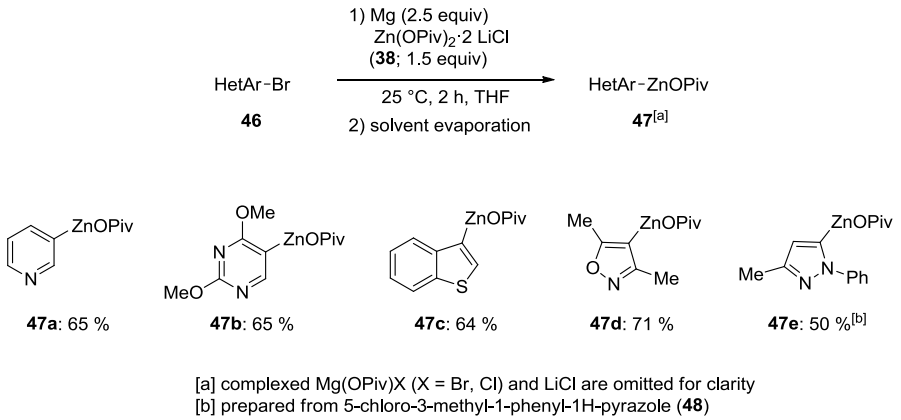
Table 5: PEPPSI-*i*Pr catalyzed cross-couplings of aromatic organozinc pivalates of type **41** in THF (or AcOEt) in 2 h at 25 °C.

Entry	Arylzinc Reagent[a]	Electrophile[b]	Product	Yield (%)[c]
1	 **41b**	 **44c**	 **45c**	86
2	**41b**	 **44d**	 **45d**	67
3	 **41d**	 **44e**	 **45e**	89[d]
4	 **41e**	 **44f**	 **45f**	83
5	 **41f**	 **44g**	 **45g**	80
6	 **41g**	 **44h**	 **45h**	80
7	**41g**	 **44i**	 **45i**	79[e]
8	 **41h**	 **44j**	 **45j**	78
9	 **41i**	 **44k**	 **45k**	99[f]
10	 **41j**	 **44l**	 **45l**	94[f]
11	**41j**	 **44m**	 **45m**	88

[a] Complexed Mg(OPiv)Br (X = Br, Cl) and LiCl are omitted for clarity. [b] 0.84 equiv of electrophile was used. [c] Isolated yield of analytically pure product. [d] The cross-coupling was perfomed at 50 °C. [e] This experiment was performed by Thomas Kunz and is given here for the sake of completeness. For further information, see: T. Kunz, *PhD Thesis*, Ludwig-Maximilians-Universität, Munich, **2011**. [f] The cross-coupling was performed in AcOEt.

2.1.3. Preparation of Solid Salt-Stabilized Heteroaryl- and Benzylzinc Reagents by Magnesium-Insertion in the Presence of $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**) and Their Application in *Negishi* Cross-Coupling Reactions

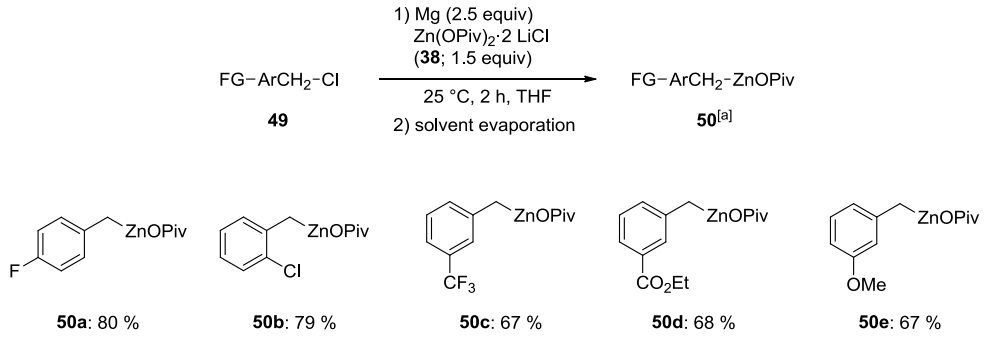
A range of heteroaromatic zinc pivalates could also be prepared from heterocyclic bromides (HetAr-Br) of type **46** using $Mg/Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**). The solid organozinc pivalates **47a-d** were obtained in 64-71 % yield under mild conditions (25 °C, 2 h, Scheme 32). The pyrazoylzinc pivalate **47e** was prepared from the corresponding heteroaryl *chloride* **48** in a moderate yield (50 %).



[a] complexed Mg(OPiv)X (X = Br, Cl) and LiCl are omitted for clarity
[b] prepared from 5-chloro-3-methyl-1-phenyl-1H-pyrazole (**48**)

Scheme 32: Preparation of solid functionalized heteroaromatic zinc pivalates of type **47** from the corresponding heteroaromatic bromides of type **46**.

Furthermore, the method was also applicable to the synthesis of various benzylic zinc pivalates of type **50** using benzyl chlorides of type **49**. The insertion with $Mg/Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**) proceeded well at 25 °C in 2 h and after evaporation of the solvent the solid organozincs **50a-e** were obtained in 67-80 % yield (Scheme 33).



[a] complexed Mg(OPiv)Cl and LiCl are omitted for clarity

Scheme 33: Preparation of solid functionalized benzylic zinc pivalates of type **50** from the corresponding benzylic chlorides **49**.

When the solid benzylzinc pivalate **50e** was exposed to air an initial lower stability compared to the corresponding aryl- and heteroarylzinc pivalates was observed (Table 6). After 5 min in air 77 % of active zinc species **50e** were detected (entry 1). After 60 min exposure to air 24 % of active zinc reagent **50e** could still be detected (entry 5).

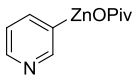
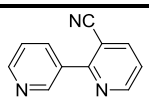
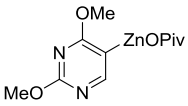
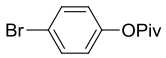
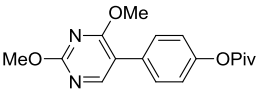
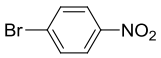
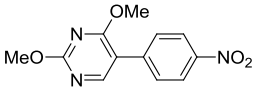
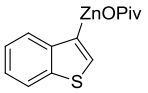
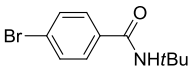
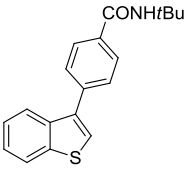
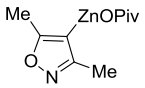
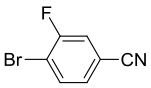
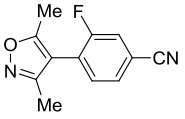
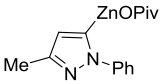
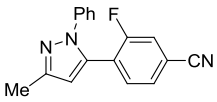
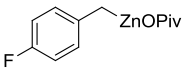
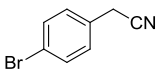
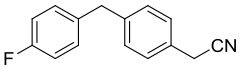
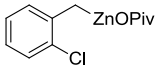
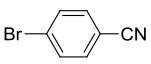
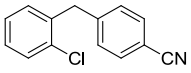
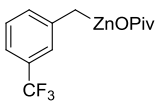
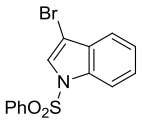
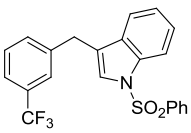
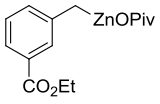
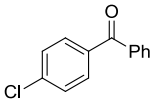
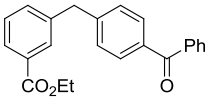
Table 6: Stability study of 3-methoxybenzylzinc pivalate (**50e**) towards the exposure to air.

Entry	t in air	Active zinc species **50e** (%)[a]
1	5 min	77
2	15 min	61
3	30 min	58
4	45 min	40
5	60 min	24

[a] Determined by titration with a stock solution of iodine (1.0 M in THF).

The heteroaromatic zinc pivalates (**47a-c**) and the benzylzinc pivalates (**50a-d**) reacted also under mild conditions (25 °C, 2 h) and PEPPSI-*i*Pr catalysis (2 mol %) with various heteroaryl halides and aryl bromides in high yields (70-99 %, Table 7). For the isoxazolyl and pyrazolyl zinc pivalates **47d** and **47e** the reaction temperature had to be increased to 50 °C to obtain full conversion with the bromobenzonitrile **44e** (entries 5 and 6). Electrophiles bearing functionalities with acidic protons like the amide **44b** and the phenylacetonitrile **44o** were also used in the cross-couplings applying our standard procedure (entries 4 and 7).

Table 7: PEPPSI-*i*Pr catalyzed cross-couplings of heteroaromatic and benzyl organozinc pivalates of type **47** and **50** in THF in 2 h at 25 °C.

Entry	Zinc Reagent[a]	Electrophile[b]	Product	Yield (%)[c]
1	 **47a**	 **44a**	 **51a**	91
2	 **47b**	 **44n**	 **51b**	80
3	**47b**	 **44o**	 **51c**	71
4	 **47c**	 **44b**	 **51d**	84
5	 **47d**	 **44e**	 **51e**	99[d]
6	 **47e**	**44e**	 **51f**	98[d]
7	 **50a**	 **44o**	 **52a**	81
8	 **50b**	 **43**	 **52b**	70
9	 **50c**	 **44p**	 **52c**	86
10	 **50d**	 **44q**	 **52d**	85

[a] Complexed Mg(OPiv)X (X = Br, Cl) and LiCl are omitted for clarity. [b] 0.84 equiv of electrophile was used. [c] Isolated yield of analytically pure product. [d] The cross-coupling was perfomed at 50 °C.

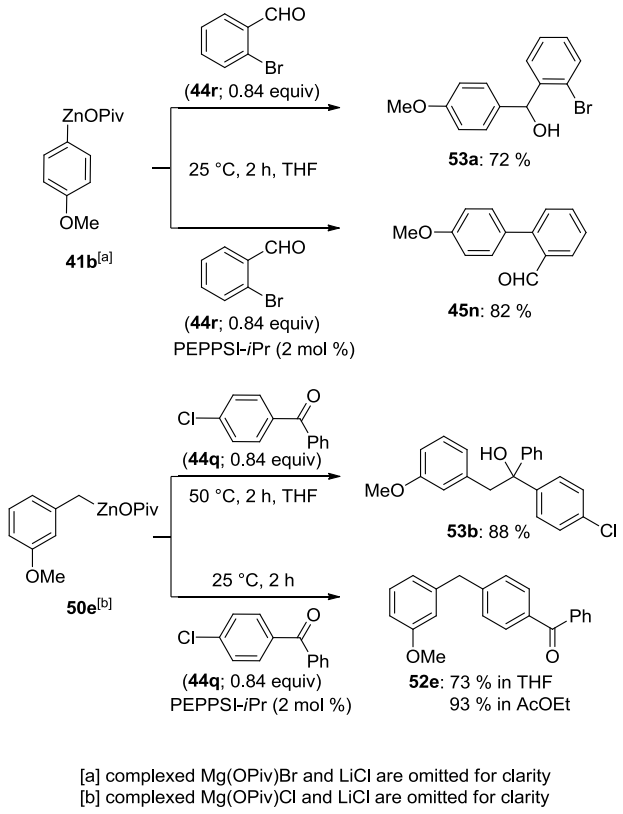
2.1.4. Tuneable Reactivity of Solid Aryl- and Benzylzinc Pivalates Towards Carbonyl Derivatives

Recently, *Knochel* and coworkers have shown that $MgCl_2$ greatly enhances the reactivity of organozinc reagents towards carbonyl derivatives.[71] In fact both, $MgCl_2$ and LiCl,[67] increase the intrinsic reactivity of organozinc reagents by boosting their nucleophilicity as well as the electrophilicity of the carbonyl compound (Lewis acid activation).[80]

Such activation was also observed for arylzinc pivalates of type **41** and **50**. Thus, the reaction of the arylzinc pivalate **41b** with 2-bromobenzaldehyde **44r** produced rapidly the benzhydryl alcohol **53a** in 72 % yield due to additional presence of magnesium salts in reagent **41b**.[81] This salt effect could be overcome by the addition of the powerful Pd-catalyst PEPPSI-*i*Pr (2 mol %)[76] which now left the formyl group of **44r** untouched and provided the *Negishi* cross-coupling product **45n** in 82 % yield (Scheme 34). This behaviour has some generality and the reaction of a benzylic zinc pivalate such as **50e** with 4-chlorobenzophenone (**44q**) produces without additional catalyst the tertiary alcohol **53b** in 88 % yield in THF. However, by the addition of 2 mol % of PEPPSI-*i*Pr, the cross-coupled benzophenone derivative **52e** is obtained as the sole product in 73 % yield in THF.[81] Repeating the reaction in AcOEt led to an improved yield of 93 %.[81]

[80] a) E. Hevia, J. Z. Chua, P. García-Álvarez, A. R. Kennedy, M. D. McCall, *Proc. Nat. Acd. Sci. USA* **2010**, *107*, 5249. b) D. R. Amstrong, W. Clegg, P. García-Álvarez, M. D. McCall, L. Nuttall, A. R. Kennedy, L. Russo, E. Hevia, *Chem. Eur. J.* **2011**, *17*, 4470; c) D. R. Amstrong, P. García-Álvarez, A. R. Kennedy, R. E. Mulvey, J. A. Parkinson, *Angew. Chem. Int. Ed*. **2010**, *49*, 3185; d) E. Hevia, R. Mulvey, *Angew. Chem. Int. Ed*. **2011**, *50*, 6448; e) J. G. Kim, P. J. Walsh, *Angew. Chem. Int. Ed*. **2006**, *45*, 4175; f) L. Salvi, J. G. Kim, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 12483.

[81] This experiment was performed by Thomas Kunz and is given here for the sake of completeness. For further information, see: T. Kunz, *PhD Thesis*, Ludwig-Maximilians-Universität, Munich, **2011**.



[a] complexed Mg(OPiv)Br and LiCl are omitted for clarity
[b] complexed Mg(OPiv)Cl and LiCl are omitted for clarity

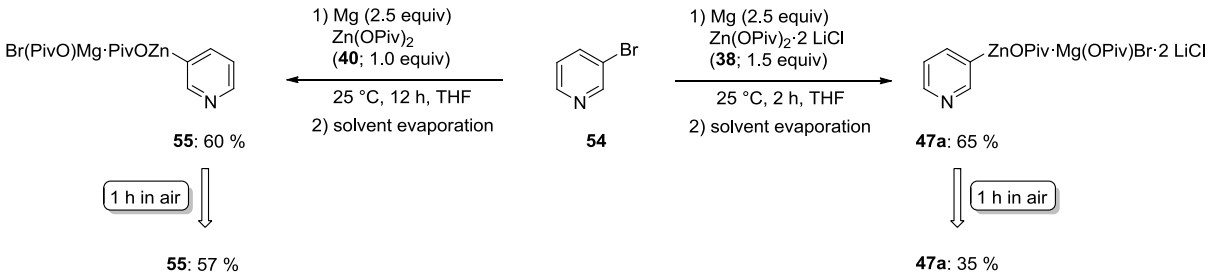
Scheme 34: Tuneable reactivity of organozincs of type **41** and **50** by the presence or absence of PEPPSI-*i*Pr.

2.1.5. Improvement of the Air-Stability of the Solid Salt-Stabilized Organozinc Reagents Prepared *via* Magnesium-Insertion in the Presence of $Zn(OPiv)_2$ (**40**)

The decomposition of the solid salt-stabilized organozincs in air could be mainly attributed to the hydrolysis of the reagents *via* air moisture. Therefore, it was assumed that a decreased hygroscopy of the reagents should lead to an improved air-stability. LiCl is known to be extremely hygroscopic.[82] Thus, organozinc reagents bearing no complexed LiCl should have a lower tendency to undergo hydrolysis in air. To proof this assumption we prepared 3-pyridylzinc pivalate with and without complexed LiCl and compared the stability of solid organozincs towards air (Scheme 35). The 3-pyridylzinc pivalate **47a** with complexed LiCl was prepared *via* magnesium-insertion in the presence of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; 1.5 equiv; compare 2.2.) at 25 °C in 2 h and obtained in 65 % yield after evaporation of the solvent. After 1 h in air a yield of 35 % was determined by iodometric titration (this corresponds to a loss of 53 % of the initial activity). 3-Pyridylzinc pivalate **55** bearing no complexed LiCl was prepared *via* magnesium insertion in the presence of $Zn(OPiv)_2$ (**40**; 1.0 equiv) into 3-

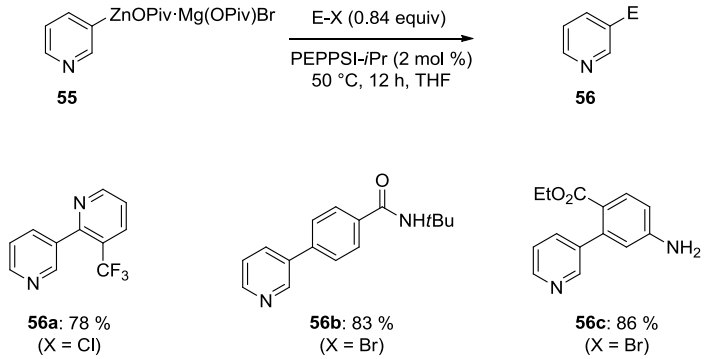
[82] U. Wietelmann, R. J. Bauer, *Lithium and Lithium Compounds* in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2012**, pp. 339-366.

bromopyridine (**54**). Given that $Zn(OPiv)_2$ (**40**) has a poor solubility in THF in the absence of LiCl, the initial appearance of the reaction mixture is heterogeneous and vigorous stirring for 12 h at 25 °C is needed for the reaction to go to completion. After evaporation of the solvent the 3-pyridylzinc pivalate **55** was obtained in 60 % yield. When the reagent was exposed to air for 1 h, only 5 % of the initial activity was lost (a yield decrement from 60 to 57 % was determined).



Scheme 35: Synthesis and air-stability of 3-pyridylzinc pivalates **47a** and **55** with and without complexed LiCl.

The 3-pyridylzinc pivalate **55** without complexed LiCl underwent *Negishi* cross-couplings under PEPPSI-*i*Pr-catalysis[76] and comparable mild conditions. Electrophiles bearing acidic protons like amides or anilines were well tolerated (Scheme 36).



Scheme 36: PEPPSI-*i*Pr-catalyzed *Negishi* cross-coupling of 3-pyridylzinc pivalate **55** bearing no complexed LiCl.

2.2. Improved Air-Stable Solid Aromatic Zinc Pivalates *via* Highly Selective Metalations and Their Application in *Negishi* Cross-Couplings

2.2.1. Introduction

Responding to the demand for more stable and easy to handle zinc organometallics, *Knochel* and coworkers have recently described the preparation of the first solid, salt-stabilized aryl, heteroaryl and benzylic zinc reagents of the general formula RZnOPiv·Mg(OPiv)X·2 LiCl (X = Cl, Br, I; OPiv = pivalate).[83] These new organozinc species, prepared by magnesium insertion on halogenated precursors and *in situ* trapping of the Grignard intermediates with $Zn(OPiv)_2$·2 LiCl (**38**), exhibit excellent reactivity in *Negishi* cross-coupling reactions and undergo Mg(II)-promoted additions to carbonyl compounds.[84] Although, the aryl and heteroaryl halides used for the preparation of the solid organozinc pivalates by insertion using $Mg/Zn(OPiv)_2$·2 LiCl (**38**) are readily available, the preparation of these organometallics by directed metalation was envisioned and thus, various arenes and heteroarenes could serve as even more convenient starting materials.[85]

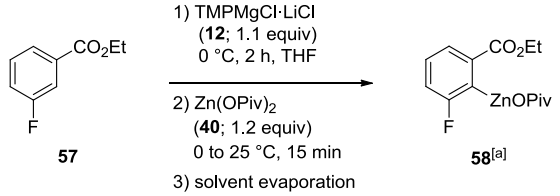
2.2.2. Preparation and Air-Stability of Aromatic Zinc Pivalates Prepared *via* Highly Selective Metalation

The metalation of ethyl 3-fluorobenzoate (**57**), using TMPMgCl·LiCl (**12**, TMP = 2,2,6,6-tetramethylpiperidide, 1.1 equiv, THF, 0 °C, 2 h) followed by transmetalation with $Zn(OPiv)_2$ (**40**) was examined as the model reaction (Table 8).[86] Thus, ethyl 3-fluorobenzoate (**57**) was treated with TMPMgCl·LiCl (**12**; 1.1 equiv) at 0 °C in THF. After 2 h at 0 °C full conversion[87] was observed and $Zn(OPiv)_2$ (**40**; 1.2 equiv, 0 to 25 °C, 15 min; Table 8, Scheme 37) was added for the transmetalation. After evaporation of the solvent in high vacuum, the solid arylzinc pivalate **58** was obtained as a yellow fine powder in 92 % yield, as determined by iodometric titration.[63] The resulting zinc compound **58** was found to exhibit

[83] See chapter **2.1.** of Results and Discussion.
[84] See chapter **2.1.4.** of Results and Discussion.
[85] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326; c) T. Kunz, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 866; d) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237; e) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; f) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.
[86] In chapter 2.1.5. of Results and Discussion it was demonstrated that the use of $Zn(OPiv)_2$ (**40**) is beneficial over the use of $Zn(OPiv)_2$·2 LiCl (**38**) in terms of air stability.
[87] GC-analysis of a reaction aliquot quenched with iodine showed no remaining starting material **57**.

increased stability compared to the organozinc pivalates prepared by magnesium insertion (100 % of its initial concentration was maintained after 1 h of air exposure (Table 8, entry 1), while this percentage drops to 90 % after 4 h (entry 4).[63] After 24 h in air still 24 % of active zinc species could be detected (entry 5).

Table 8: Air stability of (2-(ethoxycarbonyl)-6-fluorophenyl)zinc pivalate (**58**) over time.



[a] complexed Mg(OPiv)Cl and LiCl are omitted for clarity

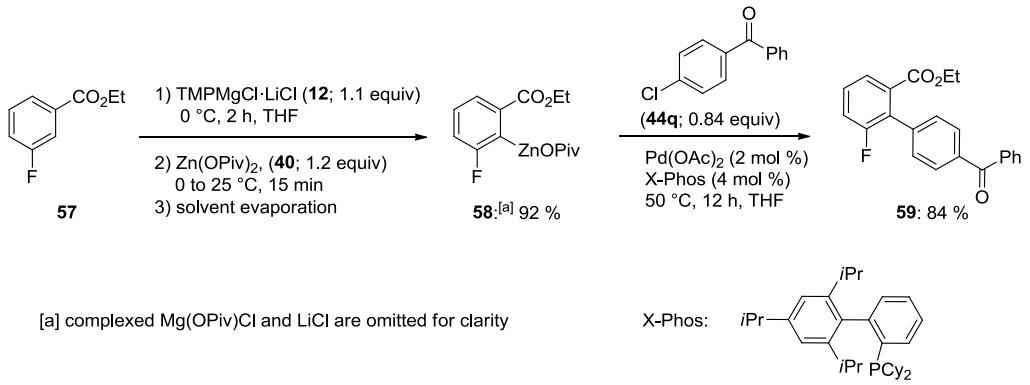
Entry	t in air	Active zinc species **58** (%)[a]
1	0 h	100
2	1 h	100
3	2 h	95
4	4 h	90
5	24 h	24

[a] Determined by titration with a stock solution of iodine (1.0 M in THF).

2.2.3. Application of Aromatic Zinc Pivalates Prepared *via* Highly Selective Metalation in *Negishi* Cross-Couplings

The 2-(ethoxycarbonyl)-6-fluorophenyl)zinc pivalate **58** proved to be an excellent nucleophile in *Negishi* cross-coupling reactions. Redissolution of the solid zinc compound **58** in dry THF (0.5 M), followed by addition of $Pd(OAc)_2$ (2 mol %) and X-Phos (4 mol %),[88] and subsequently, 4-chlorobenzophenone (**44q**; 0.84 equiv), led to biphenyl **59** in 84 % yield after heating at 50 °C for 12 h (Scheme 37).

[88] X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.

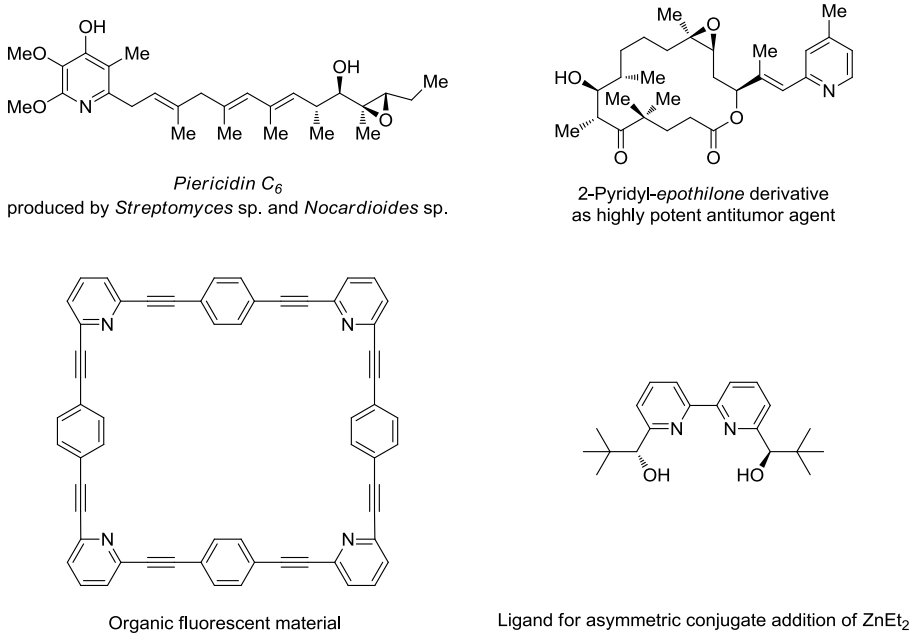


Scheme 37: Preparation of zinc pivalate **58** *via* directed metalation and subsequent *Negishi* cross-coupling using $Pd(OAc)_2$/X-Phos as the catalytic system.

2.3. Solid 2-Pyridylzinc Pivalates and Their Application to *Negishi* Cross-Coupling Reactions

2.3.1. Introduction

The 2-pyridyl subunit is an important structural motif that can be found in natural products,[89] pharmaceuticals,[90] materials[91] and metal-complexing ligands[92] (Scheme 38).

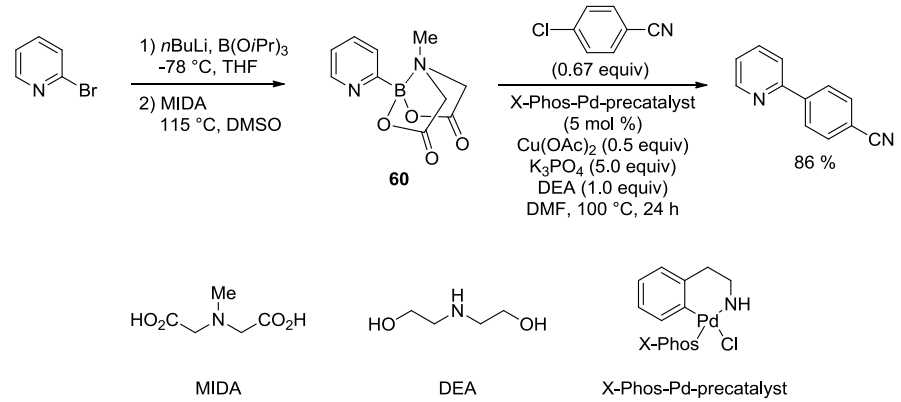


Scheme 38: Selected examples of important structures comprising the 2-pyridyl motif.

Thus, the development of efficient synthetic methods for the introduction of 2-pyridyl moieties is of great interest. Especially the use of 2-pyridyl nucleophiles in metal-catalyzed cross-coupling reactions is an important research field nowadays.[9c, 93] So far, *Stille*- and *Suzuki* cross-couplings using the corresponding 2-pyridylstannanes and -boronic acids have been the major approaches to tackle this problem.[94, 95] However, the application of organotin reagents on industrial scale is precluded by their high toxicity and their poor solubility in

[89] N. N. Kubota, E. Ohta, S. Ohta, F. Koizumi, M. Suzuki, M. Ichimura, S.Ikegami, *Bioorg. Med. Chem.* **2003**, *11*, 4569.
[90] K. C. Nicolaou, R. Scarpelli, B. Bollbuck, B. Werschkun, M. M. A. Pereira, M. Wartmann, K.-H. Altmann, D. Zaharevitz, R. Gussio, P. Giannakakou, *Chem. Biol.* **2000**, *7*, 593.
[91] Y. Yamaguchi, S. Kobayashi, S. Miyamura, Y. Okamoto, T. Wakamiya, Y. Matsubara, Z.-I. Yoshida, *Angew. Chem. Int. Ed.* **2004**, *43*, 366.
[92] C. Bolm, M. Ewald, *Tetrahedron Lett.* **1990**, *35*, 5011.
[93] G. R. Newkome, A. N. Patri, E. Holder, U. S. Schubert, *Eur. J. Org. Chem.* **2004**, 235.
[94] M. Hapke, L. Brandt, A. Lützen, *Chem. Soc. Rev.* **2008**, *37*, 2782.
[95] B. M. Coleridge, C. S. Bello, D. H. Ellenberger, A. Leitner, *Tetrahedron Lett.* **2010**, *51*, 357.

water which requires elaborate purification processes.[9c] The cross-coupling of 2-pyridyl boronic acids has been intensively studied.[93, 94, 96] However, the corresponding *Suzuki*-couplings require high reaction temperatures and the presence of stoichiometric amounts of copper-salts to promote the transmetalation to the palladium-catalyst.[97] Moreover, the 2-pyridyl boronic acids tend to decompose *via* protodeborylation reactions.[94] Recently, it was shown that the stability of boronic acids can be significantly increased in the presence of chelating N,O-ligands.[98] However, for the cross-coupling of the air-stable 2-pyridyl *N*-methyl-iminodiacetic acid (MIDA) boronate **60**, the use of 0.5 equiv of $Cu(OAc)_2$, 5.0 equiv of K_3PO_4, 1.0 equiv of diethanolamine in the presence of 5 mol % of the X-Phos-Pd-precatalyst[99] are required and the reaction has to be conducted in DMF at 100 °C for 24 h. Furthermore, the preparation of the MIDA-boronate **60** involves cryogenic as well as elevated temperatures and a subsequent purification (Scheme 39). [100]



Scheme 39: Preparation and cross-coupling of 2-pyridyl *N*-methyl-iminodiacetic acid (MIDA) boronate **60**.

The *Negishi* cross-coupling of 2-pyridylzinc reagents has been established as an attractive alternative to the corresponding *Suzuki*-couplings. The reactions can be conducted under

[96] For recent examples, see: a) K. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358; b) K. Billingsley, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 4695; c) J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissmann, S. R. Stauffer, C. S. Burgey, *Org. Lett.* **2009**, *11*, 345; d) D. X. Yang, S. L. Coletti, K. Wu, M. Song, G. Y. Li, H. C. Shen, *Org. Lett.* **2009**, *11*, 381; e) L. Ackermann, H. K. Potukochi, *Synlett* **2009**, 2852; f) B. M. Crowley, C. M. Potteiger, J. Z. Deng, C. K. Prier, D. V. Paone, C. S. Burgey, *Tetrahedron Lett.* **2011**, *52*, 5055; g) W. Ren, J. Li, D. Zou, Y. Wu, Y. Wu, *Tetrahedron* **2012**, *68*, 1351.

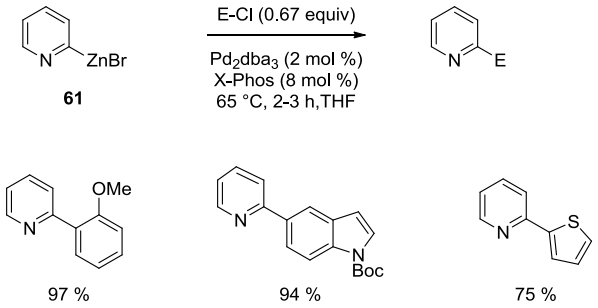
[97] M. R. Luzung, J. S. Patel, J. Yin, *J. Org. Chem.* **2010**, *75*, 8330 and references therein.

[98] a) E. P. Gillis, M. D. Burke, *Aldrichim. Acta* **2009**, *42*, 17; b) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961; c) P. H. Hodgson, F. H. Salingue, *Tetrahedron Lett.* **2004**, *45*, 685; d) A. Bouillon, J.-C. Lancelot, J. Sopkova de Oliveira Santos, V. Collot, P. B. Bovy, S. Rault, *Tetrahedron* **2003**, *59*, 10043.

[99] T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14073.

[100] G. R. Dick, E. M. Woerly, M. D. Burke, *Angew. Chem. Int. Ed.* **2012**, *51*, 2667.

comparable mild conditions and the addition of bases or Cu-salts is not required.[94, 95, 97, 101] Thus, different aryl and heteroaryl chlorides can be smoothly coupled with 2-pyridylzinc bromide (**61**) in THF at 65 °C using Pd_2dba_3 (2 mol %) and X-Phos (8 mol %) as the catalytic system (Scheme 40).[97]



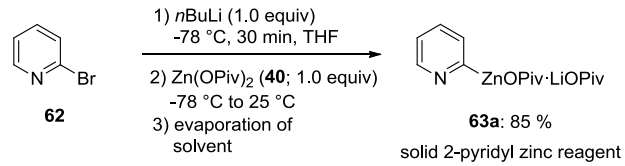
Scheme 40: *Negishi* cross-couplings of 2-pyridylzinc bromide (**61**) with aryl and heteroaryl chlorides.

So far, 2-pyridylzinc reagents are only available as solutions in THF.[95] Thus, there is a great interest in the availability of stable solid 2-pyridylzinc derivatives that can be stored for long time under argon and even be exposed to air for a certain time without significant loss of activity.

2.3.2. Preparation of Solid 2-Pyridylzinc Pivalates and Their Stability Towards Air

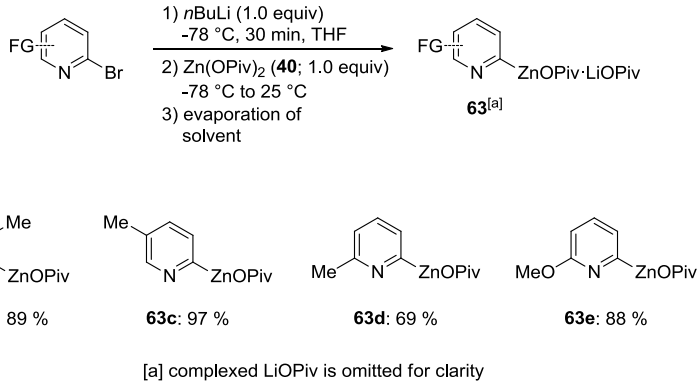
The transmetalation of organomagnesium reagents with $Zn(OPiv)_2$ (**40**) and subsequent evaporation of the solvent proved to be an efficient procedure to access solid functionalized aryl and heteroaryl zinc reagents.[102] Thus, the applicability of this process was also tested for the synthesis of solid 2-pyridylzinc reagents. In a first attempt a Br-Li exchange on 2-bromopyridine (**62**) was performed in THF at -78 °C using *n*BuLi (1.0 equiv). After 30 min at -78 °C solid $Zn(OPiv)_2$ (**40**) was added for the transmetalation and the mixture was then slowly warmed to 25 °C. After subsequent evaporation of the solvent 2-pyridylzinc pivalate (**63a**) was obtained as a slightly greenish solid in 85 % yield (Scheme 41).

[101] For recent examples for *Negishi* couplings of 2-pyridylzinc reagents, see: a) P. Walla, C. O. Kappe, *Chem. Commun.* **2004**, 564; b) U. Kiehne, J. Bunzen, H. Staats, A. Lützen, *Synthesis* **2007**, 1061; c) S.-H. Kim, R. D. Rieke, *Tetrahedron Lett.* **2010**, *51*, 2657; d) S.-H. Kim, R. D. Rieke, *Tetrahedron* **2010**, *66*, 3135; e) S.-H. Kim, R. D. Rieke, *Tetrahedron Lett.* **2011**, *52*, 244.
[102] See chapter 2.1. and 2.2. of Results and Discussion.



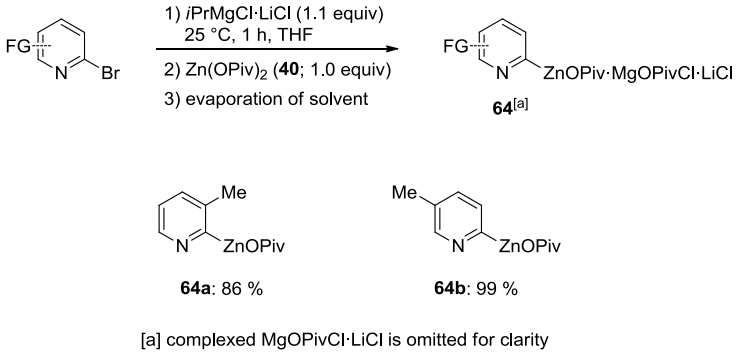
Scheme 41: Preparation of solid 2-pyridylzinc pivalate (**63a**) from 2-bromopyridine (**62**) *via* halogen-lithium exchange and subsequent transmetalation with $Zn(OPiv)_2$ (**40**).

This approach proved to be generally applicable and a range of functionalized solid 2-pyridylzinc pivalates of type **63** were accessible in good yields (69-97 %; Scheme 42).



Scheme 42: Solid 2-pyridylzinc pivalates of type **63** prepared *via* bromine-lithium exchange and subsequent transmetalation with $Zn(OPiv)_2$ (**40**).

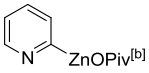
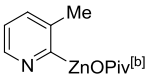
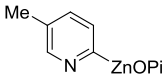
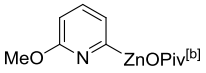
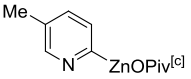
Whereas the bromine-lithium exchange has to be performed at -78 °C the corresponding bromine-magnesium exchange reaction using *i*PrMgCl·LiCl can be performed at elevated temperatures (up to 25 °C depending on the sensitivity of the functional groups).[21] Therefore, different 2-bromopyridines were reacted with 1.1 equiv of *i*PrMgCl·LiCl at 25 °C. The exchange was completed in 1 h and subsequent transmetalation with $Zn(OPiv)_2$ (**40**; 1.0 equiv) and evaporation of the solvent afforded the solid 2-pyridylzinc pivalates **64a-b** in 86-99 % yield (Scheme 43).



Scheme 43: Solid 2-pyridylzinc pivalates of type **64** prepared *via* bromine-magnesium exchange and subsequent transmetalation with $Zn(OPiv)_2$ (**40**).

Moreover, the stability of different 2-pyridylzinc pivalates towards their exposure to air for 1 h was investigated (Table 9). The unsubstituted 2-pyridylzinc pivalate (**63a**) and 6-methoxypyridin-2-ylzinc pivalate (**63e**) proved to have the highest stability, retaining 86-90 % of their initial activity after 1 h in air. The 3-methyl- and 5-methylpyridin-2-ylzinc pivalates **63b**, **63c** and **64b** preserved 69-72 % of their initial acitivity. Interestingly, the stability of 5-methylpyridin-2-ylzinc pivalate **64b** bearing 1.0 equiv of complexed LiCl is comparable to the one of the organozinc pivalates **63b** and **63c** without complexed LiCl.

Table 9: Activity of various 2-pyridylzinc pivalates after exposure to air for 1 h.

2-Pyridylzinc pivalate	 **63a**	 **63b**	 **63c**	 **63e**	 **64b**
Active zinc species (%)[a]	90	69	70	86	72

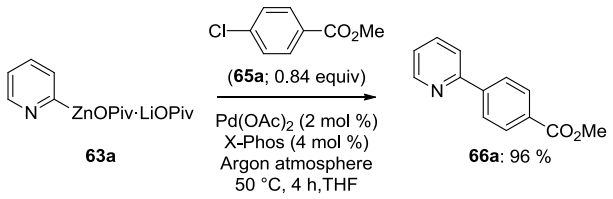
[a] After exposure to air for 1 h. [b] Complexed LiOPiv is omitted for clarity. [c] Complexed MgOPivCl·LiCl is omitted for the sake of clarity.

2.3.3. Application of Solid 2-Pyridylzinc Pivalates in *Negishi* Cross-Coupling Reactions

Furthermore, the application of the solid 2-pyridylzinc pivalates in *Negishi* cross-coupling reactions was investigated. *Buchwald*'s X-Phos-ligand[103] has been successfully applied in the coupling of 2-pyridylzinc halides with aryl chlorides.[97] Thus, 2-pyridylzinc pivalate (**63a**) was reacted with 0.84 equiv of methyl-4-chlorobenzoate (**65a**) in distilled THF in argon-

[103] X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.

atmosphere using 2 mol % $Pd(OAc)_2$ and 4 mol % X-Phos as the catalytic system. After 4 h stirring at 50 °C the coupling product **66a** could be isolated in 96 % yield (Scheme 44). Due to the sufficient air-stability of the solid zinc pivalate **63a**, the weighing of the reagent could be conveniently carried out in air.

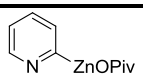
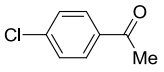
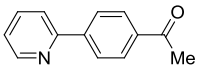
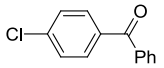
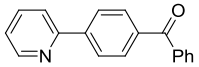
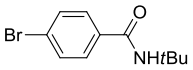
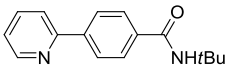
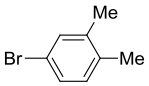
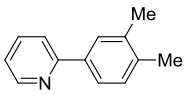
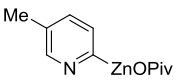
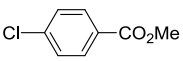
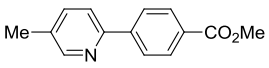
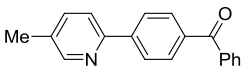
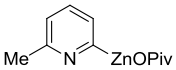
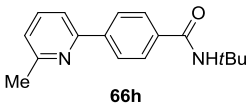
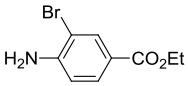
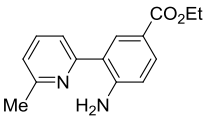
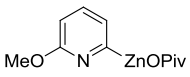
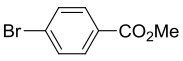
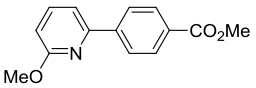
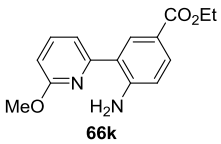
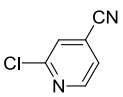
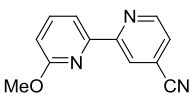


Scheme 44: *Negishi* cross-coupling of 2-pyridylzinc pivalate (**63a**).

Using these conditions the 2-pyridylzinc pivalates **63a**, **63c**, **63d**, **63e** could be coupled with different aryl bromides and chlorides as well as heteroaryl chloride **65d** in 60-98 % yield (Table 10).[104] The reactions were completed after stirring for 4 h at 50 °C. The presence of unprotected amide and amine functions in the aryl bromides was well tolerated (entries 3, 6, 8, 11) and the products could be isolated in 69-89 % yield.

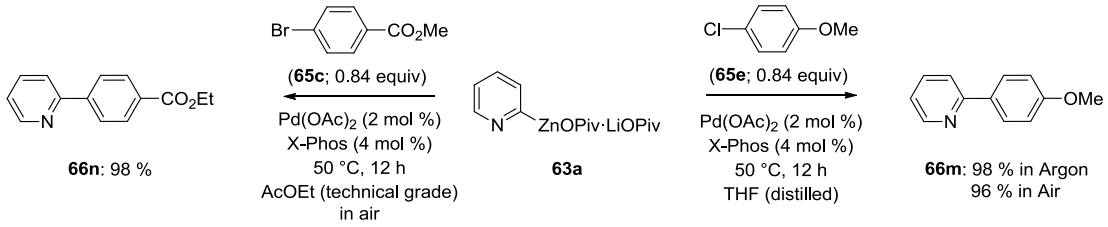
[104] 3-Methylpyridin-2-ylzinc pivalate **63b** did not undergo cross-coupling reactions under the conditions described in Scheme 44. An extensive screening of other catalyst systems and reaction conditions was also unsuccessful.

Table 10: *Negishi* cross-coupling of 2-pyridylzinc pivalates of type **63** in distilled THF under argon atmosphere in 4 h at 50 °C using $Pd(OAc)_2$ (2 mol %) and X-Phos (4 mol %) as the catalytic system.

Entry	2-Pyridylzinc pivalate[a]	Electrophile[b]	Product	Yield (%)[c]
1	 **63a**	 **44d**	 **66b**	94
2	**63a**	 **44q**	 **66c**	97
3	**63a**	 **44b**	 **66d**	89
4	**63a**	 **39**	 **66e**	75
5	 **63c**	 **65a**	 **66f**	60
6	**63c**	**44q**	 **66g**	78
8	 **63d**	**44b**	 **66h**	69
9	**63d**	 **65b**	 **66i**	83
10	 **63e**	 **65c**	 **66j**	98
11	**63e**	**65b**	 **66k**	77
12	**63e**	 **65d**	 **66l**	67

[a] Complexed LiOPiv is omitted for clarity. [b] 0.84 equiv of electrophile was used. [c] Isolated yield of analytically pure product.

To emphasize the practicability of these new 2-pyridylzinc pivalates of type **63** the compatibility of the reagents and their cross-couplings with air and technical grade solvents was further investigated. Therefore, 2-pyridylzinc pivalate **63a** was first reacted with 4-chloroanisole (**65e**) in distilled THF under argon atmosphere using 2 mol % of $Pd(OAc)_2$ and 4 mol % of X-Phos as the catalytic system. After 12 h at 50 °C the product **66m** could be isolated in 98 % yield (Scheme 45). Performing the reaction in air in a closed vial afforded the product **66m** in a slightly decreased yield of 96 %. When 2-pyridylzinc pivalate **63a** was coupled with methyl-4-bromobenzoate (**65c**) in technical grade AcOEt[77] in air, the coupling product **66n** was obtained in 98 % yield. Interestingly, the use of AcOEt as solvent led to an *in situ* transesterification to the corresponding ethylester-moiety in product **66n**.



Scheme 45: *Negishi* cross-couplings of 2-pyridylzinc pivalate (**63a**) in air and technical-grade AcOEt.

3. Preparation of Functionalized Organoindium Reagents *via* Magnesium Insertion in the Presence of $InCl_3$

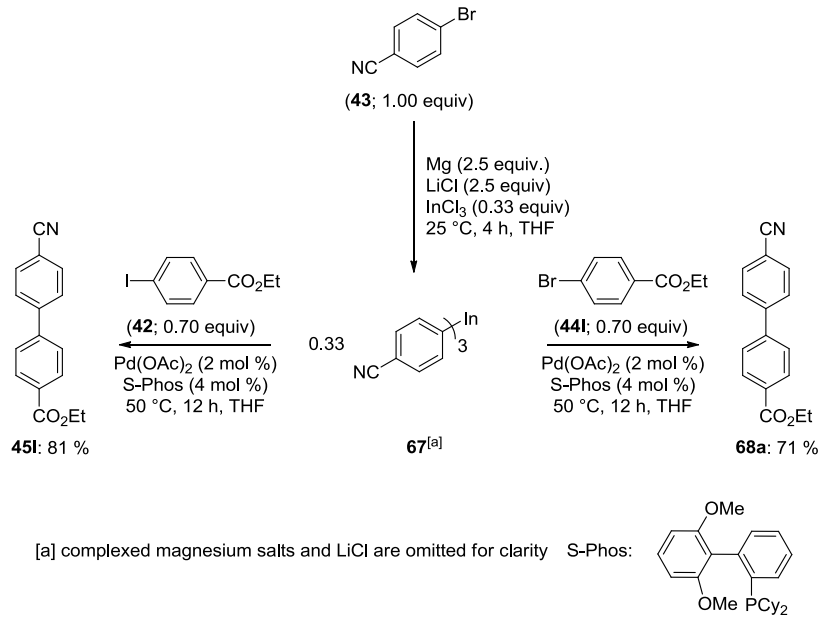
3.1. Introduction

The preparation of organoindium reagents *via* direct oxidative addition of elemental indium usually requires the use of an excess of the expensive metal source (1.2-4.0 equiv). Moreover, this approach is limited to the use of activated aryl and heteroaryl iodides as starting materials and the reactions have to be conducted at elevated temperatures.[42, 43] The preparation of organoindium reagents *via* transmetalation from the corresponding organolithium and –magnesium reagents is hampered by the lower functional group tolerance of the latter ones. Therefore, the preparation of the organolithiums or *Grignard*-reagents often involves the use of cryogenic temperatures. Thus, a methodology giving a direct access to trisorganoindium reagents under mild conditions (25 °C, THF) from cheaper aryl and heteroaryl bromides as well as benzyl chlorides would be highly desirable. Hence, the direct oxidative addition of magnesium-metal in the presence of 0.33 equiv of $InCl_3$ to organic halides was studied.

3.2. Preparation of Trisorganoindium Reagents and Their Application to Pd-Catalyzed Cross-Coupling Reactions

In a first attempt 4-bromobenzonitrile (**43**) was reacted with magnesium-turnings (2.5 equiv) in the presence of $InCl_3$ (0.33 equiv) and LiCl (2.5 equiv) in THF. After stirring for 4 h at 50 °C, GC-MS-analysis of a quenched reaction aliquot showed full conversion of the aryl bromide **43**. Thus, the trisarylindium reagent **67** was then separated from the excess magnesium-turnings *via* syringe and transferred to another reaction flask. $Pd(OAc)_2$ (2 mol %), S-Phos (4 mol %)[105] and ethyl 4-iodobenzoate (**42**; 0.7 equiv) were added and after stirring for 12 h at 50 °C the cross-coupling product **45l** could be detected as a single product and was isolated in 81 % yield. Moreover, this procedure allowed also the cross-coupling of the corresponding bromide **44l** in 71 % (Scheme 46).

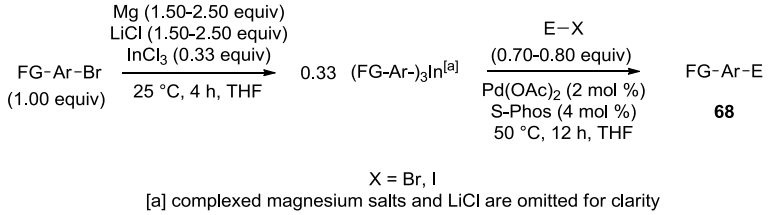
[105] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.

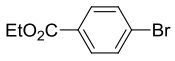
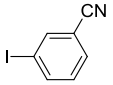
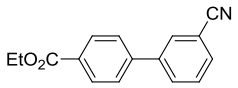
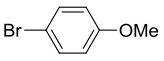
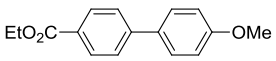
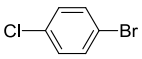
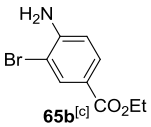
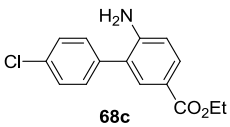
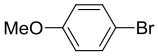
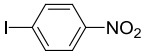
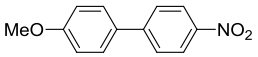
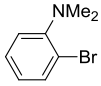
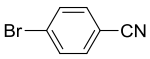
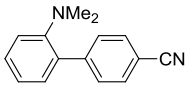
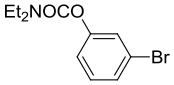
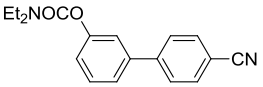
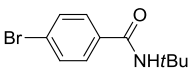
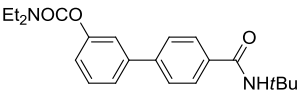
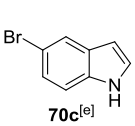
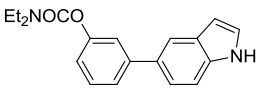


Scheme 46: Preparation of the trisarylindium reagent **67** *via* magnesium insertion in the presence of $InCl_3$ (0.33 equiv) and subsequent Pd-catalyzed cross-coupling.

This methodology could be applied for the preparation of a range of trisarylindium reagents and their subsequent cross-couplings (Table 11). Due to the fast *in situ* transmetalation of the initially formed *Grignard*-species to the organoindium reagent sensitive functionalities like a nitrile (Scheme 46), an ester-group (entries 1-2, Table 11) or a carbamate-moiety (entries 6-8) were well tolerated although the reactions were conducted at 25 °C. The insertion reaction proceeded in a comparable rate when the amount of used Mg/LiCl was reduced to 1.5 equiv (entries 6-8). Moreover, the cross-coupling reactions were all completed in between 12 h at 50 °C using THF as solvent and the products were obtained in 57-87 % yield. Electron-rich 4-bromoanisole (**31**) could be coupled (entry 2) and electrophiles bearing acidic protons like aniline **65b** (entry 3), amide **44b** (entry 7) or indole **70c** (entry 8) were well tolerated.

Table 11: Preparation of the trisarylindium reagents *via* magnesium insertion in the presence of $InCl_3$ (0.33 equiv) and subsequent Pd-catalyzed cross-coupling.

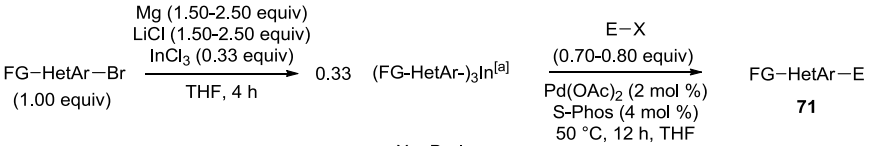


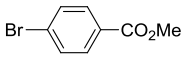
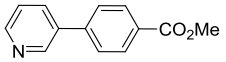
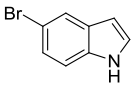
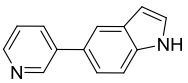
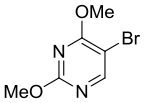
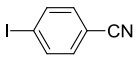
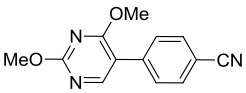
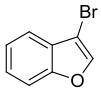
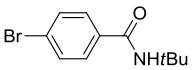
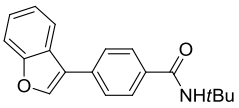
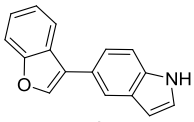
Entry	Aryl bromide	Electrophile	Product	Yield (%)[a]
1	 **44l**[b]	 **70a**[c]	 **68a**	67
2	**44l**[b]	 **31**[c]	 **68b**	57
3	 **69a**[b]	 **65b**[c]	 **68c**	82
4	 **31**[b]	 **70b**[c]	 **68d**	84
5	 **69b**[b]	 **43**[c]	 **68e**	69
6	 **69c**[d]	**43**[e]	 **68f**	74
7	**69c**[d]	 **44b**[e]	 **68g**	87
8	**69c**[d]	 **70c**[e]	 **68h**	64

[a] Isolated yield of analytically pure product. [b] Mg-turnings (2.50 equiv), LiCl (2.50 equiv), $InCl_3$ (0.33 equiv) were used for the preparation of the trisarylindium reagent. [c] 0.70 equiv of electrophile were used. [d] Mg-turnings (1.50 equiv), LiCl (1.50 equiv), $InCl_3$ (0.33 equiv) were used for the preparation of the trisarylindium reagent. [e] 0.80 equiv of electrophile were used.

Heteroaromatic indium reagents could be prepared in a similar manner starting from the corresponding heteroaryl bromides. Using $Pd(OAc)_2$/S-Phos as the catalytic systems enabled cross-coupling reactions with different aryl and heteroaryl bromides at 50 °C in THF in 68-90 % yield (Table 12).

Table 12: Preparation of the trisheteroarylindium reagents *via* magnesium insertion in the presence of $InCl_3$ (0.33 equiv) and subsequent Pd-catalyzed cross-coupling.

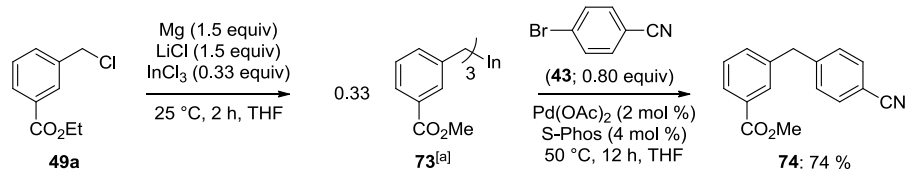


Entry	Heteroaryl bromide	Electrophile	Product	Yield (%)[a]
1	 **54**[b]	 **44l**[c]	 **71a**	82
2	**54**[b]	 **70c**[c]	 **71b**	90
3	 **72a**[d]	 **70d**[e]	 **71c**	68
4	 **72b**[b]	 **44b**[c]	 **71d**	76
5	**72b**[b]	**70c**[c]	 **71e**	69

[a] Isolated yield of analytically pure product. [b] Mg-turnings (1.50 equiv), LiCl (1.50 equiv), $InCl_3$ (0.33 equiv) were used for the preparation of the trisheteroarylindium reagent. [c] 0.80 equiv of electrophile were used. [d] Mg-turnings (2.50 equiv), LiCl (2.50 equiv), $InCl_3$ (0.33 equiv) were used for the preparation of the trisheteroarylindium reagent. [e] 0.70 equiv of electrophile were used.

Interestingly, this methodology was also applicable to the synthesis of functionalized benzylindium reagents. Thus, ethyl 3-(chloromethyl)benzoate (**49a**) is smoothly converted to the corresponding trisbenzylindium derivative **73** in 2 h at 25 °C using 1.5 equiv of Mg/LiCl in the presence of 0.33 equiv of $InCl_3$. Subsequent cross-coupling with 4-bromobenzonitrile

(**43**; 0.80 equiv) using $Pd(OAc)_2$/S-Phos as the catalytic system delivers the diarylmethane **74** in 74 % yield after 12 h at 50 °C (Scheme 47).



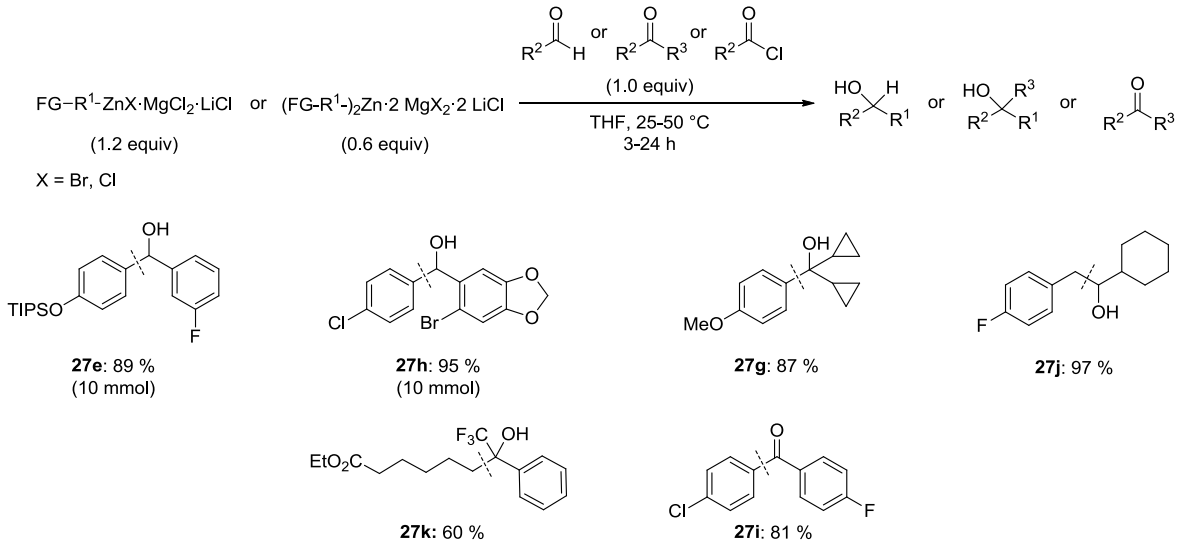
[a] complexed magnesium salts and LiCl are omitted for clarity

Scheme 47: Preparation of the trisbenzylindium reagent **73** *via* magnesium insertion in the presence of $InCl_3$ (0.33 equiv) and subsequent Pd-catalyzed cross-coupling.

4. Summary

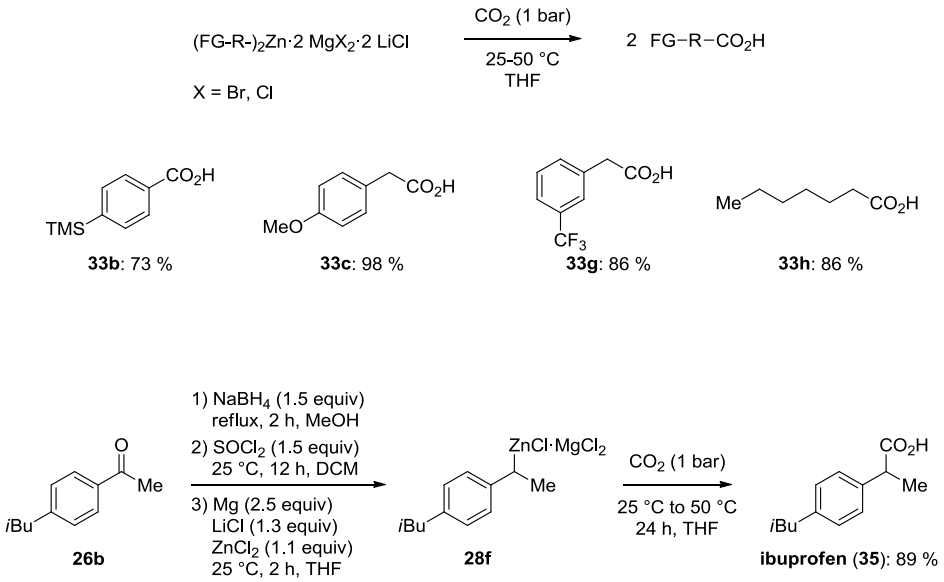
4.1. Magnesium Halide-Mediated Addition of Functionalized Organozinc Reagents to Aldehydes, Ketones and Carbon Dioxide

The addition of functionalized organozinc reagents to carbonyl derivatives and carbon dioxide in the presence of stoichiometric amounts of magnesium halide salts was investigated. The organozincs react under mild conditions with different aldehydes, ketones and acid chlorides and only a minor excess of the organometallic reagent has to be used. Furthermore, the reactions can be performed in larger scales (tested up to 10 mmol) without decrement of the yield (Scheme 48).



Scheme 48: Addition of functionalized organozinc reagents to carbonyl derivatives in the presence of stoichiometric amounts of magnesium halide salts.

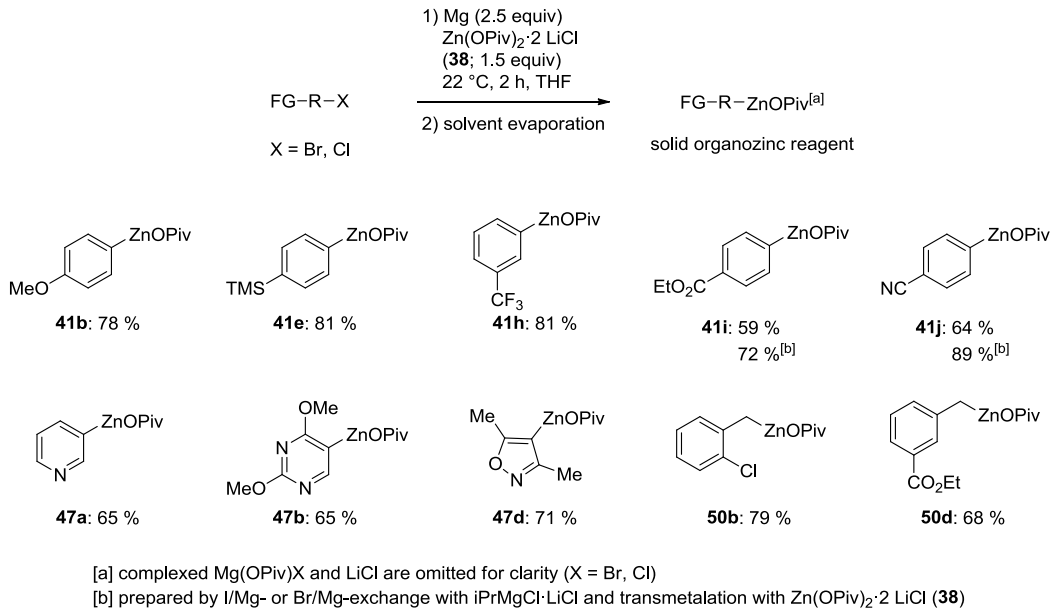
The presence of magnesium salts enables also the direct addition of functionalized aryl-, benzyl-, and alkylzinc reagents to carbon dioxide in THF at 25 to 50 °C in scales up to 10 mmol. Moreover, based on this methodology an efficient short synthesis of the blockbuster drug ibuprofen (**35**) was developed (Scheme 49).



Scheme 49: Direct addition of functionalized organozinc reagents to CO_2-gas in the presence of stoichiometric amounts of magnesium halide salts and application to the synthesis of ibuprofen (**35**).

4.2. Preparation of Solid Salt-Stabilized Organozinc Reagents

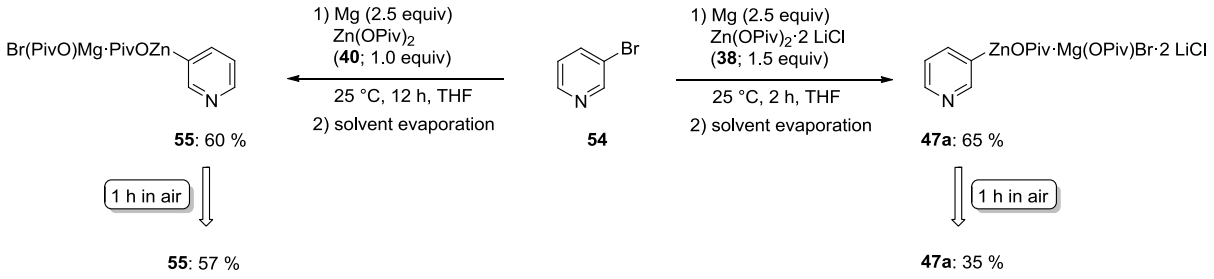
A first general approach towards the preparation of solid salt-stabilized organozinc reagents *via* magnesium insertion in the presence of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**) was developed. Thus, different functionalized aryl-, heteroaryl- and benzylzinc pivalates are accessible from the corresponding organic halides under mild conditions and are obtained as easy to handle solids after evaporation of the solvent (Scheme 50).



[a] complexed Mg(OPiv)X and LiCl are omitted for clarity (X = Br, Cl)
[b] prepared by I/Mg- or Br/Mg-exchange with iPrMgCl·LiCl and transmetalation with $Zn(OPiv)_2$·2 LiCl (**38**)

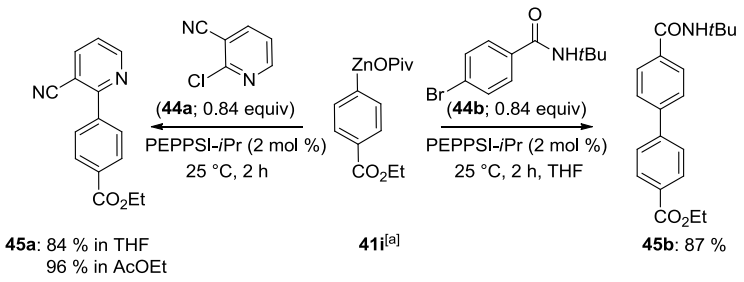
Scheme 50: Preparation of solid functionalized aryl-, heteroaryl- and benzylzinc pivalates of type **41**, **47** and **50** using Mg and $Zn(OPiv)_2$·2 LiCl (**38**).

The solid organozinc pivalates retain a substantial amount of their activity after short-time exposure to air. Furthermore, it was shown that the omittance of complexed LiCl can increase the air stability of the solid organozincs (Scheme 51).



Scheme 51: Synthesis and air-stability of 3-pyridylzinc pivalates **47a** and **55** with and without complexed LiCl.

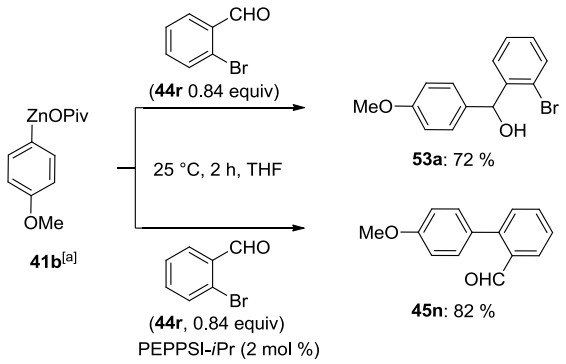
The organozinc pivalates can be efficiently applied in *Negishi* cross-couplings using PEPPSI-*i*Pr as catalyst. Electrophiles bearing relatively acidic protons are well tolerated without special precautions and the reactions can be conducted in technical grade AcOEt (Scheme 52).



[a] complexed Mg(OPiv)Br and LiCl are omitted for clarity

Scheme 52: PEPPSI-*i*Pr catalyzed one-pot cross-couplings of organozinc reagents of type **41** in THF or AcOEt.

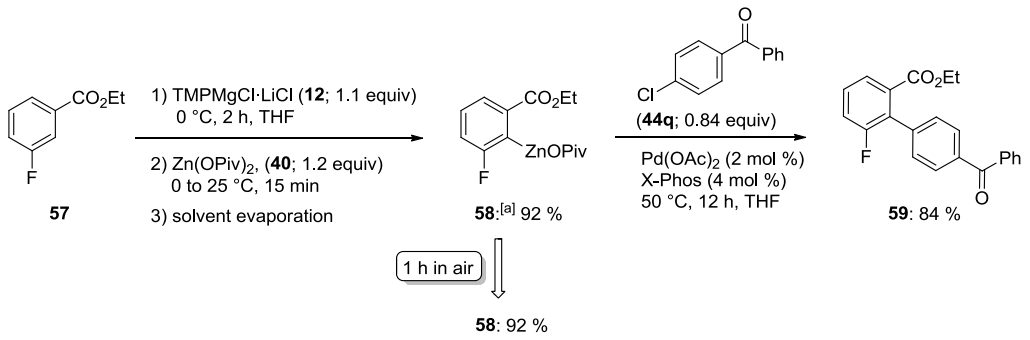
The organozinc pivalates undergo smooth addition reactions to carbonyl derivatives due to their complexed magnesium salts (Scheme 53). Moreover, using the Pd-catalyst PEPPSI-*i*Pr and electrophiles such as 2-bromobenzaldehyde (**44r**) leads to the corresponding cross-coupling products leaving the carbonyl moiety untouched.



[a] complexed Mg(OPiv)Br and LiCl are omitted for clarity

Scheme 53: Tuneable reactivity of organozincs pivalates by the presence or absence of PEPPSI-*i*Pr.

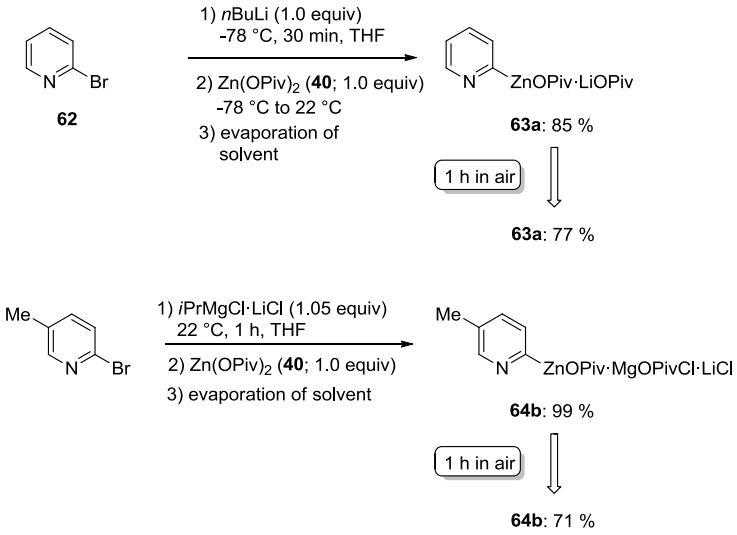
Moreover, the preparation of solid organozincs *via* directed metalation using TMPMgCl·LiCl (**12**) and subsequent transmetalation with $Zn(OPiv)_2$ (**40**) was investigated. The corresponding organozinc pivalates showed an increased stability towards air exposure compared to the ones prepared by magnesium insertion in the presence of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**) or $Zn(OPiv)_2$ (**40**) and could be efficiently applied in *Negishi* cross-couplings (Scheme 54).



[a] complexed Mg(OPiv)Cl and LiCl are omitted for clarity

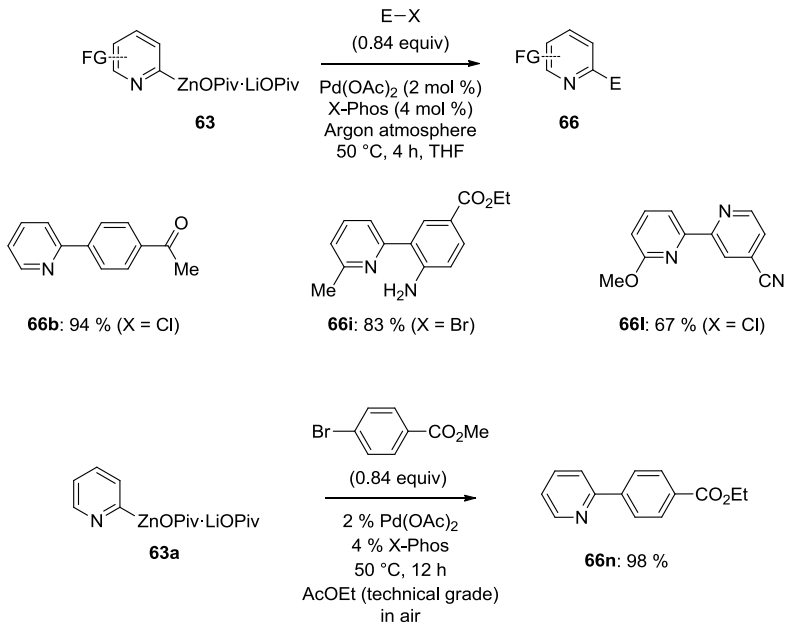
Scheme 54: Preparation of zinc pivalates *via* directed metalation and their application to *Negishi* cross-couplings.

Furthermore, the preparation of solid 2-pyridylzinc pivalates was investigated. The reagents could be conveniently prepared *via* Br/Li- or Br/Mg-exchange and subsequent transmetalation with $Zn(OPiv)_2$ (**40**). After evaporation of the solvent the reagents were obtained as powders with sufficient stability for short-term manipulation in air (loss of 10-30 % of their activity after exposure to air for 1 h, Scheme 55).



Scheme 55: Preparation and air stability of solid 2-pyridylzinc pivalates of type **63** and **64**.

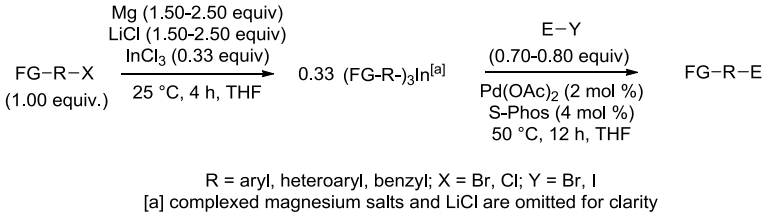
The 2-pyridylzinc pivalates underwent smooth *Negishi* cross-couplings with aryl bromides and chlorides using $Pd(OAc)_2$ (2 mol %) and X-Phos (4 mol %) as the catalytic system. Moreover, some couplings could be conducted in technical grade solvents in air (Scheme 56).

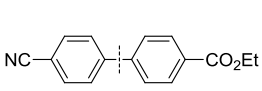


Scheme 56: *Negishi* cross-couplings of 2-pyridylzinc pivalates.

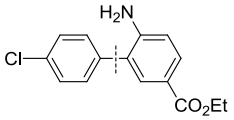
4.3. Preparation of Functionalized Organoindium Reagents *via* Magnesium Insertion in the Presence of $InCl_3$

An efficient method for the preparation of functionalized trisorganoindium reagents *via* Mg-insertion in the presence of LiCl and $InCl_3$ (0.33 equiv) was developed. The procedure gave access to functionalized aryl-, heteroaryl- and benzylindium reagents at 25 °C in 2-4 h. Moreover, the trisorganoindium reagents underwent smooth Pd-catalyzed cross-coupling reactions with different aryl and heteroaryl bromides and iodides (Scheme 57).

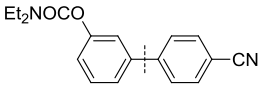




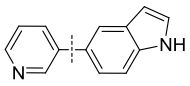
45l: 81 %



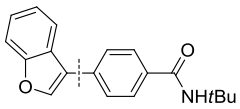
68c: 82 %



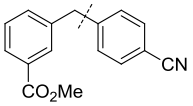
68f: 74 %



71b: 90 %



71d: 76 %



74: 74 %

Scheme 57: Preparation of the trisorganoindium reagents *via* magnesium insertion in the presence of $InCl_3$ (0.33 equiv) and subsequent Pd-catalyzed cross-coupling.

C. EXPERIMENTAL SECTION

1. General Considerations

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

1.1. Solvents

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

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.
DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.
EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.
Et_2O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.
Pyridine was dried over KOH and distilled.
THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and then stored over molecular sieves.
Solvents for column chromatography were distilled prior to use.

1.2. Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use. Following compounds were prepared according to literature procedures: ethyl 3-(chloromethyl)benzoate,[106] (4-bromophenoxy)(triisopropyl)silane,[107]
Triethylamine was dried over KOH and distilled.
***i*PrMgCl·LiCl** solution in THF was purchased from Chemetall.
***n*BuLi** solution in hexane was purchased from Chemetall.
TMPMgCl·LiCl (12) was prepared according to a literature procedure (ref. 23a).

[106] S. C. Berk, M. C. P. Yeh, N. Jeong, P. Knochel, *Organometallics* **1990**, *9*, 3053.
[107] Y. Fan, P. Feng, M. Liu, H. Pan, H. Pan, Y. Shi, *Org. Lett.* **2011**, *13*, 4494.

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

$ZnCl_2$/LiCl solution (1.10/1.50 M) was prepared by drying LiCl (15.9 g, 375 mmol) and $ZnCl_2$ (37.5 g, 275 mmol) under high vacuum (1 mbar) for 5 h at 140 °C. After cooling to 25 °C, dry THF (250 mL) was added and stirring was continued until the salts were dissolved.

1.3. Content Determination of Organometallic Reagents

Organzinc and organomagnesium reagents were titrated against I_2 in THF.[63]

Organolithium reagents were titrated against isopropanol using 1,10-phenanthroline as indicator in THF.[108]

TMPMgCl·LiCl (12) was titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

1.4. Chromatography

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

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

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

1.5. Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of $CHCl_3$ (δ_H: 7.25; δ_C: 77.0). For the characterization of

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

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

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

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

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

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

2. Typical Procedures (TP)

2.1. Typical Procedure for the Preparation of Zinc Reagents of Type $RZnX \cdot MgX_2 \cdot LiCl$ (**28**) or Diorganozinc Reagents of Type $R_2Zn \cdot 2\ MgX_2 \cdot LiCl$ (**30**) using Mg and $ZnCl_2$/LiCl Solution (**TP1**):

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (2.5 equiv). Then, $ZnCl_2$/LiCl (1.1/1.5 M) solution was added (1 mL / mmol for the preparation of organozinc reagents of type $RZnX \cdot MgX_2 \cdot LiCl$ (X = Cl, Br); 0.5 mL / mmol for the preparation of diorganozinc reagents of type $R_2Zn \cdot 2\ MgX_2 \cdot LiCl$ (X = Cl, Br)). The organic halide (1.0 equiv) was added dropwise as solution in THF using a water cooling bath to keep the temperature below 30 °C. The reaction mixture was stirred for the given time until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask through a syringe filter. The concentration of the zinc reagent was determined by iodometric titration.[63]

2.2. Typical Procedure For the Addition of Organozinc Reagents of Type $RZnX \cdot MgX_2 \cdot LiCl$ (**28**) or Diorganozinc Reagents of Type $R_2Zn \cdot 2\ MgX_2 \cdot LiCl$ (**30**) to Carbonyl Derivatives (**TP2**):

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

2.3. Typical Procedure for the Addition of Organozinc Reagents of Type $RZnX \cdot MgX_2 \cdot LiCl$ (**28**) or Diorganozinc Reagents of Type $R_2Zn \cdot 2\ MgX_2 \cdot LiCl$ (**30**) to Carbon Dioxide (**TP3**):

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

2.4. Typical Procedure for the Preparation of the Solid Organozinc Pivalates of Type **41**, **47** and **50** by Magnesium Insertion in the Presence of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**) (**TP4**):

$Zn(OPiv)_2 \cdot 2$ LiCl (**38**) was placed in a *Schlenk*-flask, equipped with a magnetic stirrer and a septum, dried for 5 min at 400 °C (heat gun) in high vacuum and then dissolved in dry THF. The organic halide (1.00 equiv) was added and the mixture was stirred for 2 min at room temperature. Magnesium turnings (2.50 equiv) were added and the *Schlenk*-flask was placed in a water bath for cooling during the initial heat evolution of the insertion reaction. The reaction mixture was stirred for the given time until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask *via* syringe filter and the solvent was removed *in vacuo*.

2.5. Typical Procedure for the Preparation of the Solid Organozinc Pivalates of Type **41** by Halogen-Magnesium Exchange and Subsequent Transmetalation with $Zn(OPiv)_2 \cdot 2$ LiCl (**38**) (**TP5**):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, the organic halide was dissolved in dry THF. *i*PrMgCl·LiCl was added dropwise at the given temperature and the reaction mixture was stirred for the given time at this temperature until GC-analysis of a quenched reaction aliquot showed complete conversion. A solution of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; the zinc salt was dried for 5 min at 400 °C (heat gun) in high vacuum and then dissolved in dry THF (0.5 M) was added dropwise and the mixture was stirred for 30 min at the given temperature. Then the solvent was removed *in vacuo*.

2.6. Typical Procedure for Palladium-Catalyzed Cross-Coupling Reactions of the Organozinc Pivalates of Type **41**, **47** and **50** with Organic Halides (**TP6**):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, the solid organozinc reagent was dissolved in the solvent of choice. The organic halide (0.84 equiv) was added followed by PEPPSI-*i*Pr (2 mol%) and the mixture was stirred for the given time at the given temperature. Then sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

2.7. Typical Procedure for the Addition of the Organozinc Pivalates of Type **41** or **50** to Carbonyl Derivatives (**TP7**):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, the solid organozinc reagent was dissolved in dry THF. The carbonyl derivative (0.84 equiv) was added and the mixture was stirred for the given time at the given temperature. Then sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

2.8. Typical Procedure for the Preparation of the Organozinc Pivalates of Type **55** by Magnesium Insertion in the Presence of $Zn(OPiv)_2$ (**40**) (**TP8**):

$Zn(OPiv)_2$ (**40**) was placed in a *Schlenk*-flask, equipped with a magnetic stirrer and a septum, dried for 5 min at 400 °C (heat gun) in high vacuum and then suspended in dry THF. The organic halide (1.00 equiv) was added and the mixture was stirred for 2 min at room temperature. Magnesium turnings (2.00 equiv) were added and the *Schlenk*-flask was placed in a water bath for cooling during the initial heat evolution of the insertion reaction. The reaction mixture was stirred for the given time until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask *via* syringe filter and the solvent was removed *in vacuo*.

2.9. Typical Procedure for the Preparation of the Organozinc Pivalates (**58**) by Metalation with TMPMgCl·LiCl (**12**) and Subsequent Transmetalation with $Zn(OPiv)_2$ (**40**) (**TP9**):

A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic substrate (3.00 mmol) and dry THF (9 mL). The reaction mixture was put to the appropriate temperature, before TMPMgCl·LiCl (**12**, 2.70 mL, 1.23 M, 3.30 mmol) was added dropwise. The progress of the deprotonation was monitored by GC-analysis of reaction aliquots quenched with I_2. Upon completion of the metalation, solid $Zn(OPiv)_2$ (**40**; 963 mg, 3.60 mmol) was added in one portion and the mixture was allowed to slowly warm up to 25 °C. After stirring at ambient temperature for 15 min, the solvent was carefully removed *in vacuo*. The complete dried material was titrated using iodine in order to determine its actual content in zinc species and the yield of the metalation.

2.10. Typical Procedure for the Palladium-Catalyzed Cross-Coupling Reactions of Organozinc Pivalates with Organic Halides (**TP10**):

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with the respective amount of the solid organozinc reagent that corresponds to 1.00 mmol of active zinc species and 2 mL of dry THF. $Pd(OAc)_2$ (4 mg, 0.02 mmol, 2 mol%) and X-Phos (16 mg, 0.03 mmol, 4 mol%) were added followed, after stirring for 2 min, by the organic halide (0.84 equiv). The mixture was stirred at the given temperature

until the full consumption of either the electrophile or the organozinc compound (checked by GC analysis of iodolyzed aliquots of the reaction). Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

2.11. Typical Procedure for the Preparation of 2-Pyridylzinc Pivalates of Type **63** *via* Bromine-Lithium Exchange and Subsequent Transmetalation with $Zn(OPiv)_2$ (**40**) (**TP11**):

The 2-bromopyridine derivative (1.00 equiv) was dissolved in dry THF. The mixture was cooled to -78 °C and *n*BuLi (1.00 equiv) was added dropwise over a period of 5 min. The mixture was stirred at -78 °C for the given time until GC-analysis of a quenched reaction aliquot showed complete conversion. $Zn(OPiv)_2$ (1.00 equiv) was added and the mixture was slowly warmed to 25 °C. Then, the solvent was removed *in vacuo*.

2.12. Typical Procedure for the Preparation 2-Pyridylzinc Pivalates of Type **64** *via* Bromine-Magnesium Exchange and Subsequent Transmetalation with $Zn(OPiv)_2$ (**40**) (**TP12**):

The 2-bromopyridine derivative (1.00 equiv) was dissolved in dry THF and *i*-PrMgCl·LiCl (1.05 equiv) was added dropwise over a period of 5 min at 25 °C. The mixture was stirred at 25 °C for the given time until GC-analysis of a quenched reaction aliquot showed complete conversion. $Zn(OPiv)_2$ (1.00 equiv) was added and the mixture was slowly warmed to 25 °C. Then, the solvent was removed *in vacuo*.

2.13. Typical Procedure for the Palladium-Catalyzed Cross-Coupling Reactions of Organozinc Reagents of Type **63** with Organic Halides in Argon-Atmosphere (**TP13**):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, the solid organozinc reagent was dissolved in the solvent of choice. The organic halide (0.84 equiv) was added followed by $Pd(OAc)_2$ (2 mol%)/X-Phos (4 mol%) and the mixture was stirred for the given time at the given temperature. Then sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic

phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

2.14. Typical Procedure for the Palladium-Catalyzed Cross-Coupling Reactions of Organozinc Reagents of Type **63** with Organic Halides in Air (**TP14**):

In a round-bottom flask, equipped with a magnetic stirring bar, the solid organozinc reagent was dissolved in the solvent of choice in air. The organic halide (0.84 equiv) was added followed by $Pd(OAc)_2$ (2 mol %)/X-Phos (4 mol %) the flask was capped with a septum and mixture was stirred for the given time at 50 °C. Then sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

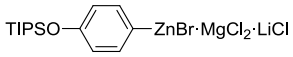
2.15. Typical Procedure for the Preparation of Organoindium Reagents of Type **67** by Magnesium Insertion in the Presence of $InCl_3$ (**TP15**):

LiCl and $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv) were placed in a *Schlenk*-flask, equipped with a magnetic stirrer and a septum, dried for 5 min at 400 °C (heat gun) in high vacuum and then dissolved in dry THF. The organic halide (2.00 mmol, 1.00 equiv) was added and the mixture was stirred for 2 min at 25 °C. Magnesium turnings were added and the reaction mixture was stirred for the given time at 25 °C until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask containing the electrophile and the catalytic system for the subsequent cross-coupling reaction.

3. Magnesium Halide Mediated Addition of Functionalized Organozinc Reagents to Aldehydes, Ketones and Carbon Dioxide

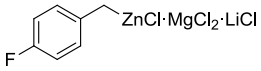
3.1. Preparation of the Organozinc Reagents

4-((Triisopropylsilyl)oxy)phenyl)zinc (28c)



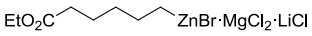
According to **TP1** (4-bromophenoxy)(triisopropyl)silane (4.94 g, 15.0 mmol, in 10 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) and a THF solution (15 mL) of $ZnCl_2$ (16.5 mmol) and LiCl (22.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **28c** indicated a concentration of 0.54 M.

4-Fluorobenzylzinc chloride (28d)



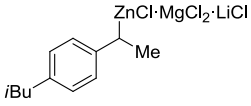
According to **TP1** 4-fluorobenzyl chloride (2.17 g, 15.0 mmol, in 8 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) and a THF solution (15 mL) of $ZnCl_2$ (16.5 mmol) and LiCl (22.5 mmol) at 25 °C for 45 min. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **28d** indicated a concentration of 0.39 M.

6-Ethoxy-6-oxohexylzinc bromide (28e)



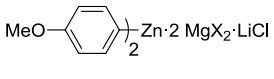
According to **TP1** ethyl 6-bromohexanoate (4.46 g, 20.0 mmol, in 10 mL THF) was reacted with magnesium turnings (1.22 mg, 50.0 mmol) and a THF solution (20 mL) of $ZnCl_2$ (22.0 mmol) and LiCl (30.0 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **28e** indicated a concentration of 0.32 M.

1-(4'-Isobutyl-phenyl)ethylzinc chloride (28f)



According to **TP1** 1-(1-chloro-ethyl)-4-isobutyl-benzene (**34**; 1.97 g, 10.0 mmol, in 10 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) and a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **28f** indicated a concentration of 0.17 M.

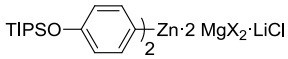
Bis(4-methoxyphenyl)zinc (30a)



X = Br, Cl

According to **TP1b** 4-bromoanisole (**31**; 2.81 g, 15.0 mmol, in 10 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) and a THF solution (7.5 mL) of $ZnCl_2$ (8.25 mmol) and LiCl (11.3 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30a** indicated a concentration of 0.39 M.

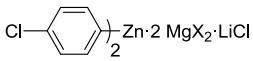
Bis(4-((triisopropylsilyl)oxy)phenyl)zinc (30b)



X = Br, Cl

According to **TP1** (4-bromophenoxy)(triisopropyl)silane (5.19 g, 15.8 mmol, in 23 mL THF) was reacted with magnesium turnings (1.03 g, 42.5 mmol) and a THF solution (8 mL) of $ZnCl_2$ (8.80 mmol) and LiCl (12.0 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30b** indicated a concentration of 0.32 M.

Bis(4-chlorophenyl)zinc (30c)

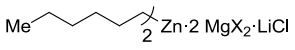


X = Br, Cl

According to **TP1** 1-bromo-4-chlorobenzene (**69a**; 3.83 g, 20.0 mmol, in 4 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) and a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 2 h. After subsequent cannulation to another

argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30c** indicated a concentration of 0.71 M.

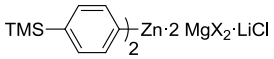
Bis(hexyl)zinc (30d)



X = Br, Cl

According to **TP1** hexyl bromide (3.30 g, 20.0 mmol, in 10 mL THF) was reacted with magnesium turnings (1.22 g, 50.0 mmol) and a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30d** indicated a concentration of 0.31 M.

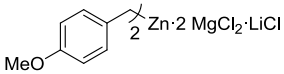
Bis(4-trimethylsilylphenyl)zinc (30e)



X =Br, Cl

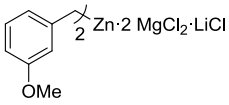
According to **TP1** (4-bromophenyl)trimethylsilane (2.29 g, 10.0 mmol, in 8 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) and a THF solution (5 mL) of $ZnCl_2$ (6.00 mmol) and LiCl (7.50 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30e** indicated a concentration of 0.28 M.

Bis(4-methoxybenzyl)zinc (30f)



According to **TP1** 4-methoxybenzyl chlorid (1.57 g, 10.0 mmol, in 8 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) and a THF solution (5 mL) of $ZnCl_2$ (5.50 mmol) and LiCl (7.50 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30f** (premix of an aliquot with excess $ZnCl_2$ (1.00 M in THF)) indicated a concentration of 0.31 M.

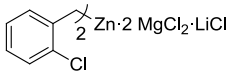
Bis(3-methoxybenzyl)zinc (30g)



According to **TP1** 3-methoxybenzyl chlorid (2.35 g, 15.0 mmol, in 8 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) and a THF solution (7.5 mL) of $ZnCl_2$

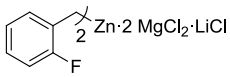
(8.25 mmol) and LiCl (11.3 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30g** (premix of an aliquot with excess $ZnCl_2$ (1.00 M in THF)) indicated a concentration of 0.31 M.

Bis(2-chlorobenzyl)zinc (30h)



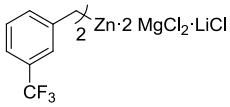
According to **TP1** 2-chlorobenzyl chloride (3.22 g, 20.0 mmol, in 5 mL THF) was reacted with magnesium turnings (1.22 g, 50.0 mmol) and a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30h** (premix of an aliquot with excess $ZnCl_2$ (1.00 M in THF)) indicated a concentration of 0.54 M.

Bis(2-fluorobenzyl)zinc (30i)



According to **TP1** 2-fluorobenzyl chlorid (1.45 g, 10.0 mmol, in 8 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) and a THF solution (5 mL) of $ZnCl_2$ (5.50 mmol) and LiCl (7.50 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30i** (premix of an aliquot with excess $ZnCl_2$ (1.00 M in THF)) indicated a concentration of 0.23 M.

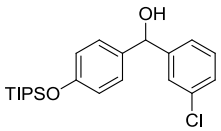
Bis(3-trifluoromethylbenzyl)zinc (30j)



According to **TP1** 3-(trifluoromethyl)benzyl chloride (3.89 g, 20.0 mmol, in 10 mL THF) was reacted with magnesium turnings (1.22 g, 50.0 mmol) and a THF solution (10 mL) of $ZnCl_2$ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 1 h. After subsequent cannulation to another argon-flushed *Schlenk*-flask, iodometric titration of the zinc reagent **30j** (premix of an aliquot with excess $ZnCl_2$ (1.00 M in THF)) indicated a concentration of 0.33 M.

3.2. Preparation of the Title Compounds

(3-Chlorophenyl)(4-((triisopropylsilyl)oxy)phenyl)methanol (27d)



According to **TP2** 3-chlorobenzaldehyde (**26d**; 211 mg, 1.50 mmol) was added to (4-[(triisopropylsilyl)oxy]phenyl)zinc bromide·$MgCl_2$ (**28c**; 3.33 mL, 1.80 mmol, 0.54 M in THF). The reaction mixture was stirred for 3 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 7:1) afforded the alcohol **27d** (499 mg, 85 %) as a colourless oil.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.36 (br, 1H), 7.33-7.2 (m, 5H), 6.81-6.77(m, 2H), 5.94 (d, *J* = 4.09, 1H), 5.64 (d, *J* = 4.29, 1H), 1.29-1.16 (m, 3H), 1.03 (d, 18H).

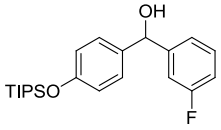
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 154.3, 148.5, 137.8, 132.7, 130.0, 127.6, 126.5, 125.8, 124.8, 119.1, 73.0, 17.7, 12.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3318 (w), 3062 (vw), 3032 (vw), 2944 (m), 2892 (w), 2866 (m), 1606 (m), 1575 (w), 1507 (vs), 1463 (m), 1427 (w), 1389 (w), 1385 (w), 1368 (w), 1263 (vs), 1184 (m), 1169 (m), 1095 (w), 1076 (w), 1012 (m), 997 (m), 911 (vs), 881 (vs), 840 (m), 815 (w), 780 (m), 740 (m), 699 (m), 680 (s).

MS (EI, 70 eV): m/z (%) = 392 (M^+, 12), 373 (34), 347 (100), 331 (16), 319 (43), 291 (44), 275 (12), 207 (29), 179 (18), 165 (16), 151 (31), 141 (26), 137 (25), 125 (10), 113 (12), 89 (14), 77 (24), 59 (11).

HRMS ($C_{22}H_{31}ClO_2Si$): calc.: 390.1782; found: 390.1773 (M^+).

(3-Fluorophenyl){4-[(triisopropylsilyl)oxy]phenyl}methanol (27e)



According to **TP2** 3-fluorobenzaldehyde (**26e**; 1.05 g, 8.44 mmol) was added to bis(4-[(triisopropylsilyl)oxy]phenyl)·2 MgX_2 (**30b**; X = Br, Cl; 22.2 mL, 5.10 mmol, 0.23 M in THF). The reaction mixture was stirred for 3 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 5:1) afforded the alcohol **27e** (2.81 g, 89 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.31-7.24 (m, 1H), 7.19-7.16 (m, 2H), 7.12-7.07 (m, 2H), 6.96-6.90 (m, 1H), 6.86-6.81 (m, 2H), 5.75 (s_{br}, 1H), 2.19 (s_{br}, 1H), 1.29-1.16 (m, 3H), 1.09 (d, *J* = 7.1 Hz, 18H).

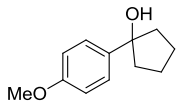
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.9 (d, *J* = 246.0 Hz), 155.8, 146.6 (d, *J* = 6.7 Hz), 135.8, 129.8 (d, *J* = 8.1 Hz), 127.9, 122.0 (d, *J* = 3.1 Hz), 119.9, 114.1 (d, *J* = 21.3 Hz), 113.3 (d, *J* = 22.2 Hz) 75.3, 18.1, 15.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3329 (w), 2866 (m), 1606 (m), 1507 (vs), 1263 (vs), 1011 (w), 911 (s), 881 (vs), 762 (s), 712 (m), 681 (s).

MS (EI, 70 eV): m/z (%) = 374 (M^+, 29), 331 (100), 303 (22), 275 (26), 207 (12), 183 (14), 151 (20), 137 (25), 125 (28), 123 (18), 97 (30), 77 (12).

HRMS ($C_{22}H_{31}FO_2Si$): calc.: 374.2077; found: 374.2076 (M^+).

1-(4-Methoxyphenyl)cyclopentanol (27f)



According to **TP2** cyclopentanone (**26f**; 126 mg, 1.50 mmol) was added to bis(4-methoxyphenyl)zinc·2 MgX_2 (**30a**; X = Br, Cl; 2.31 mL, 0.90 mmol, 0.39 M in THF). The reaction mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1 + 1 vol-% NEt_3) afforded the alcohol **27f** (243 mg, 84 %) as a colourless oil.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.37-7.34 (m, 2H), 6.86-6-82 (m, 2H), 4.65 (s, 1H), 3.71 (s, 3H), 1.87-1.66 (m, 8H).

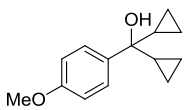
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 157.5, 140.5, 126.3, 113.0, 81.1, 55.0, 41.6, 23.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3403 (w), 2956 (m), 2872 (w), 2836 (w), 1611 (m), 1581 (w), 1511 (s), 1463 (m), 1442 (m), 1367 (w), 1297 (m), 1240 (vs), 1177 (s), 1114 (w), 1093 (w), 1033 (s), 1000 (s), 961 (w), 904 (m), 882 (w), 827 (vs), 795 (m), 732 (w).

MS (EI, 70 eV): m/z (%) = 192 (M^+, 29), 174 (96), 163 (100), 159 (39), 150 (60), 143 (42), 135 (97), 128 (21), 121 (14), 115 (19), 107 (10), 91 (15), 77 (25), 71 (14), 57 (17).

HRMS ($C_{12}H_{16}O_2$): calc.: 192.1150; found: 192.1146 (M^+).

Dicyclopropyl(4-methoxyphenyl)methanol (27g)



According to **TP2** dicyclopropylketone (**26g**; 165 mg, 1.50 mmol) was added to bis(4-methoxyphenyl)zinc·2 MgX_2 (**30a**; X = Br, Cl; 2.31 mL, 0.90 mmol, 0.39 M in THF). The

reaction mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1 + 1 vol-% NEt_3) afforded the alcohol **27g** (286 mg, 87 %) as a colourless oil.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.45-7.41 (m, 2H), 6.85-6.81 (m, 2H), 4.28 (s, 1H), 3.72 (s, 3H), 1.17-1.10 (m, 2H), 0.52-0.46 (m, 2H), 0.37-0.25 (m, 4H), 0.19-0.14 (m, 2H).

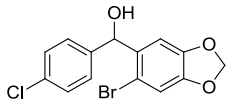
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 157.5, 140.7, 126.8, 112.6, 71.4, 54.9, 20.9, 1.4, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3457 (w), 2953 (m), 2868 (w), 2836 (w), 1610 (m), 1584 (w), 1509 (s), 1464 (m), 1412 (w), 1383 (w), 1366 (m), 1299 (m), 1247 (vs), 1176 (s), 1127 (w), 1120 (w), 1094 (m), 1068 (m), 1032 (s), 1020 (m), 913 (m), 883 (vw), 830 (vs), 817 (m), 798 (s), 778 (m), 738 (w), 657 (w).

MS (EI, 70 eV): m/z (%) = 218 (M^+, 17), 190 (81), 177 (86), 173 (27), 159 (32), 149 (22), 135 (100), 128 (14), 121 (44), 115 (19), 107 (12), 91 (18), 77 (26), 69 (31), 41 (19).

HRMS ($C_{14}H_{18}O_2$): calc.: 218.1307; found: 218.1301 (M^+).

(6-Bromo-1,3-benzodioxol-5-yl)(4-chlorophenyl)methanol (27h)



According to **TP2** 6-bromopiperonal (**26h**; 2.04 g, 8.90 mmol) was added to bis(4-chlorophenyl)zinc·2 MgX_2 (**30c**; X = Br, Cl; 12.8 mL, 5.30 mmol, 0.42 M in THF). The reaction mixture was stirred for 10 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 6:1) afforded the alcohol **27h** (2.68 g, 88 %) as a pale yellow oil.

^{1}H-NMR (400 MHz, Acetone-d6): δ / ppm = 7.44-7.38 (m, 2H), 7.35-7.30 (m, 2H), 7.12 (s, 1H), 7.02 (s, 1H), 6.07 (s, 1H), 6.05 (d, *J* = 1.0 Hz, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 2.83 (s_{br}, 1H).

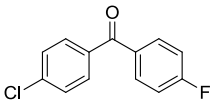
^{13}C-NMR (100 MHz, Acetone-d6): δ / ppm = 148.8, 148.7, 143.7, 138.0, 133.2, 129.3, 129.0, 112.9, 112.7, 108.8, 103.0, 73.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3316 (w), 2896 (w), 1471 (vs), 1407 (m), 1388 (m), 1231 (s), 1103 (m), 1035 (vs), 1013 (s), 931 (s), 845 (s), 780 (m).

MS (EI, 70 eV): m/z (%) = 342 (100), 340 (M^+, 76), 229 (48), 209 (13), 201 (10), 149 (14), 139 (50), 122 (35), 110 (10), 77 (18), 63 (8).

HRMS ($C_{14}H_{10}BrClO_3$): calc.: 339.9502; found: 339.9504 (M^+).

(4-Chlorophenyl)(4-fluorophenyl)methanone (27i)



According to **TP2** 4-fluorobenzoylchloride (**26i**; 238 mg, 1.50 mmol) was added to bis(4-chlorophenyl)zinc·2 MgX_2 (**30c**; X = Br, Cl; 2.90 mL, 0.90 mmol, 0.31 M in THF). The reaction mixture was stirred for 12 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 8:1) afforded the ketone **27i** (286 mg, 81 %) as a colourless solid.

M.p. (°C): 118-119.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.84-7.79 (m, 2H), 7.75-7.72 (m, 2H), 7.63-7.60 (m, 2H), 7.41-7.35 (m, 2H).

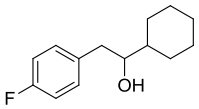
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 193.7, 164.8 (d, *J* = 251.8 Hz), 137.6, 135.6, 133.2 (d, *J* = 3.1 Hz), 132.6 (d, *J* = 9.6 Hz), 131.4, 128.7, 115.7 (d, *J* = 22.9 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1648 (s), 1591 (s), 1504 (m), 1400 (m), 1271 (s), 1227 (s), 1155 (s), 1145 (s), 1085 (s), 853 (vs), 838 (s), 757 (vs), 672 (s).

MS (EI, 70 eV): m/z (%) = 234 (M^+, 44), 199 (15), 141 (20), 138 (59), 123 (100), 111 (21), 95 (28), 75 (19).

HRMS ($C_{13}H_8ClFO$): calc.: 234.0248; found: 234.0246 (M^+).

1-Cyclohexyl-2-(4-fluorophenyl)ethanol (27j)



According to **TP2** cyclohexylcarbaldehyde (**26j**; 168 mg, 1.50 mmol) was added to 4-fluorobenzylzinc·2 $MgCl_2$ (**28d**; 4.62 mL, 1.80 mmol, 0.39 M in THF). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1 + 1 vol-% NEt_3) afforded the alcohol **27j** (327 mg, 97 %) as a colourless oil.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.24-7.19 (m, 2H), 7.08-7.02 (m, 2H), 4.3 (d, *J* = 5.9 Hz, 1H), 3.38-3.32 (m, 1H), 2.68 (dd, *J* = 13.7 Hz, *J* = 4.0 Hz, 1H), 2.53-2.47 (m, 1H), 1.79-1.59 (m, 5H), 1.24-0.96 (m, 6H).

^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 160.6 (d, *J* = 241 Hz), 136.5 (d, *J* = 3 Hz), 130.9 (d, *J* = 8 Hz), 114.5 (d, *J* = 21 Hz), 75.3, 43.0, 39.3, 29.2, 27.1, 26.3, 26.0, 25.9.

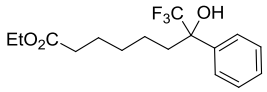
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3318 (w), 3062 (vw), 3032 (vw), 2944 (m), 2892 (w), 2866 (m), 1606 (m), 1575 (w), 1507 (vs), 1463 (m), 1427 (w), 1389 (w), 1385 (w), 1368 (w),

1263 (vs), 1184 (m), 1169 (m), 1095 (w), 1076 (w), 1012 (m), 997 (m), 911 (vs), 881 (vs), 840 (m), 815 (w), 780 (m), 740 (m), 699 (m), 680 (s).

MS (EI, 70 eV): m/z (%) = 222 (M^+, 1), 110 (100), 95 (54), 67 (13), 55 (10).

HRMS ($C_{14}H_{19}FO$): calc.: 222.1420; found: 222.1401 (M^+).

Ethyl-8,8,8-trifluoro-7-hydroxy-7-phenyloctanoate (27k)



According to **TP2** α,α,α,-trifluoroacetophenone (**26k**; 261 mg, 1.50 mmol) was added to 5-ethoxycarbonylpentyl

zinc bromide·$MgCl_2$ (**28e**; 5.63 mL, 1.80 mmol, 0.32 M in THF). The reaction mixture was stirred for 24 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 10:1 + 1 vol-% NEt_3) afforded the alcohol **27k** (287 mg, 60 %) as a colourless oil.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.52 (d, *J* = 7.4, 2H), 7.4-7.3 (m, 3H), 6.38 (s, 1H), 4.00 (q, *J* = 7.0, 2H), 2.2-2.09 (m, 3H), 1.96-1.89 (m, 1H), 1.46-1.39 (m, 2H), 1.31-1.18 (m, 3H), 1.14 (t, *J* = 7.0, 3H), 0.86-0.76 (m, 1H).

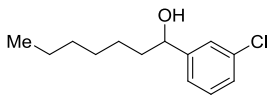
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 172.7, 137.4, 127.9, 127.8, 126.5, 126.1 (q, *J* = 287 Hz), 75.9 (q, *J* = 27 Hz), 59.6, 33.5, 28.4, 24.1, 21.5, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3457 (w), 2941 (w), 2871 (vw), 1711 (m), 1499 (vw), 1466 (w), 1450 (w), 1375 (w), 1266 (m), 1148 (vs), 1094 (m), 1074 (m), 1031 (m), 1004 (w), 987 (w), 901 (w), 860 (vw), 764 (m), 731 (w), 702 (s), 685 (m).

MS (EI, 70 eV): m/z (%) = 319 ($[M-H]^+$, 3), 281 (159), 253 (19), 249 (86), 235 (17), 213 (15), 203 (54), 185 (17), 175 (43), 157 (100), 144 (86), 125 (14), 115 (26), 105 (91), 101 (92), 97 (12), 91 (25), 88 (25), 73 (20), 69 (14), 55 (13).

HRMS ($C_{16}H_{21}F_3O_3$): calc.: 318.1443; found: 319.1511 ($[M+H]^+$).

1-(3-Chlorophenyl)heptan-1-ol (27l)



According to **TP2** 3-chlorobenzaldehyde (**26d**; 211 mg, 1.50 mmol) was added to 6 bis(hexyl)zinc·2 MgX_2 (**30d**; X = Br, Cl; 2.90 mL, 0.90 mmol, 0.31 M in THF). The reaction mixture was stirred for 14 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1 + 1 vol-% NEt_3) afforded the alcohol **27l** (295 mg, 87 %) as a colourless oil.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.35-7.34 (m, 1H), 7.32-7.30 (m, 1H), 7.26-7.23 (m, 2H), 5.25 (d, *J* = 4.7 Hz, 1H), 4.52-4.48 (m, 1H), 1.61-1.48 (m, 2H), 1.34-1.16 (m, 8H), 0.84-0.81 (m, 3H).

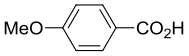
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 149.2, 132.7, 129.8, 126.4, 125.6, 124.5, 71.6, 39.2, 31.3, 28.6, 25.1, 22.1, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3334 (w), 2927 (s), 1574 (w), 1432 (m), 1198 (m), 1044 (m), 882 (m), 783 (vs), 696 (s).

MS (EI, 70 eV): m/z (%) = 226 (M^+, 4), 143 (37), 141 (100), 113 (22), 77 (29).

HRMS ($C_{13}H_{19}ClO$): calc.: 226.1124; found: 226.1119 (M^+).

4-Methoxybenzoic acid (33a)



According to **TP3** bis(4-methoxyphenyl)zinc·2 MgX_2 (**30a**; X = Br, Cl; 12.8 mL, 5.0 mmol, 0.39 M in THF) was reacted with dry $CO_{2(g)}$ at 25 °C for 3 h. After purification 4-methoxybenzoic acid (**33a**; 1.47 g, 94 %) was obtained as a white solid.

M.p. (°C): 184-185 °C.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 12.62 (s, 1H), 7.88 (dt, *J* = 9.3 Hz, *J* = 2.8 Hz, 2H), 7.00 (dt, ^{3}J = 9.5 Hz, ^{4}J = 2.7 Hz, 2H), 3.81 (s, 3H).

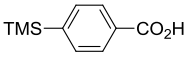
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 167.0, 162.8, 131.4, 123.0, 113.8, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2939 (w), 2842 (w), 2660 (w), 2542 (w), 1922 (w), 1746 (w), 1679 (s), 1602 (s), 1576 (m), 1515 (m), 1494 (w), 1464 (w), 1426 (m), 1414 (m), 1304 (s), 1297 (s), 1259 (vs), 1179 (m), 1165 (s), 1129 (m), 1105 (m), 1052 (w), 1025 (s), 921 (s), 852 (m), 843 (s), 823 (m), 771 (vs), 762 (s), 697 (m), 633 (m), 615 (s).

MS (EI, 70 eV): m/z (%) = 152 (M^+, 96), 135 (100), 107 (16), 92 (12), 77 (22), 64 (10).

HRMS ($C_8H_8O_3$): calc.: 152.0473; found: 152.0466 (M^+).

4-(Trimethylsilyl)benzoic acid (33b)



According to **TP3**, bis(4-trimethylsilylphenyl)zinc·2 MgX_2 (**30e**; X = Br, Cl; 3.57 mL, 1.00 mmol, 0.23 M in THF) was reacted with dry $CO_{2(g)}$ at 25 °C for 6 h. After purification 4-(trimethylsilyl)benzoic acid (**33b**; 284 mg, 73 %) was obtained as a white solid.

M.p. (°C): 116 °C.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 12.94 (s, 1H), 7.90 (dt, *J* = 7.9 Hz, *J* = 1.5 Hz, 2H), 7.63 (dt, *J* = 7.9 Hz, *J* = 1.5 Hz, 2H), 0.25 (s, 9H)

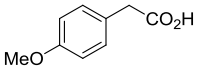
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 167.4, 145.9, 133.3, 131.1, 128.3, -1.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077 (w), 2956 (w), 2666 (w), 2543 (w), 1940 (vw), 1684 (s), 1598 (w), 1553 (w), 1498 (w), 1418 (m), 1387 (m), 1314 (w), 1290 (s), 1253 (s), 1187 (m), 1133 (w), 1110 (w), 1095 (m), 1019 (w), 942 (m), 834 (vs), 808 (s), 756 (m), 739 (s), 698 (s).

MS (EI, 70 eV): m/z (%) = 194 (M^+, 6), 179 (100), 133 (4).

HRMS ($C_{10}H_{14}O_2Si$): calc.: 194.0763; found: 194.0761 (M^+).

(4-Methoxyphenyl)acetic acid (33c)



According to **TP3** bis(4-methoxybenzyl)zinc·2 $MgCl_2$ (**30f**; 3.03 mL, 1.00 mmol, 0.33 M in THF) was reacted with dry $CO_{2(g)}$ at 25 °C for 2 h. After purification (4-methoxyphenyl)acetic acid (**33c**; 326 mg, 98 %) was obtained as a white solid.

M.p. (°C): 86-87.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 12.28 (s, 1H), 7.15 (dt, *J* = 9.3 Hz, *J* = 2.9 Hz, 2H), 6.85 (dt, *J* = 9.2 Hz, *J* = 2.9 Hz, 2H), 3.71 (s, 3H), 3.47 (s, 2H).

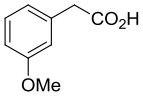
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 173.0, 158.0, 130.4, 127.0, 113.6, 55.0, 39.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2364 (vw), 1994 (vw), 1716 (m), 1692 (m), 1612 (m), 1584 (w), 1514 (m), 1469 (w), 1457 (w), 1445 (w), 1426 (m), 1405 (m), 1342 (w), 1316 (w), 1303 (m), 1238 (s), 1186 (m), 1178 (s), 1152 (m), 1109 (m), 1024 (s), 962 (w), 923 (m), 907 (m), 900 (m), 854 (m), 831 (m), 815 (vs), 789 (m), 770 (s), 748 (m), 731 (w), 726 (w), 716 (w), 707 (w), 696 (w), 693 (w), 675 (s), 635 (m).

MS (EI, 70 eV): m/z (%) = 166 (M^+, 100), 121 (80), 91 (18).

HRMS ($C_9H_{10}O_3$): calc.: 166.0630; found: 166.0624 (M^+).

(3-Methoxyphenyl)acetic acid (33d)



According to **TP3** bis(3-methoxybenzyl)zinc·2 $MgCl_2$ (**30g**; 3.13 mL, 1.00 mmol, 0.32 M in THF) was reacted with dry $CO_{2(g)}$ at 25 °C for 2 h. After purification (3-methoxyphenyl)acetic acid (**33d**; 326 mg, 98 %) was obtained as a white solid.

M.p. (°C): 67-68.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.21 (t, *J* = 8.0 Hz, 1H), 6.83-6.79 (m, 3H), 3.72 (s, 3H), 3.52 (s, 2H).

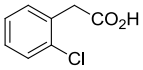
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 172.6, 159.2, 136.5, 129.3, 121.6, 115.1, 112.0, 55.0, 40.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920 (m), 1692 (s), 1492 (m), 1258 (s), 1212 (s), 1167 (s), 1035 (s), 996 (m), 893 (m), 792 (s), 756 (vs).

MS (EI, 70 eV): m/z (%) = 166.1 (M^+, 100), 121.1 (87), 91.1 (21).

HRMS ($C_9H_{10}O_3$): calc.: 166.0630; found: 166.0630 (M^+).

(2-Chlorophenyl)acetic acid (33e)



According to **TP3** *bis*(2-chlorobenzyl)zinc·2 $MgCl_2$ (**30h**; 1.85 mL, 1.00 mmol, 0.52 M in THF) was reacted with dry $CO_{2(g)}$ at 50 °C for 12 h. After purification (2-chlorophenyl)acetic acid (**33e**; 272 mg, 80 %) was obtained as a white solid.

M.p. (°C): 92-93.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.45-7.36 (m, 2H), 7.30-7.26 (m, 2H), 3.70 (s, 2H).

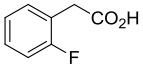
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 171.5, 133.7, 133.3, 132.2, 129.0, 128.8, 127.1, 38.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2916 (w), 1699 (s), 1402 (m), 1238 (s), 1055 (m), 926 (m), 761 (vs), 733 (s), 687 (s).

MS (EI, 70 eV): m/z (%) = 170 (M^+, 40), 135 (76), 125 (100), 91 (50), 63 (10).

HRMS ($C_8H_7ClO_2$): calc.: 170.0135; found: 170.0133 (M^+).

(2-Fluorophenyl)acetic acid (33f)



According to **TP3** bis(2-fluorobenzyl)zinc·2 $MgCl_2$ (**30i**; 4.35 mL, 1.00 mmol, 0.23 M in THF) was reacted with dry $CO_{2(g)}$ at 25 °C for 12 h. After purification (2-fluorophenyl)acetic acid (**33f**; 302 mg, 98 %) was obtained as a white solid.

M.p. (°C): 59-60 °C.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.35-7.27 (m, 2H), 7.18-7.11 (m, 2H), 3.61 (s, 2H).

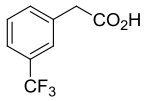
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 171.7, 160.7 (d, *J* = 244 Hz), 132.1 (d, *J* = 4.61 Hz), 129.0 (d, *J* = 8.1 Hz), 124.2 (d, *J* = 3.8 Hz), 122.3 (d, *J* = 16 Hz), 115.0 (d, *J* = 22 Hz), 34.2 (d, *J* = 2.7 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3252 (w), 3032 (w), 2962 (w), 2934 (w), 2910 (w), 2659 (w), 2629 (w), 1752 (w), 1702 (s), 1618 (w), 1588 (w), 1494 (m), 1457 (m), 1419 (m), 1405 (m), 1341 (w), 1290 (m), 1237 (m), 1220 (s), 1185 (m), 1166 (m), 1156 (m), 1108 (w), 1101 (m), 1031 (w), 988 (w), 975 (w), 954 (m), 925 (m), 922 (m), 887 (m), 877 (m), 856 (w), 788 (w), 777 (m), 762 (vs), 747 (s), 728 (m), 703 (w), 677 (m), 667 (s), 662 (s), 634 (w), 610 (m).

MS (EI, 70 eV): m/z (%) = 154 (M^+, 39), 136 (24), 109 (100), 90 (12), 83 (12), 44 (17).

HRMS ($C_8H_7FO_2$): calc.: 154.0430; found: 154.0418 (M^+).

(3-(Trifluoromethyl)phenyl)acetic acid (33g)



According to **TP3**, bis(3-trifluoromethylbenzyl)zinc·2 $MgCl_2$ (**30j**; 3.03 mL, 1.00 mmol, 0.33 M in THF) was reacted with dry $CO_{2(g)}$ at 50 °C for 12 h. After purification [3-(trifluoromethyl)phenyl]acetic acid (**33g**; 352 mg, 86 %) was obtained as a white solid.

M.p. (°C): 77-78 °C.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 12.47 (s, 1H), 7.63-7.52 (m, 4H), 3.72 (s, 2H).

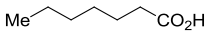
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 172.3, 136.5, 133.8 (q, *J* = 1.2 Hz), 129.2, 128.9 (q, *J* = 31.5 Hz), 126.1 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 272.1 Hz), 123.4 (q, *J* = 3.97 Hz), 39.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922 (m), 2853 (w), 2654 (w), 1697 (s), 1620 (w), 1598 (vw), 1492 (w), 1453 (m), 1411 (m), 1331 (s), 1296 (m), 1234 (s), 1165 (vs), 1115 (vs), 1096 (s), 1074 (s), 1002 (w), 928 (m), 915 (m), 906 (m), 890 (m), 810 (m), 802 (m), 783 (m), 760 (m), 744 (w), 735 (m), 723 (w), 707 (s), 700 (s), 672 (w), 658 (s), 637 (w), 620 (m), 603 (m).

MS (EI, 70 eV): m/z (%) = 204 (M^+, 49), 186 (40), 159 (100), 109 (20), 91 (27), 44 (22).

HRMS ($C_9H_7F_3O_2$): calc.: 204.0398; found: 204.0384 (M^+).

Heptanoic acid (33h)



According to **TP3**, bis(hexyl)zinc·2 MgX_2 (**30d**; X = Br, Cl; 3.03 mL, 1.00 mmol, 0.33 M in THF) was reacted with dry $CO_{2(g)}$ at 50 °C for 12 h. After purification heptanoic acid (**33h**; 223 mg, 86 %) was obtained as colourless oil.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 11.95 (s, 1H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.50-1.43 (m, 2H), 1.30 -1.19 (m, 6H), 0.86-0.83 (m, 3H).

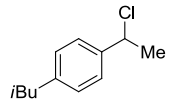
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 174.5, 33.7, 31.0, 28.2, 24.5, 22.0, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928 (m), 1704 (vs), 1412 (m), 1283 (m), 1237 (m), 1206 (w), 1106 (w), 934 (w).

MS (EI, 70 eV): m/z (%) = 130 (M^+, 1), 101 (10), 87 (30), 73 (60), 60 (100), 55 (16), 43 (16), 41 (23).

HRMS ($C_7H_{14}O_2$): calc.: 130.0994; found: 130.0987 (M^+).

1-(1-Chloro-ethyl)-4-isobutyl-benzene (34)



Sodium borohydride (1.71 g, 45.0 mmol) was added portionwise to a stirred solution of 4-isobutylacetophenone (**26b**; 5.28 g, 30.0 mmol) in methanol (75 mL). The reaction mixture was refluxed for 1 h, cooled to room temperature and then quenched with 1 M HCl (50 mL). Methanol was removed *in vacuo* and the obtained aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine solution (3 x 50 mL) and then dried over Na_2SO_4.

The crude product was dissolved in dry CH_2Cl_2 (30 mL) and the mixture was cooled to 0 °C. A solution of thionyl chloride (3.57 g, 30.0 mmol) in CH_2Cl_2 (8 mL) was added dropwise over a period of 10 min. The mixture was slowly warmed to room temperature and then stirred for further 12 h. The mixture was carefully quenched with saturated aqueous solution of $NaHCO_3$ (40 mL) and the aqueous phase was then extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. 1-(1-Chloro-ethyl)-4-isobutyl-benzene (**34**) was obtained as a slightly yellowish liquid (5.55 g, 28.2 mmol, 94 %).

M.p. (°C): 59-60 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.32 (dt, *J* = 8.1 Hz, *J* = 1.9 Hz, 2H), 7.13 (dt, *J* = 8.1 Hz, *J* = 1.9 Hz, 2H), 5.09 (q, *J* = 6.7 Hz, 1H), 2.47 (d, *J* = 7.1 Hz, 2H), 1.95-1.77 (m, 4H), 0.91 (d, *J* = 6.7 Hz, 6H).

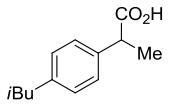
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.9, 140.1, 129.3, 126.2, 58.9, 45.1, 30.1, 26.4, 22.4, 22.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955 (s), 2926 (m), 2869 (m), 2849 (w), 1903 (vw), 1613 (w), 1512 (m), 1465 (m), 1453 (m), 1444 (m), 1421 (m), 1384 (m), 1376 (m), 1367 (m), 1335 (w), 1311 (w), 1289 (w), 1229 (m), 1206 (w), 1185 (w), 1168 (w), 1122 (w), 1087 (w), 1068 (w), 1047 (s), 1020 (m), 969 (m), 922 (vw), 882 (w), 846 (s), 801 (vs), 758 (m), 723 (s), 670 (w).

MS (EI, 70 eV): m/z (%) = 196 (M^+, 21), 161 (100), 117 (41), 91 (18).

HRMS ($C_{12}H_{17}Cl$): calc.: 196.1019; found: 196.1015 (M^+).

Ibuprofen (35)



According to **TP3** 1-(4'-isobutyl-phenyl)ethylzinc chloride·$MgCl_2$ (**28f**; 5.60 mL, 1.0 mmol, 0.17 M in THF) was reacted with dry $CO_{2(g)}$ at 25 °C for 12 h and then the mixture was heated up to 50 °C for further 12 h. After purification ibuprofen (**35**; 332 mg, 89 %) was obtained as a pale yellow solid.

M.p. (°C): 73-75 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.22 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 3.70 (q, *J* = 7.2 Hz, 1H), 2.44 (d, *J* = 7.1 Hz, 2H), 1.84 (sept, *J* = 6.7 Hz, 1H), 1.49 (d, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 180.7, 140.8, 137.0, 129.4, 127.3, 45.0, 44.9, 30.1, 22.4, 22.4, 18.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3026 (w), 2955 (s), 2926 (m), 2869 (m), 2849 (w), 1903 (vw), 1613 (w), 1512 (m), 1465 (m), 1453 (m), 1444 (m), 1421 (m), 1384 (m), 1376 (m), 1367 (m), 1335 (w), 1311 (w), 1289 (w), 1229 (m), 1206 (w), 1185 (w), 1168 (w), 1122 (w), 1087 (w), 1068 (w), 1047 (s), 1020 (m), 969 (m), 922 (vw), 882 (w), 846 (s), 801 (vs), 758 (m), 723 (s), 670 (w).

MS (EI, 70 eV): m/z (%) = 206 (M^+, 44), 161 (100), 119 (43), 91 (53).

HRMS ($C_{13}H_{18}O_2$): calc.: 206.1307; found: 206.1297 (M^+).

4. Preparation of Solid Salt-Stabilized Organozinc Reagents

4.1. Preparation of $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**)

Pivalic acid (20.4 g, 22.6 mL, 200 mmol) was placed in a dry and argon-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, and dissolved in dry THF (100 mL). The solution was cooled to 0 °C and methyllithium (135 mL, 1.63 M in diethyl ether, 220 mmol) was added dropwise over a period of 45 min. $ZnCl_2$ (100 mL, 1.00 M in THF, 100 mmol) was added and the mixture was stirred for 2 h at 25 °C. The solvent was removed *in vacuo* and $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**) was obtained as a colourless solid in quantitative yield.

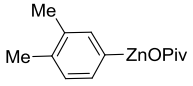
4.2. Preparation of $Zn(OPiv)_2$ (**40**)

Pivalic acid (30.6 g, 34.5 mL, 300 mmol) was placed in a dry and argon-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a pressure-relief valve, and dissolved in dry THF (150 mL). The solution was cooled to 0 °C and a solution of diethylzinc (18.8 g, 15.6 mL, 152 mmol) in THF (150 mL) was added dropwise over a period of 30 min (gas formation and partial precipitation of the product was observed). After slowly warming to 22 °C under vigorous stirring, the solvent was removed *in vacuo* and $Zn(OPiv)_2$ was obtained as a colourless solid in quantitative yield. $Zn(OPiv)_2$ was stored under argon although no sensitivity towards air or moisture was observed.

4.3. Preparation of Solid Salt-Stabilized Organozinc Reagents by Magnesium-Insertion in the Presence of $Zn(OPiv)_2$

4.3.1. Preparation of Arylzinc Pivalates of Type **41**

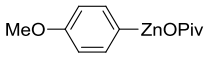
(3,4-Dimethylphenyl)zinc pivalate (41a)



According to **TP5** $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**; 2.64 g, 7.50 mmol) and 4-bromo-1,2-dimethylbenzene (**39**; 925 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium

turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 20 min at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (3,4-Dimethylphenyl)zinc pivalate (**41a**) was obtained as a grey solid (3.48 g). The content of active zinc species was determined by titration of 546 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.10 mmol/g was determined which corresponds to a yield of 77 %.

(4-Methoxyphenyl)zinc pivalate (41b)



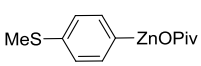
a) Magnesium insertion in the presence of 1.0 equiv of $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**)

According to **TP5** $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**; 3.52 g, 10.0 mmol) and 4-bromoanisole (**31**; 1.87 g, 10.0 mmol) were dissolved in 20 mL of dry THF. Magnesium turnings (608 mg, 25.0 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-Methoxyphenyl)zinc pivalate (**41b**) was obtained as a grey solid (5.85 g). The content of active zinc species was determined by titration of 199 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.16 mmol/g 865 mg/mmol was determined which corresponds to a yield of 78 %.

b) Magnesium insertion in the presence of 1.5 equiv of $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**)

According to **TP5** $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**; 3.97 g, 11.3 mmol) and 4-bromoanisole (1.40 g, 7.50 mmol) were dissolved in 20 mL of dry THF. Magnesium turnings (456 mg, 18.8 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-Methoxyphenyl)zinc pivalate (**41b**) was obtained as a grey solid (5.16 g). The content of active zinc species was determined by titration of 337 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.07 mmol/g was determined which corresponds to a yield of 74 %.

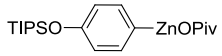
(4-(Methylthio)phenyl)zinc pivalate (41c)



According to **TP5** $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**; 3.52 g, 10.0 mmol) and 4-bromothioanisole (1.02 g, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent

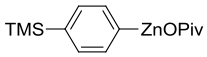
cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-Thiomethylphenyl)zinc pivalate (**41c**) was obtained as a orange solid (3.49 g). The content of active zinc species was determined by titration of 190 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.11 mmol/g was determined which corresponds to a yield of 77 %.

(4-((Triisopropylsilyl)oxy)phenyl)zinc pivalate (41d)



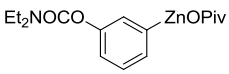
According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 3.52 g, 10.0 mmol) and (4-bromophenoxy)triisopropylsilane (3.29 g, 10.0 mmol) were dissolved in 25 mL of dry THF. Magnesium turnings (608 mg, 25.0 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-((Triisopropylsilyl)oxy)phenyl)zinc pivalate (**41d**) was obtained as a grey solid (7.82 g). The content of active zinc species was determined by titration of 184 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.98 mmol/g was determined which corresponds to a yield of 77 %.

(4-(Trimethylsilyl)phenyl)zinc pivalate (41e)



According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and (4-bromophenyl)(trimethyl)silane (1.15 g, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-(Trimethylsilyl)phenyl)zinc pivalate (**41e**) was obtained as a grey solid (4.03 g). The content of active zinc species was determined by titration of 270 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.00 mmol/g was determined which corresponds to a yield of 81 %.

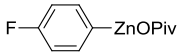
(3-((Diethylcarbamoyl)oxy)phenyl)zinc pivalate (41f)



According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and 3-bromophenyl diethylcarbamate (1.36 g, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (243 mg, 10.0 mmol) were added and the reaction mixture was stirred for 2 h at

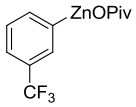
25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (3-((Diethylcarbamoyl)oxy)phenyl)zinc pivalate (**41f**) was obtained as a yellow solid (4.12 g). The content of active zinc species was determined by titration of 270 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.69 mmol/g was determined which corresponds to a yield of 57 %.

(4-Fluorophenyl)zinc pivalate (41g)



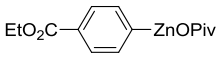
According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and 1-bromo-4-fluorobenzene (875 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-Fluorophenyl)zinc pivalate (**41g**) was obtained as a grey solid (3.34 g). The content of active zinc species was determined by titration of 171 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.05 mmol/g was determined which corresponds to a yield of 70 %.

(3-(Trifluoromethyl)phenyl)zinc pivalate (41h)



According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and 1-bromo-3-(trifluoromethyl)benzene (1.13 g, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (3-(Trifluoromethyl)phenyl)zinc pivalate (**41h**) was obtained as a grey solid (3.72 g). The content of active zinc species was determined by titration of 300 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.13 mmol/g was determined which corresponds to a yield of 84 %.

(4-(Ethoxycarbonyl)phenyl)zinc pivalate (41i)



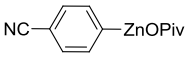
a) Magnesium insertion in the presence of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**)

According to **TP5** $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; 2.64 g, 7.50 mmol) and ethyl 4-bromobenzoate (**44l**; 1.15 g, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-(Ethoxycarbonyl)phenyl)zinc pivalate (**41i**) was obtained as a yellowish solid (4.01 g). The content of active zinc species was determined by titration of 283 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.74 mmol/g was determined which corresponds to a yield of 59 %.

b) Halogen-magnesium exchange and subsequent transmetalation with $Zn(OPiv)_2 \cdot 2$ LiCl (**38**)

According to **TP6** ethyl 4-iodobenzoate (**42**; 1.38 g, 5.00 mmol) was dissolved in 3 mL of dry THF and the mixture was cooled to -30 °C. *i*PrMgCl·LiCl (4.74 mL, 1.16 M in THF, 5.50 mmol) was added dropwise and the mixture was stirred for 30 min at -30 °C. A solution of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; 2.64 g, 7.50 mmol) in 15 mL of dry THF was added dropwise and the mixture was stirred at -30°C for 30 min and then slowly warmed to 25 °C. The solvent was removed *in vacuo* and (4-(ethoxycarbonyl)phenyl)zinc pivalate (**41i**) was obtained as a yellowish solid (4.56 g). The content of active zinc species was determined by titration of 277 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.79 mmol/g was determined which corresponds to a yield of 72 %.

(4-Cyanophenyl)zinc pivalate (41j)



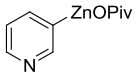
a) Magnesium insertion in the presence of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**)

According to **TP5** $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; 2.64 g, 7.50 mmol) and 4-bromobenzonitrile (**43**; 910 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-Cyanophenyl)zinc pivalate (**41j**) was obtained as a yellowish solid (3.68 g). The content of active zinc species was determined by titration of 196 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.87 mmol/g was determined which corresponds to a yield of 64 %.

b) Halogen-Magnesium exchange and subsequent transmetalation with $Zn(OPiv)_2 \cdot 2$ LiCl (**38**)
According to **TP6** 4-bromobenzonitrile (**43**; 910 mg, 5.00 mmol) was dissolved in 7 mL of dry THF and the mixture was cooled to 0 °C. *i*PrMgCl·LiCl (4.52 mL, 1.16 M in THF, 5.25 mmol) was added dropwise and the mixture was stirred for 2 h at 0 °C. A solution of $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; 2.64 g, 7.50 mmol) in 15 mL of dry THF was added dropwise and the mixture was stirred at 0°C for 30 min and then slowly warmed to room temperature. The solvent was removed *in vacuo* and (4-cyanophenyl)zinc pivalate (**41j**) was obtained as a colourless solid (4.11 g). The content of active zinc species was determined by titration of 279 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.08 mmol/g was determined which corresponds to a yield of 89 %.

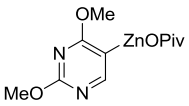
4.3.2. Preparation of Heteroarylzinc Pivalates of Type **47**

Pyridin-3-ylzinc pivalate (47a)



According to **TP5** $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; 2.64 g, 7.50 mmol) and 3-bromopyridine (**54**; 790 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. Pyridin-3-ylzinc pivalate (**47a**) was obtained as a yellow solid (3.93 g). The content of active zinc species was determined by titration of 181 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.83 mmol/g was determined which corresponds to a yield of 65 %.

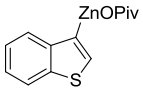
(2,4-Dimethoxypyrimidin-5-yl)zinc pivalate (47b)



According to **TP5** $Zn(OPiv)_2 \cdot 2$ LiCl (**38**; 2.64 g, 7.50 mmol) and 5-bromo-2,4-dimethoxypyrimidine (**72a**; 1.10 g, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (2,4-Dimethoxypyrimidin-5-yl)zinc pivalate (**47b**) was obtained as a yellow solid (3.62 g). The content of active zinc species was determined by

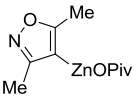
titration of 181 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.88 mmol/g was determined which corresponds to a yield of 65 %.

Benzo[*b*]thiophen-3-ylzinc pivalate (47c)



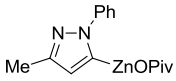
According to **TP5** $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**; 2.64 g, 7.50 mmol) and 3-bromobenzo[b]thiophene (1.07 g, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (243 mg, 10.0 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. Benzo[*b*]thiophen-3-ylzinc pivalate (**47c**) was obtained as a yellow solid (3.22 g). The content of active zinc species was determined by titration of 301 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.98 mmol/g was determined which corresponds to a yield of 64 %.

(3,5-Dimethylisoxazol-4-yl)zinc pivalate (47d)



According to **TP5** $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**; 2.64 g, 7.50 mmol) and 4-bromo-3,5-dimethylisoxazole (880 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (3,5-Dimethylisoxazol-4-yl)zinc pivalate (**47d**) was obtained as a yellow solid (3.94 g). The content of active zinc species was determined by titration of 222 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.90 mmol/g was determined which corresponds to a yield of 71 %.

(3-Methyl-1-phenyl-1H-pyrazol-5-yl)zinc pivalate (47e)

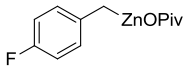


According to **TP5** $Zn(OPiv)_2 \cdot 2\ LiCl$ (**38**; 2.64 g, 7.50 mmol) and 5-chloro-3-methyl-1-phenyl-1-*H*-pyrazole (**48**; 963 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 22 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the

solvent was removed *in vacuo*. (3-Methyl-1-phenyl-1H-pyrazol-5-yl)zinc pivalate (**47e**) was obtained as a yellow solid (3.32 g). The content of active zinc species was determined by titration of 176 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.74 mmol/g was determined which corresponds to a yield of 50 %.

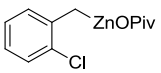
4.2.3. Preparation of Benzylzinc Pivalates of Type **50**

(4-Fluorobenzyl)zinc pivalate (50a)



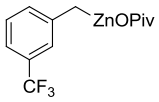
According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and 1-(chloromethyl)-4-fluorobenzene (723 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-Fluorobenzyl)zinc pivalate (**50a**) was obtained as a grey solid (3.42 g). The content of active zinc species was determined by titration of 170 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.18 mmol/g was determined which corresponds to a yield of 80 %.

(2-Chlorobenzyl)zinc pivalate (50b)



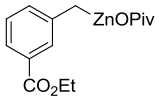
According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and 1-chloro-2-(chloromethyl)benzene (805 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (4-Chlorobenzyl)zinc pivalate (**50b**) was obtained as a grey solid (3.66 g). The content of active zinc species was determined by titration of 507 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.09 mmol/g was determined which corresponds to a yield of 79 %.

(3-(Trifluoromethyl)benzyl)zinc pivalate (50c)



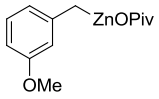
According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and 1-(chloromethyl)-3-(trifluoromethyl)benzene (973 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (3-(Trifluoromethyl)benzyl)zinc pivalate (**50c**) was obtained as a grey solid (3.61 g). The content of active zinc species was determined by titration of 108 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.93 mmol/g was determined which corresponds to a yield of 67 %.

(3-(Ethoxycarbonyl)benzyl)zinc pivalate (50d)



According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and ethyl 3-(chloromethyl)benzoate (**49a**; 993 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (3-(Ethoxycarbonyl)benzyl)zinc pivalate (**50d**) was obtained as a grey solid (3.67 g). The content of active zinc species was determined by titration of 161 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 0.93 mmol/g was determined which corresponds to a yield of 68 %.

(3-Methoxybenzyl)zinc pivalate (50e)

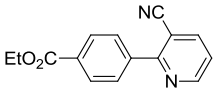


According to **TP5** $Zn(OPiv)_2 \cdot 2\,LiCl$ (**38**; 2.64 g, 7.50 mmol) and 1-(chloromethyl)-3-methoxybenzene (783 mg, 5.00 mmol) were dissolved in 15 mL of dry THF. Magnesium turnings (304 mg, 12.5 mmol) were added and the reaction mixture was stirred for 2 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. (3-Methoxybenzyl)zinc pivalate (**50e**) was obtained as a grey solid (3.02 g). The content of active zinc species was determined by titration of 260 mg of the

reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.11 mmol/g was determined which corresponds to a yield of 67 %.

4.3.4. Preparation of Cross-Coupling Products of Type **45**

Ethyl 4-(3-cyanopyridin-2-yl)benzoate (45a)



a) Cross-coupling in THF

According to **TP6** (4-(ethoxycarbonyl)phenyl)zinc pivalate (**41i**; 2.43 g, 0.61 mmol/g, 1.47 mmol) was dissolved in dry THF (5 mL). 2-Chloronicotinonitrile (**44a**; 170 mg, 1.23 mmol) and PEPPSI-*i*Pr (20 mg, 0.03 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 1:1) afforded the pyridine derivative **45a** (262 mg, 84 %) as a slightly yellow solid.

b) Cross-coupling in AcOEt

According to **TP6** (4-(ethoxycarbonyl)phenyl)zinc pivalate (**41i**; 2.02 g, 0.78 mmol/g, 1.32 mmol) was dissolved in technical grade AcOEt[77] (5 mL). 2-Chloronicotinonitrile (**44a**; 183 mg, 1.32 mmol) and PEPPSI-*i*Pr (20 mg, 0.03 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 1:1) afforded the pyridine derivative **45a** (320 mg, 96 %) as a slightly yellow solid.

M.p. (°C): 98-99.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.89 (dd, *J* = 4.9 Hz, *J* = 1.5 Hz, 1H), 8.19 (m, 2H), 8.09 (dd, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 7.99 (m, 2H), 7.41 (dd, *J* = 7.5 Hz, *J* = 4.9 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

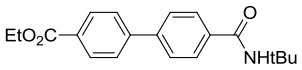
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm =166.0, 159.9, 152.7, 141.8, 141.0, 131.9, 129.8, 128.9, 122.1, 117.2, 107.8, 61.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2226 (w), 1714 (s), 1576 (w), 1550 (w), 1432 (m), 1404 (m), 1368 (m), 1270 (vs), 1176 (w), 1102 (s), 1016 (m), 862 (m), 804 (w), 786 (w), 750 (s), 718 (w), 698 (m).

MS (EI, 70 eV): m/z (%) = 252 (M^+, 44), 224 (47), 207 (100), 178 (62), 152 (33), 125 (13), 83 (12), 71 (15).

HRMS ($C_{15}H_{12}N_2O_2$): calc.: 252.0899; found: 252.0886 (M^+).

Ethyl 4'-[(*tert*-butylamino)carbonyl]biphenyl-4-carboxylate (45b)



According to **TP6** (4-(ethoxycarbonyl)phenyl)zinc pivalate (**41i**; 1.26 g, 0.79 mmol/g, 0.98 mmol) was dissolved in dry THF (5 mL). 4-Bromo-*N*-(*tert*-butyl)benzamide (**44b**; 211 mg, 0.83 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / EtOAc = 6:1 to 5:1) afforded the biphenyl **45b** (235 mg, 87 %) as colourless solid.

M.p. (°C): 98-99.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.13-8.09 (m, 2H), 7.82-7.78 (m, 2H), 7.66-7.63 (m, 4H), 5.99 (s, br, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.49 (s, 9H), 1.40 (t, *J* = 7.2 Hz, 3H).

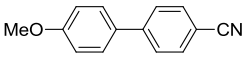
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 166.3, 144.3, 142.6, 135.4, 130.1, 129.8, 127.3, 127.3, 127.1, 61.1, 51.7, 28.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3264 (w), 2970 (w), 1708 (s), 1632 (s), 1608 (m), 1544 (s), 1492 (m), 1458 (m), 1450 (m), 1388 (m), 1362 (m), 1322 (s), 1266 (vs), 1222 (s), 1180 (m), 1104 (vs), 1022 (w), 1004 (m), 874 (m), 844 (s), 758 (vs), 674 (m), 668 (m).

MS (EI, 70 eV): m/z (%) = 325 (M^+, 16), 269 (47), 253 (100), 224 (17), 152 (36), 104 (17).

HRMS ($C_{20}H_{23}NO_3$): calc.: 325.1678; found: 325.1671 (M^+).

4'-Methoxybiphenyl-4-carbonitrile (45c)



According to **TP6** (4-methoxyphenyl)zinc pivalate (**41b**; 2.16 g, 1.16 mmol/g, 2.50 mmol) was dissolved in dry THF (5 mL). 4-Bromobenzonitrile (**44c**; 382 mg, 2.10 mmol) and PEPPSI-*i*Pr (34 mg, 0.05 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 8:1) afforded the biphenyl **45c** (377 mg, 86 %) as colourless solid.

M.p. (°C): 111-112.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.69-7.60 (m, 4H), 7.55-7.50 (m, 2H), 7.02-6.97 (m, 2H), 3.85 (s, 3H).

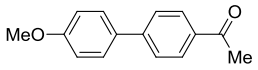
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2, 145.1, 132.5, 131.4, 128.3, 127.0, 119.0, 114.5, 110.1, 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962 (w), 2920 (w), 2842 (w), 2360 (w), 2222 (m), 1740 (w), 1604 (m), 1514 (w), 1492 (m), 1294 (m), 1240(s), 1176 (m), 1036 (m), 854 (m), 822 (vs), 812(s).

MS (EI, 70 eV): m/z (%) = 209 (M^+, 100), 194 (23), 166 (32), 140 (15).

HRMS ($C_{14}H_{11}NO$): calc.: 209.0841; found: 209.0831 (M^+).

1-(4'-Methoxybiphenyl-4-yl)ethanone (45d)



According to **TP6** (4-methoxyphenyl)zinc pivalate (**41b**; 2.10 g, 1.07 mmol/g, 1.18 mmol) was dissolved in dry THF (3 mL). 4-Chloroacetophenone (**44d**; 154 mg, 0.99 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / EtOAc = 10:1) afforded the biphenyl **45d** (149 mg, 67 %) as colourless solid.

M.p. (°C): 156-157.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.02-7.98 (m, 2H), 7.66-7.61 (m, 2H), 7.59-7.54 (m, 2H), 7.02-6.97 (m, 2H), 3.85 (s, 3H), 2.62 (s, 3H).

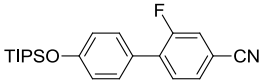
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.7, 159.9, 145.3, 135.3, 132.2, 128.9, 128.3, 126.6, 114.4, 55.4, 26.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958 (vw), 2840 (vw),1674 (s), 1598 (m), 1528 (w), 1496 (w), 1400 (w), 1360 (m), 1292 (m), 1256 (m), 1198 (m), 1186 (m), 1032 (m), 1012 (m), 958 (w), 816 (vs), 640 (w).

MS (EI, 70 eV): m/z (%) = 226 (M^+, 79), 183 (21), 168 (23), 152 (12), 139 (21), 105 (9).

HRMS ($C_{15}H_{14}O_2$): calc.: 226.0994; found: 226.0986 (M^+).

2-Fluoro-4'-[(triisopropylsilyl)oxy]biphenyl-4-carbonitrile (45e)



According to **TP6** (4-((triisopropylsilyl)oxy)phenyl)zinc pivalate (**41d**; 1.20 g, 1.22 mmol/g, 0.98 mmol) was dissolved in dry THF (3 mL). 4-Bromo-3-fluorobenzonitrile (**44e**; 198 mg, 0.99 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 50:1 to 10:1) afforded the biphenyl **45e** (327 mg, 89 %) as colourless solid.

M.p. (°C): 76-77.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.65 (m, 1H), 7.48-7.35 (m, 4H), 6.99-6.94 (m, 2H), 1.36-1.18 (m, 3H), 1.11 (d, *J* = 6.9 Hz, 18H).

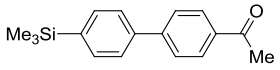
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.5 (d, *J* = 258.0 Hz), 157.5, 148.2 (d, *J* = 8.5 Hz), 133.6 (d, *J* = 1.1 Hz), 130.5 (d, *J* = 2.4 Hz), 128.3, 122.7 (d, *J* = 3.4 Hz), 120.6, 114.3, 114.0 (d, *J* = 20.4 Hz), 98.8 (d, *J* = 15.9 Hz), 17.9, 12.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2946 (m), 2866 (m), 2228 (m), 1616 (m), 1600 (s), 1556 (w), 1526 (w), 1492 (s), 1464 (m), 1432 (w), 1400 (w), 1274 (s), 1260 (s), 1216 (m), 1176 (m), 1120 (m), 1078 (w), 1010 (w), 998 (w), 908 (vs), 886 (vs), 844 (m), 824 (s), 746 (s), 726 (m), 688 (s), 654 (m), 622 (m), 614 (w).

MS (EI, 70 eV): m/z (%) = 369 (M^+, 17), 326 (64), 298 (40), 270 (100), 256 (58), 240 (20), 196 (17), 169 (14), 135 (50), 75 (15).

HRMS ($C_{22}H_{28}FNOSi$): calc.: 369.1924; found: 369.1916 (M^+).

1-[4'-(Trimethylsilyl)biphenyl-4-yl]ethanone (45f)



According to **TP6** (4-methoxyphenyl)zinc pivalate (**41e**; 813 mg, 1.00 mmol/g, 0.81 mmol) was dissolved in dry THF (3 mL). 4-Bromoacetophenone (**44f**; 135 mg, 0.68 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 8:1) afforded the biphenyl **45f** (151 mg, 83 %) as a slightly yellow solid.

M.p. (°C): 117-119.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.02-8.01 (m, 2H), 7.71-7.67 (m, 2H), 7.65-7.59 (m, 4H), 2.63 (s, 3H), 0.31 (s, 9H).

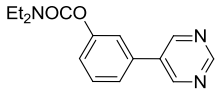
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.7, 145.7, 140.7, 140.2, 135.9, 134.0, 128.9, 127.2, 126.6, 26.7, -1.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958 (w), 1682 (m), 1602 (m), 1408 (w), 1392 (w), 1358 (w), 1264 (m), 1250 (m), 1178 (w), 1112 (m), 954 (w), 840 (vs), 808 (vs), 766 (m), 760 (m), 734 (m), 710 (m), 698 (m), 634 (w).

MS (EI, 70 eV): m/z (%) = 268 (M^+, 24), 254 (20), 253 (100).

HRMS ($C_{17}H_{20}OSi$): calc.: 268.1283; found: 268.1275 (M^+).

3-(Pyrimidin-5-yl)phenyl diethylcarbamate (45g)



According to **TP6** (3-((diethylcarbamoyl)oxy)phenyl)zinc pivalate (**41f**; 955 mg, 0.69 mmol/g, 0.66 mmol) was dissolved in dry THF (3 mL). 5-Bromopyrimidine (**44g**; 0.87 mg, 0.55 mmol) and PEPPSI-*i*Pr (7 mg, 0.01 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 2:1 to pure AcOEt) afforded the carbamate **45g** (119 mg, 80 %) as a slightly yellow solid.

M.p. (°C): 53-54.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.19 (s, 1H), 8.93 (s, 2H), 7.52-7.46 (m, 1H), 7.40-7.37 (m, 1H), 7.35-7.34 (m, 1H), 7.24-7.20 (m, 1H), 3.49-3.36 (m, 4H), 1.29-1.18 (m, 6H).

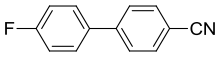
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.7, 155.0, 153.9, 152.4, 135.5, 133.7, 130.3, 123.6, 122.5, 120.5, 42.4, 42.0, 14.3, 13.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976 (w), 2937 (w), 1704 (vs), 1586 (w), 1555 (w), 1471 (m), 1411 (s), 1349 (m), 1267 (s), 1194 (s), 1183 (vs), 1153 (vs), 1086 (m), 1042 (m), 963 (s), 939 (m), 893 (s), 881 (w), 828 (m), 795 (s), 777 (s), 757 (s), 723 (vs), 695 (vs).

MS (EI, 70 eV): m/z (%) = 271 (M^+, 3), 100 (100), 72 (38).

HRMS ($C_{15}H_{17}N_3O_2$): calc.: 271.1321; found: 271.1312 (M^+).

4'-Fluorobiphenyl-4-carbonitrile (45h)



According to **TP6** (4-fluorophenyl)zinc pivalate (**41g**; 921 mg, 1.05 mmol/g, 0.97 mmol) was dissolved in dry THF (4 mL). 4-Chlorobenzonitrile (**44h**; 112 mg, 0.81 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the biphenyl **45h** (125 mg, 80 %) as colourless solid.

M.p. (°C): 116-118.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.73-7.61 (m, 4H), 7.58-7.52 (m, 2H), 7.20-7.12 (m, 2H).

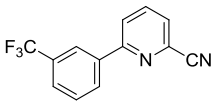
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.2 (d, *J* = 248.2 Hz), 144.6, 135.3, 132.6, 129.1 (d, *J* = 8.0 Hz), 127.6, 118.8, 116.2 (d, *J* = 21.8 Hz), 111.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2226 (w), 1738 (vw), 1606 (w), 1598 (w), 1516 (w), 1492 (m), 1228 (m), 1178 (w), 1162 (w), 856 (w), 820 (vs), 776 (w), 630 (w).

MS (EI, 70 eV): m/z (%) = 197 (M^+, 100), 169 (13), 98 (5), 85 (8), 57 (6), 43 (8).

HRMS ($C_{13}H_8FN$): calc.: 197.0641; found: 197.0635 (M^+).

6-[3-(Trifluoromethyl)phenyl]pyridine-2-carbonitrile (45j)



According to **TP6** (3-(trifluoromethyl)phenyl)zinc pivalate (**41h**; 780 mg, 1.28 mmol/g, 0.88 mmol) was dissolved in dry THF (3 mL). 6-Bromopyridine-2-carbonitrile (**44j**; 135 mg, 0.74 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 1:1) afforded the pyridine derivative **45j** (144 mg, 78 %) as colourless solid.

M.p. (°C): 79-80.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm =8.28 (s, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 8.00-7.91 (m, 2H), 7.74-7.60 (m, 3H).

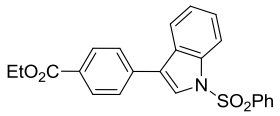
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.3, 138.1, 137.9, 134.0, 131.5 (q, *J* = 32.5 Hz), 130.2 (q, *J* = 1.3 Hz), 129.6, 127.2, 126.7 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 3.9 Hz), 123.9 (q, *J* = 272.5 Hz), 123.5, 117.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962 (vw), 2928 (vw), 2236 (w), 1738 (w), 1582 (m), 1562 (w), 1442 (m), 1334 (s), 1308 (w), 1276 (m), 1260 (m), 1190 (s), 1170 (s), 1108 (vs), 1086 (s), 1064 (s), 988 (m), 890 (w), 796 (vs), 736 (w), 694 (s), 654 (w).

MS (EI, 70 eV): m/z (%) = 248 (M^+, 100), 229 (11), 179 (26), 69 (9), 57 (12).

HRMS ($C_{13}H_7F_3N_2$): calc.: 248.0561; found: 248.0552 (M^+).

Ethyl 4-(1-(phenylsulfonyl)-1H-indol-3-yl)benzoate (45k)



According to **TP6** (4-(ethoxycarbonyl)phenyl)zinc pivalate (**41i**; 770 mg, 0.78 mmol/g, 0.60 mmol) was dissolved in technical grade AcOEt[77] (3 mL). 3-Bromo-1-(phenylsulfonyl)-1H-indole (**44k**; 168 mg, 0.50 mmol) and PEPPSI-*i*Pr (8 mg, 0.01 mmol) were added and the mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 5:1 to 3:1) afforded the title compound **45k** (201 mg, 99 %) as white solid.

M.p. (°C): 116.2-118.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.16-8.10 (m, 2H), 8.09-8.05 (m, 1H), 7.96-7.92 (m, 2H), 7.80-7.76 (m, 2H), 7.70-7.65 (m, 2H), 7.58-7.51 (m, 1H), 7.48-7.42 (m, 2H), 7.40-7.35 (m, 1H), 7.34-7.28 (m, 1H), 4.41 (t, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

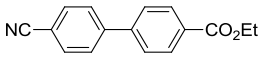
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 138.0, 137.6, 135.5, 134.0, 130.1, 129.4, 129.3, 128.8, 127.6, 126.8, 125.2, 123.9, 123.6, 123.1, 120.3, 113.9, 61.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3141 (vw), 2989 (vw), 2979 (w), 1701 (s), 1609 (m), 1581 (w), 1442 (m), 1366 (s), 1355 (m), 1346 (w), 1338 (w), 1309 (w), 1282 (s), 1272 (s), 1243 (m), 1175 (vs), 1153 (m), 1138 (vs), 1122 (m), 1106 (s), 1088 (m), 1075 (m), 1024 (m), 1010 (s), 997 (m), 974 (w), 931 (m), 854 (m), 838 (w), 826 (w), 774 (s), 767 (m), 763 (m), 745 (s), 738 (vs), 721 (s), 696 (m), 689 (s), 669 (m).

MS (EI, 70 eV): m/z (%) = 405 (M^+, 40), 264 (100), 236 (23), 191 (9), 164 (7).

HRMS ($C_{23}H_{19}O_4NS$): calc.: 405.1035 found: 405.1024 (M^+).

Ethyl 4'-cyano-[1,1'-biphenyl]-4-carboxylate (45l)



According to **TP6** (4-cyanophenyl)zinc pivalate (**41j**; 1.61 g, 0.77 mmol/g, 1.24 mmol) was dissolved in technical grade AcOEt[77] (5 mL). 4-Bromoethylbenzoate (**44l**; 239 mg, 1.04 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / EtOAc = 4:1 to 3:1) afforded the biphenyl **45l** (245 mg, 94 %) as colourless solid.

M.p. (°C): 112-114.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.16-8.11 (m, 2H), 7.76-7.68 (m, 4H), 7.66-7.62 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H).

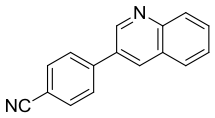
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm =166.1, 144.4, 143.3, 132.7, 130.6, 130.3, 127.9, 127.1, 118.6, 111.8, 61.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961 (w), 2222 (m), 1704 (s), 1605 (m), 1465 (w), 1396 (m), 1364 (m), 1264 (m), 1180 (m), 1098 (s), 1020 (m), 1005 (m), 871 (m), 838 (s), 770 (vs), 729 (m), 698 (m).

MS (EI, 70 eV): m/z (%) = 251. (M^+, 35), 223 (35), 206 (100), 178 (19), 151 (19), 43 (20).

HRMS ($C_{16}H_{13}NO_2$): calc.: 251.0946; found: 251.0952 (M^+).

4-Quinolin-3-ylbenzonitrile (45m)



According to **TP6** (4-cyanophenyl)zinc pivalate (**41j**; 1.60 g, 0.87 mmol/g, 1.39 mmol) was dissolved in dry THF (5 mL). 3-Bromoquinoline (**44m**; 243 mg, 1.17 mmol) and PEPPSI-*i*Pr (20 mg, 0.03 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the benzonitrile **45m** (329 mg, 88 %) as yellow solid.

M.p. (°C): 165-167.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.14 (d, *J* = 2.2 Hz, 1H), 8.32 (d, *J* = 2.2 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.80- 7.74 (m, 5H), 7.63-7.58 (m, 1H).

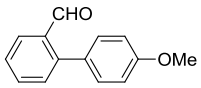
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm =148.9, 147.7, 142.3, 134.0, 132.9, 131.8, 130.3, 129.2, 128.1, 128.0, 127.7, 127.5, 118.5, 111.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3032 (w), 2922 (w), 2854 (w), 2224 (m), 1738 (w), 1602 (w), 1572 (w), 1492 (w), 1428 (w), 1360 (m), 1338 (w), 1312 (w), 1228 (w), 1182 (w), 1124 (w), 1038 (w), 956 (w), 910 (w), 862 (m), 838 (vs), 802 (m), 782 (m), 746 (s), 640 (vw).

MS (EI, 70 eV): m/z (%) = 230 (M^+, 100), 201 (7), 175 8%), 88 (5).

HRMS ($C_{16}H_{10}N_2$): calc.: 230.0844; found: 230.0842 (M^+).

4'-Methoxy-[1,1'-biphenyl]-2-carbaldehyde (45n)



According to **TP6** (4-methoxyphenyl)zinc pivalate (**41b**; 2.33 g, 1.05 mmol/g, 2.44 mmol) was dissolved in dry THF (5 mL). 2-Bromobenzaldehyde (**44r**; 379 mg, 2.05 mmol) and PEPPSI-*i*Pr (33 mg, 0.05 mmol) were added and the mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 10:1) afforded the biphenyl **45n** (349 mg, 82 %) as white solid.

M.p. (°C): 56.6-58.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.0 (s, 1H), 8.06-8.00 (m, 1H), 7.68-7.60 (m, 1H), 7.52-7.42 (m, 2H), 7.37-7.27 (m, 2H), 7.07-6.98 (m, 2H), 3.89 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 192.6, 159.7, 145.6, 133.7, 133.5, 131.2, 130.7, 130.0, 127.6, 127.3, 113.9, 55.3.

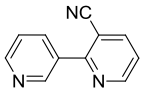
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938 (w), 2844 (w), 1689 (s), 1658 (m), 1605 (m), 1596 (s), 1576 (m), 1511 (m), 1475 (m), 1464 (m), 1456 (m), 1448 (m), 1442 (m), 1416 (w), 1393 (m), 1309 (w), 1296 (m), 1270 (m), 1243 (vs), 1196 (s), 1179 (s), 1167 (m), 1114 (m), 1099 (m), 1048 (w), 1030 (s), 1015 (m), 999 (m), 972 (w), 951 (w), 844 (s), 830 (s), 802 (m), 764 (vs), 744 (m), 724 (m), 709 (m)

MS (EI, 70 eV): m/z (%) = 212 (M^+, 100), 197 (15), 185 (10), 181 (20), 169 (29), 152 (10), 141 (30), 115 (17).

HRMS ($C_{14}H_{12}O_2$): calc.: 212.0837 found: 212.0824 (M^+).

4.3.5. Preparation of Cross-Coupling Products of Type **51**

2,3'-Bipyridine-3-carbonitrile (51a)



According to **TP6** pyridin-3-ylzinc pivalate (**47a**; 2.34 g, 0.99 mmol/g, 2.32 mmol) was dissolved in dry THF (5 mL). 2-Chloronicotinonitrile (**44a**; 270 mg, 1.95 mmol) and PEPPSI-*i*Pr (34 mg, 0.05 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, Et_2O) afforded the bipyridine **51a** (321 mg, 91 %) as colourless solid.

M.p. (°C): 110-111.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.14 (d, *J* = 2.2 Hz, 1H), 8.88 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.72 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.23 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.09 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.46-7.40 (m, 2H).

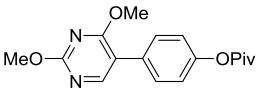
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.1, 152.9, 150.9, 149.7, 141.7, 136.0, 132.9, 123.2, 122.2, 117.0, 107.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068 (w), 2224 (w), 1738 (w), 1582 (m), 1554 (m), 1434 (s), 1406 (m), 1194 (w), 1102 (w), 1066 (w), 1016 (w), 812 (m), 762 (s), 708 (vs), 638 (w).

MS (EI, 70 eV): m/z (%) = 181 (M^+, 100), 155 (17), 129 (4), 77 (5).

HRMS ($C_{11}H_7N_3$): calc.: 181.0640; found: 181.0636 (M^+).

4-(2,4-Dimethoxypyrimidin-5-yl)phenyl pivalate (51b)



According to **TP6** (2,4-dimethoxypyrimidin-5-yl)zinc pivalate (**47b**; 1.74 g, 0.88 mmol/g, 1.54 mmol) was dissolved in dry THF (3 mL). 4-Bromophenyl pivalate (**44n**; 332 mg, 1.29 mmol) and PEPPSI-*i*Pr (20 mg, 0.03 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / EtOAc = 10:1 to 8:1) afforded the pyrimidine **51b** (321 mg, 80 %) as a yellow solid.

M.p. (°C): 72-75.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.24 (s, 1H), 7.50-7.45 (m, 2H), 7.13-7.08 (m, 2H), 4.02 (s, 3H), 4.00 (s, 3H), 1.36 (s, 9H).

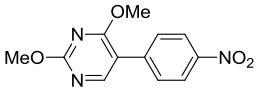
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 177.0, 168.2, 164.5, 157.3, 150.7, 130.6, 129.8, 121.5, 115.5, 54.9, 54.1, 39.1, 27.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974 (w), 2872 (vw), 1746 (m), 1596 (m), 1552 (m), 1466 (s), 1396 (s), 1382 (s), 1298 (w), 1276 (m), 1248 (m), 1238 (m), 1198 (m), 1168 (s), 1146 (w), 1118 (vs), 1086 (s), 1014 (m), 998 (m), 936 (w), 898 (m), 852 (w), 800 (w), 764 (w), 610 (w).

MS (EI, 70 eV): m/z (%) = 316 (M^+, 37), 232 (100), 217 (5), 202 (8), 57 (63).

HRMS ($C_{17}H_{20}N_2O_4$): calc.: 316.1423; found: 316.1413 (M^+).

2,4-Dimethoxy-5-(4-nitrophenyl)pyrimidine (51c)



According to **TP6** (2,4-dimethoxypyrimidin-5-yl)zinc pivalate (**47b**; 974 mg, 0.88 mmol/g, 0.86 mmol) was dissolved in dry THF (3 mL). 1-Bromo-4-nitrobenzene (**44o**; 332 mg, 0.72 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / EtOAc = 6:1) afforded the pyrimidine **51c** (133 mg, 71 %) as a yellow solid.

M.p. (°C): 176-177.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.32 (s, 1H), 8.29-8,24 (m, 2H), 7.69-7.65 (m, 2H), 4.06 (s, 3H), 4.05 (s, 3H).

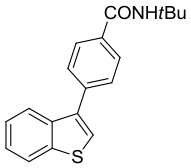
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.1, 165.2, 157.9, 147.1, 140.1, 129.4, 123.7, 114.2, 55.2, 54.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3008 (w), 2958 (w), 1740 (w), 1602 (s), 1554 (s), 1514 (s), 1454 (s), 1400 (s), 1382 (s), 1348 (vs), 1330 (vs), 1238 (s), 1186 (m), 1104 (m), 1080 (s), 1010 (s), 998 (s), 934 (m), 854 (vs), 796 (m), 740 (m), 732 (m), 696 (s).

MS (EI, 70 eV): m/z (%) = 261 (M^+, 100), 230 (32), 189 (8), 115 (8).

HRMS ($C_{12}H_{11}N_3O_4$): calc.: 261.0750; found: 261.0743 (M^+).

4-(Benzo[*b*]thiophen-3-yl)-*N*-(*tert*-butyl)benzamide (51d)



According to **TP6** benzo[b]thiophen-3-ylzinc pivalate (**47c**; 827 mg, 1.00 mmol/g, 0.83 mmol) was dissolved in dry THF (3 mL). 4-Bromo-*N*-(tert-butyl)benzamide (**44b**; 176 mg, 0.69 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the amide **51d** (180 mg, 84 %) as a yellow solid.

M.p. (°C): 120-122.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.94-7.82 (m, 4H), 7.65-7.60 (m, 2H), 7.44-7.35 (m, 3H), 1.50 (s, 9H).

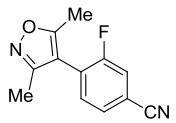
^{13}C-NMR (300 MHz, $CDCl_3$): δ / ppm = 166.6, 140.7, 138.8, 137.6, 137.1, 134.9, 128.7, 127.2, 124.6, 124.6, 124.2, 123.0, 122.7, 51.7, 28.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2971 (m), 1741 (m), 1633 (vs), 1542 (s), 1522 (s), 1451 (m), 1426 (m), 1389 (m), 1363 (s), 1314 (s), 1217 (vs), 860 (m), 832 (m), 759 (vs), 731 (s).

MS (EI, 70 eV): m/z (%) = 309 (M^+, 63), 253 (71), 237 (100), 208 (27), 165 (15).

HRMS ($C_{19}H_{19}NOS$): calc.: 309.1187; found: 309.1188 (M^+).

4-(3,5-Dimethylisoxazol-4-yl)-3-fluorobenzonitrile (51e)



According to **TP6** (3,5-dimethylisoxazol-4-yl)zinc pivalate **47d**; 1.92 g, 0.98 mmol/g, 1.88 mmol) was dissolved in dry THF (5 mL). 4-Bromo-3-fluorobenzonitrile (**44e**; 316 mg, 1.58 mmol) and PEPPSI-*i*Pr (27 mg, 0.04 mmol) were added and the mixture was stirred for

2 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / EtOAc = 3:1) afforded the benzonitrile **51e** (337 mg, 99 %) as a yellow solid.

M.p. (°C): 98-99.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.72-7.67 (m, 1H), 7.18-7.11 (m, 2H), 2.44 (s, 3H), 2.29 (s, 3H).

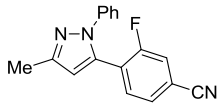
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 163.2 (d, *J* = 259.7 Hz), 157.8, 138.2 (d, *J* = 8.4 Hz), 133.8 (d, *J* = 1.1 Hz), 125.2 (d, *J* = 3.7 Hz), 116.6 (d, *J* = 19.7 Hz), 114.6 (d, *J* = 2.3 Hz), 113.6, 100.4 (d, *J* = 15.4 Hz), 11.8, 10.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3090 (vw), 3068 (vw), 2970 (vw), 2934 (vw), 2234 (m), 1742 (vw), 1630 (s), 1562 (m), 1490 (m), 1450 (m), 1402 (s), 1368 (m), 1308 (m), 1264 (m), 1246 (m), 1202 (m), 1184 (m), 1120 (w), 1032 (m), 1006 (w), 878 (vs), 846 (s), 738 (w), 636 (m).

MS (EI, 70 eV): m/z (%) = 216 (M^+, 100), 201 (26), 173 (37), 147 (60), 132 (38), 120 (14), 43 (47).

HRMS ($C_{12}H_9FN_2O$): calc.: 216.0699; found: 216.0699 (M^+).

3-Fluoro-4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)benzonitrile (51f)



According to **TP6** (3-methyl-1-phenyl-1H-pyrazol-5-yl)zinc pivalate (**47e**; 1.01 g, 0.74 mmol/g, 1.88 mmol) was dissolved in dry THF (5 mL). 4-Bromo-3-fluorobenzonitrile (**44e**; 125 mg, 0.63 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / EtOAc = 3:1) afforded the benzonitrile **51f** (172 mg, 98 %) as a colourless solid.

M.p. (°C): 74-76.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.55-7.50 (m, 1H), 7.43 (m, 3H), 7.30 -7.23 (m, 2H), 7.10-7.05 (m, 2H), 6.43 (s, 1H), 2.40 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.8 (d, *J* = 259.4 Hz), 149.9, 140.5 (d, *J* = 2.2 Hz), 139.3, 137.5 (d, *J* = 8.7 Hz), 133.4 (d, *J* = 1.1 Hz), 129.3, 128.1, 125.3, 124.6 (d, *J* = 3.4 Hz), 116.0 (d, *J* = 20.8 Hz), 113.6, 109.0, 100.6 (d, *J* = 15.8 Hz), 13.4.

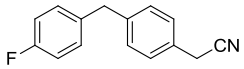
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922 (w), 2234 (m), 1738 (m), 1620 (m), 1594 (m), 1566 (m), 1540 (vw), 1502 (s), 1496 (s), 1432 (s), 1362 (s), 1236 (s), 1120 (m), 876 (s), 838 (m), 796 (s), 762 (vs), 742 (m), 696 (s).

MS (EI, 70 eV): m/z (%) = 277 (M^+, 100), 261 (5), 235 (5), 208 (6), 77 (9).

HRMS ($C_{17}H_{12}FN_3$): calc.: 277.1015; found: 277.1006 (M^+).

4.3.6. Preparation of Cross-Coupling Products of Type **52**

[4-(4-Fluorobenzyl)phenyl]acetonitrile (52a)



According to **TP6** (4-fluorobenzyl)zinc pivalate (**50a**; 737 mg, 1.18 mmol/g, 0.87 mmol) was dissolved in dry THF (4 mL). 2-(4-Bromophenyl)acetonitrile (**44o**; 143 mg, 0.73 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 4:1) afforded the acetonitrile **52a** (133 mg, 81 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.29-7.26 (m, 2H), 7.22-7.12 (m, 4H), 7.04-6.96 (m, 2H), 3.97 (s, 2H), 3.73 (s, 2H).

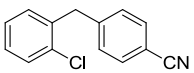
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.8 (d, *J* = 244.3 Hz), 141.0 (d, *J* = 0.8 Hz), 136.3 (d, *J* = 3.1 Hz), 130.2 (d, *J* = 7.9 Hz), 129.5, 128.1, 127.8, 117.9, 115.3 (d, *J* = 21.5 Hz), 40.6 (d, 0.8 Hz), 23.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3034 (vw), 2920 (vw), 2360 (vw), 2250 (w), 1736 (vw), 1602 (w), 1506 (vs), 1416 (m), 1220 (s), 1158 (m), 1092 (w), 1016 (w), 920 (w), 848 (m), 808 (s), 774 (m), 754 (m), 694 (w).

MS (EI, 70 eV): m/z (%) = 225 (M^+, 44), 185 (100), 165 (43), 109 (12), 74 (14), 59 (19), 45 (18).

HRMS ($C_{15}H_{12}FN$): calc.: 225.0954; found: 225.0940 (M^+).

4-(2-Chlorobenzyl)benzonitrile (52b)



According to **TP6** (2-chlorobenzyl)zinc pivalate (**50b**; 1.64 g, 1.09 mmol/g, 1.77 mmol) was dissolved in dry THF (4 mL). 4-Bromobenzonitrile (**43**; 271 mg, 1.49 mmol) and PEPPSI-*i*Pr (27 mg, 0.04 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 30:1) afforded the benzonitrile **52b** (237 mg, 70 %) as a colourless solid.

M.p. (°C): 63-64.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.61-7.58 (m, 2H), 7.44-7.39 (m, 1H), 7.32-7.28 (m, 2H), 7.26-7.18 (m, 3H), 4.18 (s, 2H).

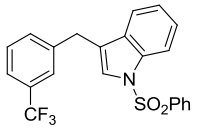
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 145.1, 136.9, 134.3, 132.2, 131.1, 129.8, 129.5, 128.3, 127.1, 118.9, 110.2, 39.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2224 (m), 1920 (vw), 1738 (w), 1606 (w), 1508 (w), 1500 (vw), 1444 (w), 1438 (w), 1414 (w), 1298 (vw), 1178 (vw), 1114 (w), 1102 (w), 1048 (w), 1034 (w), 1020 (w), 942 (vw), 916 (w), 844 (w), 806 (m), 760 (m), 742 (vs), 674 (m).

MS (EI, 70 eV): m/z (%) = 229 (14), 227 (M^+, 43), 192 (100), 165 (16), 95 (8), 43 (9).

HRMS ($C_{14}H_{10}ClN$): calc.: 227.0502; found: 227.0499 (M^+).

1-(Phenylsulfonyl)-3-(3-(trifluoromethyl)benzyl)-1*H*-indole (52c)



According to **TP6** (3-(trifluoromethyl)benzyl)zinc pivalate (**50c**; 840 mg, 0.76 mmol/g, 0.64 mmol) was dissolved in dry THF (3 mL). 3-Bromo-1-(phenylsulfonyl)-1*H*-indole (**44p**; 182 mg, 0.54 mmol) and PEPPSI-*i*Pr (7 mg, 0.01 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the indole **52c** (192 mg, 86 %) as a yellow solid.

M.p. (°C): 119-120.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.05-8.02 (m, 1H), 7.90-7.85 (m, 2H), 7.60-7.30 (m, 10H), 7.25-7.20 (m, 1H), 4.09 (s, 2H).

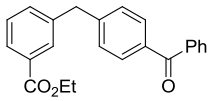
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 140.0, 138.1, 135.6, 133.8, 132.0 (q, *J* = 1.1 Hz), 130.9 (q, *J* = 32.0 Hz), 130.5, 129.2, 129.0, 126.6, 125.3 (q, *J* = 3.9 Hz), 125.0, 124.1, 124.1 (q, *J* = 272.4 Hz), 123.4 (q, *J* = 3.9 Hz), 123.4, 121.7, 119.6, 113.9, 31.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1738 (w), 1448 (m), 1368 (m), 1332 (s), 1206 (m), 1172 (s), 1160 (vs), 1132 (s), 1106 (vs), 1092 (vs), 1070 (s), 972 (m), 784 (m), 744 (s), 722 (s), 702 (m), 678 (m), 656 (m).

MS (EI, 70 eV): m/z (%) = 415 (M^+, 34), 274 (100), 204 (11), 77 (19).

HRMS ($C_{22}H_{16}F_3NO_2S$): calc.: 415.0854; found: 415.0839 (M^+).

Ethyl 3-(4-benzoylbenzyl)benzoate (52d)



According to **TP6** (3-(ethoxycarbonyl)benzyl)zinc pivalate (**50d**; 862 mg, 0.94 mmol/g, 0.74 mmol) was dissolved in dry THF (3 mL). 4-Chlorobenzophenone (**44q**; 134 mg, 0.62 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the benzophenone **52d** (181 mg, 85 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm =7.93-7.88 (m, 2H), 7.79-7.72 (m, 4H), 7.60-7.54 (m, 1H), 7.49-7.43 (m, 2H), 7.40-7.34 (m, 2H), 7.30-7.25 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.10 (s, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm =196.3, 166.5, 145.4, 140.4, 137.7, 135.7, 133.4, 132.3, 130.9, 130.5, 130.0, 129.9, 128.8, 128.7, 128.2, 127.7, 61.0, 41.7, 14.3.

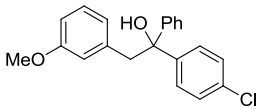
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056 (vw), 2979 (w), 2904 (vw), 1713 (s), 1654 (s), 1601 (m), 1445 (m), 1412 (w), 1366 (m), 1274 (vs), 1178 (s), 1103 (s), 1080 (m), 1019 (m), 1001 (m), 938 (m), 922 (m), 858 (m), 784 (m), 752 (s), 699 (vs).

MS (EI, 70 eV): m/z (%) = 344 (M^+, 85), 299 (23), 267 (100), 165 (23), 105 (32), 77 (14).

HRMS (ESI, $C_{23}H_{20}O_3$): calc.: 362.1748 ($[M+NH_4]^+$); found: 362.1748 ($[M+NH_4]^+$).

4.3.7. Preparation of Carbonyl Addition Products of Type **53**

1-(4-Chlorophenyl)-2-(3-methoxyphenyl)-1-phenylethanol (53b)



According to **TP7** (3-methoxybenzyl)zinc pivalate (**50e**; 675 mg, 1.12 mmol/g, 0.75 mmol) was dissolved in dry THF (3 mL). 4-Chlorobenzophenone (**44q**; 137 mg, 0.63 mmol) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1 to pure AcOEt) afforded the alcohol **53b** (188 mg, 88 %) as orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.47-7.26 (m, 9H), 7.15 (m, 1H), 6.79-6.75 (m, 1H), 6.57-6.54 (m, 1H), 6.39-6,38 (m, 1H), 3.65 (d, *J* = 13.8 Hz, 1H), 3.63 (s, 3H), 3.59 (d, *J* = 13.8 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.3, 146.2, 145.1, 136.8, 132.7, 129.2, 128.2, 128.1, 127.7, 127.1, 126.1, 123.1, 115.9, 113.0, 77.5, 55.0, 47.9.

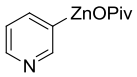
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3466 (w), 1612 (m), 1584 (m), 1488 (s), 1446 (m), 1436 (m), 1398 (w), 1378 (w), 1296 (m), 1254 (m), 1210 (m), 1196 (m), 1150 (s), 1094 (s), 1058 (s), 1046 (s), 1014 (m), 874 (m), 860 (w), 822 (s), 780 (m), 764 (m), 754 (w), 746 (s), 732 (m), 708 (vs), 698 (s).

MS (EI, 70 eV): m/z (%) = 338 (M^+, <1), 217 (100), 141 (14), 139 (49), 122 (26), 111 (11), 105 (29), 77 (18).

HRMS ($C_{21}H_{19}ClO_2$): calc.: 338.1074; found: 338.1094 (M^+).

4.4. Improvement of the Air-Stability of the Solid Salt-Stabilized Organozinc Reagents Prepared *via* Magnesium-Insertion in the Presence of $ZnOPiv_2$

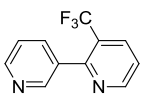
4.4.1. Preparation of 3-Pyridylzinc Pivalate (**55**)



According to **TP8** $Zn(OPiv)_2$ (**40**; 1.87 g, 7.00 mmol) and 3-bromopyridine (**54**; 1.11 g, 7.00 mmol) were dissolved in 20 mL of dry THF. Magnesium turnings (340 mg, 14.0 mmol) were added and the reaction mixture was stirred for 12 h at 25 °C. After subsequent cannulation to another argon-flushed *Schlenk*-flask the solvent was removed *in vacuo*. Pyridin-3-ylzinc pivalate (**55**) was obtained as a pale green solid (3.50 g). The content of active zinc species was determined by titration of 209 mg of the reagent with a stock solution of iodine (1.0 M in THF). A concentration of 1.20 mmol/g was determined which corresponds to a yield of 60 %.

4.4.2. Preparation of Cross-Coupling Products of Type **56**

3-(Trifluoromethyl)-2,3'-bipyridine (56a)



According to **TP6** pyridin-3-ylzinc pivalate (**55**; 911 mg, 0.98 mmol/g, 0.90 mmol) was dissolved in AcOEt (4 mL). 2-Chloro-3-(trifluoromethyl)pyridine (138 mg, 0.76 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 12 h at 50 °C.

Purification by flash chromatography (silica gel, pure AcOEt) afforded the bipyridine **56a** (132 mg, 78 %) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.88-8.86 (m, 1H), 8.76-8.75 (d, *J* = 1.5 Hz, 1H), 8.70-8.69 (m, 1H), 8.12-8.10 (m, 1H), 7.85-7.81 (m,1H), 7.49-7.46 (m, 1H), 7.40-7.37 (m, 1H).

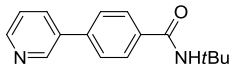
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.3 (q, *J* = 1.88 Hz), 152.2 (q, *J* = 1.17 Hz), 145.0, 149.4 (q, *J* = 1.95 Hz), 136.0 (q, *J* = 1.95 Hz), 135.0, 134.9 (q, *J* = 4.93 Hz), 125.5 (q, *J* = 32.0 Hz), 123.4 (q, *J* = 273 Hz), 122.8, 122.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053 (vw), 1590 (m), 1573 (m), 1440 (s), 1410 (m), 1317 (s), 1293 (m), 1228 (m), 1161 (s), 1115 (vs), 1091 (s), 1054 (m), 1027 (vs), 1013 (s), 816 (m), 775 (s), 712 (s), 672 (m).

MS (EI, 70 eV): m/z (%) = 224 (M^+, 100), 203 (14), 198 (15), 155 (11), 149 (13).

HRMS ($C_{11}H_7F_3N_2$): calc.: 224.0561; found: 224.0563 (M^+).

***N*-(*tert*-butyl)-4-(pyridin-3-yl)benzamide (56b)**



According to **TP6** pyridin-3-ylzinc pivalate (**55**; 1.21 g, 0.98 mmol/g, 1.19 mmol) was dissolved in dry THF (4 mL). 4-Bromo-*N*-(*tert*-butyl)benzamide (**44b**; 255 mg, 1.00 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (silica gel, pure AcOEt) afforded the benzamide **56b** (210 mg, 83 %) as a yellow solid.

M.p. (°C): 153-154.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.85-8.84 (m, 1H), 8.62-8.60 (m, 1H), 7.89-7.86 (m, 1H), 7.84-7.80 (m, 2H), 7.64-7.59 (m, 2H), 7.39-7.35 (m, 1H), 5.98 (br, 1H), 1.48 (s, 9H).

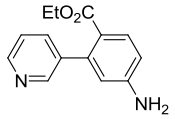
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 149.1, 148.3, 140.5, 135.6, 135.5, 134.4, 127.5, 127.2, 123.6, 51.8, 28.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3283 (w), 2958 (w), 2364 (w), 1741 (m), 1637 (s), 1610 (m), 1543 (s), 1471 (m), 1450 (m), 1425 (w), 1388 (m), 1364 (m), 1315 (s), 1224 (s), 1000 (m), 875 (m), 859 (m), 842 (w), 806 (m), 767 (vs), 708 (s), 662 (m).

MS (EI, 70 eV): m/z (%) = 224 (M^+, 18), 198 (21), 182 (100), 154 (15), 127 (12).

HRMS ($C_{16}H_{18}N_2O$): calc.: 254.1419; found: 254.1418 (M^+).

Ethyl 4-amino-2-(pyridin-3-yl)benzoate (56c)



According to **TP6** pyridin-3-ylzinc pivalate (**55**; 847 mg, 0.94 mmol/g, 0.80 mmol) was dissolved in dry THF (2 mL). Ethyl 4-amino-2-bromobenzoate (**65b**; 155 mg, 0.67 mmol) and PEPPSI-*i*Pr (14 mg, 0.02 mmol) were added and the mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (silica gel, pure AcOEt) afforded the benzamide **56c** (139 mg, 86 %) as a yellow solid.

M.p. (°C): 119-121.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.73-8.63 (m, 2H), 7.88 (dd, *J* = 8.4, 2.1, 1H), 7.80-7.77 (m, 2H), 7.42-7.38 (m, 1H), 6.75 (d, *J* = 8.4, 1H), 4.32 (q, *J* = 7.1, 2H), 4.10 (br s, 2H), 1.35 (t, *J* = 7.1, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 149.9, 148.8, 148.0, 144.9, 136.7, 132.5, 131.3, 125.7, 122.6, 120.7, 114.8, 60.5, 14.4.

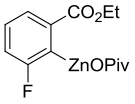
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3283 (w), 2958 (w), 2364 (w), 1741 (m), 1637 (s), 1610 (m), 1543 (s), 1471 (m), 1450 (m), 1425 (w), 1388 (m), 1364 (m), 1315 (s), 1224 (s), 1000 (m), 875 (m), 859 (m), 842 (w), 806 (m), 767 (vs), 708 (s), 662 (m).

MS (EI, 70 eV): m/z (%) = 242 (M^+, 95), 214 (16), 197 (100), 168 (14).

HRMS ($C_{14}H_{14}N_2O_2$): calc.: 242.1055; found: 242.1046 (M^+).

4.5. Improved Air-stable Solid Aromatic Zinc Pivalates *via* Highly Selective Metalations and Their Application in *Negishi* Cross-Couplings

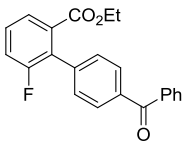
4.5.1. Preparation of (2-(Ethoxycarbonyl)-6-fluorophenyl)zinc pivalate (**58**)



According to **TP9**, ethyl 3-fluorobenzoate (**57**; 505 mg, 3.0 mmol) in 9 mL of dry THF was fully metalated using TMPMgCl·LiCl (**12**; 2.70 mL, 1.23 M, 3.30 mmol) after 2 h at 0 °C. After transmatelation with solid $Zn(OPiv)_2$ (963 mg, 3.60 mmol) and careful evaporation of the solvent the arylzinc pivalate **58** was obtained as yellow solid. The content of active zinc

species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 1.22 mmol/g, which corresponds to a yield of 92 % was determined.

4.5.2. Preparation of Ethyl 4'-benzoyl-6-fluorobiphenyl-2-carboxylate (**59**)



According to **TP10** (2-(ethoxycarbonyl)-6-fluorophenyl)zinc pivalate (**58**; 820 mg, 1.22 mmol/g, 1.00 mmol) was dissolved in dry THF (2 mL). $Pd(OAc)_2$ (4 mg, 0.02 mmol, 2 mol %) and X-Phos (16 mg, 0.03 mmol, 4 mol %) were added successively and the resulting mixture was stirred for 2 min at 25 °C, followed by the addition of 4-chlorobenzophenone (**44q**; 182 mg, 0.84 mmol). The reaction was completed after heating for 12 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / EtOAc = 20:1 to 10:1) afforded the biphenyl **59** (246 mg, 84 %) as light yellow solid.

M.p. (°C): 69.8-71.6.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.88-7.91 (m, 2H), 7.83-7.87 (m, 2H), 7.73 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.59-7.64 (m, 1H), 7.49-7.54 (m, 2H), 7.45-7.48 (m, 1H), 7.41-7.45 (m, 2H), 7.33 (ddd, *J* = 9.2, 8.2, 1.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 1.02 (t, *J* = 7.1 Hz, 3H),

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm: 196.2, 166.9 (d, *J*=3.0 Hz), 159.5 (d, *J*=246.0 Hz), 138.8, 137.6, 136.6, 133.3 (d, *J*=1.5 Hz), 132.4, 130.0, 129.7, 129.4 (d, *J*=9.0 Hz), 129.3 (d, *J*=1.5 Hz), 128.9 (d, *J*=16.5 Hz), 128.3, 125.7 (d, *J*=4.5 Hz), 119.0 (d, *J*=24.0 Hz), 61.3, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ /cm-1: 3066 (vw), 2978 (w), 1706 (s), 1654 (s), 1446 (m), 1282 (vs), 1275 (vs), 1237 (m), 1179 M), 1130 (m), 1007 (m), 940 (m), 925 (m), 860 (m), 769 (s), 752 (s), 698 (s), 684 (s).

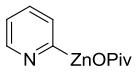
MS (EI, 70 eV): m/z (%): 349 (15), 348 (M^+, 62), 272 (17), 271 (100), 170 (11), 105 (40), 77 (18).

HRMS ($C_{22}H_{22}FO_3$): calc.: 348.1162; found: 348.1157 (M^+).

4.6. Solid 2-Pyridylzinc Pivalates and Their Application to *Negishi* Cross-Coupling Reactions

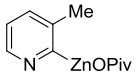
4.6.1. Preparation of the 2-Pyridylzinc Pivalates of Type **63** and **64**

Pyridin-2-ylzinc pivalate (63a)



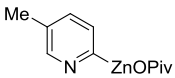
According to **TP11** 2-bromopyridine (**62**; 1.26 g, 8.00 mmol) was dissolved in dry THF (13 mL) and *n*BuLi (3.41 mL, 2.34 M in hexane, 8.00 mmol) was added. The mixture was stirred at -78 °C for further 15 min. $Zn(OPiv)_2$ (**40**; 2.14 g, 8.00 mmol) was added and the mixture was slowly warmed to 25 °C. The solvent was removed *in vacuo* and 2-pyridylzinc pivalate (**63a**) was obtained as a slightly greenish solid (3.41 g). The content of active zinc species was determined by titration of 276 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 502 mg/mmol was determined which corresponds to a yield of 85 %.

3-Methylpyridin-2-ylzinc pivalate (63b)



According to **TP11** 2-bromo-3-methylpyridine (860 mg, 5.00 mmol) was dissolved in dry THF (8 mL) and *n*BuLi (2.14 mL, 2.34 M in hexane, 5.00 mmol) was added. The mixture was stirred at -78 °C for further 15 min. $Zn(OPiv)_2$ (**40**; 1.34 g, 5.00 mmol) was added and the mixture was slowly warmed to 25 °C. The solvent was removed *in vacuo* and 3-methylpyridin-2-ylzinc pivalate (**63b**) was obtained as a slightly greenish solid (1.86 g). The content of active zinc species was determined by titration of 193 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 2.38 mmol/g was determined which corresponds to a yield of 89 %.

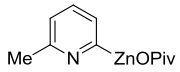
5-Methylpyridin-2-ylzinc pivalate (63c)



According to **TP11** 2-bromo-5-methylpyridine (860 mg, 5.00 mmol) was dissolved in dry THF (8 mL) and *n*BuLi (2.14 mL, 2.34 M in hexane, 5.00 mmol) was added. The mixture was stirred at -78 °C for further 15 min. $Zn(OPiv)_2$ (**40**; 1.34 g, 5.00 mmol) was added and the

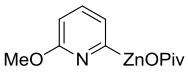
mixture was slowly warmed to 25 °C. The solvent was removed *in vacuo* and 5-methylpyridin-2-ylzinc pivalate (**63c**) was obtained as a slightly greenish solid (1.94 g). The content of active zinc species was determined by titration of 287 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 2.51 mmol/g was determined which corresponds to a yield of 97 %.

6-Methylpyridin-2-ylzinc pivalate (63d)



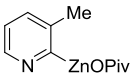
According to **TP11** 2-bromo-6-methylpyridine (860 mg, 5.00 mmol) was dissolved in dry THF (8 mL) and *n*BuLi (2.14 mL, 2.34 M in hexane, 5.00 mmol) was added. The mixture was stirred at -78 °C for further 15 min. $Zn(OPiv)_2$ (**40**;1.34 g, 5.00 mmol) was added and the mixture was slowly warmed to 25 °C. The solvent was removed *in vacuo* and 6-methylpyridin-2-ylzinc pivalate (**63d**) was obtained as a slightly greenish solid (2.07 g). The content of active zinc species was determined by titration of 90.0 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.67 mmol/g was determined which corresponds to a yield of 69 %.

6-Methoxypyridin-2-ylzinc pivalate (63e)



According to **TP11** 2-bromo-6-methoxypyridine (940 mg, 5.00 mmol) was dissolved in dry THF (8 mL) and *n*BuLi (2.14 mL, 2.34 M in hexane, 5.00 mmol) was added. The mixture was stirred at -78 °C for further 15 min. $Zn(OPiv)_2$ (**40**; 1.34 g, 5.00 mmol) was added and the mixture was slowly warmed to 25 °C. The solvent was removed *in vacuo* and 6-methoxypyridin-2-ylzinc pivalate (**63e**) was obtained as a slightly greenish solid (2.07 g). The content of active zinc species was determined by titration of 150 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 2.00 mmol/g was determined which corresponds to a yield of 88 %.

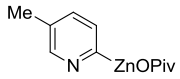
3-Methylpyridin-2-ylzinc pivalate (64a)



According to **TP12** 2-bromo-3-methylpyridine (860 mg, 5.00 mmol) was dissolved in dry THF (5 mL) and *i*PrMgCl·LiCl (4.13 mL, 1.27 M, 5.25 mmol) was added. The mixture was

stirred at 25 °C for further 2 h. $Zn(OPiv)_2$ (**40**; 1.34 g, 5.00 mmol) was added and the mixture was slowly warmed to 25 °C. The solvent was removed *in vacuo* and 3-methylpyridin-2-ylzinc pivalate (**64a**) was obtained as a slightly greenish solid (3.52 g). The content of active zinc species was determined by titration of 123 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.22 mmol/g was determined which corresponds to a yield of 86 %.

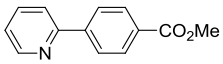
5-Methylpyridin-2-ylzinc pivalate (64b)



According to **TP12** 2-bromo-5-methylpyridine (860 mg, 5.00 mmol) was dissolved in dry THF (8 mL) and *i*PrMgCl·LiCl (4.13 mL, 1.27 M, 5.25 mmol) was added. The mixture was stirred at 25 °C for further 2 h. $Zn(OPiv)_2$ (**40**; 1.34 g, 5.00 mmol) was added and the mixture was slowly warmed to 25 °C. The solvent was removed *in vacuo* and 5-methylpyridin-2-ylzinc pivalate (**64b**) was obtained as a slightly greenish solid (3.43 g). The content of active zinc species was determined by titration of 478 mg of the reagent with a stock solution of iodine (1.00 M in THF). A concentration of 1.44 mmol/g was determined which corresponds to a yield of 99 %.

4.6.2. Preparation of Cross-Coupling Products of Type **66**

Methyl 4-(pyridin-2-yl)benzoate (66a)



According to **TP13** pyridin-2-ylzinc pivalate (**63a**; 700 mg, 700 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). Methyl 4-chlorobenzoate (**65a**; 143 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 3:1) afforded the pyridine **66a** (172 mg, 96 %) as a pale yellow solid.

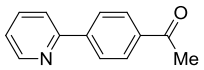
M.p. (°C): 100-101.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.72-8.70(m, 1H), 8.14-8.11 (m, 2H), 8.07-8.04 (m, 2H), 7.77-7.76 (m, 2H), 7.29-7.24 (m, 1H), 3.93 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.9, 156.2, 149.9, 143.5, 136.9, 130.3, 130.0, 126.8, 122.8, 121.0, 52.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944 (w), 2848 (w), 1708 (s), 1606 (w), 1586 (m), 1466 (w), 1435 (m), 1405 (w), 1319 (w), 1274 (s), 1194 (m), 1183 (m), 1153 (w), 1111 (s), 1014 (m), 965 (m), 868 (w), 830 (w), 797 (w), 754 (vs), 699 (m).
MS (EI, 70 eV): m/z (%) = 213 (M^+, 69), 182 (100), 154 (30), 127 (10).
HRMS ($C_{13}H_{11}NO_2$): calc.: 213.0790; found: 213.0784 (M^+).

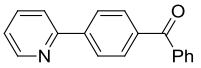
1-(4-(Pyridin-2-yl)phenyl)ethanone (66b)



According to **TP13** pyridin-2-ylzinc pivalate **63a**; 700 mg, 700 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). 4-Chloroacetophenone (**44d**; 130 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 4:1) afforded the pyridine **66b** (155 mg, 94 %) as a pale yellow solid.

M.p. (°C): 118-119.
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.72-8.70 (m, 1H), 8.10-8.07 (m, 2H), 8.05-8.03 (m, 2H), 7.78-7.76 (m, 2H), 7.30-7.24 (m, 1H), 2.63 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 212.9, 197.8, 156.0, 149.9, 143.5, 136.9, 128.8, 127.0, 122.9, 121.0, 26.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3309 (w), 2971 (w), 2928 (w), 2361 (w), 2339 (w), 1740 (w), 1634 (s), 1540 (vs), 1465 (m), 1436 (m), 1393 (m), 1366 (m), 1324 (m), 1307 (s), 1217 (s), 1157 (w), 1015 (w), 865 (m), 797 (m), 756 (vs).
MS (EI, 70 eV): m/z (%) = 197 (M^+, 44), 182 (100), 153 (36), 127 (11).
HRMS ($C_{13}H_{11}NO$): calc.: 197.0841; found: 197.0836 (M^+).

Phenyl(4-(pyridin-2-yl)phenyl)methanone (66c)



According to **TP13** pyridin-2-ylzinc pivalate (**63a**; 700 mg, 700 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). 4-Chlorobenzophenone (**44q**; 182 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 4:1) afforded the pyridine **66c** (211 mg, 97 %) as a pale yellow solid.

M.p. (°C): 100-101.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.74-8.72(m, 1H), 8.12-8.09 (m, 2H), 7.92-7.89 (m, 2H), 7.84-7.76 (m, 4H), 7.61-7.57 (m, 1H), 7.51-7.47 (m, 2H), 7.31-7.25 (m, 1H).

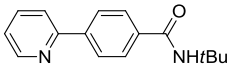
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 213.0, 196.4, 156.2, 149.9, 143.0, 137.6, 132.5, 130.6, 132.5, 130.0, 128.3, 126.7, 122.8, 123.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3746 (vw), 3008 (vw), 2361 (w), 2340 (w), 1651 (s), 1599 (m), 1577 (m), 1559 (m), 1462 (w), 1437 (m), 1399 (w), 1317 (m), 1278 (m), 1265 (m), 1152 (m), 941 (m), 924 (m), 868 (m), 804 (m), 778 (m), 766 (m), 735 (s), 699 (vs).

MS (EI, 70 eV): m/z (%) = 259 (M^+, 93), 182 (100), 154 (23), 105 (14).

HRMS ($C_{18}H_{13}NO$): calc.: 259.0997; found: 259.0992 (M^+).

***N*-(*tert*-butyl)-4-(pyridin-2-yl)benzamide (66d)**



According to **TP13** pyridin-2-ylzinc pivalate (**63a**; 700 mg, 700 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). 4-Bromo-*N*-(*tert*-butyl)benzamide (**44b**; 215 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 2:1) afforded the pyridine **66d** (190 mg, 89 %) as a pale yellow solid.

M.p. (°C): 153-155.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.71-8.69 (m, 1H), 8.06-8.02 (m, 2H), 7.83-7.79 (m, 2H), 7.77-7.73 (m, 2H), 7.29-7.21 (m, 1H), 5.99 (s, br, 1H), 1.48 (s, 9H).

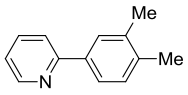
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.5, 156.3, 149.8, 141.8, 136.8, 136.1, 127.2, 126.9, 122.6, 120.8, 51.7, 28.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3309 (w), 2971 (w), 2928 (w), 2361 (w), 2339 (w), 1734 (w), 1634 (s), 1540 (vs), 1465 (m), 1436 (m), 1393 (m), 1366 (m), 1324 (m), 1307 (s), 1217 (s), 1157 (w), 1015 (w), 865 (m), 797 (m), 756 (vs).

MS (EI, 70 eV): m/z (%) = 254 (M^+, 37), 198 (27), 182 (100), 154 (25).

HRMS ($C_{16}H_{18}N_2O$): calc.: 254.1419; found: 254.1411 (M^+).

2-(3,4-Dimethylphenyl)pyridine (66e)



According to **TP13** pyridin-2-ylzinc pivalate (**63a**; 767 mg, 767 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). 4-bromo-1,2-dimethylbenzene (**39**; 156 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 5:1) afforded the pyridine **66e** (115 mg, 75 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.68-8.65 (m, 1H), 7.81-7.79 (m, 1H), 7.74-7.67 (m, 3H), 7.24-7.21 (m, 1H), 7.20-7.14 (m, 1H), 2.34 (s, 3H), 2.31 (s, 3H).

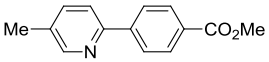
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.6, 149.5, 137.6, 137.0, 136.9, 136.6, 130.0, 128.0, 124.2, 121.7, 120.3, 19.9, 19.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3005 (w), 2918 (w), 2860 (vw), 1584 (m), 1562 (m), 1464 (s), 1449 (m), 1430 (s), 1384 (w), 1304 (w), 1273 (w), 1152 (w), 1126 (w), 1095 (w), 1021 (w), 993 (m), 882 (w), 855 (vw), 775 (vs), 740 (m), 718 (m).

MS (EI, 70 eV): m/z (%) = 183 (M^+, 100), 167 (24), 153 (36), 127 (11).

HRMS ($C_{13}H_{13}N$): calc.: 183.1048; found: 183.1041 (M^+).

Methyl 4-(5-methylpyridin-2-yl)benzoate (66f)



According to **TP13** (5-methylpyridin-2-yl)zinc pivalate (**63c**; 374 mg, 374 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). Methyl 4-chlorobenzoate (**65a**; 143 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 3:1) afforded the pyridine **66f** (115 mg, 60 %) as a pale yellow solid.

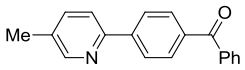
M.p. (°C): 111-113.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.54-8.53 (m, 1H), 8.13-8.10 (m, 2H), 8.05-8.02 (m, 2H), 7.68-7.66 (m, 1H), 7.59-7.56 (m, 1H), 3.93 (s, 3H), 2.38 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.9, 153.5, 150.3, 143.5, 137.4, 132.6, 130.0, 130.0, 126.5, 120.5, 52.1, 18.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953 (w), 1711 (vs), 1608 (m), 1577 (m), 1475 (m), 1440 (s), 1410 (m), 1373 (m), 1282 (vs), 1272 (vs), 1197 (m), 1189 (m), 1103 (s), 1013 (m), 962 (m), 868 (m), 835 (vs), 811 (m), 778 (s), 747 (vs), 702 (s).
MS (EI, 70 eV): m/z (%) = 227 (M^+, 100), 196 (64), 168 (28).
HRMS ($C_{14}H_{13}NO_2$): calc.: 227.0946; found: 227.0941 (M^+).

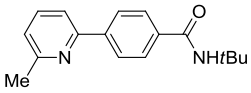
(4-(5-Methylpyridin-2-yl)phenyl)(phenyl)methanone (66g)



According to **TP13** (5-methylpyridin-2-yl)zinc pivalate (**63c**; 374 mg, 374 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). 4-Chlorobenzophenone (**44q**; 182 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 3:1) afforded the pyridine **66g** (180 mg, 78 %) as a pale yellow solid.

M.p. (°C): 133-143.
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.56-8.55 (m, 1H), 8.10-8.06 (m, 2H), 7.91-7.87 (m, 2H), 7.85-7.81 (m, 2H), 7.71-7.69 (m, 1H), 7.62-7.56 (m, 2H), 7.51-7.46 (m, 2H), 2.39 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.4, 153.5, 150.4, 143.1, 137.7, 137.4, 137.3, 132.6, 132.4, 130.6, 130.0, 128.3, 126.5, 120.5, 18.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953 (w), 2923 (m), 2855 (w), 1650 (s), 1594 (s), 1575 (m), 1554 (m), 1468 (m), 1446 (m), 1378 (m), 1311 (m), 1273 (s), 1177 (m), 1150 (m), 1028 (m), 927 (m), 870 (w), 826 (vs), 794 (s), 735 (vs), 699 (vs), 670 (m).
MS (EI, 70 eV): m/z (%) = 273 (M^+, 100), 196 (75), 168 (18), 105 (17), 65 (17).
HRMS ($C_{19}H_{15}NO$): calc.: 273.1154; found: 273.1161 (M^+).

***N*-(*tert*-butyl)-4-(6-methylpyridin-2-yl)benzamide (66h)**



According to **TP13** (6-methylpyridin-2-yl)zinc pivalate (**63d**; 540 mg, 540 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). 4-Bromo-*N*-(*tert*-butyl)benzamide (**44b**; 215 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography

(silica gel, *i*hexane / AcOEt = 3:1) afforded the pyridine **66h** (156 mg, 69 %) as a pale yellow solid.

M.p. (°C): 147-148.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.05-8.02 (m, 2H), 7.81-7.78 (m, 2H), 7.66-7.61 (m, 1H), 7.55-7.52 (m, 1H), 7.13-7.10 (m, 1H), 2.62 (s, 3H), 1.48 (s, 9H).

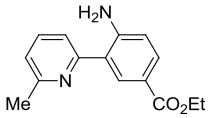
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.6, 158.6, 155.7, 142.2, 137.0, 135.8, 127.1, 127.0, 122.2, 117.8, 51.7, 28.9, 24.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3348 (w), 2978 (w), 1636 (s), 1591 (m), 1542 (vs), 1458 (s), 1398 (w), 1362 (m), 1321 (s), 1310 (s), 1287 (m), 1218 (s), 1110 (m), 1017 (w), 860 (s), 802 (m), 763 (vs), 719 (w), 706 (w).

MS (EI, 70 eV): m/z (%) = 268 (M^+, 32), 212 (31), 196 (100), 168 (22).

HRMS ($C_{17}H_{20}N_2O$): calc.: 268.1576; found: 268.1576 (M^+).

Ethyl 4-amino-2-(6-methylpyridin-2-yl)benzoate (66i)



According to **TP13** (6-methylpyridin-2-yl)zinc pivalate (**63d**; 540 mg, 540 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). Ethyl 4-amino-3-bromobenzoate (**65b**; 205 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 3:1) afforded the pyridine **66i** (179 mg, 83 %) as a pale yellow solid.

M.p. (°C): 75-76.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.30-8.29 (m, 1H), 7.83-7.80 (m, 1H), 7.69-7.64 (m, 1H), 7.59-7.56 (m, 1H), 7.06-7.03 (m, 1H), 6.70-6.67 (m, 1H), 6.45 (s, br, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.91 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

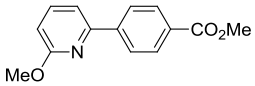
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.7, 157.9, 156.3, 150.9, 137.3, 131.5, 131.2, 120.7, 120.4, 119.0, 118.9, 116.2, 60.3, 24.5, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3404 (m), 3220 (w), 2924 (w), 1678 (s), 1608 (s), 1587 (s), 1554 (m), 1504 (m), 1451 (m), 1368 (s), 1289 (m), 1258 (s), 1223 (vs), 1134 (s), 1029 (s), 915 (m), 838 (m), 796 (s), 766 (s), 741 (m), 691 (m).

MS (EI, 70 eV): m/z (%) = 256 (100; M^+), 227 (45); 211 (33), 183 (23), 168 (10).

HRMS ($C_{15}H_{16}N_2O_2$): calc.: 256.1212; found: 256.1201 (M^+).

Methyl 4-(6-methoxypyridin-2-yl)benzoate (66j)



According to **TP13** (3-methoxyphenyl)zinc pivalate (**63e**; 500 mg, 500 mg/mmol, 1.00 mmol) was dissolved in dry THF (3 mL). Methyl 4-bromobenzoate (**65c**; 181 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 9:1) afforded the pyridine **66j** (200 mg, 98 %) as a colourless solid.

M.p. (°C): 93-94.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.12-8.09 (m, 4H), 7.67-7.61 (m, 1H), 7.40-7.37 (m, 1H), 6.74-6.71 (m, 1H), 4.04 (s, 3H), 3.93 (s, 3H).

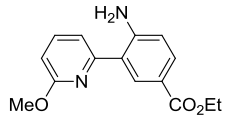
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.9, 163.8, 153.3, 143.2, 139.2, 130.2, 129.9, 126.5, 113.4, 110.3, 53.3, 52.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953 (w), 1716 (s),1602 (m), 1572 (m), 1468 (m), 1429 (m), 1423 (m), 1396 (m), 1328 (m), 1281 (s), 1255 (s), 1187 (m), 1153 (w), 1105 (m), 1012 (m), 985 (m), 964 (w), 881 (w), 861 (w), 823 (w), 801 (s), 766 (vs), 700 (m).

MS (EI, 70 eV): m/z (%) = 243 (M^+, 100), 212 (14), 154 (10).

HRMS ($C_{14}H_{13}NO_3$): calc.: 243.0895; found: 243.0888 (M^+).

Ethyl 4-amino-2-(6-methoxypyridin-2-yl)benzoate (66k)



According to **TP13** (3-methoxyphenyl)zinc pivalate (**63e**; 447 mg, 447 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). Ethyl 4-amino-3-bromobenzoate (**65b**; 205 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 6:1) afforded the pyridine **66k** (175 mg, 77 %) as a yellow solid.

M.p. (°C): 92-94.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.28-8.27 (m, 1H), 7.84-7.81 (m, 1H), 7.70-7.66 (m, 1H), 7.35-7.33 (m, 1H), 6.71-6.67 (m, 2H), 6.19 (s, br, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

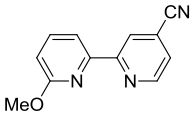
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.7, 162.6, 156.0, 150.4, 139.6, 131.7, 131.3, 120.7, 119.2, 116.2, 115.0, 108.4, 60.4, 53.4, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3461 (w), 3361 (m), 2926 (w), 2361 (w), 1684 (s), 1631 (m), 1600 (m), 1576 (m), 1504 (w), 1462 (m), 1420 (m), 1364 (m), 1343 (m), 1321 (m), 1287 (m), 1262 (m), 1228 (vs), 1158 (m), 1128 (m), 1114 (m), 1013 (m), 986 (m), 838 (w), 801 (m), 771 (m), 748 (m), 707 (w).

MS (EI, 70 eV): m/z (%) = 272 (M^+, 100), 243 (12), 227 (37).

HRMS ($C_{15}H_{16}N_2O_3$): calc.: 272.1161; found: 272.1155 (M^+).

6'-Methoxy-[2,2'-bipyridine]-4-carbonitrile (66l)



According to **TP13** (3-methoxyphenyl)zinc pivalate (**63e**; 447 mg, 447 mg/mmol, 1.00 mmol) was dissolved in dry THF (2 mL). 2-Chloro-4-cyanopyridine (**65d**; 116 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 6:1) afforded the bipyridine **66l** (118 mg, 67 %) as a colourless solid.

M.p. (°C): 142-144.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.80-8.79 (m, 1H), 8.63-8.62 (m, 1H), 8.03-8.01 (m, 1H), 7.74-7.70 (m, 1H), 7.49-7.47 (m, 1H), 6.85-6.82 (m, 1H), 4.05 (s, 3H).

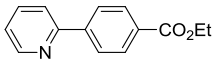
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.7, 157.4, 151.3, 149.9, 139.6, 124.4, 122.7, 121.1, 116.9, 114.1, 112.6, 53.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070 (vw), 2951 (w), 2362 (w), 2236 (w), 1739 (w), 1578 (s), 1547 (m), 1468 (s), 1438 (m), 1394 (s), 1322 (m), 1267 (s), 1112 (w), 1069 (w), 1017 (s), 988 (m), 918 (m), 852 (w), 842 (w), 799 (vs), 746 (w), 728 (m), 716 (w), 674 (w).

MS (EI, 70 eV): m/z (%) = 211 (M^+, 79), 181 (40), 155 (11).

HRMS ($C_{12}H_9N_3O$): calc.: 211.0746; found: 211.0718 (M^+).

Ethyl 4-(pyridin-2-yl)benzoate (66n)



According to **TP14** pyridin-2-ylzinc pivalate (**63a**; 700 mg, 700 mg/mmol, 1.00 mmol) was dissolved in technical grade AcOEt[77] (2 mL). Methyl 4-bromobenzoate (**65c**; 181 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 3:1) afforded the pyridine **66n** (187 mg, 98 %) as a pale yellow solid.

M.p. (°C): 61-62.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.74-8.72 (m, 1H), 8.17-8.14 (m, 2H), 8.09-8.06 (m, 2H), 7.82-7.75 (m, 2H), 7.32-7.25 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

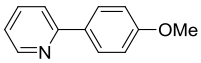
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 156.3, 149.9, 143.4, 136.8, 130.7, 130.0, 126.8, 122.8, 121.0, 61.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983 (w), 2903 (vw), 2364 (vw), 1706 (s), 1608 (w), 1586 (m), 1564 (w), 1467 (m), 1436 (w), 1404 (w), 1363 (m), 1278 (s), 1261 (s), 1182 (m), 1156 (m), 1103 (s), 1012 (m), 866 (m), 796 (w), 753 (vs), 695 (m).

MS (EI, 70 eV): m/z (%) = 227 (M^+, 70), 182 (100), 154 (30), 127 (10).

HRMS ($C_{14}H_{13}NO_2$): calc.: 227.0946; found: 227.0937 (M^+).

2-(4-Methoxyphenyl)pyridine (66m)



a) Coupling in argon atmosphere

According to **TP13** pyridin-2-ylzinc pivalate (**63a**; 586 mg, 586 mg/mmol, 1.00 mmol) was dissolved in dry THF (4 mL). 1-Chloro-4-methoxybenzene (**65e**; 120 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 1:1) afforded the pyridine **66m** (152 mg, 98 %) as a colourless solid.

b) Coupling in air

According to **TP14** pyridin-2-ylzinc pivalate (**63a**; 586 mg, 586 mg/mmol, 1.00 mmol) was dissolved in dry THF (4 mL). 1-Chloro-4-methoxybenzene (**65e**; 120 mg, 0.84 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) and X-Phos (19 mg, 0.04 mmol) were added and the mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 1:1) afforded the pyridine **66m** (149 mg, 96 %) as a colourless solid.

M.p. (°C): 66-67.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.65-8.63 (m, 1H), 7.97-7.92 (m, 2H), 7.74-7.63 (m, 2H), 7.18-7.13 (m, 1H), 7.03-6.96 (m, 2H), 3.85 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.4, 157.1, 149.5, 136.6, 132.0, 128.1, 121.4, 119.8, 114.1, 55.3.

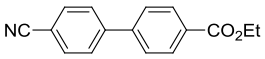
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3050 (w), 2996 (w), 2835 (w), 1600 (m), 1586 (m), 1579 (m), 1562 (m), 1513 (m), 1459 (m), 1431 (m), 1302 (m), 1272 (m), 1242 (s), 1176 (m), 1151 (m), 1112 (m), 1057 (m), 1036 (m), 1021 (m), 838 (s), 776 (vs), 735 (m), 717 (m).

MS (EI, 70 eV): m/z (%) = 185 (M^+, 100), 170 (19), 142 (24).

HRMS ($C_{12}H_{11}NO$): calc.: 185.0841; found: 185.0843 (M^+).

5. Preparation of Functionalized Organoindium Reagents *via* Magnesium Insertion in the Presence of $InCl_3$

Ethyl 4'-cyano-[1,1'-biphenyl]-4-carboxylate (45l)



a) Cross-coupling with ethyl 4-iodobenzoate

The organoindium reagent **67** was prepared according to **TP15** from 4-bromobenzonitrile (**43**; 364 mg, 2.00 mmol) in 4 h using 2.50 equiv of LiCl (212 mg, 5.0 mmol) and 2.50 equiv of magnesium turnings (122 mg, 5.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and ethyl 4-iodobenzoate (**42**; 386 mg, 1.40 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the biphenyl **45l** (284 mg, 81 %) as a colourless solid.

b) Cross-coupling with ethyl 4-bromobenzoate

The organoindium reagent **67** was prepared according to **TP15** from 4-bromobenzonitrile (**43**; 364 mg, 2.00 mmol) in 4 h using 2.50 equiv of LiCl (212 mg, 5.0 mmol) and 2.50 equiv of magnesium turnings (122 mg, 5.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and ethyl 4-bromobenzoate (**44l**; 321 mg, 1.40 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the biphenyl **45l** (250 mg, 71 %) as a colourless solid.

M.p. (°C): 120-121.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.16-8.12 (m, 2H), 7.76-7.68 (m, 4H), 7.66-7.62 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

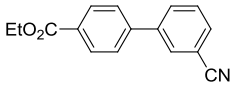
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.1, 144.5, 143.3, 132.7, 130.6, 130.3, 127.9, 127.2, 118.6, 111.8, 61.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961 (w), 2222 (m), 1704 (s), 1605 (m), 1465 (w), 1396 (m), 1364 (m), 1264 (m), 1180 (m), 1098 (s), 1020 (m), 1005 (m), 871 (m), 838 (s), 770 (vs), 729 (m), 698 (m).

MS (EI, 70 eV): m/z (%) = 252 (M^+, 34), 223 (36), 206 (100), 178 (23), 151 (23).

HRMS ($C_{16}H_{13}NO_2$): calc.: 251.0946; found: 251.0944 (M^+).

Ethyl 3'-cyano-[1,1'-biphenyl]-4-carboxylate (68a)



The organoindium reagent was prepared according to **TP15** from ethyl 4-bromobenzoate (**44l**; 458 mg, 2.00 mmol) in 4 h using 2.50 equiv of LiCl (212 mg, 5.0 mmol) and 2.50 equiv of magnesium turnings (122 mg, 5.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 3-iodobenzonitrile (**70a**; 321 mg, 1.40 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the biphenyl **68a** (236 mg, 67 %) as a colourless solid.

M.p. (°C): 89-91.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.10-8.06 (m, 2H), 7.63-7.54 (m, 4H), 7.01-6.96 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

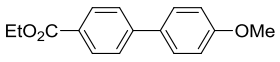
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.1, 143.0, 141.3, 131.5, 131.4, 130.8, 130.4, 130.3, 129.8, 127.0, 118.5, 113.2, 61.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2932 (w), 2361 (vw), 2230 (w), 1707 (s), 1604 (w), 1398 (w), 1370 (m), 1271 (vs), 1186 (m), 1098 (vs), 1020 (m), 906 (w), 861 (m), 838 (w), 796 (m), 764 (s), 704 (m).

MS (EI, 70 eV): m/z (%) = 251 (M^+, 33), 223 (29), 206 (100), 178 (19), 151 (16).

HRMS ($C_{16}H_{13}NO_2$): calc.: 251.0946; found: 251.0948 (M^+).

Ethyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (68b)



The organoindium reagent was prepared according to **TP15** from ethyl 4-bromobenzoate (**44l**; 229 mg, 1.00 mmol) in 4 h using 2.50 equiv of LiCl (106 mg, 2.5 mmol) and 2.50 equiv of magnesium turnings (61.0 mg, 2.50 mmol) in dry THF (2 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (5.00 mg, 0.02 mmol), S-Phos (16.0 mg, 0.04 mmol) and 4-bromoanisole (**31**; 131 mg, 0.70 mmol) in dry THF (1 mL). The mixture was stirred for

12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 6:1) afforded the biphenyl **68b** (103 mg, 57 %) as a colourless solid.

M.p. (°C): 100-103.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.15-8.11 (m, 2H), 7.88-7.87 (m, 1H), 7.85-7.81 (m, 1H), 7.68-7.65 (m, 1H), 7.64-7.54(m, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

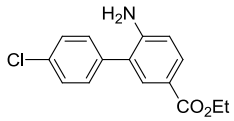
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.6, 159.8, 145.1, 132.5, 130.0, 128.6, 128.3, 126.4, 114.4, 60.9, 55.4, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1705 (s), 1601 (m), 1562 (w), 1529 (w), 1496 (w), 1472 (w), 1426 (w), 1400 (w), 1364 (w), 1311 (w), 1290 (s), 1271 (m), 1254 (m), 1198 (m), 1109 (s), 1036 (m), 1012 (m), 999 (m), 877 (w), 828 (vs), 770 (vs), 718 (m), 698 (m).

MS (EI, 70 eV): m/z (%) = 251 (M^+, 100), 228 (14), 211 (60), 139 (10).

HRMS ($C_{16}H_{16}O_3$): calc.: 256.1099; found: 256.1088 (M^+).

Ethyl 6-amino-4'-chloro-[1,1'-biphenyl]-3-carboxylate (68c)



The organoindium reagent was prepared according to **TP15** from 1-bromo-4-chlorobenzene (**69a**; 383 mg, 2.00 mmol) in 2 h using 2.50 equiv of LiCl (212 mg, 5.0 mmol) and 2.50 equiv of magnesium turnings (122 mg, 5.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and ethyl 4-amino-3-bromobenzoate (**70b**; 342 mg, 1.40 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / DCM = 3:1) afforded the biphenyl **68c** (317 mg, 82 %) as a yellow solid.

M.p. (°C): 126-128.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84 (dd, *J* = 8.2 Hz, 2.1 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.45-7.40 (m, 2H), 7.39-7.35 (m, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

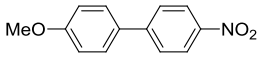
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.6, 147.6, 136.8, 133.6, 132.2, 130.7, 130.4, 129.2, 125.3, 120.5, 114.6, 60.4, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3482 (w), 3361 (m), 3214 (w), 2982 (w), 1683 (s), 1628 (s), 1590 (m), 1505 (m), 1434 (w), 1367 (m), 1320 (m), 1291 (s), 1241 (vs), 1111 (m), 1032 (m), 901 (w), 838 (m), 772 (m), 742 (m).

MS (EI, 70 eV): m/z (%) = 275 (M^+, 100), 247 (26), 230 (93), 167 (35).

HRMS ($C_{15}H_{14}ClNO_2$): calc.: 275.0713; found: 275.0711 (M^+).

4-Methoxy-4'-nitro-1,1'-biphenyl (68d)



The organoindium reagent as prepared according to **TP15** from 4-bromoanisole (**31**; 370 mg, 2.00 mmol) in 2 h using 2.50 equiv of LiCl (212 mg, 5.0 mmol) and 2.50 equiv of magnesium turnings (122 mg, 5.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 1-iodo-4-nitrobenzene (**70b**; 349 mg, 1.40 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 5:1) afforded the biphenyl **68d** (270 mg, 84 %) as a yellow solid.

M.p. (°C): 107-109.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 8.25-8.21 (m, 2H), 7.90-7.86 (m, 2H), 7.75-7.71 (m, 2H), 7.07-7.04 (m, 2H), 3.80 (s, 3H).

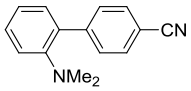
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 160.2, 146.3, 146.0, 129.9, 128.6, 127.0, 124.1, 114.7, 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930 (w), 2836 (w), 1600 (m), 1506 (vs), 1486 (s), 1468 (m), 1341 (s), 1301 (m), 1273 (m), 1250 (s), 1185 (s), 1107 (m), 1033 (m), 1016 (m), 838 (s), 816 (s), 756 (s), 722 (s), 696 (m).

MS (EI, 70 eV): m/z (%) = 229 (M^+, 100), 199 (22), 183 (24), 168 (19), 152 (14), 139 (26).

HRMS ($C_{13}H_{11}NO_3$): calc.: 229.0739; found: 229.0732 (M^+).

2'-(Dimethylamino)-[1,1'-biphenyl]-4-carbonitrile (68e)



The organoindium reagent was prepared according to **TP15** from 2-bromo-*N*,*N*-dimethylaniline (**69b**; 400 mg, 2.00 mmol) in 2 h using 2.50 equiv of LiCl (212 mg, 5.0 mmol) and 2.50 equiv of magnesium turnings (122 mg, 5.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 4-bromobenzonitrile (**43**; 254 mg, 1.40 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 16:1) afforded the biphenyl **68e** (214 mg, 69 %) as a yellow solid.

M.p. (°C): 96-98.

^{1}H-NMR (400 MHz, DMSO-d6): δ / ppm = 7.88-7.85 (m, 2H), 7.74-7.71 (m, 2H), 7.34-7.29 (m, 1H), 7.20-7.18 (m, 1H), 7.11-7.09 (m, 1H), 7.05-7.01 (m, 1H), 2.46 (s, 6H).

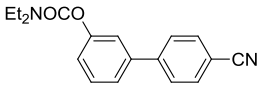
^{13}C-NMR (100 MHz, DMSO-d6): δ / ppm = 150.9, 164.4, 132.4, 131.5, 131.2, 129.3, 129.2, 121.8, 119.0, 118.1, 109.2, 43.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2943 (w), 2829 (w), 2775 (w), 2226 (m), 1596 (m), 1485 (m), 1430 (m), 1314 (m), 1189 (w), 1148 (m), 1104 (m), 1052 (m), 1004 (w), 945 (m), 849 (m), 834 (m), 760 (vs).

MS (EI, 70 eV): m/z (%) = 222 (M^+, 100), 219 (14), 205 (38).

HRMS ($C_{15}H_{14}N_2$): calc.: 222.1157; found: 222.1145 (M^+).

4'-Cyano-[1,1'-biphenyl]-3-yl diethylcarbamate (68f)

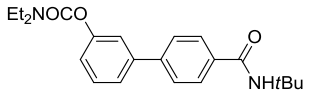


The organoindium reagent was prepared according to **TP15** from 3-bromophenyl diethylcarbamate (**69c**; 127 mg, 2.00 mmol) in 2 h using 1.50 equiv of LiCl (127 mg, 3.0 mmol) and 2.50 equiv of magnesium turnings (73 mg, 3.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 4-bromobenzonitrile (**43**; 291 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the

aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 5:2) afforded the biphenyl **68f** (349 mg, 74 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.72-7.65 (m, 4H), 7.48-7.37 (m, 2H), 7.36-7.34 (m, 1H), 7.19-7.16 (m, 1H), 3.49-3.36 (m, 4H), 1.29-1.19 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.0, 152.1, 144.9, 140.4, 132.5, 129.9, 127.8, 123.9, 122.0, 120.8, 118.8, 111.2, 42.3, 42.0, 14.3, 13.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2975 (w), 2935 (w), 2227 (m), 1710 (vs), 1605 (m), 1472 (m), 1416 (s), 1260 (s), 1187 (vs), 1151 (vs), 1097 (m), 1046 (m), 960 (s), 838 (s), 774 (s), 692 (m).
MS (EI, 70 eV): m/z (%) = 294 (M^+, 2), 100 (100), 72 (27), 43 (15).
HRMS ($C_{18}H_{18}N_2O_2$): calc.: 294.1368; found: 294.1364 (M^+).

4'-(*Tert*-butylcarbamoyl)-[1,1'-biphenyl]-3-yl diethylcarbamate (68g)



The organoindium reagent was prepared according to **TP15** from 3-bromophenyl diethylcarbamate (**69c**; 544 mg, 2.00 mmol) in 2 h using 1.50 equiv of LiCl (127 mg, 3.0 mmol) and 2.50 equiv of magnesium turnings (73 mg, 3.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 4-bromo-*N*-(*tert*-butyl)benzamide (**44b**; 410 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 1:1) afforded the biphenyl **68g** (511 mg, 87 %) as a yellow solid.

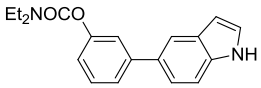
M.p. (°C): 141-142.
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.78-7.74 (m, 2H), 7.63-7.59 (m, 2H), 7.45-7.38 (m, 2H), 7.36-7.34 (m, 1H), 7.16-7.10 (m, 1H), 5.98 (br, 1H), 3.46-3.39 (m, 4H), 1.48 (s, 9H), 1.29-1.19 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 154.1, 152.0, 143.1, 141.4, 134.8, 129.6, 127.2, 123.9, 121.2, 120.6, 51.6, 42.3, 41.9, 28.9, 14.3, 13.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3374 (w), 2974 (w), 1707 (vs), 1657 (s), 1532 (m), 1416 (s), 1305 (m), 1274 (s), 1223 (m), 1184 (vs), 1097 (m), 1050 (w), 969 (m), 849 (m), 757 (m), 695 (m).

MS (EI, 70 eV): m/z (%) = 379 (10), 368 (M^+, 34), 296 (20), 197 (26), 168 (12), 100 (100), 72 (80), 44 (10).

HRMS ($C_{22}H_{28}N_2O_3$): calc.: 368.2100; found: 368.2099 (M^+).

3-(1*H*-Indol-5-yl)phenyl diethylcarbamate (68h)



The organoindium reagent was prepared according to **TP15** from 3-bromophenyl diethylcarbamate (**69c**; 544 mg, 2.00 mmol) in 2 h using 1.50 equiv of LiCl (127 mg, 3.0 mmol) and 2.50 equiv of magnesium turnings (73 mg, 3.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 5-bromo-1*H*-indole (**70c**; 314 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 5:2) afforded the indol **68h** (316 mg, 64 %) as a orange solid.

M.p. (°C): 111.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.40 (br, 1H), 7.84-7.83 (m, 1H), 7.49-7.45 (m, 1H), 7.43-7.40 (m, 2H), 7.38-7.36 (m, 2H), 7.16-7.14 (m, 1H), 7.10-7.06 (m, 1H), 6.56-6.54 (m, 1H), 3.56-3.37 (m, 4H), 1.36-1.19 (m, 6H).

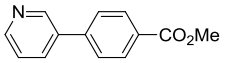
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.4, 151.8, 144.0, 135.5, 132.4, 129.3, 128.3, 124.9, 124.1, 121.7, 120.6, 119.5, 119.2, 111.2, 42.3, 41.9, 14.3, 13.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3299 (m), 2971 (w), 2931 (w), 1701 (s), 1603 (m),1419 (m), 1310 (m), 1252 (s), 1195 (s), 1163 (vs), 1098 (m), 970 (m), 880 (m), 761 (vs), 728 (s).

MS (EI, 70 eV): m/z (%) = 308 (M^+,100), 180 (18), 100 (66), 72 (16).

HRMS ($C_{19}H_{20}N_2O_2$): calc.: 308.1525; found: 308.1518 (M^+).

Methyl 4-(pyridin-3-yl)benzoate (71a)



The organoindium reagent was prepared according to **TP15** from 3-bromopyridine (**54**; 316 mg, 2.00 mmol) in 2 h using 1.50 equiv of LiCl (127 mg, 3.0 mmol) and 2.50 equiv of magnesium turnings (73 mg, 3.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and methyl 4-bromobenzoate (**44l**; 344 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:4) afforded the cross-coupling product **71a** (279 mg, 82 %) as a yellow solid.

M.p. (°C): 113-115.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.86 (m, 1H), 8.63-8.61 (m, 1H), 8.14-8.10 (m, 2H), 7.91-7.87 (m, 1H), 7.65-7.87 (m, 2H), 7.65-7.61 (m, 2H), 7.40-7.35 (m, 1H), 3.93 (s, 3).

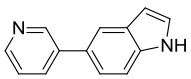
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.7, 149.2, 148.3, 142.2, 135.6, 134.5, 130.4, 129.8, 127.1, 123.7, 52.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950 (vw), 1720 (s), 1608 (w), 1562 (w), 1475 (w), 1429 (w), 1395 (w), 1274 (s), 1197 (m), 1106 (s), 1025 (w), 1001 (m), 964 (w), 870 (w), 810 (m), 765 (vs), 704 (vs).

MS (EI, 70 eV): m/z (%) = 213 (M^+,100), 182 (48), 154 (32), 127 (24).

HRMS ($C_{13}H_{11}NO_2$): calc.: 213.0790; found: 213.0795 (M^+).

5-(Pyridin-3-yl)-1*H*-indole (71b)



The organoindium reagent was prepared according to **TP15** from 3-bromopyridine (**54**; 316 mg, 2.00 mmol) in 2 h using 1.50 equiv of LiCl (127 mg, 3.0 mmol) and 2.50 equiv of magnesium turnings (73 mg, 3.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 5-bromo-1*H*-indole (**70c**; 314 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / AcOEt = 1:1) afforded the indole **71b** (278 mg, 90 %) as a yellow solid.

M.p. (°C): 158-169.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.92 (br, 1H), 8.65-8.55 (m, 2H), 7.96-7.92 (m, 1H), 7.86-7.85 (m, 1H), 7.52-7.47 (m, 1H), 7.43-7.39 (m, 1H), 7.38-7.34 (m, 1H), 7.28-7.26 (m, 1H), 6.64-6.62 (m, 1H).

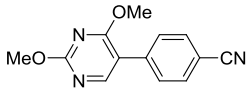
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.3, 147.2, 135.7, 134.6, 129.6, 128.5, 125.3, 123.5, 121.5, 119.4, 111.7, 103.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3120 (w), 2853 (w), 1619 (w), 1573 (w), 1457 (m), 1414 (m), 1345 (w), 1313 (m), 1246 (m), 1178 (w), 1105 (m), 1024 (m), 1013 (m), 877 (s), 765 (vs), 728 (vs), 702 (vs).

MS (EI, 70 eV): m/z (%) = 194 (M^+,100), 165 (10), 139 (10).

HRMS ($C_{13}H_{10}N_2$): calc.: 194.0844; found: 194.0837 (M^+).

4-(2,4-Dimethoxypyrimidin-5-yl)benzonitrile (71c)



The organoindium reagent was prepared according to **TP15** from 5-bromo-2,4-dimethoxypyrimidine (**72a**; 438 mg, 2.00 mmol) in 2 h using 2.50 equiv of LiCl (212 mg, 5.0 mmol) and 2.50 equiv of magnesium turnings (122 mg, 5.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 4-iodobenzonitrile (**70d**; 321 mg, 1.40 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 2:1) afforded the benzonitrile **71c** (230 mg, 68 %) as a brown solid.

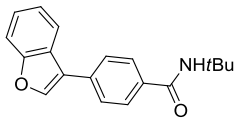
^{1}H-NMR (300 MHz, DMSO-d6): δ / ppm = 8.46 (s, 1H), 7.87 (d, *J* = 8.2, 2H), 7.74 (d, *J* = 8.2, 2H), 3.95 (s, 3H), 3.94 (s, 3H).

^{13}C-NMR (75 MHz, DMSO-d6): δ / ppm = 167.4, 164.6, 158.3, 137.9, 132.2, 129.4, 118.7, 113.8, 110.0, 54.7, 54.1.

MS (EI, 70 eV): m/z (%) = 241 (100), 226 (13), 211 (30), 169 (13), 141 (13).

HRMS ($C_{13}H_{11}N_3O_2$): calc.: 241.0851; found: 241.0845 (M^+).

4-(Benzofuran-3-yl)-*N*-(*tert*-butyl)benzamide (71d)



The organoindium reagent was prepared according to **TP15** from 3-bromobenzofuran (**72b**; 394 mg, 2.00 mmol) in 2 h using 1.50 equiv of LiCl (127 mg, 3.0 mmol) and 1.50 equiv of magnesium turnings (73 mg, 3.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 4-bromo-*N*-(*tert*-butyl)benzamide (**44b**; 410 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the benzamide **71d** (356 mg, 76 %) as a yellow solid.

M.p. (°C): 133-135.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.85-7.80 (m, 4H), 7.70-7.66 (m, 2H), 7.57-7.54 (m, 1H), 7.39-7.29 (m, 2H), 1.50 (s, 9H).

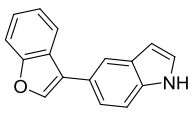
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 155.8, 141.8, 134.9, 134.7, 127.4, 127.3, 126.0, 124.8, 123.2, 121.5, 120.2, 111.9, 51.7, 28.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3392(vw), 3350(vw), 2977(w), 1635(s), 1610(m), 1534(s), 1451(s), 1318(m) ,1297(m), 1216(s), 1094(m), 962(m),854(m), 816(m), 772(m), 743(vs).

MS (EI, 70 eV): m/z (%) = 293 (M^+, 25), 237 (52), 221 (100), 165 (26).

HRMS ($C_{19}H_{19}NO_2$): calc.: 293.1416; found: 293.1416 (M^+).

5-(Benzofuran-3-yl)-1-*H*-indole (71e)

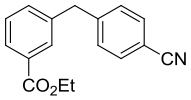


The organoindium reagent was prepared according to **TP15** from 3-bromobenzofuran (**72b**; 394 mg, 2.00 mmol) in 2 h using 1.50 equiv of LiCl (127 mg, 3.0 mmol) and 1.50 equiv of magnesium turnings (73 mg, 3.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 5-bromo-1*H*-indole (**70c**; 314 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted

with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 6:1) afforded the indole **71e** (234 mg, 63 %) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.20 (br, 1H), 7.94-7.90 (m, 2H), 7.79 (s, 1H), 7.58-7.55 (m, 1H), 7.49-7.48 (m, 2H), 7.39-7.29 (m, 2H), 7.27-7.25 (m, 1H), 6.64-6.62 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 155.8, 140.7, 135.3, 128.4, 127.2, 124.9, 124.3, 123.6, 123.2, 122.7, 122.2, 120.6, 119.7, 111.6, 111.5, 102.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3412 (m), 3053 (w), 1791 (w), 1584 (w), 1449 (s), 1414 (m), 1341 (m), 1316 (m), 1223 (m), 1090 (s), 883 (m), 856 (m), 743 (s), 723 (vs).
MS (EI, 70 eV): m/z (%) = 233 (M^+, 100), 204 (40), 176 (10).
HRMS ($C_{16}H_{11}NO$): calc.: 233.0841; found: 233.0837 (M^+).

Ethyl 3-(4-cyanobenzyl)benzoate (74)



The organoindium reagent was prepared according to **TP15** from ethyl 3-(chloromethyl)benzoate (**49a**; 397 mg, 2.00 mmol) in 2 h using 1.50 equiv of LiCl (127 mg, 3.0 mmol) and 1.50 equiv of magnesium turnings (73 mg, 3.00 mmol) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 4-bromobenzonitrile (**43**; 291 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the diphenylmethane **74** (316 mg, 74 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.93-7.90 (m, 1H), 7.87-7.85 (m, 1H), 7.59-7.55 (m, 2H), 7.40-7.30 (m, 2H), 7.28-7.25 (m, 2H), 4.36 (q, *J* = 7.1, 2H), 1.87 (s, 2H), 1.34 (t, *J* = 7.1, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 146.0, 139.6, 133.4, 132.4, 131.0, 130.0, 129.6, 128.8, 127.9, 118.9, 110.3, 61.1, 41.7, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981(w), 2227(m), 1712(vs), 1605(m), 1587(w), 1503(w), 1443(m), 1366(m), 1278(vs), 1185(s), 1104(s), 1080(m), 1020(m), 934(w), 853(m), 812(m), 758(m), 736(s), 697(m), 670(w).

MS (EI, 70 eV): m/z (%) = 265 (M^+, 45), 237 (38), 220 (100), 190 (48), 177 (27), 165 (27), 151 (15), 130 (13).

HRMS ($C_{19}H_{19}NO_2$): calc.: 265.1103; found: 265.1095 (M^+).