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 InCl₃.

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Erklärung


Eidesstattliche Versicherung

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…………………………………………

Sebastian Daniel Gerhard Bernhardt

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“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]


Direct Addition of Functionalized Organozinc Reagents to Carbon Dioxide, Ketones, and Aldehydes


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]


(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$_3$

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

B) Review Articles

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

Functionalization of Heterocyclic Compounds Using Polyfunctional Magnesium and Zinc Reagents

C) Patents

Carbonylierung von organischen Zinkverbindungen - Eine neue effiziente Darstellungsvariante von Ibuprofen

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
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<table>
<thead>
<tr>
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<th>Description</th>
</tr>
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<tbody>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>ATR</td>
<td>attenuated total reflection (IR)</td>
</tr>
<tr>
<td>br</td>
<td>broad (NMR)</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet (NMR)</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>dist.</td>
<td>distilled</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>E</td>
<td>eletrophile</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FG</td>
<td>functional group</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>Hex</td>
<td>hexyl</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>iBu</td>
<td>iso-butyl</td>
</tr>
<tr>
<td>iPr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR)</td>
</tr>
<tr>
<td>M</td>
<td>mol/L</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Met</td>
<td>metal</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>MIDA</td>
<td>N-methyl-iminodiacetic acid</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
</tbody>
</table>
M.P. melting point
MS mass spectroscopy
NMR nuclear magnetic resonance
OPiv pivalate
PEPPSI-iPr [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-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
rBu 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
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 organo-organocarbene compounds

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to interact with d-orbitals of transition metals and thus smoothly undergo transmetalation reactions.\textsuperscript{4a, 8} The most prominent applications of this behaviour are the Pd-catalyzed \textit{Negishi}-cross-coupling reactions, which proceed under milder reaction conditions and much faster than the corresponding \textit{Suzuki}-cross-couplings of boronic acids.\textsuperscript{4b, 9} A powerful application of a sequence of \textit{Negishi}-couplings is demonstrated by \textit{Gademann} in the synthesis of the highly selective tumor-growth inhibitor Anguinomycin C.\textsuperscript{10} The coupling of the vinylic zinc reagent 1 with the dibromoolefin 2 afforded selectively the (6\textit{E}, 8\textit{Z})-diene 3 in 81 \% yield. The subsequent cross-coupling with \textit{Me}_2\textit{Zn} (4) installs a methyl group at position 8 and simultaneously inverts the stereochemistry at position 9 affording exclusively the \textit{cis}-product 5 in 68 \% yield (Scheme 1).

\textbf{Scheme 1}: \textit{Negishi} cross-coupling sequence in the total synthesis of Anguinomycin C by \textit{Gademann}.

An impressive industrial application of a \textit{Negishi} cross-coupling is implemented in the synthesis of the HIV-reverse transcriptase inhibitor MIV-150 (9) by the \textit{Chiron Corporation}.\textsuperscript{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).

\textbf{Scheme 2}: \textit{Negishi} cross-coupling in the synthesis of HIV reverse transcriptase inhibitor MIV-150 (9) by the \textit{Chiron Corporation}.

INTRODUCTION

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, the direct insertion of magnesium metal into carbon-halogen bonds has been the most straightforward approach to their preparation. While the exact mechanism of this reaction is still not entirely elucidated, radical pathways are generally accepted. However, despite the efficiency of the magnesium insertion in terms of atom economy, 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, I₂) have to be added to remove the hindering oxide layers. Moreover, this part of the reaction is usually exothermic and requires suitable cooling. 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).

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

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).

![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, the halogen-magnesium reaction has been established has very useful methodology for the preparation of highly functionalized Grignard-reagents. The driving force of this reaction is the formation of an organomagnesium reagent that is more stable than the exchange reagent. Knochel and coworkers could impressively demonstrate the potential of iPrMgBr and PhMgCl in the I-Mg-

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exchange reaction.\textsuperscript{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](image)

Scheme 5: Preparation of functionalized Grignard-reagents by iodine-magnesium exchange using iPrMgBr 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).\textsuperscript{19,21}

![Scheme 6](image)

Scheme 6: LiCl-enhanced bromine-magnesium exchange reaction with iPrMgCl.

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.\textsuperscript{22} The recently developed mixed lithium and magnesium amide bases TMPMgCl·LiCl (12) and TMP\textsubscript{2}Mg·2 LiCl (13) give

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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.](image)


INTRODUCTION

3. Preparation of Organozinc Reagents

3.1. Introduction

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

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. Rieke could show that the use of highly active zinc powder (Zn*), produced by a reduction of ZnCl₂ with lithium naphthalenide, gives access to functionalized organozincs starting even from the less reactive arylbromides (Scheme 8).

![Scheme 8](image_url)

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

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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 ZnCl₂

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 ZnCl₂.17,32 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 ZnCl₂ to 0.5 equiv the method gives a convenient access to more reactive diorganozinc reagents (Scheme 10).


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. 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).

Scheme 11: Preparation of diorganozincs by an Li(acac)-catalyzed iodine-zinc exchange reaction.
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.\textsuperscript{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).\textsuperscript{24,36}

\begin{center}
\begin{tabular}{c}
\textbf{Scheme 12}: Application of hindered zinc amide bases 14 and 15 for the directed metalation and functionalization of aromatic and heteroaromatic scaffolds.
\end{tabular}
\end{center}


4. Preparation of Organoindium Reagents

4.1. Introduction

Since the initial studies on the reactivity of organoindium reagents by Gilman in 1940,\textsuperscript{37} the manifold potential of this class of organometallics in organic synthesis has started to be explored only recently.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \textit{in situ} formed allylic organoindium reagent reacts with the aldehyde \textbf{16} to give the polyol \textbf{17} in good diastereoselectivity.\textsuperscript{41}

\begin{center}
\includegraphics[width=\textwidth]{scheme13.png}
\end{center}

\textbf{Scheme 13:} Indium mediated Barbier-type addition.

Knochel and Minehan could show that in the presence of LiCl commercially available indium powder reacts even with less activated aromatic iodides.\textsuperscript{42} This methodology could be further extended to the preparation of highly functionalized benzylindium reagents (Scheme 14).\textsuperscript{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\textsubscript{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.\textsuperscript{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 alkaiode Hyrtinadine A by Sarandeses (Scheme 15).\textsuperscript{44}

**Scheme 15**: Preparation of trisorganoinium reagents by halogen-lithium exchange and subsequent transmetalation with InCl\textsubscript{3} as well as sequential cross-coupling.


INTRODUCTION

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).
INTRODUCTION

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 activity should be investigated. Furthermore, an efficient procedure for Negishi cross-couplings of these reagents under mild conditions should be developed (Scheme 18).

The preparation of functionalized trisorganoindium reagents from organic halides via magnesium insertion in the presence of InCl₃ (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).
Scheme 19: Preparation of functionalized trisorganindium reagents from organic halides via magnesium insertion in the presence of InCl₃ (0.33 equiv).
B. RESULTS AND DISCUSSION
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. 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).

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 CeCl₃, LaCl₃·2 LiCl or ZnCl₂ 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. Ishihara and coworkers could efficiently demonstrate this principle in a ZnCl₂-catalyzed alkylation of ketones with Grignard-reagents. The in situ formed trialkylzincate complexes

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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 ZnCl₂.]

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. In Scheme 22 this is exemplified for the addition of diphenylzinc (22) to the aliphatic aldehyde 23 in the presence of the H₈-binol 24 as the chiral catalyst.

![Scheme 22: Enantioselective addition of diphenylzinc (22) to the aliphatic aldehyde 23.]

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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.](image)

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.$^{32}$ 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,$^{31}$ 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

$^{57}$ The addition of MgCl$_2$ (1.0 equiv, prepared from Mg and ClCH$_2$CH$_2$Cl 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.
RESULTS AND DISCUSSION

impressively the dramatic addition rate acceleration triggered by the presence of MgCl₂ (1.0 equiv). Diorganozincs are more reactive than organozinc halides²⁸,⁵¹e 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; nBuLi, −78 °C, 2 h; then ZnCl₂ (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 ZnCl₂ 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](image)

**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 LiCl³¹c 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 MgCl₂ 28b and prepared by the reaction of (3-ethoxycarbonyl)benzyl chloride with magnesium turnings in the presence of ZnCl₂ and LiCl,³²a a full conversion was

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²⁸ 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

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-MgCl2 (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 MgX2 (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 MgX2 (30c) smoothly added to the bromopiperonal 26h in 95 % yield on a 10 mmol scale (entry 5). Interestingly, bis (4-chlorophenyl)zinc-2 MgX2 (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(C6H4)ZnBr·MgCl2·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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent[^{[a], [b]}]</th>
<th>Carbonyl derivative</th>
<th>Time (h)[^{[c]}]</th>
<th>Product</th>
<th>Yield (%)[^{[d]}]</th>
</tr>
</thead>
</table>
| 1     | TIPSO-\text{ZnBr}_2\cdot MgCl_2
28c    | 26d                 | 3                 | TIPSO-\text{OH} \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} 27d | 85      |
| 2     | TIPSO-\text{Zn}_2\cdot MgX_2
30b    | 26e                 | 6                 | TIPSO-\text{OH} \begin{array}{c} \text{F} \\ \text{Cl} \end{array} 27e | 89\[^{e}\] |
| 3     | \text{MeO}-\text{Zn}_2\cdot MgX_2
30a    | 26f                 | 3                 | \text{MeO}-\text{OH} \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} 27f | 84      |
| 4     | 30a                  | 26g                 | 12\[^{f}\]       | \text{MeO}-\text{OH} \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} 27g | 87      |
| 5     | 30c                  | 26h                 | 10               | \text{Cl}-\text{Br}-\text{OH} \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} 27h | 95\[^{f}\] |
| 6     | 30c                  | 26i                 | 12               | \text{Cl}-\text{Br}-\text{OH} \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} 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 bisalkylyzinc reagent 30d also reacted smoothly with 3-chlorobenzaldehyde (26l) leading to the addition product 27l in 87 % yield (entry 3).
RESULTS AND DISCUSSION

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent[a], [b]</th>
<th>Carbonyl derivative</th>
<th>Time (h)[c]</th>
<th>Product</th>
<th>Yield (%)[d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{F}^\text{ZnCl-MgCl}_2 ) ( \text{28d} )</td>
<td>( \text{CH}_2\text{CHO} )</td>
<td>6</td>
<td>( \text{27j} )</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>( \text{EtO}_2\text{C}	ext{ZnBr-MgCl}_2 ) ( \text{28e} )</td>
<td>( \text{O} \text{CF}_3 )</td>
<td>24</td>
<td>( \text{27k} )</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Me} \text{Zn-2 MgX}_2 ) ( \text{30d} )</td>
<td>( \text{CHO} )</td>
<td>14</td>
<td>( \text{27l} )</td>
<td>87</td>
</tr>
</tbody>
</table>

[a] Complexed LiCl has been omitted for the sake of clarity. [b] \( \text{X} = \text{Br, Cl} \). [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 \( \text{MgCl}_2 \) allows the addition of aryl-, benzyl- and alkylzinc reagents to \( \text{CO}_2 \) (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 \( \text{CO}_2 \). Thus, bis(4-methoxyphenyl)zinc·2 \( \text{MgX}_2 \) \( \text{(30a)} \) added in THF to \( \text{CO}_2 \) (1 bar, 25 °C, 3 h) providing 4-methoxybenzoic acid \( \text{(33a)} \) in 94 % yield on a 10 mmol scale (entry 1 of Table 3).\(^{60}\)

Similarly, bis(4-trimethylsilylphenyl)zinc·2 \( \text{MgX}_2 \) \( \text{(30e)} \) was carboxylated within 6 h at 25 °C leading to the benzoic acid \( \text{33b} \) in 73 % yield (entry 2). Bisbenzyl zinc reagents of type \( \text{30f} \) reacted especially well and smoothly provided the corresponding phenylacetic acids \( \text{33c-g} \) in 80-98 % yield (entries 3-7). Furthermore, bis(nhexyl)zinc·2 \( \text{MgX}_2 \) \( \text{(30k)} \) could be converted at 50 °C to heptanoic acid \( \text{(33h)} \) in 86 % yield.

\(^{60}\) Using \( \text{4-MeO(C}_6\text{H}_4)\text{ZnBr-MgCl}_2\cdot\text{LiCl} \) instead of the bisarylzinc reagent \( \text{30c} \) leads to full conversion within 6 h reaction time under similar reaction conditions.
RESULTS AND DISCUSSION

Table 3: Addition of diaryl-, dibenzyl and dialkylzinc reagents to CO₂.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Zn2MgX2_30a" /></td>
<td>3</td>
<td>25</td>
<td><img src="image" alt="CO2H_33a" /></td>
<td>94[d]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Zn2MgX2_30e" /></td>
<td>6</td>
<td>25</td>
<td><img src="image" alt="CO2H_33b" /></td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Zn2MgCl2_30f" /></td>
<td>2</td>
<td>25</td>
<td><img src="image" alt="CO2H_33c" /></td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Zn2MgCl2_30g" /></td>
<td>2</td>
<td>25</td>
<td><img src="image" alt="CO2H_33d" /></td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Cl_30h" /></td>
<td>12</td>
<td>50</td>
<td><img src="image" alt="CO2H_33e" /></td>
<td>80[d]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="F_30i" /></td>
<td>12</td>
<td>25</td>
<td><img src="image" alt="CO2H_33f" /></td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="CF3_30j" /></td>
<td>12</td>
<td>50</td>
<td><img src="image" alt="CO2H_33g" /></td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Zn2MgX2_30d" /></td>
<td>12</td>
<td>50</td>
<td><img src="image" alt="CO2H_33h" /></td>
<td>86</td>
</tr>
</tbody>
</table>

[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.\(^6^1\) Thus, a short synthesis of the blockbuster drug ibuprofen (35)\(^6^2\) 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 NaBH₄ (1.5 equiv, MeOH, reflux, 2 h) followed by...

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RESULTS AND DISCUSSION

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), ZnCl₂ (1.1 equiv), THF, 25 °C, 2 h) in 70% yield (10 mmol scale). This secondary benzylzinc halide of type 28f is sufficiently reactive to undergo an addition to CO₂ (1 bar for 12 h at 25 °C and then 12 h at 50 °C) to produce ibuprofen (35) in 89% yield.

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

1.4. Mechanistic Considerations

The acceleration effect of MgCl₂ may be rationalized by assuming that the usual 6-membered transition state (36) is modified by the presence of MgCl₂. Thus, R₃ZnCl which complexes the carbonyl group, is replaced by MgCl₂ (see the transition state 37; Scheme 27). Since MgCl₂ is a stronger Lewis acid than R₃ZnCl, 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.

63 The yield of the organozinc reagent was determined via titration with I₂: 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.
RESULTS AND DISCUSSION

Scheme 27: Tentative MgCl₂-modified six-membered transition state for the addition of R³ZnCl to a carbonyl reagent (R¹R²CO).

In a recent study based on this work Hevia and coworkers could show that in fact both MgCl₂ 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). In the presence of LiCl the formation of highly reactive mixed trimetallic Li-/Mg-/Zn-reagents is most likely.

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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$_2$Zn 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-stabilized iodomethylzinc reagent by Charette.](image)

Furthermore, Herrmann reported that methylzinc acetate can be efficiently used for the synthesis of methyltrioxorhenium (MTO) even on larger scales (Scheme 29).$^{73}$

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71 See chapter 1 of Results and Discussion.
2.1.2. Preparation of Solid Salt-Stabilized Arylzinc Reagents by Magnesium-Insertion in the Presence of Zn(OPiv)₂·2 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. Thus, the insertion of magnesium turnings to aromatic halides in the presence of the THF-soluble salt Zn(OPiv)₂·2 LiCl (38) 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)₂·2 LiCl (38) led to a fast formation of the zinc reagent at 25 °C within 2 h. The presence of Zn(OPiv)₂·2 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/ZnCl₂·2 LiCl, with the combination Mg/Zn(OPiv)₂·2 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. 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.

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

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75 Zn(OPiv)₂·2 LiCl (38) is prepared by reacting pivalic acid with MeLi in THF and subsequent addition of ZnCl₂ (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.
RESULTS AND DISCUSSION

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$_2$Et, 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 iPrMgCl-LiCl followed by a transmetalation with Zn(OPiv)$_2$.2 LiCl (38; 72-89 %).\textsuperscript{21}

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

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.
RESULTS AND DISCUSSION

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Treatment</th>
<th>Active species 41h (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>storage under inert gas (7 d)</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>exposure to air (5 min)</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>exposure to air (15 min)</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>exposure to air (30 min)</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>exposure to air (45 min)</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>exposure to air (60 min)</td>
<td>0</td>
</tr>
</tbody>
</table>

[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-Pr<sup>76</sup> 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<sup>77</sup> 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.<sup>78</sup> However, using arylzinc pivalates such as 41i combined with PEPPSI-Pr<sup>76</sup> 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).


<sup>77</sup> Ethyl acetate was purchased from Sigma-Aldrich with a purity of 99 % and was used without drying or distillation prior to use.

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Scheme 31: PEPPSI-iPr 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 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-iPr catalyzed cross-couplings of aromatic organozinc pivalates of type 41 in THF (or AcOEt) in 2 h at 25 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylzinc Reagent[a]</th>
<th>Electrophile[b]</th>
<th>Product</th>
<th>Yield (%)[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{MeO-} \text{ZnOPiv} ) 41b</td>
<td>( \text{Br-} \text{CN} ) 44c</td>
<td>( \text{MeO-} \text{ZnOPiv} ) 45c</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Cl-} \text{CN} ) 44d</td>
<td>( \text{MeO-} \text{ZnOPiv} ) 45d</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>( \text{TIPS-} \text{ZnOPiv} ) 41d</td>
<td>( \text{Br-} \text{CN} ) 44e</td>
<td>( \text{TIPS-} \text{ZnOPiv} ) 45e</td>
<td>89[d]</td>
</tr>
<tr>
<td>4</td>
<td>( \text{TMS-} \text{ZnOPiv} ) 41e</td>
<td>( \text{Br-} \text{CN} ) 44f</td>
<td>( \text{TMS-} \text{ZnOPiv} ) 45f</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>( \text{EtNOCO-} \text{ZnOPiv} ) 41f</td>
<td>( \text{Br-} \text{N} = \text{N} ) 44g</td>
<td>( \text{EtNOCO-} \text{ZnOPiv} ) 45g</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>( \text{F-} \text{ZnOPiv} ) 41g</td>
<td>( \text{Cl-} \text{CN} ) 44h</td>
<td>( \text{F-} \text{ZnOPiv} ) 45h</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>( \text{F}_{3}\text{C-} \text{ZnOPiv} ) 41h</td>
<td>( \text{Br-} \text{N} = \text{H}_{2}\text{N} ) 44i</td>
<td>( \text{F}_{3}\text{C-} \text{ZnOPiv} ) 45i</td>
<td>79[e]</td>
</tr>
<tr>
<td>8</td>
<td>( \text{ClO}_{2}\text{C-} \text{ZnOPiv} ) 41i</td>
<td>( \text{Br-} \text{N} = \text{CN} ) 44j</td>
<td>( \text{ClO}_{2}\text{C-} \text{ZnOPiv} ) 45j</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>( \text{PhO}_{2}\text{C-} \text{ZnOPiv} ) 41j</td>
<td>( \text{Br-} \text{N} = \text{SO}_{2}\text{Ph} ) 44k</td>
<td>( \text{PhO}_{2}\text{C-} \text{ZnOPiv} ) 45k</td>
<td>99[f]</td>
</tr>
<tr>
<td>10</td>
<td>( \text{NC-} \text{ZnOPiv} ) 41k</td>
<td>( \text{Br-} \text{CO}_{2}\text{Et} ) 44l</td>
<td>( \text{NC-} \text{ZnOPiv} ) 45l</td>
<td>94[f]</td>
</tr>
<tr>
<td>11</td>
<td>( \text{Br-} \text{Ni} ) 41l</td>
<td>( \text{NC-} \text{ZnOPiv} ) 44m</td>
<td>( \text{Br-} \text{Ni} ) 45m</td>
<td>88</td>
</tr>
</tbody>
</table>

[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 performed 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 Benzylic Zinc Reagents by Magnesium-Insertion in the Presence of Zn(OPiv)$_2$·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)$_2$·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 pyrazoyllic zinc pivalate 47e was prepared from the corresponding heteroaryl chloride 48 in a moderate yield (50%).

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)$_2$·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).
RESULTS AND DISCUSSION

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>t in air</th>
<th>Active zinc species 50e (%)$^{[a]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 min</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>15 min</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>30 min</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>45 min</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>60 min</td>
<td>24</td>
</tr>
</tbody>
</table>

$^{[a]}$ 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-iPr 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-iPr catalyzed cross-couplings of heteroaromatic and benzyl organozinc pivalates of type 47 and 50 in THF in 2 h at 25 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Reagent[^a]</th>
<th>Electrophile[^b]</th>
<th>Product</th>
<th>Yield (%)[^c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="47a" /></td>
<td><img src="image" alt="44a" /></td>
<td><img src="image" alt="51a" /></td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="47b" /></td>
<td><img src="image" alt="44n" /></td>
<td><img src="image" alt="51b" /></td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="47b" /></td>
<td><img src="image" alt="44o" /></td>
<td><img src="image" alt="51c" /></td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="47c" /></td>
<td><img src="image" alt="44b" /></td>
<td><img src="image" alt="51d" /></td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="47d" /></td>
<td><img src="image" alt="44e" /></td>
<td><img src="image" alt="51e" /></td>
<td>99[^d]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="47e" /></td>
<td><img src="image" alt="44f" /></td>
<td><img src="image" alt="51f" /></td>
<td>98[^d]</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="50a" /></td>
<td><img src="image" alt="44o" /></td>
<td><img src="image" alt="52a" /></td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="50b" /></td>
<td><img src="image" alt="43" /></td>
<td><img src="image" alt="52b" /></td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="50c" /></td>
<td><img src="image" alt="44p" /></td>
<td><img src="image" alt="52c" /></td>
<td>86</td>
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<tr>
<td>10</td>
<td><img src="image" alt="50d" /></td>
<td><img src="image" alt="44q" /></td>
<td><img src="image" alt="52d" /></td>
<td>85</td>
</tr>
</tbody>
</table>

[^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 performed 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-iPr (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-iPr, 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 %.$^{81}$

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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.
RESULTS AND DISCUSSION

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

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. 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)₂·2 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-

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RESULTS AND DISCUSSION

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 PEPSSI-iPr-catalysis and comparable mild conditions. Electrophiles bearing acidic protons like amides or anilines were well tolerated (Scheme 36).

Scheme 36: PEPSSI-iPr-catalyzed Negishi cross-coupling of 3-pyridylzinc pivalate 55 bearing no complexed LiCl.
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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). 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. 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.

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). 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 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. 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.
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). 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>t in air</th>
<th>Active zinc species 58 (%) [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 h</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>1 h</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>2 h</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>4 h</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>24 h</td>
<td>24</td>
</tr>
</tbody>
</table>

[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 %), 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).
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, pharmaceuticals, materials and metal-complexing ligands (Scheme 38).

![Scheme 38: Selected examples of important structures comprising the 2-pyridyl motif.](image)

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. So far, Stille- and Suzuki cross-couplings using the corresponding 2-pyridylstannanes and -boronic acids have been the major approaches to tackle this problem. However, the application of organotin reagents on industrial scale is precluded by their high toxicity and their poor solubility in

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water which requires elaborate purification processes.\(^9\) 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\(_3\)PO\(_4\), 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.](image)

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

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comparable mild conditions and the addition of bases or Cu-salts is not required.\textsuperscript{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\textsubscript{2}dba\textsubscript{3} (2 mol %) and X-Phos (8 mol %) as the catalytic system (Scheme 40).\textsuperscript{97}

\[
\begin{align*}
\text{(61)} & \xrightarrow{\text{E-Cl (0.67 equiv)}} \text{Pd\textsubscript{2}dba\textsubscript{3} (2 mol %)} & \text{X-Phos (8 mol %)} & \xrightarrow{65 \, ^\circ \text{C}, \ 2-3 \, \text{h}, \text{THF}} \\
\text{N} & \text{ZnBr} & \text{E-Cl (0.67 equiv)} & \text{Pd\textsubscript{2}dba\textsubscript{3} (2 mol %)} & \text{X-Phos (8 mol %)} & \xrightarrow{65 \, ^\circ \text{C}, \ 2-3 \, \text{h}, \text{THF}} \\
\text{N} & \text{E} & \text{N} & \text{OMe} & \text{N} & \text{Boc} & \text{N} & \text{S} & \text{Scheme 40: Negishi cross-couplings of 2-pyridylzinc bromide (61) with aryl and heteroaryl chlorides.}
\end{align*}
\]

So far, 2-pyridylzinc reagents are only available as solutions in THF.\textsuperscript{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)\textsubscript{2} (40) and subsequent evaporation of the solvent proved to be an efficient procedure to access solid functionalized aryl and heteroaryl zinc reagents.\textsuperscript{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 nBuLi (1.0 equiv). After 30 min at -78 °C solid Zn(OPiv)\textsubscript{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).

\textsuperscript{102} See chapter 2.1. and 2.2. of Results and Discussion.
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 iPrMgCl•LiCl can be performed at elevated temperatures (up to 25 °C depending on the sensitivity of the functional groups). Therefore, different 2-bromopyridines were reacted with 1.1 equiv of iPrMgCl•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).
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**Scheme 43**: Solid 2-pyridylzinc pivlates of type 64 prepared via bromine-magnesium exchange and subsequent transmetalation with Zn(OPiv)$_2$ (40).

Moreover, the stability of different 2-pyridylzinc pivlates towards their exposure to air for 1 h was investigated (Table 9). The unsubstituted 2-pyridylzinc pivlate (63a) and 6-methoxypyridin-2-ylzinc pivlate (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 pivlates 63b, 63c and 64b preserved 69-72 % of their initial activity. Interestingly, the stability of 5-methylpyridin-2-ylzinc pivlate 64b bearing 1.0 equiv of complexed LiCl is comparable to the one of the organozinc pivlates 63b and 63c without complexed LiCl.

<table>
<thead>
<tr>
<th>2-Pyridylzinc pivlate</th>
<th>Active zinc species (%)$^{[a]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>63a</td>
<td>90</td>
</tr>
<tr>
<td>63b</td>
<td>69</td>
</tr>
<tr>
<td>63c</td>
<td>70</td>
</tr>
<tr>
<td>63e</td>
<td>86</td>
</tr>
<tr>
<td>64b</td>
<td>72</td>
</tr>
</tbody>
</table>

$^{[a]}$ 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 pivlates 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 pivlate (63a) was reacted with 0.84 equiv of methyl-4-chlorobenzoate (65a) in distilled THF in argon-

---

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).](image)

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.

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$^{104}$ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Pyridylzinc pivalate$^{[a]}$</th>
<th>Electrophile$^{[b]}$</th>
<th>Product</th>
<th>Yield (%)$^{[c]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63\text{a}</td>
<td>44\text{d}</td>
<td>66\text{b}</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>63\text{a}</td>
<td>44\text{q}</td>
<td>66\text{c}</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>63\text{a}</td>
<td>44\text{b}</td>
<td>66\text{d}</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>63\text{a}</td>
<td>39</td>
<td>66\text{e}</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>63\text{c}</td>
<td>65\text{a}</td>
<td>66\text{f}</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>63\text{c}</td>
<td>44\text{q}</td>
<td>66\text{g}</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>63\text{d}</td>
<td>44\text{b}</td>
<td>66\text{h}</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>63\text{d}</td>
<td>65\text{b}</td>
<td>66\text{i}</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>63\text{e}</td>
<td>65\text{c}</td>
<td>66\text{j}</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>63\text{e}</td>
<td>65\text{b}</td>
<td>66\text{k}</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>63\text{e}</td>
<td>65\text{d}</td>
<td>66\text{l}</td>
<td>67</td>
</tr>
</tbody>
</table>

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

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).

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RESULTS AND DISCUSSION

Scheme 46: Preparation of the trisarylindium reagent 67 via magnesium insertion in the presence of InCl₃ (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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)$^{[a]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO$_2$C-Br</td>
<td>I-C$_2$H$_4$-CN</td>
<td>EtO$_2$C-S$_2$-C$_2$H$_4$-CN</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>44$^{[b]}$</td>
<td>Br-C$_2$H$_4$-OMe</td>
<td>EtO$_2$C-S$_2$-C$_2$H$_4$-OMe</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>Cl-C$_2$H$_4$-Br</td>
<td>H$_2$N-C$_2$H$_4$-NH$_2$</td>
<td>H$_2$N-C$_2$H$_4$-NH$_2$</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>MeO-C$_2$H$_4$-Br</td>
<td>I-C$_2$H$_4$-NO$_2$</td>
<td>MeO-C$_2$H$_4$-NO$_2$</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>69$^{[b]}$</td>
<td>Br-C$_2$H$_4$-CN</td>
<td>Br-C$_2$H$_4$-CN</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>69$^{[b]}$</td>
<td>Br-C$_2$H$_4$-CN</td>
<td>Br-C$_2$H$_4$-CN</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>69$^{[b]}$</td>
<td>Br-C$_2$H$_4$-NH$_2$Bu</td>
<td>Br-C$_2$H$_4$-NH$_2$Bu</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>69$^{[b]}$</td>
<td>Br-C$_2$H$_4$-NH$_2$</td>
<td>Br-C$_2$H$_4$-NH$_2$</td>
<td>64</td>
</tr>
</tbody>
</table>

$^{[a]}$ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heteroaryl bromide</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Heteroaryl bromide" /></td>
<td><img src="image" alt="Electrophile" /></td>
<td><img src="image" alt="Product" /></td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Heteroaryl bromide" /></td>
<td><img src="image" alt="Electrophile" /></td>
<td><img src="image" alt="Product" /></td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Heteroaryl bromide" /></td>
<td><img src="image" alt="Electrophile" /></td>
<td><img src="image" alt="Product" /></td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Heteroaryl bromide" /></td>
<td><img src="image" alt="Electrophile" /></td>
<td><img src="image" alt="Product" /></td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Heteroaryl bromide" /></td>
<td><img src="image" alt="Electrophile" /></td>
<td><img src="image" alt="Product" /></td>
<td>69</td>
</tr>
</tbody>
</table>

[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).

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).
RESULTS AND DISCUSSION

**Scheme 49:** Direct addition of functionalized organozinc reagents to CO₂-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)₂·2 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).
RESULTS AND DISCUSSION

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-iPr 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).
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Scheme 52: PEPPSI-iPr 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-iPr and electrophiles such as 2-bromobenzaldehyde (44r) leads to the corresponding cross-coupling products leaving the carbonyl moiety untouched.

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

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)2·2 LiCl (38) or Zn(OPiv)2 (40) and could be efficiently applied in Negishi cross-couplings (Scheme 54).
RESULTS AND DISCUSSION

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).
RESULTS AND DISCUSSION

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

4.3. Preparation of Functionalized Organoinium Reagents via Magnesium Insertion in the Presence of InCl₃

An efficient method for the preparation of functionalized trisorganoinium reagents via Mg-insertion in the presence of LiCl and InCl₃ (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 trisorganoinium reagents underwent smooth Pd-catalyzed cross-coupling reactions with different aryl and heteroaryl bromides and iodides (Scheme 57).
RESULTS AND DISCUSSION

Scheme 57: Preparation of the trisorganoinium 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$_2$Cl$_2$ 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$_2$O 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.
- iPrMgCl·LiCl solution in THF was purchased from Chemetall.
- nBuLi solution in hexane was purchased from Chemetall.
- TMPMgCl·LiCl (12) was prepared according to a literature procedure (ref. 23a).

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\[ \text{ZnCl}_2 \text{ solution (1.00 M) was prepared by drying ZnCl}_2 \text{ (100 mmol, 136 g) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL dry THF were added and stirring was continued until the salt was dissolved.} \]

\[ \text{ZnCl}_2/\text{LiCl} \text{ solution (1.10/1.50 M) was prepared by drying LiCl (15.9 g, 375 mmol) and ZnCl}_2 \text{ (37.5 g, 275 mmol) under high vacuum (1 mbar) for 5 h at 140 °C. After cooling to 25 °C, dry THF (250 mL) was added and stirring was continued until the salts were dissolved.} \]

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\(_2\)SO\(_4\) in water (300 mL).
- Phosphomolybdic acid (5.0 g), Ce(SO\(_4\))\(_2\) (2.0 g) and conc. H\(_2\)SO\(_4\) (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 \(\delta\)-values in ppm relative to the residual solvent peak of CHCl\(_3\) (\(\delta_H\) : 7.25; \(\delta_C\) : 77.0). For the characterization of

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the observed signal multiplicities the following abbreviations 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 DuraSamp\textit{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·MgX₂·LiCl (28) or Diorganozinc Reagents of Type R₂Zn-2 MgX₂·LiCl (30) using Mg and ZnCl₂/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, ZnCl₂/LiCl (1.1/1.5 M) solution was added (1 mL/mmol for the preparation of organozinc reagents of type RZnX·MgX₂·LiCl (X = Cl, Br); 0.5 mL/mmol for the preparation of diorganozinc reagents of type R₂Zn·2 MgX₂·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·MgX₂·LiCl (28) or Diorganozinc Reagents of Type R₂Zn-2 MgX₂·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·MgX₂·LiCl (1.8 mmol, 1.2 equiv; X = Cl, Br) or the diorganozinc reagent R₂Zn·2 MgX₂·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. NH₄Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic phases were dried (MgSO₄). 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·MgX₂·LiCl (28) or Diorganozinc Reagents of Type R₂Zn·2 MgX₂·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 CO₂(g) and the organozinc reagent (typically 1.0 mmol for Ar₂Zn and (ArCH₂)₂Zn) was added. Then, dry CO₂(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 I₂ and GC-analysis). The reaction mixture was diluted with Et₂O (20 mL) and sat. aq. NaHCO₃ (30 mL) was added. After filtration, the organic phase was separated and extracted with sat. aq. NaHCO₃ (3 x 30 mL). The combined aq. phases were carefully acidified with HCl (5 M) until pH < 5 and extracted with Et₂O (3 x 100 mL). The combined organic phases were dried over Na₂SO₄. 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)₂·2 LiCl (38) (TP4):

Zn(OPiv)₂·2 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)$_2$·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. iPrMgCl·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)$_2$·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-iPr (2 mol%) and the mixture was stirred for the given time at the given temperature. Then sat. aq. NH$_4$Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na$_2$SO$_4$). 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$_4$Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na$_2$SO$_4$). 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 \textit{in vacuo}.

2.9. Typical Procedure for the Preparation of the Organozinc Pivalates (58) by Metalation with TMPMgCl$\cdot$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$\cdot$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 \textit{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
EXPERIMENTAL SECTION

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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na₂SO₄). 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 nBuLi (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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic
phases were dried (Na₂SO₄). 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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na₂SO₄). 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 InCl₃ (TP15):

LiCl and InCl₃ (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 ZnCl₂ (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)

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 ZnCl₂ (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)

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 ZnCl₂ (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)

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 ZnCl₂ (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)**

![Chemical Structure](image)

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 ZnCl₂ (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)**

![Chemical Structure](image)

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 ZnCl₂ (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)**

![Chemical Structure](image)

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 ZnCl₂ (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 ZnCl₂ (1.00 M in THF)) indicated a concentration of 0.31 M.

**Bis(3-methoxybenzyl)zinc (30g)**

![Chemical Structure](image)

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 ZnCl₂
(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 ZnCl₂ (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 ZnCl₂ (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 ZnCl₂ (1.00 M in THF)) indicated a concentration of 0.54 M.

**Bis(2-fluorobenzyl)zinc (30i)**

According to TP1 2-fluorobenzyl chloride (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 ZnCl₂ (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 ZnCl₂ (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 ZnCl₂ (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 ZnCl₂ (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$_2$O = 7:1) afforded the alcohol 27d (499 mg, 85 %) as a colourless oil.

$^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta$ / ppm = 7.36 (br, 1H), 7.33 - 7.20 (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-d$_6$): $\delta$ / 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$_2$Si): 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$_2$O = 5:1) afforded the alcohol 27e (2.81 g, 89 %) as a colourless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / 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).
\textbf{13C-NMR (75 MHz, CDCl\textsubscript{3})}: \( \delta / \text{ppm} = 162.9 \) (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.

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

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

\textbf{HRMS (C\textsubscript{22}H\textsubscript{31}FO\textsubscript{2}Si)}: calc.: 374.2077; found: 374.2076 (M\textsuperscript{+}).

\textbf{1-(4-Methoxyphenyl)cyclopentanol (27f)}

According to TP\textsubscript{2} cyclopentanone (26f; 126 mg, 1.50 mmol) was added to bis(4-methoxyphenyl)zinc·2 MgX\textsubscript{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\textsubscript{2}O = 3:1 + 1 vol-% NEt\textsubscript{3}) afforded the alcohol 27f (243 mg, 84 %) as a colourless oil.

\textbf{1H-NMR (400 MHz, DMSO-d\textsubscript{6})}: \( \delta / \text{ppm} = 7.37-7.34 \) (m, 2H), 6.86-6-82 (m, 2H), 4.65 (s, 1H), 3.71 (s, 3H), 1.87-1.66 (m, 8H).

\textbf{13C-NMR (100 MHz, DMSO-d\textsubscript{6})}: \( \delta / \text{ppm} = 157.5, 140.5, 126.3, 113.0, 81.1, 55.0, 41.6, 23.6 \).

\textbf{IR (Diamond-ATR, neat)}: \( \tilde{\nu} / \text{cm}^{-1} = 3403 \) (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).

\textbf{MS (EI, 70 eV)}: m/z (%) = 192 (M\textsuperscript{+}, 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).

\textbf{HRMS (C\textsubscript{12}H\textsubscript{16}O\textsubscript{2})}: calc.: 192.1150; found: 192.1146 (M\textsuperscript{+}).

\textbf{Dicyclopropyl(4-methoxyphenyl)methanol (27g)}

According to TP\textsubscript{2} dicyclopropylketone (26g; 165 mg, 1.50 mmol) was added to bis(4-methoxyphenyl)zinc·2 MgX\textsubscript{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 / Et₂O = 3:1 + 1 vol-% NEt₃) afforded the alcohol 27g (286 mg, 87 %) as a colourless oil.

¹H-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).

¹³C-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): ν / 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 (44), 115 (19), 107 (12), 91 (18), 77 (26), 69 (31), 41 (19).

HRMS (C₁₄H₁₈O₂): 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 MgX₂ (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 / Et₂O = 6:1) afforded the alcohol 27h (2.68 g, 88 %) as a pale yellow oil.

¹H-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 (sbr, 1H).

¹³C-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): ν / cm⁻¹ = 3316 (w), 2896 (w), 1471 (vs), 1407 (m), 1388 (m), 1231 (s), 1103 (m), 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 (C₁₄H₁₀BrClO₃): calc.: 339.9502; found: 339.9504 (M⁺).
(4-Chlorophenyl)(4-fluorophenyl)methanone (27i)

According to TP2 4-fluorobenzoylechloride (26i; 238 mg, 1.50 mmol) was added to bis(4-chlorophenyl)zinc-2 MgX₂ (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 / Et₂O = 8:1) afforded the ketone 27i (286 mg, 81 %) as a colourless solid.


1H-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).

13C-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): ν / 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 (C₁₃H₈ClFO): calc.: 234.0248; found: 234.0246 (M⁺).

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

According to TP2 cyclohexylcarbaldehde (26j; 168 mg, 1.50 mmol) was added to 4-fluorobenzylzinc-2 MgCl₂ (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 / Et₂O = 3:1 + 1 vol-% NEt₃) afforded the alcohol 27j (327 mg, 97 %) as a colourless oil.

1H-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).

13C-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): ν / 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), 80
1263 (vs), 1184 (m), 1095 (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 (C₁₄H₁₉FO):** 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-MgCl₂ (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 / Et₂O = 10:1 + 1 vol-% NEt₃) afforded the alcohol 27k (287 mg, 60 %) as a colourless oil.

**¹H-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).

**¹³C-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):** ν / 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 (C₁₆H₂₁F₃O₃):** 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)zine·2 MgX₂ (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 / Et₂O = 3:1 + 1 vol-% NEt₃) afforded the alcohol 27l (295 mg, 87 %) as a colourless oil.
**EXPERIMENTAL SECTION**

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

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

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

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): $\delta / \text{ppm} = 12.62 (s, 1H), 7.88 (dt, J = 9.3 \text{ Hz, } J = 2.8 \text{ Hz, 2H}), 7.00 (dt, ^3J = 9.5 \text{ Hz, } ^4J = 2.7 \text{ Hz, 2H}), 3.81 (s, 3H).$

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

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

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

HRMS ($C_{8}H_{8}O_{3}$): 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.
**Experimental Section**

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

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

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

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

HRMS (C\(_{10}\)H\(_{14}\)O\(_2\)Si): 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.


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

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

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

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

HRMS (C\(_9\)H\(_{10}\)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 ($^{13}$C$_9$H$_{10}$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 ($^{13}$C$_8$H$_7$ClO$_2$): 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.
**EXPERIMENTAL SECTION**

**1H-NMR (400 MHz, DMSO-d6):** $\delta$ / ppm = 7.35-7.27 (m, 2H), 7.18-7.11 (m, 2H), 3.61 (s, 2H).

**13C-NMR (100 MHz, DMSO-d6):** $\delta$ / 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), 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$_8$H$_7$FO$_2$):** calc.: 154.0430; found: 154.0418 (M$^+$).

**1H-NMR (400 MHz, DMSO-d6):** $\delta$ / ppm = 12.47 (s, 1H), 7.63-7.52 (m, 4H), 3.72 (s, 2H).

**13C-NMR (100 MHz, DMSO-d6):** $\delta$ / 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$_9$H$_7$F$_3$O$_2$):** calc.: 204.0398; found: 204.0384 (M$^+$).

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(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.

**1H-NMR (400 MHz, DMSO-d6):** $\delta$ / ppm = 12.47 (s, 1H), 7.63-7.52 (m, 4H), 3.72 (s, 2H).

**13C-NMR (100 MHz, DMSO-d6):** $\delta$ / 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$_9$H$_7$F$_3$O$_2$):** calc.: 204.0398; found: 204.0384 (M$^+$).
Heptanoic acid (33h)

According to TP3, bis(hexyl)zinc·2 MgX₂ (30d; X = Br, Cl; 3.03 mL, 1.00 mmol, 0.33 M in THF) was reacted with dry CO₂(g) at 50 °C for 12 h. After purification heptanoic acid (33h; 223 mg, 86 %) was obtained as colourless oil.

¹H-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).

¹³C-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): ν / 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 (C₇H₁₄O₂): 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 Na₂SO₄.

The crude product was dissolved in dry CH₂Cl₂ (30 mL) and the mixture was cooled to 0 °C. A solution of thionyl chloride (3.57 g, 30.0 mmol) in CH₂Cl₂ (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 NaHCO₃ (40 mL) and the aqueous phase was then extracted with CH₂Cl₂ (3 x 40 mL). The combined organic layers were dried over Na₂SO₄ 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.
**EXPERIMENTAL SECTION**

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.32 (dt, $J = 8.1$ Hz, 2H), 7.13 (dt, $J = 8.1$ 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$_3$): $\delta$ / 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$_3$): $\delta$ / 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$_3$): $\delta$ / 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(O Piper)\textsubscript{2}·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\textsubscript{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 \textit{in vacuo} and Zn(O Piper)\textsubscript{2}·2 LiCl (38) was obtained as a colourless solid in quantitative yield.

4.2. Preparation of Zn(O Piper)\textsubscript{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 \textit{in vacuo} and Zn(O Piper)\textsubscript{2} was obtained as a colourless solid in quantitative yield. Zn(O Piper)\textsubscript{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(O Piper)\textsubscript{2}

4.3.1. Preparation of Arylzinc Pivalates of Type 41

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

According to TP5 Zn(O Piper)\textsubscript{2}·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)2·2 LiCl (38)
According to TP5 Zn(OPiv)2·2 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)2·2 LiCl (38)
According to TP5 Zn(OPiv)2·2 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)2·2 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-((Triisopropylsilyloxy)phenyl)zinc pivalate (41d)**

According to TP5 Zn(OPiv)₂·2 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-((Triisopropylsilyloxy)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)₂·2 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-((Diethylcarbamoyloxy)phenyl)zinc pivalate (41f)**

According to TP5 Zn(OPiv)₂·2 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(O\text{Piv})_{2}\cdot2\text{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(O\text{Piv})_{2}\cdot2\text{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 %.
**EXPERIMENTAL SECTION**

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

![Chemical structure](4EOC-ZnOPiv)

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

According to TP5 Zn(OPiv)$_2$·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 (41l) 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)$_2$·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. iPrMgCl-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)$_2$·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)

![Chemical structure](4NC-ZnOPiv)

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

According to TP5 Zn(OPiv)$_2$·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)$_2$·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)$_2$·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 (1.0 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)**

![Pyridin-3-ylzinc pivalate](image)

According to TP5 Zn(OPiv)$_2$·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)**

![2,4-Dimethoxypyrimidin-5-yl]zinc pivalate

According to TP5 Zn(OPiv)$_2$·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)$_2$·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)$_2$·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)$_2$·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)$_2$·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)$_2$·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%. 

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

According to TP5 Zn(OPiv)$_2$·2LiCl (38; 2.64 g, 7.50 mmol) and 1-(chloromethyl)-3-(trifluoromethyl)benzene (973 mg, 5.00 mmol) were dissolve 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)$_2$·2LiCl (38; 2.64 g, 7.50 mmol) and ethyl 3-(chloromethyl)benzoate (49a; 993 mg, 5.00 mmol) were dissolve 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)$_2$·2LiCl (38; 2.64 g, 7.50 mmol) and 1-(chloromethyl)-3-methoxybenzene (783 mg, 5.00 mmol) were dissolve 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)**

![](image)

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-iPr (20 mg, 0.03 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, /hexane / Et₂O = 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 (5 mL). 2-Chloronicotinonitrile (44a; 183 mg, 1.32 mmol) and PEPPSI-iPr (20 mg, 0.03 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, /hexane / Et₂O = 1:1) afforded the pyridine derivative 45a (320 mg, 96 %) as a slightly yellow solid.

**M.p. (°C):** 98-99.

**¹H-NMR (300 MHz, CDCl₃):** 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).

**¹³C-NMR (75 MHz, CDCl₃):** 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):** ν / 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 (C₁₃H₁₂N₂O₂):** calc.: 252.0899; found: 252.0886 (M⁺).
Ethyl 4’-[(tert-butilamino)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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane/EtOAc = 6:1 to 5:1) afforded the biphenyl 45b (235 mg, 87 %) as colourless solid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ 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$_3$): $\delta$/ 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), 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-Bromobenzenitrile (44c; 382 mg, 2.10 mmol) and PEPPSI-iPr (34 mg, 0.05 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane/Et$_2$O = 8:1) afforded the biphenyl 45c (377 mg, 86 %) as colourless solid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ 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$_3$): $\delta$/ 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 (C₁₄H₁₁NO): 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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane/EtOAc = 10:1) afforded the biphenyl 45d (149 mg, 67 %) as colourless solid.


¹H-NMR (300 MHz, CDCl₃): 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).

¹³C-NMR (75 MHz, CDCl₃): 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): ν / 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 (C₁₅H₁₄O₂): calc.: 226.0994; found: 226.0986 (M⁺).

2-Fluoro-4'-(triisopropylsilyl)oxybiphenyl-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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, ihexane/Et₂O = 50:1 to 10:1) afforded the biphenyl 45e (327 mg, 89 %) as colourless solid.

M.p. (°C): 76-77.

¹H-NMR (300 MHz, CDCl₃): 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).

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EXPERIMENTAL SECTION

$^{13}$C-NMR (75 MHz, CDCl$_3$): \( \delta / \text{ppm} = 163.5 \text{ (d, } J = 258.0 \text{ Hz)}, 157.5, 148.2 \text{ (d, } J = 8.5 \text{ Hz)}, 133.6 \text{ (d, } J = 1.1 \text{ Hz)}, 130.5 \text{ (d, } J = 2.4 \text{ Hz)}, 128.3, 122.7 \text{ (d, } J = 3.4 \text{ Hz)}, 120.6, 114.3, 114.0 \text{ (d, } J = 20.4 \text{ Hz)}, 98.8 \text{ (d, } J = 15.9 \text{ Hz)}, 17.9, 12.7 \).

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

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 ($^{13}$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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et$_2$O = 8:1) afforded the biphenyl 45f (151 mg, 83 %) as a slightly yellow solid.


$^1$H-NMR (300 MHz, CDCl$_3$): \( \delta / \text{ppm} = 8.02-8.01 \text{ (m, 2H)}, 7.71-7.67 \text{ (m, 2H)}, 7.65-7.59 \text{ (m, 4H)}, 2.63 \text{ (s, 3H)}, 0.31 \text{ (s, 9H)}. \)

$^{13}$C-NMR (75 MHz, CDCl$_3$): \( \delta / \text{ppm} = 197.7, 145.7, 140.7, 140.2, 135.9, 134.0, 128.9, 127.2, 126.6, 26.7, 26.7, -1.1. \)

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

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

HRMS ($^{13}$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-iPr (7 mg, 0.01 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / AcOEt = 2:1 to pure AcOEt) afforded the carbamate 45g (119 mg, 80 %) as a slightly yellow solid.

M.p. (°C): 53-54.

^1H-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).

^13C-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): v / 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$_3$O$_2$): 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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et$_2$O = 3:1) afforded the biphenyl 45h (125 mg, 80 %) as colourless solid.


^1H-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).

^13C-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): v / 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 (C₁₃H₇FN): 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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et₂O = 1:1) afforded the pyridine derivative 45j (144 mg, 78 %) as colourless solid.


¹H-NMR (300 MHz, CDCl₃): 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).

¹³C-NMR (75 MHz, CDCl₃): 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): ν / 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 (C₁₃H₇F₃N₂): 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 (3 mL). 3-Bromo-1-(phenylsulfonfonyl)-1H-indole (44k; 168 mg, 0.50 mmol) and PEPPSI-iPr (8 mg, 0.01 mmol) were added and the mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et₂O = 5:1 to 3:1) afforded the title compound 45k (201 mg, 99 %) as white solid.

M.p. (°C): 116.2-118.4.
**EXPERIMENTAL SECTION**

**1H-NMR (300 MHz, CDCl3):** \(\delta / \text{ppm} = 8.16-8.10 \text{ (m, 2H)}, 8.09-8.05 \text{ (m, 1H)}, 7.96-7.92 \text{ (m, 2H)}, 7.80-7.76 \text{ (m, 2H)}, 7.70-7.65 \text{ (m, 2H)}, 7.58-7.51 \text{ (m, 1H)}, 7.48-7.42 \text{ (m, 2H)}, 7.40-7.35 \text{ (m, 1H)}, 7.34-7.28 \text{ (m, 1H)}, 4.41 \text{ (t, } J = 7.2 \text{ Hz, 2H)}, 1.42 \text{ (t, } J = 7.2 \text{ Hz, 3H}).

**13C-NMR (75 MHz, CDCl3):** \(\delta / \text{ppm} = 166.3, 138.0, 137.6, 135.5, 134.0, 130.1, 129.4, 129.3, 128.8, 126.8, 125.2, 123.9, 123.6, 123.1, 120.3, 113.9, 61.0, 14.3.

**IR (Diamond-ATR, neat):** \(\bar{\nu} / \text{cm}^{-1} = 3141 \text{ (v, w)}, 2989 \text{ (vw)}, 2979 \text{ (w)}, 1701 \text{ (s)}, 1609 \text{ (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 \text{ (M}^+ \text{, 40), 264 (100), 236 (23), 191 (9), 164 (7).}

**HRMS (C23H19O4NS):** 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 AcOEt77 (5 mL). 4-Bromoethylbenzoate (44l; 239 mg, 1.04 mmol) and PEPPSI-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / EtOAc = 4:1 to 3:1) afforded the biphenyl 45l (245 mg, 94 %) as colourless solid.

**M.p. (°C):** 112-114.

**1H-NMR (300 MHz, CDCl3):** \(\delta / \text{ppm} = 8.16-8.11 \text{ (m, 2H)}, 7.76-7.68 \text{ (m, 4H)}, 7.66-7.62 \text{ (m, 2H)}, 4.39 \text{ (q, } J = 7.2 \text{ Hz, 2H)}, 1.41 \text{ (t, } J = 7.2 \text{ Hz, 3H}).

**13C-NMR (75 MHz, CDCl3):** \(\delta / \text{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):** \(\bar{\nu} / \text{cm}^{-1} = 2961 \text{ (w)}, 2222 \text{ (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 \text{ (M}^+ \text{, 35), 223 (35), 206 (100), 178 (19), 151 (19), 43 (20).}

**HRMS (C16H13NO2):** 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-iPr (20 mg, 0.03 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et2O = 3:1) afforded the benzonitrile 45m (329 mg, 88 %) as yellow solid.


1H-NMR (300 MHz, CDCl₃): 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).

13C-NMR (75 MHz, CDCl₃): 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): ν / 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 (m), 640 (vw).

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

HRMS (C₁₆H₁₀N₂): 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-iPr (33 mg, 0.05 mmol) were added and the mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et₂O = 10:1) afforded the biphenyl 45n (349 mg, 82 %) as white solid.

M.p. (°C): 56.6-58.4.

1H-NMR (300 MHz, CDCl₃): 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).

13C-NMR (75 MHz, CDCl₃): 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.
EXPERIMENTAL SECTION

IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 2938$ (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), 1099 (m), 1048 (w), 1030 (s), 1015 (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 ($C_{11}H_{12}O_2$): 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-iPr (34 mg, 0.05 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, Et₂O) afforded the bipyridine 51a (321 mg, 91%) as colourless solid.


$^1$H-NMR (300 MHz, CDCl₃): $\delta / \text{ppm} = 9.14$ (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, CDCl₃): $\delta / \text{ppm} = 158.1$, 152.9, 150.9, 149.7, 141.7, 136.0, 132.9, 123.2, 122.2, 117.0, 107.8.

IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 3068$ (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 ($C_{11}H_{12}N_3$): 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-iPr (20 mg, 0.03 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / 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$_3$): $\delta$ / 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$_3$): $\delta$ / 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$_2$O$_4$): 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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / 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$_3$): $\delta$ / 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$_3$): $\delta$ / ppm = 168.1, 165.2, 157.9, 147.1, 140.1, 129.4, 123.7, 114.2, 55.2, 54.4.
EXPERIMENTAL SECTION

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3008 (w), 2958 (w), 1740 (w), 1602 (s), 1554 (s), 1514 (s), 1454 (s), 1400 (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 (C₁₂H₁₁N₃O₄): 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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, hexane / Et₂O = 3:1) afforded the amide 51d (180 mg, 84 %) as a yellow solid.

M.p. (°C): 120-122.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.94-7.82 (m, 4H), 7.65-7.60 (m, 2H), 7.44-7.35 (m, 3H), 1.50 (s, 9H).

¹³C-NMR (300 MHz, CDCl₃): 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): ν / 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 (C₁₉H₁₉NOS): 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-iPr (27 mg, 0.04 mmol) were added and the mixture was stirred for
2 h at 50 °C. Purification by flash chromatography (silica gel, ihexane / EtOAc = 3:1) afforded the benzonitrile 51e (337 mg, 99 %) as a yellow solid.

**M.p. (°C):** 98-99.

**1H-NMR (300 MHz, CDCl3):** δ / ppm = 7.72-7.67 (m, 1H), 7.18-7.11 (m, 2H), 2.44 (s, 3H), 2.29 (s, 3H).

**13C-NMR (75 MHz, CDCl3):** 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):** ν / cm⁻¹ = 3090 (vw), 3068 (vw), 2970 (vw), 2934 (vw), 2234 (m), 1742 (vw), 1630 (s), 1562 (s), 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 (C₁₃H₉FN₂O):** calc.: 216.0699; found: 216.0699 (M⁺).

### 3-Fluoro-4-(3-methyl-1-phenyl-1H-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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (silica gel, ihexane / EtOAc = 3:1) afforded the benzonitrile 51f (172 mg, 98 %) as a colourless solid.

**M.p. (°C):** 74-76.

**1H-NMR (300 MHz, CDCl₃):** 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).

**13C-NMR (75 MHz, CDCl₃):** 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):** ν / 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).
**EXPERIMENTAL SECTION**

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

**HRMS (C₁₇H₁₂FN₃):** calc.: 277.1015; found: 277.1006 (M⁺).

4.3.6. Preparation of Cross-Coupling Products of Type 52

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

![Chemical Structure](#)

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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et₂O = 4:1) afforded the acetonitrile 52a (133 mg, 81 %) as a colourless oil.

**¹H-NMR (300 MHz, CDCl₃):** 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).

**¹³C-NMR (75 MHz, CDCl₃):** 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, J = 8.2 Hz), 23.2.

**IR (Diamond-ATR, neat):** ν / 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 (C₁₅H₁₂F):** calc.: 225.0954; found: 225.0940 (M⁺).

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

![Chemical Structure](#)

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-iPr (27 mg, 0.04 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et₂O = 30:1) afforded the benzonitrile 52b (237 mg, 70 %) as a colourless solid.

**M.p. (°C):** 63-64.
**EXPERIMENTAL SECTION**

**¹H-NMR (300 MHz, CDCl₃):** 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).

**¹³C-NMR (75 MHz, CDCl₃):** 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):** ν / 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 (C₁₄H₁₀ClN):** calc.: 227.0502; found: 227.0499 (M⁺).

1-(Phenylsulfonyl)-3-(3-(trifluoromethyl)benzyl)-1H-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)-1H-indole (44p; 182 mg, 0.54 mmol) and PEPPSI-iPr (7 mg, 0.01 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et₂O = 3:1) afforded the indole 52c (192 mg, 86 %) as a yellow solid.

**M.p. (°C):** 119-120.

**¹H-NMR (300 MHz, CDCl₃):** 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).

**¹³C-NMR (75 MHz, CDCl₃):** 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):** ν / 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 (C₂₂H₁₆F₃NO₂S):** calc.: 415.0854; found: 415.0839 (M⁺).
**EXPERIMENTAL SECTION**

**Ethyl 3-(4-benzyloxybenzyl)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-iPr (14 mg, 0.02 mmol) were added and the mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, ihexane / Et₂O = 3:1) afforded the benzophenone 52d (181 mg, 85 %) as a yellow oil.

1H-NMR (300 MHz, CDCl₃): 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).

13C-NMR (75 MHz, CDCl₃): 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): ν / 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, C₂₃H₂₀O₃): calc.: 362.1748 ([M+NH₄⁺]); found: 362.1748 ([M+NH₄⁺]).

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, ihexane / Et₂O = 3:1 to pure AcOEt) afforded the alcohol 53b (188 mg, 88 %) as orange oil.

1H-NMR (300 MHz, CDCl₃): 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).
13C-NMR (75 MHz, CDCl3): 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): ν / 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 (C21H19ClO2): calc.: 338.1074; found: 338.1094 (M⁺).


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-iPr (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\(_3\)): \(\delta / \text{ppm} = 8.88-8.86 (\text{m}, 1\text{H}), 8.76-8.75 (\text{d}, J = 1.5 \text{ Hz}, 1\text{H}), 8.70-8.69 (\text{m}, 1\text{H}), 8.12-8.10 (\text{m}, 1\text{H}), 7.85-7.81 (\text{m}, 1\text{H}), 7.49-7.46 (\text{m}, 1\text{H}), 7.40-7.37 (\text{m}, 1\text{H}).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 155.3 (\text{q}, J = 1.88 \text{ Hz}), 152.2 (\text{q}, J = 1.17 \text{ Hz}), 145.0, 149.4 (\text{q}, J = 1.95 \text{ Hz}), 136.0, 134.9 (\text{q}, J = 4.93 \text{ Hz}), 125.5 (\text{q}, J = 32.0 \text{ Hz}), 123.4 (\text{q}, J = 273 \text{ Hz}), 122.8, 122.4.

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

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

HRMS (C\(_{11}\)H\(_7\)F\(_3\)N\(_2\)): 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-iPr (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.


\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 8.85-8.84 (\text{m}, 1\text{H}), 8.62-8.60 (\text{m}, 1\text{H}), 7.89-7.86 (\text{m}, 1\text{H}), 7.84-7.80 (\text{m}, 2\text{H}), 7.64-7.59 (\text{m}, 2\text{H}), 7.39-7.35 (\text{m}, 1\text{H}), 5.98 (\text{br}, 1\text{H}), 1.48 (\text{s}, 9\text{H}).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta / \text{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} / \text{cm}^{-1} = 3283 (\text{w}), 3053 (\text{vw}), 2958 (\text{w}), 2364 (\text{w}), 1741 (\text{m}), 1637 (\text{s}), 1610 (\text{m}), 1543 (\text{s}), 1471 (\text{m}), 1450 (\text{m}), 1425 (\text{w}), 1388 (\text{m}), 1364 (\text{m}), 1315 (\text{s}), 1224 (\text{s}), 1000 (\text{m}), 875 (\text{m}), 859 (\text{m}), 842 (\text{w}), 806 (\text{m}), 767 (\text{vs}), 708 (\text{s}), 662 (\text{m}).

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

HRMS (C\(_{16}\)H\(_{18}\)N\(_2\)O): 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-iPr (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$_3$): $\delta$ / 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$_3$): $\delta$ / 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$_2$O$_2$): 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 transmetalation 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, ihexane / 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$_{12}$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 nBuLi (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 nBuLi (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 nBuLi (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 nBuLi (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 nBuLi (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 iPrMgCl·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 iPrMgCl·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, hexane / AcOEt = 3:1) afforded the pyridine 66a (172 mg, 96 %) as a pale yellow solid.


$^1$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.
EXPERIMENTAL SECTION

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, ihexane / AcOEt = 4:1) afforded the pyridine 66b (155 mg, 94 %) as a pale yellow solid.


$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ / 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$_3$): $\delta$ / 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, ihexane / AcOEt = 4:1) afforded the pyridine 66c (211 mg, 97 %) as a pale yellow solid.
EXPERIMENTAL SECTION


$^1$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, 138.9, 137.6, 133.0, 130.6, 132.5, 130.0, 128.3, 126.7, 122.8, 123.0.

IR (Diamond-ATR, neat): $\nu$ / cm$^{-1}$ = 3746 (vw), 3008 (vw), 2361 (w), 2340 (w), 1651 (s), 1599 (s), 1577 (m), 1599 (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, ihexane / AcOEt = 2:1) afforded the pyridine 66d (190 mg, 89 %) as a pale yellow solid.


$^1$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): $\nu$ / cm$^{-1}$ = 3309 (w), 2971 (w), 2928 (w), 2361 (w), 2339 (w), 1734 (w), 1634 (s), 1540 (vs), 1540 (m), 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$_{18}$H$_{18}$N$_2$O): calc.: 254.1419; found: 254.1411 (M$^+$).
EXPERIMENTAL SECTION

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, ihexane / Et$_2$O = 5:1) afforded the pyridine 66e (115 mg, 75 %) as a colourless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / 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$_3$): $\delta$ / 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, ihexane / AcOEt = 3:1) afforded the pyridine 66f (115 mg, 60 %) as a pale yellow solid.


$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ / 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$_3$): $\delta$ / 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): $\tilde{\nu} / \text{cm}^{-1} = 2953$ (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$^+$).

N-(tert-butyl)-4-(5-methylpyridin-2-yl)benzamide (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, ihexane / 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$_3$): $\delta$ / 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$_3$): $\delta$ / 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): $\tilde{\nu} / \text{cm}^{-1} = 2953$ (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.
EXPERIMENTAL SECTION

(silica gel, hexane / AcOEt = 3:1) afforded the pyridine 66h (156 mg, 69 %) as a pale yellow solid.


$^1$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): ν / cm$^{-1}$ = 3348 (w), 2978 (w), 1636 (s), 1591 (m), 1542 (vs), 1458 (s), 1398 (w), 1362 (m), 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$_2$O): 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, 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): ν / 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).
**EXPERIMENTAL SECTION**

**MS (EI, 70 eV):** m/z (%) = 256 (100; M⁺), 227 (45); 211 (33), 183 (23), 168 (10).

**HRMS (C₁₃H₁₆N₂O₂):** calc.: 256.1212; found: 256.1201 (M⁺).

**Methyl 4-(6-methoxypyridin-2-yl)benzoate (66j)**

![Methyl 4-(6-methoxypyridin-2-yl)benzoate](image)

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, ihexane / AcOEt = 9:1) afforded the pyridine 66j (200 mg, 98 %) as a colourless solid.

**M.p. (°C):** 93-94.

**¹H-NMR (400 MHz, CDCl₃):** 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).

**¹³C-NMR (100 MHz, CDCl₃):** 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):** ν / 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 (C₁₄H₁₃NO₃):** calc.: 243.0895; found: 243.0888 (M⁺).

**Ethyl 4-amino-2-(6-methoxypyridin-2-yl)benzoate (66k)**

![Ethyl 4-amino-2-(6-methoxypyridin-2-yl)benzoate](image)

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, ihexane / AcOEt = 6:1) afforded the pyridine 66k (175 mg, 77 %) as a yellow solid.

**M.p. (°C):** 92-94.
**EXPERIMENTAL SECTION**

^1H-NMR (400 MHz, CDCl₃): 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).

^13C-NMR (100 MHz, CDCl₃): 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): ν / 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), 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 (C₁₅H₁₆N₂O₃): 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, ihexane / AcOEt = 6:1) afforded the bipyridine 66l (118 mg, 67 %) as a colourless solid.

M.p. (°C): 142-144.

^1H-NMR (400 MHz, CDCl₃): 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).

^13C-NMR (100 MHz, CDCl₃): δ / ppm = 163.7, 157.4, 151.3, 149.9, 139.6, 124.7, 121.1, 116.9, 114.1, 112.6, 53.5.

IR (Diamond-ATR, neat): ν / 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 (C₁₂H₉N₃O): calc.: 211.0746; found: 211.0718 (M⁺).
**EXPERIMENTAL SECTION**

**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 (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, ihexane / AcOEt = 3:1) afforded the pyridine 66n (187 mg, 98%) as a pale yellow solid.


\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 8.74-8.72 \text{ (m, 1H)}, 8.17-8.14 \text{ (m, 2H)}, 8.09-8.06 \text{ (m, 2H)}, 7.82-7.75 \text{ (m, 2H)}, 7.32-7.25 \text{ (m, 1H)}, 4.41 \text{ (q, } J = 7.1 \text{ Hz, 2H)}, 1.43 \text{ (t, } J = 7.1 \text{ Hz, 3H}).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta / \text{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} / \text{cm}^{-1} = 2983 \text{ (w)}, 2903 \text{ (vw)}, 2364 \text{ (vvw)}, 1706 \text{ (s)}, 1608 \text{ (w)}, 1586 \text{ (m)}, 1564 \text{ (w)}, 1467 \text{ (m)}, 1436 \text{ (w)}, 1404 \text{ (w)}, 1363 \text{ (m)}, 1278 \text{ (s)}, 1261 \text{ (s)}, 1182 \text{ (m)}, 1156 \text{ (m)}, 1103 \text{ (s)}, 1012 \text{ (m)}, 866 \text{ (m)}, 796 \text{ (w)}, 753 \text{ (vs)}, 695 \text{ (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, ihexane / Et\(_2\)O = 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, ihexane / Et\(_2\)O = 1:1) afforded the pyridine 66m (149 mg, 96%) as a colourless solid.

^1^H-NMR (300 MHz, CDCl\textsubscript{3}): \(\delta / \text{ppm} = 8.65-8.63 \text{ (m, 1H)}, 7.97-7.92 \text{ (m, 2H)}, 7.74-7.63 \text{ (m, 2H)}, 7.18-7.13 \text{ (m, 1H)}, 7.03-6.96 \text{ (m, 2H)}, 3.85 \text{ (s, 3H)}\).

^1^3^C-NMR (75 MHz, CDCl\textsubscript{3}): \(\delta / \text{ppm} = 160.4, 157.1, 149.5, 136.6, 132.0, 128.1, 121.4, 119.8, 114.1, 55.3\).

IR (Diamond-ATR, neat): \(\tilde{\nu} / \text{cm}^{-1} = 3050 \text{ (w)}, 2996 \text{ (w)}, 2835 \text{ (w)}, 1600 \text{ (m)}, 1586 \text{ (m)}, 1579 \text{ (m)}, 1562 \text{ (m)}, 1513 \text{ (m)}, 1459 \text{ (m)}, 1431 \text{ (m)}, 1302 \text{ (m)}, 1272 \text{ (m)}, 1242 \text{ (s)}, 1176 \text{ (m)}, 1151 \text{ (m)}, 1112 \text{ (m)}, 1057 \text{ (m)}, 1036 \text{ (m)}, 1021 \text{ (m)}, 838 \text{ (s)}, 776 \text{ (vs)}, 735 \text{ (m)}, 717 \text{ (m)}\).

MS (EI, 70 eV): \(m/z \% = 185 (M^+, 100), 170 (19), 142 (24)\).

HRMS (C\textsubscript{12}H\textsubscript{11}NO): calc.: 185.0841; found: 185.0843 (M^+).
5. Preparation of Functionalized Organoindium Reagents via Magnesium Insertion in the Presence of InCl₃

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

\[ \text{NC} \quad \text{CO₂Et} \]

(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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). The combined organic phases were dried (Na₂SO₄). Purification by flash chromatography (silica gel, ihexane / Et₂O = 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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). The combined organic phases were dried (Na₂SO₄). Purification by flash chromatography (silica gel, ihexane / Et₂O = 3:1) afforded the biphenyl 45l (250 mg, 71 %) as a colourless solid.

**M.p. (°C):** 120-121.

**¹H-NMR (300 MHz, CDCl₃):** 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).

**¹³C-NMR (75 MHz, CDCl₃):** 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):** ν / 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).
EXPERIMENTAL SECTION

MS (EI, 70 eV): m/z (%) = 252 (M⁺, 34), 223 (36), 206 (100), 178 (23), 151 (23).

HRMS (C₁₆H₁₃NO₂): 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, 5.00 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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, ihexane / Et₂O = 3:1) afforded the biphenyl 68a (236 mg, 67 %) as a colourless solid.


¹H-NMR (300 MHz, CDCl₃): 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).

¹³C-NMR (75 MHz, CDCl₃): 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): $\bar{\nu}$ / 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 (C₁₆H₁₃NO₂): 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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, ihexane / Et₂O = 6:1) afforded the biphenyl 68b (103 mg, 57 %) as a colourless solid.

**M.p. (°C):** 100-103.

**¹H-NMR (300 MHz, CDCl₃):** 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).

**¹³C-NMR (75 MHz, CDCl₃):** 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):** ν / cm⁻¹ = 1705 (s), 1601 (m), 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 (s), 770 (vs), 718 (m), 698 (m).

**MS (EI, 70 eV):** m/z (%) = 251 (M⁺, 100), 228 (14), 211 (60), 139 (10).

**HRMS (C₁₆H₁₆O₃):** calc.: 256.1099; found: 256.1088 (M⁺).

**Ethyl 6-amino-4'-chloro-[1,1'-biphenyl]-3-carboxylate (68c)**

![Chemical Structure](image)

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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, ihexane / DCM = 3:1) afforded the biphenyl 68c (317 mg, 82 %) as a yellow solid.

**M.p. (°C):** 126-128.

**¹H-NMR (300 MHz, CDCl₃):** 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).
13C-NMR (75 MHz, CDCl₃): 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): ν / cm⁻¹ = 3482 (w), 3361 (m), 3214 (w), 2982 (w), 1683 (s), 1628 (s), 1590 (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 (C₁₅H₁₄ClNO₂): 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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, ihexane / AcOEt = 5:1) afforded the biphenyl 68d (270 mg, 84 %) as a yellow solid.


1H-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).

13C-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): ν / 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 (C₁₃H₁₁NO₃): 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$_4$Cl (10 mL) was added and the aqueous layer was extracted with AcOEt ($3 \times 20$ 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-d$_6$): 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-d$_6$): 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$_4$Cl (10 mL) was added and the
aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, i/hexane / Et₂O = 5:2) afforded the biphenyl 68f (349 mg, 74 %) as a yellow oil.

\( ^1 \)H-NMR (300 MHz, CDCl₃): \( \delta / ppm = 7.72-7.65 \) (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, CDCl₃): \( \delta / ppm = 154.0, 152.1, 144.9, 140.4, 132.5, 129.9, 127.8, 123.9, 122.0, 120.8, 118.8, 111.2, 42.3, 42.0, 14.3, 13.4. \)

IR (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 2975 \) (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): \( \text{m/z} / \% = 294 (M^+, 2), 100 (100), 72 (27), 43 (15). \)

HRMS (C₁₈H₁₈N₂O₂): calc.: 294.1368; found: 294.1364 (M⁺).

4'-{(tert-buty carbamoyl)-[1,1'-biphenyl]-3-yl diethyl carbamate (68g)}

\[ \text{NH}_{2} \text{Bu} \]

The organoindium reagent was prepared according to TP15 from 3-bromophenyl diethyl carbamate (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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, i/hexane / Et₂O = 1:1) afforded the biphenyl 68g (511 mg, 87 %) as a yellow solid.

M.p. (°C): 141-142.

\( ^1 \)H-NMR (300 MHz, CDCl₃): \( \delta / ppm = 7.78-7.74 \) (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, CDCl₃): \( \delta / ppm = 166.5, 154.1, 152.0, 143.1, 141.4, 134.8, 129.6, 127.2, 123.9, 121.2, 120.6, 51.6, 42.3, 41.9, 28.9, 14.3, 13.4. \)
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-(1H-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-1H-indole (70c; 314 mg, 1.60 mmol) in dry THF (2 mL). The mixture was stirred for 12 h at 50 ºC. Then, sat. aq. NH$_4$Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, i$\times$hexane / Et$_2$O = 5:2) afforded the indol 68h (316 mg, 64 %) as a orange solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / 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$_3$): $\delta$ / 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$^+$).
**EXPERIMENTAL SECTION**

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$_4$Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, i/hexane / Et$_2$O = 3:4) afforded the cross-coupling product 71a (279 mg, 82 %) as a yellow solid.


$^1$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), 7.65-7.61 (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): ν / 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)-1H-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-1H-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$_4$Cl (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.
EXPERIMENTAL SECTION


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / 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$_3$): $\delta$ / 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$_4$Cl (10 mL) was added and the aqueous layer was extracted with AcOEt ($3 \times 20$ mL). Purification by flash chromatography (silica gel, ihexane / Et$_2$O = 2:1) afforded the benzonitrile 71c (230 mg, 68 %) as a brown solid.

$^1$H-NMR (300 MHz, DMSO-d$_6$): $\delta$ / 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-d$_6$): $\delta$ / 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$^+$).
EXPERIMENTAL SECTION

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$_4$Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, ihexane / Et$_2$O = 3:1) afforded the benzamide 71d (356 mg, 76 %) as a yellow solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / 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$_3$): $\delta$ / 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$_4$Cl (10 mL) was added and the aqueous layer was extracted.
with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, i-hexane / Et₂O = 6:1) afforded the indole 71e (234 mg, 63 %) as a brown oil.

**1H-NMR (300 MHz, CDCl₃):** 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).

**13C-NMR (75 MHz, CDCl₃):** 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):** ν / 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 (C₁₆H₁₁NO):** calc.: 233.0841; found: 233.0837 (M⁺).

**Ethyl 3-(4-cyanobenzyl)benzoate (74)**

![Chemical Structure](image)

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. NH₄Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, i-hexane / Et₂O = 3:1) afforded the diphenylmethane 74 (316 mg, 74 %) as a colourless oil.

**1H-NMR (300 MHz, CDCl₃):** 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).

**13C-NMR (75 MHz, CDCl₃):** 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):** ν / 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).
EXPERIMENTAL SECTION

**MS (EI, 70 eV):** m/z (%) = 265 (M⁺, 45), 237 (38), 220 (100), 190 (48), 177 (27), 165 (27), 151 (15), 130 (13).

**HRMS (C₁₉H₁₉NO₂):** calc.: 265.1103; found: 265.1095 (M⁺).