
von

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**Erklärung**


**Ehrenwörtliche Versicherung**

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15) Sebastian Bernhardt, Albrecht Metzger, Paul Knochel, “Direct Addition of Functionalized Organozinc Reagents to Carbon Dioxide, Ketones and Aldehydes in the Presence of MgCl₂”, manuscript in preparation.


To Teresa, my love!
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<td>Ac</td>
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A. INTRODUCTION
A. Introduction

1. Overview

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

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

2. Preparation of Functionalized Organozinc Reagents

2.1. Introduction

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


\(^12\) H. E. Simmons, T. L. Cairns, A. Vladiuchick, C. M. Hoiness, Org. React. 1972, 20, 1.

\(^13\) I. Antes, G. Frenking, Organometallics 1995, 14, 4263.

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

\[ \text{R-Zn-X} + \text{L}_n-M-Y \rightarrow \left[ \text{X-Zn} \right] + \text{Y-Zn-X} + \text{L}_n-M-R \]

\( M = \text{Pd, Cu, Ni, Pt, Ti, …} \)

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

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

\[ \text{R}_2\text{ZnX} < \text{R}_2\text{Zn} < \text{R}_2\text{ZnMgX} < \text{R}_2\text{ZnLi} \]

alkynyl < alkyl < alkenyl-aryl < benzyl < allyl

**Scheme 2:** Reactivity series of organozinc reagents.

2.2. Direct zinc insertion into organic halides using zinc metal

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

\[
\text{FG-R-X} \xrightarrow{\text{Zn dust, THF}} \text{FG-R-ZnX}
\]

\(\text{FG} = \text{CO}_2\text{R}, \text{CN, halide, enolate, NH}_2, \text{RNH}, \text{(TMS)}_2\text{N}, \text{RCONH}, \) 
\(\text{(RCO)}_2\text{N}, \text{(RO)}_3\text{Si}, \text{(RO)}_2\text{PO}, \text{RS}, \text{RSO}, \text{RSO}_2\text{, PhCOS}\)

\(\text{R} = \text{aryl, alkyl, allyl, benzyl}\)

\(\text{X} = \text{I, Br, Cl}\)

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

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

---

(Zn*),\textsuperscript{21} which can, for example, insert into 3-iodoisouquinoline (2) providing the corresponding zinc reagent 3 (Scheme 4).\textsuperscript{22}

![Scheme 4](image)

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

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

![Scheme 5](image)

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

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

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

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

2.3. The iodine-zinc exchange reaction

Diorganozinc reagents are more reactive than organozinc halides. Besides the typical preparation of diorganozincs by transmetalation of organolithium or -magnesium reagents using one half-equivalent of zinc salt, a practical way for their preparation is the iodine-zinc exchange reaction using diethylzinc leading to functionalized zinc reagents of the type (FG-RCH)₂Zn (13; Scheme 7). One major advantage, compared to the transmetalations described above, is the functional group tolerance. Catalytic amounts of copper(I)-salts are necessary to achieve good exchange reactions.

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

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

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

The reaction is performed in a Et₂O:NMP mixture at 25 °C. The use of Li(acac) is crucial to promote the transfer of the second alkyl group R and the proposed intermediated 15 is shown as an “ate-complex” which can be seen in analogy to the known boranate-complex in the Suzuki cross-coupling reaction. Several sensitive functional groups can be tolerated during this exchange as exemplarily shown in Scheme 9.

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

2.4. Preparation of highly functionalized arylzinc reagents by directed metalations

Recently, the preparation of the mild and chemoselective base TMP₂Zn·2MgCl₂·2LiCl was reported. Using this base, an efficient and convenient access to functionalized diarylzinc reagents is possible. The Lewis acid LiCl is responsible for the excellent solubility of both the

---

base and the formed diarylzincs. Moreover, MgCl₂ leads to the high reactivity of the base in analogy to the presented iodine-zinc exchange presented above. Thus, the reaction of the nitro-substituted benzofuran 17 with TMP₂Zn·2MgCl₂·2LiCl provided the desired heterodiarylzinc compound 18 which led to the deuterated product 19 in 82% yield (Scheme 10).

Scheme 10: Preparation of diarylzinc reagent 18 by using TMP₂Zn·2MgCl₂·2LiCl.

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

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

However, using TMP₂Zn·2MgCl₂·2LiCl, only unsatisfactory results in terms of reaction selectivity and yield are obtained with some electron-poor heteroaromatics. Therefore, a more selective base (TMPZnCl·LiCl) was developed which showed, in contrast to the previously demonstrated base a very good chemoselectivity towards functionalized heterocycles even at

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

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

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

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

\[
\text{R}^1\text{MgX} + \text{R}^2\text{O}\text{R}^3 \xrightarrow{\text{conditions}} \text{R}^1\text{OMgX} + \text{R}^2\text{R}^3 + \text{HOMgX} \quad \text{Scheme 13: Possible products of the reaction of a Grignard reagent with enolizable ketones.}
\]

The formation of byproducts 26 and 27 can be considerably reduced by using a Lewis acid activation of the ketone. Lanthane halides, such as CeCl₃, introduced by Imamoto have proven to be especially effective. In the presence of CeCl₃, the 1,2-addition reaction of a Grignard reagent to a ketone is favored and the formation of byproducts of type 26 and 27 is

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A. Introduction

... reduced. A recent example using CeCl₃ for the addition of a Grignard reagent to a ketone is demonstrated in the reaction sequence in Scheme 14 to provided an precursor for the total synthesis of (±)-actinophilic acid.

Scheme 14: Application of CeCl₃ in natural product synthesis.

Two explanations are commonly used to describe the influence of CeCl₃ in these addition reactions. On the one hand lanthanide salts activate in a Lewis-acid fashion the ketone due to the oxophilic behavior of these salts. On the other hand, a transmetalation of the Grignard reagent to the lanthanide salt is possible. The resulting organolanthanides are less basic and therefore a deprotonation of alpha-acidic ketones should not occur. Recently, the preparation of THF-soluble LaCl₃·2LiCl complex has been reported. It was found that this complex is highly efficient in improving the addition of Grignard reagents to ketones and imines (Scheme 15).

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

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Furthermore, the direct alkylation of benzophenone (30) with Grignard reagents in the presence of a catalytic amount of ZnCl₂ (10 mol%) was very recently reported (equation 1, Scheme 16).\(^{40}\) Moreover, isopropylation of acetophenone (31) proceeds along the same way (equation 2). Interestingly, by using a catalytic amount of ZnCl₂ the addition of alkylmagnesium reagents to ketones 30 and 31 led to the tertiary alcohols 32-33 without significant formation of reduction products 34 and 35.

**Scheme 16:** Addition of alkylmagnesium reagents to ketones in the presence of ZnCl₂ (cat.).

These results were explained by assuming that the addition of an organomagnesium reagent to a carbonyl derivative in the presence of catalytic amounts of ZnCl₂ proceeds via a catalytic cycle including a six-membered transition state (Scheme 17). First, a active Zn(II)-ate complex is formed by the reaction of the Grignard reagent with ZnCl₂ followed by the addition to the ketone. Therefore, the [MgCl]⁺-moiety coordinates to the carbonyl group followed by the attack of [R₂Zn-R]⁻ and finally release of the adduct and regeneration of the active zinc intermediate.

Scheme 17: Proposed catalytic cycle for the addition of organomagnesium reagents to ketones in the presence of catalytic amounts of ZnCl₂.

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

Scheme 18: Addition of Et₂Zn to benzaldehyde 36 in the presence of the chiral ligand 37.

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

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

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

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

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A. Introduction

Bourguignon, Rossom, W. Maes, L. Kishore, M. Ovaere, L. van Meer

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

Furthermore, organostannanes\(^\text{47}\) as well as organoindium reagents\(^\text{48}\) were also used as nucleophilic partners for the direct synthesis of ketones starting from the corresponding thioesters.

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


\(^{50}\) M. Egi, L. S. Liebeskind, Org. Lett. 2003, 5, 801.
Scheme 21: Pd-catalyzed cross-couplings of organoboronic acids and organostannanes with thioether-substituted heterocycles.

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

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

Beside the known Ni-catalyzed cross-couplings of vinyl sulfides with organomagnesium reagents,\textsuperscript{44b,d} cross-coupling reactions of alkenyl sulfides with Grignard reagents in the presence
of an iron catalyst were recently reported leading to functionalized styrenes (Scheme 23).\textsuperscript{51}

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

5. Objectives

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

![Scheme 24](image)

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

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

![Scheme 25](image)

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

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

Scheme 26: Preparation of heterobenzylic zinc chlorides.

Moreover, the preparation of benzylic zinc chlorides was extended to the direct insertion of magnesium into benzylic chlorides in the presence of ZnCl₂ and LiCl and subsequent reaction with different electrophiles (Scheme 27).

Scheme 27: Preparation of benzylic zinc chlorides by direct insertion of magnesium in the presence of ZnCl₂ and LiCl into benzylic chlorides.

Lanthanide halides are often used to support an efficient addition of Grignard reagents to enolizable ketones. However, CeCl₃ and LaCl₃·2LiCl have been used so far only in a stoichiometric fashion. Therefore, in a second project, the addition of functionalized magnesium reagents to carbonyl derivatives in the presence of catalytic amounts of LaCl₃·2LiCl was investigated (Scheme 28).

Scheme 28: Addition of Grignard reagents to ketones in the presence of LaCl₃·2LiCl (cat.).

Since functionalized organozinc reagents are only rarely used towards the addition to carbonyl derivatives, the direct addition of highly functionalized organozinc compounds to aldehydes, ketones and carbon dioxide mediated by stoichiometric amounts of MgCl₂ was developed (Scheme 29).
A. Introduction

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

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

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

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

Scheme 31: Pd- or Ni-catalyzed cross-coupling reactions of heterocyclic thioethers with functionalized organozinc compounds.
B. RESULTS AND DISCUSSION
1. Preparation and Applications of Benzylic Zinc Chlorides

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

1.1.1. Introduction

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

![Scheme 32: Presence of benzylic moieties in natural products and pharmaceuticals.](image)

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

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

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

preparation for benzylic magnesium reagents was demonstrated using a sulfur-magnesium exchange (Scheme 33).^{62}

![Scheme 33](image)

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

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

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

![Scheme 34](image)

**Scheme 34:** Preparation of benzylic zinc bromides.

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64 1,2-Dibromoethane and TMSCl are used for the zinc activation; see also (ref 18).
To perform the zinc insertion into benzylic mesylates or phosphates in the presence of a lithium halide (LiBr or LiI), elevated temperatures and the use of polar cosolvents are required (Scheme 35). \(^{65,66}\)

\[
\text{FG} \xrightarrow{\text{Zn (1.2 equiv), LiI (0.2 equiv)}} \xrightarrow{\text{1,2-dibromoethane (5 mol%), TMSCl (1 mol%), DMPU, 35 °C to 60 °C, 12 h - 24 h}} \text{ZnX}
\]

\(X = \text{OMs, OP(O)(OEt)}_2\)

\(\text{FG} = \text{Br, OMe, OAc}\)

**Scheme 35:** Preparation of benzylic zinc mesylates and -phosphates. \(^{64}\)

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

The above mentioned drawbacks hamper a more general application of zinc organometallics. \(^{67}\) Recently, it has been reported that LiCl considerably facilitates the rate of zinc insertion. \(^{23,68}\)

Therefore, this new method was applied to the preparation of benzylic zinc reagents using cheap benzylic chlorides, commercially available zinc dust and LiCl. \(^{69}\) The activation of zinc dust was generally performed using 1,2-dibromoethane (5 mol%) and TMSCl (1 mol%). \(^{64}\) As a comparative example the insertion of zinc dust into benzyl chloride (53a) was examined in the absence (Scheme 36) and in the presence of LiCl (Scheme 37).
B. Results and Discussion

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

The preparation of benzylzinc chloride (54a) by the direct insertion of zinc dust into benzyl chloride (53a) in the absence of LiCl must be performed at an elevated temperature (40 °C) and full conversion is achieved only after 16 h. In contrast, the zinc insertion into benzyl chloride (53a) in the presence of LiCl proceeded easily within 6.5 h at 40 °C or at 25 °C within 18 h without the formation of significant amounts of homo-coupling products (< 5%; Scheme 37). The use of stoichiometric amounts of LiCl is essential for a fast zinc insertion.

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

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

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

70 For an investigation of the formation of organozincate anions using ESI-spectroscopy, see: K. Koszinowski, P. Böhler, Organometallics 2009, 28, 771.
Thus, the addition of 2-chlorobenzyl chloride (53b, 1.0 equiv) to zinc dust (1.5 equiv) and LiCl (1.5 equiv) at 0 °C followed by 2 h of stirring at 25 °C provided almost quantitatively 2-chlorobenzylzinc chloride 54b (in 99% yield as determined by iodometric titration, entry 1 Table 1).\textsuperscript{71} 4-Fluorobenzyl chloride 53c was smoothly converted to the corresponding benzylic zinc chloride 54c within 24 h at 25 °C in 87% yield (entry 2). Furthermore, treatment of 2-bromobenzyl chloride 53d with commercially available zinc dust in the presence of LiCl at ambient temperature led to the related benzylic zinc reagent 54d in 92% yield (entry 3). Related bromo-, iodo- and (trifluoromethyl)-substituted benzylic chlorides 53e-g reacted smoothly under these conditions leading to the benzylic zinc reagents 54e-g in 94-99% yield (entries 4-6).

<table>
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<tr>
<th>Entry</th>
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<th>Time (h)\textsuperscript{a}</th>
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<th>Yield (%)\textsuperscript{b}</th>
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<td>9</td>
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\textsuperscript{a} Reaction time at 25 °C. \textsuperscript{b} Yield determined by iodometric titration. \textsuperscript{c} Zn (1.5 equiv), LiCl (1.5 equiv) were used. \textsuperscript{d} Zn (2.0 equiv), LiCl (2.0 equiv) were used.

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

\textsuperscript{71} A. Krasovskiy, P. Knochel, Synthesis 2006, 5, 890.
conditions, these side reactions are normally disfavored. Thus, 3,4,5-trimethoxybenzyl chloride (53h) was easily converted within 3.5 h at 25 °C (zinc dust 2.0 equiv, LiCl 2.0 equiv) to the corresponding benzylic zinc compound 54h in 78% yield (entry 1 of Table 2). Similarly, the reaction of 4-methoxybenzyl chloride (53i) and 2-methoxybenzyl chlorides (53j) furnished readily the related benzylic zinc chlorides 54i-j in 73% respectively 92% yield (entries 2-3). Also, the electron-rich benzylic chlorides 53k-l led smoothly to the related zinc compound 54k and 54l within 1-2 h (Zn 1.5 equiv, LiCl 1.5 equiv) in 77-93% yield (entries 4-5).

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

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

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

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B. Results and Discussion

Table 3 continued

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</table>

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

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

![Scheme 40: Preparation of 3-acetylbenzylzinc chloride (54t).](image)

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

![Stability of 3-acetylbenzylzinc chloride (54t).](image)

**Scheme 41:** Stability of 3-acetylbenzylzinc chloride (54t).
Moreover, secondary benzylic zinc chlorides can also be prepared (Scheme 42). Thus, addition of 1-chloroethylbenzene to zinc dust (1.5 equiv) and LiCl (1.5 equiv) at 25 °C gave the desired zinc compound 54u in 85% yield. Benzhydryl chloride furnished the expected secondary benzylic zinc chloride 54v in 64% yield under the standard reaction conditions. In contrast, cumyl chloride (a tertiary benzylic chloride) did not afford the corresponding zinc species due to competitive elimination.

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

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

1.1.3. Reaction of functionalized benzylic zinc chlorides with various electrophiles

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

![Scheme 43: Reactions of various benzylic zinc chlorides of type 54 with a variety of electrophiles leading to polyfunctional products of type 56.](image)

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzyl zinc chloride</th>
<th>Electrophile</th>
<th>Temperature (°C) / Time (h)</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54b</td>
<td>55a</td>
<td>25 / 1.5</td>
<td>56a</td>
<td>94\textsuperscript{b}</td>
</tr>
<tr>
<td>2</td>
<td>54b</td>
<td>57a</td>
<td>25 / 1</td>
<td>56b</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>54b</td>
<td>58a</td>
<td>-40 to 25 / 15</td>
<td>56c</td>
<td>93\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td>54b</td>
<td>59a</td>
<td>0 / 3</td>
<td>56d</td>
<td>89\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{73} K. Fujiki, N. Tanifuji, Y. Sasaki, T. Yokoyama, *Synthesis* 2002, 343.
B. Results and Discussion

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>54b</td>
<td>56d</td>
<td>60 / 5</td>
<td>97⁴</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>54b</td>
<td>56e</td>
<td>-40 to 25 / 13.5</td>
<td></td>
<td>89⁵</td>
</tr>
<tr>
<td>7</td>
<td>54b</td>
<td>56f</td>
<td>0 / 3</td>
<td></td>
<td>87⁵</td>
</tr>
<tr>
<td>8</td>
<td>54c</td>
<td>56g</td>
<td>-60 to 0 / 2</td>
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</tr>
<tr>
<td>9</td>
<td>54c</td>
<td>56h</td>
<td>-40 to 25 / 15</td>
<td></td>
<td>95⁵</td>
</tr>
<tr>
<td>10</td>
<td>54d</td>
<td>56i</td>
<td>-60 to 0 / 15</td>
<td></td>
<td>96⁵</td>
</tr>
<tr>
<td>11</td>
<td>54e</td>
<td>56j</td>
<td>25 / 17</td>
<td></td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>54e</td>
<td>56k</td>
<td>-40 to 0 / 18</td>
<td></td>
<td>92⁵</td>
</tr>
<tr>
<td>13</td>
<td>54e</td>
<td>56l</td>
<td>-60 to -20 / 15</td>
<td></td>
<td>96⁵</td>
</tr>
<tr>
<td>14</td>
<td>54e</td>
<td>56m</td>
<td>-40 to 25 / 16</td>
<td></td>
<td>91⁴⁻⁵</td>
</tr>
<tr>
<td>15</td>
<td>54f</td>
<td>56n</td>
<td>25 / 5</td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>16</td>
<td>54f</td>
<td>56o</td>
<td>-40 to 25 / 15</td>
<td></td>
<td>72⁵</td>
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Table 4 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>Reaction Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td><img src="image1" alt="Structure" /></td>
<td>-60 to 0 / 1</td>
<td>86b</td>
</tr>
<tr>
<td>18</td>
<td><img src="image2" alt="Structure" /></td>
<td>25 / 6</td>
<td>86</td>
</tr>
</tbody>
</table>

[a] Yield of isolated analytically pure product. [b] Reaction performed in the presence of catalytic amounts of CuCN-2LiCl. [c] Stoichiometric amounts of CuCN-2LiCl and, in the case of 1,4-additions, TMSCl were used. [d] Pd(PPh₃)₄ (2 mol%) was used. [e] Reaction performed on a 20 mmol scale. [f] Reaction performed on a 5 mmol scale.

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

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

Reactions of electron-rich benzylic zinc reagents

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

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

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

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

Benzylzinc reagents 54m-n bearing an ester function in meta- or para-position reacted smoothly with various electrophiles. Thus, the reaction with 4-bromobenzaldehyde (61e; 0.8 equiv) furnished the benzylic alcohol 56x in 91% yield (entry 1 of Table 6). Also, a copper(I)-mediated 1,4-addition of 3-(ethoxycarbonyl)benzylzinc chloride (54m) to cyclohex-2-eneone (58a; 0.8 equiv) with CuCN·2 LiCl (1.0 equiv) and TMSCl (2.0 equiv) led to the Michael adduct 56y in 97% yield (entry 2). Furthermore, reaction of 54m with thiophene-3-carbaldehyde (61f) and S-methyl methanesulfonothioate (57b) provided the functionalized products 56z-aa in 88% yield (entries 3-4). A Cu(I)-mediated acylation reaction of 54n with the acid chloride 60d led...
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to the desired ketone 56ab in 43% yield (entry 5). The use of the benzylic zinc reagent 54o, which bears a cyano group on the aromatic ring, towards a Pd-catalyzed cross-coupling reaction with 3-iodoanisole (4b; 0.8 equiv) provided the diarylmethane 56ac in 88% yield (entry 6). This benzylic zinc reagent was used to prepare various ketones in 78-97% yield (56ad-ae; entries 7 and 8). Smooth reaction of the para-cyano-substituted benzylic zinc chloride 54p with ethyl (2-bromomethyl)acrylate (55b) and S-(4-fluorophenyl) benzenesulfonothioate (57c) furnished the acrylate 56af and the thioether 56ag (81-95%, entries 9-10).

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

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

| 9  | \[
| 54p | \[
| 55b | CO₂Et | -60 to 0 / 1 | 56af |
| 56af | \[
| 81\(^{c}\) | \[

| 10 | \[
| 54p | \[
| 57c | PhSO₂SOPh | 25 / 1.5 | 56ag |
| 56ag | \[
| 95 | \[

| 11 | \[
| 54q | \[
| 60f | OCl | -20 / 15 | 56ah |
| 56ah | \[
| 85\(^{b}\) | \[

| 12 | \[
| 54q | \[
| 61b | Cl₃C⁶H₃OH | 25/ 5.5 | 56ai |
| 56ai | \[
| 95 | \[

| 13 | \[
| 54r | \[
| 60g | \[
| 56aj | \[
| 51\(^{b}\) | \[

| 14 | \[
| 54s | \[
| 55b | CO₂Et | -60 to 0 / 1 | 56ak |
| 56ak | \[
| 92\(^{d}\) | \[

| 15 | \[
| 54s | \[
| 60b | OCl | -60 to -20 / 15 | 56al |
| 56al | \[
| 69\(^{b}\) | \[

| 16 | \[
| 54t | \[
| 60b | OCl | -60 to -20 / 15 | 56am |
| 56am | \[
| 74\(^{b}\) | \[

| 17 | \[
| 54t | \[
| 55b | CO₂Et | -60 to 0 / 1 | 56an |
| 56an | \[
| 97\(^{d}\) | \[

| 18 | \[
| 54t | \[
| 61b | Cl₃C⁶H₃OH | 25 / 3 | 56ao |
| 56ao | \[
| 82 | \[

[a] Yield of isolated analytically pure product. [b] Stoichiometric amounts of CuCN·2LiCl and, in the case of 1,4-additions, TMSCl were used. [c] Pd(PPh₃)₄ (2 mol%) was used. [d] Reaction performed in the presence of catalytic amounts of CuCN·2LiCl. [e] Reaction performed on a 8 mmol scale.
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Notably, the keto group on the benzylic zinc reagents is compatible with various reactions such as allylation, acylation and nucleophilic attack on an aldehyde. Thus, the products 56ah-ai were obtained in 51-95% yield after reactions with various electrophiles (entries 11-15). A Cu(I)-mediated reaction of the acetyl-substituted benzylic zinc reagent 54t with 3,3-dimethylbutyryl chloride (60b) as well as a Cu(I)-catalyzed allylation using ethyl (2-bromomethyl)acrylate (55b) furnished the highly functionalized products 56am-an in 74-97% yield (entries 16-17). Finally, the addition of 3-acetylbenzylzinc chloride (54t) to 3,4-dichlorobenzaldehyde (61b) in the absence of any catalyst provided the benzylic alcohol 56ao within 3 h at 25 °C (82%; entry 18).

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzylic zinc chloride</th>
<th>Electrophile</th>
<th>Temperature (°C) / Time (h)</th>
<th>Product</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54a</td>
<td>60f</td>
<td>-40 to 25 / 20</td>
<td>56ap</td>
<td>92bc</td>
</tr>
<tr>
<td>2</td>
<td>54a</td>
<td>55b</td>
<td>-60 to 0 / 1</td>
<td>56aq</td>
<td>93d</td>
</tr>
<tr>
<td>3</td>
<td>54u</td>
<td>60b</td>
<td>-60 to 25 / 15</td>
<td>56ar</td>
<td>96e</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>4</th>
<th>Ph (\text{ZnCl}_2)</th>
<th>(\text{CO}_2\text{Et} )</th>
<th>Cl</th>
<th>-60 to 0 / 1</th>
<th>(\text{Ph} \text{CO}_2\text{Et} )</th>
<th>96(^{\text{d}})</th>
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<tr>
<td>54v</td>
<td>55b</td>
<td>56as</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

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

Benzylic zinc reagents can also be used to prepare phenyl acetic acid derivatives which are useful intermediates and targets in pharmaceutical research.\(^{77}\) Two possible ways have been explored (Scheme 44). The first is a Pd-catalyzed acylation\(^{78}\) with ethyl chloroformate (60h) as an electrophile. Alternatively, a copper(I)-mediated acylation with ethyl cyanoformate (60i) as the electrophilic species was developed. Thus, Pd-catalyzed acylation of the benzylic zinc chloride 54b with ethyl chloroformate (60h) in the presence of Pd(PPh\(_3\))\(_4\) (5 mol\%) at 25 °C in 6.5 h led to the phenylacetic acid ethyl ester 62a in 81\% yield. To perform the copper(I)-mediated reaction, it was essential to prepare the mixed diorganozinc compound of the type ArCH\(_2\)ZnCH\(_2\)SiMe\(_3\)\(^{79}\) by adding TMSCH\(_2\)Li at -30 °C to 54b. After transmetalation to copper with CuCN·2LiCl and the addition of Mander’s reagent\(^{80}\) (ethyl cyanoformate; 60i), the expected ethyl phenylacetic ester 62a was obtained in 77\% yield.

![Scheme 44](image)

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

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

---


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| Table 8: Preparation of phenylacetic acid derivatives of type 62. |
|---|---|---|---|---|
| Entry | Benzyllic zinc chloride | Electrophile | Temperature (°C) / Time (h) | Product | Yield (%) \(^{a}\) |
| 1 | 54m | 60h | 25 / 6 | 62b | 76\(^{b,c}\) |
| 2 | 54f | 60i | 0 / 6 | 62c | 59\(^{d}\) |

[a] Yield of isolated analytically pure product. [b] \(\text{Pd(PPh)}_3\) (2.5 mol%) was used. [c] Reaction performed in a 10 mmol scale. [d] After transmetalation using LiCH\(_2\)TMS, stoichiometric amounts of CuCN-2LiCl were used; reaction scale: 5 mmol.

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

1.1.4. Synthesis of papaverine

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

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

---


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

Magnesiation of 67 with TMPMgCl-LiCl83 (TMP = 2,2,6,6-tetramethylpiperidyl) at 25 °C for 4 h, followed by iodolysis provided the iodo-substituted isoquinoline 68 in 73% yield. The preparation of the second intermediate for the papaverine synthesis started with the conversion of 3,4-dimethoxybenzyl alcohol (69) to the corresponding benzylic chloride 53w (Scheme 46). Thus, reaction of 69 with LiCl, NEt₃ and mesyl chloride furnished the chloride 53w in 69% yield within 15 h. Direct zinc insertion into 53w in the presence of LiCl within 4 h provided 3,4-dimethoxybenzylzinc chloride (54w) in 72% yield. In order to receive a good yield of 54w, it was crucial to use four equivalents of zinc and LiCl for the zinc insertion.

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

---

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

![Scheme 47: Synthesis of papaverine (63) by Pd-catalyzed cross-coupling reaction.](image)

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

1.2.1. Introduction

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

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


**Scheme 48:** Selected diarylmethane derivatives.

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

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

Since the first reported cross-coupling reaction of benzylic zinc bromides under Ni catalysis\(^ {92}\) only a few examples for diarylmethane synthesis have been reported using benzylic zinc halides under transition metal catalysis.\(^ {8c, 93}\)

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1.2.2. Ni-catalyzed cross-coupling reactions with benzylic zinc chlorides using Ni(acac)$_2$/PPh$_3$

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

![Scheme 50](image)

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

By screening of several catalytic systems, Ni(acac)$_2$ (0.5 mol%) combined with PPh$_3$ (2 mol%) in a THF:NMP = 4:1 mixture at 60 °C was found to be the most efficient system. Using this cheap and convenient catalytic system, it was possible to synthesize various functionalized diarylmethanes of type 72 (Table 9).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzylic zinc chloride</th>
<th>Electrophile</th>
<th>Time (h)$^a$</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54c</td>
<td>Cl$_2$N$_2$CO$_2$Et</td>
<td>3</td>
<td>72a</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>54m</td>
<td>Br$_2$N$_2$CO$_2$Et</td>
<td>4</td>
<td>72b</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>54o</td>
<td>Cl$_2$N$_2$CO$_2$Et</td>
<td>4</td>
<td>72c</td>
<td>43</td>
</tr>
</tbody>
</table>

$^a$ Time for completion of reaction.

$^b$ Isolated yield.

---


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

Table 9 continued

<table>
<thead>
<tr>
<th>4</th>
<th>54s</th>
<th>54t</th>
<th>54u</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>54c</td>
<td>54d</td>
<td>54e</td>
</tr>
</tbody>
</table>

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

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

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

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

---

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

\begin{align*}
\text{Scheme 51:} \quad & \text{Bioactive substances containing relatively acidic protons and the benzyl moiety.}
\end{align*}

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


\textsuperscript{100} Selected publication highlighting problems using organoboronic reagents: T. Watanabe, N. Miyaura, A. Suzuki, \textit{Synlett} \textbf{1992}, \textit{207}.

B. Results and Discussion

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

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzylic zinc chloride</th>
<th>Electrophile</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54c</td>
<td>77a</td>
<td>24</td>
<td>78a</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>54g</td>
<td>77a</td>
<td>8</td>
<td>78b</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>54i</td>
<td>77b</td>
<td>6.25</td>
<td>78c</td>
<td>77</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzylic zinc chloride</th>
<th>Electrophile</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO-PhCH2Cl2</td>
<td>Br-PhOH</td>
<td>1.5</td>
<td>77c</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>NC-PhCH2Cl2</td>
<td>Br-PhOH</td>
<td>1.5</td>
<td>77d</td>
<td>84</td>
</tr>
</tbody>
</table>

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

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

1.4.1. Introduction

Transition metal-catalyzed reactions are among the most important reactions for carbon-carbon bond formation.\(^{30}\) Especially, palladium-catalyzed reactions have found numerous applications.\(^{102}\) One of the main advantages for the Suzuki cross-coupling reaction is the use of air and moisture stable boronic acids and their derivatives. On the other hand, an important limitation of these boronic compounds is their preparation requiring the corresponding magnesium or lithium species which limits the presence of functional groups.\(^{103}\) Organozinc reagents display much higher reactivity in Pd-catalyzed cross-coupling reactions.\(^{104}\) Moreover, these reagents can be prepared in the presence of sensitive functional groups. A major drawback of these organometallics is the instability towards air and moisture.\(^{16}\)

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


\(^{105}\) The experiment was performed by Dr. Shohei Sase and Milica Jaric and is given here for the sake of completeness. For further information, see: diploma thesis M. Jaric, LMU Munich, 2007.

\(^{106}\) PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropylphenyl-imidazolium derivative.
carboxylate (79) was obtained in 83% isolated yield \textit{without prior removal of the excess of zinc powder.}

![Scheme 53: Preliminary experiments of one-pot Negishi cross-coupling reaction using the palladium catalyst PEPPSI-IPr.](image)

The palladium catalyst PEPPSI-IPr, introduced by Organ, displays a broader applicability compared to common catalysts like Pd(PPh₃)₄.\textsuperscript{107} This catalyst is easily synthesized and air-stable. Moreover, shorter reaction times and higher yields are generally observed.

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

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

B. Results and Discussion

Very low catalyst loadings are sufficient (0.25 mol%) to perform these cross-coupling reactions. Thus, 4-fluorobenzyl chloride (53c) was readily converted to the corresponding benzylic zinc intermediate 54c within 24 h at 25 °C. Subsequent cross-coupling reaction with methyl 2-bromobenzoate (71g; 0.5 equiv) furnished the desired diarylmethane 80a in 96% yield (entry 1 of Table 12). Similarly, reaction of 3,4,5-trimethoxybenzyl chloride (53h) with zinc dust (1.5 equiv) and LiCl provided the desired benzylic zinc reagent 54h within 4 h (entry 2). Pd-catalyzed cross-coupling with 4-bromobenzonitrile (71h) led to the expected product 80b in 99% yield. Moreover, 3-(ethoxycarbonyl)- as well as 3-cyano-substituted benzylic chlorides 53m-o were smoothly converted to the corresponding benzylic zinc chlorides 54m-o which led, after Pd-catalyzed cross-couplings with different aromatic bromides 71b and 71i, to the diarylmethanes 80c-d (entry 3 and 4). Several keto-functions present on benzylic chlorides can be tolerated by this protocol. Thus, direct zinc insertion into 3-pentanoylbenzyl chloride (53q) provided the desired benzylic zinc chloride intermediate 54q. After one-pot Pd-catalyzed cross-coupling with ethyl 3-bromobenzoate (71d), the disubstituted diarylmethane 80e was obtained within 2 h in 92% yield (entry 5). Similarly, 3-propionylbenzyl chloride (53s) led to 3′-propionylbiphenyl-4-carbonitrile (80f) in 79% yield (entry 6). In an analogous manner, 3-acetylbenzyl chloride (53t) was smoothly converted to the corresponding zinc intermediate 54t by direct zinc insertion within
4 h. Subsequent cross-couplings in a one-pot fashion with either 1-bromo-3-(trifluoromethyl)benzene (71j), ethyl 4-bromobenzoate (71e) or 1-bromo-3-methoxybenzene (71k) led to the desired diarylmethanes 80g–i in 60-94% yield (entries 7-9). Finally, the secondary benzylic chloride 53u was easily converted to the corresponding secondary benzylic zinc intermediate 54u which provided after Pd-catalyzed cross-coupling reaction with 4-bromobenzonitrile (71h) the expected 1,1-diarylethane derivative 80j in 94% yield (entry 10).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzylic chloride&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Electrophile</th>
<th>Time (h)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F–Cl, 53e (25 °C, 24 h)</td>
<td>Br·CO₂Me, 71g</td>
<td>24</td>
<td>80a</td>
<td>96&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>MeO–Cl, 53h (25 °C, 4 h)</td>
<td>Br·CN, 71h</td>
<td>15</td>
<td>80b</td>
<td>99&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>EtO₂C–Cl, 53m (25 °C, 4 h)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Br·CF₃, 71i</td>
<td>4</td>
<td>80c</td>
<td>94&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>NC–Cl, 53o (25 °C, 3.5 h)</td>
<td>Br·CF₃, 71b</td>
<td>15.5</td>
<td>80d</td>
<td>85&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Bu–CO₂Et, 53q (25 °C, 4 h)</td>
<td>Br·CO₂Et, 71d</td>
<td>2</td>
<td>80e</td>
<td>92&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Et–CN, 53s (25 °C, 4 h)</td>
<td>Br·CN, 71h</td>
<td>2</td>
<td>80f</td>
<td>79&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>MeO–CF₃, 53t (25 °C, 4 h)</td>
<td>Br·CF₃, 71j</td>
<td>5</td>
<td>80g</td>
<td>86&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>53t</td>
<td>Br·CO₂Et, 71e</td>
<td>2</td>
<td>80h</td>
<td>94&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
B. Results and Discussion

Table 12 continued

<table>
<thead>
<tr>
<th>9</th>
<th>53t</th>
<th>71k</th>
<th>5</th>
<th>80i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Cl</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
</tr>
</tbody>
</table>

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

1.5. Preparation of diheterobenzylc zinc reagents and heterobenzylc zinc chlorides

1.5.1. Introduction

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

![Scheme 55: Heterobenzylc groups present in various bioactive compounds.](image)

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

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

### 1.5.2. Preparation of heterobenzylic zinc reagents and further reactions

Heterobenzylic zinc reagents were prepared by two different methods. The first possibility for the preparation of these zinc reagents was the direct metalation using the mild base TMP$_2$Zn·2MgCl$_2$·2LiCl\textsuperscript{29}.\textsuperscript{111} Therefore, methyl-substituted heteroaromatics were smoothly deprotonated to furnish the heterobenzylic zinc reagent 84 (Scheme 56). However, to succeed in the formation of the heterobenzylic zinc reagent it is crucial that the methyl group is in activated position to the nitrogen atom (2- or 4-position of the pyridine ring).

![Scheme 56: General preparation of bis-heterobenzylic zinc reagents by direct metalation using TMP$_2$Zn·2MgCl$_2$·2LiCl.](image)

Thus, 2-chloro-4-methylpyridine (85) was easily metalated using TMP$_2$Zn·2MgCl$_2$·2LiCl (0.6 equiv) within 3 h at 0 °C (Scheme 57). Transmetalation of the bis-heterobenzylic zinc reagent 86 with CuCN·2LiCl and subsequent acylation using benzoyl chloride (60f) furnished the heterocyclic ketone 87 in 60%. Moreover, the zinc reagent 86 was smoothly alylated with ethyl (2-bromomethyl)acrylate (55b) under Cu(I)-catalysis to provide the desired product 88 in 98% yield.


B. Results and Discussion

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

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

However, the preparation of heterobenzylic zinc reagents by direct metalation reaction with TMP₂Zn·2MgCl₂·LiCl totally fails in the case of unactivated methyl group such as in the case of 3-picoline.¹¹² Therefore, a zinc insertion into heterobenzyl chlorides was developed. Thus, direct zinc insertion in the presence of LiCl into 2-chloro-5-(chloromethyl)pyridine (90a) led smoothly to the corresponding heterobenzylic zinc chloride 91a within 2.5 h in 78% yield (Scheme 58).

Scheme 58: Preparation of (6-chloropyridin-3-yl)methylzinc chloride (91a).¹¹⁸

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

The chloro-substituent in 2 position is absolutely crucial for the formation of the heterobenzylic zinc reagent 91a. Direct zinc insertion into (3-chloromethyl)pyridine led only to decomposition probably due to direct alkylation reactions of the starting material. Moreover, reaction of 4-(chloromethyl)-3,5-dimethylisoxazole (90b) with commercially available zinc dust in the presence of LiCl provided the expected heterobenzylic zinc reagent 91b within 4.5 h in 90% yield (Scheme 59).

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

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

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heterobenzylic zinc chloride</th>
<th>Electrophile</th>
<th>Temperature (°C) / Time (h)</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="ZnCl-LiCl" /> 91a</td>
<td><img src="image2" alt="PhCHO" /> 61g</td>
<td>0 to 25 / 17</td>
<td><img src="image3" alt="N-Ph" /> 92a</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1" alt="ZnCl-LiCl" /> 91a</td>
<td><img src="image4" alt="ClC-Ph" /> 60d</td>
<td>-40 to 25 / 20</td>
<td><img src="image3" alt="N-Ph" /> 92b</td>
<td>62^b</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1" alt="ZnCl-LiCl" /> 91b</td>
<td><img src="image4" alt="ClC-Ph" /> 60d</td>
<td>-40 to 25 / 27</td>
<td><img src="image3" alt="N-Ph" /> 92c</td>
<td>81^b</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1" alt="ZnCl-LiCl" /> 91c</td>
<td><img src="image5" alt="BrC-Ph-OEt" /> 71e</td>
<td>18 / 25</td>
<td><img src="image3" alt="N-Ph" /> 92d</td>
<td>65^c</td>
</tr>
</tbody>
</table>

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

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

![Scheme 61: Preparation of the benzylic alcohol 92e by the direct addition of (3,5-dimethylisoxazol-4-yl)methylzinc chloride (91b) to 3,4-dichlorobenzaldehyde (61b).](image6)

^113 For the preparation of (3-thienylmethyl)zinc chloride (91c) as well as additional reaction conditions, see. A. J. Wagner, Ph.D. thesis, LMU Munich.
B. Results and Discussion

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

![Figure 1: ORTEP representation of the alcohol 92e.](image)

1.6. Preparation of benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of ZnCl$_2$ and LiCl

1.6.1. Introduction

In 2008, a mild and easy preparation of arylmagnesium reagents by the direct insertion of magnesium in the presence of LiCl into halogen-substituted aromatics was reported.$^{117}$ This work extended considerably the previously documented preparation and applications of Grignard reagents.$^{118}$ However, there were also some limitations. Mainly, in the case of an ester group attached to an aromatic bromide, the method described above needed to be modified. Therefore, stoichiometric amounts of ZnCl$_2$ were added to transmetalate in situ the formed Grignard reagent to the corresponding organozinc halide. Thus, methyl 2-bromobenzoate (71g) reacted with magnesium powder in the presence of ZnCl$_2$ and LiCl to furnish the desired organozinc reagent 93a which was subsequently acylated with the acid chloride 60d providing the benzophenone 94 in 77% yield (Scheme 62).$^{119}$


1.6.2. Preparation of benzylic zinc chlorides by the Mg/ZnCl₂/LiCl method

This mild method was adapted for the preparation of benzylic organometallics. Thus, reaction of 2-chlorobenzyl chloride (53b) with magnesium turnings in the presence of LiCl led only to large amount of Wurtz-coupling product (Scheme 63). Only traces of the benzylic magnesium reagent were formed. In strong contrast, by performing the insertion reaction in the presence of stoichiometric amounts of ZnCl₂, 2-chlorobenzylzinc chloride-MgCl₂ (95b) is readily formed and the amount of homo-coupling product is below 5%. Moreover, it has to be pointed out that no activation of the magnesium is required.

\[
\text{Scheme 63: Influence of ZnCl}_2 \text{ for the preparation of benzylic zinc chlorides of type 95.}
\]

In contrast to the previously described insertion method into benzylic chlorides using zinc dust and LiCl (chapter 1, p. 23 ff.), the magnesium insertion in the presence of zinc chloride and lithium chloride allows shorter insertion times due to the use of a more strongly reducing metal and proceeds at a lower temperature. Thus, direct zinc insertion (Zn powder; 2.0 equiv) in the presence of LiCl (2.0 equiv) into 4-fluorobenzyl chloride (53c) furnished the corresponding benzylic zinc chloride 54c after a reaction time of 24 h at 25 °C. On the other hand, direct
magnesium insertion (Mg turnings; 2.5 equiv) into benzylic chloride $53c$ in the presence of ZnCl$_2$ (1.1 equiv) and LiCl (1.25 equiv) in THF resulted in complete conversion to the zinc reagent $95c$ within 45 min at 25 °C (Scheme 64).

![Scheme 64: Comparison of the preparation times for 4-fluorobenzylzinc chloride ($54c$ or $95c$) either by the Zn/LiCl method or by the Mg/ZnCl$_2$/LiCl method.](image)

Furthermore, by using 0.5 equivalents of ZnCl$_2$, this alternative method allows the preparation of bisbenzylic zinc reagents of the type (ArCH$_2$)$_2$Zn.

Ranges of functionalized benzylic zinc reagents of type $95$ have been successfully prepared by this new procedure described above, using commercially available benzylic chlorides of type $53$ and magnesium turnings in the presence of ZnCl$_2$ and LiCl. These reactions proceed via intermediate benzylic magnesium compounds $96$, which are in situ transmetalated to the corresponding benzylic zinc chlorides of type $95$. Subsequent reactions of the functionalized benzylic zinc reagents $95$ with various electrophiles (E$^+$) provided a range of benzylic derivatives of type $97$ (Scheme 65).

![Scheme 65: General procedure for the preparation of benzylic zinc chlorides by the Mg/ZnCl$_2$/LiCl method and subsequent reactions of these organometalics with common electrophiles.](image)
In a typical experiment, the reaction of 2-chlorobenzyl chloride (53b) with magnesium turnings (2.5 equiv), ZnCl₂ (1.1 equiv) and LiCl (1.25 equiv) easily occurred at 25 °C within 45 min providing the benzylic zinc reagent 95b. Its subsequent reaction with S-(4-fluorophenyl) benzenesulfonothioate (57c; 0.7 equiv) led to the asymmetrically substituted sulfide 97a within 17 h in 86% yield (Scheme 66).

Scheme 66: Insertion of magnesium into 2-chlorobenzyl chloride (53b) in the presence of ZnCl₂ and LiCl and subsequent reaction with benzenesulfonothioate 57c.

Similarly, allylation of the zinc reagent 95c with ethyl (2-bromomethyl)acrylate (55b) provided the unsaturated ester 97b in 77% yield (entry 1 of Table 14). As mentioned above, 4-fluorobenzyl chloride (53c) is readily converted to the corresponding benzylic zinc reagent 95c within 45 min. Addition of 95c to 4-bromobenzaldehyde (61e) gave the benzylic alcohol 97c in 51% yield (entry 2). 3-(Trifluoromethyl)benzyl chloride (53g) was converted to the benzylic zinc organometallic 95g within 30 min at 25 °C. Reaction with 2-chlorobenzaldehyde (61a) or S-(3-cyanobenzyl) benzenesulfonothioate (57d) gave the benzylic alcohol 97d and, respectively, the dibenzylic sulfide 97e in 85-86% yield (entries 3 and 4). Also, electron-rich benzylic chlorides are converted to the corresponding zinc reagents without the formation of homo-coupling products. Thus, 3,4,5-trimethoxybenzyl chloride 95h was obtained after reaction of 3,4,5-trimethoxybenzyl chloride (53h) with magnesium, ZnCl₂ and LiCl (25 °C, 1 h). Cu(I)-mediated treatment with 4-chlorobenzoyl chloride (60d) provided the ketone 97f in 56% yield (entry 5). Moreover, 4-methoxybenzyl chloride (53i) was readily converted to the expected benzylic zinc chloride 95i within 2 h and subsequent reaction with (S)-(4-bromophenyl) benzenesulfonothioate (57a) yielded the sulfide 97g in 88% (entry 6). Similarly, 2-methoxybenzyl chloride (53j) reacted under standard conditions to provide the corresponding benzylic zinc chloride 95j within 45 min. Its copper(I)-mediated acylation with cyclopropanecarbonyl chloride (60c) as well as reaction with 3-chlorobenzaldehyde (61e) furnished the desired products 97h-i in 89-92% yield (entries 7
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and 8). Furthermore, the direct magnesium insertion in the presence of ZnCl₂ and LiCl into (4-methylthio)benzyl chloride (53l) led to the thioether-substituted benzyl zinc chloride 95l within 1.5 h reaction time at 25 °C. Subsequent addition to 4-bromobenzaldehyde (61e) or Cu(I)-mediated addition to 3-iodocyclohex-2-enone (58b) provided the alcohol 97j as well as the substituted cyclohex-2-enone 97k in 62-82% yield (entries 9 and 10).

Table 14: Preparation of benzylic zinc chlorides 95 by the Mg/ZnCl₂/LiCl method and their subsequent reaction with various electrophiles (part 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzyl chloride&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Electrophile</th>
<th>Conditions&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53b (0.75 h)</td>
<td>CO₂Et</td>
<td>25 / 0.75</td>
<td>97b</td>
<td>77&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>53c (0.75 h)</td>
<td>Br</td>
<td>25 / 2</td>
<td>97c</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>53g (0.5 h)</td>
<td>61a</td>
<td>25 / 1</td>
<td>97d</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>53g (0.5 h)</td>
<td>61a</td>
<td>25 / 2</td>
<td>97e</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>53h (1.0 h)</td>
<td>60d</td>
<td>-20 to 25 / 2</td>
<td>97f</td>
<td>56&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>53i (2.0 h)</td>
<td>57a</td>
<td>25 / 17</td>
<td>97g</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>53j (1.0 h)</td>
<td>60c</td>
<td>-20 to 25 / 6.5</td>
<td>97h</td>
<td>89&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Sensitive functional groups are also tolerated by this method. Thus, the reaction of 3-(ethoxycarbonyl)benzyl chloride (53m) with Mg/ZnCl₂/LiCl at 25 °C for 2 h provided the corresponding zinc reagent 95m. Its copper(I)-mediated reaction with 4-chlorobenzoyl chloride (60d), as a representative acid chloride, led to the benzylic ketone 97i in 82% yield (Scheme 67).

Scheme 67: Insertion of magnesium into 3-(ethoxycarbonyl)benzyl chloride (53m) in the presence of ZnCl₂ and LiCl and subsequent Cu(I)-mediated acylation reaction.

Moreover, Pd-catalyzed cross-coupling reaction of 95m with 4-iodoanisole (4c) using PEPPSI-IPr (0.25 mol%) as catalyst led to the expected product 97m in 78% yield (entry 1 of Table 15). Additionally, the zinc reagent 95m smoothly reacted with S-(4-chlorophenyl) benzenesulfonylthioate (57e) to furnish the sulfide 97n within 2 h in 67% yield (entry 2). Analogously, a cyano function is tolerated as well. Thus, 3-cyanobenzyl chloride (53o) was cleanly converted to the corresponding zinc reagent 95o within 2 h at 25 °C and a copper(I)-catalyzed allylation of the latter with ethyl (2-bromomethyl)acrylate (55b) provided the desired
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acrylate 97o (79%; entry 3). Similarly, reaction with 3,4-dichlorobenzaldehyde (61b) and Cu(I)-mediated 1,4-addition to 3-iodocyclohex-2-enone (58b) led to the expected products 97p and 97q in 77-83% yield (entries 4 and 5). Furthermore, reaction of benzyl chloride (53a) under standard conditions led to benzylzinc chloride (95a) at 25 °C in 2 h. Then, reaction with S-(4-methoxyphenyl) benzenesulfonothioate (57f) provided the sulfide 97r in 78% yield (entry 6). Analogous to the reaction times for the direct LiCl-mediated zinc insertion into secondary benzylic chlorides 53u-v, the direct magnesium insertion in the presence of ZnCl₂ and LiCl into secondary benzylic chlorides 53u-v proceeded also faster than the magnesium insertion into benzyl chloride (53a; see also Scheme 42). Thus, 1-(chloroethyl)benzene (53u) or 1,1-diphenylchloromethane (53v) are smoothly converted to the corresponding secondary benzylic zinc reagents 95u-v within 30 min to 1 h. Subsequent reaction with 4-bromobenzaldehyde (61e) or Cu(I)-mediated acylation with acetyl chloride (60a) yielded the adducts 97s and 97t in 68-70% yield (entries 7 and 8).

Table 15: Preparation of benzylic zinc chlorides 95 by the Mg/ZnCl₂/LiCl method and their subsequent reaction with various electrophiles (part 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzylic zinc chloride*</th>
<th>Electrophile</th>
<th>Conditionsb</th>
<th>Product</th>
<th>Yield (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53m (2.0 h)</td>
<td>4c</td>
<td>25 / 21</td>
<td>97m</td>
<td>78d</td>
</tr>
<tr>
<td>2</td>
<td>53m (2.0 h)</td>
<td>57e</td>
<td>25 / 2</td>
<td>97n</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>53o (2.0 h)</td>
<td>55b</td>
<td>25 / 1</td>
<td>97o</td>
<td>79e</td>
</tr>
<tr>
<td>4</td>
<td>53o (2.0 h)</td>
<td>61b</td>
<td>25 / 2</td>
<td>97p</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>53o (2.0 h)</td>
<td>58b</td>
<td>-60 to 0 / 18</td>
<td>97q</td>
<td>77f</td>
</tr>
</tbody>
</table>
This *in situ* method (Mg, ZnCl₂, LiCl) also has the advantage of producing more reactive benzylic zinc reagents due to the *in situ* generation of MgCl₂, which accelerates the addition to carbonyl derivatives. Thus, for benzylic zinc chloride (95a) generated by using Mg/ZnCl₂/LiCl method, the reaction with electron-rich 4-(dimethylamino)benzaldehyde (61h) led to the desired benzylic alcohol 97u in 98% isolated yield after a reaction time of only 1 h at 25 °C (Scheme 68).

In contrast, by generating 54a via the Zn/LiCl-method, the addition to benzaldehyde 61h did not provide the expected product 97u in any appreciable amount. Only 20% conversion of the aldehyde 61h was observed after a reaction time of 20 h at 25 °C.

**Scheme 68:** Different reactivity of benzylic zinc chloride (54a or 95a) depending on its preparation.
2. Lewis-Acid Promoted Additions of Functionalized Organomagnesium and Organozinc Reagents to Carbonyl Derivatives

2.1. Addition of Grignard reagents to ketones in the presence of catalytic amounts of LaCl\(_3\)-2LiCl

2.1.1. Introduction

As mentioned in the general introduction, CeCl\(_3\) is commonly used to activate carbonyl groups towards the attack of an organomagnesium reagent. However, the low solubility of CeCl\(_3\) in THF requires the use of stoichiometric amounts of this relatively expensive salt. The general problem of insolubility of the lanthanide salt is elegantly solved by using the THF-soluble complex LaCl\(_3\)-2LiCl. Recently, this method was applied to the synthesis of tryptamines and related heterocycles.\(^{120,121}\) However, LaCl\(_3\)-2LiCl has been used so far only in stoichiometric amounts, while a catalytic version of this reaction would be highly appreciable considering industrial applications of this methodology.\(^{122}\)

2.1.2. LaCl\(_3\)-2LiCl-catalyzed addition of organomagnesium reagents to enolizable ketones

A comparative study of the use of LaCl\(_3\)-2LiCl in stoichiometric and catalytic amounts for 1,2-addition reactions of various Grignard reagents to ketones was investigated (Scheme 2).

![Scheme 69: Addition of Grignard reagents (28a-j) to ketones (58c-j) in the presence of variable amount of LaCl\(_3\)-2LiCl.](image)

Therefore, organomagnesium reagents of type 28 were added to ketones of type 58 premixed with either 100 mol% or 30 mol% of LaCl\(_3\)-2LiCl or in the absence of the lanthanum salt. Lowering the amount of LaCl\(_3\)-2LiCl below 30 mol% often resulted in heterogeneous reaction mixtures. Thus, the reaction of cyclohexylmagnesium bromide (28b) with the easily enolizable


\(^{122}\) The addition of Grignard reagents to imines requires only 10 mol% of LaCl\(_3\)-2LiCl. An isolated example of the addition of PhMgBr to camphor using 10 mol% of LaCl\(_3\)-2LiCl has also been reported (ref. 39).
ketone 58c in the presence of one equivalent of LaCl$_3$·2LiCl provided the tertiary alcohol 98a in 93% yield (entry 1 of Table 16). By using 30 mol% of LaCl$_3$·2LiCl a similar yield (87%) was achieved. Without the addition of LaCl$_3$·2LiCl only 33% of the alcohol 98a was isolated.

**Table 16:** Addition of Grignard reagents to different ketones in the presence of LaCl$_3$·2LiCl.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Grignard reagent</th>
<th>Ketone</th>
<th>Product</th>
<th>Yield (%)$^a$ in the presence of variable amounts of LaCl$_3$·2LiCl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mol%</td>
</tr>
<tr>
<td>1</td>
<td>MgBr·LiCl 28b$^d$</td>
<td>58c</td>
<td>98a</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>$t$-BuMgCl 28c$^d$</td>
<td>58d</td>
<td>98b</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>MeMgCl 28d$^d$</td>
<td>58e</td>
<td>98c</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>MgCl 28e$^d$</td>
<td>58d</td>
<td>98d</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>MgHCl 28f$^d$</td>
<td>58f</td>
<td>98e$^j$</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>MgCl$_3$·2LiCl 28g$^d$</td>
<td>30</td>
<td>98f</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>MgCl$_3$·2LiCl 28h$^d$</td>
<td>58g</td>
<td>98g</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>MgCl$_3$·2LiCl 28h$^d$</td>
<td>58h</td>
<td>98h</td>
<td>76</td>
</tr>
</tbody>
</table>
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Table 16 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>Product</th>
<th>Yield 1</th>
<th>Yield 2</th>
<th>Yield 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Product" /></td>
<td>73</td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Product" /></td>
<td>71</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>11</td>
<td><img src="image5" alt="Structure" /></td>
<td><img src="image6" alt="Product" /></td>
<td>59</td>
<td>65</td>
<td>75</td>
</tr>
</tbody>
</table>

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

The reaction of the secondary alkylmagnesium reagent i-PrMgCl (28c) with 1,3-diphenylacetone (58d) is strongly influenced by the addition of LaCl₂-LiCl. Thus, the alcohol 98b was obtained in 86% with stoichiometric amount of LaCl₂-LiCl and in 65% yield in the presence of 30 mol% of LaCl₂-LiCl (entry 2). In the absence of LaCl₂-LiCl, only traces of the alcohol 98b were obtained due to the occurrence of competing reduction and enolization reactions. With MeMgCl (28d) which does not possess β-hydrogen atoms, similar yields were obtained regardless of the amount of the lanthanum salt added (entry 3). Reaction of phenylmagnesium chloride (28e) with the enolizable ketone 58d led to the desired alcohol 98d in 93-97% in the presence of either 30 or 100 mol% of LaCl₂-LiCl (entry 4). Without LaCl₂-LiCl, a yield of 67% was achieved. In the reaction of naphthylmagnesium chloride (28f) with the less sterically hindered cyclohexyl methyl ketone (58f), the influence of LaCl₂-LiCl is relatively strong (entry 5). The uncatalyzed reaction afforded the product 98e in 22% yield, in the presence of 30 mol% of LaCl₂-LiCl a yield of 66% was obtained. Using stoichiometric amounts of LaCl₂-LiCl led to the product 98e in 76% yield. In the absence of a catalyst, sterically hindered Grignard reagents do not react satisfactorily with ketones bearing acidic protons. Thus, reaction of 2-(trifluoromethyl)phenylmagnesium chloride (28g) and acetophenone (30) furnished the corresponding alcohol 98g in 72% yield only in the presence of LaCl₂-LiCl, independently on whether 100 or 30 mol% were used (entry 6). A poor yield of 98f (13%) was observed in the absence of LaCl₂-LiCl. Treatment of dicyclopentyl ketone (58g), cyclopropyl methyl ketone (58h) and cyclohexanone (58i) with various
organomagnesium reagents 28h-j led to the desired alcohols 98g-i in similar yields almost regardless of the LaCl$_3$·2LiCl amount (entries 7-9). However, the positive influence of LaCl$_3$·2LiCl was well demonstrated in the case of heteroaromatic organomagnesium compounds such as 2-pyridylmagnesium chloride (28a; entry 10). Its reaction with ketone 58c led to the desired alcohol 98j in 71% yield only in the presence of LaCl$_3$·2LiCl. Using electron-rich arylmagnesium reagent 28f and enolizable ketone 58j the alcohol 98k was obtained in lower yields with LaCl$_3$·2LiCl than without the use of LaCl$_3$·2LiCl (entry 11). These results show that for the addition of electron-rich organomagnesium species the influence of LaCl$_3$·2LiCl on the product yield can be negative.

An upscaling of the above described procedure gave satisfactory results (Scheme 70). The reaction of ketone 58d either with secondary alkylmagnesium reagent 28c in the presence of LaCl$_3$·2LiCl (100 mol%) or with arylmagnesium reagent 28e in the presence of LaCl$_3$·2LiCl (30 mol%) furnished the expected alcohols 98b and 98d in 83-88% yield.

**Scheme 70:** Upscaled reaction (20 mmol) of ketone 58d with either i-PrMgCl (28c) using 100 mol% of lanthanum salt or PhMgCl (28e) using 30 mol% of LaCl$_3$·2LiCl.
2.2. Addition of functionalized organozinc reagents to aldehydes, ketones and carbon dioxide under mediation of MgCl₂

2.2.1. Introduction

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

![Scheme 71: Presence of the alcohol function in various pharmaceuticals.](attachment:image.png)

Organozinc reagents are versatile tools in organic synthesis.¹⁷ Their intrinsic moderate reactivity towards electrophiles can be dramatically increased by transmetalations with catalytic amounts of various transition metal complexes.¹²⁵ However, for reactions with a ketone or an aldehyde such transmetalations are less appropriate. In these cases, a Lewis-acid complexation¹²⁶ of the carbonyl group is usually a more suitable activation.¹²⁷ As already mentioned in the general introduction, the addition of organozinc reagents to carbonyl derivatives has widely been investigated. However, one major drawback is the fact that diorganozinc reagents have to be used due to the higher reactivity compared to organozinc halides. Moreover, these organozinc reagents have to be used in large excess, usually one to four equivalents, to achieve completeness of the

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reactions. Furthermore, the functional group tolerance is low due to the problems in the preparation methods of these organozincs species. As presented in chapter 1.6. (p. 58 ff), benzylic zinc chlorides prepared by the direct insertion of magnesium into benzylic chlorides in the presence of zinc chloride and lithium chloride showed a significantly higher rate for the addition to carbonyl derivatives. This result is explained due to the presence of magnesium chloride which is generated in situ during the preparation of the zinc reagent (Scheme 68). Therefore, the addition of functionalized aryl-, alkyl- and benzylic zinc reagents, prepared by the Mg/ZnCl₂/LiCl method, to various carbonyl derivatives was investigated.¹²⁸

2.2.2. Addition of functionalized organozinc reagents to carbonyl derivatives

Thus, the addition of PhZnI (5b) prepared by the insertion of zinc dust in the presence of LiCl into iodobenzene,²¹ to 2-chlorobenzaldehyde (61a) required 72 h at 25 °C to reach completion and afforded (2-chlorophenyl)(phenyl)methanol (101) in 60% yield (Scheme 72). In contrast, by using PhZnI-MgCl₂ (93b) prepared by the reaction of iodobenzene with magnesium turnings, ZnCl₂ and LiCl,¹¹⁷ a complete conversion was obtained within 1 h at 25 °C. The desired alcohol 101 was obtained in 88% yield. The presence of MgCl₂ (1.0 equiv) is responsible for this dramatic rate acceleration.¹²⁹

![Scheme 72: Comparison of the reactivity of phenylzinc iodide (5b) and phenylzinc iodide-MgCl₂ (93b) towards the addition to 2-chlorobenzaldehyde (61a).](image)

¹²⁸ For a crystal structure of PhZnBr·MgCl₂ obtained after transmetalation of PhMgBr with ZnCl₂, see: L. Jin, C. Liu, J. Liu, F. Hu, Y. Lan, A. S. Batsanov, J. A. K. Howard, T. B. Marder, A. Lei, J. Am. Chem. Soc. **2009**, *131*, 16656.

Also, by external addition of MgCl$_2$ to phenylzinc iodide (5b) or 2-chlorobenzaldehyde (61a), the addition rate is improved. Thus, premixing of MgCl$_2$ with phenylzinc iodide (5b) followed by the addition to 2-chlorobenzaldehyde (61a) provided the alcohol 101 within 2 h in 79% yield (Table 17). Furthermore, addition reaction of zinc reagent 5b to a premixed solution of MgCl$_2$ with 2-chlorobenzaldehyde (61a) under similar reaction conditions led to the expected product within 2 h in 78% yield.

Table 17: Reaction of phenylzinc iodide (5b) with 2-chlorobenzaldehyde (61a) under mediation of additionally added MgCl$_2$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent</th>
<th>Additive</th>
<th>Time (h)$^a$</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhZnI-LiCl</td>
<td>MgCl$_2$</td>
<td>2</td>
<td>101</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>(premixed with 61a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>MgCl$_2$</td>
<td>2</td>
<td>101</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(premixed with aldehyde 61a)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

It is known that in the case of Grignard reagents the counterion plays an important role towards the addition reaction to carbonyl groups. Therefore, the reaction described above was investigated regarding the influence of the zinc counterion. Thus, addition of phenylzinc chloride·MgCl$_2$ (93c) to 2-chlorobenzaldehyde (61a) provided the alcohol 101 in 60 min in 86% yield (entry 1 of Table 18). Reaction of PhZnBr·MgCl$_2$ (93d) with aldehyde 61a led to full conversion in 30 min and provided the expected product in 93% yield (entry 2). As already demonstrated in Scheme 72, reaction of PhZnI·MgCl$_2$ (93b) with aldehyde 61a furnished the desired alcohol 101 in 60 min in 88% (entry 3).

---

130 MgCl$_2$ was freshly prepared as 0.5 M solution in THF by the reaction of magnesium turnings with 1,2-dichloroethane.

### Table 18: Addition of various phenylzinc halides complexed with MgCl₂ to 2-chlorobenzaldehyde (61a).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent</th>
<th>Time (min)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhZnCl·MgCl₂·LiCl 93c</td>
<td>60</td>
<td><img src="image" alt="Product 101" /></td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>PhZnBr·MgCl₂·LiCl 93d</td>
<td>30</td>
<td><img src="image" alt="Product 101" /></td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>PhZnI·MgCl₂·LiCl 93b</td>
<td>60</td>
<td><img src="image" alt="Product 101" /></td>
<td>88</td>
</tr>
</tbody>
</table>

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

Diorganozinc reagents are more reactive than organozinc halides and these reagents were found particularly well suited for addition reactions to ketones. The reaction of bis(4-methoxyphenyl)zinc (102) prepared from 4-bromoanisole (n-BuLi, -78 °C, 2 h; then ZnCl₂ (0.5 equiv)) to 4-isobutylacetophenone (58k) does not proceed (25 °C, 12 h). However, the corresponding diarylzinc reagent (103a) which was prepared by direct insertion of magnesium into 4-bromoanisole in the presence of LiCl and 0.5 equivalents of ZnCl₂ underwent a smooth addition to the ketone 58k within 2 h at 25 °C and provided the tertiary alcohol 104 in 78% yield (Scheme 73). It is noteworthy that both Ar-groups are transferred to the ketone in the addition reaction.

![Scheme 73: Addition of diarylzinc reagents 102 and 103a to ketone 58k in the presence or absence of MgCl₂.](image)

---

133 This experiment was performed by Sebastian Bernhardt and is given here for the sake of completeness.
134 For further informations, see: Ph.D. thesis S. Bernhardt, LMU Munich.
B. Results and Discussion

Functionalized benzylic zinc reagents show the same behavior and the addition of the ester-substituted benzylic zinc reagent 54m prepared by the insertion of zinc dust in the presence of LiCl into 3-(ethoxycarbonyl)benzyl chloride (53m) to the aldehyde 61h did not proceed at 25 °C (Scheme 74). Heating of the reaction mixture at 50 °C for 14 h only led to a conversion of 60%. In strong contrast, by using the same zinc reagent complexed with MgCl$_2$ (95m) and prepared by the reaction of 3-(ethoxycarbonyl)benzyl chloride (53m) with magnesium turnings in the presence of ZnCl$_2$ and LiCl, a full conversion was achieved within 6 h at 25 °C and the secondary alcohol 105 was isolated in 80% yield. Bisbenzylic zinc reagents of type 106 (ArCH$_2$)$_2$Zn-2MgCl$_2$ can also be prepared, as already discussed in chapter 1.6. and used for efficient addition reactions.

\[ \text{Scheme 74: Addition of benzylic zinc chlorides 54m and 95m to benzaldehyde 61h.} \]

Finally, the functionalized alkylzinc reagent 107a (no MgCl$_2$ present) and 108a (complexed with MgCl$_2$) showed a similar reactivity difference.\(^{135}\) Thus, the reaction of 107a with trifluoromethyl phenyl ketone (58l) required 48 h at 25 °C, whereas by using 108a, a complete conversion is reached within 6 h at 25 °C leading to the tertiary alcohol 109 in 76-77% yield (Scheme 75).

---

\(^{135}\) For the preparation of alkylzinc reagents by the direct insertion of magnesium into alkyl bromides in the presence of ZnCl$_2$ and LiCl, see: T. D. Blümke, F. M. Piller, P. Knochel, Chem. Commun. 2010, in press.
Scheme 75: Addition of cyano-substituted alkylzinc reagents 107a and 108a to ketone 58l.

These MgCl₂-mediated addition reactions have an excellent reaction scope (Table 19 and Table 20). Thus, tolylzinc iodide-MgCl₂ (93e) added at 25 °C to 4-cyanobenzaldehyde (61i) within 13 h affording the alcohol 110a in 73% yield (entry 1 of Table 19). Electron-rich heteroarylzinc reagent 93f added to benzaldehyde 61i furnishing the heterobenzyl secondary alcohol 110b in 98% yield (entry 2). Interestingly, a copper-free acylation reaction is possible. Thus, the electron-rich arylzinc reagent 4-(trimethylsilyl)phenylzinc bromide-MgCl₂ (93g) reacted with 4-chlorobenzoyl chloride (60d) leading to the benzophenone derivative 110c in 81% yield (entry 3). As indicated above (Scheme 73), it is advantageous to use bisarylzinc derivative of type 103 (Ar₂Zn-2MgX₂-2LiCl; 0.6 equiv; X = Cl, Br). In these cases, both aryl-groups are transferred in the carbonyl addition reaction. Thus, the reaction of bis(2-trifluoromethylphenyl)zinc-2MgX₂ (103b; X = Cl, Br) proceeded smoothly with the heterocyclic aldehyde 61j and furnished the pyridyl alcohol 110d in 82 % yield (entry 4). Furthermore, the addition of the electron-poor zinc reagent 103c to the aldehyde 61k led to the desired alcohol 110e in 85% yield (entry 5). The addition of bis(4-methoxyphenyl)zinc-2MgX₂ (103a; X = Cl, Br) to 4-cyanoacetophenone (58m) provided the tertiary alcohol 110f within 1 h in 62% yield (entry 6). The electron-rich arylzinc reagent bis(4-trimethylsilylphenyl)zinc-2MgX₂ (103d; X = Cl, Br) reacted with 4-cyanobenzaldehyde (61i) and the benzhydryl alcohol 110g was obtained in almost quantitative yield (entry 7). Furthermore, bis(4-N,N-dimethylaninophenyl)zinc-2MgX₂ (103e; X = Cl, Br) reacted with dicyclopentyl ketone (58g) in 24 h leading to the desired product 110h (74%; entry 8). Also, bis(2-N,N-dimethylaninophenyl)zinc-2MgX₂ (103f; X = Cl, Br) reacted smoothly with the benzaldehyde 61i providing the alcohol 110i within 3 h reaction time in 93% yield (entry 9). The bis(5-pyrazolyl)zinc species 103g as well as the bis(1,2-oxazol-4-
B. Results and Discussion

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Carbonyl derivative</th>
<th>Time (h)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93e</td>
<td>61i</td>
<td>13</td>
<td>110a</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>93f</td>
<td>61i</td>
<td>10</td>
<td>110b</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>93g</td>
<td>60d</td>
<td>18</td>
<td>110c</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>103b&lt;sup&gt;c&lt;/sup&gt;</td>
<td>61j</td>
<td>8</td>
<td>110d</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>103c&lt;sup&gt;d&lt;/sup&gt;</td>
<td>61k</td>
<td>10</td>
<td>110e</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>103a&lt;sup&gt;d&lt;/sup&gt;</td>
<td>58m</td>
<td>1</td>
<td>110f</td>
<td>62</td>
</tr>
</tbody>
</table>

<sup>a</sup>FG = Me, CF<sub>3</sub>, Cl, OMe, TMS, NMe<sub>2</sub>.

<sup>b</sup>R<sup>1</sup> = aryl, alkyl.

<sup>c</sup>FG = Br, i.

<sup>d</sup>FG = Cl, Br.
B. Results and Discussion

Table 19 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>TMS-103d</td>
<td>61i</td>
<td>110g</td>
</tr>
<tr>
<td>8</td>
<td>Me2N-103e</td>
<td>58g</td>
<td>110h</td>
</tr>
<tr>
<td>9</td>
<td>NMe2-103f</td>
<td>61l</td>
<td>110i</td>
</tr>
<tr>
<td>10</td>
<td>Ph-103g</td>
<td>61m</td>
<td>110j</td>
</tr>
<tr>
<td>11</td>
<td>103g</td>
<td>61c</td>
<td>110k</td>
</tr>
<tr>
<td>12</td>
<td>103h</td>
<td>61b</td>
<td>110l</td>
</tr>
<tr>
<td>13</td>
<td>103h</td>
<td>61n</td>
<td>110m</td>
</tr>
</tbody>
</table>

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

Benzylic zinc reagents are similarly activated by the presence of MgCl₂. Thus, electron-poor 4-fluorobenzylzinc chloride·MgCl₂ (95c) added to α-tetralone (58e) and acetophenone 58m providing the products 111a-b in 74-80% yield (entries 1 and 2 of Table 20). Moreover, addition of zinc reagent 95c to benzophenone 58n provided the tertiary alcohol 111c in 78% yield (entry 3). 4-Methoxybenzylzinc chloride·MgCl₂ (95i) reacted well with 4-(dimethylamino)benzaldehyde (61h) and 4-acetylbenzonitrile (58m) furnishing the benzylic alcohols 111d-e in 74-99% yield (entries 4 and 5). The ester-substituted benzylic zinc reagent 95m smoothly added within 16 h to trifluoromethyl phenyl ketone (58l) leading to the alcohol
111f in 87% yield (entry 6). Instead of using benzylic zinc chlorides of type 95 (ArCH₂ZnCl·MgCl₂; 1.2 equiv) it is also possible to use bisbenzylic zinc compounds of type 106 ((ArCH₂)₂Zn·2MgCl₂; 0.6 equiv). Usually, both benzylic groups are transferred to the electrophile. Recently, it has been reported that both aryl N-(2-pyridylsulfonyl)aldimines and Cu(II)-catalysis are required for adding various zinc reagents. However, the presence of MgCl₂ allows a direct addition of organozincs to N-tosylimines. Thus, the reaction of bis(3-(ethoxycarbonyl)benzyl)zinc·2MgCl₂ (106a) with the N-tosylimine 61o affords the expected N-tosylamine derivative 111g in 86% yield within 24 h at 25 °C (entry 7). Furthermore, the benzylic zinc reagent 106a added to 4-fluorophenylmethyl ketone (58o; 50 °C, 24 h) leading to the tertiary alcohol 111h in 68% yield (entry 8). Electron-rich methoxy-substituted benzylic zinc reagent 106b reacted well with dicyclopentyl ketone (58g) within 1 h at 25 °C and furnished the benzylic alcohol 111i within 1 h at 25 °C in 84% yield (entry 9).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Carbonyl derivative</th>
<th>Time (h)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95c</td>
<td>58e</td>
<td>9</td>
<td>111a</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>95c</td>
<td>58m</td>
<td>15</td>
<td>111b</td>
<td>80</td>
</tr>
</tbody>
</table>

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

Table 20 continued

<table>
<thead>
<tr>
<th>No.</th>
<th>95c</th>
<th>58n</th>
<th>48</th>
<th>78</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MeO</td>
<td>61h</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>95i</td>
<td>58m</td>
<td>14</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>EtO2C</td>
<td>58l</td>
<td>16</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>106a</td>
<td>61o</td>
<td>24</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>106a&lt;sup&gt;d&lt;/sup&gt;</td>
<td>58o</td>
<td>24&lt;sup&gt;c&lt;/sup&gt;</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>106b</td>
<td>58g</td>
<td>1</td>
<td>84</td>
</tr>
</tbody>
</table>

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

Remarkably, the presence of MgCl<sub>2</sub> allows the addition of aryl and benzylic zinc reagents to CO<sub>2</sub> (1 bar) at 25 °C in THF without the need of a polar solvent<sup>137</sup> or transition metal catalysis.<sup>138</sup> Thus, bis(4-methoxyphenyl)zinc·2MgX<sub>2</sub> (103a; X = Cl, Br) added in THF to CO<sub>2</sub> (1 bar, 25 °C,

---

3 h) providing 4-methoxybenzoic acid (112) in 94% yield (Scheme 76). Furthermore, reaction of bis(benzylzinc)-2MgCl (106c) with CO₂ led to phenylacetic acid (113) in 76% yield.

\[
\begin{align*}
\text{MeO} & \quad \text{Zn} \quad \text{2MgX} \quad \text{LiCl} \\
& \xrightarrow{\text{CO}_2 \ (1 \text{ bar})} \\
& \quad \text{25 °C, 3 h} \\
103a & \quad \text{112: 94%} \\
\text{MeO} & \quad \text{Zn} \quad \text{2MgCl}_2 \quad \text{ZnCl} \\
& \xrightarrow{\text{CO}_2 \ (1 \text{ bar})} \\
& \quad \text{25 °C, 2.5 h} \\
106c & \quad \text{113: 76%}
\end{align*}
\]

**Scheme 76:** Preparation of carboxylic acids 112 and 113 by the direct reaction of organozinc reagents 103 and 106 with carbon dioxide under mediation of MgCl₂.

The acceleration effect of MgCl₂ may be rationalized by the following explanations. The usual 6-membered transition state (A) is modified by the presence of MgCl₂ (Scheme 77). Thus, the organozinc regent R₃ZnCl which complexes the carbonyl group, is replaced by MgCl₂ (see the transition state B). Since MgCl₂ is a stronger Lewis-acid than the zinc compound R₃ZnCl, a more effective activation of the carbonyl group towards the addition of the zinc reagent is expected.

\[
\begin{align*}
\text{Cl} & \quad \text{Zn} \quad \text{Cl} \\
& \quad \text{Zn} \quad \text{Cl} \\
R_1 & \quad \text{R}_2 \\
R_3 & \quad \text{R}_4 \\
\text{O} & \quad \text{Cl} \\
& \quad \text{R}_5 \\
A & \quad \text{B}
\end{align*}
\]

**Scheme 77:** Proposed MgCl₂-modified six membered transition state for the addition of R₃ZnCl to carbonyl reagents (R₁R₂CO).

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

---

139 In a comparative experiment, performed by S. Bernhardt and given here for the sake of completeness, 4-MeO(C₆H₅)Br-MgCl₂-LiCl added to carbon dioxide within 6 h reaction time under similar reaction conditions to reach full conversion of the zinc reagent; see ref. 134.

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.\textsuperscript{141,142}

3. Carbocupration of Alkynes With Functionalized Diorganozinc Reagents

3.1. Introduction

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

![Scheme 78: Possible isomers obtained by carbometalation reactions of alkynes.](image)

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


**Scheme 79:** Arylzincation of alkynes by cobalt catalysis.

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

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

### 3.2. Carbocupration reaction on thioether-substituted alkynes

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

---

Scheme 81: Influence of MgCl$_2$ on the carbometalation of alkyne 118a with phenylzinc reagents.

Thus, the transmetalation of PhZnI (5b, 3.0 equiv) which was prepared by the direct insertion into phenyliodide in the presence of LiCl with CuCN·2LiCl (1.5 equiv) provided the corresponding arylcopper reagent which did not react with alkyne 118a (1.0 equiv). On the other hand, the related organocopper compound prepared by the reaction of CuCN·2LiCl (1.5 equiv) with Ph$_2$Zn·2MgCl$_2$·2LiCl (103i, 1.5 equiv; prepared by transmetalation using PhMgCl (3.0 equiv) and ZnCl$_2$·LiCl solution (1.5 equiv)) smoothly led to the vinylic copper intermediate 119a within 23 h at 25 °C.\textsuperscript{147} One can say that in the presence of stoichiometric amounts of MgCl$_2$ the carbometalation reaction occurs. Having this novel reaction in hand, several thioether-substituted alkynes were subjected to copper(I)-mediated carbometalation reaction with functionalized diorganozinc reagents.

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

<table>
<thead>
<tr>
<th>R$^1$-SR$_2$</th>
<th>ArZn (1.5 equiv)</th>
<th>CuCN·2LiCl (1.5 equiv)</th>
<th>Ar$_2$CuX</th>
<th>Ar$^+$ (3.3 equiv)</th>
<th>Ar$^+$E</th>
<th>120b-e</th>
<th>51-91%</th>
</tr>
</thead>
<tbody>
<tr>
<td>118b-e</td>
<td>THF, 25 °C, 6-24 h</td>
<td></td>
<td>119b-e</td>
<td>conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R$^1$, R$_2$ = Alkyl, Aryl

B. Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Alkyne&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Electrophile&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Product&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103a</td>
<td>118b (25 °C, 6 h)</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (-40 °C, 10 min)</td>
<td>120b (E/Z = 99:1)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>103a</td>
<td>118b (25 °C, 6 h)</td>
<td>allyl bromide (-60 to 0 °C, 1 h)</td>
<td>120c (E/Z = 99:1)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>103j</td>
<td>118c (25 °C, 24 h)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (-40 to 0 °C, 1 h)</td>
<td>120d (E/Z = 94:6)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>103k</td>
<td>118d (25 °C, 16 h)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (-60 to -20 °C, 2 h)</td>
<td>120e (E/Z = 68:32)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>103l</td>
<td>118e (25 °C, 15 h)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (-40 °C, 10 min)</td>
<td>120f (E/Z = 96:4)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>80~148</td>
</tr>
</tbody>
</table>

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

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

<sup>148</sup> The experiment was performed by Cora Dunst and is given here for the sake of completeness. For further informations, see: Ph.D. thesis Cora Dunst, LMU Munich.
intermediate 119b within 6 h at 25 °C. Its subsequent reaction with iodine led to the vinylic iodide 120b in 82% yield with an excellent E/Z-ratio determined by 2D-NMR (entry 1 of Table 21). Similarly, the copper species 119b was smoothly allylated using allyl bromide providing the alkene 120c in 91% yield (E/Z-ration = 99:1, entry 2). Furthermore, the alkyne 118c was prone to stereoselective Cu(I)-mediated carbometalation reaction using the ester-substituted arylzinc reagent 103j and provided the expected olefin 120d after allylation reaction with ethyl (2-bromomethyl)acrylate (55b) in 68% yield (entry 3). The fluoro-substituted acetylene 118d was used in the carbometalation reaction with bis(4-cyanophenyl)zinc·2MgX₂ (104k; X = Cl, Br) and the desired vinyl sulfide 120e was obtained in 51% yield with an E/Z-ratio of 68:32 (entry 4). Finally, the alkylacetylene 118e underwent smooth carbometalation with bis(phenyl)zinc·MgCl₂ (104k) and led to the vinylic iodide 120f in 80% yield (entry 5).
4. Transition Metal-Catalyzed Cross-Coupling Reactions of Functionalized Organozinc Reagents With Methylthio-Substituted N-Heterocycles

4.1. Introduction

Transformation of a carbon-sulfur bond into a carbon-carbon bond via transition metal catalysis is an efficient tool in organic synthesis, as shown in the introduction. Nevertheless, organozinc reagents are rarely used for such cross-couplings. One of the first documented examples for the Pd-catalyzed reaction of heterocyclic thioethers with organozinc reagents was the reaction of methylthio-substituted pyridine 121 with benzylzinc bromide in the presence of Pd(Ph3)4 at elevated temperatures leading to the heterodiaryl methane 122 (Scheme 82).149

\[
\text{Scheme 82: Palladium-catalyzed cross-coupling reaction of benzylzinc bromide with 2-(methylthio)pyridine (121) at elevated temperatures.}
\]

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

\[
\text{Scheme 83: Ni-catalyzed cross-coupling reaction for the functionalization of oxazole derivatives.}
\]

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

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

\[
\text{MeO} \quad \text{NaSMe (1,1 equiv)} \quad \text{DMF, 25 °C, 24 h} \quad \text{MeO} \quad \text{SMe} \\
\text{123} \quad \text{124a 69%}
\]

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

Also, by using the selective bases TMPMgCl·LiCl or TMP₂Mg·2LiCl several heterocycles can be easily metalated and reacted with various sulfonothioates in order to introduce the thioether moiety to the heterocyclic system.\(^{154}\) Thus, 2-bromopyridine (125) was reacted with TMPMgCl·LiCl and subsequent reaction with S-methyl methanesulfonothioate (57b) led to the desired methylthio-substituted pyrimidine 124b in 70% yield (Scheme 85).\(^{155}\)

---

\(^{151}\) For reactions of organomagnesium as well as organozinc reagents with tetramethylthiuram disulfide, see: (a) A. Krasovskiy, A. Gavryushin, P. Knochel, *Synlett* 2005, 2691; (b) A. Krasovskiy, A. Gavryushin, P. Knochel, *Synlett* 2006, 792.


B. Results and Discussion

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

Furthermore, the catalytic system for the Pd-catalyzed cross-coupling of organozinc reagents with heterocyclic thioethers was optimized to perform this reaction at ambient temperature. Thus, the reaction of benzylzinc chloride (54a) with 4-methyl-2-(thiomethyl)pyrimidine (124c) in the absence of any catalyst led to no conversion of the pyrimidine 124c (entry 1 of Table 22). Using PdCl₂(dppe) as well as Pd(dba)₂/tpf no conversion of the pyrimidine 124c was observed too (entries 2 and 3). By using PEPPSI-IPr, the cross-coupling took place and after 19 h only 27% starting material was left (entry 4). The best catalytic system for the cross-coupling of organozinc reagents with heterocyclic thioethers was found to be Pd(OAc)₂/S-Phos (entry 5). Additionally, it was observed that these cross-couplings can also be performed using a cheap nickel catalyst. Thus, reaction of pyrimidine 124c with benzylzinc chloride (54a) using NiCl₂(PPh)₂ led to full conversion of the heterocyclic species 124c within 12 h at 60 °C (entry 6).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (2 mol%)</th>
<th>Ligand (4 mol%)</th>
<th>Conversion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂</td>
<td>dppe</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)₂</td>
<td>tpf</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>PEPPSI-IPr</td>
<td>-</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>S-Phos</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>NiCl₂</td>
<td>PPh</td>
<td>95 (60 °C, 12 h)</td>
</tr>
</tbody>
</table>

[a] Conversions were determined by GC-analysis of a hydrolyzed reaction aliquot using tetradecane as internal standard.
Having a robust catalytic system in hand, several organozinc reagents were reacted with different methylthio-substituted heterocyclic compounds. These cross-couplings were mainly performed at 25 °C (Scheme 86).

![Scheme 86: Pd-catalyzed cross-coupling reactions of functionalized organozinc reagents with methylthio-substituted N-heterocycles.](image)

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl- and heteroaryl zinc reagent</th>
<th>Electrophile</th>
<th>Time (h)(^b)</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="5c" /></td>
<td>124d</td>
<td>1</td>
<td>126a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="5a" /></td>
<td>124e</td>
<td>6</td>
<td>126b</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="5c" /></td>
<td>124f</td>
<td>5</td>
<td>126c</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="5d" /></td>
<td>124g</td>
<td>21</td>
<td>126d</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="5e" /></td>
<td>124h</td>
<td>1.5(^c)</td>
<td>126e</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="5f" /></td>
<td>124i</td>
<td>18</td>
<td>126f</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="5f" /></td>
<td>124a</td>
<td>5(^c)</td>
<td>126g</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="5f" /></td>
<td>124j</td>
<td>10</td>
<td>126h</td>
<td>95</td>
</tr>
</tbody>
</table>

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

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

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzylic zinc chloride</th>
<th>Electrophile</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO-(\text{ZnCl}_2)</td>
<td>CO(_2\text{Et})</td>
<td>1.5</td>
<td>126i</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>EtO(_2\text{C-}\text{ZnCl}_2)</td>
<td>N-SMe(_2)</td>
<td>24</td>
<td>126j</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>CN-(\text{ZnCl}_2)</td>
<td>N-SMe(_2)</td>
<td>14(^c)</td>
<td>126k</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>EtO(_2\text{C-}\text{ZnCl}_2)</td>
<td>N-SMe(_2)</td>
<td>12(^c)</td>
<td>126l</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>MeO-(\text{ZnCl}_2)</td>
<td>S-SMe(_2)</td>
<td>16</td>
<td>126m</td>
<td>70</td>
</tr>
</tbody>
</table>

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

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

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

A selective bis-functionalization of pyrimidines in positions 2 and 4 can be achieved. Cross-coupling occurs first in position 2 or 4 depending on the substrate. Thus, the reaction of 2-bromo-4-(methylthio)pyrimidine (124b) with 4-methoxybenzylzinc chloride (107b) using Pd(dba)/ tfp and in situ Pd(OAc)/S-Phos leading to intermediate 127a (25 °C, 3 h; equation 1, Scheme 88).

Scheme 88: Selective one-pot cross-couplings of 2-bromo-4-(methylthio)pyrimidine (124b) or 4-iodo-2-(methylthio)pyrimidine (124m) using Pd(dba)/ tfp and in situ Pd(OAc)/S-Phos.
After a direct addition of a second catalyst system (Pd(OAc)$_2$/S-Phos) to the reaction mixture, a second cross-coupling occurred with 4-(ethoxycarbonyl)phenylzinc iodide (5a) providing the 2,4-disubstituted pyrimidine 126o in 68% overall yield. Alternatively, 4-iodo-2-(methylthio)pyrimidine (124m) was converted into the regioisomeric 2,4-disubstituted pyrimidine 126p by performing first a cross-coupling with 4-methoxybenzylzinc chloride (54i) using Pd(dba)$_2$/tfp (25 °C, 10 min; leading to 127b) followed by a second cross-coupling with the arylzinc reagent 5a in the presence of Pd(OAc)$_2$/S-Phos (25 °C, 20 h). The pyrimidine 126p was obtained in 80% overall yield in this one-pot double cross-coupling sequence (equation 2).

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

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

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

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

---

156 The screening of the nickel/ligand catalytic systems was performed by Laurin Melzig. For further information, see also: Ph.D. thesis Laurin Melzig, LMU Munich.

157 DPE = bis(2-diphenylphosphinophenyl)ether.
B. Results and Discussion

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

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

---

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc reagent</th>
<th>Electrophile</th>
<th>Time (h)( ^a )</th>
<th>Product</th>
<th>Yield (%( ^b ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO₂C₆H₄ZnLiCl</td>
<td>N₂CO₂Et</td>
<td>14</td>
<td>124e</td>
<td>128a</td>
</tr>
<tr>
<td>2</td>
<td>EtO₂C₆H₄ZnLiCl</td>
<td>N₂CN</td>
<td>18</td>
<td>124i</td>
<td>128b</td>
</tr>
<tr>
<td>3</td>
<td>EtO₂C₆H₄ZnLiCl</td>
<td>N₂SMe</td>
<td>12</td>
<td>124c</td>
<td>128c</td>
</tr>
<tr>
<td>4</td>
<td>NC₆H₅ZnLiCl</td>
<td>124c</td>
<td>18</td>
<td></td>
<td>128d</td>
</tr>
<tr>
<td>5</td>
<td>EtO₂C₆H₄ZnLiCl</td>
<td>N₂SMe</td>
<td>14</td>
<td>124n</td>
<td>128e</td>
</tr>
<tr>
<td>6</td>
<td>EtO₂C₆H₄ZnLiCl</td>
<td>N₂SMe</td>
<td>18</td>
<td>124j</td>
<td>128f</td>
</tr>
<tr>
<td>7</td>
<td>S₂H₅ZnLiCl</td>
<td>N₂SMe</td>
<td>16</td>
<td>124o</td>
<td>128g</td>
</tr>
<tr>
<td>8</td>
<td>S₂H₅ZnLiCl</td>
<td>N₂SMe</td>
<td>16</td>
<td>124g</td>
<td>128h</td>
</tr>
<tr>
<td>9</td>
<td>EtO₂C₆H₄ZnLiCl</td>
<td>N₂SMe</td>
<td>24</td>
<td>124d</td>
<td>128i</td>
</tr>
</tbody>
</table>
Finally, this Ni-catalyzed cross-coupling reaction was scaled up. Thus, reaction of 4-methoxybenzylzinc chloride (54i) with the 2-(methylthio)pyrazine 124n provided the heterocyclic diarylmethane 128l within 15 h at 25 °C in 84% yield.

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

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

5.1. Preparation and applications of benzylic zinc chlorides

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

**Scheme 92:** Preparation of functionalized benzylic zinc chlorides.
These novel benzylic zinc reagents were reacted with various electrophiles leading to polyfunctionalized products (Scheme 93). Moreover, it was possible to establish an easy access to phenylacetic acid derivative as well as the alkaloid papaverine (Scheme 93).

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

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

**Scheme 94:** Ni-catalyzed cross-couplings of benzylic zinc chlorides with aromatic halides.
B. Results and Discussion

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

![Scheme 95: Pd-catalyzed cross-couplings of benzylic zinc reagents with unsaturated bromides bearing acidic protons.](image_url)

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

![Scheme 96: Pd-catalyzed cross-couplings of in situ generated benzylic zinc chloride with aromatic bromides in the presence of residual zinc dust.](image_url)

Furthermore, heterobenzylic zinc reagents were prepared by metalation reactions of methyl-substituted heterocycles using TMP\(_2\)Zn·2MgCl\(_2\)·2LiCl (Scheme 97).
Scheme 97: Application of TMP₂Zn·2MgCl₂·2LiCl to prepare heterobenzylic zinc reagents.

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

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

Furthermore, benzylic zinc chlorides were smoothly prepared by the direct insertion of magnesium into benzylic chlorides in the presence of ZnCl₂ and LiCl. Their subsequent reactions with different electrophiles led to highly functionalized products (Scheme 99).
Scheme 99: Preparation of benzylic zinc chlorides by Mg insertion into benzylic chlorides in the presence of ZnCl₂/LiCl and subsequent reactions with various electrophiles.

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

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

It was demonstrated that by using the THF-soluble complex LaCl₃·2LiCl in a catalytic fashion organomagnesium reagents easily add to enolizable ketones to provide the expected alcohols in similar yields to when using LaCl₃·2LiCl in stoichiometric amounts (Scheme 100).
Scheme 100: Addition of Grignard reagents to enolizable ketones in the presence of catalytic amounts of LaCl$_3$·2LiCl.

Furthermore, it was demonstrated that functionalized organozinc reagents add to aldehydes, ketones and even carbon dioxide in the presence of stoichiometric amounts of MgCl$_2$ under mild conditions (Scheme 101).

Scheme 101: Addition of functionalized organozinc reagents to carbonyl derivatives in the presence of stoichiometric amounts of MgCl$_2$. 
B. Results and Discussion

The catalytic use of LaCl$_3$·2LiCl for the addition of a Grignard reagent to a ketone can be extended to a catalytic use of the lanthanum salt for reductions of 1,4-systems having a positive influence for industrial processes. Furthermore, the addition of zinc organometallics to carbonyl derivatives should be performed in the presence of various magnesium or aluminum salts to change the reaction scope. Also the addition of organozinc reagents to carbonyl derivatives in the presence of a chiral ligand should be investigated. Moreover, this method can find important applications in the pharmaceutical and agrochemical industry due to the high functional group tolerance of the utilized zinc reagents which is normally not given for the corresponding Grignard compounds.

5.3. Carbocupration of alkynes with functionalized diorganozinc reagents

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

![Scheme 102: Carbometalation reactions on thioether-substituted alkynes.](image)

As an extension of this method the use of benzylic zinc reagents as well as various alkynes bearing directing groups should be possible.
5.4. Transition metal-catalyzed cross-coupling reactions of functionalized organozinc reagents with methylthio-substituted N-heterocycles

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

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

Furthermore, selective one-pot cross-coupling procedures were developed.
Scheme 104: Selective Pd-catalyzed cross-coupling reactions of organozinc halides with pyrimidines bearing a halogen and a thioether substituent.

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

Scheme 105: Ni-catalyzed cross-couplings of organozinc reagents with heterocyclic thioethers.
These methods allow smooth cross-couplings of highly functionalized organozinc reagents with stable thioether-substituted N-heterocycles and they can find several applications in fields where the cross-couplings of halogen-substituted heterocycles are not possible due to the instability of the starting materials as well as the difficulties in their preparations.
C. EXPERIMENTAL SECTION
1. **General Considerations**

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

1.1. **Solvents**

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

- **CH$_2$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.
- **NMP** was heated to reflux for 14 h over CaH$_2$ and distilled from CaH$_2$.
- **Pyridine** was dried over KOH and distilled.
- **THF** was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.
- **Toluene** was predried over CaCl$_2$ and distilled from CaH$_2$.
- **Triethylamine** was dried over KOH and distilled.

Solvents for column chromatography were distilled prior to use.

1.2. **Reagents**

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

---


C. Experimental Section

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

\textit{i-PrMgCl-LiCl} solution in THF was purchased from Chemetall.

\textit{i-PrMgCl} solution in THF was purchased from Chemetall.

\textit{PhMgCl} solution in THF was purchased from Chemetall.

\textit{n-BuLi} solution in hexane was purchased from Chemetall.

\textit{TMPMgCl-LiCl} was prepared according to a literature procedure (ref. 83).

\textit{TMP\textsubscript{2}Zn\textsubscript{2}MgCl\textsubscript{2}·2LiCl} was prepared according to a literature procedure (ref. 29a).

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

\textit{ZnCl\textsubscript{2}} solution (1.00 M) was prepared by drying ZnCl\textsubscript{2} (100 mmol, 136 g) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL dry THF were added and stirring was continued until the salt was dissolved.

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

\textit{ZnCl\textsubscript{2}/LiCl} solution (1.1/1.5 M) was prepared by drying LiCl (15.9 g, 375 mmol) and ZnCl\textsubscript{2} (37.5 g, 275 mmol) under high vacuum (1 mbar) for 5 h at 140 °C. After cooling to 25 °C, dry THF (250 mL) was added and stirring was continued until the salts were dissolved.

1.3. Content determination of organometallic reagents

Organzinc and organomagnesium reagents were titrated against I\textsubscript{2} in a 0.5 M LiCl solution in THF.\textsuperscript{71}


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


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

TMPMgCl·LiCl and TMP₂Zn·2MgCl₂·2LiCl were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

1.4. Chromatography

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

Thin layer chromatography was performed using SiO₂ 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:

- KMnO₄ (3.0 g), 5 drops of conc. H₂SO₄ in water (300 mL).
- Phosphomolybdic acid (5.0 g), Ce(SO₄)₂ (2.0 g) and conc. H₂SO₄ (12 mL) in water (230 mL).

1.5. Analytical data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AIXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of CHCl₃ (δH: 7.25, δC: 77.0). For the characterization of 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 (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an electron energy of 70 eV.

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

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

Melting points (M.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.
2. Typical Procedures (TP)

2.1. Typical procedure for the preparation of benzylic zinc chlorides by LiCl-mediated direct zinc insertion into benzylic chlorides (TP1)

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

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

In a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, the aldehyde (1.0 equiv) was dissolved in THF at 0 °C and the benzylic zinc chloride (1.3 equiv) was added dropwise. The resulting solution was allowed to warm to 25 °C and was stirred for the required time. Then, sat. aq. NH\(_4\)Cl (20 mL) solution was added. The phases were separated and the aq. layer was extracted with Et\(_2\)O (3 x 20 mL). The combined organic extracts were dried over MgSO\(_4\). Evaporation of the solvents in vacuo and purification by flash column chromatography afforded the expected alcohols.

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

Into a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, CuCN-2LiCl solution (1.4 equiv) was added: Then, the desired benzylic zinc chloride (1.4 equiv) was added dropwise at -25 °C. The resulting reaction mixture was stirred for 15 min at this temperature. Then, the solution was cooled to the required temperature and the acid chloride (1.0 equiv) was added dropwise. The reaction mixture was stirred for the given time and allowed to warm to 25 °C. Then, a mixture of sat. aq. NH\(_4\)Cl / NH\(_3\)(25% in H\(_2\)O) = 2:1 was added, the
phases were separated and the aq. layer was extracted with Et$_2$O (3 x 100 mL). The combined organic extracts were dried over MgSO$_4$. Evaporation of the solvents \textit{in vacuo} and purification by flash column chromatography afforded the expected ketones.

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

Into a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, CuCN·2LiCl solution (1.25 equiv) was added. Then, the desired benzylic zinc chloride (1.25 equiv) was added dropwise at -25°C. The resulting reaction mixture was stirred for 15 min at this temperature. Then, the solution was cooled to the required temperature and a mixture of the unsaturated ketone (1.0 equiv), trimethylsilyl chloride (2.5 equiv) and THF was added dropwise. The reaction mixture was stirred for the given time and allowed to reach 25 °C. Then, a mixture of sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 2:1 was added. The phases were separated and the aq. layer was extracted with Et$_2$O (3 x 100 mL). The combined extracts were dried over MgSO$_4$. Evaporation of the solvents \textit{in vacuo} and purification by flash column chromatography afforded the expected ketones.

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

In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the aromatic bromide or chloride (2.00 mmol, 1.0 equiv) was dissolved in NMP (0.4 mL) and PPh$_3$ (0.1 mL, 0.04 mmol, 0.4 M in THF, 2 mol%) was added. Then, Ni(acac)$_2$ (0.1 mL, 0.01 mmol, 0.1 M in THF, 0.5 mol%) was added. After the addition of the corresponding benzylic zinc reagent (2.40 mmol, 1.2 equiv), the reaction mixture was warmed to 60 °C and stirred for the given time until GC-analysis showed full conversion of the electrophile. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution and extracted with Et$_2$O (3 times). The combined organic phases were dried over MgSO$_4$ and the solvent was removed \textit{in vacuo}. The product was purified by flash column chromatography.
2.6. Typical procedure for the Pd-catalyzed cross-coupling reaction with a bromo-aniline (TP6)

A dry and argon flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with the bromo-aniline (1.0 equiv), Pd(OAc)$_2$ (1 mol%), S-Phos (2 mol%) and THF. After stirring the reaction mixture for 5 min, the zinc reagent was added. The reaction mixture was stirred for the given time at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH$_4$Cl solution, extracted with Et$_2$O (3 times). The combined organic phases were washed with an aq. thiourea solution and dried over MgSO$_4$. Purification of the crude residue obtained after evaporation of the solvents by flash column chromatography yielded the desired product.

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

A dry and argon flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with the bromo-alcohol (1.0 equiv), Pd(OAc)$_2$ (1 mol%), S-Phos (2 mol%) and THF. After stirring the reaction mixture for 5 min, the zinc reagent was added slowly over 90 min using a syringe pump at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH$_4$Cl solution, extracted with Et$_2$O (3 times). The combined organic phases were washed with an aq. thiourea solution and dried (MgSO$_4$). Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the desired product.

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

A Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (1.5 equiv). The flask was heated with a heat gun (400 °C) for 10 min under high vacuum. After cooling to 25 °C, the flask was flushed with argon (3 times). Zinc dust (1.5 equiv) was added followed by THF. 1,2-Dibromoethane was added (5 mol%) and the reaction mixture was heated to ebullition for 15 s. After cooling to 25 °C, trimethylsilyl chloride (1 mol%) was added and the mixture was heated to ebullition for 15 s. The benzylic chloride (1.0 equiv) was added at the required temperature (usually 25 °C) as a solution in THF (usually 4 M). When capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of > 98%, the aromatic bromide was added, followed by PEPPSI-IPr. The reaction mixture was stirred at 25 °C until GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of > 98%. Then, sat. aq. NH$_4$Cl solution was added (20 mL). The phases were
separated and the aq. layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 20 mL). The combined extracts were dried over MgSO\textsubscript{4}. Evaporation of the solvents \textit{in vacuo} and purification by flash chromatography afforded the expected diarylmethanes.

2.9. Typical procedure for preparation of benzylic zinc chlorides by magnesium insertion in the presence of ZnCl\textsubscript{2} and LiCl (TP9)

A dry and argon-flushed \textit{Schlenk}-flask, equipped with a magnetic stirring bar and a septum, was charged with magnesium turnings (122 mg, 5.00 mmol). LiCl (5.00 mL, 2.50 mmol, 0.5 M in THF) and ZnCl\textsubscript{2} (2.20 mL, 2.20 mmol, 1.00 M in THF) were added. The benzylic chloride (2.00 mmol) was added in one portion at the given temperature. The reaction mixture was stirred for the given time and then canulated to a new \textit{Schlenk}-flask for the reaction with an electrophile.

2.10. Typical procedure for the addition of organomagnesium reagents to carbonyl derivatives in the presence of variable amounts of LaCl\textsubscript{3}·2LiCl (TP10)

A dry and argon-flushed \textit{Schlenk}-flask, equipped with a magnetic stirring bar and a septum, was charged with the carbonyl derivative (1 equiv) in LaCl\textsubscript{3}·2LiCl solution (1 equiv) and the reaction mixture was stirred for 1 h. Then, the organomagnesium reagent (1.1 equiv) was added dropwise at 0 °C. The reaction mixture was stirred for the given time at the required temperature until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the reaction mixture was cooled to 0 °C and quenched with sat. aq. NH\textsubscript{4}Cl solution and extracted with Et\textsubscript{2}O (3 times). The combined organic phases were dried over Na\textsubscript{2}SO\textsubscript{4}. Evaporation of the solvents \textit{in vacuo} and purification by flash column chromatography afforded the expected alcohols.

2.11. Typical procedure for the preparation of zinc reagents using Mg and ZnCl\textsubscript{2}/LiCl solution (TP11)

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

2.12. **Typical procedure for the addition of organozinc reagents of type RZnX·MgX₂·LiCl or diorganozinc reagents of type R₂Zn·2MgX₂·LiCl to carbonyl derivatives (TP12)**

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with the carbonyl derivative (1.5 mmol) in THF (1 mL). Then, the organozinc reagent RZnX-MgX₂-LiCl (1.8 mmol, 1.2 equiv; X = Cl, Br) or the diorganozinc reagent R₂Zn·2MgX₂-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 over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected products.

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

A Schlenk-flask, equipped with a magnetic stirring bar and a septum, was flame-dried under high vacuum. After cooling to 25 °C, the flask was filled with dry CO₂(g) and the organozinc reagent (typically 1.0 mmol for Ar₂Zn or (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.
2.14. Typical procedure for the Pd-catalyzed cross-coupling reaction of organozinc reagents with methylthio-substituted N-heterocycles (TP14)

In a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, the aromatic thioether (1.00 mmol), Pd(OAc)$_2$ (2.5 mol%) and S-Phos (5.0 mol%) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (1.5 mmol) was added dropwise and the reaction mixture was stirred for the given time at the required temperature until GC-analysis of a hydrolyzed aliquot showed full consumption of the electrophile. The reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$. Evaporation of the solvents \textit{in vacuo} and purification by flash column chromatography afforded the expected products.

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

In a dry argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, the aromatic thioether (1.00 mmol), Ni(acac)$_2$ (2.5 mol%) and DPE-Phos (5.0 mol%) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (1.5 mmol) was added dropwise and the reaction mixture was stirred for the given time at 25 °C until GC-analysis of a hydrolyzed aliquot showed full consumption of the electrophile. The reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$. Evaporation of the solvents \textit{in vacuo} and purification by flash column chromatography afforded the expected products.
3. Preparation and Applications of Benzylic Zinc Chlorides

3.1. Preparation of the starting materials

2-Bromobenzyl chloride (53d)

To a solution of LiCl (2.54 g, 60.0 mmol, dried for 10 min under high vacuum at 400 °C using a heat gun) in THF (50 mL) was added 2-bromobenzyl alcohol (3.74 g, 20.0 mmol) at 0 °C. Then, NEt$_3$ (5.56 mL, 40.0 mmol) was added dropwise, followed by mesyl chloride (2.32 mL, 30.0 mmol). The reaction mixture was allowed to reach 25 °C within 15 h. Then, CH$_2$Cl$_2$ (300 mL) was added and the solution was washed with water (3 x 250 mL). The combined extracts were dried over MgSO$_4$. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et$_2$O = 98:2) afforded the benzylic chloride 53d (3.67 g, 89%) as a colourless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.58 (dd, $J = 8.0$ Hz, 1.2 Hz, 1H), 7.48 (dd, $J = 7.4$ Hz, 1.6 Hz, 1H), 7.35-7.28 (m, 1H), 7.22-7.15 (m, 1H), 4.70 (s, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 136.6, 133.1, 130.8, 130.0, 127.8, 124.1, 46.1.

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

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

HRMS (C$_7$H$_6$BrCl): calc.: 203.9341; found: 203.9339.

4-(Ethoxycarbonyl)benzyl chloride (53n)

N,N-Dimethylpyridin-4-amine (305 mg, 2.50 mmol) was dissolved in ethanol (4 mL) and pyridine (7.5 mL) at 0 °C. 4-(Chloromethyl)benzoyl chloride (9.45 g, 50.0 mmol, in 2.5 mL Et$_2$O) was added dropwise. Then, the reaction mixture was warmed to 25 °C and added to a dilute HCl/Et$_2$O mixture = 1:1 (200 mL). The phases were separated and the organic layer was washed successively with H$_2$O (100 mL) and brine (100 mL), then dried over MgSO$_4$. Evaporation of the solvents in vacuo afforded the benzylic chloride 53n (9.51 g, 96%) as a pale yellow liquid which was used without further purification.
H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.06-7.98 (m, 2H), 7.47-7.41 (m, 2H), 4.59 (s, 2H), 4.37 (q, $J = 7.0$ Hz, 2H), 1.38 (q, $J = 7.2$ Hz, 3H).

C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 166.0, 142.1, 130.4, 129.9, 128.4, 61.1, 45.3, 14.3.

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

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

HRMS (C$_{10}$H$_{11}$ClO$_2$): calc.: 198.0448; found: 198.0446.

3-Cyanobenzyl chloride (53o)

LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min). 3-(Bromomethyl)benzonitrile (9.80 g, 50.0 mmol) was added followed by THF (100 mL) at 0 °C. The reaction mixture was refluxed for 5 h. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over MgSO$_4$ followed by the evaporation of the solvents in vacuo. Again, LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min) and the crude product was added followed by THF (100 mL) at 0 °C. The reaction mixture was refluxed for 5 h. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over MgSO$_4$ followed by the evaporation of the solvents in vacuo. Once again, LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min) and the crude product was added followed by THF (100 mL) at 0 °C. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over MgSO$_4$ followed by the evaporation of the solvents in vacuo. Purification by flash chromatography (short column, silica gel, pentane / Et$_2$O = 9:1) afforded the benzylic chloride 53o (7.47 g, 99%) as a white solid.

M.p. (°C): 73-75.

H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.70-7.65 (m, 1H), 7.65-7.57 (m, 2H), 7.52-7.43 (m, 1H), 4.58 (s, 2H).

C-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 138.8, 132.8, 131.9, 131.9, 129.6, 118.2, 112.9, 44.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3060 (w), 2227 (m), 1584 (w), 1484 (m), 1445 (m), 1275 (m), 1240 (m), 1153 (m), 930 (w), 894 (w), 804 (s), 718 (m), 701 (vs), 679 (vs).

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

HRMS (C$_8$H$_6$ClN): calc.: 151.0189; found: 151.0183.

4-Cyanobenzyl chloride (53p)

LiCl (1.40 g, 33.0 mmol) was dried (high vacuum, heat gun ca. 400 °C, 10 min). 4-(Bromomethyl)benzonitrile (2.16 g, 11.0 mmol) was added followed by THF (20 mL) at 25 °C. The reaction mixture was refluxed for 12 h. The resulting suspension was transferred into a separation funnel, washed with water (1 x 50 mL) and dried over MgSO$_4$ followed by filtration and evaporation of the solvents in vacuo. Again, LiCl (1.40 g, 33.0 mmol) was dried (high vacuum, heat gun ca. 400 °C, 10 min) and the crude product was added followed by THF (20 mL) at 0 °C. The reaction mixture was refluxed for 12 h. The resulting suspension was transferred into a separation funnel, washed with water (1 x 50 mL) and dried over MgSO$_4$ followed by the evaporation of the solvents in vacuo. Purification by flash chromatography (short column, silica gel, pentane / Et$_2$O = 5:1) afforded the benzylic chloride 53p (1.62 g, 97%) as a white solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.64 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 8.0$ Hz, 2H), 4.59 (s, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 142.4, 132.5, 129.2, 118.4, 112.2, 45.0.

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

MS (EI, 70 eV): m/z (%) = 151 (M$^+$, 61), 117 (17), 116 (83), 89 (45), 63 (11).

HRMS (C$_8$H$_6$ClN): calc.: 151.0189; found: 151.0183.
3-Pentanoylbenzyl chloride (53q)

Butylmagnesium chloride (12.2 mL, 18.0 mmol, 1.48 M in THF/toluene) was added to ZnCl₂ (18.8 mL, 18.8 mmol, 1.00 M in THF) at -25 °C. The mixture was stirred for 30 min. CuCN·2LiCl (19.5 mL, 19.5 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched with 60 mL of a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1. The phases were separated and the organic layer was extracted with 60 mL of a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1. The combined aqueous layers were extracted with Et₂O (3 x 250 mL). The combined organic extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 2:1) afforded the benzylic chloride 53q (2.89 g, 91%) as colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.97-7.95 (m, 1H), 7.90 (dt, J = 7.7 Hz, 1.3 Hz, 1H), 7.60-7.56 (m, 1H), 7.45 (t, J = 7.7 Hz, 1H), 4.62 (s, 2H), 2.96 (t, J = 7.1 Hz, 2H), 1.77-1.66 (m, 2H), 1.47-1.34 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 200.2, 138.3, 137.8, 133.1, 129.3, 128.3, 128.3, 45.9, 38.7, 26.6, 22.7, 14.2.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2957 (m), 2931 (w), 2871 (w), 1717 (w), 1682 (s), 1443 (w), 1260 (m), 1233 (w), 1199 (w), 1179 (m), 1162 (m), 1109 (w), 1036 (w), 790 (w), 760 (w), 704 (vs), 654 (m).

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


3-Isobutyrylbenzyl chloride (53r)

ZnCl₂ solution (18.8 mL, 18.8 mmol, 1.00 M in THF) was added to i-PrMgCl·LiCl (11.3 mL, 18.0 mmol, 1.59 M in THF) at -10 °C. The mixture was stirred for 30 min. CuCN·2LiCl (19.5 mL,
C. Experimental Section

19.5 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched with 100 mL of a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 2:1. The layers were separated and the organic layer was extracted with 100 mL of a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 2:1. The combined aqueous layers were extracted with Et₂O (3 x 250 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 4:1) afforded the ketone 53r (2.91 g, 98%) as colourless liquid.

1H-NMR (300 MHz, CDCl₃): δ ppm = 7.97-7.94 (m, 1H), 7.91-7.86 (m, 1H), 7.60 -7.55 (m, 1H), 7.46 (t, J = 7.6 Hz, 1H), 4.62 (s, 2H), 3.62-3.46 (m, 1H), 1.21 (d, J = 6.9 Hz, 6H).

13C-NMR (75 MHz, CDCl₃): δ ppm = 203.9, 138.1, 136.6, 132.8, 129.1, 128.3, 128.2, 45.6, 35.4, 19.1.

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

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

HRMS (C₁₁H₁₃ClO): calc.: 196.0655; found: 196.0656.

3-Propionylbenzyl chloride (53s)

Ethylmagnesium bromide (21.2 mL, 18.0 mmol, 0.85 M in t-BuOMe) was added to ZnCl₂ (18.8 mL, 18.8 mmol, 1.00 M in THF) at -25 °C. The mixture was stirred for 30 min. CuCN·2LiCl (19.5 mL, 19.5 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched with 60 mL of a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1. The phases were separated and the organic layer was extracted with 60 mL of a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1. The combined aqueous layers were extracted with Et₂O (3 x 250 mL). The combined organic extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash...
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chromatography (silica gel, pentane / Et₂O = 1:1) afforded the benzylic chloride 53s (2.89 g, 94%) as colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.98-7.95 (m, 1 H), 7.90 (dt, J = 7.7 Hz, 1.3 Hz, 1H), 7.60-7.56 (m, 1H), 7.45 (t, J = 7.5 Hz, 1H), 4.62 (s, 2H), 3.00 (t, J = 7.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 200.5, 138.3, 137.6, 133.1, 129.3, 128.2, 128.2, 45.9, 32.1, 8.4.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2978 (w), 1682 (s), 1604 (w), 1586 (w), 1444 (w), 1378 (w), 1350 (m), 1270 (w), 1242 (s), 1184 (m), 1164 (s), 974 (m), 786 (m), 704 (vs).

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

HRMS (C₁₀H₁₁ClO): calc.: 182.0498; found: 182.0472.

3-Acetylbenzyl chloride (54t)

Methylmagnesium chloride (7.03 mL, 18.0 mmol, 2.56 M in THF) was added to ZnCl₂ (18.8 mL, 18.8 mmol, 1.00 M in THF) at -10 °C. The mixture was stirred for 30 min. CuCN·2LiCl (19.5 mL, 19.5 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched with 60 mL of a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1. The phases were separated and the organic layer was extracted with 60 mL of a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1. The combined aqueous layers were extracted with Et₂O (3 x 250 mL). The combined organic extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 3:1) afforded the benzylic chloride 53t (2.46 g, 97%) as colourless liquid.

¹H-NMR (600 MHz, C₆D₆): δ / ppm = 7.74-7.71 (m, 1H), 7.58 (dt, J = 7.7 Hz, 1.4 Hz, 1H), 7.12-7.04 (m, 1H), 6.93 (t, J = 7.7 Hz, 1H), 4.02 (s, 2H), 2.06 (s, 3H).

¹³C-NMR (150 MHz, C₆D₆): δ / ppm = 196.0, 138.2, 137.9, 132.8, 128.9, 128.4, 128.2, 45.5, 26.1.
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IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 1680$ (vs), 1604 (m), 1586 (w), 1440 (m), 1428 (m), 1356 (s), 1280 (s), 1258 (s), 1192 (s), 1174 (m), 976 (w), 956 (w), 798 (m), 702 (vs), 688 (s).

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

HRMS ($C_{9}H_{9}ClO$): calc.: 168.0342; found: 168.0317.

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

Benzylic zinc chloride (54a)

According to TP1 benzyl chloride (53a) (2.53 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH$_2$CH$_2$Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 20 h at 25 °C. After centrifugation iodometric titration of 54a indicates a yield of 87%.

2-Chlorobenzylzinc chloride (54b)

According to TP1 2-chlorobenzyl chloride (53b; 3.22 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH$_2$CH$_2$Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 15 min at 0 °C followed by 1.75 h at 25 °C. After centrifugation iodometric titration of 54b indicates a yield of 99%.

4-Fluorobenzylzinc chloride (54c)

According to TP1 4-fluorobenzyl chloride (53c; 2.17 g, 15.0 mmol, in 4 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 3.5 mL THF (activation: BrCH$_2$CH$_2$Br (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 24 h at 25 °C. After centrifugation iodometric titration of 54c indicates a yield of 87%.
2-Bromobenzylzinc chloride (54d)

According to TP1 2-bromobenzyl chloride (53d; 3.39 g, 16.5 mmol, in 4 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.05 g, 24.8 mmol) and zinc dust (1.62 g, 24.8 mmol) in 4.3 mL THF (activation: BrCH₂CH₂Br (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 10 min at 0 °C followed by 110 min at 25 °C. After centrifugation iodometric titration of 54d indicates a yield of 92%.

3-Bromobenzylzinc chloride (54e)

According to TP1 3-bromobenzyl chloride (53e; 4.11 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 3.5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 4 h at 25 °C. After centrifugation iodometric titration of 54e indicates a yield of 95%.

2-Iodobenzylzinc chloride (54f)

According to TP1 2-iodobenzyl chloride (53f; 5.05 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 20 min at 0 °C followed by 100 min at 25 °C. After centrifugation iodometric titration of 54f indicates a yield of 99%.

3-(Trifluoromethyl)benzyll zinc chloride (54g)

According to TP1 3-(trifluoromethyl)benzyl chloride (53g; 2.92 g, 15.0 mmol, in 4 mL THF) was added dropwise at 25 °C to a suspension of LiCl (954 mg, 22.5 mmol) and zinc dust (1.47 g, 22.5 mmol) in 3.5 mL THF (activation: BrCH₂CH₂Br (0.07 mL, 5 mol%), TMSCl (0.02 mL,
1 mol%). The reaction mixture was stirred for 9 h at 25 °C. After centrifugation iodometric titration of 54g indicates a yield of 94%.

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

According to TP1 3,4,5-trimethoxybenzyl chloride (53h; 2.71 g, 12.5 mmol, solution in 3 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.06 g, 25.0 mmol) and zinc dust (1.64 g, 25.0 mmol) in 3.5 mL THF (activation: BrCH₂CH₂Br (0.05 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The ice bath was removed and the reaction mixture was stirred for 3 h at 25 °C. After centrifugation iodometric titration of 54h indicates a yield of 78%.

4-Methoxybenzylzinc chloride (54i)

According to TP1 4-methoxybenzyl chloride (53i; 1.57 g, 10.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (636 mg, 15.0 mmol) and zinc dust (981 mg, 15.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.04 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 6.5 h at 25 °C. After centrifugation, iodometric titration of 54i indicates a yield of 73%.

2-Methoxybenzylzinc chloride (54j)

According to TP1 2-methoxybenzyl chloride (53j; 2.35 g, 15.0 mmol, in 4 mL THF) was added dropwise at 25 °C to a suspension of LiCl (954 mg, 22.5 mmol) and zinc dust (1.47 g, 22.5 mmol) in 3.5 mL THF (activation: BrCH₂CH₂Br (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 4.5 h at 25 °C. After centrifugation iodometric titration of 54j indicates a yield of 92%.
6-Chloro-1,3-benzodioxol-5-ylmethylzinc chloride (54k)

According to TP1 6-chloro-1,3-benzodioxol-5-ylmethyl chloride (53k; 4.10 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The ice bath was removed and the reaction mixture was stirred for 1 h at 25 °C. After centrifugation iodometric titration of 54k indicates a yield of 93%.

4-(Methylthio)benzylzinc chloride (54l)

According to TP1 4-(methylthio)benzyl chloride (53l, 2.59 g, 15.0 mmol, in 3 mL THF) was added dropwise at 0 °C to a suspension of LiCl (954 mg, 22.5 mmol) and zinc dust (1.47 g, 22.5 mmol) in 4.5 mL THF (activation: BrCH₂CH₂Br (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 2 h at 25 °C. After centrifugation, iodometric titration of 54l indicates a yield of 77%.

3-(Ethoxycarbonyl)benzylzinc chloride (54m)

According to TP1 3-(ethoxycarbonyl)benzyl chloride (53m; 3.97 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.70 g, 40.0 mmol) and zinc dust (2.62 g, 40.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation iodometric titration of 54m indicates a yield of 85%.

4-(Ethoxycarbonyl)benzylzinc chloride (54n)

According to TP1 4-(ethoxycarbonyl)benzyl chloride (53n; 1.99 g, 10.0 mmol, in 2.5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (848 mg, 20.0 mmol) and zinc dust (1.31 g, 20.0 mmol) in 2.5 mL THF (activation: BrCH₂CH₂Br (0.04 mL, 5 mol%), TMSCl (0.01 mL,
1 mol%). The reaction mixture was stirred for 10 min at 0 °C followed by 50 min at 25 °C. After centrifugation iodometric titration of 54n indicates a yield of 64%.

3-Cyanobenzylzinc chloride (54o)

According to TP1 3-cyanobenzyl chloride (53o; 3.03 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH\textsubscript{2}CH\textsubscript{2}Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The ice bath was removed and the reaction mixture was stirred for 3 h at 25 °C. After centrifugation iodometric titration of 54o indicates a yield of 93%.

4-Cyanobenzylzinc chloride (54p)

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

3-Pentanoylbenzylzinc chloride (54q)

According to TP1 3-pentanoylbenzyl chloride (53q; 4.21 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30 mmol) in 5 mL THF (activation: BrCH\textsubscript{2}CH\textsubscript{2}Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation iodometric titration of 54q indicates a yield of 72%.
3-Isobutrylbenzylzinc chloride (54r)

According to TP1, 3-isobutrylbenzyl chloride (53r; 2.18 g, 10.9 mmol, in 3 mL THF) was added dropwise at 25 °C to a suspension of LiCl (699 mg, 16.5 mmol) and zinc dust (1.08 g, 16.5 mmol) in 2.5 mL THF (activation: BrCH₂CH₂Br (0.05 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 9 h at 25 °C. After centrifugation, iodometric titration of 54r indicates a yield of 64%.

3-Propionylbenzylzinc chloride (54s):

According to TP1, 3-propionylbenzyl chloride (53s; 2.01 g, 11.0 mmol, in 3.5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (0.70 g, 16.5 mmol) and zinc dust (1.08 g, 16.5 mmol) in 3 mL THF (activation: BrCH₂CH₂Br (0.05 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 3 h at 25 °C. After centrifugation, iodometric titration of 54s indicates a yield of 72%.

3-Acetylbenzylzinc chloride (54t)

According to TP1, 3-acetylbenzyl chloride (53t; 1.85 g, 11.0 mmol, in 2.5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (0.70 g, 16.5 mmol) and zinc dust (1.08 g, 16.5 mmol) in 3 mL THF (activation: BrCH₂CH₂Br (0.05 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation, iodometric titration of 54t indicates a yield of 68%.
1-Phenylethylzinc chloride (54u)

![1-Phenylethylzinc chloride](image)

According to TP1 1-phenylethyl chloride (53u; 2.81 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol%), TMSCl (0.03 mL, 1 mol%)). The ice bath was removed and the reaction mixture was stirred for 11 h at 25 °C. After centrifugation iodometric titration of 54u indicates a yield of 85%.

(Diphenylmethyl)zinc chloride (54v)

![Diphenylmethylzinc chloride](image)

According to TP1 1,1’-(chloromethylene)dibenzene (53v; 3.04 g, 15.0 mmol, in 4 mL THF) was added dropwise at 0 °C to a suspension of LiCl (954 mg, 22.5 mmol) and zinc dust (1.47 g, 22.5 mmol) in 3.5 mL THF (activation: BrCH₂CH₂Br (0.07 mL, 5 mol%), TMSCl (0.02 mL, 1 mol%)). The reaction mixture was stirred for 15 min at 0 °C followed by 4.5 h at 25 °C. After centrifugation iodometric titration of 54v indicates a yield of 64%. (8% of the homo-coupling product was observed.

3.3. Preparation of the title compounds

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

![1-Chloro-2-(cyclohex-2-en-1-ylmethyl)benzene](image)

3-Bromocyclohexene (55a; 419 mg, 2.60 mmol) was added to 2-chlorobenzylzinc chloride (54b; 1.23 mL, 2.00 mmol, 1.62 M in THF) at 0 °C followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The mixture was stirred for 1.5 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with Et₂O (3 x 5 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane) afforded the cyclohexene 56a (389 mg, 94%) as a colourless liquid.
1H-NMR (600 MHz, CDCl₃): δ / ppm = 7.33 (dd, J = 7.7 Hz, 1.3 Hz, 1H), 7.20-7.11 (m, 3H), 5.72-5.68 (m, 1H), 5.58-5.54 (m, 1H), 2.77-2.72 (m, 1H), 2.69-2.65 (m, 1H), 2.51-2.43 (m, 1H), 2.02-1.96 (m, 2H), 1.77-1.66 (m, 2H), 1.55-1.47 (m, 1H), 1.33-1.27 (m, 1H).

13C-NMR (150 MHz, CDCl₃): δ / ppm = 138.5, 134.3, 131.4, 131.0, 129.5, 127.5, 127.3, 126.4, 40.0, 35.4, 28.8, 25.4, 21.2.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3017 (m), 2922 (s), 2857 (m), 2834 (m), 1473 (s), 1446 (m), 1439 (m), 1052 (m), 1032 (m), 746 (vs), 718 (m), 683 (m), 665 (m).

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

HRMS (C₁₃H₁₀Cl): calc.: 206.0862; found: 206.0840.

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

To a solution of S-(4-bromophenyl) benzenesulfonothioate (57a; 658 mg, 2.00 mmol) in THF (4 mL) at 25 °C was added 2-chlorobenzylzinc chloride (54b; 1.55 mL, 2.4 mmol, 1.55 M in THF). The reaction mixture was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane) afforded the sulfide 56b (559 mg, 89%) as a colourless liquid.

1H-NMR (300 MHz, CDCl₃): δ / ppm = 7.40-7.33 (m, 3H), 7.23-7.10 (m, 5H), 4.18 (s, 2H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 134.8, 134.8, 134.1, 132.4, 131.9, 130.6, 129.7, 128.7, 126.8, 120.9, 37.0.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 1567 (w), 1471 (vs), 1442 (s), 1386 (m), 1235 (w), 1090 (s), 1068 (m), 1051 (s), 1037 (s), 1006 (vs), 804 (s), 757 (s), 741 (vs), 728 (s), 698 (m), 681 (s), 666 (m).

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

HRMS (C₁₃H₁₀BrClS): calc.: 311.9375; found: 311.9366.
3-(2-Chlorobenzyl)cyclohexanone (56c)

According to TP4 a mixture of cyclohex-2-en-1-one (58a; 480 mg, 5.00 mmol) and TMSCl (1.60 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.30 mL, 6.30 mmol, 1.00 M in THF) and 2-chlorobenzylzinc chloride (54b; 3.83 mL, 6.24 mmol, 1.63 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 4:1) afforded the ketone 56c (1.03 g, 93%) as a colourless liquid.

1H-NMR (300 MHz, CDCl₃): δ / ppm = 7.33-7.27 (m, 1H), 7.18-7.05 (m, 3H), 2.81 -2.62 (m, 2H), 2.38-1.94 (m, 6H), 1.89-1.78 (m, 1H), 1.66-1.48 (m, 1H), 1.47-1.32 (m, 1H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 211.4, 137.5, 134.4, 131.5, 129.9, 128.0, 126.9, 47.9, 41.6, 40.6, 39.6, 31.2, 25.3.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2936 (w), 2864 (w), 1708 (vs), 1476 (m), 1444 (m), 1348 (w), 1312 (w), 1224 (m), 1128 (w), 1052 (m), 1036 (m), 748 (s), 680 (s), 596 (w).

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

HRMS (C₁₃H₁₅ClO): calc.: 222.0811; found: 222.0800.

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

To a solution of 4-nitrobenzyl bromide (59a; 594 mg, 2.75 mmol) in 2.7 mL THF at 0 °C was added successively 2-chlorobenzylzinc chloride (54b; 2.17 mL, 3.3 mmol, 1.62 M in THF) and CuCN-2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The mixture was stirred for 3 h at 0 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with Et₂O (5 x 5 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the diarylethane 56d (643 mg, 89%) as a white solid.

M.p. (°C): 67-68.
1H-NMR (600 MHz, CDCl₃): δ / ppm = 8.14-8.11 (m, 2H), 7.38-7.34 (m, 1H), 7.32-7.29 (m, 2H), 7.18-7.13 (m, 2H), 7.09-7.06 (m, 1H), 3.07-3.00 (m, 4H).

13C-NMR (150 MHz, CDCl₃): δ / ppm = 149.3, 146.7, 138.2, 134.1, 130.7, 129.9, 129.6, 128.1, 127.1, 123.9, 36.0, 35.4.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2932 (w), 2854 (w), 1596 (m), 1509 (s), 1470 (m), 1457 (m), 1444 (m), 1334 (m), 1313 (m), 1256 (m), 1107 (m), 1049 (m), 1036 (m), 829 (s), 750 (vs), 698 (s).

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

HRMS (C₁₄H₁₂ClNO₂): calc.: 261.0557; found: 261.0560.

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

To a solution of ethyl 4-iodobenzoate (4a; 690 mg, 2.50 mmol) in 2.5 mL THF at 25 °C was added successively 2-chlorobenzylzinc chloride (54b; 1.96 mL, 3.00 mmol, 1.53 M in THF) and Pd(PPh₃)₄ (69 mg, 2 mol%). The resulting reaction mixture was heated to 60 °C for 5 h. After cooling to 25 °C the reaction mixture was diluted with Et₂O (5 mL) and quenched with sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with Et₂O (5 x 5 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 9:1) afforded the diarylmethane 56e (667 mg, 97%) as a pale yellow liquid.

1H-NMR (300 MHz, CDCl₃): δ / ppm = 8.06-8.01 (m, 3H), 7.46-7.42 (m, 1H), 7.34-7.28 (m, 2H), 7.27-7.18 (m, 2H), 4.42 (q, J = 7.2 Hz, 2H), 4.21 (s, 2H), 1.44 (t, J = 7.2 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 166.8, 145.0, 138.0, 134.5, 131.3, 130.0, 129.9, 129.1, 128.9, 128.2, 127.2, 61.1, 39.5, 14.6.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2980 (w), 1712 (vs), 1610 (m), 1473 (w), 1443 (m), 1415 (m), 1366 (w), 1271 (vs), 1177 (m), 1103 (s), 1050 (m), 1039 (m), 1020 (m), 747 (s).

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

HRMS (C₁₆H₁₅ClO₂): calc.: 274.0671; found: 274.0748.
1-(2-Chlorophenyl)acetone (56f)

According to TP3 acetyl chloride (60a; 166 mg, 2.11 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.00 mL, 3.00 mmol, 1.00 M in THF) and 2-chlorobenzylzinc chloride (54b; 1.96 mL, 3.00 mmol, 1.53 M in THF) at –40 °C. The reaction mixture was allowed to reach 25 °C within 13.5 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (30 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the ketone 56f (315 mg, 89%) as a colourless liquid.

H-NMR (300 MHz, CDCl₃): δ / ppm = 7.41-7.34 (m, 1H), 7.26-7.16 (m, 3H), 3.83 (s, 2H), 2.19 (s, 3H).

C-NMR (75 MHz, CDCl₃): δ / ppm = 204.9, 134.4, 132.9, 131.6, 129.5, 128.6, 127.0, 48.3, 29.6.

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

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

HRMS (C₉H₉ClO): calc.: 168.0342; found: 168.0329.

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

According to TP2 2-chlorobenzylzinc chloride (54b; 18.0 mL, 28.1 mmol, 1.56 M in THF) was reacted with 2-chlorobenzaldehyde (61a; 2.81 g, 20.0 mmol, in 10 mL THF) at 0 °C. After 3 h, the reaction mixture was quenched with sat. aq. NH₄Cl (200 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 7:1) afforded the benzylic alcohol 56g (4.67 g, 87%) as a white solid.


H-NMR (300 MHz, CDCl₃): δ / ppm = 7.68-7.62 (m, 1H), 7.46-7.20 (m, 7H), 5.50 (dd, J = 8.8 Hz, 4.1 Hz, 1H), 3.33 (dd, J = 13.9 Hz, 4.1 Hz, 1H), 3.11 (dd, J = 13.7 Hz, 8.9 Hz, 1H), 2.07 (s, 1H).
\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta /\text{ppm} = 141.1, 135.5, 134.6, 132.0\) (double), 129.6, 129.4, 128.6, 128.1, 127.3, 127.1, 126.7, 70.2, 41.5.

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

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

HRMS (C\(_{14}\)H\(_{12}\)Cl\(_2\)O): calc.: 266.0265; found: 266.0251.

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

To a solution of ethyl (2-bromo)methylacrylate (55b; 965 mg, 5.00 mmol) in 3 mL THF at -60 °C was added 4-fluorobenzylzinc chloride (54c; 4.12 mL, 6.00 mmol, 1.45 M in THF) followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 1.5 h, followed by stirring at 0 °C for additional 30 min. Workup as usual and purification by flash chromatography (silica gel, pentane / Et\(_2\)O = 98:2) afforded the acrylate 56h (1.03 g, 93%) as colourless liquid.

\(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta /\text{ppm} = 7.14-7.10\) (m, 2H), 6.97-6.92 (m, 2H), 6.15-6.13 (m, 1H), 5.47-5.45 (m, 1H), 4.21 (q, \(J = 7.2\) Hz, 2H), 2.79-2.72 (m, 2H), 2.61-2.54 (m, 2H), 1.30 (t, \(J = 7.2\) Hz, 3H).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)): \(\delta /\text{ppm} = 167.0, 161.3\) (d, \(^1\)J\(_{CF}\) = 243.7 Hz), 139.9, 137.0 (d, \(^4\)J\(_{CF}\) = 3.1 Hz), 129.8 (d, \(^3\)J\(_{CF}\) = 7.6 Hz), 125.2, 115.0 (d, \(^2\)J\(_{CF}\) = 21.0 Hz), 60.6, 34.1, 34.0, 14.2.

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

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

HRMS (C\(_{13}\)H\(_{15}\)FO\(_2\)): calc.: 222.1056; found: 222.1032.
C. Experimental Section

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

According to TP3 3,3-dimethylbutyryl chloride (60b; 377 mg, 2.80 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.92 mL, 3.92 mmol, 1.00 M in THF) and 4-fluorobenzylzinc chloride (54c; 2.69 mL, 3.93 mmol, 1.46 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH₄Cl/NH₃ (25% in H₂O) = 4:1 (25 mL). Purification by flash chromatography (silica gel, pentane/Et₂O = 98:2) afforded the ketone 56i (555 mg, 95%) as a pale yellow liquid.

$^1$H-NMR (600 MHz, CDCl₃): δ ppm = 7.15-7.10 (m, 2H), 7.02-6.97 (m, 2H), 3.36 (s, 1H), 2.35 (s, 1H), 1.00 (s, 9H).

$^{13}$C-NMR (150 MHz, CDCl₃): δ ppm = 207.8, 162.1 (d, $^1$J₇-₈ = 245.1 Hz), 131.2 (d, $^3$J₇-₈ = 8.1 Hz), 130.1 (d, $^4$J₇-₈ = 3.4 Hz), 115.7 (d, $^3$J₇-₈ = 21.6 Hz), 54.4, 51.2, 31.3, 29.9.

IR (Diamond-ATR, neat): ν/cm⁻¹ = 2956 (m), 1712 (s), 1508 (vs), 1364 (m), 1352 (m), 1220 (vs), 1160 (m), 1084 (m), 1064 (m), 824 (m), 780 (m), 524 (m).

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

HRMS (C₁₃H₁₇FO): calc.: 208.1263; found: 208.1261.

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

According to TP4 3-iodocyclohex-2-en-1-one (58b; 666 mg, 3.00 mmol) was added dropwise at −60 °C to a mixture of CuCN·2LiCl (3.90 mL, 3.90 mmol, 1.00 M in THF) and 2-bromobenzylzinc chloride (54d; 2.52 mL, 3.90 mmol, 1.55 M in THF). The reaction mixture was allowed to reach slowly 0 °C within 15 h and was quenched with a mixture of sat. aq. NH₄Cl/NH₃ (25% in H₂O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane/Et₂O = 2:1) afforded the unsaturated ketone 56j (779 mg, 96%) as a colourless oil.

$^1$H-NMR (300 MHz, CDCl₃): δ ppm = 7.55 (dd, $J = 8.0$ Hz, 1.3 Hz, 1H), 7.29-7.22 (m, 1H), 7.19-7.07 (m, 2H), 5.68-5.64 (m, 1H), 3.65 (s, 2H), 2.40-2.29 (m, 4H), 2.05-1.94 (m, 2H).

$^{13}$C-NMR (75 MHz, CDCl₃): δ ppm = 199.6, 163.3, 136.6, 133.1, 131.2, 128.7, 127.6, 127.0, 125.1, 43.9, 37.3, 29.7, 22.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3054 (vw), 2944 (w), 2887 (w), 2868 (w), 2823 (vw), 1664 (vs), 1567 (w), 1470 (m), 1426 (m), 1371 (m), 1348 (m), 1323 (m), 1245 (m), 1190 (m), 1131 (w), 1023 (s), 967 (m), 884 (m), 749 (vs), 659 (s).

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

HRMS (C$_{13}$H$_{13}$BrO): calc.: 264.0150; found: 264.0142.

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

According to TP2, 3-bromobenzylzinc chloride (54e; 1.72 mL, 2.68 mmol, 1.56 M in THF) was reacted with 3,4-dichlorobenzaldehyde (61b; 361 mg, 2.1 mmol, in 1.5 mL THF). After 17 h the reaction mixture was quenched with sat. aq. NH$_4$Cl solution. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 98:2) afforded the alcohol 56k (699 mg, 98%) as a white solid.


$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ / ppm = 7.43 (d, $J = 2.0$ Hz, 1H), 7.41-7.34 (m, 3H), 7.16 (t, $J = 7.7$ Hz, 1H), 7.12 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 4.81 (dd, $J = 8.4$ Hz, 4.6 Hz, 1H), 2.96-2.85 (m, 2H), 2.09 (s, 1H).

$^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ / ppm = 143.6, 139.6, 132.6, 132.4, 131.5, 130.4, 130.1, 130.0, 128.1, 127.8, 125.1, 122.6, 73.8, 45.4.

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

HRMS (ESI; C$_{15}$H$_{12}$BrCl$_2$O$_3$): calc.: 388.9352 ([M+HCO$_2$]+); found: 388.9360 ([M+HCO$_2$]+).

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

According to TP3, cyclopropanecarbonyl chloride (60c; 320 mg, 3.07 mmol) was added dropwise to a mixture of CuCN-2LiCl (4.2 mL, 4.2 mmol, 1.00 M in THF) and 3-bromobenzylzinc chloride (54e; 2.75 mL, 4.2 mmol, 1.53 M in THF) at -40 °C. The reaction mixture was allowed to reach
0 °C within 18 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the ketone 56l (675 mg, 92%) as a colourless liquid.

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.42-7.35 (m, 2H), 7.23-7.10 (m, 2H), 3.79 (s, 2H), 2.00-1.89 (m, 1H), 1.08-1.00 (m, 2H), 0.91-0.83 (m, 2H).

**¹³C-NMR (75 MHz, CDCl₃):** δ / ppm = 207.3, 136.5, 132.5, 130.1, 130.0, 128.2, 122.6, 49.9, 20.2, 11.4.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3007 (w), 1693 (s), 1593 (w), 1567 (m), 1474 (m), 1428 (m), 1379 (s), 1205 (m), 1066 (vs), 1021 (m), 997 (m), 900 (m), 886 (m), 816 (m), 766 (s), 695 (s), 681 (m), 670 (m), 664 (m), 600 (m), 568 (m), 565 (m).

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

**HRMS (C₁₁H₁₈BrO):** calc.: 237.9993; found: 237.9983.

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

According to TP3, 3,3-dimethylbutyryl chloride (60b; 581 mg, 4.32 mmol) was added dropwise to a mixture of CuCN·2LiCl (6.02 mL, 6.02 mmol, 1.00 M in THF) and 3-bromobenzylzinc chloride (54e; 1.72 mL, 6.02 mmol, 1.53 M in THF) at -60 °C. The reaction mixture was allowed to reach -20 °C overnight and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the ketone 56m (1.11 g, 96%) as a pale yellow liquid.

**¹H-NMR (600 MHz, CDCl₃):** δ / ppm = 7.40-7.37 (m, 1H), 7.33-7.32 (m, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.11-7.08 (m, 1H), 3.62 (s, 2H), 2.35 (s, 2H), 1.00 (s, 9H).

**¹³C-NMR (150 MHz, CDCl₃):** δ / ppm = 206.9, 136.4, 132.5, 130.1, 130.0, 128.2, 122.6, 54.3, 51.3, 31.1, 29.7.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2868 (m), 1596 (m), 1188 (m), 1222 (m), 996 (m), 1428 (m), 1350 (m), 1568 (m), 2954 (m), 668 (s), 1364 (s), 696 (s), 1474 (s), 772 (s), 1072 (vs), 1714 (vs).

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

**HRMS (C₁₃H₁₇BrO):** calc.: 268.0463; found: 268.0457.
3-(3-Bromobenzyl)cyclohexanone (56n)

According to TP4 a mixture of cyclohex-2-en-1-one (58a; 480 mg, 5.00 mmol) and TMSCl (1.60 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.25 mL, 6.25 mmol, 1.00 M in THF) and 3-bromobenzylzinc chloride (56e; 4.08 mL, 6.25 mmol, 1.53 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 16 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (60 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 4:1) afforded the ketone 56n (1.22 g, 91%) as a colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.36-7.30 (m, 1H), 7.29-7.25 (m, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.07-7.00 (m, 1H), 2.65-2.50 (m, 2H), 2.43-2.17 (m, 3H), 2.12-1.94 (m, 3H), 1.91-1.79 (m, 1H), 1.70-1.52 (m, 1H), 1.43-1.28 (m 1H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 211.0, 141.7, 132.0, 129.9, 129.3, 127.7, 122.4, 47.6, 42.5, 41.3, 40.6, 30.8, 25.0.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2926 (m), 1707 (vs), 1565 (m), 1473 (m), 1447 (m), 1424 (m), 1224 (m), 1070 (m), 997 (m), 857 (m), 778 (m), 753 (m), 696 (m), 668 (m).

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

HRMS (C₁₃H₁₅BrO): calc.: 266.0306; found: 266.0297.

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

According to TP2 2-iodobenzylzinc chloride (54f; 1.28 mL, 1.96 mmol, 1.53 M in THF) was reacted with 3-chlorobenzaldehyde (61c; 211 mg, 1.5 mmol, in 1.5 mL THF). After 5 h, the reaction mixture was quenched with sat. aq. NH₄Cl solution. Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 to 7:3) afforded the alcohol 56o (470 mg, 87%) as a pale yellow solid.

1H-NMR (600 MHz, CDCl$_3$): $\delta$ / ppm = 7.86 (dd, $J = 7.8$ Hz, 1.2 Hz, 1H), 7.46-7.44 (m, 1H), 7.30-7.24 (m, 4H), 7.18 (dd, $J = 7.5$ Hz, 1.8 Hz, 1H), 6.96-6.93 (m, 1H), 5.01-4.97 (m, 1H), 3.17-3.13 (m 1H), 3.08-3.03 (m, 1 H), 1.92 (d, $J = 3.3$ Hz, 1H).

13C-NMR (150 MHz, CDCl$_3$): $\delta$ / ppm = 145.7, 140.4, 139.7, 134.4, 131.3, 129.7, 128.7, 128.3, 127.8, 125.9, 123.9, 100.9, 72.8, 50.4.

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

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

HRMS (C$_{14}$H$_{12}$ClO): calc.: 357.9621; found: 357.9629.

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

According to TP4 a mixture of cyclohex-2-en-1-one (58a; 480 mg, 5.00 mmol) and TMSCl (1.60 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.30 mL, 6.30 mmol, 1.00 M in THF) and 2-iodobenzylzinc chloride (54f; 4.81 mL, 6.25 mmol, 1.30 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 4:1) afforded the ketone 56p (1.13 g, 72%) as a colourless liquid.

1H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.80 (dd, $J = 7.8$ Hz, 1.2 Hz, 1 H), 7.28-7.22 (m, 1H), 7.13-7.09 (m, 1H), 6.91-6.85 (m, 1H), 2.82-2.64 (m, 2H), 2.43-1.98 (m, 6H), 1.95-1.83 (m, 1H), 1.70-1.53 (m, 1H), 1.53-1.37 (m, 1H).

13C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 211.3, 142.2, 139.7, 130.4, 128.1 (overlap), 101.0, 47.6, 47.2, 41.4, 39.5, 30.9, 25.1.

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

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

HRMS (C$_{13}$H$_{12}$IO): calc.: 314.0168; found: 314.0166.
Ethyl 2-[2-(2-iodophenyl)ethyl]acrylate (56p)

2-Iodobenzylzinc chloride (54f; 3.92 mL, 6.00 mmol, 1.53 m in THF) was added to a solution of ethyl (2-bromomethyl)acrylate (55b; 965 mg, 5.00 mmol) in 3 mL THF at -60 °C followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 9:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 + 1 vol-% NEt₃) afforded the acrylate 56p (1.42 g, 86%) as colourless liquid.

1H-NMR (300 MHz, CDCl₃): δ / ppm = 7.80 (d, J = 6.9 Hz, 1H), 7.32-7.14 (m, 2H), 6.93-6.81 (m, 1H), 6.17 (s, 1H), 5.53 (d, J = 1.4 Hz, 1H), 4.22 (d, J = 7.2 Hz, 2H), 2.95-2.85 (m, 2H), 2.63-2.54 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 167.0, 143.9, 139.7, 139.4, 129.6, 128.3, 127.8, 125.5, 100.4, 60.7, 39.9, 32.4, 14.2.

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

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

HRMS (C₁₃H₁₅IO₂): calc.: 330.0117; found: 330.0110.

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

According to TP2 3-(trifluoromethyl)benzylzinc chloride (54g; 1.39 mL, 2.09 mmol, 1.50 M in THF) was reacted with benzothiophene-3-carbaldehyde (61d; 260 mg, 1.60 mmol, in 0.5 mL THF) at 0 °C. The ice-bath was removed. After 6 h, the reaction mixture was quenched with sat. aq. NH₄Cl (50 mL). The phases were separated and the aq. layer was extracted with CH₂Cl₂
(3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 3:1) afforded the benzyl alcohol 56r (441 mg, 86%) as a yellow oil.

**1H-NMR (400 MHz, C₆D₆):** δ / ppm = 7.68-7.64 (m, 1H), 7.59-7.55 (m, 1H), 7.39 (s, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.20-7.15 (m, 1H), 7.12-7.07 (m, 1H), 6.92-6.88 (m, 1H), 6.86 (t, J = 7.7 Hz, 1H), 6.78-6.76 (m 1H), 4.68 (t, J = 6.3 Hz, 1H), 2.79 (d, J = 6.2 Hz, 2H), 1.24 (s, 1H).

**13C-NMR (100 MHz, C₆D₆):** δ / ppm = 141.3, 139.7, 139.2, 137.5, 133.2 (q, 4J_C-F = 1.2 Hz), 130.6 (q, 2J_C-F = 31.7 Hz), 128.7, 126.5 (q, 3J_C-F = 3.8 Hz), 125.0 (q, 1J_C-F = 272.5 Hz), 124.7, 124.2, 123.4 (q, J = 3.8 Hz), 123.2, 122.6, 122.6, 70.5, 43.4.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2970 (w), 2919 (w), 1739 (m), 1450 (m), 1428 (m), 1365 (m), 1326 (s), 1217 (m), 1201 (m), 1118 (vs), 1098 (s), 1072 (s), 797 (m), 761 (s), 732 (s), 701 (s), 657 (s).

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

**HRMS (C₁₇H₁₃F₃OS):** calc.: 322.0639; found: 322.0630.

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

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

To a solution of ethyl (2-bromomethyl)acrylate (55b; 579 mg, 3.00 mmol) in 1.5 mL THF at -60 °C was added 3,4,5-trimethoxybenzylzinc chloride (54h; 7.40 mL, 3.75 mmol, 0.51 M in THF) followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with Et₂O (3 x 20 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 7:1) afforded the acrylate 56s (867 mg, 98%) as colourless liquid.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 6.36 (s, 2H), 6.11 (s, 1H), 5.48 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.79 (s, 6H), 3.77 (s, 3H), 2.73–2.63 (m, 2H), 2.62-2.51 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 167.3, 153.3, 140.3, 137.5, 136.4, 125.3, 105.6, 61.0, 60.8, 56.2, 35.6, 34.2, 14.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2936 (w), 2840 (w), 1712 (m), 1588 (m), 1508 (m), 1456 (m), 1420 (m), 1332 (m), 1236 (s), 1184 (s), 1120 (vs), 1008 (m), 944 (m), 820 (m).

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

HRMS (C$_{16}$H$_{22}$O$_5$): calc.: 294.1467; found: 294.1457.

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

To a solution of ethyl 2-bromomethylacrylate (55b; 772 mg, 4.00 mmol) in THF (2 mL) at -40 °C was added 4-methoxybenzylzinc chloride (54i; 7.19 mL, 5.00 mmol, 0.70 M in THF) followed by CuCN·2LiCl (0.01 mL, 1.00 M in THF). The reaction mixture was stirred at -40 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH$_4$Cl solution. The phases were separated and the aq. layer was extracted with Et$_2$O (3 x 50 mL). The combined extracts were dried over MgSO$_4$. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et$_2$O = 98:2) afforded the acrylate 56t (0.91 g, 97%) as colourless liquid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.14-7.06 (m, 2H), 6.86–6.79 (m, 2H), 6.15–6.13 (m, 1H), 5.49-5.46 (m, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 2.78–2.69 (m, 2H), 2.62-2.53 (m, 2H), 1.31 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 167.1, 157.8, 140.2, 133.5, 129.3, 125.0, 113.7, 60.6, 55.2, 34.1, 34.0, 14.2.

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

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

HRMS (C$_{14}$H$_{18}$O$_3$): calc.: 234.1256; found: 234.1233.
1-(4-Chlorophenyl)-2-(2-methoxyphenyl)ethanone (56u)

According to TP3 4-chlorobenzoyl chloride (60d; 411 mg, 2.35 mmol) was added dropwise to a mixture of CuCN-2LiCl (3.29 mL, 3.29 mmol, 1.00 M in THF) and 2-methoxybenzylzinc chloride (54i; 2.19 mL, 3.29 mmol, 1.50 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 21 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 14:1) afforded the ketone 56u (605 mg, 99%) as a white solid.


¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.99-7.94 (m, 2H), 7.44-7.38 (m, 2H), 7.29 -7.22 (m, 4H), 7.16 (dd, J = 7.8 Hz, 1.7 Hz, 1H), 6.95-6.85 (m, 2H), 4.23 (s, 2H), 3.78 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 196.8, 157.0, 139.2, 135.2, 130.9, 129.8, 128.8, 128.5, 123.4, 120.7, 110.6, 55.4, 39.9.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2988 (w), 2954 (w), 2940 (w), 2912 (w), 2832 (w) , 1692 (s), 1590 (s), 1494 (s), 1466 (m), 1398 (m), 1334 (s), 1288 (m), 1238 (vs), 1208 (s), 1196 (s), 1174 (m), 1110 (s), 1086 (s), 1026 (s), 992 (s), 816 (vs), 766 (vs), 758 (vs), 568 (m).

MS (EI, 70 eV): m/z (%) = 260 (M⁺, 19), 141 (31), 139 (100), 121 (22), 111 (14), 91 (24).

HRMS (C₁₅H₁₃ClO₂): calc.: 260.0604; found: 260.0599.

1-(6-Chloro-1,3-benzodioxol-5-yl)-4,4-dimethylpentan-2-one (56v)

According to TP3 3,3-dimethylbutryl chloride (60b; 377 mg, 2.80 mmol) was added dropwise to a mixture of CuCN-2LiCl (3.92 mL, 3.92 mmol, 1.00 M in THF) and 6-chloro-1,3-benzodioxol-5-ylmethylzinc chloride (54k; 2.80 mL, 3.92 mmol, 1.40 M in THF) at -60 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 95:5) afforded the ketone 56v (703 mg, 93%) as a pale yellow liquid.

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 6.84 (s, 1H), 6.63 (s, 1H), 5.95 (s, 2H), 3.70 (s, 2H), 2.38 (s, 2H), 1.02 (s, 9H).
13C-NMR (150 MHz, CDCl3): δ / ppm = 206.5, 147.4, 146.7, 126.0, 125.7, 110.9, 109.8, 101.7, 54.3, 49.2, 31.0, 29.6.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2952 (m), 2904 (w), 1716 (m), 1504 (s), 1480 (vs), 1364 (m), 1248 (s), 1232 (s), 1120 (s), 1036 (vs), 984 (m), 932 (s), 840 (s), 724 (w), 684 (w).

MS (EI, 70 eV): m/z (%) = 268 (77), 171 (76), 169 (50), 110 (23), 99 (100), 71 (65), 57 (43), 41 (33).

HRMS (C14H17ClO3): calc.: 268.0866; found: 268.0855.

1-[4-(Methylthio)phenyl]butan-2-one (56w)

According to TP3 propanoyl chloride (60e; 95.3 mg, 1.03 mmol, in 0.5 mL THF) was added dropwise at -20 °C to a mixture of CuCN·2LiCl (0.50 mL, 0.50 mmol, 1.00 M in THF) and 4-(methylthio)benzylzinc chloride (54l; 0.85 mL, 1.20 mmol, 1.42 M in THF). The reaction mixture was stirred at 0 °C and slowly warmed to 25 °C within 4 h. Then, a mixture of sat. aq. NH4Cl / NH3 (25% in H2O) = 9:1 (25 mL) was added and the phases were separated. The aq. layer was extracted with Et2O (5 x 20 mL). The combined extracts were dried over MgSO4. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et2O = 9:1) afforded the ketone 56w (143 mg, 71%) as a white solid.


1H-NMR (600 MHz, CDCl3): δ / ppm = 7.23-7.19 (m, 2H), 7.13-7.10 (m, 2H), 3.63 (s, 2H), 2.46 (q, J = 7.3 Hz, 2H), 2.46 (s, 3H), 1.02 (t, J = 7.3 Hz, 3H).

13C-NMR (150 MHz, CDCl3): δ / ppm = 208.8, 137.0, 131.3, 129.8, 127.0, 49.2, 35.2, 16.0, 7.8.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2978 (w), 2937 (w), 2922 (w), 2903 (w), 1711 (vs), 1601 (w), 1496 (s), 1456 (m), 1438 (m), 1413 (s), 1378 (m), 1351 (m), 1317 (m), 1111 (s), 1098 (m), 1087 (m), 1038 (s), 1020 (m), 993 (m), 969 (m), 959 (m), 866 (m), 823 (m), 803 (vs), 725 (m), 667 (m).

MS (EI, 70 eV): m/z (%) = 194 (M⁺, 26), 137 (100), 122 (11), 57 (10).

HRMS (C11H14OS): calc.: 194.0765; found: 194.0747.
Ethyl 3-[2-(4-bromophenyl)-2-hydroxyethyl]benzoate (56x)

According to TP2 3-(ethoxycarbonyl)benzylzinc chloride (54m; 4.10 mL, 5.33 mmol, 1.30 M in THF) was reacted with 4-bromobenzaldehyde (61e; 775 mg, 4.2 mmol, in 3 mL THF). After 4.5 h the reaction mixture was quenched with sat. aq. NH₄Cl solution. Purification by flash chromatography (silica gel, pentane / Et₂O = 7:3) afforded the alcohol 56x (1.33 g, 91%) as a white solid.


$^1$H-NMR (600 MHz, CDCl₃): $\delta / $ppm = 7.92-7.90 (m, 1H), 7.86-7.85 (m, 1H), 7.47-7.44 (m, 2H), 7.37-7.30 (m, 2H), 7.22-7.19 (m, 2H), 4.91-4.87 (m, 1H), 4.36 (q, $J = 7.1$ Hz, 2H), 3.04-3.01 (m, 2H), 1.97 (d, $J = 3.1$ Hz, 1H), 1.39 (t, $J = 7.2$ Hz, 3H).

$^{13}$C-NMR (150 MHz, CDCl₃): $\delta / $ppm = 166.5, 142.5, 137.9, 134.1, 131.5, 130.7, 130.4, 128.5, 127.9, 127.6, 121.5, 74.6, 61.0, 45.6, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu} / $cm⁻¹ = 3466 (w), 1704 (s), 1682 (s), 1484 (m), 1446 (m), 1400 (m), 1366 (m), 1278 (s), 1200 (s), 1108 (s), 1066 (s), 1024 (s), 1004 (s), 746 (vs), 698 (s).

MS (EI, 70 eV): m/z (%) = 348 (M⁺, <1), 164 (100), 135 (29), 135 (13), 118 (10), 92 (10), 91 (16), 90 (11), 78 (10), 77 (20).

HRMS (C₁₇H₁₇BrO₃): calc.: 348.0361; found: 348.0372.

Ethyl 3-[(3-oxocyclohexyl)methyl]benzoate (56y)

According to TP4 a mixture of cyclohex-2-ene-1-one (58a; 480 mg, 5.0 mmol) and TMSCl (1.60 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.30 mL, 6.30 mmol, 1.0 M in THF) and 3-(ethoxycarbonyl)benzylzinc chloride (54m; 4.46 mL, 6.24 mmol, 1.40 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 5:1 to 1:1) afforded the cyclohexanone 56y (1.26 g, 97%) as a colourless liquid.
C. Experimental Section

\[ ^1\text{H-NMR (300 MHz, CDCl}_3\text{): } \delta / \text{ppm} = 7.82-7.78 \text{ (m, 1H), 7.74-7.72 \text{ (m, 1H), 7.28-7.24 \text{ (m, 1H), 7.24-7.21 \text{ (m, 1H), 4.28 (q, } J = 7.2 \text{ Hz, 2H), 2.63-2.53 \text{ (m, 2H), 2.28-2.21 \text{ (m, 2H), 2.20-2.13 \text{ (m, 1H), 2.01-1.89 \text{ (m, 3H), 1.79-1.73 \text{ (m, 1H), 1.57-1.47 \text{ (m, 1H), 1.33-1.25 \text{ (m, 1H), 1.30 (t, } J = 7.2 \text{ Hz, 3H).}}}

\[ ^{13}\text{C-NMR (75 MHz, CDCl}_3\text{): } \delta / \text{ppm} = 211.2, 166.7, 140.0, 133.7, 130.8, 130.2, 128.6, 127.7, 61.1, 47.8, 42.9, 41.5, 40.9, 31.0, 25.2, 14.5.\]

IR (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 2936 \text{ (w), 1708 \text{ (vs), 1444 \text{ (m), 1368 \text{ (w), 1276 \text{ (s), 1196 \text{ (s), 1108 \text{ (s), 1024 \text{ (m), 864 \text{ (w), 748 \text{ (s), 700 \text{ (m), 672 \text{ (w).}}}}}

MS (EI, 70 eV): m/z (%) = 260 (M^+; 30), 215 (36), 214 (79), 164 (26), 129 (39), 121 (83), 115 (20), 97 (80), 91 (33), 69 (100), 55 (46), 41 (50).

HRMS (C_{16}H_{20}O_{3}): calc.: 260.1412; found: 260.1386.

Ethyl 3-[2-hydroxy-2-(3-thienyl)ethyl]benzoate (56z)

According to TP2 3-(ethoxycarbonyl)benzylzinc chloride (54m; 3.07 mL, 3.90 mmol, 1.27 M in THF) was reacted with 3-thiophencarbaldehyde (61f; 337 mg, 3.00 mmol, in 1.5 mL THF) at 0 °C. After 22 h at 25 °C, the reaction mixture was quenched with sat. aq. NH_4Cl (50 mL). The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the benzylic alcohol 56z (730 mg, 88%) as a pale yellow solid.

M.p. (°C): 44-46.

\[ ^1\text{H-NMR (300 MHz, CDCl}_3\text{): } \delta / \text{ppm} = 7.94-7.82 \text{ (m, 2H), 7.37-7.26 \text{ (m, 3H), 7.14-7.08 \text{ (m, 1H), 7.09-7.03 \text{ (m, 1H), 4.99 (dd, } J = 6.9 \text{ Hz, 6.4 Hz, 1H), 4.34 (q, } J = 7.2 \text{ Hz, 2H), 3.16-3.00 \text{ (m, 2H), 2.22 (s, 1H), 1.37 (t, } J = 7.2 \text{ Hz, 3H).}}\]

\[ ^{13}\text{C-NMR (75 MHz, CDCl}_3\text{): } \delta / \text{ppm} = 166.6, 145.0, 138.2, 134.0, 130.5, 130.4, 128.3, 127.7, 126.1, 125.5, 120.9, 71.2, 60.9, 44.8, 14.3.\]

IR (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 3350 \text{ (w), 3267 \text{ (w), 3100 \text{ (w), 2980 \text{ (w), 2924 \text{ (w), 1711 \text{ (vs), 1605 \text{ (w), 1587 \text{ (w), 1472 \text{ (w), 1443 \text{ (m), 1363 \text{ (m), 1279 \text{ (s), 1261 \text{ (s), 1196 \text{ (s), 1106 \text{ (s), 1060 \text{ (s), 1029 \text{ (s), 922 \text{ (m), 853 \text{ (s), 792 \text{ (s), 757 \text{ (s), 727 \text{ (vs), 673 \text{ (m).}}}}}

\]
MS (EI, 70 eV): m/z (%) = 276 (M^+, 1), 231 (13), 164 (100), 136 (42), 118 (12), 113 (35), 91 (18), 85 (22).

HRMS \( \text{C}_{15}\text{H}_{16}\text{O}_3\text{S} \): calc.: 276.0820; found: 276.0817.

**Ethyl 3-[(methylthio)methyl]benzoate (56aa)**

\[
\text{EtO}_2\text{C} \quad \text{C} \quad \text{SMe}
\]

3-(Ethoxycarbonyl)benzylzinc chloride (54m; 1.82 mL, 2.40 mmol, 1.32 M in THF) was added dropwise to S-methyl methanethiosulfonate (57b; 254 mg, 2.01 mmol) at 25 °C. After 25 h, the reaction mixture was quenched with sat. aq. NH₄Cl (25 mL). The phases were separated and the aq. layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane) afforded the thioether 56aa (370 mg, 88%) as a yellow liquid.

\[^1\text{H}-\text{NMR (300 MHz, CDCl}_3\text{): } \delta / \text{ppm} = 7.98-7.88 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.69 (s, 2H), 1.98 (s, 3H), 1.38 (q, J = 7.2 Hz, 3H).\]

\[^{13}\text{C}-\text{NMR (75 MHz, CDCl}_3\text{): } \delta / \text{ppm} = 166.4, 138.7, 133.2, 130.7, 129.8, 128.5, 128.2, 61.0, 38.0, 14.9, 14.3.\]

IR (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 2979 (w), 2914 (w), 1713 (vs), 1605 (w), 1587 (w), 1442 (m), 1366 (m), 1303 (m), 1277 (vs), 1236 (s), 1190 (s), 1102 (s), 1078 (s), 1021 (m), 912 (w), 863 (w), 818 (w), 761 (m), 730 (s), 714 (m), 699 (s), 682 (m). \)

MS (EI, 70 eV): m/z (%) = 210 (M^+, 28), 181 (11), 163 (100), 135 (18), 119 (39), 91 (12), 77 (6).

HRMS \( \text{C}_{11}\text{H}_{14}\text{O}_2\text{S} \): calc.: 210.0715; found: 210.0711.

**Ethyl 4-[2-(4-chlorophenyl)-2-oxoethyl]benzoate (56ab)**

According to TP3 4-chlorobenzoyl chloride (60d; 350 mg, 2.00 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.60 mL, 2.60 mmol, 1.00 M in THF) and 4-(ethoxycarbonyl)benzylzinc chloride (54n; 2.20 mL, 2.60 mmol, 1.18 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 20 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in
H₂O) = 2:1 (50 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1) afforded the ketone 56ab (261 mg, 43%) as a white solid.

**M.p. (°C):** 141-143.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.03-7.97 (m, 2H), 7.95-7.89 (m, 2H), 7.46-7.39 (m, 2H), 7.34-7.28 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 4.30 (s, 2H), 1.37 (t, J = 7.1 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 195.6, 166.3, 139.9, 139.2, 134.6, 129.9 (double), 129.5, 129.3, 129.0, 60.9, 45.4, 14.3.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2981 (m), 2970 (m), 2928 (m), 1739 (s), 1728 (s), 1705 (s), 1681 (vs), 1586 (m), 1489 (m), 1399 (m), 1366 (s), 1267 (s), 1229 (s), 1216 (s), 1200 (s), 1091 (s), 1022 (s), 1015 (m), 992 (s), 930 (m), 824 (s), 797 (m), 758 (vs), 725 (s).

**MS (EI, 70 eV):** m/z (%) = 302 (M⁺, 1), 257 (8), 141 (31), 139 (100), 111 (13).

**HRMS (C₁₇H₁₅ClO₃):** calc.: 302.0710; found: 302.0716.

3-(3-Methoxybenzyl)benzonitrile (56ac)

To a solution of 3-iodoanisole (4b; 585 mg, 2.5 mmol) in 2.0 mL THF at 25 °C was added successively 3-cyanobenzylzinc chloride (54o; 2.03 mL, 3.00 mmol, 1.48 M in THF) and Pd(PPh₃)₄ (139 mg, 5.0 mol%). The resulting reaction mixture was heated to 60 °C for 5 h. After cooling to 25 °C, the reaction mixture was diluted with Et₂O (5 mL) and quenched with sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with Et₂O (5 x 5 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 9:1) afforded the diarylmethane 56ac (492 mg, 88%) as a colourless liquid.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.51-7.34 (m, 4H), 7.26-7.20 (m, 1H), 6.81-6.67 (m, 3H), 3.97 (s, 2H), 3.78 (s, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 160.2, 142.7, 141.2, 133.6, 132.6, 130.2, 130.0, 129.5, 121.5, 119.2, 115.2, 112.8, 112.0, 55.4, 41.6.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2937 (w), 2228 (s), 1596 (s), 1582 (s), 1488 (s), 1435 (m), 1257 (vs), 1151 (m), 1048 (s), 779 (m), 741 (m), 686 (s).

**MS (EI, 70 eV):** m/z (%) = 224 (15), 223 (M⁺, 100), 222 (12), 208 (13), 190 (10).

**HRMS (C₁₅H₁₃NO):** calc.: 223.0997; found: 223.0988.
C. Experimental Section

3-(3,3-Dimethyl-2-oxobutyl)benzonitrile (56ad)

According to TP4 a mixture of cyclohex-2-en-1-one (58a; 480 mg, 5.00 mmol) and TMSCl (1.60 mL, 12.5 mmol) in THF (2 mL) was added dropwise to a mixture of CuCN·2LiCl (6.30 mL, 6.30 mmol, 1.00 M in THF) and 3-cyanobenzylzinc chloride (54o; 4.05 mL, 6.25 mmol, 1.55 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 3:1) afforded the cyclohexanone 56ad (1.03 g, 97%) as a pale yellow liquid.

$^1$H-NMR (300 MHz, CDCl$_3$): δ / ppm = 7.53-7.46 (m, 1H), 7.43-7.32 (m, 3H), 2.73-2.57 (m, 2H), 2.42-2.18 (m, 3H), 2.14-1.95 (m, 3H), 1.90-1.79 (m, 1H), 1.71-1.53 (m, 1H), 1.45-1.29 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / ppm = 210.6, 140.8, 133.5, 132.5, 130.1, 129.2, 118.8, 112.5, 47.5, 42.4, 41.2, 40.5, 30.7, 24.9.

IR (Diamond-ATR, neat): ν / cm$^{-1}$ = 2933 (w), 2863 (w), 2227 (m), 1706 (vs), 1582 (w), 1483 (w), 1448 (m), 1429 (w), 1346 (w), 1312 (w), 1277 (w), 1258 (w), 1225 (m), 1100 (w), 1059 (w), 912 (w), 901 (w), 866 (w), 796 (m), 753 (w), 723 (m), 691 (s), 572 (w), 558 (w).

MS (EI, 70 eV): m/z (%) = 213 (M$^+$, 52), 155 (78), 142 (12), 116 (28), 97 (100), 89 (15), 69 (93), 55 (45).

HRMS (C$_{14}$H$_{15}$NO): calc.: 213.1154; found: 213.1153.

3-(3,3-Dimethyl-2-oxobutyl)benzonitrile (56ae)

According to TP3 2,2-dimethylpropionyl chloride (60b; 225 mg, 1.87 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.6 mL, 2.6 mmol) and 3-cyanobenzylzinc chloride (54o; 1.9 mL, 2.6 mmol, 1.37 M in THF) at -60 °C. The reaction mixture was allowed to reach -20 °C within 15 h and was quenched with a mixture of sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 6:1) afforded the ketone 56ae (292 mg, 78%) as a white solid.

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\( ^1H-NMR \) (600 MHz, C\( _6D_6 \)): \( \delta / \text{ppm} = 7.03-7.01 \) (m, 1H), 6.98-6.95 (m, 2H), 6.74 (t, \( J = 7.8 \) Hz, 1H), 3.13 (s, 2H), 0.89 (s, 9H).

\( ^13C-NMR \) (150 MHz, C\( _6D_6 \)): \( \delta / \text{ppm} = 209.7, 136.7, 134.0, 133.2, 130.2, 128.8, 118.9, 112.9, 44.3, 42.2, 26.1. \)

IR (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 2956 \) (m), 2226 (m), 1700 (s), 1482 (m), 1364 (m), 1330 (s), 1058 (vs), 1020 (s), 808 (m), 770 (vs), 684 (vs).

MS (EI, 70 eV): \( m/z (\%) = 201 \) (M\(^+\), <1), 117 (28), 116 (22), 85 (22), 57 (100), 41 (30).

HRMS (C\(_{13}\)H\(_{15}\)NO): calc.: 201.1154; found: 201.1131.

Ethyl 2-[2-(4-cyanophenyl)ethyl]acrylate (56af)

4-Cyanobenzylzinc chloride (54p; 6.90 mL, 10.0 mmol, 1.45 M in THF) was added to a solution of ethyl (2-bromomethyl)acrylate (55b; 1.54 g, 8.00 mmol) in 4 mL THF at -60 °C followed by CuCN·2LiCl (0.01 mL, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding a mixture of sat. aq. NH\(_4\)Cl / NH\(_3\) (25% in H\(_2\)O) = 9:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et\(_2\)O = 3:1) afforded the acrylate 56af (1.48 g, 81%) as colourless oil.

\( ^1H-NMR \) (300 MHz, CDCl\(_3\)): \( \delta / \text{ppm} = 7.58-7.51 \) (m, 2H), 7.29-7.22 (m, 2H), 6.17-6.10 (m, 1H), 5.48-5.43 (m, 1H), 4.19 (d, \( J = 7.1 \) Hz, 2H), 2.88-2.79 (m, 2H), 2.65-2.54 (m, 2H), 1.28 (t, \( J = 7.1 \) Hz, 3H).

\( ^13C-NMR \) (75 MHz, CDCl\(_3\)): \( \delta / \text{ppm} = 166.7, 147.0, 139.3, 132.1, 129.3, 125.6, 119.0, 109.9, 60.7, 35.0, 33.4, 14.2.

IR (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 2983 \) (w), 2936 (w), 2228 (m), 1710 (vs), 1631 (w), 1608 (m), 1506 (w), 1445 (w), 1412 (w), 1369 (m), 1309 (m), 1273 (m), 1254 (m), 1184 (vs), 1135 (s), 1105 (m), 1027 (m), 947 (m), 838 (m), 820 (s), 668 (w).

MS (EI, 70 eV): \( m/z (\%) = 229 \) (M\(^+\), 12), 183 (80), 155 (35), 127 (11), 116 (100), 89 (23), 43 (15).

HRMS (C\(_{14}\)H\(_{15}\)NO\(_2\)): calc.: 229.1103; found: 229.1096.
To S-(4-fluorophenyl) benzenesulfonylthioate (57c; 644 mg, 2.40 mmol, in 1.0 mL THF) was added dropwise 4-cyanobenzylzinc chloride (54p; 2.30 mL, 2.88 mmol, 1.25 M in THF). The reaction mixture was stirred for 1.5 h followed by the addition of sat. aq. NH₄Cl solution at 0 °C. The phases were separated and the aq. layer was extracted with Et₂O (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 95:5) afforded the thioether 56ag (552 mg, 95%) as a white solid.


³¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.58-7.52 (m, 2H), 7.30-7.21 (m, 4H), 7.01–6.91 (m, 2H), 4.03 (s, 2H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 162.4 (d, ¹³J_C-F = 248.2 Hz), 143.3, 134.2 (d, ³¹J_C-F = 8.3 Hz), 132.2, 129.5, 129.2 (d, J = 3.4 Hz), 118.7, 116.1 (d, J = 21.9 Hz), 110.9, 40.4.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3064 (w), 3044 (w), 2930 (w), 2856 (w), 2360 (w), 2342 (w), 2228 (m), 1862 (w), 1734 (w), 1606 (m), 1590 (w), 1506 (m), 1488 (s), 1416 (m), 1400 (m), 1298 (w), 1216 (s), 1180 (m), 1158 (m), 1104 (m), 1090 (m), 1014 (w), 968 (w), 924 (w), 904 (w), 856 (s), 812 (vs), 804 (vs), 760 (s), 712 (w), 630 (s).

MS (EI, 70 eV): m/z (%) = 243 (M⁺, 35), 127 (5), 117 (8), 116 (100), 89 (9) 83 (6), 63 (2).

HRMS (C₁₄H₁₀FNS): calc.: 243.0518; found: 243.0513.

1-[3-(2-Oxo-2-phenylethyl)phenyl]pentan-1-one (56ah)

According to TP3 benzoyl chloride (60f; 278 mg, 1.98 mmol) was added dropwise to a mixture of CuCN-2LiCl (2.60 mL, 2.60 mmol, 1.00 M in THF) and 3-pentanoylbenzylzinc chloride (54q; 2.30 mL, 2.64 mmol, 1.15 M in THF) at -20 °C. The reaction mixture was stirred for 15 h at this temperature followed by quenching with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1) afforded the ketone 56ah (470 mg, 85%) as a white solid.
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$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ / ppm = 8.03-8.00 (m, 2H), 7.86-7.83 (m, 2H), 7.59-7.55 (m, 1H), 7.49-7.40 (m, 4H), 4.35 (s, 2 H), 2.94 (t, $J = 7.4$ Hz, 2H), 1.73-1.67 (m, 2H), 1.43-1.35 (m, 2 H), 0.94 (t, $J = 7.4$ Hz, 3H).

$^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ / ppm = 200.4, 197.0, 137.4, 136.4, 135.0, 134.1, 133.4, 129.2, 128.8, 128.7, 128.5, 126.7, 45.1, 38.4, 26.4, 22.4, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2956 (w), 2932 (w), 1678 (vs), 1594 (m), 1580 (m ), 1446 (m), 1328 (m), 1206 (s), 1164 (m), 974 (m), 748 (s), 692 (vs).

MS (EI, 70 eV): m/z (%) = 280 (M$^+$, 6), 223 (6), 105 (100), 77 (17).

HRMS (C$_{19}$H$_{20}$O$_2$): calc.: 280.1463; found: 280.1439.

1-{3-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]phenyl}pentan-1-one (56ai)

According to TP3 3-pentanoylbenzylzinc chloride (54q; 2.40 mL, 2.59 mmol, 1.08 M in THF) was reacted with 3,4-dichlorobenzaldehyde (61b; 350 mg, 2.00 mmol, in 1.5 mL THF). After 5.5 h the reaction mixture was quenched with sat. aq. NH$_4$Cl solution. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 2:1) afforded the alcohol 56ai (665 mg, 95%) as a white solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.84-7.80 (m, 1H), 7.75-7.72 (m, 1H), 7.45-7.30 (m, 4 H), 7.16-7.11 (m, 1H), 4.92-4.85 (m, 1H), 3.04-3.00 (m, 2H), 2.01 (t, $J = 7.4$ Hz, 2H), 2.11-1.93 (s, 1H), 1.76-1.62 (m, 2H), 1.47-1.32 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 200.5, 143.8, 137.8, 137.4, 134.1, 132.6, 131.5, 130.4, 129.0, 128.8, 127.9, 126.7, 125.2, 73.9, 45.7, 38.4, 26.5, 22.5, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3427 (w), 2956 (m), 2930 (m), 2871 (w), 1673 (s), 1601 (w), 1583 (m), 1466 (s), 1440 (m), 1379 (m), 1319 (m), 1261 (m), 1231 (m), 1199 (m), 1179 (m), 1163 (m), 1129 (m), 1057 (s), 1028 (vs), 885 (m), 820 (s), 787 (m), 764 (m), 730 (m), 692 (s), 675 (s).

MS (EI, 70 eV): m/z (%) = 350 (M$^+$, <1), 293 (7), 177 (15), 176 (100), 175 (14), 119 (8).

HRMS (C$_{19}$H$_{20}$Cl$_2$O$_2$): calc.: 350.0840; found: 350.0839.
According to TP3 2-furoyl chloride (60g; 261 mg, 2.00 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.60 mL, 2.60 mmol, 1.00 M in THF) and 3-isobutyrylbenzylzinc chloride (54r; 2.36 mL, 2.60 mmol, 1.10 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 20 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (50 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 3:1) afforded the ketone 56aj (259 mg, 51%) as a yellow oil.

**1H-NMR (600 MHz, CDCl₃):** δ / ppm = 7.88 (s, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.62-7.59 (m, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 4.18 (s, 2H), 3.56-3.50 (m, 1H), 1.19 (d, J = 6.9 Hz, 6H).

**13C-NMR (150 MHz, CDCl₃):** δ / ppm = 204.3, 186.1, 152.3, 146.7, 136.5, 134.5, 134.0, 129.5, 128.9, 127.1, 117.9, 112.5, 45.0, 35.4, 19.1.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3132 (vw), 2972 (w), 2934 (w), 2873 (w), 1673 (vs), 1568 (m), 1465 (s), 1439 (m), 1384 (m), 1335 (m), 1288 (m), 1235 (s), 1149 (s), 1084 (m), 1039 (m), 1019 (s), 994 (s), 912 (m), 882 (m), 836 (m), 764 (s), 734 (s), 708 (m), 685 (m), 643 (m), 594 (s), 576 (m).

**MS (EI, 70 eV):** m/z (%) = 256 (M⁺, 10), 214 (65), 185 (21), 128 (20), 118 (11), 95 (100), 90 (20).

**HRMS (C₁₆H₁₆O₃):** calc.: 256.1099; found: 256.1097.

**Ethyl 2-[2-(3-propionylphenyl)ethyl]acrylate (56ak)**

To a solution of ethyl (2-bromomethyl)acrylate (55b; 560 mg, 2.90 mmol) in 1.5 mL THF at -60 °C was added 3-propionylbenzylzinc chloride (54s; 2.80 mL, 3.48 mmol, 1.25 M in THF) followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with Et₂O (3 x 20 mL). The combined extracts were dried over MgSO₄.
Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 95:5) afforded the acrylate 56ak (694 mg, 92%) as a pale yellow liquid.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.80-7.74 (m, 2H), 7.39-7.34 (m, 2H), 6.16-6.14 (m, 1H), 5.48 (q, J = 1.3 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.98 (q, J = 7.1 Hz, 2H), 2.89-2.80 (m, 2H), 2.66-2.59 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 200.9, 167.0, 141.9, 139.8, 137.1, 133.1, 128.5, 128.0, 125.8, 125.4, 60.7, 34.8, 33.8, 31.8, 14.2, 8.3.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2978 (w), 2938 (w), 1712 (vs), 1684 (vs), 1300 (m), 1240 (s), 1184 (vs), 1164 (s), 1132 (s), 1028 (m), 944 (m), 782 (s), 694 (s).

**MS (EI, 70 eV):** m/z (%) = 260 (M⁺, 23), 232 (16), 231 (100), 214 (11), 213 (11), 185 (16), 147 (28), 129 (14), 128 (12), 118 (10), 91 (12), 90 (19), 57 (15).

**HRMS (C₁₆H₂₀O₃):** calc.: 260.1412; found: 260.1419.

4,4-Dimethyl-1-(3-propionylphenyl)pentan-2-one (56al)

According to TP3, 3,3-dimethylbutyryl chloride (60b; 192 mg, 1.44 mmol) was added dropwise to a mixture of CuCN·2LiCl (1.88 mL, 1.88 mmol, 1.00 M in THF) and 3-propionylbenzylzinc chloride (54s; 1.76 mL, 1.88 mmol, 1.07 M in THF) at -60 °C. The reaction mixture was allowed to reach -20 °C within 15 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1) afforded the ketone 56al (246 mg, 69%) as a white solid.

**M.p. (°C):** 39.4-41.5.

**1H-NMR (600 MHz, CDCl₃):** δ / ppm = 7.86-7.83 (m, 1H), 7.77-7.75 (m, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.37-7.35 (m, 1H), 3.73 (s, 2H), 2.99 (q, J = 7.3 Hz, 2H), 2.38 (s, 2H), 1.21 (t, J = 7.2 Hz, 3H), 1.00 (s, 9H).

**13C-NMR (150 MHz, CDCl₃):** δ / ppm = 207.2, 200.6, 137.2, 134.7, 134.0, 129.0, 128.8, 126.7, 54.4, 51.6, 31.8, 31.1, 29.7, 8.2.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2947 (m), 2938 (m), 2899 (w), 2867 (w), 1711 (s), 1677 (vs), 1604 (w), 1459 (m), 1440 (m), 1411 (m), 1404 (m), 1369 (m), 1364 (m), 1340 (s), 1311 (m), 782 (s), 694 (s).
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1247 (m), 1235 (m), 1193 (m), 1167 (s), 1149 (m), 1085 (s), 1037 (m), 1024 (m), 983 (m), 898 (m), 778 (vs), 747 (m), 697 (vs), 647 (w), 571 (m).

**MS (EI, 70 eV):** m/z (%) = 246 (M⁺, 2), 217 (9), 148 (23), 147 (33), 118 (11), 99 (75), 71 (18), 57 (100), 43 (11), 41 (14).

**HRMS (C₁₆H₂₂O₂):** calc.: 246.1620; found: 246.1626.

1-(3-Acetylphenyl)-4,4-dimethylpentan-2-one (56am)

According to TP3, 3,3-dimethylbutyryl chloride (60b; 192 mg, 1.44 mmol) was added dropwise to a mixture of CuCN·2LiCl (1.88 mL, 1.88 mmol, 1.00 M in THF) and 3-acetylbenzylzinc chloride (54t; 1.68 mL, 1.88 mmol, 1.12 M in THF) at -60 °C. The reaction mixture was stirred for 15 h at -20 °C and quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 7:3) afforded the ketone 56am (248 mg, 74%) as a pale yellow liquid.

**¹H-NMR (600 MHz, CDCl₃):** δ / ppm = 7.85-7.82 (m, 1H), 7.75-7.74 (m, 1H), 7.43-7.40 (m, 1H), 7.38-7.36 (m, 1H), 3.73 (s, 2H), 2.58 (s, 3H), 2.37 (s, 2H), 1.00 (s, 9H).

**¹³C-NMR (150 MHz, CDCl₃):** δ / ppm = 207.1, 197.9, 137.4, 134.7, 134.2, 129.2, 128.8, 127.0, 54.4, 51.5, 31.1, 29.6, 26.6.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2868 (w), 1920 (w), 1602 (w), 1584 (w), 2953 (m), 1439 (m), 790 (m), 1063 (m), 1083 (m), 1189 (m), 1713 (m), 1356 (s), 693 (s), 1269 (s), 1681 (vs).

**MS (EI, 70 eV):** m/z (%) = 232 (M⁺, 3), 134 (18), 133 (50), 99 (100), 90 (15), 71 (17), 57 (72), 43 (27).

**HRMS (C₁₅H₂₀O₂):** calc.: 232.1463; found: 232.1447.

**Ethyl 2-[2-(3-acetylphenyl)ethyl]acrylate (56an)**

To a solution of ethyl 2-bromomethylacrylate (55b; 193 mg, 1.00 mmol) in THF (3 mL) at -60 °C was added 3-acetylbenzylzinc chloride (54t; 1.16 mL, 1.30 mmol, 1.12 M in THF) and CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C
for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with Et₂O (3 x 100 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and and purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 to 6:1) afforded the acrylate 56an (239 mg, 97%) as colourless liquid.

1H-NMR (600 MHz, CDCl₃): δ / ppm = 7.80-7.75 (m, 2H), 7.41-7.34 (m, 2H), 6.16 -6.14 (m, 1H), 5.50-5.47 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.87-2.81 (m, 2H), 2.65-2.60 (m, 2H ), 2.59 (s, 3H), 1.30 (q, J = 7.1 Hz, 3H).

13C-NMR (150 MHz, CDCl₃): δ / ppm = 198.3, 167.0, 142.0, 139.8, 137.3, 133.3, 128.6, 128.2, 126.2, 125.4, 60.7, 34.8, 33.8, 26.7, 14.2.

IR (Diamond-ATR, neat): ʋ / cm⁻¹ = 2980 (w), 2931 (w), 1711 (s), 1682 (vs), 1438 (m), 1357 (m), 1300 (m), 1270 (s), 1241 (m), 1184 (vs), 1133 (s), 1114 (m), 1026 (m), 946 (m), 795 (m), 693 (s).

MS (EI, 70 eV): m/z (%) = 234 (M⁺, 23), 201 (18), 200 (29), 185 (29), 157 (19), 133 (100), 129 (20), 118 (11), 90 (18), 42 (48).

HRMS (C₁₅H₁₈O₃): calc.: 246.1156; found: 246.1143.

1-{3-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]phenyl}-ethanone (56ao)

According to TP2 3-propionylbenzylzinc chloride (54t; 3.12 mL, 3.12 mmol, 1.00 M in THF) was reacted with 3,4-dichlorobenzaldehyde (61b; 420 mg, 2.40 mmol, in 2 mL THF) at 25 °C. After 3 h, the reaction mixture was quenched with sat. aq. NH₄Cl (5 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 2:1 + 1 vol-% NEt₃) afforded the benzylic alcohol 56ao (609 mg, 82%) as a white solid.


1H-NMR (300 MHz, CDCl₃): δ / ppm = 7.84-7.80 (m, 1H), 7.77-7.75 (m, 1H), 7.45-7.31 (m, 4H), 7.16-7.11 (m, 1H), 4.89 (dd, J = 7.3 Hz, 6.1 Hz, 1H), 3.03 (s, 1H), 3.01 (d, J = 1.9 Hz, 1H), 2.57 (s, 3H), 2.11 (s, 1H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 198.1, 143.9, 137.9, 137.4, 134.3, 132.6, 131.5, 130.4, 129.2, 128.8, 128.0, 127.0, 125.3, 73.9, 45.6, 26.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3353 (w), 2921 (w), 1676 (s), 1601 (m), 1583 (m), 1467 (m), 1438 (m), 1389 (m), 1357 (s), 1271 (s), 1189 (m), 1129 (m), 1056 (m), 1028 (s), 957 (m), 906 (m), 887 (m), 820 (s), 792 (s), 730 (s), 692 (vs), 674 (s).

MS (EI, 70 eV): m/z (%) = 308 (M+, <1), 212 (11), 174 (85), 147 (44), 135 (90), 119 (27), 111 (100), 91 (95), 75 (21), 43 (57).

HRMS (C$_{16}$H$_{14}$Cl$_2$O$_2$): calc.: 308.0371; found: 308.0371.

1,2-Diphenylethanone (56ap)

![1,2-Diphenylethanone](image)

According to TP3 benzoyl chloride (60f; 1.69 g, 12.0 mmol) was added dropwise to a mixture of CuCN·2LiCl (16.8 mL, 16.8 mmol, 1.00 M in THF) and benzylzinc chloride (54a; 11.1 mL, 16.8 mmol, 1.52 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 20 h and was quenched with a mixture of sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 9:1) afforded the ketone 56ap (2.17 g, 92%) as a pale yellow solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.06-7.98 (m, 2H), 7.59-7.51 (m, 1H), 7.50-7.41 (m, 2H), 7.37-7.21 (m, 5H), 4.29 (s, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 197.6, 136.6, 134.5, 133.1, 129.4, 128.6, 128.6, 128.6, 126.8, 45.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3564 (vw), 3058 (w), 3027 (w), 2922 (vw), 2904 (w), 1682 (s), 1593 (m), 1579 (m), 1496 (m), 1447 (m), 1336 (m), 1323 (m), 1216 (m), 1199 (m), 1076 (m), 1026 (m), 991 (m), 750 (s), 728 (s), 711 (m), 698 (vs), 686 (vs), 662 (s), 648 (m), 619 (m), 565 (vs).

MS (EI, 70 eV): m/z (%) = 196 (M$^+$, 2), 165 (5), 105 (100), 91 (13), 77 (41), 69 (6), 61 (5), 51 (8), 44 (32).

HRMS (C$_{14}$H$_{12}$O): calc.: 196.0888; found: 196.0872.
C. Experimental Section

**Ethyl 2-(2-phenylethyl)acrylate (56aq)**

![Chemical structure of ethyl 2-(2-phenylethyl)acrylate](image)

To a solution of ethyl 2-bromomethylacrylate (55b; 965 mg, 5.00 mmol) in THF (2.5 mL) at -60 °C was added benzylzinc chloride (54a; 3.85 mL, 6.00 mmol, 1.56 M in THF) and CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aq. NH₄Cl solution. The phases were separated and the aq. layer was extracted with Et₂O (3 x 100 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents _in vacuo_ and purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the acrylate 56aq (948 mg, 93%) as colourless liquid.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.33-7.24 (m, 2H), 7.23-7.15 (m, 3H), 6.18-6.14 (m, 1H), 5.52-5.47 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.85-2.76 (m, 2H), 2.67-2.58 (m, 2H), 1.32 (q, J = 7.2 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 167.1, 141.4, 140.1, 128.4, 128.3, 125.9, 125.0, 60.6, 34.9, 33.9, 14.2.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2980 (w), 2932 (w), 1712 (vs), 1632 (w), 1456 (w), 1308 (m), 1240 (m), 1184 (s), 1156 (m), 1132 (s), 1028 (m), 944 (m), 748 (m), 700 (vs).

**MS (EI, 70 eV):** m/z (%) = 234 (M⁺, 7), 158 (17), 130 (26), 91 (100), 65 (11), 57 (13).

**HRMS (C₁₃H₁₆O₂):** calc.: 204.1150; found: 204.1144.

**5,5-Dimethyl-2-phenylhexan-3-one (56ar)**

According to TP3 3,3-dimethylbutyl chloride (60b; 382 mg, 2.84 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.90 mL, 3.90 mmol, 1.00 M in THF) and 1-phenylethylzinc chloride (54u; 2.73 mL, 3.90 mmol, 1.43 M in THF) at -60 °C. The reaction mixture was allowed to reach 25 °C within 15 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 9:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 95:5) afforded the ketone 56ar (556 mg, 96%) as a colourless liquid.
C. Experimental Section

**1H-NMR** (600 MHz, CDCl₃): δ / ppm = 7.39-7.35 (m, 2H), 7.32-7.28 (m, 1H), 7.26-7.23 (m, 2H), 3.76 (q, J = 6.9 Hz, 1H), 2.37 (d, J = 15.3 Hz, 1H), 2.23 (d, J = 15.5 Hz, 1H), 1.40 (d, J = 6.9 Hz, 3H), 1.00 (s, 9H).

**13C-NMR** (150 MHz, CDCl₃): δ / ppm = 210.3, 140.5, 128.8, 128.0, 127.0, 54.4, 53.2, 30.9, 29.6, 17.4.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2952 (m), 2868 (w), 1712 (s), 1492 (w), 1452 (m), 1364 (m), 1068 (w), 1044 (w), 1028 (w), 1016 (w), 912 (m), 756 (m), 700 (vs), 548 (m), 520 (w).

**MS (EI, 70 eV):** m/z (%) = 204 (M⁺, 3), 105 (63), 99 (74), 83 (14), 79 (11), 71 (29), 69 (13), 57 (100), 55 (13), 43 (23).

**HRMS (C₁₄H₂₀O):** calc.: 204.1514; found: 204.1525.

**Ethyl 2-(2,2-diphenylethyl)acrylate (56as)**

(Diphenyl)methylzinc chloride (54v; 5.42 mL, 3.90 mmol, 0.72 M in THF) was added to a solution of ethyl (2-bromomethyl)acrylate (55b; 579 mg, 3.00 mmol) in THF (3 mL) at -60 °C followed by CuCN·2LiCl (0.01 mL, 1.00 M in THF). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 8:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the acrylate 56as (804 mg, 96%) as colourless oil.

**1H-NMR** (300 MHz, CDCl₃): δ / ppm = 7.39-7.21 (m, 10H), 6.16-6.14 (m, 1H), 5.40-5.37 (m, 1H), 4.34 (t, J = 7.9 Hz, 1H), 4.26 (d, J = 7.2 Hz, 2H), 3.19-3.13 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H).

**13C-NMR** (75 MHz, CDCl₃): δ / ppm = 167.1, 144.0, 138.5, 128.4, 128.0, 126.8, 126.2, 60.6, 49.9, 38.0, 14.2.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3061 (vw), 3027 (w), 2981 (w), 2936 (vw), 1709 (s), 1630 (w), 1600 (w), 1494 (w), 1464 (w), 1450 (m), 1368 (w), 1330 (w), 1300 (m), 1231 (w), 1187 (s), 1134 (s), 1082 (w), 1028 (m), 944 (m), 863 (w), 816 (w), 788 (w), 742 (s), 697 (vs), 602 (m).
C. Experimental Section

**MS (EI, 70 eV):** m/z (%) = 280 (M⁺, 2), 235 (3), 167 (100), 165 (14), 152 (9), 128 (2), 105 (3), 77 (2).

**HRMS (C₁₉H₂₀O₂):** calc.: 280.1463; found: 280.1461

**Ethyl (2-chlorophenyl)acetate (62a)**

![Structural formula of ethyl (2-chlorophenyl)acetate (62a)](image)

**Reaction 1 using ethyl chloroformate:**

To 2-chlorobenzylzinc chloride (54b; 2.62 mL, 4.00 mmol, 1.50 M in THF) at -30 °C was added THF (0.5 mL) followed by Pd(PPh₃)₄ (116 mg, 5.0 mol%). The reaction mixture was stirred for 5 min. Then, ethyl chloroformate (60h, 227 mg, 2.09 mmol) was added dropwise. Stirring was continued for 10 min at -30 °C followed by 6.25 h at 25 °C. The reaction mixture was quenched by adding a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 4:1 (15 mL). The phases were separated and the aq. layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the phenylacetic acid ester 62a (336 mg, 81%) as colourless liquid.

**Reaction 2 using ethyl cyanofomate:**

To 2-chlorobenzyl zine chloride (54b; 0.67 mL, 1.00 mmol, 1.50 M in THF) at -30 °C was added dropwise TMSCH₂Li (1.00 mL, 1.00 mmol, 1.00 M in pentane). The reaction mixture was stirred for 30 min. CuCN-2LiCl solution (1.00 mL, 1.00 mmol, 1.00 M in THF) was added dropwise and the mixture was stirred for additional 30 min. Ethyl cyanofomate (60i; 150 mg, 1.5 mmol) was added dropwise. Stirring was continued for 10 min at -30 °C followed by 6 h at 0 °C. The reaction mixture was quenched by adding a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (15 mL). The phases were separated and the aq. layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the phenylacetic acid ester 62a (152 mg, 77%) as colourless liquid.

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.42-7.34 (m, 1H), 7.32-7.17 (m, 3H), 4.17 (q, J = 7.1 Hz, 2H), 3.76 (s, 2H), 1.25 (t, J = 7.2 Hz, 3H).
C. Experimental Section

$^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$/ ppm = 170.5, 134.5, 132.5, 131.4, 129.4, 128.6, 126.8, 61.0, 39.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2981 (w), 1731 (vs), 1475 (m), 1445 (m), 1415 (w), 1367 (m), 1335 (m), 1279 (m), 1246 (m), 1216 (s), 1156 (vs), 1122 (m), 1053 (s), 1028 (s), 928 (w), 885 (w), 859 (w), 827 (w), 741 (vs), 681 (s), 626 (w).

MS (EI, 70 eV): m/z (%) = 198 (M$^+$, 4), 163 (100), 135 (23) 127 (78), 125 (35, 89 (21).

HRMS (C$_{10}$H$_{11}$ClO$_2$): calc.: 198.0448; found: 198.0462.

Ethyl 3-(2-ethoxy-2-oxoethyl)benzoate (62b)

Ethyl chloroformate (60h; 1.09 g, 10.0 mmol) was solved in THF (5 mL) at -30 °C. Then, Pd(PPh$_3$)$_4$ (290 mg, 0.25 mmol, 2.5 mol%) was added and the mixture was stirred for 10 min. 3-(Ethoxycarbonyl)benzylzinc chloride (54m; 9.09 mL, 12.0 mmol, 1.32 M in THF) was added dropwise. The reaction mixture was stirred for 6 h at 25 °C. Then, sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 9:1 (100 mL) was added. The phases were separated and the aq. layer was extracted with CH$_2$Cl$_2$ (3 x 150 mL). The combined extracts were dried over MgSO$_4$. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et$_2$O = 9:1) afforded the ester 62b (1.79 g, 76%) as colourless liquid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ ppm = 7.96-7.91 (m, 2H), 7.49-7.45 (m, 1H), 7.41 -7.35 (m, 1H), 4.36 (q, $J$ = 7.1 Hz, 2H), 4.14 (q, $J$ = 7.1 Hz, 2H), 3.65 (s, 2H), 1.38 (t, $J$ = 7.2 Hz, 3H), 1.24 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ ppm = 171.1, 166.3, 134.4, 133.7, 130.8, 130.3, 128.5, 128.3, 61.0 (double), 41.1, 14.3, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2982 (w), 1715 (vs), 1589 (w), 1446 (m), 1367 (m), 1278 (vs), 1251 (s), 1192 (s), 1156 (s), 1104 (s), 1081 (s), 1025 (s), 902 (w), 863 (w), 741 (s), 725 (m), 685 (m).

MS (EI, 70 eV): m/z (%) = 236 (M$^+$, 99), 208 (33), 192 (18), 191 (87), 164 (100), 136 (54), 135 (89), 119 (95), 77 (16), 59 (11).

HRMS (C$_{11}$H$_{16}$O$_4$): calc.: 236.1049; found: 236.1033.
C. Experimental Section

Ethyl (2-iodophenyl)acetate (62c)

TMSCH$_2$Li (5.00 mL, 5.00 mmol, 1.00 M in pentane) was added dropwise to 2-iodobenzylzinc chloride (54f; 3.76 mL, 5.00 mmol, 1.33 M in THF) at -30 °C, followed by THF (1 mL). The resulting mixture was stirred for 30 min. Then, CuCN·2LiCl (5.00 mL, 5.00 mmol, 1.00 M in THF) was added and stirring was continued for additional 30 min. Ethyl cyanoformate (60i; 625 mg, 6.31 mmol) was added dropwise and the reaction mixture was stirred for 6 h at 0 °C. The reaction mixture was quenched with 30 mL of a mixture of sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 2:1. The phases were separated and the organic layer was extracted again with 30 mL of a mixture of sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 2:1. The combined aq. layers were extracted with Et$_2$O (3 x 100 mL). The combined organic extracts were dried over MgSO$_4$. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et$_2$O = 98:2) afforded the ester 62c (859 mg, 59%) as a white solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ ppm = 7.87-7.81 (m, 1H), 7.34-7.24 (m 2H), 6.99-6.91 (m, 1H), 4.18 (q, $J$ = 7.1 Hz, 2H), 3.78 (s, 2H), 1.23 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ ppm = 170.5, 139.5, 137.9, 130.6, 128.8, 128.4, 101.0, 61.0, 46.3, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm$^{-1}$ = 2987 (w), 2944 (w), 2906 (w), 1726 (s), 1564 (w), 1469 (m), 1411 (m), 1366 (m), 1338 (s), 1277 (m), 1214 (s), 1171 (s), 1162 (s), 1113 (m), 1029 (s), 1012 (vs), 926 (m), 888 (s), 760 (s), 734 (vs), 681 (m), 647 (s), 594 (m), 574 (s).

MS (EI, 70 eV): m/z (%) = 289 (M$^+$, 4), 216 (100), 163 (60), 135 (96), 107 (11), 90 (54), 63 (13), 43 (10).

HRMS (C$_{10}$H$_{11}$IO$_2$): calc.: 289.9804; found: 289.9803.

$N$-[(1E)-(3,4-Dimethoxyphenyl)methylene]-2,2-dimethoxyethanamine (64)

To a solution of 3,4-dimethoxybenzaldehyde (60h; 8.31 g, 50.0 mmol) in 150 mL toluene was added aminoacetaldehyde dimethylacetal (8.24 mL, 76.0 mmol). The reaction mixture was refluxed for 6 h and the water was removed by using Dean–Stark apparatus. After cooling to
25 °C, the solvent was removed in vacuo. The yellow oil was dissolved in CH₂Cl₂ (50 mL) and washed with water (4 x 50 mL), then dried over Na₂SO₄. Evaporation of the solvents in vacuo gives the imine **64** (12.8 g, 100%) as a pale yellow solid which was used without further purification. The spectroscopic data match the literature.¹²¹

**M.p. (°C):** 55-56.

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.18-8.17 (m, 1H), 7.41 (d, J = 1.9 Hz, 1H), 7.14 (dd, J = 8.1 Hz, 1.9 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.65 (t, J = 5.4 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.72 (s, 2H), 3.34 (s, 6H), 2.72 (d, J = 5.8 Hz, 2H), 3.40 (s, 6H).

**¹³C-NMR (150 MHz, CDCl₃):** δ / ppm = 163.0, 151.4, 149.2, 129.3, 123.3, 110.3, 108.8, 103.9, 101.5, 95.2, 91.3, 82.3, 63.4, 55.9, 55.9, 54.1.

**IR (Diamond-ATR, neat):** ʋ / cm⁻¹ = 3001 (w), 2932 (w), 2912 (w), 2884 (w), 2832 (w), 1641 (s), 1600 (m), 1583 (s), 1512 (s), 1464 (s), 1444 (m), 1422 (s), 1396 (m), 1361 (m), 1334 (w), 1263 (vs), 1238 (vs), 1187 (m), 1158 (s), 1137 (vs), 1092 (s), 1066 (s), 1036 (s), 1015 (vs), 996 (s), 971 (s), 959 (vs), 868 (s), 850 (m), 822 (s), 809 (s), 780 (m), 752 (s), 636 (s), 621 (s)

(3,4-Dimethoxybenzyl)(2,2-dimethoxyethyl)amine (65)

To a solution of **N-[(1E)-(3,4-dimethoxyphenyl)methylene]-2,2-dimethoxyethanamine** (64; 12.8 g, 50.0 mmol) in ethanol (50 mL) was added sodium borohydride (3.78 g, 100 mmol) and the reaction mixture was stirred for 60 h at 25 °C. Then, water (150 mL) was added carefully. The phases were separated and the aq. layer was extracted with CH₂Cl₂ (3 x 300 mL). The combined extracts were washed with water (3 x 300 mL), brine (1 x 300 mL) and then dried over Na₂SO₄. Evaporation of the solvents in vacuo gives the amine **65** (11.0 g, 86%) as a pale yellow liquid which was used without further purification. The spectroscopic data match the literature.¹²¹

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 6.88-6.85 (m, 1H), 6.84-6.76 (m, 2H), 4.46 (t, J = 5.5 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (s, 2H), 3.34 (s, 6H), 2.72 (d, J = 5.8 Hz, 2H).

**¹³C-NMR (75Hz, CDCl₃):** δ / ppm = 148.8, 147.9, 132.6, 120.1, 111.2, 110.9, 103.7, 55.7, 55.7, 53.7, 53.5, 50.3.

**MS (EI, 70 eV):** m/z (%) = 255 (M⁺, 2), 180 (5), 151 (100), 107 (3), 75 (14).

**HRMS (C₁₃H₂₁NO₄):** calc.: 255.1464; found: 255.1471.
**C. Experimental Section**

*N-(3,4-dimethoxybenzyl)-N-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (66)*

![Chemical Structure](image)

Pyridine (3.40 mL, 42.0 mmol) was added dropwise at 0 °C to a solution of 3,4-dimethoxybenzyl)(2,2-dimethoxyethyl)amine (65; 7.66 g, 30.0 mmol) in CH$_2$Cl$_2$ (60 mL). Tosyl chloride (7.43 g, 39.0 mmol) was added and the reaction mixture was allowed to warm to 25 °C within 15 h and then poured on sat. aq. NaHCO$_3$ solution. The phases were separated and the aq. layer was extracted with CH$_2$Cl$_2$ (3 x 100 mL), then dried over MgSO$_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:2) afforded the sulphonamide 66 (12.2 g, 99%) as a pale yellow liquid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 7.74-7.68 (m, 2H), 7.30-7.24 (m, 2H), 6.73-6.71 (m, 2H), 6.66-6.64 (m, 1H), 4.38 (s, 2H), 4.33 (t, $J = 5.4$ Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.23 (s, 6H), 3.18 (d, $J = 5.4$ Hz, 2H), 2.39 (s, 3H).

$^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$/ppm = 149.0, 148.5, 143.1, 137.7, 129.5, 128.4, 127.1, 121.0, 111.3, 110.7, 103.8, 55.8, 55.6, 54.5, 52.2, 48.3, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm$^{-1}$ = 2935 (w), 2834 (w), 1595 (w), 1514 (s), 1438 (m), 1337 (s), 1255 (s), 1236 (s), 1155 (vs), 1066 (s), 1026 (vs), 997 (s), 911 (s), 813 (s), 760 (s), 670 (m), 658 (vs).

MS (EI, 70 eV): m/z (%) = 409 (M$^+$, <1), 254 (5), 151 (28), 91 (4), 75 (100).

HRMS (C$_{20}$H$_{27}$NO$_6$S): calc.: 409.1559; found: 409.1546.

**6,7-Dimethoxyisoquinoline (67)**

![Chemical Structure](image)

To a solution of *N-(3,4-dimethoxybenzyl)-N-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide* (66; 12.1 g, 29.5 mmol) in dioxane (280 mL) was added 6N HCl (22 mL). The reaction mixture was refluxed for 22 h. After cooling to 25 °C the solution was poured on water. The phases were separated and the aq. phase was extracted with Et$_2$O (2 x 250 mL), CH$_2$Cl$_2$ (3 x 250 mL). The combined aq. phases were treated with NaOH (10%) solution until pH >9. The aq. phase was extracted with Et$_2$O (2 x 250 mL) and CH$_2$Cl$_2$ (3 x 250 mL). The combined extracts were dried
over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, EtOAc) afforded the isoquinoline 67 (4.78 g, 86%) as a white solid.

**M.p. (°C):** 93-95.

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.98 (s, 1H), 8.33 (d, J = 5.6 Hz, 1H), 7.42 (d, J = 5.8 Hz, 1H), 7.11 (s, 1H), 6.98 (s, 1H), 3.95 (s, 6H).

**¹³C-NMR (150 MHz, CDCl₃):** δ / ppm = 152.8, 150.1, 149.8, 141.8, 132.3, 124.6, 119.0, 105.1, 104.4, 55.9, 55.9.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3015 (w), 2836 (w), 1573 (m), 1502 (s), 1477 (s), 1459 (m), 1433 (m), 1412 (s), 1335 (s), 1248 (vs), 1206 (s), 1138 (vs), 1001 (s), 923 (s), 852 (vs), 755 (s), 632 (s).

**MS (EI, 70 eV):** m/z (%) = 189 (M⁺, 100), 174 (11), 146 (24), 117 (8), 103 (6), 91 (6).

**HRMS (C₁₁H₁₁NO₂):** calc.: 189.0790; found: 189.0788.

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1-Iodo-6,7-dimethoxyisoquinoline (68)

To a solution of 6,7-dimethoxyisoquinoline (67; 946 mg, 5.00 mmol) in THF (5 mL) was added TMPMgCl·LiCl (5.13 mL, 6.00 mmol, 1.17 M in THF) at 25 °C. The reaction mixture was stirred for 4 h. Iodine (1.52 g, 6.00 mmol) was dissolved in THF (3 mL) in a second flask at -40 °C. To this solution the magnesium compound was added dropwise. The solution was stirred 10 min at -40 °C, then 10 min at 0 °C. The reaction mixture was quenched by adding a mixture of sat. aq. NH₄Cl solution and sat. aq. Na₂S₂O₃ solution, then sat. aq. NaHCO₃ until pH >7. The phases were separated and the aq. phase was extracted with CH₂Cl₂ (3 x 100 mL), then dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 1:4) afforded the iodo-substituted isoquinoline 68 (1.14 g, 73%) as a pale yellow solid.

**M.p. (°C):** 140-141 (decomposition).

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.06 (d, J = 5.6 Hz, 1H), 7.37 (d, J = 5.1 Hz, 1H), 7.29 (s, 1H), 6.59 (s, 1H), 4.03 (s, 3H), 4.00 (s, 3H).

**¹³C-NMR (150 MHz, CDCl₃):** δ / ppm = 153.3, 151.3, 141.8, 132.4, 127.9, 124.6, 120.0, 111.0, 105.0, 56.3, 56.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2936 (w), 1504 (s), 1473 (s), 1458 (s), 1431 (s), 1392 (s), 1296 (s), 1251 (s), 1226 (s), 1140 (vs), 1006 (s), 929 (s), 858 (vs), 774 (s), 671 (s).

MS (EI, 70 eV): m/z (%) = 315 (M$^+$, 53), 189 (12), 188 (100), 145 (3), 94 (6).

HRMS (C$_{11}$H$_{10}$INO$_2$): calc.: 314.9751; found: 314.9756.

4-(Chloromethyl)-1,2-dimethoxybenzene (53w)

To a solution of LiCl (2.54 g, 60.0 mmol, dried for 10 min under high vacuum at 400 °C using a heat gun) in THF (50 mL) was added 3,4-dimethoxybenzyl alcohol (69; 3.30 g, 20.0 mmol) at 0 °C. Then, NEt$_3$ (5.60 mL, 40.0 mmol) was added dropwise, followed by mesyl chloride (2.33 mL, 30.0 mmol). The reaction mixture was allowed to reach 25 °C within 15 h. Then, CH$_2$Cl$_2$ (300 mL) was added and the solution was washed with water (3 x 250 mL). The combined extracts were dried over MgSO$_4$. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / EtO = 4:1) afforded the benzylic chloride 53w (2.56 g, 69%) as a white solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 6.94-6.88 (m, 1H), 6.89 (s, 1H), 6.83-6.77 (m, 1H), 4.54 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H).

$^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ / ppm = 149.1, 149.0, 129.9, 121.0, 111.6, 110.9, 55.8, 55.8, 46.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3010 (w), 2935 (w), 2838 (w), 1593 (m), 1514 (s), 1463 (s), 1450 (m), 1437 (m), 1259 (s), 1232 (vs), 1154 (vs), 1139 (vs), 1036 (s), 1022 (vs), 848 (s), 815 (s), 685 (vs).

MS (EI, 70 eV): m/z (%) = 186 (M$^+$, 17), 151 (100), 107 (9), 91 (3), 77 (4).

HRMS (C$_9$H$_{11}$ClO$_2$): calc.: 186.0448; found: 186.0434.

3,4,-Dimethoxybenzyl zinc chloride (54w)

According to TP1 3,4-dimethoxybenzyl chloride (53w; 933 mg, 5.00 mmol, in 2 mL THF) was added dropwise at 0 °C to a suspension of LiCl (848 mg, 20.0 mmol) and zinc dust (1.31 g,
20.0 mmol) in 2 mL THF (activation: BrCH₂CH₂Br (0.02 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 2 h at 0 °C followed by stirring for 2.5 h at 25 °C. After centrifugation iodometric titration of 54w indicates a yield of 72%.

**Papaverine (63)**

![Papaverine](image)

To a solution of 1-iodo-6,7-dimethoxyisoquinoline (68; 315 mg, 1.00 mmol) in THF (3 mL) was added S-Phos (20.5 mg, 0.05 mmol, 5.0 mol%), Pd(OAc)₂ (5.6 mg, 0.03 mmol, 2.5 mol%). Then, 3,4-dimethoxybenzylzinc chloride (54w; 2.00 mL, 1.40 mmol, 0.70 M in THF) was added dropwise. The reaction mixture was stirred for 1.25 h at 25 °C, then quenched by adding a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 5:1. The phases were separated and the aq. layer was extracted with CH₂Cl₂ (5 x 50 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 1:4, + 2 vol-% NEt₃, + 2 vol-% EtOH) afforded papaverine 63 (229 mg, 68%) as pale yellow solid.

**M.p. (°C):** 144-146.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.35 (d, J = 6.0 Hz, 1H), 7.46 (d, J = 5.7 Hz, 1H), 7.37 (s, 1H), 7.06 (s, 1H), 6.83–6.80 (m, 2H), 6.75 (d, J = 8.1 Hz, 1H), 4.58 (s, 2H), 4.00 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H).

**13C-NMR (150 MHz, CDCl₃):** δ / ppm = 157.7, 152.3, 149.7, 149.0, 147.4, 140.9, 133.4, 132.2, 122.8, 120.4, 118.6, 111.8, 111.1, 105.2, 104.1, 55.9, 55.8, 55.8, 55.7, 42.2.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm⁻¹ = 2956 (w), 2939 (w), 2835 (w), 1504 (vs), 1478 (s), 1463 (s), 1454 (m), 1434 (s), 1414 (s), 1257 (vs), 1232 (vs), 1202 (s), 1157 (s), 1153 (s), 1147 (s), 1139 (vs), 1075 (m), 1045 (m), 1028 (vs), 986 (s), 875 (s), 867 (m), 860 (s), 843 (s), 822 (s), 805 (m), 785 (s), 768 (m), 736 (m), 732 (m), 661 (s), 645 (m).

**MS (EI, 70 eV):** m/z (%) = 339 (M⁺, 55), 324 (75), 308 (20), 154 (13).

**HRMS (C₂₀H₂₁NO₄):** calc.: 339.1471; found: 339.1455.
3.3 Efficient Nickel-catalyzed cross-coupling reactions of benzylic zinc chloride with aromatic halides

**Ethyl 2-(4-fluorobenzyl)nicotinate (72a)**

According to TP5 4-fluorobenzylzinc chloride (54c; 1.98 mL, 2.40 mmol, 1.21 M in THF) was reacted with ethyl 2-chloronicotinate (71a; 371 mg, 2.00 mmol in 0.4 mL NMP), PPh₃ (0.1 mL, 0.04 mmol, 0.4 M in THF) and Ni(acac)₂ (0.1 mL, 0.01 mmol, 0.1 M in THF). The reaction mixture was stirred for 3 h. Purification by flash chromatography (silica gel, pentane / Et₂O = 1:1) afforded the ester 72a (407 mg, 78%) as a pale yellow oil.

**¹H-NMR (600 MHz, CDCl₃):** δ / ppm = 8.67 (dd, J = 5.0 Hz, 1.8 Hz, 1H), 8.17 (dd, J = 7.8 Hz, 1.9 Hz, 1H), 7.25-7.20 (m, 3H), 6.94-6.89 (m, 2H), 4.54 (s, 2H), 4.32 (q, J = 7.2 Hz, 1H), 7.25-7.20 (m, 3H), 6.94-6.89 (m, 2H), 4.54 (s, 2H), 4.32 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H).

**¹³C-NMR (150 MHz, CDCl₃):** δ / ppm = 166.3, 161.4 (d, ¹J_C-F = 243.7 Hz), 161.0, 151.8, 138.8, 135.2 (d, ³J_C-F = 3.1 Hz), 130.4 (d, ³J_C-F = 7.9 Hz), 126.0, 121.3, 115.0 (d, ²J_C-F = 21.0 Hz), 61.5, 41.4, 14.1.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2988 (m), 2970 (m), 1720 (vs), 1601 (w), 1583 (w), 1568 (m), 1507 (s), 1438 (m), 1365 (s), 1296 (m), 1256 (s), 1217 (vs), 1157 (m), 1129 (s), 1094 (s), 1078 (vs), 1057 (s), 1017 (m), 860 (m), 810 (m), 790 (s), 747 (s), 607 (m).

**MS (EI, 70 eV):** m/z (%) = 259 (M⁺, 100), 230 (61), 213 (86), 184 (70), 157 (11), 109 (11), 93 (10).

**HRMS (C₁₅H₁₄O₂NF):** calc.: 259.1009; found: 259.1006.

**Ethyl 3-[3,5-bis(trifluoromethyl)benzyl]benzoate (72b)**

According to TP5 3-(ethoxycarbonyl)benzylzinc chloride (54m; 1.90 mL, 2.40 mmol, 1.26 M in THF) was reacted with 1-bromo-3,5-bis(trifluoromethyl)benzene (71b; 586 mg, 2.00 mmol in 0.4 mL NMP), PPh₃ (0.1 mL, 0.04 mmol, 0.4 M in THF) and Ni(acac)₂ (0.1 mL, 0.01 mmol, 0.1 M in THF). The reaction mixture was stirred for 4 h. Purification by flash chromatography (silica gel, pentane / Et₂O = 95:5) afforded the ester 72b (331 mg, 45%) as a white solid.

\(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 7.96-7.93\) (m, 1H), 7.90-7.88 (m, 1H), 7.73 (s, 1H), 7.62 (s, 2H), 7.41 (t, \(J = 7.6\) Hz, 1H), 7.36-7.33 (m, 1H), 4.37 (q, \(J = 7.2\) Hz, 2H), 4.14 (s, 2H), 1.38 (t, \(J = 7.2\) Hz, 3H).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 166.3, 142.9, 139.0, 133.2, 131.8\) (q, \(J_{CF} = 33.4\) Hz), 131.2, 130.0, 129.0, 128.9 (m), 128.2, 123.3 (q, \(J_{CF} = 272.6\) Hz), 120.5 (m), 61.1, 41.2, 14.3.

IR (Diamond-ATR, neat): \(\nu / \text{cm}^{-1} = 2989\) (w), 2970 (w), 2911 (w), 1739 (m), 1712 (s), 1447 (m), 1376 (s), 1278 (vs), 1255 (s), 1205 (s), 1164 (s), 1110 (vs), 1027 (m), 930 (m), 921 (m), 868 (m), 843 (m), 752 (s), 728 (m), 708 (s), 699 (s), 682 (s).

MS (EI, 70 eV): \(m/\text{z} / \% = 376 (M^+, 18), 357 (11), 348 (25), 331 (100), 283 (17), 233 (15), 165 (17).

HRMS (C\(_{17}\)H\(_{18}\)O\(_2\)): calc.: 376.0898; found: 376.0888.

Ethyl 2-(3-cyanobenzyl)nicotinate (72c)

According to TP5 3-cyanobenzylzinc chloride (54o; 0.94 mL, 1.20 mmol, 1.27 M in THF) was reacted with ethyl 2-chloronicotinate (71a; 186 mg, 1.00 mmol in 0.2 mL NMP), PPh\(_3\) (0.05 mL, 0.02 mmol, 0.4 M in THF) and Ni(acac)\(_2\) (0.05 mL, 0.005 mmol, 0.1 M in THF). The reaction mixture was stirred for 4 h. Purification by flash chromatography (silica gel, pentane / Et\(_2\)O = 1:1) afforded the ester 72c (115 mg, 43%) as a colourless oil.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 8.68\) (dd, \(J = 4.8\) Hz, 1.8 Hz, 1H), 8.23 (dd, \(J = 8.0\) Hz, 1.8 Hz, 1H), 7.57-7.52 (m, 2H), 7.47-7.43 (m, 1H), 7.37-7.31 (m, 1H), 7.28 (dd, \(J = 8.0\) Hz, 4.8 Hz, 1H), 4.59 (s, 2H), 4.33 (q, \(J = 7.1\) Hz, 2H), 1.33 (t, \(J = 7.1\) Hz, 3H).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 166.0, 159.9, 152.1, 141.0, 138.9, 133.7, 132.6, 129.9, 128.9, 125.7, 121.7, 119.0, 112.1, 61.6, 41.7, 14.2.

IR (Diamond-ATR, neat): \(\nu / \text{cm}^{-1} = 2983\) (w), 2229 (m), 1717 (vs), 1581 (m), 1568 (m), 1483 (w), 1436 (m), 1366 (w), 1259 (vs), 1172 (w), 1131 (s), 1079 (vs), 1058 (s), 1016 (m), 861 (w), 823 (w), 781 (s), 742 (s), 712 (m), 689 (s).

MS (EI, 70 eV): \(m/\text{z} / \% = 266 (M^+, 63), 265 (100), 237 (41), 221 (33), 193 (75), 164 (14).

HRMS (C\(_{16}\)H\(_{14}\)N\(_2\)O\(_2\)): calc.: 266.1055; found: 266.1057.
2-(3-Propionylbenzyl)benzonitrile (72d)

According to TP5 3-propionylbenzylzinc chloride (54s; 1.63 mL, 1.80 mmol, 1.10 M in THF) was reacted with 2-chlorobenzonitrile (71c; 206 mg, 1.50 mmol in 0.3 mL NMP), PPh₃ (0.08 mL, 0.03 mmol, 0.4 M in THF) and Ni(acac)₂ (0.075 mL, 0.0075 mmol, 0.1 M in THF). The reaction mixture was stirred for 6 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 3:1) afforded the nitrile 72d (265 mg, 71%) as a white solid.


¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.84-7.80 (m, 2H), 7.65-7.61 (m, 1H), 7.52-7.48 (m, 1H), 7.43-7.41 (m, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.33-7.29 (m, 1H), 7.27 (d, J = 8.1 Hz, 1H), 4.25 (s, 2H), 2.97 (q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H).

¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 200.6, 144.1, 139.2, 137.3, 133.4, 133.0, 133.0, 130.0, 128.9, 128.3, 127.0, 126.4, 118.0, 112.5, 40.0, 31.8, 8.1.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2970 (m), 2935 (m), 2901 (m), 2224 (m), 1739 (m), 1684 (s), 1597 (m), 1488 (m), 1445 (m), 1437 (m), 1407 (m), 1375 (s), 1347 (m), 1238 (s), 1217 (m), 1163 (s), 1080 (m), 1066 (m), 1028 (m), 980 (w), 963 (m), 944 (w), 918 (m), 851 (m), 789 (s), 765 (s), 755 (vs), 711 (m), 694 (s), 647 (m), 634 (m).

MS (EI, 70 eV): m/z (%) = 249 (M⁺, 2), 220 (100), 192 (10), 190 (19), 178 (9), 165 (19), 116 (4), 89 (3).

HRMS (C₁₇H₁₅NO): calc.: 249.1154; found: 249.1152.

Ethyl 3-(3-acetylbenzyl)benzoate (72e)

According to TP5 3-acetylbenzylzinc chloride (54t; 2.27 mL, 2.40 mmol, 1.07 M in THF, addition via syringe pump over 30 min) was reacted with ethyl 3-bromobenzoate (71d; 458 mg, 2.00 mmol in 0.4 mL NMP), PPh₃ (0.1 mL, 0.04 mmol, 0.4 M in THF) and Ni(acac)₂ (0.1 mL, 0.01 mmol, 0.1 M in THF). The reaction mixture was stirred for 16 h. Purification by flash
chromatography (silica gel, pentane / Et₂O = 4:1) afforded the ester 72e (289 mg, 51%) as a yellow oil.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.92-7.86 (m, 2H), 7.82-7.76 (m, 2H), 7.40-7.32 (m, 4H), 4.35 (q, J = 7.2 Hz, 2H), 4.07 (s, 2H), 2.57 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 198.1, 166.5, 141.1, 140.7, 137.5, 133.6, 133.3, 130.9, 129.9, 128.8, 128.6, 128.5, 127.6, 61.0, 41.5, 26.7, 14.3.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2981 (w), 2928 (w), 1714 (s), 1682 (s), 1602 (w), 1585 (m), 1484 (w), 1437 (m), 1392 (w), 1358 (m), 1268 (s), 1193 (s), 1104 (s), 1081 (m), 977 (w), 954 (w), 918 (w), 861 (w), 789 (m), 753 (s), 718 (s), 690 (s), 587 (s), 559 (m).

**MS (EI, 70 eV):** m/z (%) = 282 (M⁺, 100), 268 (52), 237 (61), 194 (9), 165 (72), 152 (10), 43 (35).

**HRMS (C₁₈H₁₈O₃):** calc.: 282.1256; found: 282.1249.

Ethyl 4-(1-phenylethyl)benzoate (72f)

According to TP5 1-phenylethylzinc chloride (54u; 1.78 mL, 2.40 mmol, 1.35 M in THF) was reacted with ethyl 4-bromobenzoate (71e; 458 mg, 2.00 mmol in 0.4 mL NMP), PPh₃ (0.1 mL, 0.4 M in THF) and Ni(acac)₂ (0.1 mL, 0.1 M in THF). The reaction mixture was stirred for 12 h. Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the ester 72f (485 mg, 95%) as a colourless liquid.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.00-7.93 (m, 2H), 7.33-7.26 (m, 4H), 7.23-7.16 (m, 3H), 4.36 (q, J = 7.1 Hz, 2H), 4.20 (q, J = 7.1 Hz, 1H), 1.66 (t, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 166.5, 151.5, 145.4, 129.7, 128.5, 128.4, 127.6, 127.5, 126.3, 60.7, 44.8, 21.6, 14.3.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3085 (vw), 3061 (vw), 3028 (vw), 2973 (w), 2934 (vw), 2905 (vw), 2876 (vw), 1712 (s), 1610 (m), 1574 (vw), 1494 (w), 1451 (w), 1415 (w), 1391 (w), 1367 (m), 1310 (w), 1271 (vs), 1178 (m), 1102 (s), 1055 (w), 1019 (s), 980 (w), 910 (w), 857 (m), 758 (m), 738 (m), 698 (vs), 646 (w), 634 (w), 595 (w).

**MS (EI, 70 eV):** m/z (%) = 254 (M⁺, 100), 239 (45), 209 (40), 181 (41), 165 (57), 91 (6).
HRMS (C$_{17}$H$_{18}$O$_2$): calc.: 254.1307; found: 254.1305.

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

\[ \text{N-}2\text{-[4-fluorobenzyl]prop-2-en-1-yl]aniline (78a)} \]

According to TP6 4-fluorobenzylzinc chloride (54c, 3.34 mL, 2.40 mmol, 0.72 M in THF) was added to a solution of (2-bromo-allyl)-phenyl-amine (77a; 424 mg, 2.00 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL). The reaction mixture was stirred for 24 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 98:2) afforded the aniline 78a (295 mg, 61%) as a pale yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$): \( \delta / \text{ppm} = 7.21-7.11 \text{ (m, } 4\text{H}), 7.05-6.94 \text{ (m, } 2\text{H}), 6.74-6.67 \text{ (m, } 1\text{H}), 6.59-6.51 \text{ (m, } 2\text{H}), 5.14-5.10 \text{ (m, } 1\text{H}), 4.95-4.91 \text{ (m, } 1\text{H}), 3.88 \text{ (s, } 1\text{H}), 3.65 \text{ (s, } 2\text{H}).$

$^{13}$C NMR (75 MHz, CDCl$_3$): \( \delta / \text{ppm} = 161.5 \text{ (d, } ^1J_{\text{C-F}} = 244.0 \text{ Hz}), 148.0, 146.0, 134.7 \text{ (d, } ^4J_{\text{C-F}} = 3.1 \text{ Hz}), 130.3 \text{ (d, } ^3J_{\text{C-F}} = 7.7 \text{ Hz}), 129.1, 117.4, 115.2 \text{ (d, } ^2J_{\text{C-F}} = 21.1 \text{ Hz}), 112.8, 112.5, 48.1, 40.1).$

IR (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 3419 \text{ (vw), } 3051 \text{ (vw), } 2909 \text{ (vw), } 2839 \text{ (vw), } 1651 \text{ (w), } 1601 \text{ (s), } 1504 \text{ (vs), } 1432 \text{ (w), } 1313 \text{ (m), } 1268 \text{ (m), } 1252 \text{ (m), } 1218 \text{ (s), } 1180 \text{ (m), } 1156 \text{ (m), } 1092 \text{ (m), } 1071 \text{ (w), } 1016 \text{ (w), } 993 \text{ (w), } 901 \text{ (m), } 852 \text{ (m), } 812 \text{ (m), } 777 \text{ (m), } 747 \text{ (vs), } 690 \text{ (s).}$

MS (EI, 70 eV): m/z (%) = 241 (M$^+$, 100), 147 (55), 132 (28), 109 (25), 106 (72), 93 (16), 77 (25).

HRMS (C$_{16}$H$_{16}$FN): calc.: 241.1267; found: 241.1262.

\[ \text{N-}2\text{-[3-(trifluoromethyl)benzyl]prop-2-en-1-yl]aniline (78b)} \]

According to TP6 3-(trifluoromethyl)benzylzinc chloride (54g; 1.60 mL, 2.40 mmol, 1.50 M in THF) was added to a solution of (2-bromo-allyl)-phenyl-amine (77a; 424 mg, 2.00 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL). The reaction
mixture was stirred for 8 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the aniline 78b (437 mg, 87%) as a yellow oil.

1H NMR (600 MHz, CDCl₃): δ / ppm = 7.51-7.46 (m, 2H), 7.43-7.38 (m, 2H), 7.17-7.12 (m, 2H), 6.72-6.68 (m, 1H), 6.65-6.52 (m, 2H), 5.17 (d, J = 0.9 Hz, 1H), 4.94 (d, J = 0.9 Hz, 1H) 3.82 (s, 1H), 3.66 (s, 2H), 3.47 (s, 2H).

13C NMR (150 MHz, CDCl₃): δ / ppm = 148.0, 145.3, 140.1, 132.3 (q, J_C-F = 1.3 Hz), 130.8 (q, J_C-F = 32.1 Hz), 129.2, 128.8, 125.5 (q, J_C-F = 3.9 Hz), 124.2 (q, J_C-F = 272.3 Hz), 123.2 (q, J_C-F = 4.0 Hz), 117.5, 113.2, 112.8, 48.1, 40.6.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3420 (vw), 3054 (vw), 2913 (vw), 1603 (s), 1506 (m), 1448 (w), 1327 (vs), 1161 (s), 1117 (vs), 1093 (s), 1072 (s).

MS (EI, 70 eV): m/z (%) = 291 (M⁺, 100), 276 (18), 132 (29), 129 (21), 106 (95).

HRMS (C₁₇H₁₆F₃N): calc.: 291.1235; found: 291.1227.

2-Chloro-4-(4-methoxybenzyl)aniline (78c)

According to 4-methoxybenzylzinc chloride (54i; 1.94 mL, 2.40 mmol, 1.24 M in THF) was added to a solution of 4-bromo-2-chloroaniline (77b; 413 mg, 2.00 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL). The reaction mixture was stirred for 6.25 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 to 3:1) afforded the aniline 78c (381 mg, 77%) as a yellow oil.

1H NMR (600 MHz, CDCl₃): δ / ppm = 7.10-7.06 (m, 2H), 7.06 (d, J = 1.9 Hz, 1H), 6.87 (dd, J = 8.1 Hz, 1.9 Hz, 1H), 6.85-6.81 (m, 2H), 6.68 (d, J = 8.1 Hz, 1H), 3.92 (s, 2H), 3.79 (s, 2H), 3.78 (s, 3H).

13C NMR (150 MHz, CDCl₃): δ / ppm = 157.9, 140.9, 133.2, 132.6, 129.7, 129.4, 128.0, 119.3, 115.9, 113.9, 55.2, 39.8.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3465 (vw), 3054 (vw), 3029 (vw), 2913 (vw), 1603 (s), 1506 (m), 1448 (w), 1327 (vs), 1161 (s), 1117 (vs), 1093 (s), 1072 (s).

MS (EI, 70 eV): m/z (%) = 247 (M⁺, 100), 212 (69), 180 (12), 168 (12), 140 (13), 106 (17).

HRMS (C₁₄H₁₄ClNO): calc.: 247.0764; found: 247.0756.
3,4,5-Trimethoxybenzylphenol (78d)

According to TP7, 3,4,5-trimethoxybenzylzinc chloride (54h, 2.47 mL, 2.40 mmol, 0.97 M in THF) was slowly added over 90 min using a syringe pump to a solution of 4-bromophenol (77c; 346 mg, 2.00 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL) at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:1) afforded the phenol 78d (232 mg, 42%) as a white solid.

**M.p. (°C):** 119-120.

**$^1$H NMR (300 MHz, CDCl$_3$):** δ / ppm = 7.07-7.00 (m, 2H), 6.79-6.73 (m, 2H), 6.38 (s, 2H), 5.22 (s, 1H), 3.84 (s, 2H), 3.82 (s, 3H), 3.79 (s, 6H).

**$^{13}$C NMR (75 MHz, CDCl$_3$):** δ / ppm = 154.0, 153.1, 137.3, 136.0, 132.8, 129.9, 115.3, 105.7, 60.8, 56.0, 41.2.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1}$ = 3338 (w), 1612 (w), 1592 (m), 1511 (m), 1462 (m), 1444 (w), 1438 (w), 1420 (m), 1342 (w), 1318 (w), 1262 (w), 1240 (s), 1224 (m), 1189 (w), 1172 (w), 1126 (vs), 1040 (w), 1001 (m), 971 (w), 862 (w), 846 (w), 824 (m), 783 (w), 720 (vw), 669 (m).

**MS (EI, 70 eV):** m/z (%) = 274 (M$^+$, 100), 259 (19), 227 (9), 184 (8), 107 (5).

**HRMS (C$_{16}$H$_{18}$O$_4$):** calc.: 274.1205; found: 274.1208.

3-cyanobenzylzinc chloride (54o, 1.89 mL, 2.40 mmol, 1.27 M in THF) is slowly added over 90 min using a syringe pump to a solution of (4-bromophenyl)methanol (77d; 374 mg, 2.00 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL) at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:1) afforded the nitrile 78e (375 mg, 84%) as a yellow solid.

**M.p. (°C):** 53-55.

**$^1$H NMR (600 MHz, CDCl$_3$):** δ / ppm = 7.51-7.33 (m, 4H), 7.31 (d, $J$ = 8.2 Hz, 2H), 7.15 (d, $J$ = 8.4 Hz, 2H), 4.65 (s, 2H), 3.99 (s, 2H), 1.95 (s, 1H).
13C NMR (150 MHz, CDCl3): δ / ppm = 142.5, 139.3, 138.7, 133.3, 132.2, 129.9, 129.2, 129.0, 127.4, 118.8, 112.4, 64.9, 41.0.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3404 (m), 2921 (m), 2853 (m), 2228 (s), 1582 (w), 1512 (w), 1482 (m), 1419 (m), 1209 (w), 1031 (s), 1016 (s), 794 (s), 750 (m), 730 (m), 686 (vs).

MS (EI, 70 eV): m/z (%) = 223 (M⁺, 80), 221 (18), 224 (12), 192 (63), 165 (41), 116 (40), 107 (100), 91 (14), 79 (35), 44 (38).

HRMS (C15H13NO2): calc.: 244.0900; found: 244.0895.

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

Methyl 2-(4-fluorobenzyl)benzoate (80a)

According to TP8 – zinc insertion: 4-fluorobenzyl chloride (53c; 723 mg, 5.00 mmol), LiCl (318 mg, 7.50 mmol) and Zn (490 mg, 7.50 mmol) in THF (2.5 mL), t₁ = 25 °C for 24 h; cross-coupling: methyl 2-bromobenzoate (71g; 645 mg, 3.00 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), t₂ = 25 °C for 24 h; work-up and purification: extracted with Et₂O (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et₂O = 98:2) to give the diarylmethane 80a as a colourless liquid (702 mg, 96%).

1H-NMR (300 MHz, CDCl3): δ / ppm = 7.90 (dd, J = 7.9 Hz, 1.3 Hz, 1H), 7.47-7.39 (m, 1H), 7.33-7.25 (m, 1H), 7.22-7.17 (m, 1H), 7.13-7.06 (m, 2H), 6.98-6.89 (m, 2H), 4.34 (s, 2H), 3.82 (s, 3H).

13C-NMR (75 MHz, CDCl3): δ / ppm = 167.9, 161.2 (d, 1JC-F = 243.8 Hz), 142.0 (d, 6JC-F = 1.0 Hz), 136.5 (d, 4JC-F = 3.4 Hz), 132.1, 131.5, 130.8, 130.2 (d, 3JC-F = 7.7 Hz), 129.8, 126.4, 115.0 (d, 2JC-F = 21.4 Hz), 51.9, 38.8 (d, 5JC-F = 0.5 Hz).

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2952 (w), 2360 (w), 2342 (w), 1718 (vs), 1602 (m), 1576 (w), 1508 (s), 1434 (m), 1258 (vs), 1220 (s), 1192 (m), 1158 (m), 1128 (s), 1094 (s), 1076 (s), 1048 (m), 1016 (w), 966 (w), 914 (w), 844 (m), 822 (m), 802 (m), 776 (s), 732 (vs), 704 (m), 664 (m).

MS (EI, 70 eV): m/z (%) = 244 (M⁺, 3), 212 (100), 183 (38), 133 (10), 109 (5), 91 (5).

HRMS (C15H13FO2): calc.: 244.0900; found: 244.0895.
4-(3,4,5-Trimethoxybenzyl)benzonitrile (80b)

According to **TP8 – zinc insertion**: 3,4,5-trimethoxybenzyl chloride (53h; 1.08 g, 5.00 mmol), LiCl (318 mg, 7.50 mmol) and Zn (490 mg, 7.50 mmol) in THF (2.5 mL), \( t_1 = 25 ^\circ \text{C} \) for 4 h; **cross-coupling**: 4-bromobenzonitrile (71h; 455 mg, 2.50 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), \( t_2 = 25 ^\circ \text{C} \) for 15 h; **work-up and purification**: extracted with Et\(_2\)O (3 \( \times \) 20 mL), purified by flash chromatography (silica gel, pentane / Et\(_2\)O = 3:1) to give the diarylmethane 80b as a white solid (698 mg, 99%).

**M.p. (°C)**: 60-62.

**\(^1\)H-NMR (300 MHz, CDCl\(_3\))**: \( \delta / \text{ppm} = 7.60-7.54 (\text{m, 2H}), 7.31-7.25 (\text{m, 2H}), 6.34 (\text{s, 2H}), 3.95 (\text{s, 2H}), 3.81 (\text{s, 3H}), 3.80 (\text{s, 6H}). \)

**\(^13\)C-NMR (75 MHz, CDCl\(_3\))**: \( \delta / \text{ppm} = 153.4, 146.5, 136.6, 134.8, 132.3, 129.5, 118.9, 110.1, 105.9, 60.8, 56.0, 42.2. \)

**IR (Diamond-ATR, neat)**: \( \tilde{\nu} / \text{cm}^{-1} = 2990 (\text{w}), 2940 (\text{w}), 2836 (\text{w}), 2360 (\text{w}), 2342 (\text{w}), 2224 (\text{w}), 1590 (\text{s}), 1508 (\text{m}), 1500 (\text{m}), 1464 (\text{m}), 1422 (\text{m}), 1338 (\text{w}), 1324 (\text{w}), 1238 (\text{s}), 1186 (\text{w}), 1128 (\text{vs}), 1016 (\text{w}), 998 (\text{s}), 978 (\text{m}), 944 (\text{w}), 924 (\text{w}), 854 (\text{w}), 832 (\text{m}), 818 (\text{m}), 808 (\text{m}), 734 (\text{m}), 666 (\text{m}), 644 (\text{m}). \)

**MS (EI, 70 eV)**: m/z (%) = 283 (M\(^+\), 100), 268 (54), 240 (12), 225 (9), 209 (6), 166 (4), 154 (4), 127 (5), 116 (10).

**HRMS (C\(_{17}\)H\(_{17}\)NO\(_3\))**: calc.: 283.1208; found: 283.1203.

Ethyl 3-[4-(trifluoromethyl)benzyl]benzoate (80c)

According to **TP8 – zinc insertion**: 3-(ethoxycarbonyl)benzyl chloride (53m; 993 mg, 5.00 mmol), LiCl (424 mg, 10.0 mmol) and Zn (654 mg, 10.0 mmol) in THF (2.5 mL), \( t_1 = 25 ^\circ \text{C} \) for 4 h; **cross-coupling**: 1-bromo-4-(trifluoromethyl)benzene (71i; 667 mg, 2.97 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), \( t_2 = 25 ^\circ \text{C} \) for 4 h; **work-up and purification**: extracted with CH\(_2\)Cl\(_2\) (3 \( \times \) 20 mL), purified by flash chromatography (silica gel, pentane / Et\(_2\)O = 95:5) to give the diarylmethane 80c as a colourless liquid (857 mg, 94%).
C. Experimental Section

$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ / ppm = 7.93-7.90 (m, 1H), 7.90-7.88 (m, 1H), 7.54 (d, $J = 8.1$ Hz, 2H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.35-7.33 (m, 1H), 7.28 (d, $J = 8.1$ Hz, 2H), 4.36 (q, $J = 7.2$ Hz, 2H), 4.07 (s, 2H), 1.38 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ / ppm = 166.5, 144.5 (q, $^4J_{C,F} = 1.3$ Hz), 140.2, 133.3, 130.9, 130.0, 129.1, 128.7, 128.7 (q, $^2J_{C,F} = 32.3$ Hz), 127.7, 125.5 (q, $^3J_{C,F} = 3.9$ Hz), 124.2 (q, $^1J_{C,F} = 271.9$ Hz), 61.0, 41.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2985 (vw), 1715 (s), 1619 (w), 1588 (w), 1445 (w), 1418 (w), 1368 (w), 1322 (vs), 1278 (s), 1188 (m), 1161 (s), 1119 (s), 1065 (vs), 1018 (s), 939 (w), 852 (m), 816 (m), 764 (w), 742 (vs), 695 (m), 672 (m), 639 (m), 596 (m).

MS (EI, 70 eV): m/z (%) = 308 (M$^+$, 39), 280 (20), 263 (100), 235 (23), 215 (9), 165 (30).

HRMS (C$_{17}$H$_{15}$F$_3$O$_2$): calc.: 308.1024; found: 308.1022.

3-[3,5-Bis(trifluoromethyl)benzyl]benzonitrile (80d)

According to TP8 – zinc insertion: 3-cyanobenzyl chloride (53o; 758 mg, 5.00 mmol), LiCl (318 mg, 7.50 mmol) and Zn (490 mg, 7.50 mmol) in THF (2.5 mL), $t_1 = 25$ °C for 3.5 h; cross-coupling: 1-bromo-3,5-bis(trifluoromethyl)benzene (879 mg, 3.00 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), $t_2 = 25$ °C for 15.5 h; work-up and purification: extracted with Et$_2$O (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et$_2$O = 95:5 to 9:1) to give the diarylmethane 80d as a white solid (844 mg, 85%).


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.77 (m, 1H), 7.60 (m, 2H), 7.59-7.54 (m, 1H), 7.49-7.43 (m, 2H), 7.43-7.38 (m, 1H), 4.14 (s, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 141.8, 140.2, 133.3, 132.3, 132.1 (q, $^2J_{C,F} = 33.3$ Hz), 130.8, 129.8, 128.9 (m), 123.1 (q, $^1J_{C,F} = 273.1$ Hz), 120.9 (m), 118.5, 113.1, 40.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3675 (w), 2989 (m), 2970 (m), 2229 (w), 1739 (s), 1374 (s), 1275 (s), 1229 (s), 1217 (s), 1165 (s), 1123 (vs), 1109 (vs), 944 (m), 911 (m), 903 (m), 881 (m), 842 (m), 804 (m), 737 (m), 726 (m), 708 (s), 692 (s), 682 (s).

MS (EI, 70 eV): m/z (%) = 329 (M$^+$, 100), 309 (68), 289 (13), 260 (33), 240 (30), 190 (25), 116 (8).
Ethyl 3-(3-pentanoylbenzyl)benzoate (80e)

According to TP8 – zinc insertion: 3-pentanoylbenzyl chloride (53q; 843 mg, 4.00 mmol), LiCl (254 mg, 6.00 mmol) and Zn (392 mg, 6.00 mmol) in THF (2.0 mL), $t_1 = 25 \, ^\circ\!\!C$ for 4 h; cross-coupling: ethyl 3-bromobenzoate (71d; 458 mg, 2.00 mmol), PEPPSI-IPr (6.8 mg, 0.01 mmol), THF (1.0 mL), $t_2 = 25 \, ^\circ\!\!C$ for 2 h; work-up and purification: extracted with CH$_2$Cl$_2$ (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et$_2$O = 15:1 to 7:1) to give the diarylmethane 80e as a colourless liquid (595 mg, 92%).

$^1$H-NMR (300 MHz, CDCl$_3$): δ / ppm = 7.92-7.86 (m, 2H), 7.82-7.75 (m, 2H), 7.40-7.31 (m, 4H), 4.35 (q, $J = 7.1$ Hz, 2H), 4.07 (s, 2H), 2.92 (t, $J = 7.3$ Hz, 2H), 1.76-1.62 (m, 2H), 1.45-1.30 (m, 2H), 1.37 (t, $J = 7.1$ Hz, 3H), 0.93 (t, $J = 7.3$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / ppm = 200.5, 166.5, 141.0, 140.7, 137.4, 133.3 (overlap), 130.8, 129.9, 128.8, 128.6, 128.3, 127.6, 126.2, 60.9, 41.5, 38.4, 26.4, 22.4, 14.3, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2957 (m), 2931 (m), 2871 (w), 1714 (vs), 1681 (s), 1443 (m), 1366 (m), 1276 (vs), 1190 (s), 1159 (m), 1104 (m), 1081 (m), 1022 (m), 745 (m), 703 (m).

MS (EI, 70 eV): m/z (%) = 324 (M$^+$, 3), 282 (25), 267 (100), 237 (10), 236 (51), 166 (12), 165 (30), 161 (13).

HRMS (C$_{21}$H$_{24}$O$_3$): calc.: 324.1725; found: 324.1714.

4-(3-Propionylbenzyl)benzonitrile (80f)

According to TP8 – zinc insertion: 3-propionylbenzyl chloride (53s; 365 mg, 2.00 mmol), LiCl (127 mg, 3.00 mmol) and Zn (196 mg, 3.00 mmol) in THF (1.0 mL), $t_1 = 25 \, ^\circ\!\!C$ for 4 h; cross-coupling: 4-bromobenzonitrile (71h; 182 mg, 1.0 mmol), PEPPSI-IPr (3.4 mg, 0.005 mmol), THF (1.0 mL), $t_2 = 25 \, ^\circ\!\!C$ for 2 h; work-up and purification: extracted with CH$_2$Cl$_2$ (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et$_2$O = 7:1) to give the diarylmethane 80f as a white solid (196 mg, 79%).
M.p. (°C): 83-84.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.83-7.71 (m, 2H), 7.53 (d, $J = 8.3$ Hz, 2H), 7.42-7.20 (m, 4H), 4.04 (s, 2H), 2.93 (q, $J = 7.1$ Hz, 2H), 1.17 (t, $J = 7.3$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 200.6, 146.0, 139.9, 137.4, 133.3, 132.4, 129.6, 129.0, 128.3, 126.5, 118.8, 110.3, 41.8, 31.8, 8.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1} = 2978$ (w), 2938 (w), 2227 (m), 1683 (vs), 1602 (m), 1506 (m), 1413 (m), 1349 (m), 1240 (s), 1177 (m), 1160 (s), 1020 (m), 973 (m), 859 (m), 813 (s), 783 (s), 746 (s), 695 (s).

MS (EI, 70 eV): m/z (%) = 249 (M$^+$, 100), 221 (26), 220 (31), 191 (42), 190 (86), 165 (75), 152 (11).

HRMS (C$_{17}$H$_{15}$NO): calc.: 249.1154; found: 249.1131.

1-{3-[3-(Trifluoromethyl)benzyl]phenyl}ethanone (80 g)

According to TP8 – zinc insertion: 3-acetylbenzyl chloride (53t; 674 mg, 4.00 mmol), LiCl (254 mg, 6.00 mmol) and Zn (392 mg, 6.00 mmol) in THF (2.0 mL), t$_1$ = 25 °C for 3 h; cross-coupling: 1-bromo-3-(trifluoromethyl)benzene (71j; 450 mg, 2.00 mmol), PEPPSI-IPr (6.8 mg, 0.01 mmol), THF (1.0 mL), t$_2$ = 25 °C for 5 h; work-up and purification: extracted with ether (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et$_2$O = 4:1) to give the diarylmethane 80g as a colourless liquid (476 mg, 86%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.84-7.78 (m, 2H), 7.51-7.31 (m, 6H), 4.09 (s, 2H), 2.58 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 198.0, 141.3, 140.6, 137.6, 133.6, 132.2 (q, $^4$J$_{C-F}$ = 1.3 Hz), 130.9 (q, $^2$J$_{C-F}$ = 32.2 Hz), 129.1, 129.0, 128.6, 126.7, 125.5 (q, $^3$J$_{C-F}$ = 3.8 Hz), 124.1 (m, $^1$J$_{C-F}$ = 272.1 Hz), 123.3 (q, $^3$J$_{C-F}$ = 3.9 Hz), 41.5, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1} = 1682$ (s), 1436 (w), 1358 (m), 1329 (s), 1268 (s), 1159 (s), 1117 (vs), 1094 (s), 1072 (vs), 915 (m), 790 (s), 749 (m), 719 (m), 701 (s), 692 (s), 655 (m).

MS (EI, 70 eV): m/z (%) = 278 (M$^+$, 21), 263 (100), 215 (12), 165 (23), 43 (13).

HRMS (C$_{16}$H$_{13}$F$_3$O): calc.: 278.0918; found: 278.0921.
Ethyl 4-(3-acetylbenzyl)benzoate (80h)

According to TP8 – zinc insertion: 3-acetylbenzyl chloride (53t; 337 mg, 2.00 mmol), LiCl (127 mg, 3.00 mmol) and Zn (196 mg, 3.00 mmol) in THF (1.0 mL), $t_1 = 25^\circ$C for 3 h; cross-coupling: ethyl 4-bromobenzoate (71e; 229 mg, 1.00 mmol), PEPPSI (3.4 mg, 0.005 mmol), THF (1.0 mL), $t_2 = 25^\circ$C for 2 h; work-up and purification: extracted with CH$_2$Cl$_2$ (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et$_2$O = 7:1) to give the diarylmethane 80h as a white solid (264 mg, 94%).

M.p. (°C): 78-80.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.99-7.93 (m, 2H), 7.82-7.77 (m, 2H), 7.41-7.32 (m, 2H), 7.26-7.21 (m, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 4.07 (s, 2H), 2.56 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 198.1, 166.5, 145.6, 140.8, 137.5, 133.7, 129.9, 128.9, 128.9 (overlap), 128.8, 128.6, 126.6, 60.9, 41.7, 26.7, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2984 (w), 1706 (vs), 1673 (vs), 1609 (m), 1580 (m), 1478 (m), 1416 (m), 1363 (s), 1288 (s), 1274 (vs), 1194 (s), 1177 (s), 1125 (s), 1103 (s), 1021 (s), 958 (m), 920 (s), 856 (m), 792 (s), 763 (s), 720 (vs), 698 (vs).

MS (EI, 70 eV): m/z (%) = 282 (M$^+$, 48), 267 (100), 237 (26), 165 (20), 111 (12), 43 (11).

HRMS (C$_{18}$H$_{18}$O$_3$): calc.: 282.1256; found: 282.1234.

1-[3-(3-Methoxyphenyl)phenyl]ethanone (80i)

According to TP8 – zinc insertion: 3-acetylbenzyl chloride (53t; 337 mg, 2.00 mmol), LiCl (127 mg, 3.00 mmol) and Zn (196 mg, 3.00 mmol) in THF (1.0 mL), $t_1 = 25^\circ$C for 3 h; cross-coupling: 1-bromo-3-methoxybenzene (71k; 187 mg, 1.00 mmol), PEPPSI-IPr (3.4 mg, 0.005 mmol), THF (1.0 mL), $t_2 = 25^\circ$C for 5 h; work-up and purification: extracted with CH$_2$Cl$_2$ (3 × 20 mL), purified by flash chromatography (silica gel, pentane / Et$_2$O = 7:1) to give the diarylmethane 80i as a white solid (145 mg, 60%).

M.p. (°C): 78-80.
C. Experimental Section

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.84-7.74 (m, 2H), 7.43-7.33 (m, 2H), 7.21 (t, $J$ = 7.9 Hz, 1H), 6.81-6.69 (m, 3H), 4.00 (s, 2H), 3.76 (s, 3H), 2.57 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 198.2, 159.8, 141.9, 141.5, 137.4, 133.7, 129.5, 128.7, 128.6, 126.3, 121.3, 114.8, 111.5, 55.1, 41.8, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3003 (vw), 2938 (w), 2836 (w), 1680 (s), 1598 (s), 1583 (s), 1488 (s), 1454 (m), 1434 (m), 1356 (m), 1267 (vs), 1257 (vs), 1162 (m), 1148 (s), 1047 (s), 778 (s), 740 (s).

MS (EI, 70 eV): m/z (%) = 240 (M$^+$, 84), 226 (20), 225 (100), 197 (21), 182 (18), 165 (43), 153 (21), 44 (17), 42 (23).

HRMS (C$_{16}$H$_{16}$O$_2$): calc.: 240.1150; found: 240.1132.

Ethyl 3-[(4-(trifluoromethyl)benzyl]benzoate (80j)

According to TP8 – zinc insertion: (1-chloroethyl)benzene (53u; 703 mg, 5.00 mmol), LiCl (318 mg, 7.50 mmol) and Zn (490 mg, 7.50 mmol) in THF (1.0 mL), $t_1$ = 25 °C for 15 h; cross-coupling: 4-bromobenzonitrile (71h; 546 mg, 3.00 mmol), PEPPSI-IPr (8.5 mg, 0.013 mmol), THF (1.0 mL), $t_2$ = 25 °C for 8 h; work-up and purification: extracted with CH$_2$Cl$_2$ (3 x 20 mL), purified by flash chromatography (silica gel, pentane / Et$_2$O = 98:2) to give the 1,1-diarylethane 80j as a colourless liquid (586 mg, 94%).

$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ / ppm = 7.56 (d, $J$ = 8.6 Hz, 2H), 7.33-7.27 (m, 4H), 7.21 (t, $J$ = 7.4 Hz, 1H), 7.18 (d, $J$ = 7.2 Hz, 2H), 4.19 (q, $J$ = 7.5 Hz, 1H), 1.64 (d, $J$ = 7.2 Hz, 3H).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3031 (vw), 2973 (w), 2876 (w), 2222 (m), 1912 (v), 1606 (w), 1598 (w), 1502 (w), 1491 (m), 1452 (m), 1416 (w), 1374 (w), 1302 (w), 1176 (w), 1122 (w), 1086 (w), 1045 (w), 1028 (w), 1019 (w), 982 (w), 840 (s), 771 (s), 730 (s), 702 (vs), 600 (s), 559 (s).

MS (EI, 70 eV): m/z (%) = 207 (M$^+$, 36), 192 (100), 165 (18), 95 (5), 83 (4).

HRMS (C$_{15}$H$_{13}$N): calc.: 207.1048; found: 207.1038.
3.6. Preparation of diheterobenzylic zinc reagents and heterobenzylic zinc chlorides

2-(2-Chloropyridin-4-yl)-1-phenylethanone (87)

To a solution of 2-chloro-4-methylpyridine (85; 357 mg, 2.80 mmol) in THF (1.5 mL) was added TMP$\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$ (4.19 mL, 1.55 mmol, 0.37 M in THF) at 0 °C. The reaction mixture was stirred for 3 h. Then, the reaction mixture was cooled to -30 °C. CuCN·2LiCl (3.10 mL, 3.10 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for 30 min. Then, benzoyl chloride (60f; 281 mg, 2.00 mmol) was added at -78 °C and the reaction mixture was slowly warmed to -20 °C within 22 h. Then, a mixture of sat. aq. NH$_4$Cl / NH$_3$ (25% in H$_2$O) = 2:1 was added (50 mL). The phases were separated and the aq. layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined extracts were dried over MgSO$_4$. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:4) afforded the pyridine 87 (279 mg, 60%) as a white solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta / $ppm = 8.33 (d, $J = 5.1$ Hz, 1H), 8.02-7.93 (m, 2H), 7.65-7.56 (m, 1H), 7.53-7.44 (m, 2H), 7.26-7.24 (m, 1H), 7.15-7.09 (m, 1H), 4.27 (s, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta / $ppm = 195.0, 151.7, 149.6, 146.7, 136.0, 133.8, 128.9, 128.4, 125.4, 123.7, 44.0.

IR (Diamond-ATR, neat): $\tilde{\nu} / $cm$^{-1} = 3062$ (vw), 2914 (vw), 1688 (s), 1597 (m), 1579 (w), 1550 (w), 1446 (w), 1416 (w), 1388 (m), 1325 (m), 1290 (w), 1230 (m), 1208 (m), 1184 (w), 1124 (w), 1088 (m), 992 (m), 915 (w), 898 (w), 886 (w), 860 (w), 792 (m), 756 (vs), 722 (m), 690 (s), 674 (m).

MS (EI, 70 eV): m/z (%) = 231 (M$^+$, 1), 105 (100), 77 (32), 63 (1), 51 (8).

HRMS ($C_{13}H_{10}ClNO_3$): calc.: 231.0451; found: 231.0439.
Ethyl 4-(2-chloropyridin-4-yl)-2-methylidenebutanoate (88)

To a solution of 2-chloro-4-methylpyridine (85; 255 mg, 2.00 mmol) in THF (1 mL) was added TMP·Zn·2MgCl·2LiCl (3.24 mL, 1.20 mmol, 0.37 M in THF) at 0 °C. The reaction mixture was stirred for 3 h. Then, the reaction mixture was cooled to -60 °C and ethyl 2-(bromomethyl)acrylate (55b; 541 mg, 2.80 mmol) was added followed by CuCN·2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF). The reaction mixture was stirred for 30 min at -60 °C and additional 30 min at 0 °C. Then, sat. aq. NH₄Cl solution (20 mL) was added. The phases were separated and the aq. layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 4:1) afforded the pyridine 88 (472 mg, 98%) as a yellow liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.25 (d, J = 5.1 Hz, 1H), 7.16-7.12 (m, 1H), 7.04-7.00 (m, 1H), 6.18-6.15 (m, 1H), 5.48 (q, J = 1.3 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 2.83-2.73 (m, 2H), 2.64-2.55 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 166.6, 153.7, 151.6, 149.5, 138.9, 125.9, 124.2, 122.7, 60.8, 33.9, 32.5, 14.2.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2982 (w), 2930 (w), 1711 (vs), 1631 (w), 1593 (s), 1548 (m), 1466 (m), 1445 (w), 1386 (s), 1311 (m), 1296 (m), 1277 (m), 1256 (m), 1241 (m), 1183 (vs), 1135 (s), 1086 (s), 1028 (m), 990 (m), 945 (m), 900 (m), 875 (m), 835 (s), 818 (m), 721 (m), 711 (w), 684 (w), 635 (w).

MS (EI, 70 eV): m/z (%) = 239 (M⁺, 12), 210 (18), 194 (24), 165 (100), 151 (16), 140 (12), 130 (82), 103 (16), 91 (18), 77 (20), 63 (11), 51 (15).

HRMS (C₁₂H₁₄ClNO₂): calc.: 239.0713; found: 239.0701.
2-(2-Chloropyridin-4-yl)-1-phenylethanol (89)

To a solution of 2-chloro-4-methylpyridine (85; 357 mg, 2.80 mmol) in THF (1.5 mL) was added TMP₂Zn·2MgCl₂·2LiCl (4.19 mL, 1.55 mmol, 0.37 M in THF) at 0 °C. The reaction mixture was stirred for 3 h. Then, benzaldehyde (60g; 228 mg, 2.15 mmol) was added and the reaction mixture was slowly warmed to 25 °C and stirred for 4.5 h. Sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 8:1 was added (10 mL). The phases were separated and the aq. layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined extracts were dried over Na₂SO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 1:1) afforded the pyridine 89 (485 mg, 97%) as a white solid.

M.p. (°C): 80-82.

¹H-NMR (400 MHz, DMSO-d₆): δ / ppm = 8.25 (dd, J = 5.1 Hz, 0.6 Hz, 1H), 7.38-7.27 (m, 5H), 7.25-7.19 (m, 2H), 5.43 (d, J = 4.7 Hz, 1H), 4.87-4.80 (m, 1H), 2.98-2.92 (m, 1H), 2.91-2.84 (m, 1H).

¹³C-NMR (100 MHz, DMSO-d₆): δ / ppm = 152.4, 149.9, 149.1, 145.0, 127.9, 126.9, 125.8, 125.0, 124.4, 72.2, 44.1.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3311 (w), 3063 (w), 2946 (w), 2909 (w), 2834 (vw), 1596 (s), 1547 (m), 1452 (w), 1431 (m), 1387 (s), 1332 (m), 1277 (w), 1237 (w), 1220 (w), 1204 (w), 1124 (w), 1086 (s), 1051 (vs), 1026 (m), 1010 (m), 996 (m), 918 (w), 900 (w), 888 (w), 847 (m), 816 (m), 761 (m), 752 (m), 735 (m), 717 (s), 700 (vs).

MS (EI, 70 eV): m/z (%) = 233 (M⁺, <1), 215 (1), 180 (1), 127 (100), 107 (63), 79 (36).

HRMS (C₁₃H₁₂ClNO): calc.: 233.0607; found: 233.0595.

6-Chloropyridin-3-yl)methylzinc chloride (91a)

According to TP1 2-chloro-5-(chloromethyl)pyridine (90a; 1.62 g, 10.0 mmol, in 4 mL THF) was added dropwise at 0 °C to a suspension of LiCl (848 mg, 20.0 mmol) and zinc dust (1.31 g, 20.0 mmol) in THF (1 mL) (activation: BrCH₂CH₂Br (0.04 mL, 5 mol%), TMSCl (0.01 mL,
1 mol%). The reaction mixture was stirred for 2.5 h at 25 °C. After centrifugation iodometric titration of 91a indicates a yield of 78%.

(3,5-Dimethylisoxazol-4-yl)methylzinc chloride (91b)

According to TP1 4-(chloromethyl)-3,5-dimethylisoxazole (90b; 1.02 g, 7.00 mmol) was added dropwise at 25 °C to a suspension of LiCl (455 mg, 10.5 mmol) and zinc dust (687 mg, 10.5 mmol) in THF (3.5 mL) (activation: BrCH₂CH₂Br (0.03 mL, 5 mol%), TMSCl (0.01 mL, 1 mol%)). The reaction mixture was stirred for 4 h at 25 °C. After centrifugation iodometric titration of 91b indicates a yield of 90%.

2-(6-Chloropyridin-3-yl)-1-phenylethanol (92a)

According to TP2 (6-chloropyridin-3-yl)methylzinc chloride (91a; 2.33 mL, 2.40 mmol, 1.03 mL in THF) was reacted with benzaldehyde (60g; 212 mg, 2.00 mmol, in 1.0 mL THF) at 0 °C. The reaction mixture was slowly warmed to 25 °C within 17 h and was quenched with sat. aq. NaCl solution (50 mL). The phases were separated and the aq. layer was extracted with EtOAc (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 1:1) afforded the benzylic alcohol 92a (463 mg, 99%) as a white solid.


^{1}H-NMR (400 MHz, DMSO): δ / ppm = 8.14 (d, J = 2.5 Hz, 1H), 7.63 (dd, J = 8.2, 2.5 Hz, 1H), 7.37 (dd, J = 8.2, 0.6 Hz, 1H), 7.34-7.27 (m, 4H), 7.25-7.19 (m, 1H), 5.40 (d, J = 4.5 Hz, 1H (‘OH’)), 4.76 (dt, J = 7.9, 4.8 Hz, 1H), 2.93 (dd, J = 13.7, 4.9 Hz, 1H), 2.86 (dd, J = 13.7, 8.0 Hz, 1H).

^{13}C-NMR (100 MHz, DMSO): δ / ppm = 150.5, 147.8, 144.9, 140.7, 134.0, 127.9, 126.8, 125.8, 123.3, 72.6, 41.4.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3346 (w), 1738 (w), 1586 (w), 1568 (m), 1459 (s), 1434 (m), 1387 (m), 1312 (m), 1215 (m), 1203 (m), 1111 (m), 1092 (m), 1076 (m), 1060 (s), 1027 (m), 826 (s), 763 (s), 738 (m), 700 (vs), 685 (s), 638 (s), 615 (m).
C. Experimental Section

MS (EI, 70 eV): m/z (%) = 233 (M⁺, <1), 129 (83), 107 (100), 91 (26), 79 (64), 51 (8).
HRMS (C₁₃H₁₃ClNO): calc.: 234.0686; found: 234.0686.

1-(4-Chlorophenyl)-2-(6-chloropyridin-3-yl)ethanone (92b)

According to TP3 4-chlorobenzoyl chloride (60d; 404 mg, 2.31 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.00 mL, 3.00 mmol, 1.00 M in THF) and (6-chloropyridin-3-yl)methylzinc chloride (91a; 2.42 mL, 3.00 mmol, 1.24 M in THF) at -40 °C. The reaction mixture was allowed to reach 25 °C within 20 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 1:1) afforded the ketone 92b (379 mg, 62%) as a white solid.


¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.25 (d, J = 2.4 Hz, 1H), 7.96-7.89 (m, 2H), 7.55 (dd, J = 8.2 Hz, 2.6 Hz, 1H), 7.48-7.42 (m, 2H), 7.30 (d, J = 7.7 Hz, 1H), 4.24 (s, 2H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 194.6, 150.3, 150.2, 140.2, 140.1, 134.3, 129.7, 129.2, 128.7, 124.1, 41.3.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3091 (vw), 1938 (vw), 1678 (s), 1586 (m), 1568 (m), 1490 (w), 1457 (s), 1401 (m), 1382 (m), 1323 (m), 1289 (m), 1248 (w), 1226 (m), 1204 (m), 1184 (m), 1169 (m), 1133 (w), 1108 (m), 1087 (s), 1026 (m), 1014 (m), 988 (s), 858 (m), 833 (vs), 820 (s), 793 (s), 741 (m), 716 (m), 635 (m), 627 (m).

MS (EI, 70 eV): m/z (%) = 265 (M⁺, 5), 141 (100), 126 (4), 111 (52), 75 (14), 63 (3), 50 (3).

HRMS (C₁₃H₀Cl₂NO): calc.: 265.0061; found: 265.0057.

1-(4-Chlorophenyl)-2-(3,5-dimethylisoxazol-4-yl)ethanone (92c)

According to TP3 4-chlorobenzoyl chloride (60d; 350 mg, 2.00 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.80 mL, 2.80 mmol, 1.00 M in THF) and (3,5-dimethylisoxazol-4-yl)methylzinc chloride (91b; 2.37 mL, 2.80 mmol, 1.18 M in THF) at -40 °C. The reaction
mixture was allowed to reach 25 °C within 27 h and was quenched with a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (100 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 1:1) afforded the ketone 92c (403 mg, 81%) as a white solid.

**M.p. (°C):** 139-141.

**¹H-NMR (300 MHz, C₆D₆):** δ / ppm = 7.51-7.45 (m, 2H), 7.06-7.00 (m, 2H), 3.22 (s, 2H), 1.95 (s, 3H), 1.79 (s, 3H).

**¹³C-NMR (75 MHz, C₆D₆):** δ / ppm = 193.5, 166.0, 159.6, 139.7, 134.9, 129.8, 129.0, 107.3, 32.1, 10.7, 10.2.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2930 (vw), 1687 (vs), 1647 (m), 1586 (m), 1571 (m), 1486 (w), 1455 (m), 1420 (m), 1398 (m), 1333 (m), 1263 (m), 1212 (s), 1194 (s), 1089 (s), 1015 (m), 987 (vs), 957 (m), 888 (s), 840 (s), 759 (vs), 748 (vs), 692 (s).

**MS (EI, 70 eV):** m/z (%) = 249 (M⁺, 3), 206 (40), 141 (100), 113 (17), 111 (53), 75 (19), 68 (25), 43 (20).

**HRMS (C₁₃H₁₂ClNO₂):** calc.: 249.0557; found: 249.0559.

Ethyl 4-(thiophen-3-ylmethyl)benzoate (92d)

(3-Thienylmethyl)zinc chloride (91c; 1.67 mL, 1.20 mmol, 0.72 M in THF) was added dropwise to a mixture of ethyl 4-bromobenzoate (71e; 229 mg, 1.00 mmol), Pd(OAc)₂ (4.5 mg, 2.0 mol%) and S-Phos (16.4 mg, 4.0 mol%) in THF (1 mL) at 25 °C. The reaction mixture was stirred for 18 h. Then, sat. aq. NH₄Cl solution (20 mL) was added. The phases were separated and the aq. layer was extracted with EtOAc (3 x 20 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 9:1) afforded the thiophene 92d (160 mg, 65%) as a yellow liquid.

**¹H-NMR (400 MHz, C₆D₆):** δ / ppm = 8.13-8.08 (m, 2H), 6.96-6.91 (m, 2H), 6.86 (dd, J = 4.9 Hz, 2.9 Hz, 1H), 6.59 (dd, J = 4.9 Hz, 1.4 Hz, 1H), 6.54-6.51 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.58 (s, 2H), 1.03 (t, J = 7.1 Hz, 3H).

**¹³C-NMR (100 MHz, C₆D₆):** δ / ppm = 166.2, 146.0, 140.6, 130.1, 129.3, 129.0, 128.4, 125.9, 121.7, 60.7, 36.5, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3101 (vw), 2981 (w), 2906 (vw), 1713 (s), 1610 (w), 1576 (vv), 1416 (w), 1366 (w), 1275 (vs), 1176 (m), 1102 (s), 1021 (m), 942 (w), 919 (vw), 859 (w), 832 (w), 764 (m), 713 (m).

MS (EI, 70 eV): m/z (%) = 246 (M$^+$, 100), 218 (10), 201 (84), 173 (77), 128 (11), 97 (20).

HRMS ($C_{14}H_{14}O_2$): calc.: 246.0715; found: 246.0715.

3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)(phenyl)methanol (92e; rac)

According to TP2 (3,5-dimethylisoxazol-4-yl)methylzinc chloride (91b: 2.49 mL, 3.03 mmol, 1.22 M in THF) was reacted with 3,4-dichlorobenzaldehyde (61b: 408 mg, 2.33 mmol, in 0.5 mL THF) at 0 °C. The reaction mixture was slowly warmed to 25 °C within 5 h and was quenched with sat. aq. NH$_4$Cl solution (20 mL). The phases were separated and the aq. layer was extracted with Et$_2$O (5 x 50 mL). Purification by flash chromatography (silica gel, pentane / EtO = 1:1 + 1 vol-% NEt$_3$) afforded the racemic alcohol 92e (541 mg, 81%, d:r = 95:5) as a white solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.49-7.46 (m, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.25-7.20 (m, 1H), 5.33 (d, $J = 0.8$ Hz, 1H), 4.72-4.70 (m, 1H), 4.66-4.64 (s, 1H), 2.71 (s, $J_{	ext{HH}} = 8.4$ Hz, 1H), 2.00 (s, 3H), 1.39 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 155.6, 150.3, 137.7, 132.0, 131.8, 129.7, 129.6, 127.1, 110.0, 88.7, 76.6, 22.4, 9.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3510 (m), 2987 (m), 2970 (m), 2925 (m), 1648 (m), 1562 (m), 1468 (m), 1453 (m), 1434 (m), 1401 (m), 1395 (m), 1370 (m), 1351 (m), 1333 (m), 1295 (m), 1282 (m), 1250 (m), 1202 (m), 1170 (m), 1129 (m), 1086 (m), 1062 (s), 1028 (s), 939 (m), 902 (s), 889 (vs), 854 (m), 833 (s), 821 (m), 745 (vs), 727 (s), 695 (m), 671 (s), 616 (m).

MS (EI, 70 eV): m/z (%) = 286 ([M+H]$^+$, <1), 265 (100), 145 (39), 113 (14), 108 (14), 96 (11), 82 (15), 74 (24), 68 (34), 43 (53).

HRMS ($C_{13}H_{13}Cl_2NO_2$): calc.: 286.0402 ([M+H]$^+$); found: 286.0396 ([M+H]$^+$).
3.7. Preparation of benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of ZnCl$_2$ and LiCl

2-Chlorobenzyl 4-fluorophenyl sulfide (97a)

The zinc reagent 95b was prepared according to TP9 from 2-chlorobenzyl chloride (53b; 322 mg, 2.00 mmol) in 45 min at 25 °C. The freshly prepared zinc reagent 95b was added to S-(4-fluorophenyl) benzenesulfonothioate (57c; 376 mg, 1.4 mmol) in 1 mL THF at 25 °C and the mixture was stirred for 17 h. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution (100 mL) and extracted with Et$_2$O (3 x 100 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et$_2$O = 95:5) furnished the sulfide 97a (306 mg, 86%) as a yellow liquid.

$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ / ppm = 7.37-7.33 (m, 1H), 7.32-7.27 (m, 2H), 7.19 -7.15 (m, 1H), 7.14-7.08 (m, 2H), 6.97-6.92 (m, 2H), 4.13 (s, 2H).

$^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ / ppm = 162.3 (d, $^1$J$_{C\cdot F}$ = 247.4 Hz), 135.2, 134.3 (d, $^3$J$_{C\cdot F}$ = 8.1 Hz), 134.0, 130.7, 130.1 (d, $^4$J$_{C\cdot F}$ = 3.4 Hz), 129.7, 128.6, 126.6, 115.9 (d, $^2$J$_{C\cdot F}$ = 21.9 Hz), 38.3 (d, $^6$J$_{C\cdot F}$ = 1.1 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 1739 (vw), 1589 (m), 1488 (vs), 1472 (m), 1443 (m), 1420 (w), 1396 (w), 1289 (w), 1226 (s), 1155 (m), 1090 (m), 1051 (m), 1037 (m), 1013 (w), 944 (w), 880 (w), 820 (s), 758 (s), 742 (s), 733 (s), 683 (m), 668 (m), 629 (m).

MS (EI, 70 eV): $m/z$ (%) = 252 (M$^+$, 21), 127 (36), 125 (100), 89 (11), 63 (5).

HRMS (C$_{13}$H$_{10}$ClF$_2$): calc.: 252.0176; found: 252.0176.

Ethyl 2-[2-(2-chlorophenyl)ethyl]acrylate (97b)

The zinc reagent 95b was prepared according to TP9 from 2-chlorobenzyl chloride (53b; 322 mg, 2.00 mmol) in 45 min at 25 °C. The freshly prepared zinc reagent 95b was added to ethyl (2-bromomethyl)acrylate (55b; 309 mg, 1.60 mmol) in 0.5 mL THF at 25 °C. CuCN-2LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF) was added and the mixture was stirred for 45 min. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution (45 mL) followed by 25% aq. NH$_3$.
solution (5 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 98:2) furnished the acrylate 97b (295 mg, 77%) as a colourless liquid.

**¹H-NMR (600 MHz, CDCl₃):** δ / ppm = 7.33 (dd, J = 7.6 Hz, 1.3 Hz, 1H), 7.21-7.10 (m, 3H), 6.15 (d, J = 1.3 Hz, 1H), 5.49 (d, J = 1.3 Hz, 1H), 4.21 (q, J = 7.3 Hz, 2H), 2.94-2.89 (m, 2H), 2.64-2.59 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H).

**¹³C-NMR (150 MHz, CDCl₃):** δ / ppm = 167.0, 139.8, 138.9, 134.0, 130.5, 129.4, 127.5, 126.7, 125.4, 60.7, 32.7, 32.1, 14.2.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2982 (w), 2936 (w), 1713 (vs), 1631 (w), 1475 (m), 1443 (m), 1303 (m), 1182 (s), 1139 (s), 1113 (m), 1052 (m), 1035 (s), 944 (m), 816 (m), 749 (vs), 673 (m).

**MS (EI, 70 eV):** m/z (%) =  238 (M⁺, 11), 193 (12), 164 (10), 157 (39), 129 (13), 127 (31), 125 (100), 89 (8).

**HRMS (C₁₃H₁₅O₂Cl):** calc.: 238.0761; found: 238.0762.

1-(4-Bromophenyl)-2-(4-fluorophenyl)ethanol (97c)

The zinc reagent 95c was prepared according to TP9 from 4-fluorobenzyl chloride (53c; 289 mg, 2.00 mmol) in 45 min at 25 °C. The freshly prepared zinc reagent 95c was added to 4-bromobenzaldehyde (61e; 259 mg, 1.40 mmol) in 1 mL THF at 0 °C. The mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 1:1 + 1 vol-% NEt₃) furnished the alcohol 97c (209 mg, 51%) as a pale yellow solid.

**M.p. (°C):** 62-64.

**¹H-NMR (300 MHz, C₆D₆):** δ / ppm = 7.21-7.21 (m, 2H), 6.79-6.63 (m, 6H), 4.25 (dd, J = 7.6 Hz, 5.5 Hz, 1H), 2.65-2.48 (m, 2H), 1.19 (s, 1H).

**¹³C-NMR (75 MHz, C₆D₆):** δ / ppm = 162.1 (d, ¹JC-F = 244.3 Hz), 143.3, 133.7 (d, ⁴JC-F = 3.1 Hz), 131.5, 131.3 (d, ³JC-F = 7.7 Hz), 127.9, 121.4, 115.2 (d, ²JC-F = 21.1 Hz), 74.4, 45.1.
C. Experimental Section

**IR (Diamond-ATR, neat):** \( \tilde{\nu} / \text{cm}^{-1} = 3603 \) (w), 2923 (w), 2875 (vw), 2854 (vw), 1601 (w), 1507 (m), 1486 (w), 1402 (w), 1274 (w), 1212 (m), 1157 (m), 1092 (w), 1049 (m), 1009 (m), 873 (w), 821 (vs), 806 (m), 762 (w), 713 (w).

**MS (EI, 70 eV):** \( m/z \% = 294 (M^+, <1), 276, (3), 185 (100), 157 (20), 110 (90), 77 (42), 51 (5). \)

**HRMS (C_{14}H_{12}BrFO):** calc.: 294.0056; found: 294.0059.

**1-(2-Chlorophenyl)-2-[3-(trifluoromethyl)phenyl]ethanol (97d)**

![Chemical Structure](image)

The zinc reagent 95g was prepared according to TP9 from 3-(trifluoromethyl)benzyl chloride (53g; 389 mg, 2.00 mmol) in 30 min at 25 °C. The freshly prepared zinc reagent 95g was added to 2-chlorobenzaldehyde (61a; 197 mg, 1.40 mmol) and the mixture was stirred for 1 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 7:1) furnished the alcohol 97d (357 mg, 85%) as a colourless solid.

**M.p. (°C):** 44-45.

**1H-NMR (300 MHz, CDCl₃):** \( \delta / \text{ppm} = 7.62-7.15 \) (m, 8H), 5.33 (dd, \( J = 8.8 \) Hz, 3.3 Hz, 1H), 3.18 (dd, \( J = 13.8 \) Hz, 3.3 Hz, 1H), 2.89 (dd, \( J = 13.8 \) Hz, 8.8 Hz, 1H), 1.99 (s, 1H).

**13C-NMR (150 MHz, CDCl₃):** \( \delta / \text{ppm} = 140.9, 139.1, 133.0 \) (q, \( 4J_{CF} = 1.5 \) Hz), 131.5, 130.7 (q, \( 2J_{CF} = 32.1 \) Hz), 129.4, 128.8, 128.7, 127.2, 127.0, 126.3 (q, \( 3J_{CF} = 4.0 \) Hz), 124.2 (q, \( 1J_{CF} = 272.3 \) Hz), 123.5 (q, \( 3J_{CF} = 4.0 \) Hz), 71.5, 43.7.

**IR (Diamond-ATR, neat):** \( \tilde{\nu} / \text{cm}^{-1} = 3332 \) (w), 3254 (w), 2932 (w), 1476 (w), 1448 (m), 1332 (s), 1322 (s), 1254 (w), 1198 (m), 1172 (s), 1160 (s), 1114 (vs), 1098 (s), 1072 (s), 1048 (s), 1034 (s), 1004 (m), 910 (m), 854 (m), 794 (s), 758 (s), 722 (m), 708 (s), 698 (s), 660 (m), 650 (m), 622 (m), 586 (s).

**MS (EI, 70 eV):** \( m/z \% = 300 (M^+, <1), 283 (4), 281 (10), 159 (15), 143 (100), 141 (32), 139 (12), 113 (22), 77 (46). \)

**HRMS (C_{15}H_{12}ClF_{3}O):** calc.: 300.0529; found: 300.0535.
3-([3-(Trifluoromethyl)benzyl]thio)methyl)benzonitrile (97e)

The zinc reagent 95g was prepared according to TP9 from 3-(trifluoromethyl)benzyl chloride (53g; 389 mg, 2.00 mmol) in 30 min at 25 °C. The freshly prepared zinc reagent 95g was added to S-(3-cyanobenzyl) benzenesulfonothioate (57d; 405 mg, 1.40 mmol) in THF (1 mL) at 25 °C. The mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 9:1) furnished the sulfide 97e (372 mg, 86%) as a colourless oil.

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.56-7.35 (m, 8H), 3.64 (s, 2H), 3.60 (s, 2H).

**¹³C-NMR (75 MHz, CDCl₃):** δ / ppm = 139.4, 138.6, 133.3, 132.3, 132.2 (q, J₀= 1.3 Hz), 131.0 (q, J₀= 32.3 Hz), 129.9, 129.1, 125.6 (q, J₀= 3.8 Hz), 124.1 (q, J₀= 3.9 Hz), 123.9 (q, J₀= 272.4 Hz), 118.5, 112.7, 35.5, 35.1.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2230 (w), 1598 (vw), 1582 (w), 1482 (w), 1450 (w), 1430 (w), 1328 (vs), 1240 (w), 1226 (w), 1162 (s), 1118 (vs), 1092 (s), 1070 (s), 1002 (w), 900 (m), 800 (m), 738 (m), 700 (s), 684 (s), 658 (s), 606 (w), 558 (w).

**MS (EI, 70 eV):** m/z (%) = 307 (M⁺, 33), 191 (10), 159 (100), 148 (13), 116 (25).

**HRMS (C₁₆H₁₂F₂NS):** calc.: 307.0643; found: 307.0638.

1-(4-Chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (97f)

The zinc reagent 95h was prepared according to TP9 from 3,4,5-trimethoxybenzyl chloride (53h; 433 mg, 2.00 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent 95h was cooled to -20 °C and CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) was added. After stirring for 15 min 4-chlorobenzoyl chloride (60d; 245 mg, 1.40 mmol) was added and the mixture warmed to 25 °C and stirred for 2 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (20 mL) followed by 25% aq. NH₃ solution (5 mL) and extracted with Et₂O (3 x 30 mL). The combined
organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 1:1) furnished the ketone 97f (253 mg, 56%) as a yellow solid.

**M.p. (°C):** 109-111.

1H-NMR (300 MHz, CDCl₃): δ / ppm = 7.97-7.90 (m, 2H), 7.45-7.39 (m, 2H), 6.44 (s, 2H), 4.17 (s, 2H), 3.81 (s, 6H), 3.81 (s, 3H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 196.3, 153.3, 139.7, 136.9, 134.7, 129.9, 129.6, 129.0, 106.3, 60.8, 56.0, 45.7.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3061 (vw), 3011 (vw), 2943 (w), 2842 (w), 2754 (vw), 1681 (m), 1589 (m), 1505 (m), 1458 (m), 1424 (m), 1391 (m), 1322 (s), 1233 (m), 1123 (vs), 1089 (m), 1036 (w), 993 (m), 846 (m), 812 (w), 788 (w), 758 (w), 728 (m).

**MS (EI, 70 eV):** m/z (%) = 320 (M⁺, 18), 181 (100), 148 (4), 139 (11), 111 (4).

**HRMS (C₁₇H₁₇ClO₄):** calc.: 320.0815; found: 320.0812.

1-Bromo-4-[(4-methoxybenzyl)thio]benzene (97g)

The zinc reagent 95i was prepared according to TP9 from 4-methoxybenzyl chloride (53i; 313 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent 95i was added to S-(4-bromophenyl) benzenesulfonothioate (57a; 461 mg, 1.40 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 17 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 9:1) furnished the sulfide 97g (379 mg, 88%) as a white solid.

**M.p. (°C):** 100-102.

1H-NMR (400 MHz, C₆D₆): δ / ppm = 7.09-7.04 (m, 2H), 7.02-6.97 (m, 2H), 6.86-6.80 (m, 2H), 6.71-6.64 (m, 2H), 3.67 (s, 2H), 3.24 (s, 3H).

13C-NMR (100 MHz, C₆D₆): δ / ppm = 159.4, 136.4, 132.0, 131.3, 130.2, 129.1, 120.1, 114.2, 54.7, 38.2.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3015 (w), 2962 (w), 2921 (w), 2837 (w), 1738 (w), 1611 (m), 1583 (w), 1511 (m), 1473 (m), 1454 (m), 1441 (m), 1382 (w), 1302 (m), 1254 (m),
1233 (m), 1176 (m), 1128 (w), 1089 (m), 1027 (s), 1005 (m), 837 (s), 806 (vs), 755 (s), 741 (m), 702 (m), 637 (w).

**MS (EI, 70 eV):** \( m/z \) (%) = 308 (M\(^+\), 4), 241 (3), 189 (5), 121 (100), 108 (18), 91 (12), 77 (18), 51 (7).

**HRMS (C\(_{14}\)H\(_{13}\)BrOS):** calc.: 307.9870; found: 307.9864.

1-Cyclopropyl-2-(2-methoxyphenyl)ethanone (97h)

The zinc reagent 95j was prepared according to TP9 from 2-methoxybenzyl chloride (53j; 313 mg, 2.00 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent 95j was added to CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) at -20 °C. After stirring for 15 min cyclopropanecarbonyl chloride (60c; 146 mg, 1.4 mmol) was added and the mixture was slowly warmed to 25 °C within 6.5 h. The reaction mixture was quenched with sat. aq. NH\(_4\)Cl solution (200 mL) followed by 25% aq. NH\(_3\) solution (50 mL) and extracted with Et\(_2\)O (3 x 250 mL). The combined organic layers were dried over MgSO\(_4\) and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et\(_2\)O = 8:1) furnished the ketone 97h (238 mg, 89%) as a colourless liquid.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta / \text{ppm} = 7.29-7.21 \) (m, 1H), 7.18-7.13 (m, 1H), 6.96-6.85 (m, 2H), 3.80 (s, 3H), 3.79 (s, 2H), 2.00-1.90 (m, 1H), 1.06-0.99 (m, 2H), 0.84-0.76 (m, 2H).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta / \text{ppm} = 208.7, 157.5, 131.1, 128.3, 123.7, 120.6, 110.5, 55.3, 45.0, 19.6, 10.8.

**IR (Diamond-ATR, neat):** \( \tilde{\nu} / \text{cm}^{-1} = 3008 \) (w), 2838 (vw), 1694 (s), 1602 (w), 1590 (w), 1494 (s), 1464 (m), 1440 (m), 1378 (s), 1320 (w), 1290 (w), 1244 (vs), 1200 (m), 1112 (m), 1070 (s), 1048 (m), 1024 (s), 930 (w), 898 (m), 818 (w), 750 (vs), 658 (w), 604 (w), 576 (w).

**MS (EI, 70 eV):** \( m/z \) (%) = 190 (M\(^+\), 58), 121 (44), 91 (62), 65 (47), 41 (100).

**HRMS (C\(_{12}\)H\(_{14}\)O\(_2\)):** calc.: 190.0994; found: 190.0983.
1-(3-Chlorophenyl)-2-(2-methoxyphenyl)ethanol (97i)

The zinc reagent 95j was prepared according to TP9 from 2-methoxybenzyl chloride (53j; 313 mg, 2.00 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent 95j was added to 3-chlorobenzaldehyde (61c; 197 mg, 1.40 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 4 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 4:1) furnished the alcohol 97i (338 mg, 92%) as a colourless solid.


¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.42-7.39 (m, 1H), 7.30-7.21 (m, 4H), 7.10-7.05 (m, 1H), 6.95-6.87 (m, 2H), 4.98-4.91 (m, 1H), 3.87 (s, 3H), 3.13 (dd, J = 13.6 Hz, 4.1 Hz, 1H), 2.95 (dd, J = 13.6 Hz, 8.8 Hz, 1H), 2.64 (d, J = 2.9 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 157.5, 146.6, 134.1, 131.5, 129.4, 128.2, 127.3, 126.1, 126.0, 123.9, 120.8, 110.5, 73.7, 55.4, 41.2.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3322 (w), 3252 (w), 2946 (w), 2922 (w), 2838 (w), 1600 (m), 1492 (s), 1468 (s), 1438 (m), 1420 (m), 1292 (m), 1238 (vs), 1200 (m), 1182 (m), 1114 (s), 1080 (m), 1062 (s), 1050 (s), 1032 (s), 1008 (m), 872 (m), 786 (s), 764 (s), 750 (vs), 728 (m), 708 (s), 692 (s), 642 (m), 604 (s), 558 (s).

MS (EI, 70 eV): m/z (%) = 262 (M⁺, <1), 165 (2), 122 (100), 91 (25), 77 (13).

HRMS (C₁₅H₁₅ClO₂): calc.: 262.0761; found: 262.0747.

1-(4-Bromophenyl)-2-[4-(methylthio)phenyl]ethanol (97j)

The zinc reagent 95l was prepared according to TP9 from 4-(methylthio)benzyl chloride (53l; 345 mg, 2.00 mmol) in 1.5 h at 25 °C. The freshly prepared zinc reagent 95l was added to 4-bromobenzaldehyde (61e; 259 mg, 1.40 mmol) in 1 mL THF at 25 °C. The mixture was stirred for 2 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated.
in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 3:1) furnished the alcohol \(97j\) (372 mg, 82%) as a colourless solid.

**M.p. (°C):** 117-119.

**\(^1\)H-NMR (300 MHz, CDCl₃):** \(\delta / ppm = 7.48-7.42\) (m, 2H), 7.22-7.16 (m, 4H), 7.09-7.03 (m, 2H), 4.81 (dd, \(J = 7.6\) Hz, 5.5 Hz, 1H), 2.98-2.88 (m, 2H), 2.46 (s, 3H), 1.86 (s, 1H).

**\(^1\)C-NMR (75 MHz, CDCl₃):** \(\delta / ppm = 142.6, 136.7, 134.3, 131.5, 130.0, 127.6, 126.9, 121.4, 74.6, 45.4, 16.0\).

**IR (Diamond-ATR, neat):** \(\tilde{\nu} / \text{cm}^{-1} = 3310\) (w), 2914 (w), 1494 (m), 1488 (m), 1434 (m), 1424 (m), 1404 (m), 1092 (m), 1058 (s), 1000 (m), 882 (m), 716 (w).

**MS (EI, 70 eV):** \(m/z\) (%) = 322 (M⁺, 3), 187 (14), 185 (16), 138 (100), 123 (30), 91 (7), 77 (14). **HRMS (C₁₅H₁₅BrOS):** calc.: 322.0027; found: 322.0018.

3-[4-(Methylthio)benzyl]cyclohex-2-en-1-one (97k)

The zinc reagent \(95l\) was prepared according to TP9 from 4-(methylthio)benzyl chloride (53l; 345 mg, 2.00 mmol) in 1.5 h at 25 °C. The freshly prepared zinc reagent \(95l\) was added to CuCN·2LiCl (2.00 mL, 2.0 mmol, 1.00 M in THF) at -20 °C. After stirring for 15 min, 3-iodocyclohex-2-enone (58b; 311 mg, 1.40 mmol) was added at -40 °C and the mixture was slowly warmed to 0 °C within 18 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (100 mL) followed by 25% aq. NH₃ solution (50 mL) and extracted with Et₂O (3 x 150 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 1:1) furnished the cyclohexenone \(97k\) (201 mg, 62%) as a yellow oil.

**\(^1\)H-NMR (300 MHz, CDCl₃):** \(\delta / ppm = 7.22-7.16\) (m, 2H), 7.09-7.03 (m, 2H), 5.84-5.81 (m, 1H), 3.44 (s, 2H), 2.45 (s, 3H), 2.37-2.30 (m, 2H), 2.26-2.19 (m, 2H), 1.99-1.87 (m, 2H).

**\(^1\)C-NMR (75 MHz, CDCl₃):** \(\delta / ppm = 199.8, 164.6, 136.9, 133.7, 129.5, 126.9, 126.8, 43.9, 37.2, 29.1, 22.6, 15.9\).

**IR (Diamond-ATR, neat):** \(\tilde{\nu} / \text{cm}^{-1} = 3675\) (w), 2989 (m), 2970 (m), 2920 (m), 1739 (s) (vs), 1624 (m), 1493 (m), 1425 (m), 1404 (m), 1370 (s), 1349 (m), 1323 (m), 1230 (s), 1217 (s), 1191 (m), 1092 (m), 1066 (m), 1016 (m), 968 (m), 886 (m), 834 (w), 807 (m), 794 (m), 756 (m), 728 (w), 660 (w).
**C. Experimental Section**

**MS (EI, 70 eV):** $m/z$ (%) = 232 (M$^+$, 100), 176 (22), 157 (15), 137 (28), 129 (26), 122 (11), 115 (9).

**HRMS (C$_{14}$H$_{16}$OS):** calc.: 232.0922; found: 232.0922.

**Ethyl 3-[2-(4-chlorophenyl)-2-oxoethyl]benzoate (97l)**

![Chemical Structure](image)

The zinc reagent 95m was prepared according to TP9 from 3-(ethoxycarbonyl)benzyl chloride (53m; 397 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent 95m was added to CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) at -20 °C. After stirring for 15 min, 4-chlorobenzoyl chloride (60d; 245 mg, 1.40 mmol) was added and the mixture was stirred for 1.5 h at 0 °C followed by 30 min at 25 °C. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution (40 mL) followed by 25% aq. NH$_3$ solution (20 mL) and extracted with Et$_2$O (3 x 50 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et$_2$O = 9:1) furnished the ketone 97l (347 mg, 82%) as a colourless solid.

**M.p. (°C):** 76-78.

**$^1$H-NMR (300 MHz, CDCl$_3$):** δ / ppm = 7.97-7.90 (m, 4H), 7.46-7.35 (m, 4H), 4.35 (q, $J$ = 7.1 Hz, 2H), 4.30 (s, 2H), 1.37 (t, $J$ = 7.2 Hz, 3H).

**$^{13}$C-NMR (75 MHz, CDCl$_3$):** δ / ppm = 195.8, 166.3, 139.8, 134.7, 134.4, 133.9, 130.9, 130.6, 129.9, 129.0, 128.7, 128.3, 61.0, 45.0, 14.3.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1}$ = 2984 (w), 2914 (w), 1694 (vs), 1588 (m), 1394 (m), 1332 (s), 1280 (s), 1208 (vs), 1170 (s), 1108 (s), 1088 (s), 1030 (s), 1000 (s), 990 (s), 944 (m), 832 (s), 814 (vs), 796 (m), 752 (vs), 722 (s), 710 (m), 584 (m), 562 (s).

**MS (EI, 70 eV):** $m/z$ (%) = 302 (M$^+$, 1), 259 (6), 257 (20), 141 (100), 139 (13), 113 (12), 111 (40).

**HRMS (C$_{17}$H$_{15}$ClO$_3$):** calc.: 302.0710; found: 302.0702.
Ethyl 3-(4-methoxybenzyl)benzoate (97m)

The zinc reagent 95m was prepared according to TP9 from 3-(ethoxycarbonyl)benzyl chloride (53m; 397 mg, 2.00 mmol) in 2 h at 25 °C. A dry and argon-flushed Schlenk-flask was charged with 4-iodoanisole (4c; 328 mg, 1.40 mmol) and PEPPSI-IPr (3.4 mg, 0.25 mol%). THF (1.0 mL) was added. The freshly prepared zinc reagent 95m was added and the reaction mixture was stirred for 21 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (10 mL) and extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 10:1) furnished the diarylmethane 97m (295 mg, 78%) as a colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.92-7.83 (m, 2H), 7.37-7.31 (m, 2H), 7.13 -7.06 (m, 2H), 6.86-679 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.96 (s, 2H), 3.77 (s, 3H), 1.38 (t , J = 7.2 Hz, 2H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 166.7, 158.1, 141.8, 133.3, 132.6, 130.6, 129.9, 129.8, 128.4, 127.3, 114.0, 60.9, 55.2, 40.8, 14.3.

IR (Diamond-ATR, neat): δ / cm⁻¹ = 2982 (w), 2934 (w), 2906 (w), 2836 (w), 1714 (s), 1610 (m), 1586 (w), 1510 (s), 1464 (m), 1442 (m), 1366 (m), 1276 (s), 1244 (vs), 1176 (s), 1102 (s), 1080 (s), 1030 (s), 928 (w), 810 (m), 764 (s), 738 (s), 690 (m), 670 (m), 606 (m).

MS (EI, 70 eV): m/z (%) = 270 (M⁺, 100), 241 (20), 225 (23), 197 (32), 165 (13), 232 (23).

HRMS (C₁₇H₁₈O₃): calc.: 270.1256; found: 270.1252.

Ethyl 3-[(4-chlorophenyl)thio)methyl]benzoate (97n)

The zinc reagent 95m was prepared according to TP9 from 3-(ethoxycarbonyl)benzyl chloride (53m; 397 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent 95m was added to S-(4-chlorophenyl) benzenesulfonothioate (57e; 399 mg, 1.40 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were dried
over MgSO\textsubscript{4} and concentrated in vacuo. Flash chromatography (silica gel, pentane to pentane / Et\textsubscript{2}O = 98:2) furnished the sulfide \textit{97n} (288 mg, 67\%) as a yellow solid.

\textbf{M.p. (°C):} 41-43.

\textbf{\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}):} \(\delta / \text{ppm} = 7.94-7.88 \) (m, 2H), 7.45-7.39 (m, 1H), 7.37-7.30 (m, 1H), 7.20 (s, 4H), 4.36 (q, \(J = 7.2 \text{ Hz}, 2\H\)), 4.09 (s, 2H), 1.38 (t, \(J = 7.2 \text{ Hz}, 3\H\)).

\textbf{\textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}):} \(\delta / \text{ppm} = 166.2, 137.6, 134.0, 133.1, 132.8, 131.9, 130.8, 129.9, 129.0, 128.5, 128.5, 61.0, 39.1, 14.3.\)

\textbf{IR (Diamond-ATR, neat):} \(\tilde{\nu} / \text{cm}^{-1} = 3052 \) (w), 2992 (w), 2934 (w), 1708 (s), 1584 (w), 1470 (s), 1444 (m), 1390 (m), 1282 (s), 1264 (m), 1234 (s), 1194 (s), 1176 (m), 1108 (s), 1090 (s), 1022 (m), 1006 (m), 944 (m), 934 (m), 806 (s), 778 (s), 730 (vs), 688 (s), 674 (m), 586 (m).

\textbf{MS (EI, 70 eV):} \(m/z (%) = 306 (M^+ 23), 163 (100), 135 (12), 119( 18) 89 (6).\)

\textbf{HRMS (C\textsubscript{16}H\textsubscript{15}ClO\textsubscript{2}S):} calc.: 306.0481; found: 306.0481.

**Ethyl 2-[2-(3-cyanophenyl)ethyl]acrylate (97o)**

![Structure of Ethyl 2-[2-(3-cyanophenyl)ethyl]acrylate](image)

The zinc reagent \textit{95o} was prepared according to TP\textit{9} from 3-cyanobenzyl chloride (\textit{53o}; 303 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent \textit{95o} was added to ethyl (2-bromomethyl)acrylate (\textit{55b}; 270 mg, 1.40 mmol) in 0.5 mL THF at 25 °C. CuCN·2 LiCl (0.01 mL, 0.01 mmol, 1.00 M in THF) was added and the mixture was stirred for 60 min. The reaction mixture was quenched with sat. aq. NH\textsubscript{4}Cl solution (45 mL) followed by 25% aq. NH\textsubscript{3} solution (5 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 50 mL). The combined organic layers were dried over MgSO\textsubscript{4} and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et\textsubscript{2}O = 1:1) furnished the acrylate \textit{97o} (255 mg, 79\%) as a colourless liquid.

\textbf{\textsuperscript{1}H-NMR (600 MHz, CDCl\textsubscript{3}):} \(\delta / \text{ppm} = 7.49-7.45 \) (m, 2H), 7.42-7.39 (m, 1H), 7.37 (t, \(J = 7.6 \text{ Hz}, 1\H\)), 6.15 (d, \(J = 1.3 \text{ Hz}, 1\H\)), 5.46 (q, \(J = 1.2 \text{ Hz}, 1\H\)), 4.21 (q, \(J = 7.0 \text{ Hz}, 2\H\)), 2.84-2.80 (m, 2H), 2.62-2.57 (m, 2H), 1.30 (t, \(J = 7.2 \text{ Hz}, 3\H\)).

\textbf{\textsuperscript{13}C-NMR (150 MHz, CDCl\textsubscript{3}):} \(\delta / \text{ppm} = 166.7, 142.7, 139.3, 133.1, 132.0, 129.8, 129.1, 125.7, 118.9, 112.3, 60.8, 34.4, 33.5, 14.2.\)

\textbf{IR (Diamond-ATR, neat):} \(\tilde{\nu} / \text{cm}^{-1} = 2983 \) (w), 2935 (w), 2230 (m), 1710 (vs), 1631 (w), 1583 (w), 1483 (w), 1445 (w), 1369 (w), 1300 (m), 1256 (m), 1186 (vs), 1134 (s), 1095 (m), 1028 (m), 945 (m), 917 (w), 797 (s), 690 (s).
C. Experimental Section

**MS (EI, 70 eV):** m/z (%) = 229 (M⁺, 10), 183 (71), 155 (34), 116 (100), 89 (14).

**HRMS (C₁₄H₁₅NO₂):** calc.: 229.1103; found: 229.1090.

3-[(3,4-Dichlorophenyl)-2-hydroxyethyl]benzonitrile (97p)

The zinc reagent 95o was prepared according to TP9 from 3-cyanobenzyl chloride (53o; 303 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent 95o was added to 3,4-dichlorobenzaldehyde (61b; 245 mg, 1.40 mmol) in 1 mL THF at 0 °C. The mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography (silica gel, pentane / Et₂O = 7:3) furnished the alcohol 97p (341 mg, 83%) as a white solid.

**M.p. (°C):** 96-97.

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.55-7.47 (m, 2H), 7.44-7.33 (m, 4H), 7.11 (dd, J = 8.2 Hz, 2.0 Hz, 1H), 4.86 (t, J = 6.4 Hz, 1H), 2.99 (d, J = 6.4 Hz, 2H), 2.02-1.89 (s, 1H).

**¹³C-NMR (75 MHz, CDCl₃):** δ / ppm = 143.5, 138.9, 134.1, 133.1, 132.7, 131.8, 130.5, 130.5, 129.2, 127.8, 125.1, 118.7, 112.5, 73.6, 45.1.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3328 (m), 3260 (m), 2232 (m), 1484 (m), 1470 (s), 1426 (m), 1398 (m), 1202 (m), 1142 (m), 1058 (s), 1028 (s), 1014 (m), 904 (m), 818 (s), 690 (s), 650 (s), 602 (m).

**MS (EI, 70 eV):** m/z (%) = 291 (M⁺, 2), 179 (13), 177 (100), 175 (61), 147 (29), 117 (71), 111 (19), 90 (13), 75 (12).

**HRMS (C₁₅H₁₁Cl₂NO):** calc.: 291.0218; found: 291.0214.

3-[(3-Oxocyclohex-1-en-1-yl)methyl]benzonitrile (97q)

The zinc reagent 95o was prepared according to TP9 from 3-cyanobenzyl chloride (53o; 303 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent 95o was added to CuCN-2LiCl (2.00 mL, 2.00 mmol 1.00 M in THF) at -20 °C. After stirring for 15 min, 3-iodocyclohex-2-
Cyclohexenone (58b; 311 mg, 1.40 mmol) was added at -60 °C and the mixture was slowly warmed to 0°C within 18 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (100 mL) followed by 25% aq. NH₃ solution (50 mL) and extracted with Et₂O (3 x 150 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 1:2) furnished the cyclohexenone 97q (227 mg, 77%) as a yellow liquid.

1H-NMR (300 MHz, CDCl₃): δ / ppm = 7.58-7.52 (m, 1H), 7.47-7.36 (m, 3H), 5.80-5.76 (m, 1H), 3.53 (s, 2H), 2.40-2.32 (m, 2H), 2.27-2.20 (m, 2H), 2.03-1.91 (m, 2H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 199.3, 162.6, 138.4, 133.6, 132.5, 130.7, 129.5, 127.4, 118.5, 112.9, 43.7, 37.2, 29.3, 22.5.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2926 (w), 2228 (m), 1660 (vs), 1626 (m), 1600 (w), 1582 (w), 1484 (w), 1428 (m), 1348 (m), 1324 (m), 1250 (m), 1192 (m), 1128 (w), 968 (m), 906 (m), 884 (m), 796 (s), 758 (m), 724 (m), 694 (s), 672 (m), 556 (m).

MS (EI, 70 eV): m/z (%) = 211 (M⁺, 62), 183 (100), 154 (48), 140 (16), 67 (23).

HRMS (C₁₄H₁₃NO): calc.: 211.0997; found: 211.0994.

1-(Benzylthio)-4-methoxybenzene (97r)

The zinc reagent 95a was prepared according to TP9 from benzyl chloride (53a; 253 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent 95a was added to S-(4-methoxyphenyl) benzenesulfonothioate (57f; 393 mg, 1.40 mmol) in THF (1 mL) at 25 °C. The mixture was stirred for 13 h at 25 °C. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 15:1) furnished the sulfide 97r (252 mg, 78%) as a pale yellow solid.


1H-NMR (300 MHz, CDCl₃): δ / ppm = 7.33-7.19 (m, 7H), 6.86-6.78 (m, 2H), 4.01 (s, 2H), 3.80 (s, 3H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 159.1, 138.1, 134.0, 128.8, 128.3, 126.9, 126.0, 114.4, 55.2, 41.2.
C. Experimental Section

IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 3675 \text{ (w)}, 2989 \text{ (m)}, 2970 \text{ (m)}, 1739 \text{ (s)}, 1595 \text{ (m)}, 1571 \text{ (m)}, 1492 \text{ (s)}, 1465 \text{ (m)}, 1453 \text{ (s)}, 1435 \text{ (m)}, 1365 \text{ (m)}, 1307 \text{ (w)}, 1284 \text{ (m)}, 1232 \text{ (s)}, 1217 \text{ (s)}, 1203 \text{ (s)}, 1180 \text{ (s)}, 1117 \text{ (m)}, 1105 \text{ (m)}, 1095 \text{ (m)}, 1070 \text{ (m)}, 1023 \text{ (s)}, 1004 \text{ (m)}, 914 \text{ (m)}, 808 \text{ (vs)}, 794 \text{ (m)}, 778 \text{ (m)}, 710 \text{ (vs)}, 695 \text{ (vs)}, 637 \text{ (s)}, 626 \text{ (m)}.

MS (EI, 70 eV): m/z (%): 230 (M$^+$, 100), 139 (22), 91 (98), 65 (7).

HRMS (C$_{14}$H$_{14}$OS): calc.: 230.0765; found: 230.0745.

1-(4-Bromophenyl)-2-phenylpropan-1-ol (97s)

The zinc reagent 95u was prepared according to TP9 from 1-(chloroethyl)benzene (54v; 281 mg, 2.00 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent 54u was added to 4-bromobenzaldehyde (61e; 259 mg, 1.40 mmol) in THF (1 mL) at 25 °C. The mixture was stirred for 2 h. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution (50 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et$_2$O = 9:1) furnished the alcohol 97s (285 mg, 70%) as a colourless solid. Two diastereomers were observed with a ratio of 2:1. Analitical data for the main diastereomer is given.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.57-7.07 (m, 9H), 4.66 (d, $J = 8.5$ Hz, 1H), 3.06-2.94 (m, 1H), 1.90 (s$_{br}$, 1H), 1.13 (d, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 142.8, 141.4, 131.3, 128.7, 128.7, 128.0, 127.1, 121.5, 79.0, 48.1, 18.0.

IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 3378 \text{ (w)}, 3028 \text{ (w)}, 2968 \text{ (w)}, 2896 \text{ (w)}, 2878 \text{ (w)}, 2360 \text{ (vw)}, 1602 \text{ (w)}, 1488 \text{ (m)}, 1450 \text{ (m)}, 1406 \text{ (m)}, 1378 \text{ (w)}, 1198 \text{ (w)}, 1092 \text{ (m)}, 1070 \text{ (m)}, 1036 \text{ (m)}, 1026 \text{ (m)}, 1004 \text{ (s)}, 992 \text{ (m)}, 906 \text{ (m)}, 834 \text{ (m)}, 820 \text{ (s)}, 774 \text{ (m)}, 756 \text{ (s)}, 698 \text{ (vs)}, 658 \text{ (m)}, 628 \text{ (m)}, 620 \text{ (m)}, 608 \text{ (m)}, 580 \text{ (s)}, 568 \text{ (m)}, 556 \text{ (m)}.

MS (EI, 70 eV): m/z (%) = 290 (M$^+$, 2), 211 (8), 185 (22), 91 (100), 78 (66), 51 (20).

HRMS (C$_{15}$H$_{15}$BrO): calc.: 290.0306; found: 290.0302.
1,1-Diphenylacetone (97t)

![Chemical Structure: 1,1-Diphenylacetone](image)

The zinc reagent 95v was prepared according to TP9 from 1,1'-(chloromethylene)dibenzene (53v; 405 mg, 2.00 mmol) in 30 min at 0 °C. The freshly prepared zinc reagent 95v was added to CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.00 M in THF) at -20 °C. After stirring for 15 min, acetyl chloride (60a; 110 mg, 1.40 mmol) was added and the mixture was slowly warmed to 10 °C within 24 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (90 mL) followed by 25% aq. NH₃ solution (30 mL) and extracted with Et₂O (3 x 120 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 5:1) furnished the ketone 97t (199 mg, 68%) as a colourless liquid.

M.p. (°C): 100-102.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.34-7.17 (m, 10H), 5.09 (s, 1H), 2.21 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 206.4, 138.2, 128.9, 128.7, 127.2, 65.0, 30.0.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3669 (vw), 2989 (m), 2970 (m), 1738 (s), 1714 (s ), 1598 (w), 1494 (m), 1451 (m), 1419 (w), 1354 (s), 1228 (m), 1217 (m), 1152 (m), 1080 (m), 1032 (m), 893 (w), 753 (m), 695 (vs), 629 (w).

MS (EI, 70 eV): m/z (%) = 210 (M⁺, 1), 167 (100), 152 (15), 139 (4), 43 (11).


1-[4-(Dimethylamino)phenyl]-2-phenylethanol (97u)

![Chemical Structure: 1-[4-(Dimethylamino)phenyl]-2-phenylethanol](image)

The zinc reagent 95a was prepared according to TP9 from benzyl chloride (53u; 253 mg, 2.00 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent 95a was added to 4-(dimethylamino)benzaldehyde (61h; 209 mg, 1.40 mmol) at 25 °C. The mixture was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 1:1) furnished the alcohol 97u (331 mg, 98 %) as a yellow solid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.34-7.18 (m, 7H), 6.78-6.70 (m, 2H), 4.81 (t, $J$ = 6.7 Hz, 1H), 3.02 (d, $J$ = 6.7 Hz, 2H), 2.95 (s, 6H), 1.94 (s, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 150.1, 138.5, 131.9, 129.4, 128.4, 126.9, 126.3, 112.5, 75.1, 45.7, 40.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3312 (m), 3054 (w), 3026 (w), 2922 (m), 2856 (m), 2812 (w), 1618 (s), 1526 (s), 1448 (m), 1358 (s), 1336 (m), 1324 (m), 1232 (m), 1188 (m), 1170 (m), 1068 (m), 1020 (s), 1002 (m), 946 (m), 814 (s), 794 (m), 746 (s), 732 (s), 696 (vs), 638 (m), 620 (m), 608 (s).

HRMS (ESI; C$_{16}$H$_{20}$NO): calc.: 242.1545 ([M+H]$^+$); found: 242.1540 ([M+H]$^+$).
4. Lewis-Acid Promoted Additions of Functionalized Organomagnesium and Organozinc Reagents to Carbonyl Derivatives

4.1. Addition of Grignard reagents to ketones in the presence of catalytic amounts of LaCl₃·2LiCl

2-Cyclohexyl-1-phenylpropan-2-ol (98a)

Condition A (100 mol% LaCl₃·2LiCl): according to TP10 cyclohexylmagnesium bromide (28b; 5.79 mL, 2.20 mmol, 0.38 M in THF) was added to a solution of phenylacetone (58c; 268 mg, 2.00 mmol) in LaCl₃·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 15 min at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 + 1 vol-% NEt₃) afforded the alcohol 98a (406 mg, 93%) as a colourless liquid.

Condition B (30 mol% LaCl₃·2LiCl): cyclohexylmagnesium bromide (28b; 5.79 mL, 2.20 mmol, 0.38 M in THF), phenylacetone (58c; 268 mg, 2.00 mmol, in 2.5 mL THF), LaCl₃·2LiCl (1.15 mL, 0.60 mmol, 0.52 M in THF), 15 min at 25 °C. The alcohol 98a (382 mg, 87%) was obtained as a colourless liquid.

Condition C (no LaCl₃·2LiCl present): cyclohexylmagnesium bromide (28b; 5.79 mL, 2.20 mmol, 0.38 M in THF), phenylacetone (98a; 268 mg, 2.00 mmol, in 3.5 mL THF), 1.75 h at 25 °C. The alcohol 58c was obtained in 33% yield (yield determined by ¹H-NMR after purification by flash chromatography).

¹H-NMR (300 MHz, C₆D₆): δ / ppm = 7.18-7.04 (m, 5H), 2.66 (d, J = 13.1 Hz, 1H), 2.50 (d, J = 13.3 Hz, 1H), 1.89-1.54 (m, 5H), 1.30-0.87 (m, 7H), 0.87 (s, 3H).

¹³C-NMR (75 MHz, C₆D₆): δ / ppm = 138.4, 131.1, 128.3, 126.5, 73.8, 48.0, 45.6, 28.1, 27.3, 27.1 (double), 27.0, 23.9.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3467 (vw), 3028 (vw), 2923 (m), 2852 (m), 1604 (vw), 1494 (w), 1451 (m), 1377 (w), 1346 (w), 1195 (w), 1138 (w), 1107 (w), 1083 (m), 1060 (w), 1031 (w), 937 (w), 892 (m), 849 (w), 802 (w), 769 (w), 736 (m), 726 (m), 700 (vs).

MS (EI, 70 eV): m/z (%) = 218 (M⁺, < 1), 200 (2), 180 (10), 127 (100), 109 (42), 92 (75), 83 (43), 67 (18), 55 (25).

HRMS (C₁₅H₂₂O): calc.: 218.1617; found: 218.1649.
2-Benzyl-3-methyl-1-phenylbutan-2-ol (98b)

Condition A (100 mol% LaCl$_3$·2LiCl): according to TP10 $i$-PrMgCl (28c; 1.29 mL, 2.20 mmol, 1.70 M in THF) was added to a solution of 1,3-diphenylacetone (58d; 421 mg, 2.00 mmol) in LaCl$_3$·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 5 min at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 98:2 + 1 vol-% NEt$_3$) afforded the alcohol 98b (436 mg, 86%) as a white solid.

Condition B (30 mol% LaCl$_3$·2LiCl): $i$-PrMgCl (28c; 1.29 mL, 2.20 mmol, 1.70 M in THF), 1,3-diphenylacetone (58d; 421 mg, 2.00 mmol, in 2.5 mL THF), LaCl$_3$·2LiCl (1.15 mL, 0.60 mmol, 0.52 M in THF), 5 min at 25 °C. The alcohol 98b (333 mg, 65%) was obtained as a white solid.

Condition C (no LaCl$_3$·2LiCl present): $i$-PrMgCl (28c; 1.29 mL, 2.20 mmol, 1.70 M in THF), 1,3-diphenylacetone (58d; 421 mg, 2.00 mmol, in 3.5 mL THF), 1.75 h at 25 °C. The alcohol 98b was obtained in < 3% yield (GC).

Condition D (100 mol% LaCl$_3$·2LiCl; upscaled reaction): $i$-PrMgCl (28c; 14.4 mL, 22.3 mmol, 1.55 M in THF), 1,3-diphenylacetone (58d; 4.27 g, 20.3 mmol), LaCl$_3$·2LiCl (39.0 mL, 20.3 mmol, 0.52 M in THF), 1 h at 25 °C. The alcohol 98b (4.30 g, 83%) was obtained as a white solid.

M.p. (°C): 59-60.

$^1$H-NMR (300 MHz, C$_6$D$_6$): δ / ppm = 7.21-7.08 (m, 10H), 2.78 (d, J = 13.7 Hz, 2H), 2.54 (d, J = 13.7 Hz, 2H), 1.78-1.67 (m, 1H), 1.09 (s, 1H), 0.90 (d, J = 6.7 Hz, 6H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$): δ / ppm = 138.0, 131.2, 128.3, 126.5, 76.1, 41.8, 34.2, 17.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3560 (w), 3064 (vw), 3024 (vw), 2983 (vw), 2958 (w), 2942 (w), 2930 (w), 2911 (w), 2877 (vw), 2852 (vw), 2852 (vw), 1602 (w), 1494 (m), 1470 (w), 1454 (w), 1434 (w), 1366 (w), 1350 (w), 1272 (w), 1235 (w), 1195 (w), 1181 (w), 1080 (m), 1049 (w), 1031 (m), 985 (w), 893 (w), 861 (w), 770 (w), 751 (s), 709 (s), 701 (vs).

MS (EI, 70 eV): m/z (%) = 236 ([M-H$_2$O]$^+$, <1), 163 (53), 145 (11), 119 (11), 91 (100), 71 (11), 43 (12).

HRMS (C$_{18}$H$_{22}$O): calc.: 236.1551 ([M-H$_2$O]$^+$); found: 236.1551 ([M-H$_2$O]$^+$).
C. Experimental Section

1-Methyl-1,2,3,4-tetrahydronaphthalen-1-ol (98c)

\[
\text{HO} \quad \text{Me}
\]

Condition A (100 mol% LaCl$_3$·2LiCl): according to TP10 MeMgCl (28d; 0.74 mL, 2.20 mmol, 2.99 M in THF) was added to a solution of α-tetralone (58e; 292 mg, 2.00 mmol) in LaCl$_3$·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, pentane/Et$_2$O = 9:1 + 1 vol-% NEt$_3$) afforded the alcohol 98c (307 mg, 95%) as a white solid.

Condition B (30 mol% LaCl$_3$·2LiCl): MeMgCl (28d; 0.74 mL, 2.20 mmol, 2.99 M in THF), α-tetralone (58e; 292 mg, 2.00 mmol, in 2.5 mL THF), LaCl$_3$·2LiCl (1.15 mL, 0.60 mmol, 0.52 M in THF), 2 h at 25 °C. The alcohol 98c (306 mg, 94%) was obtained as a white solid.

Condition C (no LaCl$_3$·2LiCl present): MeMgCl (28d; 0.74 mL, 2.20 mmol, 2.99 M in THF), α-tetralone (58e; 292 mg, 2.00 mmol, in 3.5 mL THF), 2 h at 25 °C. The alcohol 98c (224 mg, 69%) was obtained as a white solid.


$^1$H-NMR (300 MHz, C$_6$D$_6$): $\delta$ / ppm = 7.58-7.52 (m, 1H), 7.11-7.04 (m, 1H), 7.04-6.98 (m, 1H), 6.90-6.84 (m, 1H), 2.60-2.39 (m, 2H), 1.70-1.42 (m, 5H), 1.39 (s, 3H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$): $\delta$ / ppm = 143.7, 136.2, 128.8, 127.1, 126.9, 126.5, 70.2, 40.0, 31.1, 30.2, 20.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3313 (m), 2969 (w), 2933 (m), 2865 (w), 1487 (m), 1440 (m), 1366 (m), 1337 (m), 1284 (m), 1230 (w), 1184 (m), 1152 (m), 1103 (s), 1066 (m), 1048 (m), 990 (m), 949 (m), 930 (s), 854 (m), 761 (vs), 728 (s), 686 (s).

MS (EI, 70 eV): $m/z$ (%) = 162 (M$^+$, 1), 147 (100), 129 (56), 119 (17), 91 (32), 84 (34), 44 (6).

HRMS (C$_{11}$H$_{14}$O): calc.162.1045; found: 162.1040.

1,2,3-Triphenylpropan-2-ol (98d)

\[
\text{Ph} - \text{CH} - \text{Ph}
\]

Condition A (100 mol% LaCl$_3$·2LiCl): according to TP10 PhMgCl (28e; 1.38 mL, 2.20 mmol, 1.60 M in THF) was added to a solution of 1,3-diphenylacetone (58d; 421 mg, 2.00 mmol) in LaCl$_3$·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 1 h at
C. Experimental Section

25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2 + 1 vol-% NEt₃) afforded the alcohol 98d (582 mg, 97%) as a white solid.

Condition B (25 mol% LaCl₃·2LiCl): PhMgCl (28e; 1.38 mL, 2.20 mmol, 1.60 M in THF), 1,3-diphenylacetone (58d; 421 mg, 2.00 mmol, in 3.0 mL THF), LaCl₃·2LiCl (0.96 mL, 0.50 mmol, 0.52 M in THF), 2.5 h at 25 °C. The alcohol 98d (538 mg, 93%) was obtained as a white solid.

Condition C (no LaCl₃·2LiCl present): PhMgCl (28e; 1.38 mL, 2.20 mmol, 1.60 M in THF), 1,3-diphenylacetone (58d; 421 mg, 2.00 mmol, in 3.5 mL THF), 2.5 h at 25 °C. The alcohol 98d was obtained in 67% yield (yield determined by ¹H-NMR after purification by flash chromatography).

Condition D (30 mol% LaCl₃·2LiCl; upscaled reaction): PhMgCl (28e; 12.9 mL, 20.7 mmol, 1.60 M in THF), 1,3-diphenylacetone (58d; 3.96 g, 18.8 mmol, in 25 mL THF), LaCl₃·2LiCl (10.8 mL, 5.64 mmol, 0.52 M in THF), 1 h at 25 °C. The alcohol 98d (4.75 g, 88%) was obtained as a white solid.

M. p. (°C): 85-86.

¹H-NMR (400 MHz, C₆D₆): δ / ppm = 7.15-7.10 (m, 3H), 7.10-7.04 (m, 2H), 7.04 -6.97 (m, 6H), 6.97-6.90 (m, 4H), 3.11 (d, J = 13.5 Hz, 2H), 2.99 (d, J = 13.5 Hz, 2H), 1.72 (s br, 1H).

¹³C-NMR (100 MHz, C₆D₆): δ / ppm = 146.0, 136.9, 131.1, 128.1, 127.9, 126.7, 126.6, 126.2, 76.9, 49.0.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3565 (w), 3058 (vw), 3027 (w), 2925 (w), 1598 (w), 1495 (m), 1454 (m), 1444 (w), 1349 (w), 1324 (w), 1273 (w), 1256 (w), 1158 (vw), 1103 (w), 1080 (w), 1064 (w), 1033 (w), 1008 (w), 918 (w), 867 (w), 799 (w), 774 (m), 755 (s), 711 (s), 697 (vs), 647 (s).

MS (EI, 70 eV): m/z (%) = 288 (M⁺, <1), 197 (100), 179 (7), 105 (90), 77 (28), 44 (6).

HRMS (C₂₁H₂₀O): calc.: 288.1514; found: 288.1503.

1-Phenyl-1-[2-(trifluoromethyl)phenyl]ethanol (98f)

Condition A (100 mol% LaCl₃·2LiCl): into a flame dried and argon-flushed flask, 2-(trifluoromethyl)bromobenzene (495 mg, 2.20 mmol) was added followed by i-PrMgCl-LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF). The reaction mixture was stirred for 1.5 h. Then, the resulting aromatic Grignard reagent 28g was added to acetophenone (30; 240 mg, 2.00 mmol) in LaCl₃·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF) according to TP10. The reaction mixture was
stirred for 2 h at 0 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 7:1 + 
1 vol-% NEt₃) afforded the alcohol **98f** (384 mg, 72%) as a pale yellow liquid.

Condition B (30 mol% LaCl₃·2LiCl): 2-(trifluoromethyl)bromobenzene (495 mg, 2.20 mmol),
i-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), acetophenone (**30**; 240 mg, 2.00 mmol, in 
2.5 mL THF), LaCl₃·2LiCl (1.15 mL, 0.60 mmol, 0.52 M in THF), 2 h at 0 °C. The alcohol **98f**
(381 mg, 72%) was obtained as a pale yellow liquid.

Condition C (no LaCl₃·2LiCl present): 2-(trifluoromethyl)bromobenzene (495 mg, 2.20 mmol),
i-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), acetophenone (**30**; 240 mg, 2.00 mmol, in 
3.5 mL THF), 2 h at 0 °C. The alcohol **98f** (67 mg, 13%) was obtained as a pale yellow liquid.

**1H-NMR (600 MHz, C₄D₁₀O):** δ / ppm = 7.80 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.49 
(t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.18 (t, J = 7.6 Hz, 2H), 
7.11 (t, J = 7.4 Hz, 1H), 4.31 (s, 1H), 1.93 (s, 3H).

**13C-NMR (150 MHz, C₄D₁₀O):** δ / ppm = 149.9 (q, 4J_C-F = 1.6 Hz), 148.4 (q, 4J_C-F = 1.4 Hz), 
131.6 (q, 5J_C-F = 1.1 Hz), 129.9, 129.5 (q, 2J_C-F = 31.6 Hz), 128.8 (q, 3J_C-F = 6.7 Hz), 128.4, 
127.7, 127.1, 126.5 (q, 5J_C-F = 0.8 Hz), 125.4 (q, 1J_C-F = 273.4 Hz), 76.7, 33.0 (q, 4J_C-F = 1.7 Hz).

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3463 (vw), 2983 (vw), 1602 (w), 1494 (w), 1446 (m), 
1304 (vs), 1271 (s), 1164 (s), 1122 (vs), 1095 (s), 1032 (vs), 928 (m), 910 (m), 765 (vs), 754 (s), 
698 (vs).

**MS (EI, 70 eV):** m/z (%) = 266 (M⁺, 2), 251 (100), 231 (61), 211 (29), 183 (6), 169 (5), 121 (5).

**HRMS (C₁₅H₁₃F₃O):** calc.: 266.0918; found: 266.0905.

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**4-[Dicyclopropyl(hydroxy)methyl]benzonitrile (98g)**

Condition A (100 mol% LaCl₃·2LiCl): into a flame dried and argon-flushed flask, 4-
iodobenzonitrile (504 mg, 2.20 mmol, in 1 mL THF) was added followed by i-PrMgCl-LiCl 
(1.32 mL, 2.16 mmol 1.64 M in THF) at 0 °C. The reaction mixture was stirred for 2 h. Then, the 
resulting aromatic Grignard reagent **28h** was added to dicyclopropylmethanone (**58g**; 220 mg, 
2.00 mmol) in LaCl₃·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF) according to **TP10**. The 
reaction mixture was stirred for 2.5 h at 25 °C. Purification by flash chromatography (silica gel,
pentane / Et\textsubscript{2}O = 3:1 + 1 vol-% NEt\textsubscript{3}) afforded the alcohol \textbf{98g} (328 mg, 77%) as a pale yellow solid.

Condition B (30 mol% LaCl\textsubscript{3}·2LiCl): 4-iodobenzonitrile (504 mg, 2.20 mmol, in 1 mL THF), \textit{i}-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), dicyclopropylmethanone (\textbf{58g}; 220 mg, 2.00 mmol, in 2.5 mL THF), LaCl\textsubscript{3}·2LiCl (1.15 mL, 0.60 mmol, 0.52 M in THF), 2.5 h at 25 °C. The alcohol \textbf{98g} (357 mg, 84%) was obtained as a pale yellow solid.

Condition C (no LaCl\textsubscript{3}·2LiCl present): 4-iodobenzonitrile (504 mg, 2.20 mmol, in 1 mL THF), \textit{i}-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), dicyclopropylmethanone (\textbf{58g}; 220 mg, 2.00 mmol, in 3.5 mL THF), 2.5 h at 25 °C. The alcohol \textbf{98g} (371 mg, 87%) was obtained as a pale yellow solid.

\textbf{M.p. (°C)}: 78-80.

\textbf{\textit{1}H-NMR (300 MHz, C\textsubscript{6}D\textsubscript{6})}: δ / ppm = 7.29-7.23 (m, 2H), 7.15-7.10 (m, 2H), 1.01 (s\textsubscript{br}, 1H), 0.75-0.63 (m, 2H), 0.43-0.33 (m, 2H), 0.30-0.17 (m, 4H), 0.10-(-0.01) (m, 2H).

\textbf{\textit{13}C-NMR (75 MHz, C\textsubscript{6}D\textsubscript{6})}: δ / ppm = 153.1, 131.6, 126.4, 119.1, 110.9, 73.0, 20.7, 2.3, 0.1.

\textbf{IR (Diamond-ATR, neat)}: ν / cm\textsuperscript{-1} = 3518 (m), 3089 (vw), 3004 (w), 2226 (m), 1735 (vw), 1605 (m), 1500 (w), 1460 (w), 1400 (m), 1332 (w), 1191 (m), 1161 (m), 1106 (m), 1052 (w), 1028 (s), 1003 (m), 965 (m), 909 (m), 881 (m), 853 (m), 831 (vs), 656 (m).

\textbf{MS (EI, 70 eV)}: m/z (%) = 213 (M\textsuperscript{+}, <1), 185 (100), 170 (37), 154 (7), 143 (20), 130 (80), 127 (8), 102 (19), 69 (13), 41 (6).

\textbf{HRMS (C\textsubscript{14}H\textsubscript{15}NO)}: calc.: 213.1154; found: 213.1145.

\textbf{Ethyl 4-\(\text{-}(1\text{-cyclopropyl-1-hydroxyethyl}\)benzoate (98h)}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

Condition A (100 mol% LaCl\textsubscript{3}·2LiCl): into a flame dried and argon-flushed flask, ethyl 4-iodobenzoate (607 mg, 2.20 mmol, in 1 mL THF) was added followed by \textit{i}-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF) at -20 °C. The reaction mixture was stirred for 30 min at -20 °C. Then, the resulting aromatic Grignard reagent \textbf{28i} was added to 1-cyclopropylethanone (\textbf{58h}; 220 mg, 2.00 mmol) in LaCl\textsubscript{3}·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF) according to \textbf{TP10}. The reaction mixture was stirred for 2.5 h at 25 °C. Purification by flash chromatography
(silica gel, pentane / Et₂O = 3:1 + 1 vol-% NEt₃) afforded the alcohol 98h (354 mg, 76%) as a yellow oil.

Condition B (30 mol% LaCl₃·2LiCl): ethyl 4-iodobenzoate (607 mg, 2.20 mmol, in 1 mL THF), i-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), 1-cyclopropylethanone (58h: 220 mg, 2.00 mmol, in 2.5 mL THF), LaCl₃·2LiCl (1.15 mL, 0.60 mmol, 0.52 M in THF), 2.5 h at 25 °C. The alcohol 98h (389 mg, 83%) was obtained as a yellow oil.

Condition C (no LaCl₃·2LiCl present): ethyl 4-iodobenzoate (607 mg, 2.20 mmol, in 1 mL THF), i-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), 1-cyclopropylethanone (58h: 220 mg, 2.00 mmol, in 3.5 mL THF), 3 h at 25 °C. The alcohol 98h (378 mg, 81%) was obtained as a yellow oil.

¹H-NMR (300 MHz, C₆D₆): δ / ppm = 8.24-8.16 (m, 2H), 7.49-7.42 (m, 2H), 4.15 (d, J = 7.0 Hz, 2H), 1.27 (sbr, 1H), 1.24 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H), 0.97-0.84 (m, 1H), 0.45-0.22 (m, 3H), 0.20-0.09 (m, 1H).

¹³C-NMR (75 MHz, C₆D₆): δ / ppm = 166.4, 154.0, 129.7, 129.4, 125.5, 72.3, 60.8, 28.9, 23.1, 14.3, 2.0, 1.1.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3490 (w), 2980 (w), 1698 (s), 1610 (w), 1574 (vw), 1448 (w), 1406 (m), 1368 (m), 1272 (vs), 1182 (m), 1100 (s), 1046 (m), 1018 (s), 926 (w), 900 (m), 860 (m), 770 (s), 706 (m).

MS (EI, 70 eV): m/z (%) = 234 (M⁺, <1), 219 (22), 206 (100), 193 (23), 189 (17), 161 (19), 143 (5), 133 (6), 91 (7), 43 (10).

HRMS (C₁₄H₁₈O₃): calc.: 234.1256; found: 234.1238.

1-(4-Methoxyphenyl)cyclohexanol (98i)

Condition A (100 mol% LaCl₃·2LiCl): into a flame dried and argon-flushed flask, 4-idoanisole (515 mg, 2.20 mmol, in 1 mL THF) was added followed by i-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF) at 25 °C. The reaction mixture was stirred for 1 h at 25 °C. Then, the resulting aromatic Grignard reagent 28j was added to cyclohexanone (58i; 196 mg, 2.00 mmol) in LaCl₃·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF) according to TP10. The reaction mixture was
C. Experimental Section

stirred for 2 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 4:1 + 1 vol-% NEt₃) afforded the alcohol 98i (303 mg, 73%) as a colourless liquid.

Condition B (30 mol% LaCl₃·2LiCl): 4-iodoanisole (515 mg, 2.20 mmol, in 1 mL THF), i-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), cyclohexanone (58i; 196 mg, 2.00 mmol, in 2.5 mL THF), LaCl₃·2LiCl (1.15 mL, 0.60 mmol, 0.52 M in THF), 2 h at 25 °C. The alcohol 98i (306 mg, 74%) was obtained as a colourless liquid.

Condition C (no LaCl₃·2LiCl present): 4-iodoanisole (515 mg, 2.20 mmol, in 1 mL THF), i-PrMgCl·LiCl (1.32 mL, 2.16 mmol, 1.64 M in THF), cyclohexanone (58i; 196 mg, 2.00 mmol, in 3.5 mL THF), 2 h at 25 °C. The alcohol 98i (348 mg, 84%) was obtained as a colourless liquid.

1H-NMR (300 MHz, C₆D₆): δ / ppm = 7.39-7.33 (m, 2H), 6.88-6.81 (m, 2H), 3.36 (s, 3H), 1.88-1.56 (m, 7H), 1.54-1.43 (m, 2H), 1.19 (s, 1H), 1.17-1.04 (m, 1H).

13C-NMR (75 MHz, C₆D₆): δ / ppm = 158.8, 142.5, 126.1, 113.7, 72.5, 54.8, 39.3, 25.9, 22.5.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3443 (w), 2930 (m), 2856 (w), 1739 (w), 1608 (m), 1582 (w), 1510 (s), 1447 (m), 1298 (m), 1244 (vs), 1212 (m), 1177 (s), 1132 (w), 1112 (m), 1036 (s), 1021 (m), 966 (m), 904 (w), 849 (m), 824 (vs), 792 (m).

MS (EI, 70 eV): m/z (%) = 206 (M⁺, 38), 163 (100), 150 (24), 135 (33), 77 (5), 55 (6).
HRMS (C₁₃H₁₈O₂): calc.: 206.1307; found: 206.1300.

1-(1-Naphthyl)cyclopentanol (98k)

\[ \text{\includegraphics[width=1cm]{image}} \]

Condition A (100 mol% LaCl₃·2LiCl): according to TP10 naphthylmagnesium chloride (28f; 3.44 mL, 2.20 mmol, 0.64 M in THF) was added to a solution of cyclopentanone (58j; 168 mg, 2.00 mmol) in LaCl₃·2LiCl (3.85 mL, 2.00 mmol, 0.52 M in THF). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 + 1 vol-% NEt₃) afforded the alcohol 98k (251 mg, 59%) as a yellow solid.

Condition B (30 mol% LaCl₃·2LiCl): naphthylmagnesium chloride (28f; 3.44 mL, 2.20 mmol, 0.64 M in THF), cyclopentanone (58j; 168 mg, 2.00 mmol, in 2.5 mL THF), LaCl₃·2LiCl (1.15 mL, 0.60 mmol, 0.52 M in THF), 2 h at 25 °C. The alcohol 98k (277 mg, 65%) was obtained as a yellow solid.
Condition C (no LaCl\textsubscript{3}·2LiCl present): naphthylmagnesium chloride (28f; 3.44 mL, 2.20 mmol, 0.64 M in THF), cyclopentanone (58j; 168 mg, 2.00 mmol, in 3.5 mL THF), 2 h at 25 °C. The alcohol 98k (317 mg, 75%) was obtained as a yellow solid.

**M.p. (°C):** 74-75.

\textsuperscript{1}H-NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta / \text{ppm} = 8.84 \text{ (dd, } J = 8.6 \text{ Hz, 0.8 Hz, 1H)}, 7.70 \text{ (dd, } J = 8.0 \text{ Hz, 1.7 Hz, 1H)}, 7.61 \text{ (d, } J = 8.2 \text{ Hz, 1H)}, 7.41-7.33 \text{ (m, 2H)}, 7.33-7.26 \text{ (m, 1H)}, 7.25-7.18 \text{ (m, 1H)}, 2.16-1.83 \text{ (m, 6H)}, 1.66-1.49 \text{ (m, 2H)}, 1.32 \text{ (s, br, 1H)}.

\textsuperscript{13}C-NMR (100 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta / \text{ppm} = 142.6, 135.4, 132.5, 129.1, 128.7, 128.1, 125.5, 124.8, 122.8, 83.8, 40.8, 23.9.

IR (Diamond-ATR, neat): \(\tilde{\nu} / \text{cm}^{-1} = 3296 \text{ (w)}, 3043 \text{ (vw)}, 2955 \text{ (w)}, 2871 \text{ (w)}, 1735 \text{ (vw)}, 1598 \text{ (w)}, 1508 \text{ (w)}, 1385 \text{ (w)}, 1317 \text{ (w)}, 1241 \text{ (w)}, 1191 \text{ (w)}, 1109 \text{ (w)}, 1061 \text{ (w)}, 997 \text{ (m)}, 951 \text{ (w)}, 935 \text{ (w)}, 907 \text{ (w)}, 880 \text{ (w)}, 861 \text{ (w)}, 797 \text{ (m)}, 774 \text{ (vs)}, 656 \text{ (m)}, 641 \text{ (m)}.

MS (EI, 70 eV): m/z (%) = 212 (M\textsuperscript{+}, 78), 194 (9), 183 (42), 170 (23), 165 (32), 155 (100), 141 (26), 127 (27).

HRMS (C\textsubscript{15}H\textsubscript{16}O): calc.: 212.1201; found: 212.1191.

#### 4.2. Addition of functionalized organozinc reagents to aldehydes, ketones and carbon dioxide under mediation of MgCl\textsubscript{2}

#### 4.2.1. Preparation of the organozinc reagents

**Phenylzinc iodid (93b)**

![Phenylzinc iodid (93b)](image)

According to TP11 iodobenzene (3.06 g, 15.0 mmol, in 10.0 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) in a THF solution (15 mL) of ZnCl\textsubscript{2} (16.5 mmol) and LiCl (22.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 93b indicated a concentration of 0.68 M.

**Tolylzinc iodid (93e)**

![Tolylzinc iodid (93e)](image)

According to TP11 4-iodotoluene (2.17 g, 10.0 mmol, in 6.00 mL THF) was reacted with magnesium powder (608 mg, 25.0 mmol) in a THF solution (10 mL) of ZnCl\textsubscript{2} (11.0 mmol) and
LiCl (15.0 mmol) at 25 °C for 45 min. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 93e indicated a concentration of 0.52 M.

(3-Methyl-1-phenyl-1\(H\)-pyrazol-5-yl)zinc chloride (93f)

According to TP11 5-chloro-3-methyl-1-phenyl-1\(H\)-pyrazole (963 mg, 5.00 mmol, in 2.5 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) in a THF solution (7.5 mL) of ZnCl\(_2\) (8.25 mmol) and LiCl (11.3 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 93f indicated a concentration of 0.57 M.

Bis(4-methoxyphenyl)zinc (103a)

According to TP11 4-bromoanisole (2.81 g, 15.0 mmol, in 10.0 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) in a THF solution (7.5 mL) of ZnCl\(_2\) (8.25 mmol) and LiCl (11.3 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 103a indicated a concentration of 0.39 M.

Bis[2-(trifluoromethyl)phenyl]zinc (103b)

According to TP11 1-bromo-2-(trifluoromethyl)benzene (6.75 g, 30.0 mmol, in 15.0 mL THF) was reacted with magnesium turnings (729 mg, 75.0 mmol) in a THF solution (15 mL) of ZnCl\(_2\) (16.5 mmol) and LiCl (22.5 mmol) at 25 °C for 3 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 103b indicated a concentration of 0.42 M.
Bis(4-chlorophenyl)zinc (103c)

According to TP11 1-bromo-4-chlorobenzene (3.83 g, 20.0 mmol, in 4.0 mL THF) was reacted with magnesium turnings (1.22 g, 50.0 mmol) in a THF solution (10 mL) of ZnCl₂ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 1.5 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 103c indicated a concentration of 0.71 M.

Bis(4-trimethylsilylphenyl)zinc (103d)

According to TP11 (4-bromophenyl)trimethylsilane (2.29 g, 10.0 mmol, in 8.0 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (5 mL) of ZnCl₂ (6.0 mmol) and LiCl (7.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 103d indicated a concentration of 0.28 M.

Bis[4-(dimethylamino)phenyl]zinc (103e)

According to TP11 (4-bromophenyl)dimethylamine (8.00 g, 40.0 mmol, in 16.0 mL THF) was reacted with magnesium turnings (2.43 g, 100 mmol) in a THF solution (20 mL) of ZnCl₂ (22.0 mmol) and LiCl (30.0 mmol) at 25 °C for 1 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 103e indicated a concentration of 0.41 M.

Bis[2-(dimethylamino)phenyl]zinc (103f)

According to TP11 (2-bromophenyl)dimethylamine (2.00 g, 10.0 mmol, in 6.7 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (5.0 mL) of ZnCl₂ (5.5 mmol) and LiCl (7.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another
argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 103f indicated a concentration of 0.29 M.

**Bis(3-methyl-1-phenyl-1H-pyrazol-5-yl)zinc (103g)**

According to TP11 5-chloro-3-methyl-1-phenyl-1H-pyrazole (2.70 g, 14.0 mmol, in 9.3 mL THF) was reacted with magnesium turnings (851 mg, 34.9 mmol) in a THF solution (7 mL) of ZnCl₂ (7.7 mmol) and LiCl (10.5 mmol) at 25 °C for 4 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 103g indicated a concentration of 0.34 M.

**Bis(3,5-dimethylisoxazol-4-yl)zinc (103h)**

According to TP11 4-bromo-3,5-dimethylisoxazole (3.52 g, 20.0 mmol, in 10.0 mL THF) was reacted with magnesium turnings (1.22 mg, 50.0 mmol) in a THF solution (10 mL) of 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 103h indicated a concentration of 0.20 M.

**(5-Cyano-5-methylhexyl)zinc bromide (107a)**

According to TP11 6-bromo-2,2-dimethylhexanitrile (2.04 g, 10.0 mmol, in 5.0 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (10 mL) of ZnCl₂ (11.0 mmol) and LiCl (15.0 mmol) at 25 °C for 4 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 107a indicated a concentration of 0.79 M.
C. Experimental Section

4-Fluorobenzylzinc chloride (95c)

According to TP11 4-fluorobenzyl chloride (2.17 g, 15.0 mmol, in 7.5 mL THF) was reacted with magnesium turnings (911 mg, 37.5 mmol) in a THF solution (15 mL) of ZnCl$_2$ (16.5 mmol) and LiCl (22.5 mmol) at 25 °C for 45 min. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 95c indicated a concentration of 0.39 M.

4-Methoxybenzylzinc chloride (95i)

According to TP11 4-methoxybenzyl chloride (1.10 g, 7.00 mmol, in 1.0 mL THF) was reacted with magnesium powder (425 mg, 17.5 mmol) in a THF solution (7.0 mL) of ZnCl$_2$ (7.7 mmol) and LiCl (10.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 95i indicated a concentration of 0.72 M.

3-(Ethoxycarbonyl)benzylzinc chloride (95m)

According to TP11 3-(ethoxycarbonyl)benzyl chloride (1.39 g, 7.00 mmol, in 3.75 mL THF) was reacted with magnesium turnings (425 mg, 17.5 mmol) in a THF solution (15 mL) of ZnCl$_2$ (7.70 mmol) and LiCl (10.5 mmol) at 25 °C for 2 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 95m indicated a concentration of 0.40 M.

Bis(3-ethoxycarbonyl)benzylzinc (106a)

According to TP11 3-(ethoxycarbonyl)benzyl chloride (2.71 g, 13.6 mmol, in 12 mL THF) was reacted with magnesium turnings (826 mg, 34.0 mmol) in a THF solution (6.80 mL) of ZnCl$_2$ (7.45 mmol) and LiCl (10.2 mmol) at 25 °C for 1.5 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 106a (premix of an aliquot with excess ZnCl$_2$ solution (1.00 M in THF)) indicated a concentration of 0.33 M.
Bis(3-methoxybenzyl)zinc (106b)

According to TP11 3-methoxybenzyl chloride (2.35 g, 15.0 mmol, in 8.0 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (7.5 mL) of 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 106b (premix of an aliquot with excess ZnCl₂ solution (1.00 M in THF)) indicated a concentration of 0.31 M.

Bis(benzyl)zinc (106c)

According to TP11 benzyl chloride (1.27 g, 10.0 mmol, in 2.0 mL THF) was reacted with magnesium turnings (608 mg, 25.0 mmol) in a THF solution (5.0 mL) of ZnCl₂ (5.5 mmol) and LiCl (7.5 mmol) at 25 °C for 1 h. After subsequent cannulation to another argon-flushed Schlenk-flask, iodometric titration of the zinc reagent 106c (premix of an aliquot with excess ZnCl₂ solution (1.00 M in THF)) indicated a concentration of 0.42 M.

4.2.2. Preparation of the title compounds

(2-Chlorophenyl)(phenyl)methanol (101)

According to TP12 phenylzinc iodide·MgCl₂ (93b; 2.65 mL, 1.80 mmol, 0.68 M in THF) was added to 2-chlorobenzaldehyde (61a; 211 mg, 1.50 mmol, in 3.87 mL THF). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 + 1 vol-% NEt₃) afforded the alcohol 101 (289 mg, 88%) as a pale yellow solid.

M.p. (°C): 71-73.

¹H-NMR (400 MHz, C₆D₆): δ / ppm = 7.59-7.52 (m, 1H), 7.37-7.31 (m, 2H), 7.13-7.06 (m, 3H), 7.05-6.99 (m, 1H), 6.94-6.87 (m, 1H), 6.78-6.71 (m, 1H), 6.04 (s, 1H), 1.66 (s, 1H).

¹³C-NMR (100 MHz, C₆D₆): δ / ppm = 143.1, 142.1, 132.7, 129.5, 128.7, 128.5, 128.5, 127.7, 127.2, 127.1, 72.6.
C. Experimental Section

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1} = 3174$ (w), 1570 (vw), 1465 (w), 1456 (w), 1440 (w), 1315 (w), 1236 (w), 1183 (m), 1122 (w), 1075 (w), 1059 (w), 1024 (m), 953 (w), 916 (vw), 877 (vw), 853 (w), 824 (w), 760 (vs), 725 (m), 696 (s).

**MS (EI, 70 eV):** m/z (%) = 218 (M$^+$, 100), 201 (13), 183 (13), 165 (47), 140 (24), 112 (20), 105 (70), 77 (38).

**HRMS (C$_{13}$H$_{11}$ClO):** calc.: 218.0498; found: 218.0493.

Ethyl 3-{2-[4-(dimethylamino)phenyl]-2-hydroxyethyl}benzoate (105)

According to TP12 3-(ethoxycarbonyl)benzylzinc chloride·MgCl$_2$ (95m; 3.90 mL, 1.56 mmol, 0.40 M in THF) was added to 4-(dimethylamino)benzaldehyde (61h; 194 mg, 1.30 mmol, in 1.0 mL THF). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:1 + 1 vol-% NEt$_3$) afforded the alcohol 105 (326 mg, 80%) as a yellow oil.

**$^1$H-NMR (300 MHz, CD$_6$D$_6$):** $\delta$ / ppm = 8.21-8.17 (m, 1H), 8.08-8.02 (m, 1H), 7.19 -7.15 (m, 3H), 7.03 (t, $J = 7.7$, 1H), 6.61-6.54 (m, 2H), 4.66 (dd, $J = 7.9$ Hz, 5.5 Hz, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 3.09-2.98 (m, 1H), 2.97-2.88 (m, 1H), 2.51 (s, 6H), 1.70 (br, 1H) 1.02 (t, $J = 7.2$ Hz, 3H).

**$^{13}$C-NMR (75 MHz, CD$_6$D$_6$):** $\delta$ / ppm = 166.5, 150.4, 139.8, 134.5, 132.7, 131.2, 131.1, 128.6, 127.7, 127.2, 112.7, 75.1, 60.7, 46.1, 40.3, 14.3.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1} = 3412$ (w), 2980 (w), 2885 (w), 2801 (w), 1713 (s), 1614 (m), 1521 (s), 1444 (m), 1348 (m), 1277 (vs), 1193 (vs), 1163 (s), 1104 (s), 1082 (s), 1022 (s), 946 (m), 817 (s), 751 (s), 691 (m), 672 (w).

**MS (EI, 70 eV):** m/z (%) = 313 (M$^+$, <1), 295 (100), 267 (13), 222 (2), 178 (4), 125 (3), 110 (3).

**HRMS (C$_{19}$H$_{23}$NO$_3$):** calc.: 313.1678; found: 313.1669.
8,8,8-Trifluoro-7-hydroxy-2,2-dimethyl-7-phenyloctanenitrile (109)

According to TP12 (5-cyano-5-methylhexyl)zinc bromide-MgCl2 (107a; 1.40 mL, 1.09 mmol, 0.78 M in THF) was added to 2,2,2-trifluoro-1-phenylethanone (58l; 146 mg, 0.84 mmol). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et2O = 4:1) afforded the alcohol 109 (192 mg, 76%) as a white solid.

M.p. (°C): 76-78.

1H-NMR (400 MHz, CDCl3): δ / ppm = 7.46 (d, J = 7.8 Hz, 2H), 7.13-7.07 (m, 2H), 7.05-6.99 (m, 1H), 2.40-2.19 (s, 6H), 1.96-1.85 (m, 1H), 1.69-1.59 (m, 1H), 1.13-0.92 (m, 3H), 0.78-0.66 (m, 3H), 0.73 (s, 3H), 0.71 (s, 3H).

13C-NMR (100 MHz, CDCl3): δ / ppm = 137.0, 128.5, 128.5. 126.7 (q, 1JCF = 286.1 Hz), 124.7, 77.3 (q, 2JCF = 27.8 Hz), 40.6, 35.1, 32.0, 26.4, 26.1, 25.5, 22.5.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3443 (w), 2978 (vw), 2941 (w), 2858 (vw), 2242 (vw), 1502 (vw), 1470 (w), 1452 (w), 1406 (w), 1372 (w), 1307 (w), 1275 (m), 1243 (m), 1212 (m), 1182 (m), 1151 (vs), 1075 (m), 987 (m), 934 (w), 916 (w), 895 (w), 767 (m), 734 (w), 704 (s), 689 (m).

HRMS (ESI; C16H20F5NO): calc.: 322.1395 ([M+Na]+); found: 322.1390 ([M+Na]+).

4-[Hydroxy(4-methylphenyl)methyl]benzonitrile (110a)

According to TP12 tolylzinc iodide-MgCl2 (93e; 3.46 mL, 1.80 mmol, 0.52 M in THF) was added to 4-formylbenzonitrile (61i; 197 mg, 1.50 mmol, in 0.5 mL THF). The reaction mixture was stirred for 13 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et2O = 1:1) afforded the alcohol 110a (244 mg, 73%) as a pale yellow solid.

M.p. (°C): 44-46.

1H-NMR (400 MHz, CDCl3): δ / ppm = 7.03-6.97 (m, 6H), 6.96-6.91 (m, 2H), 5.26 (d, J = 2.7 Hz, 1H), 2.07 (s, 3H), 1.80 (d, J = 3.3 Hz, 1H).

13C-NMR (100 MHz, CDCl3): δ / ppm = 149.3, 140.8, 137.7, 132.0, 129.4, 127.0, 126.9, 118.9, 111.3, 75.3, 21.0.
IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 3448$ (m), 2234 (m), 1607 (m), 1503 (w), 1404 (m), 1322 (w), 1265 (w), 1230 (m), 1189 (m), 1173 (m), 1120 (w), 1052 (s), 1018 (m), 871 (m), 812 (vs), 770 (vs), 744 (m).

MS (EI, 70 eV): m/z (%) = 223 (M$^+$, 26), 208 (30), 189 (13), 130 (40), 121 (17), 118 (33), 104 (29), 93 (100), 76 (35), 65 (25); 51 (14).

HRMS (C$_{15}$H$_{13}$NO): calc.: 223.0997; found: 223.0991.

4-[Hydroxy(3-methyl-1-phenyl-1H-pyrazol-5-yl)methyl]benzonitrile (110b)

According to TP12 (3-methyl-1-phenyl-1H-pyrazol-5-yl)zinc chloride·MgCl$_2$ (93f; 3.16 mL, 1.80 mmol, 0.57 M in THF) was added to 4-formylbenzonitrile (61i; 197 mg, 1.50 mmol, in 2.0 mL THF). The reaction mixture was stirred for 10 h at 25 ºC. Purification by flash chromatography (silica gel, pentane/Et$_2$O = 1:1 to Et$_2$O) afforded the alcohol 110b (425 mg, 98%) as a white solid.


$^1$H-NMR (300 MHz, C$_6$D$_6$): $\delta$ / ppm = 7.56-7.50 (m, 2H), 7.36 (s, 5H), 7.34-7.28 (m, 2H), 5.91 (s, 1H), 5.75 (s, 1H), 3.43 (s, 1H), 2.22 (s, 3H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$): $\delta$ / ppm = 149.1, 146.7, 145.1, 139.1, 132.1, 129.2, 128.4, 126.9, 125.5, 118.5, 111.5, 106.6, 67.1, 13.3.

IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 3265$ (w), 2927 (w), 2228 (m), 1598 (w), 1538 (m), 1502 (m), 1440 (m), 1407 (m), 1370 (m), 1323 (w), 1230 (w), 1197 (w), 1055 (s), 1034 (s), 1028 (m), 860 (m), 810 (vs), 797 (s), 770 (s), 748 (m), 698 (s), 685 (m), 660 (w).

MS (EI, 70 eV): m/z (%) = 289 (M$^+$, 100), 272 (8), 159 (36), 130 (11), 118 (6), 77 (19).

HRMS (C$_{18}$H$_{15}$N$_3$O): calc.: 289.1215; found: 289.1204.

(4-Chlorophenyl)[4-(trimethylsilyl)phenyl]methanone (110c)

According to TP12 4-(trimethylsilylphenyl)zinc bromide·2MgCl$_2$ (93g; 2.40 mL, 1.80 mmol, 0.75 M in THF) was added to 4-chlorobenzoyl chloride (60d; 525 mg, 3.00 mmol, in 6.0 mL
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THF) and the reaction mixture was stirred for 18 h at 50 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the ketone 110c (423 mg, 81%) as white solid.

**M.p. (°C):** 67-69.

**1H-NMR (400 MHz, C₆D₆):** δ / ppm = 7.70-7.66 (m, 2H), 7.50-7.45 (m, 2H), 7.42-7.38 (m, 2H), 7.03-6.97 (m, 2H), 0.18 (s, 9H).

**13C-NMR (100 MHz, C₆D₆):** δ / ppm = 194.6, 145.9, 138.6, 138.1, 136.3, 133.5, 131.6, 129.1, 128.7, -1.4.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2956 (w), 1725 (vw), 1646 (m), 1586 (m), 1543 (w), 1482 (w), 1387 (m), 1300 (m), 1283 (m), 1254 (m), 1173 (w), 1151 (w), 1085 (m), 1012 (w), 967 (w), 958 (w), 929 (m), 824 (vs), 754 (s), 741 (s), 706 (m), 672 (s).

**MS (EI, 70 eV):** m/z (%) = 288 (M⁺, 29), 275 (100), 139 (10), 73 (7).

**HRMS (C₁₆H₁₇ClOSi):** calc.: 288.0737; found: 288.0736.

Pyridin-4-yl[2-(trifluoromethyl)phenyl]methanol (110d)

According to TP12 isonicotinaldehyde (61j; 161 mg, 1.50 mmol) was added to bis[2-(trifluoromethyl)phenyl]zinc·2MgX₂ (103b; X = Cl, Br; 2.20 mL, 0.90 mmol, 0.41 M in THF). The reaction mixture was stirred for 8 h at 25 °C. Purification by flash chromatography (silica gel, Et₂O + 1 vol-% NEt₃) afforded the alcohol 110d (311 mg, 82%) as a white solid.

**M.p. (°C):** 159-160.

**1H-NMR (400 MHz, DMSO-d6):** δ / ppm = 8.50 (d, J = 1.6 Hz, 1H), 8.49 (d, J = 1.6 Hz, 1H), 7.75-7.70 (m, 1H), 7.70-7.64 (m, 1H), 7.63-7.58 (m, 1H), 7.54-7.46 (m, 1H), 7.27-7.22 (m, 2H), 6.48 (d, J = 4.7 Hz, 1H), 5.99 (d, J = 4.5 Hz, 1H).

**13C-NMR (100 MHz, DMSO-d6):** δ / ppm = 152.7, 149.6, 142.2 (q, 4J_C-F = 1.5 Hz), 132.9 (q, 4J_C-F = 1.1 Hz), 129.8, 128.1, 126.0 (q, 2J_C-F = 29.6 Hz), 125.3 (q, 3J_C-F = 5.8 Hz), 124.4 (q, 1J_C-F = 274.0 Hz), 121.3, 68.4 (q, 4J_C-F = 2.3 Hz).

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3042 (w), 2924 (w), 2850 (w), 1738 (w), 1602 (m), 1583 (w), 1452 (m), 1416 (m), 1310 (s), 1282 (m), 1247 (w), 1152 (s), 1109 (vs), 1063 (s), 1051 (s), 1032 (s), 1006 (s), 791 (s), 766 (s), 752 (s), 669 (m).
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MS (EI, 70 eV): m/z (%) = 253 (M⁺, 72), 237 (17), 233 (18), 204 (60), 184 (28), 155 (100), 145 (19), 127 (58), 106 (33), 80 (59), 51 (20).

HRMS (C₁₃H₁₀F₃NO): calc.: 253.0714; found: 253.0711.

(6-Bromo-1,3-benzodioxol-5-yl)(4-chlorophenyl)methanol (110e)

According to TP12 bis(4-chlorophenyl)zinc·2MgX₂ (103c; X = Cl, Br; 6.00 mL, 0.90 mmol, 0.15 M in THF) was added to 6-bromo-1,3-benzodioxole-5-carbaldehyde (61k; 344 mg, 1.50 mmol, in 1.0 mL THF). The reaction mixture was stirred for 10 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 6:1 + 1 vol-% NEt₃) afforded the alcohol 110e (438 mg, 85%) as 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 (s, 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), 2973 (w), 2896 (w), 1596 (vw), 1501 (m), 1471 (vs), 1407 (m), 1388 (m), 1231 (s), 1103 (m), 1090 (m), 1035 (vs), 1013 (s), 966 (m), 931 (s), 845 (s), 780 (m), 728 (w), 672 (w).

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

HRMS (C₁₄H₁₀BrClO₃): calc.: 339.9502; found: 339.9504.

4-[1-Hydroxy-1-(4-methoxyphenyl)ethyl]benzonitrile (110f)

According to TP12 bis(4-methoxyphenyl)zinc·2MgX₂ (103a; X = Cl, Br; 2.31 mL, 0.90 mmol, 0.39 M in THF) was added to 4-acetylbenzonitrile (58m; 218 mg, 1.50 mmol, in 0.5 mL THF) and the reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 + 1 vol-% NEt₃) afforded the alcohol 110f (236 mg, 62%) as white solid.
C. Experimental Section

M.p. (°C): 77-79.

$^1$H-NMR (400 MHz, $C_6D_6$): $\delta$/ ppm = 7.13-7.07 (m, 4H), 7.05-7.00 (m, 2H), 6.76-6.70 (m, 2H), 3.30 (s, 3H), 1.70 (s, 1H), 1.50 (s, 3H).

$^{13}$C-NMR (100 MHz, $C_6D_6$): $\delta$/ ppm = 159.3, 153.7, 139.5, 131.8, 127.4, 126.6, 118.9, 113.8, 111.0, 75.2, 54.8, 30.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm$^{-1}$ = 3494 (m), 2967 (w), 2231 (m), 1607 (m), 1504 (s), 1448 (m), 1403 (m), 1367 (m), 1299 (w), 1245 (vs), 1194 (m), 1178 (s), 1134 (m), 1090 (m), 1061 (m), 1028 (vs), 960 (w), 919 (m), 840 (s), 816 (s), 696 (w).

MS (EI, 70 eV): m/z (%) = 253 (M$^+$, 12), 235 (100), 220 (27), 190 (9), 151 (8), 130 (21), 43 (5).

HRMS (C$_{16}$H$_{15}$NO$_2$): calc.: 253.1103; found: 253.1094.

4-{Hydroxy[4-(trimethylsilyl)phenyl]methyl}benzonitrile (110g)

According to TP2b bis[4-(trimethylsilyl)phenyl]zinc·2MgX$_2$ (103d; X = Cl, Br; 3.21 mL, 0.90 mmol, 0.28 M in THF) was added to 4-formylbenzonitrile (61i; 197 mg, 1.50 mmol, in 0.5 mL THF). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 12:1 + 1 vol-% NEt$_3$) afforded the alcohol 110g (401 mg, 95%) as a pale yellow solid.

M.p. (°C): 73-75.

$^1$H-NMR (300 MHz, $C_6D_6$): $\delta$/ ppm = 7.45-7.40 (m, 2H), 7.18-7.12 (m, 2H), 7.04-6.96 (m, 4H), 5.27 (s, 1H), 1.82 (s, 1H), 0.20 (s, 9H).

$^{13}$C-NMR (75 MHz, $C_6D_6$): $\delta$/ ppm = 149.0, 144.2, 140.2, 133.9, 132.0, 127.0, 126.3, 118.8, 111.5, 75.4, -1.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm$^{-1}$ = 3243 (w), 2956 (w), 2902 (w), 2231 (w), 1598 (w), 1500 (w), 1404 (w), 1328 (w), 1275 (w), 1250 (m), 1187 (w), 1172 (w), 1108 (w), 1028 (m), 1014 (m), 836 (vs), 808 (vs), 745 (m), 678 (m).

MS (EI, 70 eV): m/z (% = 281 (M$^+$, 5), 266 (100), 250 (17), 190 (6), 119 (3), 73 (7).

HRMS (C$_{17}$H$_{19}$NO$_2$Si): calc.: 281.1236; found: 281.1223.
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Dicyclopentyldimethylamine (110h)

According to TP12 dicyclopropylmethanone (58g; 165 mg, 1.50 mmol) was added to bis[4-(dimethylamino)phenyl]zinc-2MgX₂ (103e; X = Cl, Br; 2.14 mL, 0.90 mmol, 0.42 M in THF). The reaction mixture was stirred for 24 h at 50 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 8:1 + 1 vol-% NEt₃) afforded the alcohol 110h (257 mg, 74%) as a yellow oil.

¹H-NMR (400 MHz, CD₆D₆) δ / ppm = 7.61-7.53 (m, 2H), 6.71-6.64 (m, 2H), 2.56 (s, 6H), 1.17-1.08 (m, 2H), 1.05 (s br, 1H), 0.67-0.58 (m, 2H), 0.52-0.44 (m, 2H), 0.41-0.33 (m, 2H), 0.31-0.20 (m, 2H).

¹³C-NMR (100 MHz, CD₆D₆) δ / ppm = 149.8, 135.7, 127.1, 112.4, 73.1, 40.4, 21.5, 1.9, 0.7.

IR (Diamond-ATR, neat): v / cm⁻¹ = 3084 (w), 3005 (w), 2882 (w), 2799 (w), 1612 (s), 1563 (w), 1519 (vs), 1480 (m), 1444 (m), 1424 (w), 1346 (m), 1221 (m), 1191 (m), 1157 (s), 1056 (m), 1024 (s), 992 (m), 947 (m), 871 (m), 849 (m), 812 (vs), 751 (w), 732 (w).

MS (EI, 70 eV): m/z (%) = 231 (M⁺, 32), 213 (100), 198 (24), 190 (27), 185 (19), 172 (38), 141 (14).

HRMS (C₁₅H₂₁NO): calc.: 231.1623; found: 231.1616.

[2-(Dimethylamino)phenyl][4-(trifluoromethyl)phenyl]methanol (110i)

According to TP12 bis[2-(dimethylamino)phenyl]zinc-2MgX₂ (103f; X = Cl, Br; 3.00 mL, 0.90 mmol, 0.30 M in THF). was added to 4-(trifluoromethyl)benzaldehyde (61l; 261 mg, 1.5 mmol) The reaction mixture was stirred for 3 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 8:1 + 1 vol-% NEt₃) afforded the alcohol 110i (413 mg, 93%) as a yellow oil.

¹H-NMR (400 MHz, DMSO-d₆): δ / ppm = 7.63 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.32-7.26 (m, 1H), 7.24-7.18 (m, 2H), 7.09-7.02 (m, 1H), 6.27 (d, J = 4.3 Hz, 1H), 6.01 (d, J = 4.9 Hz, 1H), 2.61 (s, 6H).
$^{13}$C-NMR (100 MHz, DMSO-d6): $\delta$/ ppm = 151.6, 150.7 (q, $^4 J_{C-F} = 1.5$ Hz), 139.7, 128.0, 128.0, 127.0 (q, $^2 J_{C-F} = 31.9$ Hz), 126.8, 124.8 (q, $^3 J_{C-F} = 3.8$ Hz), 124.4 (q, $^1 J_{C-F} = 271.7$ Hz), 124.1, 120.3, 68.3, 45.4.

IR (Diamond-ATR, neat): $\nu$/ cm$^{-1}$ = 3390 (vw), 2945 (w), 2866 (w), 2833 (w), 2790 (w), 1618 (w), 1599 (w), 1489 (m), 1454 (w), 1412 (w), 1322 (vs), 1160 (s), 1110 (s), 1065 (s), 1035 (m), 1016 (s), 936 (m), 805 (m), 768 (m), 744 (m), 664 (m).

MS (EI, 70 eV): m/z (%) = 295 (M$^+$, 94), 280 (100), 276 (20), 262 (65), 242 (69), 173 (16), 145 (12), 106 (9), 91 (10), 77 (11).

HRMS (C$_{16}$H$_{16}$F$_3$NO): calc.: 295.1184; found: 295.1178.

[4-(Allyloxy)phenyl](3-methyl-1-phenyl-1H-pyrazol-5-yl)methanol (110j)

According to TP12 4-(allyloxy)benzaldehyde (61m; 243 mg, 1.50 mmol) was added to bis(3-methyl-1-phenyl-1H-pyrazol-5-yl)zinc·2MgCl$_2$ (103g; 2.65 mL, 0.90 mmol, 0.34 M in THF). The reaction mixture was stirred for 15 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 1:2 + 1 vol-% NEt$_3$) afforded the alcohol 110j (439 mg, 91%) as a pale yellow oil.

$^1$H-NMR (400 MHz, C$_6$D$_6$): $\delta$/ ppm = 7.63-7.58 (m, 2H), 7.14-7.03 (m, 4H), 7.00 -6.94 (m, 1H), 6.77-6.71 (m, 2H), 6.05 (s, 1H), 5.86-5.74 (m, 1H), 5.66 (s, 1H), 5.25-5.17 (m, 1H), 5.05-4.99 (m, 1H), 4.14-4.09 (m, 2H), 2.70 (s, 1H), 2.26 (s, 3H).

$^{13}$C-NMR (100 MHz, C$_6$D$_6$): $\delta$/ ppm = 158.6, 148.9, 146.9, 140.7, 135.1, 133.7, 129.0, 128.1, 127.4, 125.4, 117.0, 114.7, 107.2, 68.6, 68.0, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm$^{-1}$ = 3241 (w), 3070 (w), 2923 (w), 2866 (w), 1609 (m), 1598 (m), 1548 (w), 1502 (vs), 1458 (m), 1425 (m), 1366 (m), 1302 (m), 1239 (s), 1222 (s), 1173 (s), 1127 (m), 1020 (vs), 997 (s), 920 (m), 793 (s), 763 (vs), 695 (vs), 673 (s), 659 (s).

MS (EI, 70 eV): m/z (%) = 320 (M$^+$, 100), 303 (35), 279 (96), 261 (34), 233 (13), 185 (24), 169 (9), 159 (17), 77 (17), 41 (17).

HRMS (C$_{20}$H$_{20}$N$_2$O$_2$): calc.: 320.1525; found: 320.1512.
(3-Chlorophenyl)(3-methyl-1-phenyl-1H-pyrazol-5-yl) methanol (110k)

According to TP12 3-chlorobenzaldehyde (61c; 211 mg, 1.50 mmol) was added to bis(3-methyl-1-phenyl-1H-pyrazol-5-yl)zinc·2MgCl₂ (103g; 2.65 mL, 0.90 mmol, 0.34 M in THF). The reaction mixture was stirred for 6 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 1:1 + 1 vol-% NEt₃) afforded the alcohol 110k (358 mg, 80%) as a white solid.

**M.p. (°C):** 100-102.

**¹H-NMR (400 MHz, C₆D₆):** δ / ppm = 7.53-7.47 (m, 2H), 7.28-7.25 (m, 1H), 7.07-6.94 (m, 4H), 6.87-6.83 (m, 1H), 6.74 (t, J = 7.7 Hz, 1H), 5.78 (s, 1H), 5.45 (s, 1H), 2.92 (s, 1H), 2.16 (s, 3H).

**¹³C-NMR (100 MHz, C₆D₆):** δ / ppm = 149.0, 145.8, 144.9, 140.3, 134.4, 129.6, 129.1, 127.8, 127.7, 126.9, 125.5, 124.8, 107.3, 67.3, 13.5.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3261 (w), 2926 (vw), 1597 (w), 1575 (w), 1543 (w), 1504 (m), 1481 (w), 1437 (m), 1370 (m), 1338 (w), 1298 (w), 1232 (w), 1194 (m), 1146 (w), 1130 (w), 1098 (w), 1079 (w), 1050 (m), 1032 (s), 1000 (w), 918 (vw), 888 (w), 874 (w), 826 (w), 797 (vs), 772 (vs), 726 (s), 697 (vs), 660 (m).

**MS (EI, 70 eV):** m/z (%) = 298 (M⁺, 100), 221 (5), 204 (7), 185 (12), 159 (48), 139 (9), 116 (4), 77 (11).

**HRMS (C₁₇H₁₁ClN₂O):** calc.: 298.0873; found: 298.0869.

(3,4-Dichlorophenyl)(3,5-dimethylisoxazol-4-yl)methanol (110l)

According to TP12 bis(3,5-dimethylisoxazol-4-yl)zinc·2MgX₂ (103h; X = Cl, Br; 3.64 mL, 1.20 mmol, 0.33 M in THF) was added to 3,4-dichlorobenzaldehyde (61b; 350 mg, 2.00 mmol, in 1.0 mL THF). The reaction mixture was stirred for 24 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 2:1 + 1 vol-% NEt₃) afforded the alcohol 110l (451 mg, 83%) as a white solid.

**M.p. (°C):** 108-110.

**¹H-NMR (300 MHz, C₆D₆):** δ / ppm = 7.54-7.50 (m, 1H), 7.01 (dd, J = 8.1 Hz, 1.4 Hz, 1H), 6.69 (t, J = 7.9 Hz, 1H), 5.56 (s, 1H), 2.64 (s, 1H), 1.95 (s, 3H), 1.81 (s, 3H).
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\[^{13}\text{C-NMR (75 MHz, C}_6\text{D}_6\text{): \(\delta / ppm = 166.5, 158.9, 142.1, 133.5, 130.5, 129.5, 127.1, 126.3, 114.5, 64.8, 11.2, 10.6\).}**

**IR (Diamond-ATR, neat):**  
\(\tilde{\nu} / \text{cm}^{-1} = 3541 (\text{vw}), 3301 (\text{w}), 2954 (\text{w}), 2923 (\text{m}), 2853 (\text{m}), 1624 (\text{m}), 1446 (\text{m}), 1414 (\text{s}), 1381 (\text{m}), 1323 (\text{w}), 1269 (\text{m}), 1176 (\text{s}), 1153 (\text{m}), 1063 (\text{s}), 1036 (\text{s}), 877 (\text{s}), 818 (\text{m}), 776 (\text{vs}), 748 (\text{s}), 680 (\text{s}).\)

**MS (EI, 70 eV):**  
m/z (%) = 271 (M\(^{+}\), 54), 236 (21), 228 (13), 212 (10), 195 (100), 173 (19), 126 (76), 108 (14), 84 (25), 42 (35).

**HRMS (C\(_{12}\)H\(_11\)Cl\(_2\)NO\(_2\)):** calc.: 271.0167; found: 271.0165.

(3,5-Dimethylisoxazol-4-yl)[4-(1H-1,2,4-triazol-1-yl)phenyl]methanol (110m)

According to TP12 bis(3,5-dimethylisoxazol-4-yl)zinc·2MgX\(_2\) (103h; X = Cl, Br; 3.64 mL, 1.20 mmol, 0.33 M in THF) was added to 4-(1H-1,2,4-triazol-1-yl)benzaldehyde (61n; 346 mg, 2.00 mmol, in 1 mL THF). The reaction mixture was stirred for 14 h at 25 °C. Purification by flash chromatography (silica gel, EtOAc + 1 vol-% NEt\(_3\)) afforded the alcohol 110m (413 mg, 76%) as a white solid.

**M.p. (°C):** 129-130.

\[^{1}\text{H-NMR (400 MHz, acetone-d6): \(\delta / ppm = 9.01 (s, 1H), 8.08 (s, 1H), 7.89-7.81 (m, 2H), 7.62-7.55 (m, 2H), 5.93 (s, 1H), 2.91 (s, 3H), 2.36 (s, 3H).}\]**

\[^{13}\text{C-NMR (100 MHz, acetone-d6): \(\delta / ppm = 166.4, 159.4, 153.2, 144.0, 142.4, 137.1, 128.0, 120.2, 117.7, 66.2, 11.3, 10.8.}\)**

**IR (Diamond-ATR, neat):**  
\(\tilde{\nu} / \text{cm}^{-1} = 3560 (\text{vw}), 3328 (\text{m}), 3124 (\text{w}), 2954 (\text{w}), 2853 (\text{m}), 1608 (\text{m}), 1522 (\text{vs}), 1458 (\text{m}), 1438 (\text{m}), 1424 (\text{s}), 1360 (\text{m}), 1320 (\text{w}), 1274 (\text{s}), 1248 (\text{m}), 1226 (\text{m}), 1194 (\text{m}), 1174 (\text{m}), 1154 (\text{s}), 1050 (\text{s}), 1032 (\text{s}), 982 (\text{s}), 958 (\text{m}), 862 (\text{s}), 792 (\text{vs}), 674 (\text{vs}), 648 (\text{m}).\)

**MS (EI, 70 eV):** m/z (%) = 270 (M\(^{+}\), 29), 253 (8), 211 (7), 172 (9), 146 (100), 124 (13), 82 (7), 43 (9).

**HRMS (C\(_{14}\)H\(_{14}\)N\(_4\)O\(_4\)):** calc.: 270.1117; found: 270.1115.
1-(4-Fluorobenzyl)-1,2,3,4-tetrahydronaphthalen-1-ol (111a)

According to TP12 4-fluorobenzylzinc chloride-MgCl$_2$ (95c; 3.12 mL, 2.40 mmol, 0.77 M in THF) was added to $\alpha$-tetralone (58e; 292 mg, 2.00 mmol, in 1 mL THF). The reaction mixture was stirred for 9 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 10:1 + 1 vol-% NEt$_3$) afforded the alcohol 111a (378 mg, 74%) as a pale yellow oil.

$^1$H-NMR (400 MHz, C$_6$D$_6$): $\delta$/ppm = 7.52-7.48 (m, 1H), 7.13-7.03 (m, 2H), 7.00 -6.93 (m, 2H), 6.93-6.89 (m, 1H), 6.83-6.75 (m, 2H), 2.98 (d, $J = 13.8$ Hz, 1H), 2.70 (d, $J = 13.8$ Hz, 1H), 2.56-2.40 (m, 2H), 1.67-1.59 (m, 1H), 1.52-1.44 (m, 2H), 1.42-1.35 (s, 1H), 1.33-1.24 (m, 1H).

$^{13}$C-NMR (100 MHz, C$_6$D$_6$): $\delta$/ppm = 162.2 (d, $^1$J$_{C-F}$ = 243.7 Hz), 143.1, 136.5, 133.8 (d, $^4$J$_{C-F}$ = 3.1 Hz), 132.5 (d, $^3$J$_{C-F}$ = 7.7 Hz), 128.8, 127.2, 127.2, 126.3, 114.8 (d, $^2$J$_{C-F}$ = 21.1 Hz), 72.4, 47.7, 35.9, 29.9, 20.2.

IR (Diamond-ATR, neat): $\nu$/cm$^{-1}$ = 3435 (w), 3064 (w), 3020 (w), 2933 (m), 2868 (w), 1603 (m), 1507 (vs), 1488 (m), 1449 (m), 1345 (w), 1219 (vs), 1157 (s), 1095 (m), 1078 (m), 1016 (s), 971 (m), 946 (m), 834 (s), 792 (m), 776 (s), 764 (s), 733 (vs).

MS (EI, 70 eV): m/z (%) = 255 ([M-H]$^-$, <1), 238 (19), 147 (100), 129 (45), 109 (13), 91 (26).

HRMS (C$_{17}$H$_{17}$FO): calc.: 255.1185 ([M-H]$^-$); found: 255.1209 ([M-H]$^-$).

4-[2-(4-Fluorophenyl)-1-hydroxy-1-methylethyl]benzonitrile (111b)

According to TP12 4-fluorobenzylzinc chloride-MgCl$_2$ (95c; 4.62 mL, 1.80 mmol, 0.39 M in THF) was added to 4-acetylbenzonitrile (58m; 218 mg, 1.50 mmol, in 0.5 mL THF) and the reaction mixture was stirred for 15 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:1 + 1 vol-% NEt$_3$) afforded the alcohol 111b (305 mg, 80%) as yellowish solid.

M.p. (°C): 93-95.

$^1$H-NMR (300 MHz, C$_6$D$_6$): $\delta$/ppm = 7.07-7.01 (m, 2H), 6.91-6.85 (m, 2H), 6.73-6.64 (m, 2H), 6.61-6.53 (m, 2H), 2.54 (d, $J = 13.6$ Hz, 1H), 2.49 (d, $J = 13.6$ Hz, 1H), 1.22 (sbr, 1H), 1.05 (s, 3H).
C. Experimental Section

$^{13}$C-NMR (75 MHz, C$_6$D$_6$): $\delta$ / ppm = 162 (d, $^1$J$_{C\cdots F}$ = 244.8 Hz), 152.5, 132.2 (d, $^3$J$_{C\cdots F}$ = 7.9 Hz), 132.2 (d, $^4$J$_{C\cdots F}$ = 3.1 Hz), 131.7, 125.9, 118.9, 115.0 (d, $^2$J$_{C\cdots F}$ = 21.0 Hz), 111.0, 73.9 (d, $^5$J$_{C\cdots F}$ = 1.4 Hz), 49.3, 28.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3468 (m), 2234 (m), 1739 (w), 1606 (m), 1504 (m), 1404 (m), 1379 (m), 1298 (w), 1220 (s), 1198 (m), 1144 (m), 1098 (m), 1075 (m), 1018 (m), 933 (m), 836 (vs), 821 (s), 770 (m), 734 (m), 709 (m), 679 (m).

HRMS (ESI; C$_{16}$H$_{14}$FNO): calc.: 273.1403 ([M+NH$_4$]$^{+}$); found: 273.1397 ([M+NH$_4$]$^{+}$).

1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2-(4-fluorophenyl)ethanol (111c)

According to TP12 4-fluorobenzylzinc chloride·MgCl$_2$ (95c; 4.62 mL, 1.80 mmol, 0.39 M in THF) was added to (2-chlorophenyl)(4-chlorophenyl)methanone (58n; 377 mg, 1.50 mmol, in 0.5 mL THF) and the reaction mixture was stirred for 48 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O / CH$_2$Cl$_2$ = 18:1:1) afforded the alcohol 111c (422 mg, 78%) as yellow solid.


$^1$H-NMR (400 MHz, C$_6$D$_6$): $\delta$ / ppm = 7.39 (dd, $J = 7.8$ Hz, 1.8 Hz, 1H), 7.07-7.00 (m, 3H), 6.88-6.63 (m, 8H), 3.70 (d, $^1$J$_{C\cdots F}$ = 13.1 Hz, 1H), 3.04 (d, $^2$J$_{C\cdots F}$ = 13.1 Hz, 1H), 2.31 (s, 1H).

$^{13}$C-NMR (100 MHz, C$_6$D$_6$): $\delta$ / ppm = 161.8 (d, $^1$J$_{C\cdots F}$ = 244.2 Hz), 144.3, 142.2, 132.9, 132.2 (d, $^3$J$_{C\cdots F}$ = 7.8 Hz), 132.0, 132.0 (d, $^4$J$_{C\cdots F}$ = 3.3 Hz), 130.8, 128.6, 128.5, 128.0, 127.9, 126.1, 114.1 (d, $^2$J$_{C\cdots F}$ = 21.0 Hz), 77.3 (d, $^5$J$_{C\cdots F}$ = 1.4 Hz), 43.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3524 (vw), 3465 (vw), 1606 (w), 1510 (s), 1488 (m), 1433 (m), 1401 (w), 1342 (w), 1269 (w), 1224 (s), 1159 (m), 1129 (w), 1092 (m), 1056 (w), 1035 (m), 1014 (m), 1002 (m), 944 (w), 925 (w), 886 (vw), 822 (vs), 756 (vs), 748 (s), 724 (m), 696 (m).

HRMS (ESI; C$_{20}$H$_{15}$Cl$_3$FO): calc.: 405.0466 ([M+HCO$_2$]$^{+}$); found: 405.0462 ([M+HCO$_2$]$^{+}$).
1-[4-(Dimethylamino)phenyl]-2-(4-methoxyphenyl)ethanol (111d)

According to TP12 4-methoxybenzylzinc chloride-MgCl₂ (95i; 36.1 mL, 13.0 mmol, 0.36 M in THF) was added to 4-(dimethylamino)benzaldehyde (61h; 1.49 g, 10.0 mmol, in 5 mL THF) and the reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 2:5) afforded the alcohol 111d (2.68 g, 99%) as yellow solid.

**M.p. (°C):** 113-115.

**¹H-NMR (400 MHz, CDCl₃):** δ / ppm = 7.27-7.22 (m, 2H), 7.04-6.99 (m, 2H), 6.76-6.71 (m, 2H), 6.63-6.58 (m, 2H), 4.75-4.70 (m, 1H), 3.30 (s, 3H), 3.06 (dd, J = 13.5 Hz, 7.4 Hz, 1H), 2.98 (dd, J = 13.5 Hz, 5.7 Hz, 1H), 2.53 (s, 6H), 1.66 (s, 1H).

**¹³C-NMR (100 MHz, CDCl₃):** δ / ppm = 158.7, 150.4, 133.0, 131.0, 130.9, 127.3, 114.0, 112.7, 75.6, 54.7, 45.7, 40.3.

**IR (Diamond-ATR, neat):** ʋ / cm⁻¹ = 3556 (w), 2961 (w), 2931 (w), 2908 (w), 2856 (w), 2835 (w), 1614 (m), 1522 (s), 1508 (s), 1440 (m), 1386 (m), 1304 (m), 1243 (s), 1204 (m), 1184 (m), 1175 (m), 1156 (m), 1106 (m), 1045 (m), 1027 (s), 995 (w), 947 (w), 875 (w), 825 (vs), 762 (w), 706 (w), 638 (w).

**MS (EI, 70 eV):** m/z (%) = 271 (M⁺, 2), 253 (58), 238 (27), 165 (6), 150 (100), 122 (7), 120 (6).

**HRMS (C₁₇H₂₁NO):** calc.: 271.1572; found: 271.1570.

4-[1-Hydroxy-2-(4-methoxyphenyl)-1-methylethyl]benzonitrile (111e)

According to TP12 4-methoxybenzylzinc chloride-MgCl₂ (95i; 2.23 mL, 1.61 mmol, 0.72 M in THF) was added to 4-acetylbenezonitrile (58m; 195 mg, 1.34 mmol, in 0.5 mL THF). The reaction mixture was stirred for 14 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 4:1 to 1:1 + 1 vol-% NEt₃) afforded the alcohol 111e (264 mg, 74%) as a pale yellow solid.

**M.p. (°C):** 120-121.

**¹H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.10-7.04 (m, 2H), 7.00-6.94 (m, 2H), 6.74-6.63 (m, 4H), 3.29 (s, 3H), 2.69 (d, J = 13.4 Hz, 1H), 2.61 (d, J = 13.6 Hz, 1H), 1.39 (s, 1H), 1.15 (s, 3H).
C. Experimental Section

$^{13}$C-NMR (75 MHz, C$_6$D$_6$): $\delta$/ppm = 159.2, 152.9, 131.7, 131.7, 128.2, 126.1, 119.0, 113.9, 110.9, 74.1, 54.7, 49.4, 29.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm$^{-1}$ = 3485 (m), 2974 (w), 2915 (w), 2840 (w), 2229 (m), 1609 (m), 1582 (w), 1512 (s), 1443 (m), 1370 (w), 1302 (m), 1284 (w), 1249 (vs), 1174 (m), 1142 (m), 1109 (m), 1074 (m), 1054 (m), 1030 (s), 763 (m).

MS (EI, 70 eV): m/z (%) = 267 (M$^+$, 1), 146 (6), 121 (100), 77 (5), 43 (6).

HRMS (C$_{17}$H$_{17}$NO$_2$): calc.: 267.1259; found: 267.1250.

Ethyl 3-(3,3,3-trifluoro-2-hydroxy-2-phenylpropyl)benzoate (111f)

According to TP12 3-(ethoxycarbonyl)benzylzinc chloride-MgCl$_2$ (95m; 3.00 mL, 1.20 mmol, 0.40 M in THF) was added to 2,2,2-trifluoro-1-phenylethanone (58l; 174 mg, 1.00 mmol). The reaction mixture was stirred for 16 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 4:1 + 1 vol-% NEt$_3$) afforded the alcohol 111f (296 mg, 87%) as a colourless oil.

$^1$H-NMR (400 MHz, acetone-d$_6$): $\delta$/ppm = 7.80-7.78 (m, 1H), 7.76-7.72 (m, 1H), 7.62-7.57 (m, 2H), 7.36-7.26 (m, 4H), 7.22-7.16 (m, 1H), 4.33-4.20 (m, 2H), 3.65 (d, $J_{C,F}$ = 14.1 Hz, 1H), 3.49 (d, $J_{C,F}$ = 14.3 Hz, 1H), 2.82 (br, 1H), 1.30 (t, $J_{C,F}$ = 7.1 Hz, 3H).

$^{13}$C-NMR (100 MHz, acetone-d$_6$): $\delta$/ppm = 167.2, 138.2, 136.9, 136.7, 133.4, 131.4, 129.6, 129.3, 129.0, 128.9, 128.4 (q, $^3J_{C,F}$ = 1.6 Hz), 127.8 (q, $^1J_{C,F}$ = 286.3 Hz), 77.3 (q, $^2J_{C,F}$ = 28.9 Hz), 61.9, 41.9, 15.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm$^{-1}$ = 3445 (w), 2984 (vw), 1696 (s), 1608 (w), 1589 (w), 1449 (m), 1370 (m), 1281 (s), 1205 (s), 1150 (vs), 1106 (s), 1084 (m), 1074 (m), 1019 (s), 966 (m), 909 (w), 866 (w), 756 (m), 735 (m), 709 (s), 671 (m).

MS (EI, 70 eV): m/z (%) = 339 ([M+H]$^+$, 5), 293 (19), 175 (16), 164 (100), 136 (33), 118 (15), 105 (19), 91 (14), 77 (6).

HRMS (C$_{18}$H$_{17}$F$_3$O$_3$): calc.: 339.1208 ([M+H]$^+$); found: 339.1196 ([M+H]$^+$).
Ethyl 3-(2-[(4-methylphenyl)sulfonyl]amino)-2-phenylethyl)benzoate (111g)

According to TP12 bis(3-(ethoxycarbonyl)benzyl)zinc·2MgCl₂ (106a; 3.33 mL, 1.1 mmol, 0.33 M in THF) was added to 4-methyl-N-[(1E)-phenylmethylene]benzenesulfonamide (61o; 519 mg, 2.00 mmol, in 1.0 mL THF). The reaction mixture was stirred for 24 h at 25 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 3:1 + 1 vol-% NEt₃) afforded the amine 111g (728 mg, 86%) as a white solid.


1H-NMR (400 MHz, DMSO-d₆): δ / ppm = 8.34 (d, J = 9.0 Hz, 1H), 7.73-7.68 (m, 1H), 7.67-7.63 (m, 1H), 7.40-7.33 (m, 1H), 7.30-7.21 (m, 5H (incl. NH)), 7.21-7.10 (m, 3H), 7.00 (d, J = 8.0 Hz, 2H), 4.47-4.38 (m, 1H), 4.29 (q, J = 7.2 Hz, 2H), 2.94-2.79 (m, 2H), 2.24 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

13C-NMR (100 MHz, DMSO-d₆): δ / ppm = 165.6, 142.2, 141.6, 138.5, 138.4, 134.1, 130.0, 129.5, 128.9, 128.3, 128.0, 127.0, 126.8, 126.5, 125.9, 60.6, 59.2, 43.0, 20.8, 14.2.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3269 (m), 2924 (m), 2856 (w), 1696 (vs), 1603 (w), 1589 (w), 1494 (w), 1445 (m), 1426 (m), 1370 (m), 1328 (s), 1284 (vs), 1201 (s), 1158 (vs), 1107 (s), 1092 (s), 1070 (m), 1027 (s), 963 (m), 908 (m), 837 (m), 812 (m), 755 (vs), 699 (m), 692 (m), 664 (s).

MS (EI, 70 eV): m/z (%) = 424 ([M+H]⁺, <1), 378 (6), 260 (100), 155 (25), 91 (26), 65 (3).

HRMS (C₂₄H₂₅NO₅S): calc.: 424.1583 ([M+H]⁺); found: 424.1564 ([M+H]⁺).

Ethyl 3-[2-(4-fluorophenyl)-2-hydroxypropyl]benzoate (111h)

According to TP12 1-(4-fluorophenyl)ethanone (58o; 276 mg, 2.0 mmol) was added to bis(3-(ethoxycarbonyl)benzyl)zinc·2MgCl₂ (106a; 6.67 mL, 2.2 mmol, 0.33 M in THF). The reaction mixture was stirred for 24 h at 50 °C. Purification by flash chromatography (silica gel, pentane / EtOAc = 4:1 + 1 vol-% NEt₃) afforded the alcohol 111h (444 mg, 68%) as a pale yellow oil.
1H-NMR (400 MHz, C$_6$D$_6$): $\delta$ / ppm = 8.07-8.01 (m, 1H), 7.95-7.92 (m, 1H), 7.02-6.95 (m, 3H), 6.95-6.91 (m, 1H), 6.82-6.74 (m, 2H), 4.17-4.08 (m, 2H), 2.76 (d, $J$ = 13.3 Hz, 1H), 2.69 (d, $J$ = 13.3 Hz, 1H), 1.23 (s, 1H), 1.16 (s, 3H), 1.03 (t, $J$ = 7.1 Hz, 3H).

13C-NMR (100 MHz, C$_6$D$_6$): $\delta$ / ppm = 166.4, 162.0 (d, $^{1}J_{C\text{-}F}$ = 244.4 Hz), 143.6 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 137.8, 135.1, 132.2, 130.8, 128.0, 128.0, 127.1 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 114.8 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz), 73.9, 60.8, 50.5, 29.2, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3480 (w), 2980 (w), 2930 (w), 1699 (s), 1603 (m), 1508 (s), 1444 (m), 1368 (m), 1277 (vs), 1223 (s), 1199 (s), 1160 (m), 1106 (s), 1088 (s), 1015 (m), 952 (w), 932 (w), 863 (m), 836 (s), 815 (m), 755 (s), 720 (s), 700 (m).

MS (EI, 70 eV): m/z (%) = 302 (M$^+$, <1), 184 (15), 257 (23), 211 (13), 196 (11), 164 (100), 139 (88), 136 (42), 118 (11), 91 (18), 43 (36).

HRMS (C$_{18}$H$_{19}$FO$_3$): calc.: 302.1318; found: 302.1306.

1,1-Dicyclopropyl-2-(3-methoxyphenyl)ethanol (111i)

According to TP12 dicyclopropylmethanone (58g; 156 mg, 1.50 mmol) was added to bis(4-methoxybenzyl)zinc·2MgCl$_2$ (106a; 2.90 mL, 0.90 mmol, 0.31 M in THF). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (silica gel, pentane / Et$_2$O = 9:1 + 1 vol-% NEt$_3$) afforded the alcohol 111i (292 mg, 84%) as a colourless oil.

1H-NMR (300 MHz, C$_6$D$_6$): $\delta$ / ppm = 7.16-7.08 (m, 1H), 7.02-6.98 (m, 1H), 6.94-6.88 (m, 1H), 6.78-6.71 (m, 1H), 3.39 (s, 3H), 2.80 (s, 2H), 0.67-0.55 (m, 3H (incl. OH)), 0.44-0.32 (m, 4H), 0.27-0.06 (m, 4H).

13C-NMR (75 MHz, C$_6$D$_6$): $\delta$ / ppm = 159.9, 139.7, 129.0, 123.5, 117.2, 111.8, 70.6, 54.7, 49.4, 19.0, 1.3, -0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3517 (w), 3084 (w), 3006 (w), 2919 (w), 2835 (w), 1601 (m), 1584 (m), 1488 (s), 1453 (m), 1437 (m), 1312 (m), 1260 (vs), 1167 (s), 1153 (s), 1117 (m), 1043 (s), 1022 (s), 994 (s), 913 (m), 875 (m), 865 (m), 826 (m), 778 (s), 749 (m), 738 (m), 703 (s).

MS (EI, 70 eV): m/z (%) = 232 (M$^+$, <1), 214 (11), 185 (10), 122 (40), 111 (100), 91 (18), 77 (13), 69 (77), 57 (11), 41 (26).
HRMS (C₁₅H₂₀O₂): calc.: 232.1463; found: 232.1453.

4-Methoxybenzoic acid (112)

According to TP13 bis(4-methoxyphenyl)zinc·2MgX₂ (103a; X = Br, Cl; 2.56 mL, 1.00 mmol, 0.39 M in THF) was reacted with dry CO₂(g) at 25 °C for 3 h. After purification, 4-methoxybenzoic acid (112; 286 mg, 94%) was obtained as a white solid.

M.p. (°C): 185-186 °C.

¹H-NMR (400 MHz, DMSO-d₆):  δ / ppm = 12.59 (s, 1H), 7.91-7.85 (m, 2H), 7.03-6.96 (m, 2H), 3.81 (s, 3H).

¹³C-NMR (100 MHz, DMSO-d₆): δ / ppm = 166.9, 162.8, 131.3, 122.9, 113.8, 55.4.

IR (Diamond-ATR, neat):  ν / cm⁻¹ = 2982 (w), 2940 (w), 2842 (w), 2542 (w), 1924 (w), 1678 (s), 1602 (s), 1576 (s), 1516 (m), 1426 (m), 1298 (s), 1260 (vs), 1166 (s), 1130 (s), 1106 (s), 1024 (s), 924 (s), 844 (s), 824 (m), 772 (s), 696 (m), 634 (m), 614 (s).

MS (EI, 70 eV):  m/z (%) = 152 (M⁺, 100), 135 (86), 107 (10), 92 (16), 77 (25), 63 (12).

HRMS (C₈H₈O₃): calc.: 152.0473; found: 152.0468.

Phenylacetic acid (113)

According to TP13 bis(benzyl)zinc·2MgCl₂ (106c; 2.38 mL, 1.00 mmol, 0.42 M in THF) was reacted with dry CO₂(g) at 25 °C for 2.5 h. After purification, phenylacetic acid (113; 208 mg, 76%) was obtained as a white solid.

M.p. (°C): 80-82.

¹H-NMR (400 MHz, DMSO-d₆):  δ / ppm = 12.29 (s, 1H), 7.33-7.28 (m, 2H), 7.27-7.20 (m, 3H), 3.56 (s, 2H).

¹³C-NMR (100 MHz, DMSO-d₆):  δ / ppm = 172.7, 135.0, 129.3, 128.2, 126.5, 40.7.

IR (Diamond-ATR, neat):  ν / cm⁻¹ = 2921 (w), 1692 (s), 1498 (w), 1454 (w), 1407 (m), 1336 (m), 1290 (w), 1228 (m), 1186 (m), 1074 (w), 892 (m), 839 (m), 751 (m), 699 (vs), 676 (s).

MS (EI, 70 eV):  m/z (%) = 136 (M⁺, 100), 91 (100), 65 (12), 44 (5).

HRMS (C₈H₈O₂): calc.: 136.0524; found: 136.0509.
5. Carbocupration of Alkynes With Functionalized Diorganozinc Reagents

5.1. Preparation of the starting materials

1-Bromo-2-[(4-methoxyphenyl)thio]ethynylbenzene (118b)

To 1-bromo-2-ethynylbenzene (958 mg, 5.29 mmol) in THF (5 mL) was added MeMgCl (1.77 mL, 5.29 mmol, 2.99 M in THF) at 25 °C and the reaction mixture was stirred for 1 h. Then, S-(4-methoxyphenyl) benzenesulfonothioate (57f; 1.48 g, 5.29 mmol, in 5 mL THF) was added at -40 °C and the resulting reaction mixture was slowly warmed to 0 °C within 12 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 95:5) furnished the alkyne 118b (1.48 g, 86%) as a yellow oil.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.60-7.55 (m, 1H), 7.53-7.44 (m, 3H), 7.28 -7.22 (m, 1H), 7.18-7.11 (m, 1H), 6.94-6.88 (m, 2H), 3.80 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 159.1, 133.0, 132.4, 129.2, 129.0, 127.0, 125.3, 125.0, 122.5, 115.1, 95.0, 82.4, 55.4.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2834 (w), 2169 (w), 1590 (m), 1491 (s), 1290 (m), 1243 (vs), 1174 (s), 1025 (s), 820 (s), 749 (s), 681 (m).

MS (EI, 70 eV): m/z (%) = 318 (M⁺, 90), 305 (23), 239 (100), 195 (34), 152 (21), 140 (19), 43 (11).

HRMS (C₁₅H₁₁BrOS): calc.: 317.9714; found: 317.9709.

1-Fluoro-4-[(4-methoxyphenyl)thio]ethynylbenzene (118d)

To 1-ethynyl-4-fluorobenzene (1.20 g, 10.0 mmol) in THF (10 mL) was added n-BuLi (4.20 mL, 10.5 mmol, 2.50 M in THF) at -20 °C and the reaction mixture was stirred for 30 min. Then, freshly prepared MgCl₂ (21.0 mL, 10.5 mmol 0.50 M in THF; prepared by the reaction of 1,2-dichloroethane with magnesium turnings in THF) was added and the reaction mixture was stirred...
for additional 30 min. Then, S-(4-methoxyphenyl) benzenesulfonothioate (57f; 3.08 g, 11.0 mmol, in 10 mL THF) was added at -40 °C and the resulting reaction mixture was slowly warmed to 25 °C within 18 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (silica gel, pentane / Et₂O = 98:2) furnished the alkyne 118d (2.08 g, 80%) as a yellow solid.

M.p. (°C): 40-42.

^1^H-NMR (400 MHz, CDCl₃): δ / ppm = 7.49-7.39 (m, 4H), 7.05-6.97 (m, 2H), 6.93-6.87 (m, 2H), 3.80 (s, 3H).

^13^C-NMR (75 MHz, CDCl₃): δ / ppm = 162.6 (d, ^1^J_C-F = 249.9 Hz), 159.1, 133.7 (d, ^3^J_C-F = 8.8 Hz), 129.0, 122.8, 119.1 (d, ^4^J_C-F = 3.5 Hz), 115.6 (d, ^2^J_C-F = 22.3 Hz), 115.1, 95.0, 76.8, 55.4.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2936 (w), 2836 (w), 1652 (vw), 1596 (m), 1574 (w), 1492 (s), 1456 (m), 1438 (m), 1402 (w), 1294 (m), 1246 (m), 1230 (s), 1214 (s), 1176 (s), 1154 (s), 1106 (m), 1092 (m), 1084 (m), 1024 (s), 1006 (m), 834 (vs), 814 (vs), 796 (s), 634 (w), 622 (w).

MS (EI, 70 eV): m/z (%) = 258 (M⁺, 100), 243 (50), 215 (17), 199 (7), 183 (10), 170 (11), 107 (12).

HRMS (C₁₅H₁₁FOS): calc.: 258.0515; found: 258.0505.

5.2. Preparation of the title compounds

1-Bromo-2-{[(E)-2-iodo-1-(4-methoxyphenyl)-2-[(4-methoxyphenyl)thio]vinyl}benzene (120b)

Bis(4-methoxyphenyl)zinc-2MgX₂ (103a; X = Br, Cl; 8.11 mL, 3.00 mmol, 0.37 m in THF) was added dropwise to CuCN-2LiCl (3.00 mL, 3.00 mmol, 1.00 m in THF) at -20 °C. The mixture was stirred for 30 min. Then, 1-bromo-2-{{(4-methoxyphenyl)thio}ethynyl}benzene (118b; 638 mg, 2.00 mmol, in 1 mL THF) was added and the reaction mixture was stirred for 6 h at 25 °C. The reaction mixture was added dropwise to another flask containing iodine (7.78 g, 7.00 mmol) in THF (7 mL) at -40 °C. After stirring for 10 min, a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 2:1 (100 mL) was added. The phases were separated and the aq.
layer was extracted with Et₂O (3 x 100 mL). The combined extracts were dried over Na₂SO₄. Evaporation of the solvents in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 3:1 + 1 vol-% NEt₃) afforded the vinylic iodide 120b (908 mg, 82%, E/Z = 99:1) as a yellow oil.

**1H-NMR (400 MHz, acetone-d6):** δ / ppm = 7.63 (dd, J = 8.1 Hz, 1.1 Hz, 1H), 7.51 (dd, J = 7.6 Hz, 1.8 Hz, 1H), 7.45-7.37 (m, 5H), 7.27-7.21 (m, 1H), 6.99-6.93 (m, 2H), 6.91-6.86 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H).

**13C-NMR (100 MHz, acetone-d6):** δ / ppm = 161.1, 160.3, 152.4, 143.2, 136.7, 135.1, 133.7, 131.4, 131.0, 128.6, 127.6, 122.9, 115.5, 114.0, 97.7, 55.7, 55.5.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2956 (w), 2932 (w), 2870 (w), 2834 (w), 1590 (m), 1572 (w), 1504 (m), 1492 (s), 1462 (m), 1440 (m), 1288 (m), 1244 (vs), 1172 (s), 1106 (w), 1064 (w), 1028 (s), 952 (w), 910 (w), 826 (s), 770 (m), 742 (s), 708 (w), 656 (w), 640 (w).

**MS (EI, 70 eV):** m/z (%) = 552 (M⁺, 14), 473 (24), 427 (69), 346 (100), 331 (24), 172 (9), 139 (24).

**HRMS (C₂₂H₁₈BrIO₂S):** calc.: 551.9256; found: 551.9249.

1-Bromo-2-{(1Z)-1-(4-methoxyphenyl)-2-[(4-methoxyphenyl)thio]penta-1,4-dien-1-yl}-benzene (120c)

Bis(4-methoxyphenyl)zinc-2MgX₂ (103a; X = Br, Cl; 4.05 mL, 1.50 mmol, 0.37 M in THF) was added dropwise to CuCN·2LiCl (1.50 mL, 1.50 mmol, 1.00 M in THF) at -20 °C. The mixture was stirred for 30 min. Then, 1-bromo-2-{[(4-methoxyphenyl)thio]ethynyl}benzene (118b; 318 mg, 1.00 mmol, in 1 mL THF) was added and the reaction mixture was stirred for 6 h at 25 °C. The reaction mixture was cooled to -50 °C and allyl bromide (436 mg, 3.60 mmol, in 5 mL THF) was added. Then, the mixture was stirred for 30 min at -50 °C followed by 45 min at -30 °C. Then, a mixture of sat. aq. NH₄Cl / NH₃ (25% in H₂O) = 4:1 (100 mL) was added. The phases were separated and the aq. layer was extracted with Et₂O (3 x 100 mL). The combined extracts were dried over Na₂SO₄. Evaporation of the solvents in vacuo and purification by flash.
C. Experimental Section

Chromatography (silica gel, pentane / Et<sub>2</sub>O = 12:1 + 2 vol-% NEt<sub>3</sub>) afforded the olefine 120c (426 mg, 91%, E/Z = 99:1) as a yellow oil.

<sup>1</sup>H-NMR (400 MHz, acetone-d<sub>6</sub>): δ / ppm = 7.63-7.59 (m, 1H), 7.47-7.43 (m, 1H), 7.42-7.36 (m, 3H), 7.34-7.28 (m, 2H), 7.22-7.16 (m, 1H), 6.93-6.84 (m, 4H), 5.89-5.78 (m, 1H), 5.06-4.97 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.01-2.96 (m, 2H).

<sup>13</sup>C-NMR (100 MHz, acetone-d<sub>6</sub>): δ / ppm = 160.7, 159.8, 144.7, 141.6, 136.5, 136.0, 135.7, 133.6, 133.0, 132.1, 131.1, 129.5, 128.4, 124.6, 124.1, 116.6, 115.4, 114.2, 55.6, 55.5, 36.1.

IR (Diamond-ATR, neat): ν / cm<sup>-1</sup> = 3002 (w), 2932 (w), 2834 (w), 1592 (m), 1508 (m), 1492 (s), 1462 (m), 1440 (m), 1284 (m), 1242 (vs), 1172 (s), 1104 (m), 1028 (s), 914 (m), 828 (s), 800 (m), 766 (m), 742 (s), 656 (w), 626 (w).

MS (EI, 70 eV): m/z (%) = 466 (M<sup>+</sup>, 6), 387 (100), 346 (39), 279 (1), 215 (2), 139 (2).

HRMS (C<sub>25</sub>H<sub>23</sub>BrO<sub>2</sub>S): calc.: 466.0602; found: 466.0600.

Ethyl 4-[(1Z)-4-(ethoxycarbonyl)-1-(4-methoxyphenyl)-2-(methylthio)penta-1,4-dien-1-yl]benzoate (120d)

Into a flame dried and argon-flushed flask, ethyl 4-iodobenzoate (828 mg, 3.00 mmol) was added followed by i-PrMgCl·LiCl (1.96 mL, 2.95 mmol, 1.50 M in THF) at -20 °C. The reaction mixture was stirred for 60 min at -20 °C. Then, ZnCl<sub>2</sub> (1.50 mL; 1.50 mmol, 1.00 M in THF) was added and the reaction mixture was stirred for 30 min. CuCN·2LiCl (1.50 mL, 1.50 mmol, 1.00 M in THF) was added and the mixture was stirred for additional 30 min at -20 °C. Then, 1-methoxy-4-[(methylthio)ethynyl]benzene (118c; 178 mg, 1.00 mmol) was added and the reaction mixture was stirred for 24 h at 25 °C. The reaction mixture was cooled to -40 °C and ethyl (2-bromomethyl)acrylate (695 mg, 3.60 mmol) was added. Then, the mixture was stirred for 30 min at -40 °C followed by 30 min at 0 °C. Then, a mixture of sat. aq. NH<sub>4</sub>Cl / NH<sub>3</sub> (25% in H<sub>2</sub>O) = 4:1 (100 mL) was added. The phases were separated and the aq. layer was extracted with Et<sub>2</sub>O (3 x 100 mL). The combined extracts were dried over MgSO<sub>4</sub>. Evaporation of the solvents
C. Experimental Section

in vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 9:1 + 2 vol-% NEt₃) afforded the alkene 120d (301 mg, 68%, E/Z = 94:6) as a yellow oil.

**¹H-NMR (400 MHz, acetone-d₆):** \( \delta / ppm = 7.95-7.89 \) (m, 2H), 7.33-7.27 (m, 2H), 7.24-7.18 (m, 2H), 6.92-6.85 (m, 2H), 6.36-6.30 (m, 1H), 5.95-5.91 (m, 1H), 4.31 (q, \( J = 7.0 \) Hz, 2H), 4.15 (q, \( J = 7.1 \) Hz, 2H), 3.77 (s, 3H), 3.39 (t, \( J = 1.7 \) Hz, 2H), 2.09 (s, 3H), 1.32 (t, \( J = 7.1 \) Hz, 3H), 1.23 (t, \( J = 7.1 \) Hz, 3H).

**¹³C-NMR (100 MHz, acetone-d₆):** \( \delta / ppm = 166.8, 166.4, 159.7, 148.2, 140.5, 138.9, 134.8, 134.0, 131.6, 130.0, 129.8, 129.6, 125.8, 125.6, 124.4, 123.8 (s), 123.7 (s), 117.2 (s), 1134 (s), 1098 (s), 1020 (s), 946 (w), 860 (m), 832 (m), 784 (m), 750 (m), 704 (m), 658 (w).

**IR (Diamond-ATR, neat):** \( \nu / cm^{-1} = 2982 \) (w), 1710 (vs), 1604 (m), 1508 (m), 1464 (w), 1444 (w), 1402 (w), 1366 (w), 1244 (vs), 1172 (s), 1134 (s), 1098 (s), 1020 (s), 946 (w), 860 (m), 832 (m), 784 (m), 750 (m), 704 (m), 658 (w).

**MS (EI, 70 eV):** m/z (%) = 440 (M⁺, 100), 392 (46), 363 (94), 335 (15), 320 (12), 135 (15).

**HRMS (C₂₅H₂₈O₅S):** calc.: 440.1657; found: 440.1655.

Ethyl (4Z)-5-(4-cyanophenyl)-5-(4-fluorophenyl)-4-[(4-methoxyphenyl)thio]-2-methylene-pent-4-enoate (120e)

Into a flame dried and argon-flushed flask, 4-iodobenzonitrile (481 mg, 2.10 mmol, in 1 mL THF) was added followed by \( i-\)PrMgCl·LiCl (1.42 mL, 2.10 mmol, 1.48 M in THF) at 0 °C. The reaction mixture was stirred for 40 min at 0 °C. Then, ZnCl₂ (1.05 mL, 1.05 mmol, 1.00 M in THF) was added at -20 °C and the reaction mixture was stirred for 30 min. CuCN·2LiCl (1.05 mL, 1.05 mmol, 1.00 M in THF) was added at -20 °C and the mixture was stirred for additional 30 min at -20 °C. Then, 1-fluoro-4-[(4-methoxyphenyl)thio]ethynyl]benzene (181 mg, 0.70 mmol) was added and the reaction mixture was stirred for 16 h at 25 °C. The reaction mixture was cooled to -60 °C and ethyl (2-bromomethyl)acrylate (444 mg, 2.30 mmol) was added. Then, the mixture was stirred for 30 min at -60 °C followed by 90 min at -20 °C. Then, a mixture of sat. aq. NH₄Cl / NH₄OH (25% in H₂O) = 4:1 (100 mL) was added. The phases were separated and the aq. layer was extracted with Et₂O (3 x 100 mL). The combined extracts
were dried over Na$_2$SO$_4$. Evaporation of the solvents \textit{in vacuo} and purification by flash chromatography (silica gel, pentane / Et$_2$O = 9:1 + 2 vol-% NEt$_3$) afforded the alkene **120e** (172 mg, 51\%, $E/Z = 68:32$) as a yellow oil.

$^1$H-NMR (400 MHz, acetone-d$_6$): $\delta$ / ppm = 7.75-7.70 (m, 2H), 7.50-7.46 (m, 2H), 7.43-7.37 (m, 2H), 7.33-7.29 (m, 2H), 7.17-7.12 (m, 2H), 6.90-6.86 (m, 2H), 6.26-6.23 (m, 1H), 5.77-5.74 (m, 1H), 4.42(q, $J = 7.0$ Hz, 2H), 3.78 (s, 3H), 3.16 (t, $J = 1.6$ Hz, 2H), 1.15 (t, $J = 7.0$ Hz, 3H).

$^{13}$C-NMR (100 MHz, acetone-d$_6$): $\delta$ / ppm = 166.4, 162.9 (d, $^1J_{C-F} = 245.2$ Hz), 161.0, 147.4, 141.1, 138.5 (d, $^4J_{C-F} = 3.5$ Hz), 138.3, 136.3, 135.9, 133.0, 132.5 (d, $^3J_{C-F} = 8.2$Hz), 130.6, 126.7, 123.7, 119.1, 115.9 (d, $^2J_{C-F} = 21.6$Hz), 115.6, 111.7, 61.1, 55.7, 34.9, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2980 (w), 2938 (w), 2906 (w), 2838 (w), 2228 (m), 1712 (s), 1630 (w), 1592 (m), 1504 (s), 1492 (vs), 1464 (m), 1442 (w), 1402 (m), 1368 (w), 1286 (m), 1246 (vs), 1222 (s), 1172 (s), 1136 (s), 1102 (m), 1028 (s), 944 (m), 828 (vs), 750 (m), 698 (w), 640 (w).

MS (EI, 70 eV): m/z (%) = 473 (M$^+$, 45), 334 (21), 306 (12), 260 (11), 140 (100), 108 (8).

HRMS (C$_{28}$H$_{24}$FNO$_3$S): calc.: 473.1461; found: 473.1461.
6. Transition Metal-Catalyzed Cross-Coupling Reactions of Functionalized Organozinc Reagents With Methylthio-Substituted N-Heterocycles

6.1. Preparation of the starting materials

3-Methoxy-6-(methylthio)pyridazine (124a)

![Chemical Structure](image)

3-Chloro-6-methoxypyridazine (123; 1.86 g, 12.9 mmol) and sodium thiomethanolate (1.03 g, 14.2 mmol) were dissolved in DMF (6 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (30 mL) followed by extraction using EtOAc (3 x 30 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 3:1) afforded the pyridazine 124a (1.38 g, 69%) as a white solid.

**M.p. (°C):** 93-94.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 7.21 (d, J = 9.3 Hz, 1H), 6.81 (d, J = 9.3 Hz, 1H), 4.06 (s, 3H), 2.67 (s, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 163.3, 156.6, 129.1, 117.7, 54.7, 13.5.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 3059 (w), 2982 (w), 2949 (w), 2922 (w), 1596 (w), 1545 (vw), 1456 (m), 1400 (s), 1300 (s), 1196 (m), 1175 (m), 1146 (m), 1006 (vs), 964 (m), 838 (s), 812 (m), 723 (m), 672 (s), 622 (m).

**MS (EI, 70 eV):** m/z (%) = 156 (M⁺, 100), 111 (6), 98 (9), 84 (20), 80 (8), 45 (6).

**HRMS (C₆H₈N₂OS):** calc.: 156.0357; found: 156.0345.

2-(Methylthio)-5-(trifluoromethyl)pyridine (124d)

![Chemical Structure](image)

5-(Trifluoromethyl)pyridine-2-thiol (2.69 g, 15.0 mmol) was dissolved in THF (13.5 mL) and CH₃CN (1.5 mL) at 0 °C. DBU (2.51 g, 16.5 mmol) was added dropwise and the resulting reaction mixture was stirred for 20 min. Then, MeI (2.34 g, 16.5 mmol) was added, the ice-bath was removed and the reaction mixture was stirred for 12.5 h. Addition of H₂O (50 mL) was followed by extraction using EtOAc (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 3:1) afforded the pyridine 124d (1.59 g, 55%) as a pale yellow liquid.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.71-8.63 (m, 1H), 7.70-7.60 (m, 1H), 7.30-7.21 (m, 1H), 2.58 (s, 3H).
13C-NMR (75 MHz, CDCl₃): δ / ppm = 164.9 (q, 4J_C-F = 1.5 Hz), 146.2 (q, 3J_C-F = 4.4 Hz), 132.3 (q, 3J_C-F = 3.4 Hz), 123.8 (q, 1J_C-F = 271.6 Hz), 122.0 (q, 2J_C-F = 33.0 Hz), 121.0, 13.2.

IR (Diamond-ATR, neat): \(\tilde{\nu} / \text{cm}^{-1} = 2932 \text{ (vw)}, 1596 \text{ (m)}, 1475 \text{ (w)}, 1377 \text{ (w)}, 1321 \text{ (vs)}, 1251 \text{ (w)}, 1166 \text{ (m)}, 1073 \text{ (s)}, 967 \text{ (w)}, 938 \text{ (w)}, 827 \text{ (m)}, 791 \text{ (w)}, 746 \text{ (w)}.

MS (EI, 70 eV): m/z (%) = 193 (M⁺, 100), 147 (44), 127 (19), 78 (8).

HRMS (C₇H₆F₃NS): calc.: 193.0173; found: 193.0176.

3-(Methylthio)pyrazine-2-carbonitrile (124f)

3-Chloropyrazine-2-carbonitrile (2.61 g, 18.7 mmol) and sodium thiomethanolate (2.10 g, 30.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (20 mL) followed by extraction using EtOAc (3 x 20 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 7:2) afforded the pyrazine 124f (793 mg, 28%) as a yellow solid.

M.p. (°C): 83-84.

1H-NMR (300 MHz, CDCl₃): δ / ppm = 8.53 (d, J = 2.4 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 2.62 (s, 3H).

13C-NMR (75 MHz, CDCl₃): δ / ppm = 161.8, 145.9, 139.1, 128.1, 114.3, 12.9.

IR (Diamond-ATR, neat): \(\tilde{\nu} / \text{cm}^{-1} = 2230 \text{ (w)}, 1512 \text{ (m)}, 1424 \text{ (w)}, 1354 \text{ (s)}, 1339 \text{ (m)}, 1317 \text{ (m)}, 1196 \text{ (m)}, 1161 \text{ (s)}, 1153 \text{ (s)}, 1142 \text{ (m)}, 1085 \text{ (vs)}, 1074 \text{ (s)}, 1060 \text{ (s)}, 964 \text{ (m)}, 854 \text{ (s)}, 835 \text{ (m)}, 719 \text{ (m)}, 663 \text{ (m)}.

MS (EI, 70 eV): m/z (%) = 151 (M⁺, 100), 137 (10), 122 (40), 112 (13), 93 (15), 84 (11), 77 (24), 52 (35).

HRMS (C₆H₅N₂S): calc.: 151.0204; found: 151.0190.
2-(Methylthio)nicotinonitrile (124i)

![2-(Methylthio)nicotinonitrile](image)

2-Chloronicotinonitrile (2.77 g, 20.0 mmol) and sodium thiomethanolate (2.31 g, 33.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aq. K$_2$CO$_3$ solution (50 mL) followed by extraction using EtOAc (3 x 100 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 3:1) afforded the pyridine 124i (665 mg, 22%) as a yellow solid.


$^1$H-NMR (300 MHz, CDCl$_3$): δ / ppm = 8.57 (dd, J = 5.0 Hz, J = 1.8 Hz, 1H), 7.77 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.05-6.96 (m, 2H), 3.87 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / ppm = 163.4, 152.0, 140.3, 118.2, 115.5, 107.2, 13.1.

IR (Diamond-ATR, neat): ν / cm$^{-1}$ = 3046 (w), 2929 (w), 2224 (m), 1574 (m), 1546 (m), 1391 (vs), 1316 (m), 1232 (m), 1184 (m), 1143 (m), 1078 (m), 959 (w), 801 (vs), 736 (m), 721 (m), 667 (m).

MS (EI, 70 eV): m/z (%) = 150 (M$^+$, 100), 123 (27), 104 (40), 79 (30), 75 (11), 45 (10), 43 (16).

HRMS (C$_7$H$_6$N$_3$S): calc.: 150.0252; found: 150.0245.

### 6.2. Preparation of the title compounds via Pd-catalyzed cross-couplings

2-(4-Methoxyphenyl)-5-(trifluoromethyl)pyridine (126a)

According to TP14 2-(methylthio)-5-(trifluoromethyl)pyridine (124d; 193 mg, 1.00 mmol, in 1 mL THF) was reacted with (4-methoxyphenyl)zinc iodide (5c; 1.61 mL, 1.50 mmol, 0.93 M in THF), Pd(OAc)$_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 1 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 12:1) afforded the pyridine 126a (241 mg, 95%) as a white solid.

M.p. (°C): 121-123.

$^1$H-NMR (300 MHz, CDCl$_3$): δ / ppm = 8.91-8.86 (m, 1H), 8.05-7.96 (m, 2H), 7.96-7.88 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.05-6.96 (m, 2H), 3.87 (s, 3H).
**Ethyl 2-[4-(ethoxycarbonyl)phenyl]nicotinate (126b)**

According to TP14 ethyl 2-(methylthio)nicotinate (124e; 197 mg, 1.00 mmol, in 1 mL THF) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide (5a; 2.14 mL, 1.50 mmol, 0.70 M in THF), Pd(OAc)$_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 6 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O / CH$_2$Cl$_2$ = 3:2:3) afforded the pyridine 126b (201 mg, 67%) as a yellow oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.80 (dd, $J = 5.0$ Hz, 1.6 Hz, 1H), 8.19 (dd, $J = 7.9$ Hz, 1.9 Hz, 1H), 8.14-8.08 (m, 2H), 7.63-7.57 (m, 2H), 7.42 (dd, $J = 7.8$ Hz, 4.8 Hz, 1H), 4.39 (q, $J = 7.0$ Hz, 2H), 4.15 (q, $J = 6.9$ Hz, 2H), 1.40 (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.3$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 167.2, 166.3, 157.6, 150.8, 143.7, 138.6, 130.7, 129.4, 128.7, 127.7, 122.4, 61.8, 61.1, 14.3, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2982 (w), 1710 (vs), 1612 (w), 1582 (w), 1560 (w), 1432 (m), 1404 (w), 1367 (m), 1268 (vs), 1209 (m), 1175 (m), 1128 (s), 1096 (s), 1054 (s), 1015 (s), 863 (m), 792 (m), 761 (s), 704 (m).

MS (EI, 70 eV): m/z (%) = 299 (M$^+$, 12), 270 (100), 254 (33), 242 (26), 198 (12), 181 (11), 153 (8), 127 (6).

HRMS (C$_{17}$H$_{17}$NO$_4$): calc.: 299.1158; found: 299.1153.
3-(4-Methoxyphenyl)pyrazine-2-carbonitrile (126c)

According to TP14 3-(methylthio)pyrazine-2-carbonitrile (124f; 151 mg, 1.00 mmol, in 1 mL THF) was reacted with (4-methoxyphenyl)zinc iodide (5c; 1.61 mL, 1.50 mmol, 0.93 M in THF), Pd(OAc)$_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 5 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:2 + 5 vol-% NEt$_3$) afforded the pyrazine 126c (121 mg, 57%) as a yellow solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.78 (d, $J = 2.4$ Hz, 1H), 8.57 (d, $J = 2.4$ Hz, 1H), 8.04-7.94 (m, 2H), 7.10-7.02 (m, 2H), 3.89 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 162.1, 156.5, 146.3, 142.2, 130.6, 127.1, 126.6, 116.7, 114.5, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2925 (w), 2846 (w), 2232 (w), 1606 (s), 1576 (m), 1525 (vs), 1515 (m), 1444 (w), 1435 (m), 1418 (m), 1398 (m), 1386 (m), 1313 (m), 1289 (w), 1254 (vs), 1183 (s), 1170 (s), 1118 (w), 1065 (w), 1033 (m), 1016 (s), 1005 (m), 966 (w), 874 (m), 842 (vs), 822 (m), 798 (m), 792 (m), 667 (w).

MS (EI, 70 eV): m/z (%) = 211 (M$^+$, 100), 196 (16), 168 (10), 158 (11), 133 (14), 114 (6), 90 (6).

HRMS (C$_{12}$H$_9$N$_3$O): calc.: 211.0746; found: 211.0736.

Ethyl 3-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzoate (126d)

According to TP14 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (124g; 187 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenyl zinc iodide (5d; 2.21 mL, 1.50 mmol, 0.68 M in THF), Pd(OAc)$_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 21 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by
extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O / EtOAc = 8:1:1) afforded the triazine **126d** (242 mg, 84%) as a yellow solid.

**M.p. (°C):** 103-105.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ ppm = 9.12-9.07 (m, 1H), 8.69-8.60 (m, 1H), 8.25-8.18 (m, 1H), 7.55 (t, $J$ = 7.8 Hz, 1H), 4.40 (q, $J$ = 7.0 Hz, 2H), 4.12 (s, 6H), 1.40 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ ppm = 174.1, 172.9, 166.0, 135.5, 133.6, 133.1, 131.1, 131.1, 130.0, 128.6, 61.2, 55.3, 14.3.

IR (Diamond-ATR, neat): $\nu$/ cm$^{-1}$ = 3310 (vw), 3232 (vw), 1720 (s), 1592 (m), 1566 (s), 1549 (s), 1536 (s), 1504 (s), 1458 (m), 1436 (m), 1356 (vs), 1298 (s), 1267 (vs), 1191 (m), 1177 (m), 1164 (m), 1118 (m), 1108 (m), 1074 (m), 1039 (s), 1022 (m), 922 (w), 873 (w), 830 (w), 818 (w), 768 (m), 714 (s), 672 (w).

MS (EI, 70 eV): m/z (%) = 289 (M$^+$, 100), 259 (27), 244 (91), 217 (90), 186 (11), 176 (11), 159 (18), 72 (10).

HRMS (C$_{14}$H$_{15}$N$_3$O$_4$): calc.: 289.1063; found: 289.1064.

**4-(1-Methyl-1H-pyrazol-5-yl)benzonitrile (126e)**

According to TP14, 1-methyl-5-(methylthio)-1H-pyrazole (**124h**; 128 mg, 1.00 mmol, in 1 mL THF) was reacted with (4-cyanophenyl)zinc iodide (**5e**; 2.31 mL, 1.50 mmol, 0.65 m in THF), Pd(OAc)$_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 1.5 h at 50 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:4) afforded the pyrazole **126e** (96 mg, 52%) as a pale yellow oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ ppm = 7.79-7.69 (m, 2H), 7.58-7.49 (m, 3H), 6.37 (d, $J$ = 2.1 Hz, 1H), 3.91 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ ppm = 141.7, 138.7, 135.0, 132.5, 129.1, 118.3, 112.2, 107.0, 37.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm$^{-1}$ = 2921 (w), 2224 (m), 1608 (m), 1489 (m), 1468 (w), 1425 (w), 1381 (m), 1279 (m), 1224 (w), 1182 (w), 1113 (w), 1067 (w), 1035 (w), 980 (m), 928 (m), 853 (s), 838 (s), 793 (m), 777 (vs), 708 (m), 664 (w), 649 (m).
MS (EI, 70 eV): m/z (%) = 183 (M⁺, 100), 155 (14), 140 (7), 128 (10), 102 (5).
HRMS (C₁₁H₉N₃): calc.: 183.0796; found: 183.0792.

2-(2-Thienyl)nicotinonitrile (126f)

According to TP14 2-(methylthio)nicotinonitrile (124i; 150 mg, 1.00 mmol, in 1 mL THF) was reacted with 2-thienylzinc iodide (5f; 1.95 mL, 1.50 mmol, 0.77 M in THF), Pd(OAc)₂ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 4:1) afforded the pyridine 126f (173 mg, 93%) as a yellow solid.
M.p. (°C): 74-75.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.72 (dd, J = 4.8 Hz, J = 1.8 Hz, 1H), 8.26 (dd, J = 7.9 Hz, J = 1.8 Hz, 1H), 7.54 (d, J = 5.1 Hz, J = 0.9 Hz, 1H), 7.23 (dd, J = 7.9 Hz, J = 4.8 Hz, 1H), 7.17 (dd, J = 5.2 Hz, J = 3.9 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 153.5, 152.5, 142.1, 141.6, 130.7, 128.9, 128.7, 120.8, 117.8, 103.8.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3066 (vw), 2921 (w), 2850 (vw), 2225 (w), 1574 (w), 1552 (w), 1528 (w), 1472 (vw), 1439 (s), 1414 (m), 1394 (w), 1358 (w), 1229 (w), 1109 (w), 1067 (w), 976 (w), 860 (w), 844 (w), 806 (w), 798 (w), 762 (s), 716 (vs), 676 (s), 619 (w).

MS (EI, 70 eV): m/z (%) = 186 (M⁺, 100), 175 (7), 159 (12), 142 (15), 69 (9), 57 (18), 55 (12), 44 (13).

HRMS (C₁₀H₆N₂S): calc.: 186.0252; found: 186.0239.

3-Methoxy-6-(2-thienyl)pyridazine (126g)

According to TP14 3-methoxy-6-(methylthio)pyridazine (124a; 156 mg, 1.00 mmol, in 1 mL THF) was reacted with 2-thienylzinc iodide (5f; 1.94 mL, 1.50 mmol, 0.77 M in THF), Pd(OAc)₂ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 5 h at 50 °C, the reaction mixture
was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, EtOAc pure) afforded the pyridazine 126g (175 mg, 91%) as a white solid.

**M.p. (°C):** 79-80.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 7.68 (d, $J = 9.2$ Hz, 1H), 7.49 (dd, $J = 3.6$ Hz, 1.21 Hz, 1H), 7.40-7.37 (m, 1H), 7.89 (dd, $J = 5.1$ Hz, 3.6 Hz, 1H), 6.96 (d, $J = 9.2$ Hz, 1H), 4.13 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 163.9, 151.2, 140.7, 128.1, 127.7, 125.8, 125.0, 117.7, 54.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm$^{-1}$ = 3104 (w), 3068 (w), 3001 (w), 2958 (w), 1600 (w), 1550 (w), 1528 (w), 1462 (s), 1437 (m), 1409 (m), 1334 (m), 1301 (m), 1279 (m), 1228 (m), 1110 (m), 1025 (s), 852 (m), 830 (s), 812 (m), 707 (vs), 685 (m).

MS (EI, 70 eV): m/z (%) = 192 (M$^+$, 100), 163 (23), 121 (60), 108 (19), 77 (8), 69 (7), 45 (8).

HRMS (C$_9$H$_8$N$_2$OS): calc.: 192.0357; found: 192.0352.

6,7-Dimethoxy-4-(2-thienyl)quinazoline (126h)

According to TP14 6,7-dimethoxy-4-(methylthio)quinazoline (124j; 236 mg, 1.00 mmol, in 1 mL THF) was reacted with 2-thienylzinc iodide (5f; 1.95 mL, 1.50 mmol, 0.77 M in THF), Pd(OAc)$_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 10 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:4 + 2-Vol% NEt$_3$) afforded the quinazoline 126h (259 mg, 95%) as a yellow solid.

**M.p. (°C):** 149-150.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 9.10 (s, 1H), 7.83 (dd, $J = 3.7$ Hz, 1.2 Hz, 1H), 7.74 (s, 1H), 7.64 (dd, $J = 5.1$ Hz, 1.1 Hz, 1H), 7.38 (s, 1H), 7.27 (dd, $J = 3.7$ Hz, 1.5 Hz, 1H), 4.08 (s, 3H), 4.03 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 157.4, 155.8, 153.1, 150.9, 149.2, 141.3, 130.0, 130.0, 128.1, 117.5, 107.0, 103.4, 56.4, 56.2.
**C. Experimental Section**

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1} = 3102$ (w), $2961$ (w), $2920$ (w), $2829$ (vw), $1615$ (w), $1572$ (w), $1535$ (w), $1499$ (s), $1466$ (s), $1450$ (m), $1427$ (s), $1367$ (m), $1352$ (m), $1296$ (m), $1271$ (w), $1236$ (s), $1217$ (s), $1194$ (m), $1131$ (m), $1101$ (m), $1084$ (w), $1021$ (m), $996$ (s), $960$ (m), $942$ (m), $867$ (m), $838$ (s), $778$ (m), $739$ (vs), $702$ (m), $662$ (m), $642$ (m), $618$ (m).

**MS (EI, 70 eV):** m/z (%) = 272 (M$^+$, 100), 257 (24), 242 (18), 202 (6), 159 (6), 86 (25).

**HRMS (C$_{14}$H$_{12}$N$_2$O$_2$S):** calc.: 272.0619; found: 272.0615.

**Ethyl 4-[2-(4-methoxybenzyl)pyrimidin-4-yl]benzoate (126i)**

According to **TP14** ethyl 4-[2-(methylthio)pyrimidin-4-yl]benzoate (**124k**: 261 mg, 0.95 mmol, in 1 mL THF) was reacted with 3,4,5-trimethoxybenzylzinc chloride (**54h**: 1.67 mL, 1.50 mmol, 0.90 M in THF), Pd(OAc)$_2$ (5.3 mg, 2.5 mol%) and S-Phos (19.5 mg, 5.0 mol%). After 1.5 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, EtOAc) afforded the pyrimidine **126i** (343 mg, 88%) as a yellow solid.

**M.p. (°C):** 121-122.

**$^1$H-NMR (300 MHz, CDCl$_3$):** $\delta$/ ppm = 8.75 (d, $J = 5.5$ Hz, 1H), 8.16 (s, 4H), 7.59 (d, $J = 5.2$ Hz, 1H), 6.69 (s, 2H), 4.41 (q, $J = 7.1$ Hz, 2H), 4.29 (s, 2H), 3.84 (s, 6H), 3.80 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H).

**$^{13}$C-NMR (75 MHz, CDCl$_3$):** $\delta$/ ppm = 169.8, 166.0, 163.3, 157.8, 153.1, 140.6, 136.7, 133.7, 132.6, 130.1, 127.1, 127.1, 116.7, 110.6, 61.3, 60.8, 56.1, 46.2, 14.3.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1} = 2939$ (w), $2838$ (vw), $2826$ (vw), $1712$ (m), $1591$ (m), $1570$ (m), $1542$ (w), $1506$ (m), $1462$ (m), $1444$ (m), $1422$ (m), $1408$ (m), $1381$ (w), $1369$ (w), $1336$ (m), $1280$ (s), $1246$ (m), $1124$ (vs), $1009$ (m), $845$ (m), $829$ (m), $784$ (w), $754$ (m), $700$ (m), $658$ (w), $650$ (w), $636$ (w), $619$ (m).

**MS (EI, 70 eV):** m/z (%) = 408 (M$^+$, 100), 393 (58), 363 (5), 307 (4), 279 (3), 175 (4), 181 (3).

**HRMS (C$_{23}$H$_{24}$N$_2$O$_5$):** calc.: 408.1685; found: 408.1677.
Ethyl 3-[(4-methylpyrimidin-2-yl)methyl]benzoate (126j)

![ Chemical structure of ethyl 3-[(4-methylpyrimidin-2-yl)methyl]benzoate (126j) ]

According to TP14 4-methyl-2-(methylthio)pyrimidine (124c; 140 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)benzylzinc chloride (54m; 1.19 mL, 1.50 mmol, 1.26 M in THF), Pd(OAc)₂ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 24 h at 25 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica, pentane / Et₂O = 1:3) afforded the pyrimidine 126j (188 mg, 73%) as a yellow oil.

^1H-NMR (300 MHz, CDCl₃): δ / ppm = 8.49 (d, J = 5.2 Hz, 1H), 8.03 (s, 1H), 7.94-7.81 (m, 11H), 7.54 (d, J = 7.7 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 5.2 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.28 (s, 2H), 2.48 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H).

^13C-NMR (75 MHz, CDCl₃): δ / ppm = 168.8, 167.4, 166.5, 156.8, 138.5, 133.6, 130.6, 130.2, 128.4, 127.7, 118.3, 60.8, 45.5, 24.1, 14.3.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 2981 (w), 1714 (vs), 1578 (s), 1555 (m), 1439 (s), 1387 (m), 1368 (m), 1279 (vs), 1190 (vs), 1105 (s), 1081 (m), 1023 (m), 929 (w), 839 (w), 754 (s), 740 (s), 697 (s), 672 (m), 651 (m).

MS (EI, 70 eV): m/z (%) = 256 (M⁺, 97), 255 (100), 227 (54), 182 (62), 168 (21), 116 (13), 89 (19), 43 (39).

HRMS (C₁₅H₁₆N₂O₂): calc.: 256.1212; found: 256.1189.

3-[(6-Methoxypyridazin-3-yl)methyl]benzonitrile (126k)

![ Chemical structure of 3-[(6-Methoxypyridazin-3-yl)methyl]benzonitrile (126k) ]

According to TP14 3-methoxy-6-(methylthio)pyridazine (124a; 156 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-cyanobenzylzinc chloride (54o; 1.05 mL, 1.50 mmol, 1.43 M in THF), Pd(OAc)₂ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 14 h at 50 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, EtOAc) afforded the pyridazine 126k (160 mg, 71%) as a yellow solid.

M.p. (°C): 76-78.
C. Experimental Section

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ / ppm = 7.57-7.49 (m, 3H), 7.43-7.39 (m, 1H), 7.18 (d, $J = 9.2$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 4.26 (s, 2H), 4.10 (s, 3H).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ / ppm = 164.2, 156.5, 139.9, 133.5, 132.4, 130.5, 129.5, 129.5, 118.6, 118.2, 112.7, 54.8, 41.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3065 (vw), 2961 (w), 2923 (w), 2854 (w), 2227 (w), 1595 (w), 1458 (s), 1438 (m), 1412 (m), 1306 (s), 1260 (m), 1234 (w), 1091 (m), 1010 (vs), 900 (m), 858 (m), 784 (s), 718 (m), 688 (s).

MS (EI, 70 eV): m/z (%) = 225 (M$^+$, 30), 224 (100), 153 (4), 127 (5), 89 (3).

HRMS (C$_{13}$H$_{11}$N$_3$O): calc.: 225.0902; found: 225.0900.

Ethyl 3-[(6,7-dimethoxyquinazolin-4-yl)methyl]benzoate (126l)

According to TP14 6,7-dimethoxy-4-(methylthio)quinazoline (124j; 236 mg, 1.00 mmol, in 1 mL THF) was reacted with (3-ethoxycarbonyl)benzylzinc chloride (54m; 1.74 mL, 1.50 mmol, 0.86 M in THF), Pd(OAc)$_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 12 h at 50 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / EtOAc = 1:6) afforded the quinazoline 126l (275 mg, 78%) as a pale yellow solid.

M.p. (°C): 119-121.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ / ppm = 9.06 (s, 1H), 8.03-7.98 (m, 1H), 7.89-7.83 (m, 1H), 7.46-7.40 (m, 1H), 7.31 (t, $J = 7.7$ Hz, 1H), 7.27 (s, 1H), 7.21 (s, 1H), 4.54 (s, 2H), 4.31 (q, $J = 7.2$ Hz, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 166.3, 165.3, 155.9, 153.1, 150.4, 148.3, 138.0, 133.2, 130.9, 129.9, 128.8, 128.0, 119.4, 107.1, 102.1, 61.0, 56.4, 56.1, 41.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2982 (vw), 1709 (m), 1615 (w), 1552 (w), 1505 (s), 1425 (s), 1365 (s), 1288 (vs), 1270 (s), 1234 (vs), 1193 (s), 1123 (m), 1027 (m), 985 (m), 850 (s), 753 (s), 728 (m), 700 (m).

MS (EI, 70 eV): m/z (%) = 352 (M$^+$, 32), 323 (18), 321 (100), 307 (14), 291 (19), 277 (5), 263 (6).
HRMS (C\textsubscript{20}H\textsubscript{20}N\textsubscript{2}O\textsubscript{4}): calc.: 352.1423; found: 352.1414.

2-(3,4,5-Trimethoxybenzyl)-1,3-benzothiazole (126m)

According to TP14 2-(methylthio)-1,3-benzothiazole (124l; 181 mg, 1.00 mmol, in 1 mL THF) was reacted with 3,4,5-trimethoxybenzylzinc chloride (54h; 1.56 mL, 1.50 mmol, 0.95 M in THF), Pd(OAc)\textsubscript{2} (5.6 mg, 2.5 mol%), S-Phos (20.5 mg, 5.0 mol%) and Zn(OAc)\textsubscript{2} (183 mg, 1.00 mmol). After 16 h at 25 °C, the reaction mixture was quenched with sat. aq. Na\textsubscript{2}CO\textsubscript{3} solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et\textsubscript{2}O = 1:1) afforded the benzothiazole 126m (222 mg, 70%) as a white solid.


\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): δ / ppm = 8.01-7.96 (m, 1H), 7.82-7.76 (m, 1H), 7.47-7.41 (m, 1H), 7.36-7.29 (m, 1H), 6.57 (s, 2H), 4.35 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H).

\textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): δ / ppm = 171.0, 153.4, 153.0, 137.1, 135.5, 132.6, 125.9, 124.8, 122.7, 121.5, 106.0, 60.8, 56.1, 40.9.

IR (Diamond-ATR, neat): ν / cm\textsuperscript{-1} = 3051 (vw), 2936 (w), 2839 (w), 2361 (vv), 1590 (m), 1501 (m), 1422 (m), 1334 (m), 1238 (s), 1203 (w), 1154 (w), 1119 (vs), 1063 (m), 996 (s), 977 (m), 856 (m), 834 (m), 764 (vs), 732 (m), 722 (s), 663 (m), 642 (m).

MS (EI, 70 eV): m/z (%) = 315 (M\textsuperscript{+}, 100), 300 (53), 268 (5), 257 (5), 186 (10).

HRMS (C\textsubscript{17}H\textsubscript{17}NO\textsubscript{2}S): calc.: 315.0929; found: 315.0925.

4-[5-(Trifluoromethyl)pyridin-2-yl]butanenitrile (126n)

According to TP14 2-(methylthio)-5-(trifluoromethyl)pyridine (124d; 193 mg, 1.0 mmol, in 1 mL THF) was reacted with (3-cyanopropyl)zinc bromide (127a; 3.66 mL, 1.5 mmol, 0.41 M in THF), Pd(OAc)\textsubscript{2} (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%). After 16 h at 25 °C, the reaction mixture was quenched with sat. Na\textsubscript{2}CO\textsubscript{3} solution (25 mL) followed by extraction using
EtOAc (3 x 25 mL). Purification by flash chromatography (pentane / Et₂O = 1:1 + 2 vol-% NEt₃) furnished the pyridine **126n** (180 mg, 0.84 mmol, 84%) as a yellow oil.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.83-8.76 (m, 1H), 7.85 (dd, J = 8.1 Hz, 2.4 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 3.02 (t, J = 7.3 Hz, 2H), 2.43 (t, J = 7.0 Hz, 2H), 2.23-2.09 (m, 2H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 163.5 (q, 4J_C-F = 1.4 Hz), 146.4 (q, 3J_C-F = 4.0 Hz), 133.7 (q, 3J_C-F = 3.5 Hz), 124.8 (q, 2J_C-F = 33.1 Hz), 123.5 (q, 1J_C-F = 272.3 Hz), 122.9, 119.2, 36.2, 24.4, 16.6.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2941 (vw), 2248 (vw), 1609 (m), 1574 (w), 1496 (vw), 1430 (w), 1396 (w), 1325 (vs), 1166 (m), 1121 (vs), 1079 (s), 1017 (s), 940 (w), 854 (w), 738 (w), 654 (w).

**MS (EI, 70 eV):** m/z (%) = 214 (M⁺, <1), 195 (5), 174 (47), 161 (100), 147 (6), 86 (11).

**HRMS (C₁₀H₉F₃N₂):** calc.: 214.0718; found: 214.0697.

**Ethyl 4-[2-(4-methoxybenzyl)pyrimidin-4-yl]benzoate (126o)**

To a solution of 2-bromo-4-(methylthio)pyrimidine (**124b**; 205 mg, 1.00 mmol), Pd(dba)₂ (14.4 mg, 2.5 mol%) and tfp (11.6 mg, 5.0 mol%) in THF (1 mL) was added dropwise 4-methoxybenzylzinc chloride (**54i**; 0.82 mL, 1.02 mmol, 1.24 M in THF). After stirring for 3 h at 25 °C Pd(OAc)₂ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) were added followed by 4-(ethoxycarbonyl)phenylzinc iodide (**5a**; 2.14 mL, 1.50 mmol, 0.70 M in THF) and the reaction mixture was stirred for additional 24 h. Then, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, CH₂Cl₂ / Et₂O = 1:1) afforded the pyrimidine **126o** (236 mg, 68%) as a yellow solid.

**M.p. (°C):** 70-71.

**1H-NMR (600 MHz, C₆D₆):** δ / ppm = 8.28 (d, J = 5.3 Hz, 1H), 8.23-8.20 (m, 2H), 8.00-7.92 (m, 2H), 7.48-7.41 (m, 2H), 6.83-6.77 (m, 2H), 6.68 (d, J = 5.3 Hz, 1H), 4.38 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.27 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H).
C-NMR (150 MHz, C$_6$D$_6$): $\delta$ / ppm = 171.0, 165.8, 162.6, 159.0, 158.1, 141.2, 132.9, 131.1, 130.7, 130.2, 127.4, 114.3, 114.2, 61.1, 54.7, 45.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2980 (w), 2934 (w), 2835 (vw), 1712 (s), 1611 (w), 1569 (s), 1547 (m), 1510 (s), 1438 (m), 1409 (m), 1383 (m), 1270 (vs), 1242 (vs), 1176 (s), 1105 (s), 1018 (s), 818 (m), 776 (s), 740 (s), 700 (s).

MS (EI, 70 eV): m/z (%) = 348 (M$^+$, 100), 333 (26), 305 (15), 160 (4), 121 (10).

HRMS (C$_{23}$H$_{24}$N$_2$O$_5$): calc.: 348.1474; found: 348.1467.

Ethyl 4-[4-(4-methoxybenzyl)pyrimidin-2-yl]benzoate (126p)

To a solution of 4-iodo-2-(methylthio)pyrimidine (124m; 252 mg, 1.00 mmol), Pd(dba)$_2$ (14.4 mg, 2.5 mol%) and tfp (11.6 mg, 5.0 mol%) in THF (1 mL) was added dropwise 4-methoxybenzylzinc chloride (54i; 1.31 mL, 1.02 mmol, 0.78 M in THF). After stirring for 10 min at 25 °C Pd(OAc)$_2$ (5.6 mg, 2.5 mol%), S-Phos (20.5 mg, 5.0 mol%) and THF (0.5 mL) were added followed by 4-(ethoxycarbonyl)phenylzinc iodide (5a; 2.14 mL, 1.50 mmol, 0.70 M in THF) and the reaction mixture was stirred for additional 20 h. Then, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / CH$_2$Cl$_2$ / Et$_2$O = 12:4:1) afforded the pyrimidine 126p (280 mg, 80%) as a yellow solid.

M.p. (°C): 71-73.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.67 (d, $J = 5.2$ Hz, 1H), 8.59-8.50 (m, 2H), 8.20-8.11 (m, 2H), 7.28-7.18 (m, 2H), 6.99 (d, $J = 5.1$ Hz, 1H), 6.93-6.81 (m, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 4.12 (s, 2H), 3.79 (s, 3H), 1.42 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 170.4, 166.4, 163.2, 158.6, 157.1, 141.5, 132.2, 130.3, 129.7, 129.5, 128.1, 118.5, 114.2, 61.1, 55.2, 43.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2992 (w), 2980 (w), 2898 (w), 2836 (w), 1709 (vs), 1611 (w), 1583 (m), 1552 (s), 1512 (s), 1456 (w), 1438 (m), 1401 (s), 1386 (m), 1274 (vs), 1245 (vs).
C. Experimental Section

1178 (s), 1110 (s), 1099 (s), 1018 (w), 884 (w), 875 (w), 845 (m), 820 (m), 763 (m), 755 (s), 699 (m), 614 (w).

**MS (EI, 70 eV):** m/z (%) = 348 (M⁺, 100), 333 (24), 303 (8), 151 (5), 121 (15).

**HRMS (C₂₃H₂₄N₂O₅):** calc.: 348.1474; found: 348.1462.

**Ethyl 3-(4-methylpyrimidin-2-yl)benzoate (126q)**

\[
\text{Me} \\ \text{N} \\ \text{CO}_2\text{Et}
\]

According to TP14 4-methyl-2-(methylthio)pyrimidine (124c; 1.40 g, 10.0 mmol, in 5 mL THF) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide (5a; 20.0 mL, 15.0 mmol, 0.75 M in THF), Pd(OAc)$_2$ (56 mg, 2.5 mol%) and S-Phos (205 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (250 mL) followed by extraction using EtOAc (3 x 250 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 4:1) afforded the pyrimidine 126o (2.20 g, 91%) as a yellow solid.


**$^1$H-NMR (300 MHz, CDCl$_3$):** $\delta$ / ppm = 8.66 (d, $J = 5.1$ Hz, 1H), 8.54-8.48 (m, 2H), 8.18-8.08 (m, 2H), 7.08 (dd, $J = 5.1$ Hz, 0.5 Hz, 1H), 4.39 (q, $J = 7.1$ Hz, 2H), 2.59 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H).

**$^{13}$C-NMR (75 MHz, CDCl$_3$):** $\delta$ / ppm = 167.6, 166.4, 163.3, 156.7, 141.6, 132.1, 129.7, 128.1, 119.1, 61.1, 24.4, 14.3.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1}$ = 2986 (w), 2904 (w), 1706 (s), 1586 (m), 1568 (m), 1550 (m), 1510 (w), 1480 (w), 1430 (w), 1400 (m), 1364 (m), 1304 (w), 1266 (vs), 1126 (m), 1106 (s), 1090 (m), 1026 (m), 1018 (m), 880 (m), 850 (m), 838 (m), 760 (s), 698 (m), 610 (w).

**MS (EI, 70 eV):** m/z (%) = 242 (M⁺, 45), 214 (38), 197 (100), 169 (25), 129 (3), 102 (4).

**HRMS (C$_{14}$H$_{14}$N$_2$O$_2$):** calc.: 242.1055; found: 242.1051.
6.3. Preparation of the title compounds via Ni-catalyzed cross-couplings

Ethyl 2-[3-(ethoxycarbonyl)phenyl]nicotinate (128a)

According to TP15 ethyl 2-(methylthio)nicotinate (124e; 197 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (5d; 2.24 mL, 1.50 mmol, 0.67 M in THF), Ni(acac)₂ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 14 h at 25 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane/EtOAc = 4:1) afforded the pyridine 128a (273 mg, 91%) as colourless liquid.

^1H-NMR (300 MHz, CDCl₃): δ ppm = 8.78 (dd, J = 4.7 Hz, 1.7 Hz, 1H), 8.22-8.19 (m, 1H), 8.17 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 8.13-8.08 (m, 1H), 7.77-7.71 (m, 1H), 7.55-7.47 (m, 1H), 7.38 (dd, J = 7.9 Hz, 4.7 Hz, 1H), 4.37 (q, J = 7.0 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H).

^13C-NMR (75 MHz, CDCl₃): δ ppm = 167.4, 166.2, 157.9, 151.1, 140.2, 138.3, 132.9, 130.4, 129.8, 129.8, 128.2, 127.3, 122.0, 61.6, 61.0, 14.3, 13.7.

IR (Diamond-ATR, neat): ν cm⁻¹ = 2982 (w), 1713 (vs), 1582 (w), 1562 (m), 1420 (m), 1391 (w), 1367 (m), 1283 (s), 1245 (vs), 1207 (s), 1170 (m), 1111 (s), 1097 (s), 1056 (s), 1015 (m), 855 (w), 822 (w), 787 (m), 753 (vs), 694 (s).

MS (El, 70 eV): m/z (%) = 299 (M⁺, 16), 270 (100), 254 (37), 242 (27), 227 (28), 208 (12), 198 (14), 182 (14), 155 (18), 127 (8), 91 (5).

HRMS (C₁₂H₁₂NO₄): calc.: 299.1158; found: 299.1155.

Ethyl 4-(3-cyanopyridin-2-yl)benzoate (128b)

According to TP15 2-(methylthio)nicotinonitrile (124i; 150 mg, 1.00 mmol, in 1 mL THF) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide (5a; 2.14 mL, 1.50 mmol, 0.70 M in THF), Ni(acac)₂ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (25 mL) followed by extraction...
using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 1:1 + 2 vol-% NEt₃) afforded the pyridine 128b (173 mg, 69%) as white solid.

**M.p. (°C):** 98-100.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.89 (dd, J = 4.9 Hz, 1.7 Hz, 1H), 8.22-8.16 (m, 2H), 8.09 (dd, J = 8.0 Hz, 1.9 Hz, 1H), 8.03-7.96 (m, 2H), 7.42 (dd, J = 7.8 Hz, 4.9 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 166.0, 160.0, 152.7, 141.8, 141.0, 131.9, 129.8, 122.1, 117.2, 107.9, 61.2, 14.3.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2977 (vw), 2225 (w), 1714 (m), 1581 (w), 1551 (w), 1432 (m), 1405 (w), 1368 (w), 1319 (vw), 1271 (vs), 1226 (w), 1184 (w), 1175 (w), 1102 (s), 1016 (m), 966 (w), 862 (m), 806 (m), 787 (w), 750 (vs), 719 (w), 698 (m).

**MS (EI, 70 eV):** m/z (%) = 252 (M⁺, 43), 224 (36), 207 (100), 179 (36), 152 (15), 90 (4).

**HRMS (C₁₅H₁₂N₂O₂):** calc.: 252.0899; found: 252.0902.

Ethyl 3-(4-methylpyrimidin-2-yl)benzoate (128c)

According to TP15 4-methyl-2-(methylthio)pyrimidine (124c; 140 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (5d; 2.21 mL, 1.50 mmol, 0.68 M in THF), Ni(acac)₂ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 12 h at 25 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 20:1) afforded the pyrimidine 128c (230 mg, 95%) as a yellow oil.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 9.10-9.06 (m, 1H), 8.68-8.60 (m, 2H), 8.17-8.11 (m, 1H), 7.58-7.51 (m, 1H), 7.07 (d, J = 5.1 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.59 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 167.6, 166.4, 163.4, 156.7, 138.0, 132.4, 131.5, 131.0, 129.3, 128.6, 119.0, 61.0, 24.4, 14.4.
IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 2976 (w), 2928 (vw), 1712 (s), 1572 (s), 1552 (m), 1422 (m), 1386 (m), 1365 (m), 1280 (s), 1255 (s), 1237 (vs), 1164 (m), 1126 (s), 1103 (s), 1078 (m), 1021 (s), 916 (m), 849 (m), 822 (m), 746 (vs), 685 (s).

MS (EI, 70 eV): $m/z (%) = 242 (M^+, 53), 214 (11), 197 (80), 170 (100), 129 (6), 102 (9).

HRMS ($C_{14}H_{14}N_2O_2$): calc.: 242.1055; found: 242.1052.

4-(4-Methylpyrimidin-2-yl)benzonitrile (128d)

According to TP15 4-methyl-2-(methylthio)pyrimidine (124c; 140 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-cyanophenylzinc iodide (5e; 2.31 mL, 1.50 mmol, 0.65 M in THF), Ni(acac)$_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O / EtOAc = 2:6:1) afforded the pyrimidine 129d (143 mg, 73%) as a white solid.


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ ppm = 8.66 (d, $J = 5.2$ Hz, 1H), 8.60-8.52 (m, 2H), 7.78-7.71 (m, 2H), 7.11 (d, $J = 5.6$ Hz, 1H), 2.59 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ ppm = 167.7, 162.4, 156.9, 141.8, 132.3, 128.6, 119.5, 118.8, 113.8, 24.3.

IR (Diamond-ATR, neat): $\tilde{\nu} / \text{cm}^{-1} = 3047 (w), 2224 (w), 1678 (w), 1606 (w), 1583 (s), 1550 (s), 1378 (s), 1288 (m), 1254 (w), 1197 (w), 1108 (w), 1018 (w), 994 (w), 949 (w), 868 (m), 860 (m), 836 (vs), 789 (vs), 706 (w).

MS (EI, 70 eV): $m/z (%) = 195 (M^+, 100), 180 (13), 128 (29), 101 (5), 67 (5).

HRMS ($C_{12}H_{10}N_3$): calc.: 195.0796; found: 195.0796.
Ethyl 3-pyrazin-2-ylbenzoate (128e)

According to TP15 2-(methylthio)pyrazine (124n; 26 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (5d; 2.31 mL, 1.50 mmol, 0.65 m in THF), Ni(acac)$_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 14 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 1:1) afforded the pyrazine 128e (170 mg, 74%) as a white solid.

M.p. (°C): 121-123.

$^1$H-NMR (400 MHz, CD$_3$D$_6$): δ / ppm = 8.95 (t, $J = 1.6$ Hz, 1H), 8.76 (d, $J = 1.6$ Hz, 1H), 8.18-8.13 (m, 1H), 8.08-8.06 (m, 1H), 8.03 (d, $J = 2.5$ Hz, 1H), 7.95-7.91 (m, 1H), 7.73 (t, $J = 7.7$ Hz, 1H), 4.14 (q, $J = 7.0$ Hz, 2H), 1.03 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (100 MHz, CD$_3$D$_6$): δ / ppm = 165.9, 151.6, 144.2, 143.6, 142.2, 137.1, 131.9, 131.0, 130.9, 129.1, 128.4, 61.0, 14.2

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3090 (vw), 3053 (w), 2983 (w), 2939 (w), 1705 (s), 1606 (w), 1465 (m), 1392 (m), 1367 (m), 1278 (s), 1247 (vs), 1176 (m), 1147 (m), 1123 (m), 1109 (s), 1081 (m), 1024 (s), 1014 (s), 936 (m), 896 (m), 856 (s), 820 (m), 765 (s), 745 (s), 689 (s), 652 (m).

MS (EI, 70 eV): m/z (%) = 228 (M$^+$, 61), 200 (31), 183 (100), 155 (49), 102 (10), 77 (6).

HRMS (C$_{13}$H$_{12}$N$_2$O$_2$): calc.: 228.0899; found: 228.0883.

Ethyl 3-(6,7-dimethoxyquinazolin-4-yl)benzoate (128f)

According to TP15 6,7-dimethoxy-4-(methylthio)quinazoline (124j; 236 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)phenylzinc iodide (5d; 2.31 mL, 1.50 mmol, 0.65 m in THF), Ni(acac)$_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 18 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction
using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / EtOAc / CH₂Cl₂ = 1:1:2) afforded the quinazoline **128f** (270 mg, 80%) as a white solid.

**M.p. (°C):** 174-175.

**1H-NMR (600 MHz, CDCl₃):** δ / ppm = 9.20 (s, 1H), 8.46 (t, J = 1.8 Hz, 1H), 8.24-8.21 (m, 1H), 7.99-7.97 (m, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.43 (s, 1H), 7.27 (s, 1H), 4.40 (q, J = 7.0 Hz, 2H), 4.08 (s, 3H), 3.89 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H).

**13C-NMR (150 MHz, CDCl₃):** δ / ppm = 165.9, 164.0, 156.1, 153.2, 150.7, 148.9, 137.8, 133.7, 131.1, 130.8, 130.6, 129.0, 118.6, 106.8, 103.5, 61.3, 56.5, 56.1, 14.3.

**IR (Diamond-ATR, neat):** ν / cm⁻¹ = 2920 (w), 2851 (w), 1730 (s), 1617 (w), 1569 (w), 1540 (m), 1501 (vs), 1464 (m), 1427 (s), 1371 (m), 1321 (m), 1302 (m), 1261 (s), 1214 (s), 1143 (m), 1122 (m), 1080 (m), 1030 (m), 974 (w), 850 (m), 753 (m), 694 (m).

**MS (EI, 70 eV):** m/z (%) = 338 (M⁺, 100), 323 (22), 309 (22), 277 (24), 265 (20), 249 (8), 221 (13), 192 (6), 147 (5), 84 (8).

**HRMS (C₁₉H₁₈N₂O₄):** calc.: 338.1267; found: 338.1265.

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**2,4-Di-2-thienyl-6-(trifluoromethyl)pyrimidine (128g)**

According to **TP15** 2-(methylthio)-4-(2-thienyl)-6-(trifluoromethyl)pyrimidine (**124o**; 276 mg, 1.00 mmol, in 1.5 mL THF) was reacted with 2-thienylzinc iodide (**5f**; 1.95 mL, 1.50 mmol, 0.77 M in THF), Ni(acac)₂ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 16 h at 25 °C, the reaction mixture was quenched with sat. aq. Na₂CO₃ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 500:1) afforded the pyrimidine **128g** (294 mg, 94%) as a yellow solid.

**M.p. (°C):** 102-104.

**1H-NMR (300 MHz, CDCl₃):** δ / ppm = 8.14 (dd, J = 3.7 Hz, 1.3 Hz, 1H), 7.87 (dd, J = 3.7 Hz, 1.1 Hz, 1H), 7.60 (dd, J = 5.0 Hz, 1.2 Hz, 1H), 7.58 (s, 1H), 7.54 (dd, J = 5.0 Hz, 1.2 Hz, 1H), 7.21-7.15 (m, 2H).

**13C-NMR (75 MHz, CDCl₃):** δ / ppm = 162.1, 161.2, 156.4 (q, ²J_C-F = 35.8 Hz), 141.9, 141.3, 131.6, 131.2, 130.6, 128.9, 128.6, 128.3, 120.6 (q, ¹J_C-F = 275.4 Hz), 107.7 (q, ³J_C-F = 2.8 Hz).
C. Experimental Section

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3101 (vw), 1739 (w), 1586 (m), 1542 (m), 1427 (s), 1410 (m), 1379 (s), 1334 (w), 1263 (s), 1215 (m), 1182 (s), 1137 (vs), 1102 (m), 1034 (m), 998 (m), 860 (m), 724 (m), 712 (s), 697 (vs).

MS (EI, 70 eV): m/z (%) = 312 (M$^+$, 100), 134 (47), 109 (18), 90 (6), 45 (10).

HRMS (C$_{13}$H$_7$F$_3$N$_2$S$_2$): calc.: 312.0003; found: 311.9985.

2,4-Dimethoxy-6-(2-thienyl)-1,3,5-triazine (128h)

According to TP15 dimethoxy-6-(methylthio)-1,3,5-triazine (124p; 187 mg, 1.00 mmol, in 1 mL THF) was reacted with 2-thienylzinc iodide (5f; 1.95 mL, 1.50 mmol, 0.77 M in THF), Ni(acac)$_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 16 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O / CH$_2$Cl$_2$ = 8:1:1) afforded the pyrimidine 128h (194 mg, 87%) as a pale yellow solid.

M.p. (°C): 93-95.

$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ / ppm = 8.14 (dd, $J =$ 3.8 Hz, 1.3 Hz, 1H), 7.57 (dd, $J =$ 5.0 Hz, 1.2 Hz, 1H), 7.14 (dd, $J =$ 4.9 Hz, 3.7 Hz, 1H), 4.07 (s, 6H).

$^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ / ppm = 172.5, 170.6, 140.6, 132.5, 131.9, 128.3, 55.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3079 (w), 2953 (w), 1563 (s), 1544 (s), 1531 (s), 1490 (s), 1452 (s), 1428 (s), 1378 (s), 1350 (vs), 1335 (s), 1231 (m), 1194 (m), 1096 (s), 1085 (m), 1041 (s), 1011 (m), 931 (m), 813 (s), 738 (s), 722 (s).

MS (EI, 70 eV): m/z (%) = 223 (M$^+$, 100), 193 (33), 178 (21), 152 (31), 110 (30), 109 (19), 69 (18).

HRMS (C$_9$H$_9$N$_3$O$_2$S): calc.: 223.0415; found: 223.0399.
Ethyl 3-[(5-(trifluoromethyl)pyridin-2-yl)methyl]benzoate (128i)

According to TP15 2-(methylthio)-5-(trifluoromethyl)pyridine (124i; 193 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-(ethoxycarbonyl)benzylzinc chloride (54m; 1.19 mL, 1.50 mmol, 1.26 M in THF), Ni(acac)$_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 24 h at 25 ºC, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O = 9:1) afforded the pyridine 128i (230 mg, 74%) as colourless liquid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ ppm = 8.82-8.79 (m, 1H), 7.97-7.89 (m, 2H), 7.81 (dd, $J$ = 8.1 Hz, 2.4 Hz, 1H), 7.48-7.42 (m, 1H), 7.38 (t, $J$ = 7.6 Hz, 1H), 7.24 (d, $J$ = 9.0 Hz, 1H), 4.35 (q, $J$ = 7.2 Hz, 2H), 4.26 (s, 2H), 1.37 (t, $J$ = 7.2 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ ppm = 166.4, 164.3 (q, $^4$J$_{C-F}$ = 1.4 Hz), 146.3 (q, $^3$J$_{C-F}$ = 4.0 Hz), 138.6, 133.8 (q, $^3$J$_{C-F}$ = 3.4 Hz), 133.6, 131.0, 130.2, 128.8, 128.1, 124.6 (q, $^2$J$_{C-F}$ = 33.0 Hz), 123.6 (q, $^1$J$_{C-F}$ = 272.1 Hz), 122.8, 61.0, 44.3, 14.3.

IR (Diamond-ATR, neat): $\nu$/ cm$^{-1}$ = 2984 (vw), 1715 (s), 1605 (m), 1574 (w), 1490 (w), 1445 (w), 1392 (w), 1368 (w), 1326 (vs), 1277 (s), 1192 (s), 1164 (m), 1123 (vs), 1105 (s), 1077 (vs), 1016 (s), 944 (w), 860 (w), 836 (w), 742 (s), 695 (m), 673 (w), 650 (w).

MS (EI, 70 eV): m/z (%) = 309 (M$^+$, 41), 308 (100), 290 (11), 280 (93), 264 (44), 235 (86), 208 (16), 167 (32), 132 (13), 118 (11), 44 (21).

HRMS (C$_{16}$H$_{14}$F$_3$NO$_2$): calc.: 309.0977; found: 309.0957.

2-(2-Chlorobenzyl)nicotinonitrile (128j)

According to TP15 2-(methylthio)nicotinonitrile (124i; 150 mg, 1.00 mmol in 1 mL THF) was reacted with 2-chlorobenzylzinc chloride (54b; 2.14 mL, 1.50 mmol, 0.70 M in THF), Ni(acac)$_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.8 mg, 5.0 mol%). After 24 h at 25 ºC, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et$_2$O / CH$_2$Cl$_2$ = 5:1:1 + 2 vol-% NEt$_3$) afforded the pyridine 128j (258 mg, 69%) as white solid.
M.p. (°C): 74-76.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 8.71 \text{ (dd, } J = 5.0 \text{ Hz, 1.8 Hz, 1H)}, 7.96 \text{ (dd, } J = 7.9 \text{ Hz, 1.7 Hz, 1H)}, 7.41-7.34 \text{ (m, 1H)}, 7.29 \text{ (dd, } J = 7.9 \text{ Hz, 4.7 Hz, 1H)}, 7.26-7.18 \text{ (m, 3H), 4.53 (s, 2H)}.

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 162.1, 152.3, 140.7, 135.2, 134.4, 131.4, 129.6, 128.5, 126.9, 121.4, 116.4, 109.8, 40.3\).

IR (Diamond-ATR, neat): \(\tilde{\nu} / \text{cm}^{-1} = 3057 \text{ (vw), 2923 (vw), 2228 (w), 1579 (m), 1562 (m), 1474 (m), 1434 (s), 1164 (w), 1127 (w), 1090 (m), 1050 (m), 1038 (m), 987 (w), 949 (w), 910 (w), 805 (m), 752 (vs), 717 (m), 704 (m), 678 (m), 623 (m).}

MS (EI, 70 eV): \(m/z (\%) = 228 (M^+ +, <1), 193 (100), 164 (4), 96 (4), 82 (2), 63 (2)\).

HRMS (C\(_{13}\)H\(_9\)ClN\(_2\)): calc.: 227.0376 ([M-H]\(^+\)); found: 227.0377 ([M-H]\(^+\)).

3-[(4-Methylpyrimidin-2-yl)methyl]benzonitrile (128k)

According to TP15 4-methyl-2-(methylthio)pyrimidine (124c; 140 mg, 1.00 mmol, in 1 mL THF) was reacted with 3-cyanobenzylzinc chloride (54o; 1.05 mL, 1.50 mmol, 1.43 M in THF), Ni(acac)\(_2\) (6.4 mg, 25 mol%) and DPE-Phos (26.8 mg, 50 mol%). After 7 h at 25 °C, the reaction mixture was quenched with sat. aq. Na\(_2\)CO\(_3\) solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et\(_2\)O / EtOAc = 2:6:1) afforded the pyrimidine 128k (197 mg, 94%) as a white solid.

M.p. (°C): 67-68.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 8.50 \text{ (d, } J = 5.2 \text{ Hz, 1H)}, 7.65-7.62 \text{ (m, 1H), 7.51-7.56 (m, 1H), 7.37 (t, } J = 7.8 \text{ Hz, 1H), 7.01 (d, } J = 5.2 \text{ Hz, 1H), 4.25 (s, 2H), 2.50 (s, 3H).}

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 168.1, 167.6, 156.9, 139.7, 133.7, 132.7, 130.2, 129.1, 118.9, 118.6, 112.4, 45.2, 24.2\).

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

MS (EI, 70 eV): \(m/z (\%) = 209 (M^+, 46), 208 (100), 193 (5), 116 (8), 104 (4), 89 (7), 44 (8).\)
C. Experimental Section

HRMS (C_{13}H_{11}N_{3}): calc.: 209.0953; found: 209.0936.

2-(4-Methoxybenzyl)pyrazine (128l)

According to TP15 2-(methylthio)pyrazine (126n; 1.26 g, 10.0 mmol, in 5 mL THF) was reacted with 4-methoxybenzylzinc chloride (54i; 20.8 mL, 15.0 mmol, 0.72 M in THF), Ni(acac)$_2$ (64 mg, 2.5 mol%) and DPE-Phos (268 mg, 5.0 mol%). After 15 h at 25 °C, the reaction mixture was quenched with sat. aq. Na$_2$CO$_3$ solution (250 mL) followed by extraction using EtOAc (3 x 250 mL). Purification by flash chromatography (silica gel, pentane/ Et$_2$O = 1:4) afforded the pyrazine 128l (1.69 g, 84%) as a yellow liquid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.48 (dd, $J = 2.5$ Hz, 1.6 Hz, 1H), 8.44 (d, $J = 1.7$ Hz, 1H), 8.38 (d, $J = 2.6$ Hz, 1H), 7.21-7.14 (m, 2H), 6.87-6.81 (m, 2H), 4.10 (s, 2H), 3.76 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 158.4, 156.8, 144.6, 144.0, 142.2, 130.1, 130.0, 114.2, 55.2, 41.1.

IR (Diamond-ATR, neat): $\vec{\nu}$ / cm$^{-1}$ = 3004 (w), 2956 (w), 2932 (w), 2908 (w), 2836 (w), 1610 (m), 1584 (w), 1510 (vs), 1472 (m), 1440 (w), 1400 (m), 1300 (m), 1246 (vs), 1176 (s), 1126 (m), 1104 (w), 1056 (m), 1032 (s), 1018 (s), 808 (s), 772 (m), 648 (w).

MS (EI, 70 eV): m/z (%) = 200 (M$^+$; 100), 185 (31), 157 (7), 121 (42), 77 (5).

HRMS (C$_{12}$H$_{12}$N$_2$O): calc.: 200.0950; found: 200.0940.
D. APPENDIX
1. Data of the X-ray Analysis

3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)(phenyl)methanol (92e)

![Chemical Structure](image)

### Crystal Data

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### Data Collection

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### Refinement

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CCDC 778844 contains the supplementary crystallographic data for this compound. This data has been deposit in the Cambridge Crystallographic Data Centre and can be obtained free of charge via the internet: www.ccdc.cam.ac.uk/data_request/cif
2. Curriculum Vitae

Albrecht Metzger

Personal Informations
Adress   Schönstraße 12
         81543 München
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E-Mail   AlbrechtMetzger@web.de
Date of Birth  24.10.1981
Place of Birth  Halle (Saale)
Citizenship  German
Marital Status  married

Education
01/2006  diploma exams (all over diploma average grade: 1.2)
05/2005 – 10/2005  Diploma thesis in the group of Prof. Dr. Armin de Meijere on “New Polymerisable Adhesives for Dental Composites”
10/2001 – 09/2003  Basic Studies in Chemistry at the Martin-Luther-Universität Halle (Saale)
09/1996 – 07/2000  Georg-Cantor-Gymnasium Halle (Saale)
Languages
German: mother tongue
English: fluently
French: basic proficiency

Awards
12/2008 Römer-Fellowship 2008 of the Dr. Klaus Römer Stiftung

Personal Interests
Playing bass guitar and violoncello
Hiking, Diving
Sports (Cycling)

Publications


(special issue in honor of Professor Ryoji Noyori (Nobel prize 2001) on the occasion of his 70th birthday)


D. Appendix


15. Sebastian Bernhardt, Albrecht Metzger, Paul Knochel, “Direct Addition of Functionalized Organozinc Reagents to Carbon Dioxide, Ketones and Aldehydes in the Presence of MgCl2”, *manuscript in preparation*.

16. Andreas J. Wagner, Albrecht Metzger, Paul Knochel, "Preparation and Applications of Heterobenzylic Zinc Reagents”, *manuscript in preparation*.


Reviews

Patents

1. Sebastian Bernhardt, Albrecht Metzger, Georg Manolikakes, Paul Knochel
   “Carbonylierung von organischen Zinkverbindungen” patent pending.

Posters

1. “Preparation of Highly Functionalized Benzylic Zinc Reagents by the Direct Insertion of Zn or Mg Into Benzylic Chlorides in the Presence of LiCl” Synthesefest, 17.3.-18.3.2009, Ludwig-Maximilians-Universität München