New Preparations and Reactions of Organometallic Reagents of Mg, Zn and B for the Functionalization of Aromatics and Heteroaromatics, Allylic and Vinylic Compounds as well as for Adamantyl Derivatives

von

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Erklärung


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**Reviews**


*Heterocycles, Heterocycles, 2014, 88, 827.*
Meiner Familie
“We choose to go to the Moon in this decade and do the other things, not because they are easy, but because they are hard!“

- John F. Kennedy -
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A. INTRODUCTION
1. OVERVIEW

“In the 21st century, the field of chemistry will face more than just academic challenges. Indeed, our ability to devise straightforward and practical chemical syntheses is indispensable to the survival of our species.”

With this statement, Ryoji Noyori precisely summarizes the rising challenges chemical and pharmaceutical industry has to face nowadays. Increasing concerns about climate change, resource depletion, and environmental degradation has created new targets for the scientific community. Advanced chemical processes must be economical, safe, environmentally benign, and resource- and energy-saving. Thus, production of the myriad of substances that are required to serve the needs of society, stretching from the world of material science to health care, must address synthetic efficiency not only in terms of selectivity (chemo-, regio-, diastereo- and enantioselectivity) but increasingly in terms of atom economy, that is, in terms of maximizing the number of atoms of all raw materials that end up in the product. Organometallic chemistry has already proven its potential to play an important role in the development of green chemistry. A plethora of very versatile reagents and synthetic transformations are provided and synthetic organic chemists can choose from an ever growing toolbox of organometallic derivatives, each possessing a unique reactivity and selectivity depending on the nature of the metal used.

The reactivity of organometallic reagents is strongly determined by the polarity of the incorporated carbon-metal bond. An appropriate selection of the metal atom and the organic moiety creates versatile tools for specific synthetic applications. Due to their strongly polarized carbon-metal bond, organolithium reagents represent a highly reactive class of organometallics but are incompatible with sensitive functional groups. In contrast, organoboron reagents have been established as air- and moisture-stable building blocks with a high functional group tolerance. However, their almost covalent carbon-boron bond enforces harsh conditions and highly developed catalytic systems for the reaction with electrophiles. Organomagnesium, -copper and -zinc reagents can be considered as a compromise between these two extremes. Although Grignard reagents

are highly reactive towards electrophiles, they show an excellent functional group
tolerance at appropriate low temperatures. Also organocopper reagents possess a well-balanced reactivity. They undergo smoothly reactions with various electrophilic substrates but still tolerate various versatile functional groups. A main drawback is the thermal instability as well as the need of the preparation from other organometallic species such as organolithium or organomagnesium reagents. The big advantages of organozinc reagents are their stability at elevated temperatures and the outstanding functional group tolerance. The slightly lower reactivity compared to other organometallic reagents can readily be overcome by suitable transition metal catalysts readily facilitating reactions with electrophiles. The availability of empty low-energy p-orbitals in organozinc reagents enables readily the interaction with d-orbitals of transition metals and thus leads to smooth transmetalation reactions. For this reason, Pd-catalyzed Negishi coupling reactions usually proceed much faster and under milder conditions than the corresponding Stille or Suzuki cross-coupling reactions.

An elegant example for the utility of the Negishi cross-coupling is demonstrated with the stereoselective synthesis of β-carotene (Scheme 1). The key feature of this approach is the regio- and stereoselective zirconium-catalyzed methylalumination of terminal alkyne precursors, followed by transmetalation with ZnCl\textsubscript{2} and subsequent Negishi cross-coupling of the resulting vinylzinc intermediates with the appropriate vinyl halide electrophiles furnishing β-carotene in >99% stereoisomeric purity.

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

Scheme 2: Negishi cross-coupling in the synthesis of HIV-reverse transcriptase inhibitor MIV-150.

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2. ORGANO MAGNESIUM REAGENTS

More than 100 years ago, Victor Grignard prepared organomagnesium compounds for the very first time.\(^{16}\) These so called Grignard reagents turned out to be exceptionally versatile nucleophiles and are nowadays widely used in chemical laboratories and have even found their way into chemical industry.\(^{17}\)

The direct insertion of magnesium metal into carbon-halogen bonds is still the most straightforward approach for the preparation of organomagnesium compounds.\(^{17}\) The exact mechanism of this reaction is still not entirely elucidated, but radical pathways are generally accepted.\(^{18}\) Despite the efficiency of the magnesium insertion in terms of atom economy\(^4\) the reaction suffers from a limited functional group tolerance since the standard protocol for the insertion is highly exothermic and normally performed at the boiling point of the solvent (e.g. Et\(_2\)O or THF). Therefore the preparation in plant scale is accompanied with serious safety risks.\(^{19}\)

These drawbacks have been elegantly bypassed by Rieke and coworkers using highly reactive magnesium powder (Mg\(^*\)) prepared by the reduction of magnesium salts with lithium naphthalide. This methodology allowed the preparation of the organomagnesium reagents at very low temperatures and thus enabled the tolerance of very sensitive groups like nitriles and esters (Scheme 3).\(^{20}\)

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

In order to avoid the drawback of the prior preparation of the highly active magnesium, Knochel and coworkers developed a methodology applying stoichiometric amounts of LiCl in the insertion reaction (Scheme 4).\(^{21}\) This gives access to a range of

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new functionalized aryl and heteroaryl magnesium species from the corresponding chlorides and bromides under mild reaction conditions.

$$\text{FG-R-X} \xrightarrow{\text{Mg, LiCl}} \text{FG-R-MgX-LiCl}$$

\( R = \text{aryl, heteroaryl} \)
\( X = \text{Cl, Br} \)
\( \text{FG}=\text{CO}_2\text{R, CN, Hal, CF}_3, \text{OR} \)

**Scheme 4**: Preparation of functionalized organomagnesium reagents using Mg in the presence of LiCl.

A more convenient preparation of organomagnesium compounds with high functional group tolerance, avoiding many of the flaws of the direct insertion, is the halogen-magnesium exchange reaction. The driving force for this reaction class is the formation of an organometallic reagent possessing a higher stability than the exchange reagent itself \( (sp^2 > sp^2_{\text{vinyl}} > sp^2_{\text{aryl}} > sp^3_{\text{prim}} > sp^3_{\text{sec}}) \). Based on the preliminary work of Prévost\(^2\) and Villiers, Knochel could impressively demonstrate the potential of the iodine-magnesium exchange with \( \text{iPrMgBr} \) and \( \text{PhMgCl} \) on substrates bearing sensitive functionalities (Scheme 5).\(^2\)

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Scheme 5: Preparation and reactivity of functionalized Grignard reagents by iodine-magnesium exchange using iPrMgBr or PhMgCl.

This method could further be improved by the addition of stoichiometric amounts of LiCl to the exchange reagent iPrMgCl resulting in the formation of an organomagnesium species with the formal composition iPrMgCl·LiCl. Noteworthy, this so called Turbo-Grignard reagent shows a remarkably higher reactivity, broadening the scope of the exchange reaction. A huge variety of aromatic and heteroaromatic bromides could now be converted into the corresponding magnesium reagents. However, the increased reactivity does not limitate the functional group tolerance (Scheme 6).

Scheme 6: Preparation and reactivity of functionalized Grignard reagents by bromine-magnesium exchange using the Turbo-Grignard reagent (iPrMgCl·LiCl).

The formation of a magnesium-lithium ate complex as intermediate of the Turbo-Grignard reagent leads to deaggregation of the organometal species and is assumed to be responsible for the higher solubility and the enhanced reactivity of the Grignard reagent (Scheme 7).

Scheme 7: Effect of LiCl on Grignard reagents.

Since electron-rich aromatic compounds resisted to undergo a bromine-magnesium exchange, reagents of type $\text{RMg}_2\cdot\text{LiCl}$ had been developed.\textsuperscript{26b} Quantum calculations on exchange reactions indicated that the reaction becomes more likely when the exchange reagent’s ate character is increased. Thus, bis-magnesium reagents of type $\text{RMg}_2\cdot\text{LiCl}$ complete the exchange reaction methodology on substrates where $i\text{PrMgCl}\cdot\text{LiCl}$ fails.\textsuperscript{26b}

Besides these two halogen-metal interconversions, a direct metalation using magnesium amide bases is the third major pathway to magnesium organometallics.\textsuperscript{27} The recently developed mixed lithium-magnesium amide bases $\text{TMPMgCl}\cdot\text{LiCl}$ and $\text{TMP}_2\text{Mg}\cdot2\text{LiCl}$ (Turbo-Hauser bases) give access to a large number of functionalized aromatic, heteroaromatic and vinylic organomagnesium reagents (Scheme 8).\textsuperscript{28,29}

\[\text{FG} = \text{CO}_2\text{R, CN, Hal, CF}_3\text{, OR}\]

\[\text{FG} = \text{CO}_2\text{R, CN, Hal, CF}_3\text{, OR}\]

\[\text{FG} = \text{CO}_2\text{R, CN, Hal, CF}_3\text{, OR}\]

\textbf{Scheme 8:} Direct magnesiation using Turbo-Hauser bases $\text{TMPMgCl}\cdot\text{LiCl}$ and $\text{TMP}_2\text{Mg}\cdot2\text{LiCl}$.


\textsuperscript{29} For a recent review article about metalation reactions using hindered amide bases, see: B. A. Haag, M. Mosrin, H. Ila, V. Malakhov, P Knochel, \textit{Angew. Chem. Int. Ed.} 2011, 50, 9794.
3. ORGANOBORON REAGENTS

From the first isolation of an organoboron compound by Frankland in 1860\textsuperscript{30} to the report of their palladium-catalyzed cross-coupling reactions with organic halides by Suzuki and Miyaura in 1979,\textsuperscript{31} the chemistry of organoboron compounds has experienced a tremendous development. Brown and coworkers intensively explored the preparation and application of boron-containing compounds in organic synthesis.\textsuperscript{32} For his pioneering work in this field, Brown received the Nobel Prize in 1979.

One of the most significant reasons for the success and the extensive use of organoboron compounds in modern organic synthesis is the highly covalent character of the carbon-boron bond and their high compatibility with a broad range of functional groups,\textsuperscript{33} their water stability as well as their relatively low toxicity.\textsuperscript{32} Hence, these reagents have emerged to a versatile class of synthons in organic chemistry.\textsuperscript{7,32,34}

The most general route for the generation of organoboron reagents is the transmetalation reaction of various metalorganic species with trihalogenboranes or trialkoxyboranes like BCl\textsubscript{3} or B(OMe)\textsubscript{3}.\textsuperscript{35,36} Organoboron compounds with all kinds of organic groups, whether alkyl, aryl, alkenyl, or alkylnyl can be obtained in this way. The first preparation of an organoborane by Frankland over a century ago used triethoxyborane and diethylzinc,\textsuperscript{30,32} which was later superseded by the more readily prepared Grignard reagents. For metals significantly more electropositive than boron, the equilibrium of the transmetalation reactions lies entirely on the side of the organoborane.
and the metal halide (order of reactivity: K, Na > Li > Mg > Al > Zn, Cd > Pb, Hg, Sn). The ease of displacement of various groups X of BX₃ follows the order Hal > OR > NR₂. Recently, Vedsø and Begtrup reported an efficient method for the synthesis of ortho-substituted arylboronic esters via ortho-lithiation and in situ trapping of the corresponding lithium species with triisopropyl borate (Scheme 9). A very efficient method for the preparation of organoboron reagents is the hydroboration of unsaturated compounds. The first hydroboration was reported by Brown et al. using diborane (B₂H₆) generated from BF₃ and NaBH₄. With the years the hydroboration proved to be one of the most important transformations for the synthesis of complex molecules due to its high regioselectivity and the excellent functional group tolerance. The syn-addition of hydroboranes to unsaturated compounds occurs with predictable selectivity, wherein the boron adds preferentially to the least hindered carbon. This selectivity is enhanced if sterically demanding boranes like pinacolborane or 9-borabicyclo[3.3.1]nonane (9-BBN) are used. Combining the hydroboration with a subsequent oxidation of the newly formed borane gives readily access to anti-Markovnikov alcohols. The hydroboration/oxidation sequence constitutes a powerful method for the regio- and stereoselective synthesis of alcohols (Scheme 10).

![Scheme 9: Preparation of organoboron reagents via transmetalation.](image)

![Scheme 10: Hydroboration and subsequent oxidation for the regio- and stereoselective synthesis of alcohols.](image)

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For the synthesis of chiral, enantiomerically enriched stereocenters in organoboron species, hydroboration is by far the most general method. In the early days of organoboron chemistry, chirality was introduced via chiral auxiliaries obtained from the chiral pool. Isopinene for instance can be converted into a chiral hydroborating reagent $\text{IpcBH}_2$ by addition of BH$_3$. A drawback of this methodology is the attachment of the chiral auxiliary via a boron-carbon bond, complicating its recycling. The chiral auxiliary needs to be removed prior subsequent carbon-carbon bond forming chemistry limiting this otherwise elegant chemistry (Scheme 11).

**Scheme 11:** Preparation and application of $\text{IpcBH}_2$.

*Soderquist* and coworkers developed an improved stoichiometric chiral auxiliary derived from 9-BBN-related derivatives for the hydroboration of a broad variety of olefins proceeding with extremely high selectivity. Most importantly, transformation of the resulting boron-carbon bond can be accomplished without removal of the chiral auxiliary (Scheme 12).

**Scheme 12:** Stereoselective hydroboration with *Soderquist’s* chiral borane and subsequent oxidation.

In terms of a catalytic enantioselective process, *Hayashi et al.* described the use of catechol borane (1,3,2-benzodioxaborole, HBCat) as achiral hydroborating reagent in combination with a rhodium catalyst and the chiral ligand BINAP.

Another convenient approach for the preparation of organoboron reagents is the transition metal-catalyzed borylation of aryl halides and triflates. The cross-coupling

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reaction of these aryl derivatives with pinacolborane\textsuperscript{46} or bis(pinacolato)diboron\textsuperscript{47} in the presence of a palladium catalyst and a base enables readily the synthesis of highly functionalized arylboron compounds containing sensitive groups such as carbonyl, cyano or nitro (Scheme 13). By using more active catalytic systems Miyaura and Fürstner could also employ aryl chlorides as precursors.\textsuperscript{48}

\begin{center}
\begin{align*}
\text{X} = \text{Br, I, OTf} \\
\text{FG} = \text{CO}_2 \text{R, COR, CHO, CN, Hal, OR, SR, NO}_2
\end{align*}
\end{center}

\textbf{Scheme 13:} Preparation of organoboron reagents via Pd-catalysed borylation of aryl halides and triflates.

Since Suzuki and Miyaura introduced in 1979 organoboron reagents into the realm of cross-coupling chemistry by demonstrating a palladium-catalysed reaction of 1-alkenylboranes with aryl and alkynyl halides in presence of a base,\textsuperscript{31} this reaction has seen significant advancement and has become one of the most powerful carbon-carbon bond forming methods in organic synthesis (Scheme 14).\textsuperscript{7,34,49} The availability of the reagents and the mild reaction conditions all contribute to the versatility of this reaction. The coupling reaction offers several additional advantages, such as being largely unaffected by the presence of water, tolerating a broad range of functional groups and proceeding generally regio- and stereoselective. Moreover, the inorganic by-product of the reaction is non-toxic and easily removed from the reaction mixture thereby making this reaction suitable not only for laboratories but also for industrial processes.\textsuperscript{50} For instance, the

\begin{thebibliography}{99}
\end{thebibliography}
**Suzuki-Miyaura** coupling has been used in the total synthesis of Capparatriene, a natural product that is highly active against leukemia (Scheme 14).

\[
R^1\text{-}BY_2 + R^2\text{-}X \xrightarrow{[\text{Pd}] \text{Base}} R^1\text{-}R^2
\]

\[R^1, R^2 = \text{alkyl, vinyl, allyl, (hetero)aryl}\]

\[X = \text{Cl, Br, I, OTf}\]

\[Y = \text{OH, OR, alkyl}\]

**Scheme 14:** Standard **Suzuki-Miyaura** cross-coupling and its application in the total synthesis of Capparatriene.

Until now, organoboronic acids\(^{52}\) are the most frequently used reagents in the **Suzuki-Miyaura** cross-coupling reaction although they are far from ideal. For example, though there are currently over 450 boronic acids commercially available, many of these reagents are difficult to purify due to their waxy constitution. Moreover, boronic acids tend to form trimeric cyclic anhydrides (boroxines) which can influence the reaction stoichiometry. Thus, it is difficult to determine the concentration of boronic acid *versus* boroxine in a mixture. Consequently, many literature protocols for **Suzuki-Miyaura** cross-couplings employ excess of the boronic acid to ensure a complete conversion of the electrophilic component in the reaction.\(^{53}\) Therefore, various boronic derivatives, such as trifluoroborates,\(^{53,54}\) MIDA boronates\(^{55}\) or DAN reagents\(^{56}\) have been developed to overcome these drawbacks. The reagents exist as monomeric complexes with defined structures aiding for precise adjustment of stoichiometry.

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An impressive demonstration of biaryl synthesis employing trifluoroborates was disclosed with the preparation of Trityrosine.\textsuperscript{57} The analogous boronic acid gave none of the double coupling product while the aryltrifluoroborate afforded the desired product in 74% overall yield (Scheme 15).

Scheme 15: Synthesis of Trityrosine employing trifluoroborates as nucleophile.

4. ORGANOZINC REAGENTS

In the first years after the discovery of the carbon-zinc bond by Frankland,\textsuperscript{58} organozinc reagents found only little attention due to the excellent accessibility of organolithium compounds and the well-established procedures for the preparation of organomagnesium reagents described by Grignard.\textsuperscript{16,59} Since organozinc compounds possess an intrinsically lower reactivity compared to the aforementioned analogs, they found only few applications in organic synthesis, such as the Simmons-Smith cyclopropanation reaction\textsuperscript{60} or the Reformatsky reaction of zinc enolates.\textsuperscript{61} However, one of the main advantages of organozinc reagents is the significantly higher tolerance of functional groups present in both the organometallic substrate and the electrophile. This can be explained by the higher covalent character of the carbon-zinc bond in comparison to the carbon-magnesium or carbon-lithium bond. For this reason, organozinc reagents can be handled at elevated temperatures not tolerated by the corresponding Grignard or organolithium reagents.\textsuperscript{58,11,62}

Similarly to organomagnesium compounds, the most common method for the direct synthesis of organozinc reagents is the insertion of zinc powder into organic halides. However, the reaction suffers from the use of expensive organic iodides and elevated reaction temperatures. To avoid these drawbacks, Rieke et al. used highly active zinc (Zn*), prepared by reduction of ZnCl\textsubscript{2} with lithium naphthalide to obtain functionalized organozinc reagents from less reactive arylbromides (Scheme 16).\textsuperscript{20b-d,63}

![Scheme 16: Preparation and reactivity of a functionalized organozinc reagent using highly reactive Rieke-Zn (Zn*).](image)

In 2006, Knochel and coworkers reported a LiCl-facilitated insertion of zinc metal into organic halides.\textsuperscript{64} Besides aromatic and heteroaromatic bromides and iodides, the presence of stoichiometric amounts of LiCl enabled also the use of alkyl bromides and benzyl chlorides in insertion reactions (Scheme 17).

![Scheme 17: Preparation of functionalized organozinc reagents using Zn in the presence of LiCl.](image)


By using a LiCl-mediated magnesium insertion in the presence of ZnCl₂, Knochel et al. were able to further improve the aforementioned insertion reaction.²¹,⁶⁵ Due to the higher reduction potential of magnesium, the insertion times could be shortened and aryl bromides as well as heteroaryl bromides and chlorides replaced the corresponding iodides as cheaper starting materials. Furthermore, by using only 0.5 equivalents of ZnCl₂ more reactive diorganozinc reagents could be obtained (Scheme 18).

Another convenient approach for the preparation of diorganozinc reagents is the iodine-zinc exchange reaction using dialkylzinc species such as diethylzinc or diisopropylzinc. A range of alkyl iodides reacted with diethylzinc in the presence of Cu(i) salts to the corresponding dialkylzinc reagents.⁶⁶ Moreover, this methodology could be improved by using Li(acac) as catalytic additive. Thus, highly functionalized aryl and heteroaryl iodides could be converted into the corresponding diorganozinc species and trapped with a broad range of electrophiles (Scheme 19).⁶⁷

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A. INTRODUCTION

Scheme 19: Preparation and reactivity of functionalized zinc reagents by iodine-zinc exchange using iPr₂Zn.

Inspired by the work on the Turbo-Hauser bases, Knochel et al. developed the mild and chemoselective bases TMP₂Zn·2MgCl₂·2LiCl and TMPZnCl·LiCl for hydrogen-metal interconversion on sensitive substrates. A variety of sensitive aromatic and heteroaromatic compounds could be smoothly zinctated and subsequently functionalized. (Scheme 20).²⁹,⁶⁸

Scheme 20: Direct zinctation using TMPZnCl·LiCl and TMP₂Zn·2MgCl₂·2LiCl.

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5. ADAMANTANE AND ITS CHEMISTRY

The originality of adamantane structure showing also in the properties of its
derivatives is the main factor governing the constant interest to the chemistry of this
compound.\textsuperscript{69} The development of the adamantane chemistry makes it possible both to
solve a series of theoretical problems and to design molecules of substances promising
for the practical application in the fields of medicine, supramolecular chemistry,
nanotechnologies, etc.\textsuperscript{70} Thus, adamantane derivatives found numerous applications in
medicinal chemistry and drug development. No other singular hydrocarbon moiety (apart
from the methyl group) is as successful as adamantane in improving or providing
pharmacological activity for pharmaceuticals. Having the “lipophilic bullet” (adamantane
is assumed to provide the critical lipophilicity) readily available as an “add-on” for
known pharmacophors, it was used for example in the modification of hypoglycemic
sulfonylureas,\textsuperscript{71} anabolic steroids,\textsuperscript{72} and nucleosides.\textsuperscript{73} The adamantane modifications
were chosen to enhance lipophilicity and stability of the drugs, thereby improving their
pharmacokinetics. Aminoadamantanes, such as Amantadine,\textsuperscript{74} Rimantadine,\textsuperscript{75} or
Tromantadine,\textsuperscript{76} are \textit{anti-Influenza A} agents and were among the first compounds on the
pharmaceutical market containing an adamantyl moiety (Figure 1).\textsuperscript{77}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{adamantane_modifications.png}
\caption{Pharmaceutical active substances containing an adamantyl moiety.}
\end{figure}

The aminoadamantanes are synthetic drugs that have not been inspired by natural
products like numerous other drugs. There are, however, also natural products that
incorporate the adamantane skeleton, showing interesting biological properties
(Figure 2).

\textsuperscript{74} W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts,
**Figure 2:** Naturally occurring substrates bearing an adamantyl moiety.

Plukenetione A for example was first isolated from *Clusia plukenetii* in 1996\(^78\) and displayed cytotoxicity in a panel of cell lines for different cancer entities.\(^79\) Also Sampsonione I, isolated from *Hypericum sampsonii*, showed cytotoxicity toward a P388 cell line.\(^80\) However, Hyperbone K, isolated from the Uzbek medicinal plant *Hypericum scrabum*, provided only moderate cytotoxicity in two human cancer cell lines,\(^81\) and no anti-HIV activity.

Noteworthy, the addition of adamantane moieties increases the permeability of the modified compounds through the blood-brain barrier.\(^82\) Therefore, targets of the central nervous system are today most promising both academically and commercially. With the discovery that Amantadine gives symptomatic benefits in *Parkinson* disease\(^83\) and the application of Memantine for the treatment of *Alzheimer* disease,\(^84\) two neurodegenerative diseases of increasing importance in the aging society are being addressed with structurally remarkably simple adamantane derivatives (Figure 3).

**Figure 3:** Simple adamantane derivatives as pharmaceuticals against *Parkinson* and *Alzheimer* disease.

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An emerging field with respect to the application of adamantane derivatives is the inhibition of enzymes using adamantane based scaffolds. Most important are the DPP-IV inhibitors Vildagliptin and Saxagliptin,\(^85\) that currently enter the multibillion dollar market of diabetes management (Figure 4).

![Figure 4](image1.png)

**Figure 4:** Adamantane derivatives as pharmaceuticals against diabetes.

Moreover, there are three classes of adamantane derivatives of relevance in cancer research. The add-on strategy is followed by adamantane derivatives of cisplatin (e.g. LA-12) and Adaphostin. Adamantyl retinoids (e.g. CD437) however represent an alternative strategy to fight cancer cell proliferation (Figure 5).

![Figure 5](image2.png)

**Figure 5:** Adamantane derivatives as pharmaceutically active substrates against cancer.

LA-12 was found to provide a higher degree of cytotoxicity against both cisplatin-sensitive and cisplatin-resistant ovarian cancer cells compared to other cisplatin-analogous substrates.\(^86\) Furthermore, Adaphostin is the adamantyl ester of the protein tyrosine kinase inhibitor AG957.\(^87\) Both AG957 and Adaphostin are classified as tyrphostins (tyrosine phosphorylation inhibitors) and were shown to induce chronic...
myelogenous leukemia cell death.\textsuperscript{88} The adamantyl-based retinoid CD437 shows high activity against a broad spectrum of cancers, including lung, prostate, ovarian, breast, melanoma and leukemia.\textsuperscript{89}

The synthesis of adamantane derivatives is commonly based on the application of well known efficient procedures of selective monofunctionalization of adamantane and on the availability of its polyfunctional derivatives with the same substituents at the bridgehead positions.\textsuperscript{90} The synthesis of adamantyl derivatives includes mainly two approaches: selective functionalization of tertiary C–H bonds in mono- and polysubstituted adamantanes and the selective modification of functional groups on adamantane derivatives.

Among the methods of activation of the tertiary C–H bond in substituted adamantane derivatives with the use of nitric acid, the application of the nitrating mixture HNO\textsubscript{3}/H\textsubscript{2}SO\textsubscript{4} found the widest spread. In this mixture an efficient single-electron oxidant NO\textsubscript{2}\textsuperscript{+} is generated \textit{in situ}. The reaction most probably proceeds \textit{via} a single-electron transfer mechanism (SET mechanism) with the formation of adamantyl cation-radicals that can be trapped by various nucleophiles. Thus, the use of 1,1-dichloroethene as a nucleophile introduces a fragment of the acetic acid onto the bridgehead position of the adamantane frame in almost quantitative yield (Scheme 21).\textsuperscript{91}

\begin{center}
\textbf{Scheme 21:} Functionalization of 1-adamantlyacetic acid \textit{via} SET and subsequent trapping with 1,1-dichloroethene as electrophile.
\end{center}

Under similar conditions, 1-adamantanecarboxylic acid can be converted to the corresponding acetylamino derivative by using acetonitrile as nucleophile in the HNO\textsubscript{3}/H_{2}SO\textsubscript{4} medium. The bifunctional derivative has been obtained in 77\% yield (Scheme 22).\textsuperscript{92}

\begin{thebibliography}{99}
\end{thebibliography}
**Scheme 22:** Functionalization of 1-adamantanecarboxylic acid via SET and subsequent trapping with acetonitrile as electrophile.

Moreover, the treatment of 1-bromoadamantane with 1,2-diethoxy-1,2-bis(trimethylsiloxy)ethene in dry CH$_2$Cl$_2$ in the presence of catalytic amounts of ZnCl$_2$ gives the desired $\alpha,\alpha$-dichloroester in excellent yield (Scheme 23).

**Scheme 23:** ZnCl$_2$-promoted addition of 1,2-diethoxy-1,2-bis(trimethylsiloxy)ethene to 1-bromoadamantane.

Adamantane is readily brominated at elevated temperatures with liquid bromine forming 1-bromoadamantane.$^{93}$ The major drawback of this methodology is the poor functional group tolerance. The bromination of functionalized adamantane derivatives succeeded without catalysts only with a few compounds such as 1-adamantylacetic acid,$^{94}$ 1-(4-nitrophenyl)adamantane,$^{95}$ or 1-($\alpha$-acetylamino)ethyladamantane$^{96}$ (Scheme 24).

**Scheme 24:** Bromination of 1-(4-nitrophenyl)adamantane.

However, bromination of the 1-adamantanecarboxylic acid requires already a catalyst to furnish the corresponding bromo-derivative in good yield. 3-Bromo-1-adamantanecarboxylic acid has been obtained in 68% yield by treating 1-adamantane-carboxylic acid with anhydrous bromine in the presence of AlBr$_3$.$^{97}$

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Furthermore, by treating adamantane derivatives with fluorooxytrifluoromethane (CF$_3$OF) under conditions preventing radical processes (in the dark or in the presence of radical inhibitors) the tertiary position of the adamantane framework undergoes a selective fluorination.$^{98}$ Besides CF$_3$OF, also IF$_5$ proved to be an effective fluorinating agent.$^{99}$ Substituted adamantane derivatives are only monofluorinated, whereas the unsubstituted adamantane reacts with IF$_5$ to both mono- and difluoro derivatives depending on the amount of the fluorinating reagent (Scheme 25).

![Scheme 25: Fluorination of adamantane derivatives using CF$_3$OF, and IF$_5$.](image)

The hydroxylation of the tertiary C–H bonds in functionalized adamantane derivatives can be performed with oxidation systems containing metal complexes or salts. Thus, potassium permanganate in a 2% NaOH solution converts 3,5-difluoroadamantane-1-carboxylic acid to the corresponding hydroxyl derivative in 83% yield (Scheme 26).$^{94}$

![Scheme 26: Hydroxylation of adamantane derivatives using KMnO$_4$/NaOH.](image)

Recently an efficient procedure has been developed for the selective hydroxylation of tertiary C–H bonds applying RuO$_4$ as oxidant.$^{100}$ The latter is generated in situ under the reaction conditions and is responsible for the selectivity of the process. The generation of RuO$_4$ from catalytic amounts of RuCl$_3$ is performed by stoichiometric amounts of the cheap oxidant KBrO$_3$. The procedure permits the hydroxylation of substrates with various functional groups like ester, oxazolidine, carbamate or sulfamate (Scheme 27).

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An efficient system for the preparation adamantylacetamides proved to be a mixture of cerium ammonium nitrate (CAN) with sodium azide in acetonitrile (Scheme 28).\textsuperscript{101} The corresponding alcohols are formed as side products.

Scheme 28: Amidation of adamantane derivatives using CAN/NaN$_3$.

\textit{Friedel-Crafts} alkylation of aromatics with diverse alkylating agents including tertiary alkyl halides has been extensively investigated.\textsuperscript{102} Also the related adamantylation of aromatics is of great interest since an increasing variety of pharmaceuticals containing the phenyladamantane moiety have been discovered.

\textit{De Meijere et al.}, for instance use Pd/C as catalyst for \textit{Friedel-Crafts} type arylation reactions of adamantane. The reaction of 1-bromoadamantane with different arenes in the presence of Pd/C furnishes the corresponding 1-aryl adamantane derivatives in excellent yields (Scheme 29).\textsuperscript{103} Noteworthy, \textit{Stetter et al.} have discovered earlier that donor-substituted arenes like toluene and acetanilide can be easily adamantylated by heating with 1-bromoadamantane in the presence of water.\textsuperscript{104}

Scheme 29: \textit{Friedel-Crafts} type arylation of 1-bromoadamantane.

Furthermore, the arylation of 1-bromoadamantane with the use of substoichiometric (35 mol%) or even stoichiometric amounts of FeCl$_3$ or AlCl$_3$ has been known much longer, and is well documented. However, recently Nakamura and coworkers developed an efficient cross-coupling reaction of 1-chloroadamantane with aryl Grignard reagents using catalytic amounts of an N-heterocyclic carbene ligand (NHC-ligand) and FeCl$_3$ (Scheme 30).

![Scheme 30](image)

**Scheme 30:** FeCl$_3$-catalyzed cross-coupling reaction of 1-chloroadamantane and an aryl Grignard reagent.

Also the silver-catalysed reaction of tertiary alkyl bromides with aryl Grignard reagents in dichloromethane affords the corresponding cross-coupling products in reasonable yields (Scheme 31).

![Scheme 31](image)

**Scheme 31:** Silver-catalyzed phenylation of 1-bromoadamantane.

Hafnium(IV) trifluoromethanesulfonate has been found to be an efficient catalyst for Friedel-Crafts alkylation. The adamantylation of toluene with 1-chloroadamantane in the presence of 5 mol% Hf(OTf)$_4$ furnishes the corresponding product in 92% yield (Scheme 32).

![Scheme 32](image)

**Scheme 32:** Hf(OTf)$_4$-catalyzed Friedel-Crafts arylation of 1-chloroadamantane.

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Furthermore, Laali et al. have reported a TfOH-promoted adamantylation of aromatic substrates using the ionic liquid n-butylmethylimidazolium triflate ([BMIM][OTf]) as solvent (Scheme 33).\(^{110}\)

![Scheme 33: TfOH-promoted adamantylation of anisol in the ionic liquid n-butylmethylimidazolium triflate ([BMIM][OTf]).](image)

Recently, a method for {Suzuki-Miyaura} cross-coupling reactions of tertiary alkyl bromides, using the commercially available catalyst components NiBr\(_2\)-diglyme and 4,4′-di-tert-butyl-2,2′-bipyridine, was disclosed.\(^{111}\) Thus, the reaction of 1-iodoadamantane with the isopropylphenyl-substituted 9-borabicyclo[3.3.1]nonane (9-BBN) furnished the desired product in 61% yield (Scheme 34).

![Scheme 34: Suzuki-Miyaura cross-coupling of 1-iodoadamantane with the isopropylphenyl-substituted 9-borabicyclo[3.3.1]nonane.](image)

6. IMIDAZOLE AND ITS CHEMISTRY

The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine or nucleic acid. Due to its polarity and its ionisable aromatic character, it leads to improved pharmacokinetic characteristics of lead molecules and is therefore used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble molecules.\(^{112}\)

Marine sponges produce a plethora of structurally diverse secondary metabolites usually containing both imidazole and pyrrole moieties.\(^{113}\) Since the discovery in 1971 of the first alkaloid of this family, Oroidin,\(^{114}\) many hundreds of such compounds have been isolated. Members of this family range from relatively simple compounds containing

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\(^{112}\) K. Shalini, P. K. Sharma, N. Kumar, *Der Chemica Sinica* 2010, 1, 36.


intact imidazole systems such as Hymenidine, Parazoanthoxanthin A and Cribrostatin 6 to considerably more complex metabolites such as Palau’amine or Axinellamine A (Figure 6).

![Figure 6](image1.png)

Figure 6: Natural products occurring in marine sponges containing the imidazole moiety.

However, the most important natural product derived from imidazole is the proteinogenic amino acid histidine. With its physiological pH value of 7.4, the histidine acts in protein building blocks as a free base and as a conjugated acid (pKₐ = 7.00) due to a regulating acid-base equilibrium. Especially in enzymes, imidazole acts as Brønsted base or Brønsted acid. Moreover it also has the possibility to form complexes with metal ions. These properties are unique among the proteinogenic amino acids (Figure 7). Histamine is formed by enzymatic decarboxylation of histidine. It acts as a vasodilator and thus lowers the blood pressure. Moreover, it can contract smooth muscles and regulate the gastric acid secretion. Too high histamine level in the blood can cause allergic reactions like hay fever, which can be surpressed by antihistamines blocking the allergy-causing histamine receptors (H₁ receptors). Cimetidine is used for treatment of duodenal and gastric ulcers. By blocking the histamine receptors stimulating the gastric acid secretion (H₂ receptors), it reduces the gastric acid production (Figure 7).

![Figure 7](image2.png)

Figure 7: Natural products containing the imidazole moiety.

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Among imidazole derivatives a huge variety of pharmacological active molecules can be found. Metronidazole is a nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal and the drug of choice for first episodes of mild-to-moderate *Clostridium difficile* infection. Bifonazole shows antifungal activity. It has dual mode of action. It blocks transformation of 24-methylendihydrolanosterol to desmethylsterol in fungi together with inhibition of HMG-CoA. This enables fungicidal properties against dermatophytes and distinguishes bifonazole from other antifungal drugs. Eprosartan is an Angiotensin II receptor antagonist used for the treatment of high blood pressure. It blocks the binding of Angiotensin II to AT₁ receptors in vascular smooth muscle, causing vascular dilatation and inhibits sympathetic norepinephrine production (Figure 8).

![Figure 8](image-url): Pharmaceutically relevant imidazole derivatives.

Ionic liquids have received attention in recent years for their various desirable properties. Imidazolium-based ionic liquids and ionic liquid monomers are becoming increasingly popular in a variety of areas including biphasic reaction catalysis, electromechanical actuator membranes and diluents, separation science membranes, as well as water purification agents or green solvents (Figure 9). Imidazole was targeted for its ability to form cationic compounds, which are molten salts at low molar mass. Ionic liquids offer several beneficial attributes including fixed charge, potential as green solvents, and relatively high thermal stability. The imidazole ring has gained much attention for its ability to tune the properties of the resulting ionic liquid. The type of substituents on any of the positions in the ring and exchange of the counteranion influences many physical properties such as the melting point, the boiling point, and the

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viscosity. Furthermore, imidazolium ionic liquids utilize two of their unique properties in biphasic catalysis, i.e. their ability to coordinate transition metals and their hydrophilic ionic nature. Several imidazolium-based ionic liquid molecules have displayed the ability to catalyze atom transfer radical polymerization and facilitate the synthesis of polymers with a narrow molecular weight distribution.\(^{123}\)

![Figure 9: Imidazole-based ionic liquids.](image)

Imidazoles react with electrophilic reagents like halogenoalkanes via the nucleophilic pyridine-like N-atom to give quarternary salts as primary products. These salts readily undergo deprotonation and react with a second halogenoalkane to afford 1,3-dialkylimidazolium salts (Scheme 35).\(^{116}\)

![Scheme 35: Reaction with electrophilic reagents.](image)

In the presence of strong bases, imidazoles form the corresponding imidazolyl anion and easily undergo 1-alkylation with halogenoalkanes and dialkyl sulfates.\(^{124}\) Due to the ambient character of unsymmetrical imidazolyl anions, base-induced alkylation of substituted imidazoles furnishes product mixtures (Scheme 36). Imidazolyl anions also react with acid chlorides, sulfonyl chlorides and trialkylchlorosilanes to give the corresponding 1-substituted imidazoles.\(^{125}\)

![Scheme 36: Base-induced reaction with electrophilic reagents leading to product mixtures.](image)

\(S_{\text{E}}\text{Ar}\) reactions like halogenations or azo couplings are mostly performed in neutral or basic medium. Chlorination with \(\text{SO}_2\text{Cl}_2\) furnishes 4,5-dichloroimidazole\(^{116}\) whereas

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bromination with Br$_2$ in water or HOAc/NaOAc$^{126}$ and iodination with I$_2$ in H$_2$O/NaOH$^{127}$ produce the corresponding 2,4,5-trihalogenated imidazoles. Azo couplings in aqueous alkaline solution lead to 2-substituted products, since the negative charge of the intermediate imidazolyl anion is delocalized over positions 1-3 of the ring (Scheme 37).$^{128}$

**Scheme 37:** Azo coupling of imidazole in basic medium.

Reactions of N-substituted imidazole derivatives with nucleophiles occur rather slowly and demand vigorous conditions. For instance, the S$_{N}$Ar reaction of 2-halogeno-1-alkylimidazoles require high temperatures (Scheme 38).$^{129}$

**Scheme 38:** S$_{N}$Ar reaction of N-substituted imidazole derivatives.

The treatment of 1,3-dialkylimidazolium salts with strong bases leads to deprotonation at position 2 generating 1,3-dialkylimidazolium ylides. Due to their electronic distribution, these ylides exhibit the behavior of nucleophilic carbenes and undergo electrophilic reactions like alkylation, acylation, halogenations, etc. at position 2 (Scheme 39).$^{130}$

**Scheme 39:** Preparation of 1,3-dialkylimidazolium ylides and their subsequent reaction with electrophiles.

1,3-dialkyl- and 1,3-diacylimidazolium ions show high reactivity against OH-ions, usually with addition at position 2 followed by ring-cleavage. For instance, the reaction

$^{127}$ A. Schmidt, T. Mordhorst, Heterocycles 2006, 68, 1393.
of imidazole with PhCOCl in NaOH/H₂O leads to the cleaved product 1,2-(dibenzoylamido)ethane and formate (Scheme 40).\textsuperscript{131}

\textbf{Scheme 40}: Ring cleavage of 1,3-diacylimidazolium ions under basic conditions.

7. OBJECTIVES

As functionalized five- and six-membered heterocycles are highly important building blocks for the synthesis of pharmaceuticals, agrochemicals and materials (e.g. regio-regular polymers), a simple and general method for the regioselective preparation of metalated heterocycles would be highly desirable. Hence, a selective Br/Mg-exchange reaction of unsymmetrically substituted five- and six-membered dibromo-heterocycles should be developed (Scheme 41).\[132\]

![Scheme 41: Regioselective Br/Mg-exchange on unsymmetrically substituted dibromoheterocycles and subsequent functionalization.](image)

Arylboron derivatives have found broad applications for the performance of Suzuki-Miyaura cross-couplings. In general, most arylboronic compounds are prepared via lithium or magnesium organometallics in a two-step process. The aim of the project lay on the development of a convenient, general and atom-economical method for the one-pot preparation of boronic derivatives using inexpensive starting materials with little toxicity and their subsequent use in Suzuki-Miyaura cross-coupling reactions (Scheme 42).\[133\]

![Scheme 42: One-pot preparation and subsequent cross-coupling of magnesium diarylboronates.](image)

\[132\] Project was developed in cooperation with B. A. Haag (see: Dissertation, LMU-München, 2010).

\[133\] Project was developed in cooperation with B. A. Haag (see: Dissertation, LMU-München, 2010) and A. Jana.
procedure involving the reaction of substituted allylic zinc reagents, prepared via direct metal insertion into substituted allylic halides, with a broad range of acid chlorides and chloroformates was envisioned to furnish the corresponding α-substituted β,γ-unsaturated ketones and esters (Scheme 43).

\[
\begin{align*}
R^1 && R^3 & \xrightarrow{\text{Zn}, \text{LiCl}} & R^1 && R^3 & \xrightarrow{\text{R}^4 \text{Cl}} & R^1 && R^2 && R^3 \\
X = \text{Cl, Br}
\end{align*}
\]

**Scheme 43:** Preparation of α-substituted β,γ-unsaturated ketones and esters via addition of allylic zinc reagents to various acid chlorides and chloroformates.

Functionalized alkenes bearing aldehyde, keto or ester functions are found in a plethora of naturally occurring products as well as in pharmaceutically active substances. This makes functionalized alkenyl organometallics bearing such sensitive carbonyl groups important intermediates in organic synthesis. Since the addition of LiCl to various insertion reactions allows the simple preparation of alkyl, aryl, and benzylic zinc reagents, this method should be extended to alkenyl zinc reagents starting from their corresponding unsaturated bromides (Scheme 44).

**Scheme 44:** Preparation of alkenylzinc reagents and subsequent functionalization.

Adamantane derivatives found numerous applications in medicinal chemistry and drug development. The development of the adamantane chemistry allows it to design molecules of substances promising for the practical application in the fields of medicine, supramolecular chemistry, nanotechnologies, etc. Until now, no general methodology has been reported for the selective synthesis of adamantyl organometallic reagents. Hence, a mild and convenient procedure for the selective synthesis of adamantyl organometallics was envisioned also tolerating functional groups on the adamantyl scaffold (Scheme 45).

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134 Project was developed in cooperation with M. A. Schade (see: Dissertation, LMU-München, 2011) and S. Yamada.

135 Project was developed in cooperation with V. Dhayalan.
**Scheme 45:** Preparation of adamantylzinc reagents and subsequent functionalization.

The imidazole scaffold can be found in a plethora of naturally occurring products. Moreover, among imidazole derivatives a huge variety of pharmacological active molecules can be found and are therefore important targets in pharmaceutical industry. For this reason, a methodology for the selective and predictable functionalization of all positions of the imidazole ring starting from simple imidazole by directed metalation and sulfoxide/magnesium exchange is highly desirable (Scheme 46).\(^{136}\)

**Scheme 46:** Fully functionalization of imidazole scaffold starting from plain N-protected imidazole.

\(^{136}\) Project was developed in cooperation with E. Coya.
A. INTRODUCTION
B. RESULTS AND DISCUSSION
RESULTS AND DISCUSSION
1. HIGHLY REGIOSELECTIVE PREPARATION OF HETEROARYLMAGNESIUM REAGENTS USING A Br/Mg-EXCHANGE

1.1 INTRODUCTION

The functionalization of heterocycles is of key importance for the preparation of pharmaceuticals, agrochemicals and materials (regioregular polymers) and has attracted a lot of attention in recent years. Especially important is the regioselective preparation of metalated five- and six-membered heterocycles. Substituted pyridines react with a variety of metallic bases leading to the corresponding metalated intermediates. Using a proper set of reaction conditions and an appropriate metal base enables the performance of a range of selective metalations. The nature of the substituents attached to the pyridine scaffold deeply influences the regioselectivity and the rate of the metalation. The deprotonation of 5-bromonicotinic acid with lithium 2,2,6,6-tetramethylpiperidide (TMPLi) for example proceeds smoothly leading regioselectively after iodolysis to the desired product with the iodo-substituent in position 4 (Scheme 47).

Scheme 47: Regioselective deprotonation on 5-bromonicotinic acid with TMPLi.

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Another way of controlling the regioselectivity in metalation reactions of pyridine derivatives is the addition of strong Lewis acids such as BF$_3$·OEt$_2$. It turns out that the sterically hindered base TMPMgCl·LiCl reacts reversibly with BF$_3$·OEt$_2$ at temperatures below -20 °C leading to the frustrated Lewis pair TMPMgCl·BF$_3$. This adduct decomposes only at temperatures above -10 °C. Through a coordination of the BF$_3$ group at the N-heterocyclic nitrogen the acidity of the pyridyl hydrogens increases and the deprotonation of even electron-rich pyridines such as 2-methoxypyridine proceeds readily. Moreover, the addition of BF$_3$·OEt$_2$ also changes dramatically the direction of the deprotonation. Thus, 3-bromoisonicotinonitrile is magnesiated with TMPMgCl·LiCl in position 2 providing the corresponding 2-allylated pyridine in 65% yield after Cu(I)-catalyzed allylation. In the presence of BF$_3$·OEt$_2$, a complete switch of regioselectivity is observed and the 4-allylated pyridine is obtained after a Cu(I)-catalyzed allylation in 63% yield (Scheme 48).

![Scheme 48: Effect of BF$_3$·OEt$_2$ on the deprotonation of 3-bromoisonicotinonitrile with TMPMgCl·LiCl.](image)

The presence of a bromo or an iodo substituent attached to the pyridine ring allows the performance of halogen/metal exchange. The use of alkyllithium reagents leads to fast exchange reactions. However, the reaction conditions and the nature of the lithium reagent used are of special importance since lithiation of the pyridine ring may be a competitive process.

In the reaction with 5-bromo-2-chloropyridine tBuLi plays the role of a base and the ortho-lithiation leads selectively after addition of TMSCl to the trisubstituted product 5-bromo-2-chloro-4-(trimethylsilyl)pyridine in 92% yield. In contrast, nBuLi selectively exchanges the bromine of 5-bromo-2-chloropyridine and furnishes, after addition of TMSCl, selectively the disubstituted heterocycle 2-chloro-5-(trimethylsilyl)pyridine in 90% yield (Scheme 49).

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Scheme 49: Br/Li exchange versus ortho-lithiation depending on the nature of the lithium reagent.

Furthermore, Knochel et al. found that a tosyloxy substituent in position 2 of 3,5-dibromopyridine allows a highly regioselective Br/Mg exchange reaction using \( \text{iPrMgCl·LiCl} \). The bromine substituent in position 3 undergoes a Br/Mg exchange with 99:1 regioselectivity, showing the strong influence of the tosyloxy group. The reaction of the pyridylmagnesium reagent with DMF affords the corresponding pyridyaldehyde in 88% yield (Scheme 50).

Scheme 50: Regioselective Br/Mg exchange on 3,5-dibromopyridin-2-yl 4-tosylate with \( \text{iPrMgCl·LiCl} \).

Based on these results, we envisioned a convenient and general regioselective Br/Mg-exchange reaction for unsymmetrically substituted dibromoheterocycles allowing the preparation of various thienyl-, furyl- and pyridyl-magnesium derivatives.

1.2 Regioselective Br/Mg-Exchange on Unsymmetrical Dibromo-Heterocycles Using iPrMgCl·LiCl

Preliminary experiments have shown that the treatment of unsymmetrically substituted dibromo-heterocycles like 2,5-dibromo-3-(methylthio)thiophene (2a) with \( \text{iPrMgCl·LiCl} \) (1a) (1.05 equiv) in THF at 0 °C leads within 1 h to the corresponding magnesium reagent 3a in >95% yield and with a regioselectivity of >99:1. Its addition to 3-chloro-4-methoxybenzaldehyde (4a, 0.9 equiv) at -20 °C provides the corresponding alcohol 5a in 74% yield (Scheme 51). With these conditions in hand, several unsymmetrically substituted dibromo-thiophenes and -benzo[b]thiophenes have been converted into their corresponding magnesium species (Table 1) and subsequently functionalized using a broad range of electrophiles, such as aldehydes, aryl iodides or acyl chlorides in the presence of an appropriate catalyst.
**Scheme 51:** Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromothiophene 2a using iPrMgCl-LiCl (1a).

This regioselective exchange has been performed with a number of unsymmetrically substituted dibromothiophenes in excellent regioselectivities. Thio-substituents such as MeS, PhS or PyrS on the dibromothiophene direct the Br/Mg-exchange in position 5 with a regioselectivity of >99:1 (Table 1). Subsequent functionalization reactions furnish the corresponding products in excellent yields. Hence, (5-bromo-4-(methylthio)thiophen-2-yl)magnesium bromide (3a) has been transmetalated with ZnCl₂ and submitted to a Pd-catalysed Negishi cross-coupling with electrophiles 4b and 4c furnishing the highly functionalized products 5b and 5c in 82% and 84% yield respectively (entries 1 and 2). The reaction of organomagnesium compound 3a with di-tert-butyl dicarbonate (4d) produces the ester-substituted thiophene 5d in 82% yield (entry 3). Furthermore, the magnesium reagent 3b of the PhS-substituted dibromothiophene smoothly adds to anisaldehyde (4e) furnishing the corresponding alcohol in 91% yield (entry 4). Also Pd-catalyzed Negishi cross-couplings of 3b after transmetalation with an electron-poor as well as an electron-rich electrophile (4f and 4g) proceed well and lead to the desired products 5f and 5g in high yields (entries 5 and 6). Noteworthy, the exchange reaction as well as the subsequent cross-coupling with 4g has been carried out in a 15 mmol scale without any loss in regioselectivity or yield. Finally, also Mg-species 3c of the PyrS-substituted dibromothiophene has been successfully submitted to a Negishi cross-coupling with ethyl 4-iodobenzoate (4h) producing thiophene 5h in 92% yield (entry 7).

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144 The corresponding regioisomers of 3a-e and 3h were not observed in 1H NMR measurements of the hydrolyzed crude reaction mixtures (H2O, 10 equiv., -20 to 25 °C).

### Table 1: Preparation of functionalized thiophenes via regioselectively generated heteroaryl-magnesium reagents of type 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent[a]</th>
<th>Electrophile</th>
<th>Product, Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a: &gt;99:1</td>
<td>4b</td>
<td>5b: 82%[c]</td>
</tr>
<tr>
<td>2</td>
<td>3a: &gt;99:1</td>
<td>4c</td>
<td>5c: 84%[c]</td>
</tr>
<tr>
<td>3</td>
<td>3a: &gt;99:1</td>
<td>4d</td>
<td>5d: 82%</td>
</tr>
<tr>
<td>4</td>
<td>3b: &gt;99:1</td>
<td>4e</td>
<td>5e: 91%</td>
</tr>
<tr>
<td>5</td>
<td>3b: &gt;99:1</td>
<td>4f</td>
<td>5f: 86%[c]</td>
</tr>
<tr>
<td>6</td>
<td>3b: &gt;99:1</td>
<td>4g</td>
<td>5g: 96%[c][d]</td>
</tr>
<tr>
<td>7</td>
<td>3c: &gt;99:1</td>
<td>4h</td>
<td>5h: 92%[c]</td>
</tr>
</tbody>
</table>

[a] Obtained after exchange reaction with iPrMgCl-LiCl (1a; 1.05 equiv) in THF at 0 °C in 1 h. Ratio of regioisomers determined by $^1$H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv).

[b] Yield of analytically pure isolated product as determined by $^1$H NMR analysis.

[c] Obtained after a Negishi cross-coupling (ZnCl$_2$ (1 equiv); then 4% Pd(PPh$_3$)$_4$) with ArI (0.9 or 1.1 equiv).

[d] Reaction was performed on a 15 mmol scale.
Also the TMS-substituted dibromothiophene 2d undergoes readily the Br/Mg-exchange with iPrMgCl-LiCl (1a) (1.05 equiv) in THF at 0 °C and leads within 1 h to the corresponding magnesium reagent 3d in >95% yield and with a regioselectivity of >99:1. Its addition to 2,3-dichlorobenzaldehyde (4i, 0.9 equiv) at -20 °C provides the corresponding alcohol 5i in 86% yield (Scheme 52).

![Scheme 52: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromothiophene 2d using iPrMgCl-LiCl (1a).](image)

After transmetalation with ZnCl$_2$ (1 equiv), the Negishi cross-coupling reaction of magnesium species 3d with 4-iodoanisol (4g) using 4% Pd(PPh$_3$)$_4$ as catalyst furnishes the corresponding arylated thioephene 5j in 87% yield (Table 2, entry 1). Moreover, transmetalation of 3d with ZnCl$_2$ (1 equiv) followed by a Cu(I)-catalyzed$^{146}$ acylation (10% CuCN·2LiCl) with furan-3-carbonyl chloride (4j) gives access to the functionalized ketone 5k in 72% yield (entry 2). Since benzo[b]thiophenes are important building blocks for the preparation of organic materials,$^{147}$ regioselective functionalizations of this scaffold have been performed with iPrMgCl-LiCl (1a). The Br/Mg-exchange of dibromo-thienothiophene 2e leads to the corresponding magnesium reagent 3e in >95% and >99:1 regioselectivity. Its subsequent addition to anisaldehyde (4e) proceeds readily and furnishes the expected alcohol 5l in 81% yield (entry 3). The arylated thienothiophene 5m has been obtained in almost quantitative yield after Pd-catalysed cross-coupling of magnesium reagent 3e with 4-iodoanisol (4g).

---


Table 2: Preparation of functionalized thiophenes and benzo[b]thiophenes via regioselectively generated heteroarylmagnesium reagents of type 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent[a]</th>
<th>Electrophile</th>
<th>Product, Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3d: &gt;99:1</td>
<td>4g</td>
<td>5j: 87%[c],[d]</td>
</tr>
<tr>
<td>2</td>
<td>3d: &gt;99:1</td>
<td>4j</td>
<td>5k: 72%[e]</td>
</tr>
<tr>
<td>3</td>
<td>3e: &gt;99:1</td>
<td>4e</td>
<td>5l: 81%</td>
</tr>
<tr>
<td>4</td>
<td>3e: &gt;99:1</td>
<td>4g</td>
<td>5m: 96%[e]</td>
</tr>
</tbody>
</table>

\[a\] Obtained after exchange reaction with \(\text{iPrMgCl-LiCl}\) (1a; 1.05 equiv) in THF at 0 °C in 1 h. Ratio of regioisomers determined by \(^1\)H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv).

\[b\] Yield of analytically pure isolated product as determined by \(^1\)H NMR analysis.

\[c\] Obtained after a Negishi cross-coupling (ZnCl\(_2\) (1 equiv); then 4% Pd(PPh\(_3\)), with ArI (0.9 or 1.1 equiv).

\[d\] Reaction was performed on a 10 mmol scale.

\[e\] Obtained after acylation (ZnCl\(_2\) (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 equiv).

Besides thio- and TMS-substituted thiophenes, also other substituents on the dibromothiophene have been tested. Interestingly, by using 2,5-dibromo-3-phenylthiophene, no regioselective Br/Mg-exchange could be achieved under various conditions. However by introducing a substituent at the ortho position of the phenyl group like Me, MeO or Me\(_2\)N selectivities from 20:1 up to >99:1 could be obtained. This effect may be explained by assuming a conformation change by moving the aryl group out of plane due to the substituent on position 2' of the aryl ring and therefore shielding the bromine at position 2.

The Br/Mg-exchange of 2,5-dibromo-3-(o-toly)thiophene (2f) with \(\text{iPrMgCl-LiCl}\) (1a) (1.05 equiv) in THF at 0 °C leads within 1 h to the corresponding magnesium reagent (3f) in >95% yield and with a regioselectivity of 22:1. After transmetalation with ZnCl\(_2\), the Negishi cross-coupling with 4-idoanisol (4g) furnishes the highly functionalized thiophene 5n in almost quantitative yield (Scheme 53).
Employing 2-$N,N$-dimethylaniline as substituent on the dibromothiophene, the ratio of the regioisomers of the Br/Mg-exchange could be increased and the corresponding magnesium reagent $3g$ has been obtained in a regioselectivity of 39:1 (Table 3, entry 1). The subsequent Negishi cross-coupling with 4-iodobenzonitrile ($4k$) furnished the desired bisarylated bromothiophene $5o$ in 91% yield. Furthermore, a 2-anisyl-substituent on the dibromothiophene directs the Br/Mg-exchange in position 5 with a regioselectivity of $>99:1$ (entry 2). The cross-coupling product $5p$ is obtained after a Negishi cross-coupling of the magnesium species $3h$ with 4-iodobenzonitrile ($4k$) in 90% yield. Noteworthy, a satisfactory regioselectivity of 20:1 has also been achieved with heterocyclic substituents like a 2-pyridyl or a 2-thienyl group (entries 3 and 4). The subsequent cross-coupling reactions of the magnesium reagents $3i$ and $3j$ with the electrophiles $4h$ and $4l$ lead to the expected products $5q$ and $5r$ in 89% and 83% yield respectively. It is worth mentioning, that no chelating effect with the MeO- or Me$_2$N-substituent of the phenyl ring as well as with the pyridyl- or the thienyl-substituent could be observed. It is assumed that this might be a result of the too long distance between the bromine in position 2 of the thiophene ring and the heteroatom of the MeO- or Me$_2$N-group of the phenyl ring or the pyridyl- and the thienyl-substituent caused by the almost perpendicular orientation of the thiophene ring and the substituents in position 3.
### Table 3: Preparation of functionalized thiophenes via regioselectively generated heteroaryl-magnesium reagents of type 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent(^{[a]})</th>
<th>Electrophile</th>
<th>Product, Yield(^{[b]})</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{Br} \\
\text{Me}_2\text{N} \\
\text{S} \\
\text{Me} \\
\text{Br} \\
\text{MgBr}
\end{array}
\] \(3g\): 39:1 | \[
\begin{array}{c}
\text{NC} \\
\text{I}
\end{array}
\] | \[
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{S} \\
\text{Br} \\
\text{I} \\
\text{Me} \\
\text{CN}
\end{array}
\] 4k: 91%\(^{[c]}\) |
| 2     | \[
\begin{array}{c}
\text{MeO} \\
\text{Br} \\
\text{S} \\
\text{MgBr}
\end{array}
\] \(3h\): >99:1 | \[
\begin{array}{c}
\text{NC} \\
\text{I}
\end{array}
\] | \[
\begin{array}{c}
\text{MeO} \\
\text{Br} \\
\text{S} \\
\text{Me} \\
\text{CN}
\end{array}
\] 4k: 90%\(^{[c]}\) |
| 3     | \[
\begin{array}{c}
\text{Br} \\
\text{S} \\
\text{MgBr}
\end{array}
\] \(3i\): 20:1 | \[
\begin{array}{c}
\text{EtO}_2\text{C}
\end{array}
\] | \[
\begin{array}{c}
\text{Br} \\
\text{S} \\
\text{Me} \\
\text{CO}_2\text{Et}
\end{array}
\] 4h: 89%\(^{[c]}\) |
| 4     | \[
\begin{array}{c}
\text{Br} \\
\text{S} \\
\text{MgBr}
\end{array}
\] \(3j\)^{[d]}: 20:1 | \[
\begin{array}{c}
\text{OMe}
\end{array}
\] | \[
\begin{array}{c}
\text{Br} \\
\text{S} \\
\text{OMe}
\end{array}
\] 4l: 83%\(^{[c]}\) |

\(^{[a]}\) Obtained after exchange reaction with iPrMgCl\(\cdot\)LiCl (1a; 1.05 equiv) in THF at 0 °C in 1 h. Ratio of regioisomers determined by \(^1\)H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). \(^{[b]}\) Yield of analytically pure isolated product as determined by \(^1\)H NMR analysis. \(^{[c]}\) Obtained after a Negishi cross-coupling (ZnCl\(_2\) (1 equiv); then 4% Pd(PPh\(_3\))\(_4\)) with ArI (0.9 or 1.1 equiv). \(^{[d]}\) Exchange reaction performed at -20 °C in 1 h.

#### 1.2.1 TUNABLE REACTIVITY OF THIENYL-MAGNESIUM REAGENTS TOWARDS CARBONYL DERIVATIVES

By the reaction of magnesium species like \(3h\) with formyl-substituted heterocyclic iodides, it has been possible to either perform an addition to the aldehyde-group or a Negishi cross-coupling using the iodide substituent (Scheme 54). After transmetalation with ZnCl\(_2\) (0.5 equiv), the reaction with 5-iodofuran-2-carbaldehyde (4m) produces rapidly the corresponding alcohol 5s in 60% yield.\(^{148}\) By the addition of 4% Pd(PPh\(_3\))\(_4\)

\(^{148}\) Preliminary transmetalation with ZnCl\(_2\) (0.5 equiv) proved to be necessary for performing the addition to the carbonyl group. Otherwise only a I/Mg-exchange was observed.
the formyl group remains untouched and the Negishi cross-coupling takes place leading to \(5t\) in 76% yield (Scheme 2).

![Scheme 54: Tuneable reactivity of heteroarylmagnesium reagent 3h towards 4m by the presence or absence of Pd(PPh\(_3\))\(_4\).](image)

1.2.2 Further Functionalization of Monobromothiophenes

In order to exemplify the further functionalization of monobromo-thiophenes of type 5 obtained after the selective Br/Mg-exchange, the previously prepared monobromo-thiophene 5g has been submitted to a second Br/Mg-exchange reaction using iPrMgCl·LiCl (1a; 1.1 equiv) at ambient temperature. The resulting magnesium reagent 6 was readily used in different types of functionalization reactions (Scheme 55 and Table 4).

![Scheme 55: Further functionalization of cross-coupling product 5g via Br/Mg-exchange and subsequent reactions with different electrophiles.](image)

Thus, thienylmagnesium reagent 6 easily adds to aldehyde 4n providing the corresponding alcohol 7a in 77% yield (Table 4, entry 1). After transmetalation with ZnCl\(_2\) (1 equiv), a Negishi cross-coupling reaction with aryl iodide 4h using 5% Pd(PPh\(_3\))\(_4\) as catalyst leads to the expected product 7b in 73% yield (entry 2). Moreover, transmetalation with ZnCl\(_2\) (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN-2LiCl) with the acyl chloride 4o gives the functionalized ketone 7c in 70% yield (entry 3).
Table 4: Preparation of functionalized thiophenes of type 7 via regioselectively generated heteroarylmagnesium reagent 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent[^a]</th>
<th>Electrophile</th>
<th>Product, Yield[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>4n</td>
<td>7a: 77%</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>4h</td>
<td>7b: 73%[^c]</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>4o</td>
<td>7c: 70%[^d]</td>
</tr>
</tbody>
</table>

[^a] Obtained after exchange reaction with iPrMgCl·LiCl (1a; 1.1 equiv) in THF at 25 °C in 1 h. [^b] Yield of analytically pure isolated product as determined by $^1$H NMR analysis. [^c] Obtained after a Negishi cross-coupling (ZnCl$_2$ (1 equiv); then 5% Pd(PPh$_3$)$_4$) with ArI (0.9 equiv). [^d] Obtained after acylation (ZnCl$_2$ (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 equiv).

1.3 Regioselective Br/Mg-Exchange on Unsymmetrical 3,5-Dibromo-Pyridines Using iPrMgCl·LiCl

The regioselective Br/Mg-exchange has also been extended to various 3,5-dibromo-pyridine derivatives (Scheme 56). The corresponding magnesium-species 9a-d have been obtained in satisfactory regioselectivities up to 28:1 (Table 5). Subsequent Negishi cross-coupling reactions after transmetalation with ZnCl$_2$ lead to trisubstituted pyridine derivatives 10a-d in good yields (60-88%, entries 1-4). Both electron-poor and electron-rich aryl iodides have been used successfully. The cross-coupling reactions are usually completed within 1 h reaction time at 25 °C.

Scheme 56: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromo pyridines of type 8 using iPrMgCl·LiCl (1a).
Table 5: Preparation of functionalized pyridines of type 10 via regioselectively generated heteroarylmagnesium reagents of type 9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent (Conditions [T, t])(^{[a]})</th>
<th>Electrophile</th>
<th>Product, Yield(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Br-MgBr} (\text{CF}_3)) (-55 °C, 2 h): 27:1</td>
<td>(\text{Et}_2\text{C})</td>
<td>(\text{CO}_2\text{Et})</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Br-MgBr} (\text{OMe})) (-78 °C, 2 h): 13:1</td>
<td>(\text{Et}_2\text{C})</td>
<td>(\text{CO}_2\text{Et})</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Br-MgBr} (\text{SPh})) (0 °C, 1 h): 28:1</td>
<td>(\text{MeO})</td>
<td>(\text{Ar}+\text{CN})</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Br-MgBr} (\text{SPh})) (-65 °C, 1 h):(^{[d]}) 17:1</td>
<td>(\text{MeO})</td>
<td>(\text{Ar}+\text{CN})</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Obtained after exchange reaction with \(\text{iPrMgCl-LiCl (1a; 1.05 equiv)}\) in THF. Ratio of regioisomers determined by \(^1\text{H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv).}\)

\(^{[b]}\) Yield of analytically pure isolated product as determined by \(^1\text{H NMR analysis.}\)

\(^{[c]}\) Obtained after a Negishi cross-coupling (ZnCl\(_2\) (1 equiv); then 4% Pd(PPh\(_3\))\(_4\)) with ArI (0.9 equiv).\(^{[d]}\) Exchange reaction was performed using \(\text{iPr}_2\text{Mg-LiCl (0.55 equiv).}\)

1.4 REGIOSELECTIVE Br/Mg-EXCHANGE ON UNSYMMETRICAL DIBROMO-HETEROCYCLES USING IsitylMgBr·LiCl

Preliminary experiments showed that the regioselectivity of the Br/Mg-exchange reaction with \(\text{iPrMgCl-LiCl (1a)}\) on 2,5-dibromothiophenes with an alkyl substituent in position 3 resulted only in poor regioselectivities. Therefore, we envisioned that by increasing the steric hindrance of the Grignard reagent \(\text{R}^1\text{MgX-LiCl}\) of type 1 as well as its aggregation in solution by adding typical chelating amines as ligand \((\text{L}^1\) or \(\text{L}^2\)) would allow to improve the regioselectivity of the Br/Mg-exchange reaction (Scheme 57).
Thus, treatment of 2,5-dibromo-3-methylthiophene (11a) with iPrMgCl-LiCl (1a; 1.05 equiv) furnishes a regioisomeric mixture of the thienylmagnesium chlorides 12a and 13a in a ratio of 80:20 (Table 6, entry 1). However, the addition of tridentate ligands like N-[2-(dimethylamino)ethyl]-N,N',N'-trimethylethane-1,2-diamine (L¹; 1.05 equiv) or 2,2'-oxy-bis(N,N-dimethylethaneamine) (L²; 1.05 equiv) leading to the sterically more hindered complexes 1a·L¹ and 1a·L² significantly improves the regioisomeric ratio of the resulting magnesium reagents in favour of 12a (85:15 and 87:13; entries 2-3). Moreover, lower temperatures (-60 °C, 1 h) further increase the regioisomeric ratio up to 90:10 favouring the formation of 12a (entry 4). In comparison to secondary alkylmagnesium reagents like 1a, arylmagnesium bromides, such as mesitylmagnesium bromide (1b) or isitylmagnesium bromide (1c), displayed lower exchange reaction rates, but lead to a regioselectivity increase from 84:16 to 96:4 (compare entry 1 with entries 5 and 7). Remarkably, the addition of 2,2'-oxy-bis(N,N-dimethylethananime) (L²; 1.05 equiv) to LiCl-solubilized mesitylmagnesium bromide (1b; 1.05 equiv) convertes 11a (-20 °C, 12 h) predominantly into the Grignard species 12a with a regioisomeric ratio of 97:3 (entry 6). The even more sterically hindered exchange reagent isitylmagnesium bromide (1c) furnishes with 2,2'-oxy-bis(N,N-dimethylethanamine) (L², 1.05 equiv) at -10 °C in 16 h now a perfect regioselectivity ratio of >99:1 for 12a:13a (entry 8).\footnote{The regioisomer 13a was not observed in \textsuperscript{1}H NMR measurements of the hydrolyzed crude reaction mixture (HOAc, 10 equiv, -20 to 25 °C).}

These results were extended to various 2,5-dibromo-heterocycles (11b-d; entries 9-14). In each case the use of the sterically hindered Grignard reagent 1c in combination with (Me₂NCH₂CH₂)₂O (L²; 1.05 equiv) gives the best results (compare entries 9, 11, 13 with 10, 12 and 14). However, the use of the bulky reagent 1c·L² lead to significantly lower exchange rates and the Br/Mg-exchanges requires ca. 16 h compared to 1-6 h.

Table 6: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromoheterocycles bearing alkyl substituents using various complexed and uncomplexed Grignard reagents of type 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹MgX·LiCl</th>
<th>Ligand</th>
<th>Conditions [T, t][a]</th>
<th>Product of Type 10, Ratio Regioisomers[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>-</td>
<td>-20 °C, 20 min</td>
<td>12a: 80:20</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>L¹</td>
<td>-20 °C, 20 min</td>
<td>12a: 85:15</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>L²</td>
<td>-20 °C, 20 min</td>
<td>12a: 87:13</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>L²</td>
<td>-60 °C, 1 h</td>
<td>12a: 90:10</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>-</td>
<td>-20 °C, 12 h</td>
<td>12a: 84:16</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>L²</td>
<td>-20 °C, 12 h</td>
<td>12a: 97:3</td>
</tr>
<tr>
<td>7</td>
<td>1c</td>
<td>-</td>
<td>-10 °C, 12 h</td>
<td>12a: 96:4</td>
</tr>
<tr>
<td>8</td>
<td>1c</td>
<td>L²</td>
<td>-10 °C, 16 h</td>
<td>12a: &gt;99:1 [c]</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>L²</td>
<td>-10 °C, 20 min</td>
<td>12b: 85:15</td>
</tr>
<tr>
<td>10</td>
<td>1c</td>
<td>L²</td>
<td>-10 °C, 16 h</td>
<td>12b: &gt;99:1 [c]</td>
</tr>
<tr>
<td>11</td>
<td>1a</td>
<td>L²</td>
<td>-10 °C, 6 h</td>
<td>12c: 80:20</td>
</tr>
<tr>
<td>12</td>
<td>1c</td>
<td>L²</td>
<td>-10 °C, 16 h</td>
<td>12c: &gt;99:1</td>
</tr>
<tr>
<td>13</td>
<td>1a</td>
<td>L²</td>
<td>-10 °C, 6 h</td>
<td>12d: 75:25</td>
</tr>
<tr>
<td>14</td>
<td>1c</td>
<td>L²</td>
<td>-10 °C, 16 h</td>
<td>12d: 91:9</td>
</tr>
</tbody>
</table>

[a] Complete conversion as determined by GC analysis of an iodolyzed reaction aliquot. [b] Determined by ¹H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [c] The regioisomer of type 13 was not observed in ¹H NMR analysis of the hydrolyzed crude reaction mixture (HOAc, 10 equiv, -20 to 25 °C).
With these conditions in hand (1c·L², -10 °C, 16 h) various five-membered heterocyclic species have been selectively magnesiated with a regioselectivity of >99:1. Thus, 2,5-dibromo-3-methylthiophene (11a) undergoes readily the Br/Mg-exchange with isitylmagnesium bromide (1c, 1.05 equiv) in combination with 2,2'-oxy-bis(N,N-dimethylethanamine) (L², 1.05 equiv) at -10 °C in 16 h in perfect regioselectivity of >99:1. The reaction of the corresponding organomagnesium reagent 12a with di-tert-butyl dicarbonate (4d) leads to the ester-substituted thiophene derivative 14a in 83% yield (Scheme 58).

Scheme 58: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromothiophene 11a using isitylmgBr·LiCl (1c) in combination with ligand L².

After transmetalation with ZnCl₂ (1 equiv), the Negishi cross-coupling reaction of magnesium species 12a with ethyl 4-iodobenzoate (4h) using 4% Pd(PPh₃)₄ as catalyst furnishes the corresponding arylated thiophene 14b in 86% yield (Table 7, entry 1). Moreover, transmetalation of 12a with ZnCl₂ (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN·2LiCl) with thiophene-2-carbonyl chloride (4p) produces the functionalized ketone 14c in 85% yield (entry 2). Similarly, the transmetalation of 12a with ZnCl₂ (0.5 equiv) followed by CuCN·2LiCl (0.5 equiv) and the addition of chloranil (1.5 equiv) generates the substituted thiophenyl dimer 14d in 87% yield (entry 3). Furthermore, also the n-hexyl-substituted dibromothiophene 11b can be converted to the corresponding magnesium reagent 12b in perfect regioselectivity by applying this methodology. The addition of 12b to anisaldehyde (4e) leads to the expected alcohol 14e in 71% yield (entry 4). Moreover, the direct reaction of 4-methoxybenzenesulfinyl chloride (4q) with the heterocyclic magnesium-species 12b furnishes sulfoxide 14f in 70% yield (entry 5). Besides alkyl-substituted dibromothiophenes, also the methyl-substituted furan 11c has been regioselectively converted to its magnesium species 12c. Through transmetalation of 12c with ZnCl₂ (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN·2LiCl) with acyl chloride 4p the functionalized ketone 14g has been obtained in 79% yield (entry 6). The Pd-catalyzed cross-coupling of 12c with

4-iodobenzonitril (4k) furnishes after transmetalation with ZnCl₂ the desired product 14h in 78% yield (entry 7). Finally, alcohol 14i has been obtained in 73% yield by addition of magnesium species 12c to pivalaldehyde (4r) (entry 8).

Table 7: Preparation of functionalized five-membered heterocycles of type 14 via regioselectively generated heteroarylmagnesium reagents of type 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent[\textsuperscript{[a]}]</th>
<th>Electrophile</th>
<th>Product, Yield[\textsuperscript{[b]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12a: &gt;99:1</td>
<td>4h</td>
<td>14b: 86%[\textsuperscript{[c]}]</td>
</tr>
<tr>
<td>2</td>
<td>12a: &gt;99:1</td>
<td>4p</td>
<td>14c: 85%[\textsuperscript{[d]}]</td>
</tr>
<tr>
<td>3</td>
<td>12a: &gt;99:1</td>
<td>-</td>
<td>14d: 87%[\textsuperscript{[e]}]</td>
</tr>
<tr>
<td>4</td>
<td>12b: &gt;99:1</td>
<td>4e</td>
<td>14e: 71%</td>
</tr>
<tr>
<td>5</td>
<td>12b: &gt;99:1</td>
<td>4q</td>
<td>14f: 70%</td>
</tr>
<tr>
<td>6</td>
<td>12c: &gt;99:1</td>
<td>4p</td>
<td>14g: 79%[\textsuperscript{[d]}]</td>
</tr>
</tbody>
</table>
B. RESULTS AND DISCUSSION

Remarkably, also the tribromothiophene 11e undergoes a smooth Br/Mg-exchange with perfect regioselectivity. The reaction of 11e with isitylmagnesium bromide (1c, 1.05 equiv) in combination with 2,2'-oxy-bis(N,N-dimethylethanamine) (L², 1.05 equiv) proceeds at 0 °C within 1 h furnishing the magnesium species 12e in >99:1 regioselectivity (Scheme 59). In this case, the exchange reaction is faster compared to the dibromo-analogon 11a due to the inductive effect of the additional bromine atom in position 3 of the thiophene ring. After transmetalation of 12e with ZnCl₂ a Pd-catalyzed cross-coupling with 4-iodobenzonitril (4k) furnishes the tetrasubstituted thiophene 14j in 77% yield.

Scheme 59: Regioselective Br/Mg-exchange on unsymmetrical 2,3,5-tribromothiophene 11e using isitylMgBr·LiCl (1c) in combination with ligand L².

Moreover, transmetalation of 12e with ZnCl₂ (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN·2LiCl) with the acyl chloride 4s gives the functionalized ketone 14k in 86% yield (Table 8, entry 1). The addition reaction of 12e and anisaldehyde (4e) produces the desired alcohol 14l in 88% yield (entry 2). Finally, the direct reaction of 4-methoxybenzenesulfinyl chloride (4q) with the heterocyclic magnesium-species 12e furnishes sulfoxide 14m in 94% yield (entry 3).
Table 8: Preparation of functionalized five-membered heterocycles of type 14 via regioselectively generated heteroarylmagnesium reagents of type 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent[^a]</th>
<th>Electrophile</th>
<th>Product, Yield[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12e: &gt;99:1</td>
<td>4s</td>
<td>14k: 86%[^c]</td>
</tr>
<tr>
<td>2</td>
<td>12e: &gt;99:1</td>
<td>4e</td>
<td>14l: 88%</td>
</tr>
<tr>
<td>3</td>
<td>12e: &gt;99:1</td>
<td>4q</td>
<td>14m: 94%</td>
</tr>
</tbody>
</table>

[^a] Obtained after exchange reaction with 1c (1.05 equiv) and L^2 (1.05 equiv) in THF at 0 °C in 1 h. Ratio of regioisomers determined by ^1^H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [^b] Yield of analytically pure isolated product as determined by ^1^H NMR analysis. [^c] Obtained after acylation (ZnCl_2 (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 or 1.2 equiv).

Interestingly, the Br/Mg-exchange reaction of 2,5-dibromo-3-methoxythiophene with isitylmagnesium bromide (1c) in combination with 2,2'-oxy-bis(N,N-imethylethanamine) leads to the 2-magnesiated thiophene 12f (Scheme 60) and not to the 5-magnesiated one (as for the other dibromo-thiophene derivatives 11a-c and 11e). It is assumed that this selectivity resulted from a preliminary coordination of the bulky magnesium reagent to the oxygen of the methoxy substituent. This complexation seems to be essential for the Br/Mg-exchange reaction to proceed. In contrast, by using iPrMgCl·LiCl (1a) in the exchange reaction, the opposite selectivity has been observed (4:1 ratio in favour of the 5-magnesiated thiophene).[^154] This might be a result of the high reactivity of iPrMgCl·LiCl (1a) that allows the exchange reaction to proceed without prior chelation in an ethereal solvent like THF.

[^154] The exchange reaction was carried out under the same conditions as described in Scheme 58 and Table 7 but at -78 °C. Higher temperatures deteriorated the ratio. At ambient temperature, the observed ratio was 2.4:1 in favour of the 5-magnesiated derivative.
Scheme 60: Regioselective Br/Mg-exchange on 2,5-dibromo-3-methoxythiophene 11f using isitylMgBr-LiCl (1c) in combination with ligand L\textsuperscript{2}.

Thus, thienylmagnesium reagent 12f easily adds to aldehyde 4a providing the corresponding alcohol 14n in 73% yield (Table 9, entry 1). After transmetalation with ZnCl\textsubscript{2} (1 equiv), a Negishi cross-coupling reaction with aryl iodide 4k using 5% Pd(PPh\textsubscript{3})\textsubscript{4} as catalyst leads to the expected product 14o in 69% yield (entry 2). Moreover, transmetalation with ZnCl\textsubscript{2} (1 equiv) followed by a Cu(i)-catalyzed acylation (10% CuCN·2LiCl) with the acyl chloride 4o gives the functionalized ketone 14p in 66% yield (entry 3).

Table 9: Preparation of functionalized five-membered heterocycles of type 14 via regioselectively generated heteroarylmagnesium reagents of type 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent\textsuperscript{[a]}</th>
<th>Electrophile</th>
<th>Product, Yield\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12f: &gt;99:1</td>
<td>4a</td>
<td>14n: 73%</td>
</tr>
<tr>
<td>2</td>
<td>12f: &gt;99:1</td>
<td>4k</td>
<td>14o: 69%\textsuperscript{[c]}</td>
</tr>
<tr>
<td>3</td>
<td>12f: &gt;99:1</td>
<td>4o</td>
<td>14p: 66%\textsuperscript{[d]}</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Obtained after exchange reaction with 1c (1.05 equiv) and L\textsuperscript{2} (1.05 equiv) in THF at -10 °C in 16 h. Ratio of regioisomers determined by \textsuperscript{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). \textsuperscript{[b]} Yield of analytically pure isolated product as determined by \textsuperscript{1}H NMR analysis. \textsuperscript{[c]} Obtained after a Negishi cross-coupling (ZnCl\textsubscript{2} (1 equiv); then 4% Pd(PPh\textsubscript{3})\textsubscript{4}) with ArI (0.9 or 1.2 equiv). \textsuperscript{[d]} Obtained after acylation (ZnCl\textsubscript{2} (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 or 1.2 equiv).
The regioselective Br/Mg-exchange with $1c\cdot L^2$ has also been extended to 3,5-dibromo-2-(trimethylsilyl)pyridine (15) leading to the corresponding magnesium reagent 16 at -25 °C within 2 h (Scheme 61). The subsequent Negishi cross-coupling reactions after transmetalation with ZnCl$_2$ led to trisubstituted pyridine derivatives 17a-b in satisfactory yields (60-61%, Scheme 61).

Scheme 61: Preparation of functionalized pyridines of type 17 via regioselectively generated heteroarylmagnesium reagent 16.
2. ONE-POT PREPARATION OF MAGNESIUM DI(HETERO)ARYL- AND DIALKENYLBORONATES FOR SUZUKI-MIYURA CROSS-COUPlings

2.1 INTRODUCTION

Organoboron derivatives have found broad applications for the performance of Suzuki-Miyaura cross-couplings. In particular, various boronic acids, esters and their derivatives, such as trifluoroborates, MIDA boronates or DAN reagents have been used very successfully as synthetic tools in the preparation of natural products and pharmaceutically active compounds. Shultz et al. for example described a convenient synthetic route for the preparation of a Bradykinin B1 antagonist including a Suzuki-Miyaura cross-coupling as key step (Scheme 62). Bradykinin B1 is a kinin responsible for the mediation of physiological processes accompanying acute and chronic pain and inflammation.

![Scheme 62: Suzuki-Miyaura cross-coupling as key step in the synthesis of a Bradykinin B1 antagonist.](image)

However, the known methods for preparation of the aforementioned organoboron reagents suffer from major drawbacks, such as multi-step syntheses, low atom-economy, expensive transition-metal catalysis or low tolerance towards functional groups. In general, most arylboronic compounds are prepared via Li- or Mg-organometallics in a

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two-step process, although direct transition metal-catalyzed borylations can be realized (Scheme 63).

Scheme 63: Common syntheses of arylboronate esters and acids.

In the search of a convenient, general and atom-economic method for the preparation of boronic derivatives suitable for cross-coupling reactions, we investigated a one-pot procedure using inexpensive aryl bromides, magnesium as a low-cost reducing agent with little toxicity and trialkylborate as cheap boron source. Thus, we utilized the accelerating effect of LiCl as additive in direct metal insertions allowing the presence of a broad range of sensitive functional groups in organometallic reagents recently reported by Knochel et al.\textsuperscript{21,64,159} 2-bromo-4-fluorobenzonitrile for instance undergoes smoothly a direct Mg-insertion in the presence of LiCl furnishing the corresponding organo-magnesium compound at room temperature tolerating the nitril-group (Scheme 64).

Scheme 64: LiCl-mediated preparation of (2-cyano-5-fluorophenyl)magnesium bromide and subsequent Negishi cross-coupling.

---


Based on this methodology, we explored various borate sources for the \textit{in situ} trapping of the generated organomagnesium intermediate. The treatment of methyl 2-bromobenzoate (18a) with commercially available Mg turnings (1.6 equiv), B(OBu)$_3$ (1.0 equiv) and LiCl (1.1 equiv) furnishes within 1 h the magnesium arylboronate 19a in full conversion at ambient temperature. Its cross-coupling with 4-bromobenzonitrile (22a) using 4\% Pd(dppf)Cl$_2$ and Cs$_2$CO$_3$ (2 equiv) in a 1:1 THF/EtOH mixture provides the desired cross-coupling product 21a in 65\% yield (Scheme 65).

Scheme 65: Preparation of magnesium arylboronate 19a and subsequent Suzuki-Miyaura cross-coupling.

Interestingly, the alternative conversion of 18a to the corresponding zinc reagent using Mg turnings (1.6 equiv), ZnCl$_2$ (1.0 equiv) and LiCl (1.1 equiv) in THF\textsuperscript{21} requires 3 h reaction time showing that the presence of B(OBu)$_3$ significantly accelerates the Mg-insertion. Besides B(OBu)$_3$ also other boron compounds such as B(OMe)$_3$, B(OEt)$_3$, B(OiPr)$_3$, B(OAc)$_3$, and even NaB(OMe)$_4$ or LiB(OMe)$_4$, proved to be feasible for \textit{in situ} trapping of the magnesium reagent. However B(OBu)$_3$ was found to be the most promising boron source since no transesterification reactions with sensitive substrates like methyl 2-bromobenzoate (18a) were observed.

\subsection*{2.2 Preparation of Magnesium Diarylboronates via Magnesium-Insertion for Suzuki-Miyaura Cross-Couplings}

With these results in hands, the methodology has been optimized considering both sufficiently fast reaction times while using only minimal amounts of the boron source. A better atom economy can be achieved without a loss of yield by using 0.5 equiv of B(OBu)$_3$ and forming therefore magnesium diarylboronates of type 20 (Scheme 66).\textsuperscript{161}

Remarkably, both aryl groups (Ar$^1$) are transferred under typical Suzuki-Miyaura cross-
coupling conditions using various aryl halides or pseudo-halides of type \( \text{Ar}^2-X \) (22-24, \( \text{X} = \text{Cl}, \text{Br}, \text{I}, \text{ONf}, \text{OTs}, \text{OTf}\)).

\[
\begin{array}{cccc}
\text{Ar}^1-\text{Br} & \text{B(OBu)}_3, \text{Mg}, \text{LiCl} & \text{THF, 25 °C, 1 h} & \frac{1}{2} \left[ (\text{Ar}^1)_{2}\text{B(OBu)}_2\text{MgBr} \right] \\
18 (1 \text{ equiv}) & 20: >85\% & \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{Ar}^2-X (22-24, 0.8 \text{ equiv}) & \text{Pd(dppf)}\text{Cl}_2, \text{Cs}_2\text{CO}_3 & \text{THF/EtOH/DMF} & 65 °C, 2-12 \text{ h} \\
21: 70-95\% & \\
\end{array}
\]

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

**Scheme 66:** General equation for the synthesis and cross-coupling of magnesium diarylboronates of type 20.

Thus, under typical reaction conditions, the sensitive Boc-protected bromophenol 18b reacted with B(OBu)_3 (0.5 equiv), Mg (1.6 equiv) and LiCl (1.1 equiv) in THF within 1 h at 25 °C providing the magnesium diarylboronate 20a (>85% yield, Scheme 67). Its Pd-cross-coupling with the bromobenzamide 22b proceeds within 3 h at 65 °C using 4% Pd(dppf)Cl_2 and Cs_2CO_3 (2 equiv) in a 4:4:1 THF/EtOH/DMF mixture and leads to the functionalized biphenyl 21b in 91% yield clearly demonstrating that both aryl groups of 20a are available for the cross-coupling.

**Scheme 67:** Preparation and subsequent cross-coupling of magnesium diarylboronate 20a.

This behaviour was general and a wide range of diarylboronates of type 20 bearing various functional groups (ester, cyanid, Boc-, (thio)methoxy-, amino- or silyl-group) were prepared conveniently at 25 °C within 15 min to 1 h. The subsequent cross-coupling reactions of the magnesium diarylboronates 20b-i with a broad variety of aryl and heteroaryl bromides as electrophiles produce under standard conditions the desired products 21c-k in excellent yields (Table 10). In particular, 1-bromo-bis(trifluoromethyl)-benzene (18c) was efficiently converted into the corresponding diarylboronate 20b via the direct magnesium insertion (Mg (1.6 equiv), LiCl (1.1 equiv))

---


in the presence of trisbutylborate (B(OBu)_3 (0.5 equiv)). Subsequent *Suzuki-Miyaura* cross-coupling with 5-bromovanillin (22c) bearing an aldehyde-, a methoxy- and a hydroxy-function furnishes successfully the substituted vanillin 21c in 83% yield (entry 1). The diarylboronate 20c bearing a nitril group has been prepared under standard conditions and undergoes smoothly the cross-coupling reaction with 4-bromoacetophenone (22d) leading to the functionalized biphenyl 21d in 82% yield (entry 2). Furthermore, using the same conditions, the dithioanisylboronate 20d readily furnishes after the Pd-catalyzed cross-coupling the desired products 21e and 21f in 87-92% yield (entries 3 and 4). Noteworthy, the unprotected 5-bromoindole (22e) could be used as electrophile without hempering the cross-coupling. Moreover, also the corresponding diarylboronate 20e of 3-bromophenyl diethylcarbamate (18f) has been successfully cross-coupled with the secondary amide 22b bearing an acidic proton. The desired product 21g has been obtained in 90% yield (entry 5). Also the ester-substituted bromopyridine 22f could be successfully applied as electrophile. The fluoro- and amino-substituted diarylboronates 20f and 20g react readily in the cross-coupling reaction furnishing the corresponding products 21h and 21i in 79% and 90% yield respectively (entries 6 and 7). The cross-coupling reactions of the diarylboronates 20h and 20i with the electron-poor electrophiles 22g and 22h proceed well under standard conditions and the highly substituted biphenyls 21j and 21k have been obtained in high yields (entries 8 and 9).

Table 10: *Suzuki-Miyaura* cross-couplings performed with magnesium diarylboronates of type 20 and aryl bromides of type 22 as electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar_2B(OBu)_2MgBr (conditions [T, t])</th>
<th>Electrophile</th>
<th>Product (t, Yield[a])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20b (25 °C, 15 min)</td>
<td>22c</td>
<td>21c (12 h, 83%)</td>
</tr>
<tr>
<td>2</td>
<td>20c (25 °C, 1 h)</td>
<td>22d</td>
<td>21d (12 h, 82%)</td>
</tr>
</tbody>
</table>
B. RESULTS AND DISCUSSION

3. **20d** (25 °C, 1 h)

4. **20d** (25 °C, 1 h)

5. **20e** (25 °C, 1 h)

6. **20f** (25 °C, 1 h)

7. **20g** (25 °C, 1 h)

8. **20h** (25 °C, 1 h)

9. **20i** (25 °C, 1 h)

[a] Yield of isolated, analytically pure product.
As shown in Scheme 68, also alkenyl bromides can be used as electrophiles in the *Suzuki-Miyaura* cross-coupling. Thus, the highly functionalized styrene derivative 21l has been obtained via the Pd-catalyzed cross-coupling of dithioanisylboronate 20d and alkenyl bromide 22i in 75% yield.

![Scheme 68: Preparation and subsequent cross-coupling of magnesium diarylboronate 20d with the alkenyl bromide 22i.](image)

Although aryl bromides have been used mostly as electrophiles (Table 10), also heteroaryl chlorides readily undergo the *Suzuki-Miyaura* cross-coupling with diarylboronates of type 20 without any further optimization (Scheme 69). Thus, dianisylboronate 20j readily furnishes after the Pd-catalyzed cross-coupling with 2-chloronicotinonitrile (23a) the desired product 21m in 78% yield. Moreover, the highly functionalized pyridine derivative 21n could be synthesized in high yield via the Pd-catalyzed reaction of the trimethylsilyl-substituted diarylboronate 20k with the chloropyridine 23b.

![Scheme 69: Preparation and subsequent cross-coupling of magnesium diarylboronates 20j and 20k with aryl chlorides of type 23 as electrophiles.](image)

Furthermore, also aryl pseudo-halides proved to be versatile electrophiles for the cross-coupling reaction with diarylboronates of type 20 (Table 11). The diarylboronate 20a prepared from the corresponding Boc-protected bromophenol 18b undergoes smoothly the Pd-catalyzed cross-coupling with nonaflate 24a and furnishes the desired...
product \(21o\) in 78% yield (entry 1). Also the tosylate \(24b\) has been successfully employed in the cross-coupling reaction with the trifluoromethyl-substituted diarylboronate \(20l\) leading to the functionalized quinoline derivative \(21p\) in 70% yield (entry 2). Finally, dithioanisyl-boronate \(20d\) readily reacts in the Pd-catalyzed cross-coupling with the triflate \(24c\) to the functionalized biphenyl \(21q\) in 81% yield (entry 3).

Table 11: Suzuki-Miyaura cross-couplings performed with magnesium diarylboronates of type \(20\) and aryl pseudo-halides of type \(24\) as electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar(_2)B(OBu)(_2)MgBr (conditions [T, t])</th>
<th>Electrophile</th>
<th>Product (t, Yield(^{[a]}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(20a) (25 °C, 1 h)</td>
<td>(24a)</td>
<td>(21o) (3 h, 78%)</td>
</tr>
<tr>
<td>2</td>
<td>(20l) (25 °C, 1 h)</td>
<td>(24b)</td>
<td>(21p) (12 h, 70%)</td>
</tr>
<tr>
<td>3</td>
<td>(20d) (25 °C, 1 h)</td>
<td>(24c)</td>
<td>(21q) (12 h, 81%)</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Yield of isolated, analytically pure product.

In some cases, when the aryl bromide is sterically hindered (18n) or strongly electron-deficient (18o and 18p), the preparation of the \(\text{mono-arylboronate} (\text{ArB(OBu)}_3\text{MgBr})\) was preferable\(^{165}\) leading to a significant yield improvement in the subsequent Suzuki-Miyaura cross-coupling (Table 12). Thus, \(\text{mono-arylboronate} 19b\), containing the sterically demanding Boc-protected alcohol in meta-position of the aryl, furnishes after the Pd-catalyzed cross-coupling with the unprotected bromoaniline \(22j\) the highly

\(^{165}\) This proved to be necessary in less than 10% of all cases studied.
functionalized biphenyl 21r in 86% yield (entry 1). Noteworthy, the alcohol group gets unprotected during the cross-coupling reaction leading to the free phenol derivative. The mono-arylboronate 19c of the highly electron-deficient aryl bromide 18o undergoes a smooth cross-coupling reaction with ethyl 4-bromobenzoate (22k) leading to the desired product 21s in 72% yield (entry 2). Analogously, also for tert-butyl 4-bromobenzoate (18p) the mono-arylboronate 19d reacts more efficiently than the corresponding diarylboronate with the electrophiles 22l and 22m in the cross-coupling reaction. For this reason, the resulting functionalized biphenyl derivates 21t and 21u could be obtained in excellent yields (entries 3 and 4).

Table 12: Suzuki-Miyaura cross-couplings performed with magnesium mono-arylboronates of type 19 and aryl bromides of type 22 as electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArB(OBu)₃MgBr (conditions [T, t])</th>
<th>Electrophile</th>
<th>Product (t, Yield[a])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19b (25 °C, 1 h)[b]</td>
<td>22j</td>
<td>21r (6 h, 86%)</td>
</tr>
<tr>
<td>2</td>
<td>19c (25 °C, 1 h)[b]</td>
<td>22k</td>
<td>21s (12 h, 72%)</td>
</tr>
<tr>
<td>3</td>
<td>19d (25 °C, 1 h)[b]</td>
<td>22l</td>
<td>21t (12 h, 89%)</td>
</tr>
<tr>
<td>4</td>
<td>19d (25 °C, 1 h)[b]</td>
<td>22m</td>
<td>21u (4 h, 78%)</td>
</tr>
</tbody>
</table>

[a] Yield of isolated, analytically pure product. [b] 1 equiv of B(OBu)₃ was used.
2.3 Preparation of Magnesium Dialkenylboronates via Magnesium-Insertion for Suzuki-Miyaura Cross-Couplings

The method described above also proved to be suitable for alkenyl halides. Suzuki-Miyaura cross-coupling reactions with mono- and dialkenylboronic derivatives such as 19e-f and 20m proceed in high yields. Thus, the treatment of cyclohexenyl iodide (25a) with B(OBu)₃ (1 equiv), Mg (1.6 equiv) and LiCl (1.1 equiv) in THF at 25 °C produces within 1 h the corresponding magnesium alkenyl-boronate 19e in >85% yield (Scheme 70). Similarly, the reaction of 2-iodostyrene (25b) furnishes under the same conditions the desired alkenylboronate 19f (>85% yield). Cross-coupling of 6a-b with 4-bromo-benzonitrile (22a) furnishes the functionalized alkenes 26a-b in 71% and 95% yield respectively.

![Scheme 70: Preparation and subsequent cross-coupling of magnesium alkenylboronates 19e and 19f with aryl bromide 22a as electrophile.](image)

The magnesium dialkenylboronate 20m was prepared from 1-bromostyrene (25c), B(OBu)₃ (0.5 equiv), Mg (1.6 equiv) and LiCl (1.1 equiv). Pd-catalyzed cross-coupling with ethyl 4-bromobenzoate (22k) under standard conditions gives the diaryl ethylene 26c in 95% yield (Scheme 71).

![Scheme 71: Preparation and subsequent cross-coupling of magnesium alkenylboronate 20m with aryl bromide 22k as electrophile.](image)
2.4 Preparation of Magnesium Diheteroarylboronates via Magnesium-Insertion for Suzuki-Miyaura Cross-Couplings

Remarkably, the aforementioned method could also be applied in the synthesis of functionalized diheteroarylboronates without any further optimization. Thus, 3-bromo-benzofuran (27a) readily reacts with Mg (1.6 equiv) and LiCl (1.1 equiv) in the presence of B(OBu)₃ (0.5 equiv) in THF within 1 h at room temperature to the diheterocyclic magnesium boronate 20n in >85% yield (Scheme 72). A subsequent Suzuki-Miyaura cross-coupling reaction with the aryl bromide 22n furnishes the corresponding heterocyclic product 28a in 84% yield. As expected, the unprotected amine did not hamper the cross-coupling reaction.

Furthermore, the reaction of diheteroarylboronate 20n with aryl bromide 22o leads to the desired substituted benzofuran 28bf in 86% yield (Table 13, entry 1). The related diheterocyclic magnesium boronates 20o and 20p have been obtained in an analogous approach. 3-bromothiophene (27b) and 3-bromobenzothiophene (27c) provide after LiCl-mediated Mg-insertion with magnesium turnings (1.6 equiv) and in situ borylation with B(OBu)₃ (0.5 equiv) the corresponding diheteroarylboronates 20o and 20p in >85% yield. The Suzuki-Miyaura cross-coupling reaction of 20o with the aryl bromides 22g and 22p furnish the highly functionalized heterocycles 28c and 28d in 72% and 79% yield, respectively (entries 2 and 3). Finally, also diheteroarylboronate 20p undergoes readily a Pd-catalysed reaction with the aryl bromide 22b and produces the substituted benzothiophene 28e in 72% yield (entry 4).
Table 13: *Suzuki-Miyaura* cross-couplings performed with magnesium diheteroarylboronates of type 20 and aryl bromides of type 22 as electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Het₂B(OBu)₂MgBr (conditions [T, t])</th>
<th>Electrophile</th>
<th>Product (t, Yield[a])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20n (25 °C, 30 min)</td>
<td>22o</td>
<td>28b (3 h, 86%[b])</td>
</tr>
<tr>
<td>2</td>
<td>20o (0 °C, 30 min)</td>
<td>22g</td>
<td>28c (3 h, 72%[b])</td>
</tr>
<tr>
<td>3</td>
<td>20o (0 °C, 30 min)</td>
<td>22p</td>
<td>28d (12 h, 79%[b])</td>
</tr>
<tr>
<td>4</td>
<td>20p (0 °C, 1 h)</td>
<td>22b</td>
<td>28e (12 h, 77%[b])</td>
</tr>
</tbody>
</table>

[a] Yield of isolated, analytically pure product. [b] Obtained after Pd-catalyzed cross-coupling (4% Pd(dppf)Cl₂, Cs₂CO₃ (2 equiv), THF/EtOH/DMF (4:4:1), 65 °C).

For 4-bromo-3-methylisoxazole (27d) the corresponding diheteroarylboronate showed only poor reactivity in the *Suzuki-Miyaura* cross-coupling. Therefore, the mono-heteroarylboronate 19g has been synthesized using magnesium turnings (1.6 equiv), B(OBu)₃ (1.0 equiv) and LiCl (1.1 equiv) and has been submitted to the Pd-catalysed cross-coupling reaction. The functionalized heterocyclic derivate 28f could then be obtained in a good yield (Scheme 73).

Scheme 73: Preparation and subsequent cross-coupling of magnesium mono-heteroarylboronate 19g and subsequent cross-coupling with aryl bromide 22k as electrophile.
Remarkably, not only heterocyclic bromides can be converted to their corresponding diheteroarylboronates, also 2-chlorothiophene (27e) provides after LiCl-mediated Mg-insertion with magnesium turning (1.6 equiv) and *in situ* borylation with B(ODB)₃ (0.5 equiv) the corresponding dithienylboronate 20q in >85% yield (Scheme 74). The subsequent *Suzuki-Miyaura* cross-coupling with the chloropyridine derivative 23c furnishes the highly functionalized thiophene 28g in 86% yield.

![Scheme 74: Preparation and subsequent cross-coupling of magnesium dithienylboronate 20q and subsequent cross-coupling with aryl chloride 23c as electrophile.](image)

Furthermore, under typical reaction conditions, also bromopyridine derivatives react effectively to the corresponding dipyridylboronates. Thus, 3-bromopyridine 27f is converted to its dipyridylboronate 20r in >85% yield within 1 h by using B(ODB)₃ (0.5 equiv), magnesium turnings (1.6 equiv) and LiCl (1.1 equiv) in THF at ambient temperature (Table 14, entry 1). The *Suzuki-Miyaura* cross-coupling employing the substituted 2-bromo-furan 22q as electrophile leads to the corresponding cross-coupling product 28h in 82% yield. The related dipyridyl magnesium boronates 20s and 20t have been obtained in an analogous approach. 5-bromo-2-methoxypyridine (27g) and 5-bromo-2-chloropyridine (27h) provided after LiCl-mediated Mg-insertion with magnesium turnings (1.6 equiv) and *in situ* borylation with B(ODB)₃ (0.5 equiv) the functionalized dipyridylboronates 20s and 20t in >85% yield. The subsequent *Suzuki-Miyaura* cross-coupling reaction of 20s with the aryl bromide 22r furnishes the highly functionalized pyridine derivative 28i 85% yield (entry 2). The dipyridylboronate 20t undergoes readily a Pd-catalysed reaction with the heteroaryl bromide 22s and produces the substituted pyridine 28j in 72% yield (entry 3).
Table 14: *Suzuki-Miyaura* cross-couplings performed with magnesium dipyridylboronates of type 20 and aryl bromides of type 22 as electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Het$_2$B(OBu)$_2$MgBr (conditions [T, t])</th>
<th>Electrophile</th>
<th>Product (t, Yield$^a$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B(OBu)$_2$MgBr (25 °C, 1 h)</td>
<td>22q$^b$</td>
<td>28h (24 h, 82%$^c$)</td>
</tr>
<tr>
<td>2</td>
<td>B(OBu)$_2$MgBr (25 °C, 1 h)</td>
<td>22r</td>
<td>28i (12 h, 85%$^d$)</td>
</tr>
<tr>
<td>3</td>
<td>B(OBu)$_2$MgBr (25 °C, 1 h)</td>
<td>22s$^b$</td>
<td>28j (12 h, 72%$^e$)</td>
</tr>
</tbody>
</table>

[a] Yield of isolated, analytically pure product. [b] 0.7 equiv of electrophile were used. [c] Obtained after Pd-catalyzed cross-coupling (4% Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, 10H$_2$O (1.3 equiv), THF/dioxane/H$_2$O (4:4:1), 110 °C). [d] Obtained after Pd-catalyzed cross-coupling (4% Pd(dppf)Cl$_2$, Cs$_2$CO$_3$ (2 equiv), THF/EtOH/DMF (4:4:1), 65 °C). [e] Obtained after Pd-catalyzed cross-coupling (4% Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$ (2 equiv), THF/EtOH (1:1), 65 °C).
B. RESULTS AND DISCUSSION

3. PREPARATION OF $\alpha$-SUBSTITUTED $\beta,\gamma$-UNSATURATED KETONES AND ESTERS VIA THE DIRECT ADDITION OF SUBSTITUTED ALLYLIC ZINC REAGENTS

3.1 INTRODUCTION

The reaction of allylic organometallic reagents with carbonyl derivatives is of high importance in synthetic organic chemistry.\(^{166}\) Since allylic moieties can be found in a plethora of natural occurring products, allylic organometallics play a significant role in their total synthesis (Figure 10).\(^{167}\) Psymberin for example has been isolated from the sea sponge \textit{Psammocinia sp.} and shows a high and selective cytotoxic activity against different human cancer cell lines.\(^{168}\) In 2005 De Brabander and coworkers described its first total synthesis.\(^{169}\)

\[\text{Psymberin} \quad (+)\text{-Strictifolione} \quad \text{Salinosporamide A}\]

Figure 10: Naturally occurring substrates bearing allylic moieties.

\[\text{Cossy et al.} \text{ used a stereoselective allyltitanation as key step in the synthesis of (}+)\text{-Strictifolione, which was isolated from the stem bark of \textit{Cryptocaria strictifolia} growing in Indonesian tropical rainforests.}^{170,171}\text{ (+}-\text{Strictifolione exhibits a potent antifungal activity. Salinosporamide A was found in the marine actinomycete}\]


Salinospora tropica distributed in ocean sediments around the Bahamas. One of the key steps of its synthesis reported by Corey and coworkers was the reaction of 2-cyclohexenylzinc chloride with a chiral aldehyde bearing three stereogenic centers. In this process, two stereogenic centers were formed stereoselectively (20:1 dr) with the right configuration.

Especially allylic zinc reagents are very versatile organometallic species since their behaviour is much more predictable than the behaviour of the corresponding allylic magnesium or lithium reagents. Moreover, the magnesium and lithium compounds suffer from their instability as well as from their difficult and inconvenient preparation.

Cyclohexenylzinc bromide for instance is readily prepared from zinc foil and the corresponding bromide at -15 °C in 60% yield (Scheme 75). However, higher yields are prevented by accompanying side reactions such as homocoupling and hydrolysis.

Scheme 75: Preparation of cyclohexenylzinc bromide from zinc and its corresponding bromide.

Recently Knochel and coworkers have reported the use of commercially available zinc powder in the presence of lithium chloride in THF as a cheap and convenient method for the synthesis of substituted allylic zinc reagents from allyl halides or phosphonates reducing unwanted side reactions on a minimum. Thus, the LiCl-mediated zinc insertion provided cyclohexenylzinc chloride in 84% yield (Scheme 76).
Scheme 76: LiCl-mediated preparation of cyclohexenylzinc chloride.

β,γ-Unsaturated ketones and esters are versatile building blocks in organic chemistry.\textsuperscript{179} Although a number of synthetic methods have been disclosed, only a few have been proven practical and useful. The acylation of olefins for example allows the synthesis of β,γ-unsaturated ketones, but generates α,β-unsaturated ketones as side-products and suffers from poor functional group tolerance (Scheme 77).\textsuperscript{180}

Scheme 77: Preparation of β,γ-unsaturated ketones via acylation of olefines.

The reaction of various allylic organometallics with acyl halides has also been reported in literature. Silicon,\textsuperscript{181} tin,\textsuperscript{182} copper,\textsuperscript{183} rhodium,\textsuperscript{184} manganese,\textsuperscript{185} titanium,\textsuperscript{186} mercury,\textsuperscript{187} cadmium,\textsuperscript{188} and indium\textsuperscript{189} are some of the metal powders used in the synthesis of β,γ-unsaturated ketones. But these protocols are mostly neither simple nor straightforward and are therefore of limited application. Since the reaction of allylic zinc reagents with acid chlorides\textsuperscript{190} or nitriles\textsuperscript{191} seemed to be a promising approach, our focus

\textsuperscript{179} M. Demuth, G. Mikhail, Synthesis 1989, 145.
lay on the investigation of addition reactions using the now readily available substituted allylic zinc reagents. This led finally to the development of a simple and flexible method for the synthesis of α-substituted β,γ-unsaturated ketones and esters through the addition of substituted allylic zinc reagents to a broad range of acid chlorides and chloroformates.

3.2 PREPARATION OF SUBSTITUTED ALLOYLIC ZINC REAGENTS

As preliminary experiments had shown, the LiCl-mediated zinc insertion into allylic halides provided the corresponding allylic zinc reagents almost without formation of homocoupling products (Scheme 78).

![Scheme 78: Preparation of allylic zinc reagents 30 from allylic halides 29 via LiCl-mediated zinc insertion.](image)

Thus, under optimized conditions but-2-en-1-ylzinc bromide (30a) is formed within 1 h at 25 °C in 83% yield by dropwise addition of 1-bromobut-2-ene (29a, 1 equiv) to a suspension of commercially available zinc powder (2.0 equiv) and dry lithium chloride (1.1 equiv) in THF (Scheme 79).

![Scheme 79: LiCl-mediated preparation of the substituted allylic zinc organometallics 30 by direct insertion of zinc powder (yields determined by iodometric titration).](image)

This procedure has been successfully extended to other allylic halides leading to cinnamylzinc chloride (30b, 86%), (3-methylbut-2-en-1-yl)zinc bromide (30c, 92%), (3,7-dimethylocta-2,6-dien-1-yl)zinc bromide (30e, 83%) and cyclohex-2-en-1-ylzinc bromide (30f, 89%). Especially the preparation of zinc reagent 30b is remarkable, since cinnamyl chloride is known to readily undergo extensive homocoupling reaction during the synthesis of the corresponding zinc reagent. It is noteworthy, that also functional groups like an ester or a nitrile are tolerated in this insertion reaction. Hence, 2-enecarboxylic acid ethyl ester-6-cyclohexenylzinc chloride (30h) and 2-cyano-5-cyclopentenylzinc chloride (30i) have been obtained from their corresponding chlorides in 90% and 69% yield, respectively. Starting from 2-chloromethyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (29g), also zinc reagent 30g could be synthesized in 73% yield (25 °C, 30 h).\footnote{178a} (2-(Trimethylsilyl)but-2-en-1-yl)zinc chloride (30d) has been generated from its chloride in the presence of zinc powder (10 equiv) and lithium chloride (3 equiv) in 18 h at 25 °C in 81% yield.\footnote{178b}

3.3 Preparation of \(\alpha\)-Substituted \(\beta,\gamma\)-Unsaturated Ketones

We then decided to concentrate our studies on the addition of these highly reactive allylic zinc reagents to a broad range of acid chlorides. It turned out that this reaction proceeds under exceedingly mild conditions (-78 °C, 1-2 h) and furnishes selectively \(\beta,\gamma\)-unsaturated ketones 32 without any traces of the \(\alpha,\beta\)-unsaturated isomers (Scheme 80).

\begin{align*}
\text{Scheme 80: } & \text{Preparation of } \alpha\text{-substituted } \beta,\gamma\text{-unsaturated ketones of type 32 via addition of allylic zinc reagents 30 to various acid chlorides of type 31.} \\
\end{align*}

Thus, the addition of but-2-en-1-ylzinc bromide (30a) to 4-(tert-butyl)benzoyl chloride (31a) leads selectively to the corresponding \(\alpha\)-substituted \(\beta,\gamma\)-unsaturated ketone 32a in 85% yield (Scheme 81).

\begin{align*}
\text{Scheme 81: } & \text{Preparation of } \alpha\text{-substituted } \beta,\gamma\text{-unsaturated ketone 32a from disubstituted allylic zinc reagent 30a.} \\
\end{align*}
Moreover, also addition of organozinc reagent 30a to the (hetero)aromatic acid chlorides 31b and 31c furnishes selectively the corresponding α-substituted β,γ-unsaturated ketones 32b-c in high yields (Table 15, entries 1-2). Regardless of the substitution pattern of the (hetero)aromatic acid chloride, the reaction proceeds within 1 h at -78 °C. Noteworthy, the configuration of the double bond in the zinc reagent does not affect the reaction course, allowing the use of E- and Z-isomeric mixtures.

Table 15: Preparation of α-substituted β,γ-unsaturated ketones 32b-g from disubstituted allylic zinc reagents 30a-b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Acid Chloride</th>
<th>Product, Yield[a]</th>
<th>Conditions (T, t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30a</td>
<td>31b</td>
<td>32b: 71%</td>
<td>-78 °C, 1 h</td>
</tr>
<tr>
<td>2</td>
<td>30a</td>
<td>31c</td>
<td>32c: 65%</td>
<td>-78 °C, 1 h</td>
</tr>
<tr>
<td>3</td>
<td>30b</td>
<td>31a</td>
<td>32d: 90%</td>
<td>-78 °C, 1 h</td>
</tr>
<tr>
<td>4</td>
<td>30b</td>
<td>31b</td>
<td>32e: 77%</td>
<td>-78 °C, 1 h</td>
</tr>
<tr>
<td>5</td>
<td>30b</td>
<td>31d</td>
<td>32f: 84%</td>
<td>-78 °C, 1 h</td>
</tr>
<tr>
<td>6</td>
<td>30b</td>
<td>31e</td>
<td>32g: 72%</td>
<td>-20 to 25 °C, 2 h</td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure isolated product as determined by ¹H NMR analysis.
Cinnamylzinc chloride (30b) reacts in a similar manner. The α-substituted β,γ-unsaturated ketones 32d-f are obtained by addition to the corresponding (hetero)aromatic acid chlorides 31a, 31b and 31d in excellent yields (entries 3-5). Interestingly, also with aliphatic acid chloride 31e the addition proceeds smoothly (-20 to 25 °C, 2 h) and leads to ketone 32g in 72% yield (entry 6).

This procedure could also be successfully applied to trisubstituted allylic zinc derivatives. Thus, (3-methylbut-2-en-1-yl)zinc bromide (30c) reacted selectively in 1 h at -78 °C with 4-(tert-butyl)benzoyl chloride (31a) to afford the corresponding α,α-disubstituted β,γ-unsaturated ketone 32h in 93% yield (Scheme 82).

Scheme 82: Preparation of α,α-substituted β,γ-unsaturated ketone 32h from trisubstituted allylic zinc reagent 30c.

Remarkably, the addition of (2-(trimethylsilyl)but-2-en-1-yl)zinc chloride (30d) to the acid chlorides 31a and 31b furnishes the corresponding ketones 32i and 32j in the almost quantitative yield of 98% and 99%, respectively (Table 16, entries 1 and 2). Also the trisubstituted allylic zinc reagent 30e, containing another double bond besides the allylic one, could be employed in the addition reaction. (Hetero)aromatic acid chlorides (31a and 31d) as well as an aliphatic one (31e) have been used to synthesize the corresponding ketones 32k-m leaving the non-allylic double bond untouched (entries 3-5).

Table 16: Preparation of α- and α,α-substituted β,γ-unsaturated ketones 32i-m from trisubstituted allylic zinc reagents 30d-e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Acid Chloride</th>
<th>Product, Yield[^a]</th>
<th>Conditions (T, t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30d</td>
<td>31a</td>
<td>32i: 98%</td>
<td>25 °C, ovn</td>
</tr>
<tr>
<td>2</td>
<td>30d</td>
<td>31b</td>
<td>32j: 99%</td>
<td>-78 °C, 1 h</td>
</tr>
</tbody>
</table>
The cyclic allylic zinc reagents \textbf{30f-i} show an analogous behaviour. The addition of cyclohexy-2-en-1-ylzinc bromide (\textbf{30f}) to acid chloride \textbf{31f} affords selectively the corresponding \(\alpha\)-substituted \(\beta,\gamma\)-unsaturated ketone \textbf{32n} in 75\% yield (Scheme 83).

![Scheme 83: Preparation of \(\alpha\)-substituted \(\beta,\gamma\)-unsaturated ketone \textbf{32n} from cyclic allylic zinc reagent \textbf{30f}.](image)

Furthermore, the allylic zinc reagent \textbf{30f} smoothly adds to acid chloride \textbf{31a} affording selectively the corresponding \(\alpha\)-substituted \(\beta,\gamma\)-unsaturated ketone \textbf{32o} in 83\% yield (Table 17, entry 1). Moreover, the cyclic zinc reagent \textbf{30g} reacts readily with the (hetero)aromatic acid chlorides \textbf{31a} and \textbf{31b} to the ketones \textbf{32p} and \textbf{32q} in 67\% and 89\% yield, containing a terminal double bond (entries 2 and 3). Also, zinc reagent \textbf{30h} undergoes the addition reaction with the (hetero)aromatic acid chlorides \textbf{31d} and \textbf{32g} smoothly and furnishes the corresponding ketones \textbf{32r} and \textbf{32s} in high yields (90\% and 80\%, entries 4 and 5). The addition of 2-cyano-5-cyclopentenylzinc chloride (\textbf{30i}) to acid chloride \textbf{31g} leads to the \(\alpha\)-substituted \(\beta,\gamma\)-unsaturated ketone \textbf{32t} (70\% yield, entry 6).
Table 17: Preparation of α-substituted β,γ-unsaturated ketones 32o-t from cyclic allylic zinc reagents 30f-i.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Acid Chloride</th>
<th>Product, Yield(^{[a]})</th>
<th>Conditions (T, t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30f</td>
<td>31a</td>
<td>32o: 83%</td>
<td>-78 °C, 1 h</td>
</tr>
<tr>
<td></td>
<td>[ZnBr·LiCl]</td>
<td>[tBu]Cl</td>
<td>[tBu]Cl</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30g</td>
<td>31a</td>
<td>32p: 67%</td>
<td>-78 °C, 1 h</td>
</tr>
<tr>
<td></td>
<td>[ZnCl·LiCl]</td>
<td>[tBu]Cl</td>
<td>[tBu]Cl</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30g</td>
<td>31b</td>
<td>32q: 89%</td>
<td>-78 to 25 °C, 2 h</td>
</tr>
<tr>
<td></td>
<td>[ZnCl·LiCl]</td>
<td>[EtO]Cl</td>
<td>[EtO]Cl</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>30h</td>
<td>31d</td>
<td>32r: 90%</td>
<td>-78 to 25 °C, ovn</td>
</tr>
<tr>
<td></td>
<td>[ZnCl·LiCl]</td>
<td>[Cl]Cl</td>
<td>[Cl]Cl</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30h</td>
<td>31g</td>
<td>32s: 80%</td>
<td>-78 to 25 °C, ovn</td>
</tr>
<tr>
<td></td>
<td>[ZnCl·LiCl]</td>
<td>[Cl]Cl</td>
<td>[Cl]Cl</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>30i</td>
<td>31g</td>
<td>32t: 70%</td>
<td>-78 to 25 °C, ovn</td>
</tr>
<tr>
<td></td>
<td>[ZnCl·LiCl]</td>
<td>[Cl]Cl</td>
<td>[Cl]Cl</td>
<td></td>
</tr>
</tbody>
</table>

\(^{[a]}\) Yield of analytically pure isolated product as determined by \(^1\)H NMR analysis.
3.3.1 Further Functionalization of α-Substituted β,γ-Unsaturated Ketones

Ring-closing metathesis (RCM) represents one of the most powerful and versatile tools in organic synthesis for the formation of carbon-carbon double bonds\(^{193}\) and has proven to be highly important for natural product synthesis.\(^{194}\) With the α-substituted β,γ-unsaturated ketones in hands, the diene-precursor 33 for a RCM has readily been synthesized in only one step via the diastereoselective addition\(^{166}\) of allyl magnesium chloride to the carbonyl moiety of 32d in almost quantitative yield (Scheme 84). The subsequent RCM using the second generation of Grubbs’ catalyst\(^{195}\) furnishes diastereoselectively cyclopentene derivative 34 in 97% yield.

\[
\text{Scheme 84: Diastereoselective addition of allyl magnesium chloride to 32d and subsequent ring-closing metathesis forming the cyclopentene derivative 34.}
\]

3.4 Preparation of α-Substituted β,γ-Unsaturated Esters

Due to the lack of a convenient and practical direct synthesis for α-substituted β,γ-unsaturated esters in the literature, we extended our method to this direction. As shown in Scheme 85, the allylic zinc reagent 30b reacts readily under the optimized conditions with chloroformate 35a and forms selectively the desired α-substituted β,γ-ununsaturated ester 36a in 64% yield.

\[
\text{Scheme 85: Preparation of α-substituted β,γ-ununsaturated ester 36a from disubstituted allylic zinc reagent 30b.}
\]


Furthermore, cinnamylzinc chloride (30b) adds to aromatic (35b) as well as to allylic chloroformates (35c) affording the corresponding α-substituted β,γ-unsaturated esters 36b and 36c in 78% and 82% yield, respectively (Table 18, entries 1 and 2). The trisubstituted allylic zinc reagent 30c shows a similar behaviour and furnishes ester 36d in 70% yield (entry 3).

Table 18: Preparation of α-substituted β,γ-unsaturated esters of type 36.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Chloroformate</th>
<th>Product, Yield&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>Conditions (T, t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30b</td>
<td>35b</td>
<td>36b: 78%</td>
<td>-78 to 25 °C, 2 h</td>
</tr>
<tr>
<td>2</td>
<td>30b</td>
<td>35c</td>
<td>36c: 82%</td>
<td>-78 to 25 °C, 2 h</td>
</tr>
<tr>
<td>3</td>
<td>30c</td>
<td>35b</td>
<td>36d: 70%</td>
<td>-20 to 25 °C, 2 h</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> Yield of analytically pure isolated product as determined by <sup>1</sup>H NMR analysis.
4. PREPARATION OF FUNCTIONALIZED ALKENYLZINC REAGENTS BEARING CARBONYL GROUPS VIA DIRECT METAL INSERTION

4.1 INTRODUCTION

Functionalized alkenes bearing aldehyde, keto or ester functions are found in a plethora of naturally occurring products as well as in pharmaceutically active substances (Figure 11). Thuggacin A, for example, has been isolated from the myxobacterium Sorangium cellulosum and shows strong antibiotic activity against Mycobacterium tuberculosis by targeting the bacterial respiratory chain. Moreover, Rapamycin, found in Streptomyces hygroscopicus, is a known immunosuppressant drug used to prevent rejection in organ transplantations (especially for kidney transplants). Its first total synthesis was reported by Nicolaou et al. in 1993. Upenamide is a macrocyclic marine natural product from a branching sponge of the genus Echinochalina, containing an all-trans triene chain system.

Figure 11: Naturally occurring substrates bearing functionalized alkene moieties.

Olefin metathesis is one of the most important methods in organic synthesis for the formation of carbon-carbon double bonds and has proven to be highly useful for natural

RESULTS AND DISCUSSION

However, for the synthesis of highly functionalized double bonds an approach via cross-coupling reactions of alkenyl organometallics derived from the corresponding alkenyl halides seems to be more promising. The synthesis of Rapamycin for instance contains as key step a Stille-coupling of two alkenyl iodides with vinylendistannane for the stereoselective ring closure and the introduction of the conjugated double bond system (Scheme 86).

Scheme 86: Stille-coupling as key step in the total synthesis of Rapamycin.

For this reason a simple and efficient method for the preparation of functionalized alkenyl organometallics bearing sensitive groups is highly desirable. Especially alkenylzinc halides are useful targets due to their high functional group tolerance and their excellent reactivity in the presence of an appropriate catalysts. In general, functionalized alkenyl organometallic compounds are mostly prepared via halogen-metal exchange reactions of the corresponding iodoalkenes. Thus, an iodine-lithium exchange with n-butyllithium at -80 °C on 5-chloro-1-iodopent-1-ene combinded with a subsequent transmetalation allows the synthesis of the corresponding alkenyl zinc reagent (Scheme 87). Moreover, Knochel et al. described the use of iPrMgCl-LiCl as exchange reagent for the formation of alkenyl magnesium reagents.

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iodocyclo-hex-1-ene, for example, could readily be converted into its corresponding magnesium reagent (Scheme 87).

\[ \text{Scheme 87: Preparation of alkenyl organometallics via iodine-metal exchange reactions.} \]

The major drawbacks of this method are the low reaction temperatures required and the use of expensive and unstable alkenyl iodides as starting materials. To avoid these drawbacks, direct insertion reactions could be used. However, up to now, only unfunctionalized alkenyl organometallics could be employed in direct insertion reactions. Rieke et al. for instance described the use of highly active zinc (Zn*) prepared via reduction of ZnCl\(_2\) with lithium naphthalide for the synthesis of styrylzinc or (1-phenylvinyl)zinc bromide (Scheme 88).

\[ \text{Scheme 88: Preparation of (1-phenylvinyl)zinc bromide from its corresponding bromide using Rieke-Zn (Zn*).} \]

Recently, Knochel and coworkers have developed a practical and useful method for the synthesis of alkyl-, aryl-, and benzylzinc halides via LiCl-mediated metal-insertion into the corresponding chlorides and bromides. Based on these results, we searched for a convenient, mild and atom economical methodology for the preparation of highly functionalized alkenylzinc reagents starting from readily available alkenyl bromides bearing for the first time sensitive functional moieties.

4.2 Direct Insertion of Zinc into Activated Alkenyl Bromides

Since the addition of LiCl enables a smooth zinc insertion into alkyl bromides, aromatic halides as well as benzylic chlorides, this method has been applied to activated alkenyl bromides for the effective preparation of functionalized alkenyl zinc reagents (Scheme 89).

**Scheme 89:** Preparation of alkenyl zinc reagents 38 from activated alkenyl bromides 37 via direct zinc insertion and subsequent functionalization.

Thus, 2-bromocyclohex-1-encarbaldehyde (37a) undergoes a smooth zinc insertion using commercially available zinc powder (1.5 equiv, 25 °C, 1 h) in the presence of LiCl (1.5 equiv) leading to the zinc reagent 38a (86% yield, Scheme 90). A Pd-catalyzed Negishi cross-coupling reaction with 4-bromobenzonitrile (39a) using 2% Pd(PPh₃)₄ affords the highly functionalized benzonitrile 40a in 82% yield. The presence of the electron-withdrawing formyl group on the double bond accelerates the electron-transfer from the zinc to the organic halide through conjugation and therefore enables this exceptionally fast insertion reaction.

**Scheme 90:** LiCl-mediated zinc insertion in alkenyl bromide 37a leading to zinc reagent 38a and subsequent cross-coupling.

Moreover, a Cu(I)-catalyzed allylation reaction with ethyl 2-((bromomethyl)acrylate (39b) leads to the desired product 40b in 94% yield (Table 19, entry 1). The copper-catalyzed alkynylation reaction of 38a with the bromoacetylene 39c affords the highly functionalized acetylene 40c in 80% yield (entry 2). Furthermore, the acylation reaction using 2-bromobenzoyl chloride (39d) affords ketone 40d in 51% yield (entry 3). Additionally, Pd-catalyzed cross-coupling reactions with 5-bromo-3-cyanopyridine

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(39e) and 4-bromobenzotrifluoride (39f) produce the highly functionalized cyclohexenyl derivatives 40e and 40f in 65-73% yield (entries 4 and 5). Finally, the reaction of 38a with the Tietze immonium reagent 39g210 leads to the aminoaldehyde 40g (68% yield, entry 6).

Table 19: Reactions of alkenylzinc reagent 38a with electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Reagent (Yield [%])</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38a (86)</td>
<td>39b</td>
<td>40b</td>
<td>94[c]</td>
</tr>
<tr>
<td>2</td>
<td>38a</td>
<td>39c</td>
<td>40c</td>
<td>80[d]</td>
</tr>
<tr>
<td>3</td>
<td>38a</td>
<td>39d</td>
<td>40d</td>
<td>51[d]</td>
</tr>
<tr>
<td>4</td>
<td>38a</td>
<td>39e</td>
<td>40e</td>
<td>65[e]</td>
</tr>
<tr>
<td>5</td>
<td>38a</td>
<td>39f</td>
<td>40f</td>
<td>73[e]</td>
</tr>
<tr>
<td>6</td>
<td>38a</td>
<td>39g</td>
<td>40g</td>
<td>68</td>
</tr>
</tbody>
</table>

[a] Determined via titration with I₂. [b] Isolated yield of analytically pure product. [c] 3% CuCN·2LiCl was used. [d] 1 equiv CuCN·2LiCl was used. [e] 2% Pd(PPh₃)₄ was used and the reaction was performed at 50 °C.

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Analogous to aldehyde 38a, the heterocyclic dihydropyranylzinc derivative 38b has been prepared by a direct zinc insertion using zinc powder (1.5 equiv) in the presence of LiCl (1.5 equiv, 25 °C, 1 h, 77% yield). After reaction with immonium salt 39g, the N,N-dimethyl-aminomethyl substituted dihydropyran derivative 40h was isolated in 88% yield (Scheme 91).

Scheme 91: LiCl-mediated zinc insertion in 37b leading to 38b and subsequent functionalization.

A direct insertion of zinc dust in 3-iodocyclohex-2-en-1-one and related structures is also possible. However, the corresponding iodides are often unstable at room temperature which makes a synthesis starting from the corresponding bromide highly desirable. Hence, applying the method described above to 3-bromo-cyclohex-2-en-1-one (37c), a smooth insertion reaction occurs furnishing the 3-zincated cyclohexenone 38c in 86% yield (Scheme 92). A Pd-catalyzed cross-coupling reaction with 4-bromo-benzonitrile (39a) affords the 3-substituted cyclohexenone derivative 40i in 88% yield.

Scheme 92: LiCl-mediated zinc insertion in 37c leading to 38c and subsequent cross-coupling.

The Pd-catalyzed cross-coupling of 38c with ethyl 4-iodobenzoate (39h) affords the 3-substituted cyclohexenone derivative 40j in 76% yield (Table 20, entry 1). Cu(I)-mediated reactions of 38c with 3-bromocyclohexene (39i) or the bromoacetylene 39c produce the unsaturated ketones 40k and 40l in 71-76% yield (entries 2 and 3). Analogously, 3-bromo-cyclopentenone (37d) is converted to the corresponding alkenylzinc reagent 38d in 94% yield (25 °C, 5 h). Pd-catalyzed cross-coupling with 4-(trifluoromethyl)bromobenzene (39f) leads to the substituted cyclopentenone 40m in 74% yield (entry 4).

**Table 20:** Reactions of alkenylzinc reagents \(38c\) and \(38d\) with electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Reagent (Yield [%])[^a]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(38c) (86)</td>
<td>(39h)</td>
<td>(40j)</td>
<td>76[^c]</td>
</tr>
<tr>
<td>2</td>
<td>(38c)</td>
<td>(39i)</td>
<td>(40k)</td>
<td>76[^e]</td>
</tr>
<tr>
<td>3</td>
<td>(38c)</td>
<td>(39c)</td>
<td>(40l)</td>
<td>71[^e]</td>
</tr>
<tr>
<td>4</td>
<td>(38d) (94)</td>
<td>(39f)</td>
<td>(40m)</td>
<td>74[^c]</td>
</tr>
</tbody>
</table>

\[^{a}]^\text{Determined via titration with I\(_2\). \[^{b}]^\text{Isolated yield of analytically pure product. \[^{c}]^\text{2\% Pd(PPh\(_3\))\(_4\) was used and the reaction was performed at 50 °C. \[^{d}]^\text{3\% CuCN·2LiCl was used. \[^{e}]^\text{1 equiv CuCN·2LiCl was used.}

Furthermore, also alkenyl bromides bearing a keto function can be directly converted into the corresponding zinc reagents via LiCl-mediated zinc insertion. Thus (2-bromocyclopent-1-en-1-yl)(phenyl)methanone (37e) reacts readily with zinc powder (1.5 equiv) and LiCl (1.5 equiv) at 25 °C within 1 h to the corresponding organozinc compound \(38e\) in 62 % yield (Scheme 93). A Pd-catalyzed cross-coupling of \(38e\) with ethyl 4-bromobenzoate (39j) leads to \(40n\) in 70% yield. A Cu(i)-catalyzed allylation reaction with ethyl 2-(bromomethyl)acrylate (39b) furnishes the desired product \(40o\) in 79% yield.
Due to chelation of the zinc center with the carbonyl group, acyclic alkenylzinc reagents bearing a vicinal aldehyde have been prepared without losing the stereochemical information of the alkenyl precursors. In general, the formation of a five-membered ring chelate stabilizes the corresponding organometallic compound by several kcal/mol and reduces the nucleophilicity of the carbonyl group. Thus, (Z)-3-bromo-4,4-dimethylpent-2-enal (37f) reacts with zinc powder (1.5 equiv) in the presence of LiCl (1.5 equiv) leading to the alkenylzinc reagent 38f in 67% yield (Scheme 94). A Pd-catalyzed cross-coupling with 2-bromobenzaldehyde (39k) furnishes the unsaturated aldehyde 40p in 92% yield and with a Z:E-selectivity of >99:1.

A Cu(I)-catalyzed allylation of 38f with 3-bromocyclohexene (39i) leads to the desired unsaturated product 40q in 96% yield (Table 21, entry 1). Moreover, also the 4-fluoro and the 4-methoxy substituted derivatives 37g and 37h of (Z)-3-bromo-3-phenylprop-2-enal react to the corresponding zinc species 38g and 38h in 35-41% yield. The following Cu(I)-catalyzed allylation reaction with ethyl 2-(bromomethyl)-acrylate (3b) furnishes the cinnamyl-aldehydes 40r and 40s in 89-95% yield (Z:E >99:1, entries 2 and 3).

Scheme 93: LiCl-mediated Zn-insertion in 37e leading to 38e and subsequent functionalizations.

Scheme 94: LiCl-mediated Zn-insertion in 37f leading to 38f and subsequent cross-coupling.

Table 21: Reactions of acyclic alkenylzinc reagents 38f-h with electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Reagent (Yield [%])[a]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38f (67)</td>
<td>39i</td>
<td>40q</td>
<td>96[c][e]</td>
</tr>
<tr>
<td>2</td>
<td>38g (35)</td>
<td>39b</td>
<td>40r</td>
<td>95[d][e]</td>
</tr>
<tr>
<td>3</td>
<td>38h (41)</td>
<td>39b</td>
<td>40s</td>
<td>89[d][e]</td>
</tr>
</tbody>
</table>

[a] Determined via titration with I₂. [b] Isolated yield of analytically pure product. [c] 3% CuCN-2LiCl was used. [d] 1 equiv CuCN-2LiCl was used. [e] Ratio of Z:E >99:1.

Noteworthy, the developed method has also been applied on an acyclic alkenyl bromide bearing an ester function. Hence, (Z)-ethyl 3-bromo-3-phenylacrylate (37i) has been converted into the corresponding zinc reagent 38i with zinc powder (1.5 equiv) and LiCl (1.5 equiv; 25 °C, 1 h) in 62% yield (Scheme 95). The copper-mediated reaction of 38i with 4-chlorobenzoyl chloride (39l) and ethyl 2-(bromomethyl)acrylate (39b) affords the highly functionalized cinnamyl esters 40t and 40u in 79-85% yield with a Z:E-selectivity of >99:1.

Scheme 95: LiCl-mediated zinc insertion in 37i leading to 38i and subsequent functionalizations.
4.2.1 Preparation of 1-Substituted Tetrahydrophthalazines

Unsaturated 1,4-dicarbonyl compounds are highly reactive and undergo condensation reactions with hydrazine providing tetrahydrophthalazines.\(^{213}\) Thus, zinc reagent 38a was acylated with benzoyl chloride using 3% CuCN·2LiCl as catalyst affording the 1,4-dicarbonyl derivative 40v. After aqueous workup, the crude 40v undergoes without further purification a smooth condensation reaction with hydrazine hydrate (NH\(_2\)NH\(_2\)·H\(_2\)O) in methanol to afford the 1-substituted tetrahydrophthalazine 41a in 54% yield (Scheme 96). Following this protocol, compounds 41b and 41c, bearing a 3-chlorophenyl- and a 2-thienyl-substituent, respectively, have been prepared (49-54% yield, Scheme 96).

![Scheme 96: Synthesis of substituted tetrahydrophthalazines of type 41.](image)

4.3 Magnesium Insertion in the Presence of ZnCl\(_2\) into Less Activated Alkenyl Bromides

The direct insertion of zinc into alkenyl bromides requires the presence of adjacent electron-withdrawing groups. Alkenyl bromides without such electronic activation either do not undergo an insertion reaction or react only at elevated temperatures and require long reaction times. To avoid these drawbacks, we have used the stronger reducing metal magnesium. The LiCl-mediated Mg insertion in the presence of ZnCl\(_2\) allows an efficient synthesis of alkenylzinc halides starting from weakly activated alkenyl bromides (Scheme 97).

B. RESULTS AND DISCUSSION

Scheme 97: Preparation of alkenylzinc reagents 43 from less activated alkenyl bromides 42 via magnesium insertion in presence of ZnCl$_2$ and subsequent functionalization.

Whereas a vicinal ethyl ester does not sufficiently activate the alkenyl bromide 42a for a LiCl-mediated zinc insertion, it undergoes a selective magnesium insertion in the presence of ZnCl$_2$ and LiCl furnishing the alkenylzinc reagent 43a in 70% yield (Scheme 98). Its Pd-catalyzed cross-coupling with (5-bromothiophen-2-yl)trimethylsilane (39m) leads to the substituted thiophene 44a in 71% yield.

Scheme 98: Selective insertion of Mg in the presence of ZnCl$_2$ and LiCl in the ester-substituted alkenyl bromides 42a and subsequent cross-coupling.

In an analogous way to 42a, the ester-substituted cyclopentene derivative 42b has been converted to its corresponding zinc reagent 43b and submitted to a Pd-catalyzed cross-coupling with bromothiophene 39n furnishing the substituted thiophene 44b in 86% yield. The Cu(i)-mediated allylation with 39b afforded the unsaturated product 44c in 77% yield (Scheme 99).

Scheme 99: Selective insertion of Mg in the presence of ZnCl$_2$ and LiCl in the ester-substituted alkenyl bromide 42b and subsequent functionalizations (additional complexed salts are omitted for the sake of clarity).
Remarkably, the zinc insertion proceeds also well with the acyclic unsaturated bromoester 42c. The LiCl-mediated Mg insertion in the presence of ZnCl$_2$ furnishes the corresponding zinc reagent 43c in 50% yield without any loss of stereochemical information due to the chelation of the zinc center with the carbonyl group. The subsequent copper-catalyzed reaction of 43c with 4-chlorobenzoyl chloride (39l) and ethyl 2-(bromomethyl)acrylate (39b) produces the functionalized acyclic compounds 44d and 44e in 77-86% yield (Z:E >99:1, Scheme 100).

![Scheme 100: Selective insertion of Mg in the presence of ZnCl$_2$ and LiCl in the ester-substituted alkenyl bromide 42c and subsequent functionalizations (additional complexed salts are omitted for the sake of clarity).](image)

Although 1,2-dibromocyclopentene (42d) can be converted to the corresponding magnesium reagent by a Br/Mg-exchange with iPrMgCl-LiCl$^{214}$ a more atom economical approach using Mg/ZnCl$_2$/LiCl is possible. Thus, the treatment of 42d with magnesium in the presence of ZnCl$_2$ and LiCl leads to the desired alkenylzinc reagent 43d in quantitative yield (Scheme 101). Its Cu(I)-catalyzed reaction with 3-bromocyclohexene (39i) affords 44f in 86% yield.

![Scheme 101: Selective mono-insertion of Mg in the presence of ZnCl$_2$ and LiCl into alkenyl dibromide 42d and subsequent allylation (additional complexed salts are omitted for the sake of clarity).](image)

Furthermore, an acylation reaction of 43d using 2-bromobenzoyl chloride (39d) affords the unsaturated ketone 44g in 64% yield (Table 22, entry 1). Additional Cu(I)-mediated reactions with cyclohexenone (39o), 3-iodocyclo-hexenone (39p) and bromoacetylene 39c lead to the expected products 44h-j in 65-78% yield (entries 2-4). Finally, the Pd-catalyzed cross-coupling reaction of 43d with 3-bromo-5-cyanopyridine (3e) furnishes the substituted pyridine 44k in 54% yield (entry 5).

Table 22: Reactions of alkenylzinc reagent 43d with electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Reagent[a]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43d (98)</td>
<td>39d</td>
<td>44g</td>
<td>64[d]</td>
</tr>
<tr>
<td>2</td>
<td>43d</td>
<td>39o</td>
<td>44h</td>
<td>70[d]</td>
</tr>
<tr>
<td>3</td>
<td>43d</td>
<td>39p</td>
<td>44i</td>
<td>65[d]</td>
</tr>
<tr>
<td>4</td>
<td>43d</td>
<td>39c</td>
<td>44j</td>
<td>78[e]</td>
</tr>
<tr>
<td>5</td>
<td>43d</td>
<td>39e</td>
<td>44k</td>
<td>54[f]</td>
</tr>
</tbody>
</table>

[a] Additional complexed salts are omitted for the sake of clarity. [b] Determined via titration with I₂. [c] Isolated yield of analytically pure product. [d] 1 equiv of CuCN·2LiCl was used. [e] 2% CuCN·2LiCl was used. [f] 2% Pd(PPh₃)₄ was used and the reaction was performed at 50 °C.

A functionalization of the related 1,2-dibromocyclohexene employing this method has not been possible. Since the 6-membered ring has a smaller ring strain, the initially formed organomagnesium reagent presumably eliminates MgBr₂ leading to cyclohexyne which undergoes fast side reactions such as trimerisation (Scheme 102).
Scheme 102: Reaction of 1,2-dibromocyclohexene with Mg in the presence of ZnCl₂ and LiCl leading to elimination and subsequent trimerisation.

However, the increased ring strain in the dibromo-norbornadiene derivative 42e prevents this elimination reaction and the corresponding zinc reagent 43e is obtained within 1 h in 70% yield using Mg (2.5 equiv) in the presence of LiCl (1.5 equiv) and ZnCl₂ (1.1 equiv) (Scheme 103). A Pd-catalyzed cross-coupling of 43e with ethyl 4-iodobenzoate (39h) produces the arylated norbornadiene 44l in 60% yield. A Cu(i)-catalyzed allylation reaction with ethyl 2-(bromomethyl)acrylate (39b) leads to the desired product 44m in 61% yield.

Scheme 103: Selective insertion of Mg in the presence of ZnCl₂ and LiCl in the alkenyl dibromide 42e and subsequent functionalizations (additional complexed salts are omitted for the sake of clarity).

As expected, alkenyl bromides bearing an electron-donating substituent such as (2-bromocyclopent-1-en-1-yl)(phenyl)sulfane (42f) do not undergo a direct zinc insertion. However, using Mg (2.5 equiv) in the presence of LiCl (1.5 equiv) and ZnCl₂ (1.1 equiv) furnishes 43f within 1 h in 69% yield (Scheme 104). A subsequent Pd-catalyzed cross-coupling reaction with ethyl 4-iodobenzoate (39h) leads to the arylated cyclopentene 44n in 81% yield. A Cu(i)-mediated acylation of 43f with 4-chlorobenzoyl chloride (39l) furnishes the unsaturated ketone 44o in 86% yield.
Scheme 104: Selective insertion of Mg in the presence of ZnCl$_2$ and LiCl in the alkenyl bromide 42f and subsequent functionalizations (additional complexed salts are omitted for the sake of clarity).
5. SYNTHESIS OF FUNCTIONALIZED ADAMANTYLZINC REAGENTS USING A Br/Mg-INSERTION IN THE PRESENCE OF ZnCl₂

5.1 INTRODUCTION

Synthesis of organomagnesium reagents is known for many years.\textsuperscript{16-21} Nevertheless, none of these many studies provides an explanation for the systematic failures encountered in attempts at synthesizing cage-structure organomagnesium compounds. Thus, at no time does 1- or 2-adamantyl bromide yield an organometallic compound, whereas secondary or tertiary halides such as isopropyl chloride, tert-butyl chloride, and 3-chloro-3-ethylpentane give excellent yields of organomagnesium compounds.\textsuperscript{215} The reaction of 1-adamantylmagnesium bromide with highly reactive magnesium (Mg\textsuperscript{*}) obtained \textit{in situ} by the standard method of Rieke and coworkers\textsuperscript{216} could not furnish any trace of organomagnesium compound. Instead, a 60% yield of hydrolysed adamantane and a 30% yield of homocoupling product can be isolated (Scheme 105).\textsuperscript{215}

\begin{equation}
\text{Br} + \text{Mg}^* \rightarrow \text{MgBr} + \text{H} + \text{C}_9\text{H}_{16}
\end{equation}

\textbf{Scheme 105:} Reaction of adamantyl bromide with \textit{Rieke}-Mg (Mg\textsuperscript{*}).

However, Dubois \textit{et al.} develop a so-called "static" method whereby the entire reaction was conducted without any stirring of the reaction medium leading to 58% yield of 1-adamantylmagnesium bromide (Scheme 106).\textsuperscript{217} When this process was extended to 2-AdBr, the yield of 2-adamantylmagnesium bromide lay at 60%.

\begin{equation}
\text{Br} + \text{Mg} \rightarrow \text{MgBr} \quad \text{(58\% \textit{no stirring})}
\end{equation}

\textbf{Scheme 106:} Successful synthesis of adamantylmagnesium bromide.

It was shown, that the success of this “static” method lay in the preservation of the surface state of the magnesium. The formation of organomagnesium compounds is a typical surface reaction, whereas the side reactions occur in the medium. Competition

\begin{footnotes}
\end{footnotes}
between these two reaction pathways is depending on the degree of adsorption of the transient species at the metal surface. Since the volume of cage-structure adamantane has a steric effect on the degree of adsorption of the transient species, the reactions in the medium are favoured. This explains the failures to obtain an organometallic compound with stirring. In contrast, with less hindered molecules, surface reactions are favored, and the organometallic compounds are formed readily.\textsuperscript{215}

Until 1983, all attempts for the direct synthesis of organolithium compounds\textsuperscript{218} had failed, and only the halogene/lithium exchange reactions furnished a few cage-structure organolithium compounds.\textsuperscript{219} The syntheses using secondary or tertiary adamantyl halides and methyl or \textit{tert}-butyllithium, tertiary\textsuperscript{220} and secondary\textsuperscript{220a,221} adamantyl organolithium compounds could be obtained only when an excess of \textit{tert}-butyllithium was used. Extension of the previously described method used for magnesium compounds\textsuperscript{215} to organolithium compounds was unsuccessful since tertiary organolithium compounds are known to attack diethyl ether at a temperature above -30 °C. Moreover, in the absence of stirring, lithium chloride slowly coats the metal with a film rapidly inhibiting the attack by the halogenated derivative.\textsuperscript{222} By using a 2\% sodium lithium alloy in an apolar solvent, \textit{Dubois} and coworker prevented scouring the metal surface during synthesis and limited solvent-attack side reactions. Under these conditions, 1-adamantyllithium could be obtained for the first time in a high yield (Scheme 107).\textsuperscript{222}

![Scheme 107: Synthesis of adamantyllithium using a 2\% sodium lithium alloy.](image)

In 1973, \textit{Rieke} and coworkers reported a general approach for the preparation of highly reactive zinc (Zn\textsuperscript{*}) allowing for the first time the oxidative addition to primary alkyl bromides as well as to aryl iodides and bromides.\textsuperscript{223} In 1991, they published an improved method which was not only safer but also furnished a more reactive zinc
enabling the synthesis of secondary and tertiary alkyl bromides to yield the corresponding organozinc reagents in good yields under mild conditions. Thus, 1-adamantyl bromide reacts within 2 h under reflux with Zn* furnishing the corresponding organozinc species in 65% yield (Scheme 108).

Scheme 108: Synthesis of adamantylzinc chloride using Rieke-Zn (Zn*).

The trimethylstannylation of 1-bromo- and 1-iodoadamantanes as well as of 2-bromo-adamantane has been shown to occur by free radical intermediates in an S_N1 like reaction. Also 1,3-dihaloadamantane derivatives undergo the trimethylstannylation exclusively in a S_N1 like manner (Scheme 109).

Scheme 109: Trimethylstannylation of 1-bromo-3-chloroadamantane.

Noteworthy, the photostimulated reaction of Me_3Sn^- anions with 1-chloro- and 1-bromoadamantane in liquid ammonia afforded within a few minutes the corresponding stannylated products in good yields.

Recently, Knochel and coworkers have developed a practical and useful method for the synthesis of alkyl-, aryl-, and benzylzinc halides via LiCl-mediated metal-insertion into the corresponding chlorides and bromides. Based on these results, we searched for a convenient, mild and atom economical methodology for the preparation of functionalized adamantylzinc reagents starting from readily available adamantyl bromides bearing for the first time sensitive functional moieties.

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5.2 **Preparation of Functionalized adamantylzinc reagents**

Preliminary experiments have shown that only the use of the highly reactive \textit{Rieke-zinc} (Zn*) provides a direct zinc insertion. Since we wanted to avoid the use of stochiometric amounts of lithium naphthalide, the main focus lay on the use of a stronger reducing metal than zinc. Thus, the LiCl-mediated Mg insertion in the presence of ZnCl₂ allowed an efficient synthesis of adamantylzinc reagents 46 starting from the corresponding tertiary bromides 45 (Scheme 110).

\[
\begin{align*}
\text{R} & \quad + \quad \text{Mg} \quad + \quad \text{LiCl} \quad + \quad \text{ZnCl}_2 \\
(2 \text{ equiv}) & \quad (1.1 \text{ equiv}) \quad (1.1 \text{ equiv}) \\
\text{THF} & \quad 0 \text{ to } 25 \, ^\circ\text{C} \quad 2-3 \, \text{h} \\
& \quad \rightarrow \\
\text{R} & \quad + \quad \text{ZnCl}_2 \cdot \text{MgBrCl} \cdot \text{LiCl} \\
\end{align*}
\]

\textbf{Scheme 110:} Preparation of functionalized adamantylzinc reagents 46 via the LiCl-mediated Mg-insertion in the presence of ZnCl₂ (additional complexed salts are omitted for the sake of clarity).

As illustrated in Scheme 110, the zinc species 46a was obtained from 1-bromoadamantane 45a within 2 h at ambient temperature in 85% yield using Mg (2 equiv) in the presence of LiCl (1.1 equiv) and ZnCl₂ (1.1 equiv). Remarkably, also the functionalized adamantylzinc reagents 46b and 46c have been obtained for the very first time in 63% and 57% yield, following this procedure. Noteworthy, the acetal protection of the keto-function of 5-bromoadamantan-2-one was compulsory since the preparation of the zinc reagent from the unprotected ketone caused the cleavage of the cage structure.

5.3 **Functionalization of adamantylzinc reagents**

The obtained adamantylzinc reagents 46a-c have proven to be highly reactive and readily undergo a broad variety of functionalization reactions in the presence of an appropriate catalyst. Thus, zinc reagent 46a smoothly reacts in a Pd-catalyzed \textit{Negishi} cross-coupling reaction\textsuperscript{145,208} with aryl halides 47a-m. Using 1% Pd(OAc)\textsubscript{2} and 2% SPhos\textsuperscript{227} as catalytic system, zinc reagent 46a reacts within 2 h at 50 °C with the ester substituted aryl iodide 47a, aryl bromide 47b and even the aryl chloride 47c to the corresponding cross-coupling product 48a in excellent yields (Scheme 111).

Scheme 111: Negishi cross-coupling reaction of adamantylzinc reagent 46a with aryl halides of type 47 (additional complexed salts are omitted for the sake of clarity).

Various electron-rich and electron-poor electrophiles (0.9 equiv) are used in the cross-coupling reaction at 50 °C affording the corresponding arylated adamantyl derivatives 48b-i in good to excellent yields, tolerating functional groups like nitril, aldehyde, ketone or carbamate (Table 23, entries 1-8). Noteworthy, also double cross-coupling could be achieved under these reaction conditions (entries 9 and 10), furnishing the corresponding products 48l and 48m in 82% and 55% yield, respectively.

Table 23: Negishi cross-coupling reactions of adamantylzinc reagent 46a with aryl bromides of type 47.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn-Reagent</th>
<th>Electrophile</th>
<th>Product, Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46a</td>
<td>47d</td>
<td>48b: 88%$^b$</td>
</tr>
<tr>
<td>2</td>
<td>46a</td>
<td>47e</td>
<td>48c: 84%$^b$</td>
</tr>
<tr>
<td>3</td>
<td>46a</td>
<td>47f</td>
<td>48d: 94%$^b$</td>
</tr>
<tr>
<td>4</td>
<td>46a</td>
<td>47g</td>
<td>48e: 62%$^b$</td>
</tr>
<tr>
<td>5</td>
<td>46a</td>
<td>47h</td>
<td>48f: 80%$^b$</td>
</tr>
<tr>
<td>6</td>
<td>46a</td>
<td>47i</td>
<td>48g: 88%$^b$</td>
</tr>
</tbody>
</table>
As illustrated in Scheme 112, also heteroaryl bromides have been employed in the Negishi cross-coupling reactions. Adamantyl zinc reagent 46a reacts smoothly with 3-bromobenzothiophene (49a, 0.9 equiv) at 50 °C within 2 h to the corresponding substituted adamantane 48l in 84% yield.

\[
\begin{align*}
\text{ZnX} + \text{Br} & \xrightarrow{\text{Pd(OAc)}_2 (1 \text{ mol\%}) \text{ SPhos (2 mol\%)} \text{ THF, 50 °C, 2 h}} \text{48l: 84\%}
\end{align*}
\]

Scheme 112: Negishi cross-coupling reaction of adamantylzinc reagent 46a with 3-bromobenzothiophene (49a) (additional complexed salts are omitted for the sake of clarity).
Table 24: Negishi cross-coupling reactions of adamantylzinc reagent 46a with heteroaryl bromides of type 49.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn-Reagent</th>
<th>Electrophile</th>
<th>Product, Yield&lt;sup&gt;[[a]]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46a</td>
<td>49b</td>
<td>48m: 57%&lt;sup&gt;[[b]]&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>46a</td>
<td>49c</td>
<td>48n: 91%&lt;sup&gt;[[b]]&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>46a</td>
<td>49d</td>
<td>48o: 71%&lt;sup&gt;[[b]]&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>46a</td>
<td>49e</td>
<td>48p: 61%&lt;sup&gt;[[b]]&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>46a</td>
<td>49f</td>
<td>48q: 53%&lt;sup&gt;[[b]]&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>46a</td>
<td>49g</td>
<td>48r: 58%&lt;sup&gt;[[b]]&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>[[a]]</sup> Yield of analytically pure isolated product as determined by $^1$H NMR analysis. <sup>[[b]]</sup> Obtained after a Negishi cross-coupling (Pd(OAc)$_2$ (1 mol%) and SPhos (2 mol%)) with heteroaryl bromide (0.9 equiv).

Adamantylzinc reagent 46a also undergoes Cu(I)-catalyzed acylation reactions leading to the desired ketone derivatives 51a-d in good to excellent yields (Scheme 113 and Table 25). 46a reacted with 4-fluorobenzoyl chloride (50a, 0.9 equiv) and 20% CuCN-2LiCl to the corresponding ketone 51a in 89% yield (Scheme 113).

![Scheme 113: Cu(I)-catalyzed acylation reaction of adamantylzinc reagent 46a with 4-fluorobenzoyl chloride (50a) (additional complexed salts are omitted for the sake of clarity).](image-url)
Under the same reaction conditions, also other acid chlorides 50b-d have been employed in the Cu(I)-catalyzed acylation reaction. Not only the substituted benzyol chlorides 5b-c undergo the acylation reaction with adamantylzinc species 46a in good yields (Table 25, entries 1 and 2), also the heteroaromatic 6-chloronicotinoyl chloride (50d) furnished the corresponding ketone 51d in the acceptable yield of 44% (entry 3).

Table 25: Cu(I)-catalyzed acylation reactions of adamantylzinc reagent 46a with acid chlorides of type 50.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn-Reagent</th>
<th>Electrophile</th>
<th>Product, Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46a</td>
<td>50b</td>
<td>51b: 70%</td>
</tr>
<tr>
<td>2</td>
<td>46a</td>
<td>50c</td>
<td>51c: 80%</td>
</tr>
<tr>
<td>3</td>
<td>46a</td>
<td>50d</td>
<td>51d: 44%</td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure isolated product as determined by 1H NMR analysis. [b] Obtained after a acylation reaction (CuCN·2LiCl (0.2 equiv)) with acid chloride (0.9 equiv).

Besides Pd-catalyzed Negishi cross-coupling reactions and Cu(I)-catalyzed acylation reactions the highly reactive adamantylzinc reagent 46a also reacts in a a Cu(I)-catalyzed allylation reaction\textsuperscript{146} with ethyl 2-(bromomethyl)acrylate (52a, 0.9 equiv) leading to the desired product 53a in 91% yield (Table 26, entry 1). Moreover, the copper-catalyzed reaction\textsuperscript{11a,146} of 46a with the bromoacetylene 52b\textsuperscript{209} (0.9 equiv) affords the highly functionalized acetylene 53b in 66% yield (entry 2). Furthermore, the adamantylzinc reagent 46a also reacts smoothly with S-phenyl benzenesulphonothioate (52c, 0.9 equiv) affording thioether 9c in almost quantitative yield (entry 3). Additionally, the Cu(I)-mediated reaction with cyclohex-2-enone (52d, 0.9 equiv) furnishes the desired 1,4-addition product 53d in 91% yield (entry 4).
**Table 26:** Further functionalization reactions of adamantylzinc reagent 46a with various electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn-Reagent</th>
<th>Electrophile</th>
<th>Product, Yield[^a][^b][^c][^d][^e]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46a</td>
<td>CO₂EtBr</td>
<td>53a: 91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EtO₂C ≡ Br</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>46a</td>
<td>52b</td>
<td>53b: 66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PhSSO₂Ph</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46a</td>
<td>52c</td>
<td>53c: 98%</td>
</tr>
<tr>
<td>4</td>
<td>46a</td>
<td>52d</td>
<td>53d: 91%</td>
</tr>
</tbody>
</table>

[^a]: Yield of analytically pure isolated product as determined by ¹H NMR analysis.  
[^b]: Obtained after allylation reaction (CuCN·2LiCl (0.2 equiv)) with ethyl 2-(bromomethyl)acrylate (0.9 equiv).  
[^c]: Obtained after alkylation reaction (CuCN·2LiCl (0.2 equiv)) with ethyl 3-bromopropiolate (0.9 equiv).  
[^d]: Obtained after addition to S-aryl benzenethiosulfonate (0.9 equiv).  
[^e]: Obtained after 1,4-addition (CuCN·2LiCl (1.1 equiv) and TMSCl (2.0 equiv)) with cyclohex-2-ene (0.9 equiv).

Amination reactions are well known in literature. Recently, several Pd(0)-[^229] and Cu(I)-catalyzed[^230] reactions between aromatic halides and various amines have been reported. Moreover, Knochel and coworkers found that this synthetic transformation can also be realized by reacting various arylmagnesium species with nitroarenes leading after a reductive workup to polyfunctional amines. In order to avoid the use of 2 equivalents of arylmagnesium species, they employed nitrosoarenes for the amination reaction.

It turned out that also the adamantylzinc reagent 46a readily reacts at ambient temperature within 2 h with nitroarenes of type 54. After reductive workup, the substituted amino derivatives 55a and 55b could be obtained in 89% and 71% yield, respectively (Scheme 114).

Scheme 114: Addition of adamantylzinc reagent 46a aryl nitroso compounds 54 and subsequent reduction to amines of type 55 (additional complexed salts are omitted for the sake of clarity).

Analogous to the unfunctionalized adamantylzinc reagent 46a, the ester-substituted adamantylzinc derivative 46b readily reacts in a Pd-catalyzed Negishi cross-coupling with 4-bromothioanisole (47f, 0.9 equiv) at 50 °C within 2 h to the highly functionalized adamantyl derivate 56a in 87% yield (Scheme 115).

Scheme 115: Negishi cross-coupling reaction of adamantylzinc reagent 46b with 4-bromothioanisole (47f) (additional complexed salts are omitted for the sake of clarity).

Under the same reaction conditions, also ethyl 4-bromobenzoate (47b, 0.9 equiv) and 5-bromo-2-methylbenzothiazole (49c, 0.9 equiv) have been employed in the Pd-catalyzed Negishi reaction with the ester-substituted adamantylzinc species 46b. The corresponding cross-coupling products 56b and 56c have been obtained in 84% and 70%, respectively (Table 27, entries 1 and 2). Moreover, adamantylzinc reagent 46b also undergoes smoothly Cu(I)-catalyzed acylation reactions with 4-chlorobenzoyl chloride (50b, 0.9 equiv) and 2-furoyl chloride (50e, 0.9 equiv) leading to the desired ketone derivatives 57a and 57b in good to excellent yields (entries 3 and 4).
Table 27: Functionalization reactions of adamantylzinc reagent 46b with various electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn-Reagent</th>
<th>Electrophile</th>
<th>Product, Yield[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46b</td>
<td>47b</td>
<td>56b: 84%[^b]</td>
</tr>
<tr>
<td>2</td>
<td>46b</td>
<td>49c</td>
<td>56c: 70%[^b]</td>
</tr>
<tr>
<td>3</td>
<td>46b</td>
<td>50b</td>
<td>57a: 82%[^c]</td>
</tr>
<tr>
<td>4</td>
<td>46b</td>
<td>50e</td>
<td>57b: 54%[^c]</td>
</tr>
</tbody>
</table>

[^a]: Yield of analytically pure isolated product as determined by 1H NMR analysis.  
[^b]: Obtained after a Negishi cross-coupling (Pd(OAc)\(_2\) (1 mol%) and SPhos (2 mol%)) with (hetero)aryl bromide (0.9 equiv).  
[^c]: Obtained after a acylation reaction (CuCN·2LiCl (0.2 equiv)) with acid chloride (0.9 equiv).

Also the adamantylzinc reagent 46c could easily be functionalized by Pd-catalyzed Negishi cross-coupling reactions with both electron-poor and electron-rich aryl bromides. The highly functionalized cross-coupling products 58a-c have been obtain in high yields (Scheme 116).

Scheme 116: Negishi cross-coupling reactions of adamantylzinc reagent 46c with aryl bromides of type 47 (additional complexed salts are omitted for the sake of clarity).
5.4 APPLICATION OF ADAMANTYLZINC REAGENTS

The synthesis and investigation of well-defined model oligomers has recently become useful to gain insight into the structural and electronic properties of the corresponding polymers. Depending on their size and substitution pattern the oligothiophenes are usually more soluble than polymers allowing the precise characterization of the electronic and geometric structure both in solution and in solid state.233

In analogy to the polymers, the solubility of oligothiophenes decreases dramatically with increasing chain length, which is due to the stiffness of the conjugated \(\pi\)-system and the strong interactions between the chains. The problem of low solubility can be solved by the synthesis of corresponding oligothiophenes bearing alkyl substituents.234 Several \(\alpha\)-alkyl and \(\alpha,\alpha'\)-dialkyl-substituted oligothiophenes were synthesized and characterized by different research groups. Especially, monosubstituted derivatives are attractive candidates since they offer the possibility of dimerizing them to the corresponding \(\alpha,\alpha'\)-disubstituted oligothiophenes with doubled conjugated chain length.233

Following this idea, adamantylzinc reagent 46a has been submitted to a Negishi cross-coupling reaction with the 5-bromo-terthiophene 49h furnishing the corresponding \(\alpha\)-substituted oligothiophene 48s in 64% yield (Scheme 117).

![Scheme 117: Negishi cross-coupling reactions of adamantylzinc reagent 46a with 5-bromo-2,2':5',2''-terthiophene (49h) (additional complexed salts are omitted for the sake of clarity).](image)

Subsequently, the adamantyl-substituted oligothiophene 48s has been selectively brominated at the \(\alpha\)-position of the oligothiophene with NBS leading to the corresponding product 59 in an almost quantitative manner (Scheme 118).

![Scheme 118: Selective bromination of the adamantyl-substituted oligothiophene 4s using N-bromosuccinimide.](image)

The Kumada cross-coupling reaction together with the homocoupling of thienyl-Grignard reagents have become the most frequently used methods in the synthesis of

---

various oligothiophenes. From the large variety of catalysts examined for thiophene synthesis, Ni(dppp)Cl$_2$, Ni(dppf)Cl$_2$, and Ni(dppe)Cl$_2$ turned out to be the most effective.

Thus, the $\alpha,\alpha'$-diadamantyl-sexithiophene 60 could be synthesized in 77% yield by the reaction of the corresponding Grignard reagent of the brominated adamantyl-substituted oligothiophene 59 by using Ni(dppp)Cl$_2$ as catalyst in the homocoupling (Scheme 119).

Scheme 119: Synthesis of $\alpha,\alpha'$-diadamantyl-sexithiophene 60 via Ni-catalyzed dimerisation of 59.

Since the solubility of unsubstituted sexithiophene is lower than 50 mg/l chloroform and even the $\alpha,\alpha'$-di-$n$-hexyl-substituted sexithiophene shows only a low solubility, it is noteworthy that the $\alpha,\alpha'$-diadamantyl-sexithiophene 60 is excellent soluble in all common organic solvents. The high solubility arises most probably from two reasons; on one hand, the apolar adamantyl-moiety is known to strongly increase the lipophilicity of molecules and on the other hand its bulkiness should prevent the $\pi$-stacking of the oligothiophenes.

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6. FULL FUNCTIONALIZATION OF THE IMIDAZOLE SCAFFOLD BY SELECTIVE METALATION AND SULFOXIDE/MAGNESIUM EXCHANGE

6.1 INTRODUCTION

Among functionalized imidazole derivatives a huge variety of compounds are known to possess a broad range of significant biological properties or are important templates in medicinal chemistry (e.g. as antibacterial, anticancer or anti-inflammatory pharmaceuticals). Due to their importance a number of methods has been described in the literature allowing the construction of the heteroaromatic core of these substances by cyclization protocols. However, recently much more attention lay on the design and development of efficient protocols that are based on the selective functionalization of the imidazole ring via transition metal-catalyzed reactions. This enabled the synthesis of imidazole derivatives, including bioactive and/or naturally occurring compounds, which cannot be accessed by other means.

Rossi et al. described in 2007 a attractive, convenient and practical procedure for the synthesis of free (NH)-2-arylimidazoles. Free (NH)-imidazoles were reacted with 2 equivalents of electron-deficient, electron-rich or electron-neutral aryl iodides in DMF in the presence of a catalytic amount of Pd(OAc)$_2$ and 2 equivalents of CuI under base-free and ligandless conditions to give the required 2-arylimidazoles in satisfactory yields and with excellent regioselectivity (Scheme 120).

Scheme 120: Pd-catalyzed Cu-mediated arylation at position 2 with aryl iodides.

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Sessler and coworkers reported a procedure for the synthesis of 2,2’-biimidazoles via a Pd-catalyzed homocoupling of 2-iodoimidazoles in toluene in the presence of Et₃N (Scheme 121). These 2-iodo derivatives were synthesized by treatment of the corresponding 2-unsubstituted imidazoles with N-iodosuccinimide (NIS) in refluxing THF (Scheme 121).

Scheme 121: Synthesis of free (NH)-2,2’-biimidazole derivatives.

Starting from 1987, Stille-type reactions have frequently been used to introduce organic groups at the 2-position of 1-methylimidazole derivatives. 1-Methyl-2-tributylstannylimidazole, commercially available but also readily accessible in high yield by C-2 lithiation of 1-methylimidazole followed by treatment with tributyltin chloride, has been used in Pd-catalyzed reactions. Wasserscheid et al. used catalytic amounts of PdCl₂(PPh₃)₂ in a Stille-type reaction of 1-methyl-2-tributylstannylimidazole with 4-fluoroiodobenzene in THF under reflux to synthesize 2-(4-fluorophenyl)-1-methylimidazole in 70% yield (Scheme 122).

Scheme 122: Stille-type reaction of 1-methyl-2-tributylstannylimidazole.

In 2003, Sudhçlter and coworkers prepared a 2,6-diimidazol-2-ylpyridine derivative in 79% yield via Pd(PPh₃)₄-catalyzed double cross-coupling reaction of 1-methyl-2-tributylstannylimidazole with 2,6-dibromo-4-ethoxycarbonylpyridine in toluene under reflux (Scheme 123).

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B. RESULTS AND DISCUSSION

Scheme 123: Stille-type reaction of 1-methyl-2-tributylstannylimidazole.

Also Suzuki-Miyaura cross-coupling reactions have been employed successfully to introduce aryl and alkenyl groups into the 2-position of imidazole derivatives. In 2005, Langhammer and Erker reported the Pd(PPh\textsubscript{3})\textsubscript{4}-catalyzed reaction of 2-iodo-1-[(4-methylthio)phenyl]imidazole with 3-methoxyphenylboronic acid in the presence of K\textsubscript{2}CO\textsubscript{3} as the base to give the arylated imidazole in 78% yield (Scheme 124). 2-iodo-1-[(4-methylthio)phenyl]imidazole, which was employed as the electrophile, was obtained by C-2 lithiation of 1-[(4-methylthio)phenyl]-imidazole and subsequent quenching with iodine.\(^{246}\)

Scheme 124: Suzuki-Miyaura cross-coupling reaction of 2-iodo-1-[(4-methylthio)phenyl]-imidazole.

Stille-type cross-couplings have also frequently been used to efficiently introduce organic groups into the 4-position of 1-substituted imidazoles. In 1996, Cliff and Pyne described a Pd\textsubscript{2}(dba)\textsubscript{3}/AsPh\textsubscript{3}/CuI-catalyzed reaction of 1-ethoxymethyl-4-trimethylstannylimidazole with \(\beta\)-bromostyrene (\(E/Z=10:1\)) furnishing (\(E\))- and (\(Z\))-1-ethoxymethyl-4-(2-phenylethenyl)imidazole in 68% and 12% yield, respectively (Scheme 125). The 1-substituted 4-trialkylstannylimidazole was prepared by treatment of the corresponding iodo-imidazole derivative with EtMgBr in CH\textsubscript{2}Cl\textsubscript{2} followed by quenching with Me\textsubscript{3}SnCl (Scheme 125).\(^{247}\)

\(^{246}\) I. Langhammer, T. Erker, Heterocycles 2005, 65, 2721.
**Scheme 125:** Stille-type reaction for the functionalization of position 4 on the imidazole ring.

In 2000, Wrobel et al. developed a three-step synthesis for the selective arylation in position 5 of the imidazole ring. The iodoimidazole was prepared by C-2 lithiation of 1-methylimidazole followed by treatment with diphenyl disulfide. The resulting compound was then sequentially treated with nBuLi in THF at -78 °C and iodine to give 5-iodo-1-methyl-2-phenylsulfonylimidazole in 80% yield (Scheme 126).\(^{248}\) Subsequently, a **Suzuki-Miyaura** reaction of 5-iodo-1-methyl-2-phenylsulfonylimidazole with phenylboronic acid furnished the arylated imidazole in 73% yield (Scheme 126). It should be mentioned that the PdCl\(_2\)(PPh\(_3\))\(_2\)-catalyzed Stille-type reaction of the iodoimidazole derivative with phenyltrimethylstannane in DMF led to the cross-coupling product in less yield (62%) than in the Suzuki-Miyaura reaction with phenylboronic acid under the conditions shown in Scheme 126.\(^{249}\)

**Scheme 126:** Three-step synthesis for the selective functionalization of position 5 on the imidazole ring.

In 2010, Sames and coworkers reported a general and comprehensive approach for the synthesis of complex aryl imidazoles, in which all three C–H bonds of the imidazole core have been arylated in a regioselective and sequential manner.\(^{250}\) To circumvent the low reactivity of the C-4 position, a transfer from the protecting group on N-1 to N-3 nitrogen was introduced. This enabled the preparation of 4-arylimidazoles and sequential C4-C5-arylation of the imidazole core (Scheme 127), providing rapid access to all regioisomers of mono-, di-, and triarylimidazoles.\(^{250}\)


There are a number of established protocols for the synthesis of substituted imidazoles where the imidazole ring is constructed via cyclo-condensation as well as via direct arylation reactions. Although these approaches have been improved over the past decade, each method has its scope and efficiency limitations like generation of isomers or unselective functionalization reactions. In contrast to conventional condensation and arylation methods, selective metalation reactions would enable the derivatization and elaboration of the imidazole ring in a regioselective manner and provide new possibilities for the synthesis of complex imidazole derivatives. Hence, we were looking for a mild and general metalation protocol allowing the flexible synthesis of individually substituted imidazole derivatives.

### 6.2 Overview

TMP-bases like TMPMgCl-LiCl or TMPZnCl-LiCl are known as mild and chemoselective metalating reagents for hydrogen-metal interconversion on sensitive substrates. A variety of sensitive aromatic and heteroaromatic compounds could be smoothly metalated and subsequently functionalized. Hence, we decided in the search for a general, selective and flexible methodology for the full functionalization of the imidazole scaffold to focus on metalation reactions using these type of bases.

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Scheme 128 illustrates a general overview for the fully functionalization of the imidazole scaffold starting from the double protected imidazole 61.

**Scheme 128:** Selective fully functionalization of the imidazole ring in a regioselective manner.

The protected imidazole 61 was regioselective metalated in position 5 by using TMPMgCl-LiCl (62). The subsequent sulfonylation employing 4-methoxy-3,5-dimethyl-benzenesulfonyl chloride\(^{253c,252,253,254}\) (68a) led to imidazole 67. The sulfoxide group on position 5 was found to be essential for the full functionalization procedure, since it allows both the direct metalation in \textit{ortho} position and its replacement by a sulfoxide/magnesium exchange. Hence, the sulfoxide substituent enabled the subsequent metalation with TMPMgCl-LiCl (62) in position 4. After functionalization of the magnesium species 69 imidazoles of type 70 were obtained. The next functionalization step was performed in position 5 by means of a sulfoxide/magnesium exchange. Thus, treatment of imidazole derivatives 70 with \textit{i}PrMgCl-LiCl (63) led to the corresponding magnesium intermediates 71 which could readily be functionalized leading to imidazoles of type 72. The protecting group in position 2 was then selectively removed followed by metalation using either TMPMgCl-LiCl (62) or TMPZn-2MgCl-2LiCl (65). The metalated imidazole derivatives 74 and 75 were then functionalized to give imidazoles of type 76. In the final step, the N-3 nitrogen was selectively alkylated by using Meerwein’s reagent (66, triethylxonium tetrafluoroborate) furnishing the corresponding imidazolium salts 77. Afterwards, nitrogen N-1 was deprotected and the alkylated imidazoles of type 78 were obtained. Using this protocol, all positions of the imidazole scaffold could be functionalized in a selective manner.

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6.3 SELECTIVE FUNCTIONALIZATION ON POSITION 4 OF THE IMIDAZOLE RING

Preliminary experiments have shown that the best combination of protecting groups for the use of TMP-bases in the full functionalization of the imidazole scaffold is a TBDMS-group in position 2 and a $N,N$-dimethylsulfamoyl group at nitrogen N-1 (position 1). The TBDMS-group has proven to be stable under the metalation conditions but is also easily removable by treatment with TBAF.  

Since the main challenge faced by the regioselective functionalization of imidazoles is the differentiation of positions 4 and 5 we envisioned an elegant way to solve this issue by introduction of a protecting group on the N-1 nitrogen directing the metalation to position 5. When positioned on an aromatic ring, the $N,N$-dimethylsulfamoyl group is known to direct lithiation in the ortho position. Moreover, if position 2 of the imidazole is already substituted, the presence of this sulfamoyl group on N-1 enables highly selective deprotonation in position 5.

Thus, metalation of the protected imidazole with the highly chemoselective base TMPMgCl·LiCl ($\text{62, 1.1 equiv, 25 °C, 1 h}$) leads to magnesiation in position 5, directed by the sulfamoyl group on nitrogen N-1. Subsequent sulfonylation employing 4-methoxy-3,5-dimethyl-benzenesulfonyl chloride ($\text{68a, 0.9 equiv, -20 to 25 °C, 4 h}$) furnishes imidazole $\text{67 in 86% yield (Scheme 129).}$

Scheme 129: Selective metalation in position 5 of the imidazole ring with TMPMgCl·LiCl ($\text{62}$) and subsequent sulfoxide synthesis.

As mentioned before, the sulfoxide group on position 5 was found to be essential for the full functionalization procedure, since it allows the direct metalation in ortho position (position 4). Hence, the sulfoxide substituent enables the selective metalation of imidazole 67 in position 4 with TMPMgCl·LiCl (62, 1.1 equiv, -30 °C, 1 h) in an almost quantitative manner. The resulting magnesium reagent 69 was readily used in different types of functionalization reactions furnishing the corresponding 4-substituted imidazoles of type 70 (Schemes 130-133 and Table 28).

![Scheme 130: Selective metalation in position 4 of the imidazole ring with TMPMgCl·LiCl (62) and subsequent functionalization (additional complexed salts are omitted for the sake of clarity).](image)

Thus, after transmetalation with ZnCl$_2$ (1.1 equiv, -30 °C, 15 min), the magnesium reagent 69 undergoes smooth Pd-catalyzed Negishi cross-coupling reactions. Using 5% Pd(PPh$_3$)$_4$ as catalyst, various electron-rich and electron-poor electrophiles (0.9 equiv) are used in the cross-coupling at 50 °C affording the 4-substituted imidazole derivatives 70a-f in good to excellent yields (Table 28, entries 1-6). Noteworthy, not only the simple aryl iodides 68b-e could be used in the cross-coupling reactions (entries 1-4), also a pyridyl (68f, entry 5) and a vinylic iodide (68g, entry 6) lead to good results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent[a]</th>
<th>Electrophile</th>
<th>Product, Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>68b</td>
<td>70a: 84%[c]</td>
</tr>
</tbody>
</table>

Table 28: Selective metalation in position 4 of the imidazole 67 with TMPMgCl·LiCl (62) and subsequent Negishi cross-coupling reactions.
B. RESULTS AND DISCUSSION

2 69 68c 70b: 72%[c]

3 69 68d 70c: 71%[c]

4 69 68e 70d: 60%[c]

5 69 68f 70e: 60%[c]

6 69 68g 70f: 83%[c]

[a] Obtained after metalation with TMPMgCl·LiCl (1.1 equiv) in THF at -30 °C in 1 h. [b] Yield of analytically pure isolated product as determined by 1H NMR analysis. [c] Obtained after a Negishi cross-coupling (ZnCl₂ (1.1 equiv); then 5% Pd(PPh₃)₄) with R-I (0.9 equiv).
Moreover, magnesium reagent 69 also undergoes after transmetalation with ZnCl₂ (1.1 equiv) a Cu(I)-catalyzed allylation reaction\textsuperscript{146} with ethyl 2-(bromomethyl)acrylate (68h, 0.9 equiv) leading to the desired product 70g in 98% yield (Scheme 131).

Scheme 131: Selective metalation in position 4 of the imidazole ring with TMPMgCl·LiCl (62) and subsequent Cu-catalyzed allylation (additional complexed salts are omitted for the sake of clarity).

Furthermore, the Cu(I)-catalyzed acylation reaction\textsuperscript{146} of magnesium reagent 69 using 4-chlorobenzoyl chloride (68i, 0.9 equiv) affords the corresponding ketone 70h in 82% yield (Scheme 132).

Scheme 132: Selective metalation in position 4 of the imidazole ring with TMPMgCl·LiCl (62) and subsequent Cu-catalyzed acylation (additional complexed salts are omitted for the sake of clarity).

The Cu(I)-catalyzed reaction\textsuperscript{11a,146} of magnesium reagent 69 with the bromoacetylene 68j\textsuperscript{260} (0.9 equiv) affords the highly functionalized acetylene 70i in 53% yield (Scheme 133).

RESULTS AND DISCUSSION

Scheme 133: Selective metalation in position 4 of the imidazole ring with TMPMgCl-LiCl (62) and subsequent Cu-catalyzed alkynylation (additional complexed salts are omitted for the sake of clarity).

6.4 SELECTIVE FUNCTIONALIZATION ON POSITION 5 OF THE IMIDAZOLE RING

The next functionalization was performed in position 5 by means of a sulfoxide/magnesium exchange.\textsuperscript{153c,252,253} Thus, treatment of imidazole derivatives of type 70 with \textit{i}PrMgCl-LiCl (63, 1.2 equiv) at -78 °C leads within 1 h to the corresponding magnesium intermediates of type 71 in almost quantitative yield (Scheme 134). Subsequently, different types of functionalization reactions have been carried out furnishing the corresponding 4- and 5-substituted imidazoles of type 72 (Schemes 134-136 and Table 29).

After transmetalation with ZnCl\textsubscript{2} (1.2 equiv, -78 °C, 15 min), the magnesium reagents of type 71 readily undergo Pd-catalyzed \textit{Negishi} cross-coupling reactions. Thus, the allyl-substituted imidazole derivative 71a reacts with 5% of Pd(PPh\textsubscript{3})\textsubscript{4} as catalyst at 50 °C and ethyl 4-iodobenzoate (68b, 0.9 equiv) and 4-iodobenzonitrile (68k, 0.9 equiv) to the corresponding cross-coupling products 72a-b in good to excellent yields (Table 29, entries 1 and 2). Also the vinylic substituted imidazole derivative 70f readily undergoes after the sulfoxide/magnesium exchange and transmetalation with ZnCl\textsubscript{2} (1.2 equiv, -78 °C, 15 min) Pd-catalyzed \textit{Negishi} cross-coupling reactions (entries 3 and 4). Noteworthy, the double bond stays untouched and no isomerisation occurs.
magnesium species 71c-e of the arylated imidazole derivatives have also been submitted to Pd-catalyzed Negishi reactions furnishing the corresponding cross-coupling products 72c-i in high yields (entries 5-9).

Table 29: Selective sulfoxide/Mg exchange in position 5 of imidazole derivatives of type 70 with iPrMgCl·LiCl (63) and subsequent Negishi cross-coupling reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent[a]</th>
<th>Electrophile</th>
<th>Product, Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71a</td>
<td>68b</td>
<td>72a: 71%</td>
</tr>
<tr>
<td>2</td>
<td>71a</td>
<td>68k</td>
<td>72b: 90%</td>
</tr>
<tr>
<td>3</td>
<td>71b</td>
<td>68g</td>
<td>72c: 88%</td>
</tr>
<tr>
<td>4</td>
<td>71b</td>
<td>68l</td>
<td>72d: 100%</td>
</tr>
<tr>
<td>5</td>
<td>71c</td>
<td>68g</td>
<td>72e: 60%</td>
</tr>
</tbody>
</table>
In order to prove the existence of the magnesium species and to clarify whether the cross-coupling is a Negishi reaction and not a Heck-type reaction, the magnesium species 71c of imidazole derivative 70a has been submitted to a reaction with 4-fluorobenzaldehyde (68m, 0.9 equiv) after the sulfoxide/magnesium exchange. The obtained alcohol 72j clearly demonstrated the availability of magnesium species 71c (Scheme 135).
Cu(I)-catalyzed acylation reactions of magnesium reagents of type 71 furnished only hydrolyzed species. Hence, a Pd-catalyzed acylation reaction has been employed leading to the desired ketone derivatives in good to excellent yields (Scheme 136). The vinylic substituted imidazole 70f reacted with 4-chlorobenzoyl chloride (68i, 0.9 equiv) and 5% Pd(PPh₃)₄ after sulfoxide/magnesium exchange and transmetalation with ZnCl₂ (1.2 equiv, -78 °C, 15 min) to the corresponding ketone 72k in 79% yield. Also the arylated imidazole 70a furnishes under the same reaction conditions the corresponding ketone 72l in 66% yield (Scheme 136).

Scheme 135: Selective sulfoxide/Mg exchange in position 5 of the imidazole ring with iPrMgCl·LiCl (63) and subsequent addition to aldehyde 68m (additional complexed salts are omitted for the sake of clarity).

Scheme 136: Selective sulfoxide/Mg exchange in position 5 of the imidazole ring with iPrMgCl·LiCl (63) and subsequent Pd-catalyzed acylation (additional complexed salts are omitted for the sake of clarity).

---

6.5 Selective Functionalization on Position 2 of the Imidazole Ring

6.5.1 Selective Deprotection on Position 2

In order to be able to functionalize in position 2, the TBDMS-group had to be selectively removed from the imidazole ring. As illustrated in Scheme 137 imidazole derivatives of type 72 have been treated with tetra-n-butylammonium fluoride (64, 1 equiv) at 0 °C to cleave the C–Si-bond and furnish the unprotected imidazoles 73 in quantitative yield while leaving the N,N-dimethylsulfamoyl group at the N-1 untouched.

Scheme 137: Selective deprotection with TBAF·3H₂O (64) in position 2 of the imidazole ring.

Thus, the double functionalized imidazole derivatives 72f and 72h-i could selectively deprotected leading to the corresponding imidazoles 73a-c in excellent yields (Table 30).

Table 30: Selective deprotection with TBAF·3H₂O (64) at position 2 of imidazoles of type 72.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imidazole Derivative</th>
<th>Deprotection Reagent</th>
<th>Product, Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72f</td>
<td>TBAF·3H₂O</td>
<td>73a: 93%[b]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>72h</td>
<td>TBAF·3H₂O</td>
<td>73b: 94%[b]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>72i</td>
<td>TBAF·3H₂O</td>
<td>73c: 100%[b]</td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure isolated product as determined by 'H NMR analysis. [b] Obtained after addition of tetra-n-butylammonium fluoride (1 equiv).
6.5.2 **Selective Functionalization on Position 2**

For the metalation of position 2 of the imidazole scaffold two pathways were developed. Preliminary experiments have shown that either TMP$_2$Zn·2MgCl·2LiCl (65) or TMPMgCl·LiCl (65) could be employed as metalating reagents.

Due to the mild and chemoselective properties of TMP$_2$Zn·2MgCl·2LiCl (65), the metalating reaction of imidazoles derivatives of type 73 can be carried out at -20 °C furnishing the corresponding diimidazolylyzinc derivatives 74 in almost quantitative yield within 1 h (Scheme 138). Subsequent functionalization reactions lead to the fully functionalized imidazole derivatives 76 (Table 31).

![Scheme 138: Selective metalation in position 2 of the imidazole ring TMP$_2$Zn·2MgCl·2LiCl (65) and subsequent functionalization (additional complexed salts are omitted for the sake of clarity).](image)

The Cu(i)-catalyzed allylation reaction of the imidazole zinc reagent 74a with ethyl 2-(bromomethyl)acrylate (68h, 1.1 equiv) leads to the desired full functionalized imidazole 76a in 81% yield (Table 31, entry 1). Additionally, a Pd-catalyzed Negishi cross-coupling reaction with 1-iodo-4-nitrobenzene (68l, 0.9 equiv) produces the highly functionalized imidazole derivative 76b in 76% yield (entry 2). Furthermore, also the imidazole zinc reagent 74b undergoes smoothly a Cu(i)-catalyzed allylation with ethyl 2-(bromomethyl)acrylate (68h, 0.9 equiv) furnishing imidazole 76c in 86% yield (entry 3). The Pd-catalyzed Negishi cross-coupling reactions with ethyl 4-iodobenzoate (68b, 1.1 equiv) and 4-iodobenzonitrile (68k, 0.9 equiv) produces the highly functionalized imidazole derivatives 76d and 76e in 72% and 95% yield (entries 4 and 5).

**Table 31: Selective metalation in position 2 of imidazole derivatives of type 73 with TMP$_2$Zn·2MgCl·2LiCl (65) and subsequent functionalization.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn-Reagent $^{[a]}$</th>
<th>Electrophile</th>
<th>Product, Yield $^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74a</td>
<td>68h</td>
<td>76a: 81% $^{[c]}$</td>
</tr>
</tbody>
</table>
As illustrated in Scheme 139, position 2 of the imidazole scaffold could also be metalated using TMPMgCl-LiCl (62, 1.2 equiv) at -78 °C. Within 1 h, the reaction furnished the imidazol magnesium derivatives 75 in an almost quantitative manner. Functionalization reactions lead to the highly substituted imidazoles 76 (Table 32).

Scheme 139: Selective metalation in position 2 of the imidazole ring with TMPMgCl-LiCl (62) and subsequent functionalization (additional complexed salts are omitted for the sake of clarity).
B. RESULTS AND DISCUSSION

In order to demonstrate the higher reactivity of the magnesium reagents of type 75 compared to the diimidazolylzinc reagents of type 74, imidazole derivative 75a has been submitted to an addition reaction with 4-fluorobenzaldehyde (68m, 1.1 equiv) furnishing the corresponding alcohol 76f in 92% yield (Table 32, entry 1). Moreover, the magnesium reagent 75a also reacts smoothly with S-(3,4-dichlorophenyl) benzenesulphonothioate (68n, 0.9 equiv) affording thioether 76g in 93% yield (entry 2). The corresponding diimidazolylzinc reagent 74b could not undergo these two reactions and led only to the hydrolyzed species. Since Cu(I)-catalyzed acylation reaction does not proceed, a Pd-catalyzed acylation reaction has been employed leading to the desired ketone derivative in a good yield. The magnesium derivative 75a reacts with 4-chlorobenzoyl chloride (68i, 1.1 equiv) and 5% Pd(PPh$_3$)$_4$ after transmetalation with ZnCl$_2$ (1.2 equiv, -78 °C, 15 min) to the corresponding ketone 76h in 58% yield (entry 3). Furthermore, after transmetalation with ZnCl$_2$ (1.2 equiv, -78 °C, 15 min), the magnesium species 75b successfully undergoes a Pd-catalyzed Negishi cross-coupling reaction furnishing imidazol 76i in 75% yield (entry 4). Moreover, the magnesium reagent 75b also reacts readily with S-(3,4-dichlorophenyl) benzenesulphonothioate (68n, 0.9 equiv) affording the corresponding thioether 76j in 70% yield (entry 5).

Table 32: Selective metalation in position 2 of imidazole derivatives of type 73 with TMPMgCl·LiCl (62) and subsequent functionalization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg-Reagent$[^a]$</th>
<th>Electrophile</th>
<th>Product, Yield$[^b]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75a</td>
<td>68m</td>
<td>76f: 92%$[^c]$</td>
</tr>
<tr>
<td>2</td>
<td>75a</td>
<td>68n</td>
<td>76g: 93%$[^e]$</td>
</tr>
</tbody>
</table>
B. RESULTS AND DISCUSSION

3  
75a  
68i  
76h: 58%[d]

4  
75b  
68k  
76i: 75%[f]

5  
75c  
68n  
76j: 70%[e]

[a] Obtained after metatation with TMPMgCl·LiCl (1.2 equiv) in THF at -78 °C in 1 h. [b] Yield of analytically pure isolated product as determined by 1H NMR analysis. [c] Obtained after addition to 4-fluorobenzaldehyde (1.1 equiv). [d] Obtained after a Negishi acylation (ZnCl2 (1.1 equiv); then 5% Pd(PPh3)4 with 4-chlorobenzyl chloride (1.1 equiv)). [e] Obtained after addition to S-aryl benzenethiosulfonate (0.9 equiv). [f] Obtained after a Negishi cross-coupling (ZnCl2 (1.2 equiv); then 5% Pd(PPh3)4 with 4-iodobenzonitrile (0.9 equiv)).

6.6 SELECTIVE N-3-ALKYLATION AND SUBSEQUENT N-1-DEPROTECTION

Depending on the substitution pattern, N-protected imidazoles have shown the tendency to tautomerize leading to mixtures of isomers after deprotection (due to steric factors). N-sulfamoylimidazoles are known to react with alkylating reagents exclusively via their nonsubstituted nitrogen atom since alkylation on N-1 is hampered. Moreover, the formation of an imidazolium salt by N-3-alkylation increases the lability of the dimethylsulfamoyl group allowing its removal via the addition of

concentrated HCl.\textsuperscript{264} The outcome of this procedure is thus the \(N\)-alkylation of the imidazole ring selectively at the previously nonsubstituted nitrogen atom.\textsuperscript{265}

Hence, the fully functionalized imidazole derivatives of type 76 have been treated with \textit{Meerwein’s} reagent (66, trimethyloxonium tetrafluoroborate, 1 equiv) generating the corresponding imidazolium salts 77. The \(N,N\)-dimethylsulfamoyl group at the N-1 is then cleaved by addition of concentrated HCl furnishing the alkylated imidazoles of type 78 in good yields (Scheme 140).

![Scheme 140: Selective methylation with \textit{Meerwein’s} reagent (66) at position N-3 of the imidazole ring and subsequent deprotection at position N-1.](image)

Thus, the fully functionalized imidazole 76e undergoes smoothly the described alkylation/deprotection procedure leading to the methylated imidazole 78a in 72% yield as the only isomer (Table 33, entry 1). By using regioisomer 76i of imidazole 76e, the corresponding alkylated isomer 78b could be obtained (entry 2). Additionally, also the thioether-substituted isomeric imidazoles 76g and 76j have been alkylated successfully furnishing the regioisomeric imidazoles 78c and 78d in 65% and 72% yield, respectively (entries 3 and 4).

![Table 33: Selective methylation with \textit{Meerwein’s} reagent (66) at position N-3 of imidazole derivatives of type 76 and subsequent deprotection at position N-1.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imidazole Derivative</th>
<th>Methylating Reagent</th>
<th>Product, Yield\textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76e</td>
<td>66</td>
<td>78a: 72%\textsuperscript{[b]}</td>
</tr>
</tbody>
</table>


B. RESULTS AND DISCUSSION

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>[76i]</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>[78b] 74%[b]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>[76g]</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>[78c] 65%[b]</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>[76j]</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>[78d] 72%[b]</td>
<td></td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure isolated product as determined by $^1$H NMR analysis. [b] Obtained after addition of trimethyloxonium tetrafluoroborate (1 equiv) and subsequent treatment with HCl (excess).
7. SUMMARY AND OUTLOOK

This work focused on the development of a convenient and general regioselective Br/Mg-exchange reaction for unsymmetrically substituted dibromoheterocycles allowing the preparation of various thienyl-, furyl- and pyridyl-magnesium derivatives. Furthermore, in the search of a general and atom-economical method for preparing boronic derivatives suitable for cross-coupling reactions, a one-pot procedure using inexpensive aryl bromides, magnesium as a low-cost reducing agent with little toxicity and atrialkylborate as cheap boron source was established. In order to overcome the lack of a convenient and practical direct synthesis for α-substituted β,γ-unsaturated ketones and esters, their preparation via the addition of readily available substituted allylic zinc reagents to a broad range of acid chlorides and chloroformates was disclosed. Moreover, the LiCl-mediated metal insertion into alkyl bromides, aromatic halides as well as benzylic chlorides was extended to highly functionalized alkenyl bromides for the effective preparation of alkenyl zinc reagents bearing for the first time sensitive functional moieties. Due to the lack of a general methodology for the selective synthesis of adamantyl organometallic reagents, a mild and convenient procedure for the selective synthesis of adamantyl organometallics and their subsequent functionalization was developed. Furthermore, the adamantyl moiety was introduced as substituent in oligothiophenes, dramatically increasing their solubility. Finally, a methodology for the selective and predictable functionalization of all positions of the imidazole scaffold starting from simple imidazole by directed metalation and sulfoxide/magnesium exchange was developed.

7.1 HIGHLY REGIOSELECTIVE PREPARATION OF HETEROARYL-MAGNESIUM REAGENTS USING A Br/Mg-EXCHANGE

A highly regioselective preparation of five- and six-membered heteroarylmagnesium derivatives was developed. The efficient Br/Mg-exchange reagents iPrMgCl·LiCl (1a) and isitylMgBr·LiCl (1c) proved to undergo highly regioselective Br/Mg-exchange reactions with unsymmetrically substituted dibromo-heterocycles 2 derived from thiophenes, benzo[b]thiophenes or pyridines. Ring-substituents such as thioether or trimethylsilyl groups, as well as pyridyl and thienyl groups or ortho-substituted aryl groups directed the Br/Mg-exchange in position 5 with a regioselectivity of up to >99:1 (Scheme 141). The corresponding magnesium reagents 3 were readily functionalized through e.g. Negishi cross-coupling reactions, acylations or addition to aldehydes.
B. RESULTS AND DISCUSSION

Scheme 141: Regioselective Br/Mg-exchange on unsymmetrical dibromoheterocycles using iPrMgCl·LiCl (1a).

Scheme 142: Further functionalization of cross-coupling product 5g via Br/Mg-exchange and subsequent reactions with different electrophiles.

In order to exemplify the further functionalization of monobromo-thiophenes of type 5 obtained after the selective Br/Mg-exchange, the previously prepared monobromo-thiophene 5g was submitted to a second Br/Mg-exchange reaction using iPrMgCl·LiCl (1a). The resulting magnesium reagent 6 was readily used in different types of functionalization reactions (Scheme 142).

In case of alkyl substituted dibromo-thiophene or -furan derivatives the sterically hindered Grignard reagent 2,4,6-trisopropylphenylmagnesium bromide (isitylMgBr·LiCl, 1c) furnished in combination with the chelating diamine 2,2'-oxy-
bis(N,N-dimethylethanamine) \((L^2)\) the best regioselectivities in the Br/Mg-exchange. The selectively magnesiated heterocyclic scaffolds \(12\) were subsequently functionalized with a broad range of different electrophiles like aldehydes, aryl iodides, acyl chlorides or aryl sulfinyl chlorides (Scheme 143).

Scheme 143: Regioselective Br/Mg-exchange on unsymmetrical dibromoheterocycles of using isitylMgBr·LiCl (1c) and ligand \(L^2\).

The disclosed method is very versatile and might find application e.g. for the synthesis of poly(3-hexylthiophene) (P3HT),\(^{266}\) in which the regioregularity determines macroscopic physical properties of the polymers.\(^{267}\)


7.2 One-pot Preparation of Magnesium Di(hetero)aryl- and Diallyl-boronates for Suzuki-Miyaura Cross-Couplings

Organoboronic derivatives are essential reagents for modern cross coupling chemistry. Since there is a continuous need for efficient synthetic routes for their preparation, a convenient, general and atom-economical method for preparing boronic derivatives in one step was investigated. The treatment of aryl and heteroaryl bromides as well as alkenyl halides with Mg turnings, B(OBu)$_3$ and LiCl in THF at ambient temperature leads within 1 h to the corresponding magnesium organoboronates tolerating a broad variety of functional groups. This atom-economical synthesis gives readily access to functionalized diaryl and diheteroaryl as well as to dialkenylboronates from their corresponding organic bromides and might find its way into industrial syntheses. A good atom economy was achieved without loss of yield by using 0.5 equiv of B(OBu)$_3$ and forming therefore magnesium diorganoboronates of type 20 (Scheme 144).

\[
\begin{align*}
R^1\text{-Br} + \text{B(OBu)$_3$, Mg, LiCl} \rightarrow \text{Mg(OR)$_2$} \rightarrow \text{R}^1\text{-R}^2
\end{align*}
\]

Scheme 144: General equation for the synthesis and cross-coupling of magnesium diorganoboronates of type 20.

Remarkably, both organo-groups (R$^1$) were transferred under typical Suzuki-Miyaura cross-coupling conditions with various aryl halides or pseudo-halides of type R$^2$-X furnishing the corresponding products in excellent yields (Figure 12).

Figure 12: Cross-coupling products generated from diorganoboronates of type 20.
7.3 Preparation of α-substituted β,γ-unsaturated ketones and esters via the direct addition of substituted allylic zinc reagents

A practical and convenient procedure for the synthesis of α-substituted β,γ-unsaturated ketones and esters was developed. Substituted allylic zinc reagents, prepared via direct metal insertion in substituted allylic halides, react readily with a broad range of acid chlorides and chloroformates furnishing the corresponding α-substituted β,γ-unsaturated ketones and esters in high yield and perfect regioselectivity.

The recently by Knochel et al. developed method allowed the preparation of poly-substituted allyl zinc reagents starting from the corresponding allyl halides almost without formation of homocoupling products. In order to expand this protocol, a broad variety of new allylic zinc organometallics was synthesized (Scheme 145).

![Scheme 145: LiCl-mediated preparation of substituted allylic zinc organometallics 30 via direct insertion of zinc powder.](image)

The addition of these highly reactive allylic zinc reagents (30a-i) to a broad range of acid chlorides 31 and chloroformates 35 proceeded under exceedingly mild conditions (-78 °C, 1-2 h) and furnished selectively β,γ-unsaturated ketones 32 and esters 36 without any traces of the α,β-unsaturated isomers (Scheme 146).
**Scheme 146:** Preparation of $\alpha$-substituted $\beta,\gamma$-unsaturated ketones (32) and esters (36) from allylic zinc reagents of type 30.

The diene-precursor 33 for a ring-closing metathesis (RCM) was readily synthesized from a $\alpha$-substituted $\beta,\gamma$-unsaturated ketone 32d in only one step via the diastereoselective addition of allyl magnesium chloride to the carbonyl moiety of 32d in almost quantitative yield (Scheme 147). The subsequent RCM using the second generation of *Grubbs’* catalyst furnished diastereoselectively cyclopentene derivative 34 in 97% yield.

**Scheme 147:** Diastereoselective addition of allyl magnesium chloride to 32d and subsequent ring-closing metathesis forming the cyclopentene derivative 34.
7.4 Preparation of Functionalized Alkenylzinc Reagents Bearing Carbonyl Groups via Direct Metal Insertion

A convenient, mild and atom-economical protocol for the synthesis of highly functionalized alkenylzinc reagents bearing sensitive carbonyl groups such as an aldehyde, a ketone or an ester was developed. Activated alkenyl bromides 37 underwent a direct insertion of zinc in the presence of LiCl furnishing the corresponding organozinc compounds 38. Subsequent functionalization reactions like Negishi cross-couplings, acylations or allylations were performed readily leading to polyfunctional compounds 40 in excellent yields (Scheme 148).

Scheme 148: Preparation of alkenylzinc reagents 38 from activated alkenyl bromides 37 via direct zinc insertion and subsequent functionalization.

Furthermore, acyclic alkenylzinc reagents 38f-i could be prepared from the corresponding acyclic bromides 37f-i without losing their stereochemistry due to the chelating effect of the Zn-center with the vicinal carbonyl group and allowed therefore the synthesis of trisubstituted olefins with excellent Z-selectivity (Scheme 149).

Scheme 149: LiCl-mediated zinc insertion into acyclic alkenyl bromides 37f-i leading to zinc reagents 38f-i and subsequent cross-coupling.
Electronically less activated alkenyl bromides 42 were converted to their corresponding zinc reagents 43 by using the stronger reducing metal magnesium in the presence of LiCl and ZnCl₂. Their subsequent functionalization with a broad variety of electrophiles furnished the substituted alkenyl derivatives 44 in high yields (Scheme 150).

Scheme 150: Preparation of alkenylzinc reagents 43 from less activated alkenyl bromides 42 via magnesium insertion in presence of ZnCl₂ and subsequent functionalization.

Due to their highly reactive nature, unsaturated 1,4-dicarbonyl compounds readily undergo condensation reactions with hydrazine providing tetrahydrophthalazines. Therefore, compound 40v smoothly reacted with hydrazine hydrate (NH₂NH₂·H₂O) in methanol to the corresponding 1-substituted tetrahydrophthalazine 41a in 54% yield (Scheme 151). Following this protocol, compounds 41b and 41c, bearing a 3-chlorophenyl- and a 2-thienyl-substituent respectively were prepared in 49-54% yield.

Scheme 151: Synthesis of substituted tetrahydrophthalazines of type 41.
7.5 Synthesis of Functionalized Adamantylzinc Reagents Using a Br/Mg-Insertion in the Presence of ZnCl₂

A practical and convenient procedure for the synthesis of substituted adamantyl zinc reagents was developed. The LiCl-mediated Mg insertion in the presence of ZnCl₂ allowed an efficient synthesis of adamantylzinc reagents starting from the corresponding functionalized tertiary bromides (Scheme 152).

![Chemical reaction]

Scheme 152: Preparation of functionalized adamantylzinc reagents 46 via the LiCl-mediated Mg-insertion in the presence of ZnCl₂ (additional complexed salts are omitted for the sake of clarity).

The highly reactive adamantylzinc species 46a-c readily undergo a broad variety of functionalization reactions in the presence of an appropriate catalyst. As illustrated in Scheme 153, Negishi cross-couplings, Cu(I)-catalyzed acylation and allylation as well as 1,4-addition reactions and many more could be successfully employed to generate highly functionalized adamantyl derivatives in high yields.

![Functionalization results]

Scheme 153: Highly functionalized adamantyl derivatives synthesized via functionalization of the corresponding adamantylzinc species 46a-c.
Furthermore, the adamantyl moiety could be introduced as substituent in oligothiophenes, dramatically increasing their solubility. Adamantylzinc reagent 46a readily underwent a Negishi cross-coupling reaction with the 5-bromo-terthiophene 49h furnishing the corresponding α-substituted oligothiophene 48s. Selective bromination of 48s followed by a Ni-catalyzed homocoupling reaction of the corresponding Grignard reagent of the bromo-oligothiophene 59 led to the α,α’-diadamantyl-sexithiophene 60 (Scheme 154).

![Scheme 154: Synthesis of α,α’-diadamantyl-sexithiophene 60.](image)

The presence of the apolar adamantyl-moiety strongly increases the lipophilicity of the sexithiophene. Combined with the bulkiness of the adamantine substituents preventing the π-stacking of the oligothiophenes, this explains the excellent solubility of compound 60 compared to the unsubstituted sexithiophene (solubility lower than 50 mg/l in chloroform234).

Recently Garnier et al. reported, that β-alkyl substituted oligothiophenes show an even higher solubility than the corresponding α-substituted ones.234 Since the adamantyl-substituents in α-position already proved to have an excellent impact on the solubility, it should be worth to investigate their effect as β-substituents. The increased solubility should provide the opportunity to synthesize much longer oligomers which would serve as desired models for the better understanding of polymeric systems.233
7.6 Full Functionalization of the Imidazole Scaffold by Selective Metalation and Sulfoxide/Magnesium Exchange

A general, selective and flexible approach for the synthesis of complex substituted imidazoles was developed. All three C–H bonds of the imidazole core could be functionalized in a regioselective and sequential manner by metalation using TMPMgCl–LiCl (62) and TMP₂Zn·2MgCl·2LiCl (65) as bases as well as by a selective sulfoxide/magnesium exchange triggered by iPrMgCl–LiCl (63) (Scheme 155).

Scheme 155: Selective fully functionalization of the imidazole ring in a regioselective manner.

The N,N-dimethylsulfamoyl group at nitrogen N-1 directed the metalation of imidazole 61 with TMPMgCl–LiCl (62) regioselectively in position 5. The subsequent sulfinylation employing 4-methoxy-3,5-dimethyl-benzenesulfinyl chloride (68a) led to imidazole 67. This substituent was found to be essential for the full functionalization procedure, since it allows both the direct metalation in ortho position and its replacement by a sulfoxide/magnesium exchange. Hence, the subsequent metalation with TMPMgCl–LiCl (62) occurred in position 4 enabling the selective functionalization in this position. The next functionalization step was performed in position 5 by means of a sulfoxide/magnesium exchange. Treatment of imidazole derivatives 70 with iPrMgCl–LiCl (63) led to the corresponding magnesium intermediates 71 which could readily be functionalized leading to imidazoles of type 72. After selective removal of the TBDMS-group in position 2 with TBAF·3H₂O (64), metalation either using TMPMgCl–LiCl (62) or TMP₂Zn·2MgCl·2LiCl (65) furnished the corresponding organometallic reagents 74 and 75 that were subsequently functionalized to give the fully substituted imidazoles of type 76 (Scheme 156).
Scheme 156: Fully functionalized imidazole derivatives of type 76.

*N*-sulfamoylimidazoles are known to react with alkylating reagents exclusively via their nonsubstituted nitrogen atom since alkylation on N-1 is blocked. Moreover, the formation of an imidazolium salt by N-3-alkylation increases the lability of the dimethylsulfamoyl group allowing its removal via the addition of concentrated HCl. Hence, the fully functionalized imidazole derivatives of type 76 were treated with Meerwein's reagent (66, trimethyloxonium tetrafluoroborate) generating the corresponding imidazolium salts 77. The N,N-dimethylsulfamoyl group at the N-1 was then cleaved by addition of concentrated HCl furnishing the alkylated imidazoles of type 78 (Scheme 157).

Scheme 157: Selective methylation with Meerwein's reagent (66) at position N-3 of the imidazole ring and subsequent deprotection at position N-1.
C. EXPERIMENTAL SECTION
1. General Considerations

All reactions were carried out under argon or nitrogen atmosphere in glassware dried with a heat gun. Syringes which were used to transfer anhydrous solvents or reagents were purged thrice with argon or nitrogen prior to use. THF was freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Indicated yields are isolated yields of compounds estimated to be >95% pure as determined by $^1$H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO$_2$ (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. Unless otherwise indicated, all reagents were obtained from commercial sources. Liquid starting materials were distilled prior to use. Magnesium turnings (> 99.5%), magnesium powder (> 99%) and zinc dust (> 90%) were obtained from Riedel-de Haën. CuCN, ZnCl$_2$ and LiCl were obtained from Fluka.

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$_2$.

CHCl$_3$ 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.

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

Toluene was predried over CaCl$_2$ and distilled from CaH$_2$.

NEt$_3$ was dried over KOH and distilled.

Solvents for column chromatography were distilled on a rotary evaporator prior to use.
1.2 REAGENTS

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid reagents were distilled prior to use.

*iPrMgCl·LiCl* solution in THF was purchased from Chemetall.

*nBuLi* solution in hexane was purchased from Chemetall.

TMPMgCl·LiCl was prepared according to a literature procedure.$^{28a}$

TMP₂Zn·2MgCl₂·2LiCl was prepared according to a literature procedure.$^{68a}$

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-flask under vacuum at 140 °C for 5 h. After cooling, 80 mL dry THF were added and stirring was continued until the salts were dissolved.

ZnCl₂ solution (1.00 M) was prepared by drying ZnCl₂ (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.

1.3 CONTENT DETERMINATION OF ORGANOMETALLIC REAGENTS

Organozinc and organomagnesium reagents were titrated with *I₂* in THF.$^{192}$

Organolithium reagents were titrated with dry 2-propanol and 1,10-phenanthroline as indicator in THF.$^{268}$

TMPMgCl·LiCl and TMP₂Zn·2MgCl₂·2LiCl were titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF.$^{28a, 68}$

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 254 nm UV irradiation, by

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incubating the plates in an iodine chamber and/or by staining of the TLC plate with one of the reagents 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).
- Ninhydrin (0.3 g) and AcOH (3.0 mL) in butanol (100 mL).

1.5 Analytical Data

¹H-NMR and ¹³C-NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to tetramethylsilane. The following abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet),qn (quintet), spt (septet), m (multiplet) as well as br (broadened).

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 ionization energy of 70 eV.

For coupled gas chromatography/mass spectrometry, a HEWLETT-PACKARD HP 6890/MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10%.

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. Wavenumbers are reported in cm⁻¹ starting at an absorption of 10%.

Melting points (m.p.) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected. Compounds decomposing upon melting are indicated by (decomp.).
2. HIGHLY REGIOSELECTIVE PREPARATION OF HETEROARYL-MAGNESIUM REAGENTS USING A BR/MG-EXCHANGE

2.1 PREPARATION OF STARTING MATERIALS

Preparation of 2,4,6-triisopropylphenylmagnesium bromide (1c)

Preparation of 2,4,6-triisopropylphenylmagnesium bromide (1c)

![MgBr-LiCl](image)

Magnesium turnings (3.64 g, 150 mmol, 1.5 equiv) and anhydrous LiCl (4.20 g, 100 mmol, 1.0 equiv) were placed in an Ar-flushed flask and dried with a heatgun at 450 °C for 10 min in vacuo. After cooling to 25 °C and purging with argon, THF (50 mL) was added. After addition of THF (60 mL), the magnesium was activated using 1,2-dibromoethane (2 mol %) and Me₃SiCl (5 mol %). Subsequently, a solution of 1-bromo-2,4,6-triisopropylbenzene (28.3 g, 100 mmol) in THF (40 mL) was slowly added at 25 °C. After addition, the reaction mixture was stirred for 12 h at 25 °C. Residual Mg was removed by cannulating the grey solution of 2,4,6-triisopropylmagnesium bromide (1c) to a dry and argon-flushed flask. The reagent was titrated prior to use by the method of Paquette or the method developed in our laboratory.

Dibromo-heteroaryl compounds 2a, 2b, 2d, 2i, 11c, 11e, and 11f were prepared according to literature procedures; compounds 11a, 11b and 11e were commercially available.

2,5-dibromo thiophenes 2b-c and 2e-h and 2j were prepared from 2,5-dibromo thiophene following a literature procedure. For 2b and 2c, the (2,5-dibromothiophen-3-yl)lithium was quenched with the corresponding diorgano disulfide at -78 °C followed by a standard aqueous workup and column chromatography. For the compounds 2f-h and 2j (2,5-dibromothiophen-3-yl)lithium was transmetalated with ZnCl₂ at -40 °C followed by a Negishi cross-coupling reaction with 4% Pd(PPh₃)₄ and 0.9 equiv of the corresponding aryl iodide in THF at 50 °C over night. After a standard workup the crude was purified via column chromatography.

2,5-dibromothieno[3,2-b]thiophene (2e) was prepared following a literature procedure\textsuperscript{147c} replacing NCS by NBS. The NBS was used as purchased without recrystallization.

2,5-dibromo pyridines 8a-8d and 15 were prepared from 2,5-dibromo pyridine following a literature procedure.\textsuperscript{28a} For 8a-8c, the magnesiated 2,5-dibromo pyridine derivative was transmetalated with ZnCl\textsubscript{2} at -40 °C followed by a Negishi cross-coupling reaction with 4 mol % Pd(PPh\textsubscript{3})\textsubscript{4} and 0.9 equiv of the corresponding aryl iodide in THF at 50 °C over night. After a standard workup the crude was purified via column chromatography. For 8d and 15, the magnesiated 2,5-dibromo pyridine derivative was quenched either with S-phenyl benzenesulfonothioate or TMSCN at -78 °C followed by a standard aqueous workup and column chromatography.

2,5-dibromo-3-(phenylthio)thiophene (2b)

\[
\text{m.p.: } 46.6-48.1 \degree C.
\]

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta \) (ppm) = 7.22-7.32 (m, 5H), 7.07 (s, 1H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta \) (ppm) = 135.6, 133.4, 130.1, 129.3, 128.4, 127.1, 119.6, 116.2.

\textbf{MS} (70 eV, EI), \(m/z \) (%) = 350 (M\textsuperscript{+}, 45), 348 (M\textsuperscript{+}, 21), 271 (24), 269 (22), 192 (10), 191 (14), 190 (100), 146 (13), 77 (9).

\textbf{HRMS} (EI), \(m/z \) calc. for C\textsubscript{10}H\textsubscript{6}Br\textsubscript{2}S\textsubscript{2} (349.8257): 349.8245 (M\textsuperscript{+}).

\textbf{IR} (ATR) \(\nu \) (cm\textsuperscript{-1}) = 3092, 3043, 3017, 3007, 2360, 2338, 1966, 1947, 1883, 1865, 1805, 1733, 1646, 1578, 1489, 1476, 1437, 1390, 1302, 1138, 1078, 1009, 965, 824, 737, 686, 678.
2-((2,5-dibromothiophen-3-yl)thio)pyridine (2c)

![Chemical structure of 2c](image)

**m.p.:** 45.8-47.5 °C.

**$^1$H NMR** (400 MHz, d6-DMSO) $\delta$ (ppm) = 8.42 (ddd, $J=4.8$Hz, 1.8Hz, 1.0Hz, 1H), 7.72 (td, $J=7.8$Hz, 1.9Hz, 1H), 7.21 (ddd, $J=7.4$Hz, 4.9Hz, 2.0Hz, 1H) 7.58 (s, 1H), 7.04 (d, $J=8.2$Hz, 1H).

**$^{13}$C NMR** (100 MHz, d6-DMSO) $\delta$ (ppm) = 157.5, 150.2, 138.4, 134.4, 126.0, 121.8, 121.7, 120.7, 118.1.

**MS** (70 eV, EI), $m/z$ (%) = 351 (M$^+$, 8), 349 (M$^+$, 4), 274 (10), 273 (13), 272 (100), 270 (88), 191 (25), 147 (5), 78 (7).

**HRMS** (EI), $m/z$ calc. for C$_9$H$_5$Br$_2$S$_2$ (348.8230): 348.8215 (M$^+$).

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3085, 3045, 2996, 2971, 1739, 1570, 1557, 1485, 1451, 1444, 1414, 1391, 1377, 1366, 1299, 1229, 1217, 1117, 1012, 969, 830, 806, 756, 717, 679.

(2,5-dibromothieno[3,2-b]thiophen-3-yl)trimethylsilane (2e)

![Chemical structure of 2e](image)

**m.p.:** 45.3-47.2 °C.

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.28 (s, 1 H), 0.43 (s, 9 H).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ (ppm) = 143.4, 141.0, 136.1, 122.7, 115.2, 107.7, -0.9.

**MS** (70 eV, EI), $m/z$ (%) = 370 (M$^+$, 52), 368 (M$^+$, 24), 358 (10), 357 (62), 356 (16), 355 (100), 353 (54), 261 (12), 259 (11), 233 (44), 231 (46), 137 (11), 73 (22).

**HRMS** (EI), $m/z$ calc. for C$_9$H$_{10}$Br$_2$S$_2$Si (369.8339) = 369.8331 (M$^+$).

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3100, 2955, 2895, 1739, 1478, 1417, 1409, 1313, 1246, 1152, 1012, 970, 833, 799, 756, 712, 698.

2,5-dibromo-3-(o-tolyl)thiophene (2f)

![Chemical structure of 2f](image)

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.20-7.39 (m, 4H), 7.03 (s, 1H), 2.28 (s, 3H).
**C. Experimental Section**

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 139.7, 138.1, 132.3, 131.3, 131.2, 130.3, 129.4, 125.7, 111.9, 109.2, 20.1.

**MS (70 eV, EI), m/z (%) = 332 (M$^+$, 32), 330 (M$^+$, 17), 252 (10), 173 (14), 172 (100), 171 (37), 128 (14), 86 (16), 80 (9), 42 (12).**

**HRMS (EI), m/z calc. for C$_{11}$H$_8$Br$_2$S (329.8713): 329.8703 (M$^+$).**

**IR (ATR) ν (cm$^{-1}$) = 3094, 3062, 3045, 3020, 2970, 2952, 2921, 1531, 1482, 1451, 1379, 1301, 1128, 979, 816, 751, 721, 685.**

2-(2,5-dibromothiophen-3-yl)-N,N-dimethylaniline (2g)

![Structure of 2-(2,5-dibromothiophen-3-yl)-N,N-dimethylaniline (2g)]

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.37-7.42 (m, 1H), 7.28-7.35 (m, 1H), 6.99 (s, 3H), 2.63 (s, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 152.2, 139.3, 132.4, 132.0, 129.8, 124.6, 121.2, 118.2, 112.7, 108.0, 43.2.

**MS (70 eV, EI), m/z (%) = 361 (M$^+$, 20), 359 (M$^+$, 10), 283 (12), 280 (14), 279 (80), 277 (12), 266 (48), 265 (10), 264 (53), 202 (12), 201 (44), 200 (100), 185 (14), 168 (30), 167 (10), 115 (16), 101 (27), 93 (10).**

**HRMS (EI), m/z calc. for C$_{12}$H$_{11}$Br$_2$NS (360.8958): 360.8971 (M$^+$).**

**IR (ATR) ν (cm$^{-1}$) = 3093, 3062, 2979, 2938, 2860, 2829, 2782, 1594, 1483, 1451, 1428, 1323, 1303, 1191, 1159, 1131, 1098, 1049, 979, 955, 942, 935, 811, 758, 741, 684.**

2,5-dibromo-3-(2-methoxyphenyl)thiophene (2h)

![Structure of 2,5-dibromo-3-(2-methoxyphenyl)thiophene (2h)]

m.p.: 65.0-67.0 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.33-7.48 (m, 2H), 6.93-7.10 (m, 3H), 3.85 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 156.9, 136.3, 132.4, 132.0, 130.6, 120.7, 120.4, 112.2, 111.3, 109.0, 55.6.

**MS (70 eV, EI), m/z (%) = 348 (M$^+$, 100), 346 (M$^+$, 53), 254 (83), 253 (12), 252 (88), 188 (40), 187 (40), 174 (17), 173 (12), 115 (13), 82 (12), 80 (12).**
HRMS (EI), m/z calc. for C_{11}H_{8}Br_{2}OS (347.8642): 347.8659 (M^+).

IR (ATR) υ (cm\(^{-1}\)) = 3094, 3082, 3019, 2967, 2936, 2835, 1595, 1579, 1481, 1476, 1461, 1455, 1432, 1286, 1250, 1182, 1132, 1111, 1052, 1027, 980, 813, 805, 791, 744, 734.

2',5'-dibromo-2,3'-bithiophene (2j)

```
\begin{center}
\includegraphics[width=1.0	extwidth]{image.png}
\end{center}
```

m.p.: 43.2-45.1 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) δ (ppm) = 7.35 (dd, \(J=5.7\)Hz, 4.3Hz, 2H), 7.07 (dd, \(J=5.1\)Hz, 3.7Hz, 1H), 6.99 (s, 1H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ (ppm) = 134.0, 133.8, 133.4, 127.3, 127.1, 126.6, 111.1, 107.0.

MS (70 eV, EI), m/z (%) = 324 (M^+, 100), 322 (M^+, 51), 245 (10), 244 (10), 165 (9), 164 (77), 93 (7), 82 (15).

HRMS (EI), m/z calc. for C\(_8\)H\(_4\)Br\(_2\)S\(_2\) (323.8101): 323.8085 (M^+).

IR (ATR) υ (cm\(^{-1}\)) = 3096, 3064, 3027, 2956, 2924, 2851, 2238, 1606, 1536, 1505, 1436, 1397, 1107, 1015, 971, 909, 858, 841, 832, 823, 774, 704, 662.

3,5-dibromo-2-(4-(trifluoromethyl)phenyl)pyridine (8a)

```
\begin{center}
\includegraphics[width=1.0	extwidth]{image.png}
\end{center}
```

m.p.: 73.8-75.2 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) δ (ppm) = 8.69 (d, \(J=1.9\)Hz, 1H), 8.18 (d, \(J=2.2\)Hz, 1H), 7.76-7.82 (m, 2H), 7.69-7.75 (m, 2H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ (ppm) = 155.2, 149.3, 143.3, 141.8, 131.0 (q, \(J=32.7\)Hz), 129.7, 125.1 (q, \(J=4.0\)Hz), 124.0 (q, \(J=272.4\)Hz), 119.7, 119.6.

MS (70 eV, EI), m/z (%) = 381 (M^+, 66), 379 (M^+, 32), 303 (14), 301 (14), 300 (100), 221 (61), 220 (15), 194 (13), 171 (10), 50 (11).

HRMS (EI), m/z calc. for C\(_{12}\)H\(_8\)Br\(_2\)F\(_3\)N (380.8799): 380.8778 (M^+).

IR (ATR) υ (cm\(^{-1}\)) = 3090, 3053, 2970, 1931, 1739, 1618, 1554, 1428, 1409, 1328, 1193, 1170, 1100, 1075, 1056, 1023, 1009, 888, 857, 842, 814, 762, 736, 690.
3,5-dibromo-2-(4-methoxyphenyl)pyridine (8b)

\[
\text{Br} \quad \text{Br} \\
\text{N}  \\
\text{OMe}
\]

m.p.: 100.8-108.8 °C.

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 8.64 (d, \(J=1.9\text{Hz}, 1\text{H}\)), 8.12 (d, \(J=1.9\text{Hz}, 1\text{H}\)), 7.65 (d, \(J=9.1\text{Hz}, 2\text{H}\)), 6.82-7.07 (m, 2H), 3.86 (s, 3H).

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 160.2, 156.2, 149.0, 143.1, 130.8, 130.7, 119.6, 118.1, 113.4, 55.3.

\text{MS} (70 eV, EI), \(m/z\) (%) = 343 (M\(^+\), 100), 341 (M\(^+\), 48), 300 (12), 264 (40), 249 (11), 247 (12), 221 (19), 183 (25), 140 (32), 113 (17).

\text{HRMS} (EI), \(m/z\) calc. for C\(_{12}\)H\(_6\)Br\(_2\)NO (342.9030): 342.9031 (M\(^+\)).

\text{IR (ATR)} \nu (\text{cm}^{-1}) = 3085, 3034, 3010, 2971, 2937, 2912, 2836, 1739, 1607, 1578, 1508, 1434, 1366, 1250, 1218, 1173, 1104, 1060, 1026, 1013, 1000, 905, 844, 836, 770, 756.

3,5-dibromo-2-(thiophen-2-yl)pyridine (8c)

\[
\text{Br} \quad \text{Br} \\
\text{N}  \\
\text{S}
\]

m.p.: 69.6-71.0 °C.

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 8.56 (d, \(J=2.2\text{Hz}, 1\text{H}\)), 8.13 (dd, \(J=3.9\text{Hz}, 1.1\text{Hz}, 1\text{H}\)), 8.09 (d, 1H), 7.49 (dd, \(J=5.0\text{Hz}, 1.11\text{Hz}, 1\text{H}\)), 7.13 (dd, \(J=5.3\text{Hz}, 3.9\text{Hz}, 1\text{H}\)).

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 149.3, 148.6, 143.9, 142.0, 129.4, 129.2, 127.7, 117.4, 117.1.

\text{MS} (70 eV, EI), \(m/z\) (%) = 319 (M\(^+\), 100), 317 (M\(^+\), 43), 278 (18), 277 (43), 240 (16), 238 (17), 183 (10), 159 (38).

\text{HRMS} (EI), \(m/z\) calc. for C\(_9\)H\(_5\)Br\(_2\)NS (318.8489): 318.8527 (M\(^+\)).

\text{IR (ATR)} \nu (\text{cm}^{-1}) = 3066, 3055, 3019, 3006, 1739, 1530, 1475, 1434, 1412, 1370, 1353, 1272, 1108, 1090, 1043, 1025, 966, 896, 852, 833, 775, 754, 740, 708, 692.
3,5-dibromo-2-(phenylthio)pyridine (8d)

\[
\begin{array}{c}
\text{Br} \\
\text{\text{\text{\text{\text{N}}}}}
\end{array}
\begin{array}{c}
\text{Br} \\
\text{\text{\text{\text{\text{S}}}}} \\
\text{Ph}
\end{array}
\]

m.p.: 67.5-69.6 °C.

\( ^1 \text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 8.29 (d, \( J=2.2 \text{Hz} \), 1H), 7.89 (d, \( J=2.2 \text{Hz} \), 1H), 7.51-7.59 (m, 2H), 7.41-7.48 (m, 3H).

\( ^{13} \text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 158.0, 148.8, 141.4, 135.5, 129.7, 129.3, 129.2, 118.2, 115.8.

MS (70 eV, EI), \( m/z \) (%): 345 (M\(^+\), 31), 344 (M\(^+\), 100), 342 (M\(^+\), 45), 185 (11), 133 (7), 109 (8), 65 (7).

HRMS (EI), \( m/z \) calc. for C\(_{11}\)H\(_7\)Br\(_2\)NS: 344.8645: 344.8656 (M\(^+\)).

IR (ATR) \( \upsilon \) (cm\(^{-1}\)) = 3076, 3050, 3037, 2985, 1575, 1544, 1476, 1438, 1414, 1396, 1347, 1228, 1213, 1138, 1097, 1018, 1000, 886, 786, 744, 713, 705, 687.

3,5-dibromo-2-(trimethylsilyl)pyridine (15)

\[
\begin{array}{c}
\text{Br} \\
\text{\text{\text{\text{\text{N}}}}}
\end{array}
\begin{array}{c}
\text{Br} \\
\text{TMS}
\end{array}
\]

\( ^1 \text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 8.72 (d, \( J=2.2 \text{Hz} \), 1H), 7.93 (d, \( J=1.9 \text{Hz} \), 1H), 0.41 (s, 9H).

\( ^{13} \text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 165.5, 148.9, 140.2, 126.5, 120.4, -1.1.

MS (70 eV, EI), \( m/z \) (%): 308 (M\(^+\), 21), 306 (M\(^+\), 12), 296 (42), 295 (12), 294 (100), 292 (37), 230 (16), 228 (17), 215 (10).

HRMS (EI), \( m/z \) calc. for C\(_8\)H\(_{11}\)Br\(_2\)NSi: 306.9028: 306.9008 (M\(^+\)).

IR (ATR) \( \upsilon \) (cm\(^{-1}\)) = 3356, 2989, 2965, 2910, 2890, 1729, 1710, 1553, 1524, 1473, 1326, 1277, 1251, 1178, 1158, 1148, 1129, 1101, 1049, 1020, 1012, 905, 855, 788, 760, 725, 658.

2.2 Typical Procedures

Typical procedure 1 (TP1): Regioselective preparation of heteroarylmagnesium reagents using 1a

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with iPrMgCl\(\cdot\)LiCl (1a; 1.05 equiv, 1.2 M in THF). The substituted dibromoheterocycle (1 equiv) was added as a solution in THF (1.0 M) at the given temperature and continuously stirred for the indicated time. Complete Br/Mg-exchange
was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard.

**Typical procedure 2 (TP2): Regioselective preparation of heteroarylmagnesium reagents using 1c and \( \text{L}^2 \)**

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 2,4,6-trisopropylmagnesium bromide (1c; 1.05 equiv, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (\( \text{L}^2 \); 1.05 equiv). After stirring for 15 min at 25 °C, the substituted dibromoheterocycle (1 equiv) was added as a solution in THF (1.0 M) at the given temperature and continuously stirred for the indicated time. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard.

**Typical procedure 3 (TP3): Cross-coupling reactions of heteroarylmagnesium reagents**

To the freshly prepared heteroarylmagnesium reagent was added ZnCl\(_2\) (1.0 M in THF, 1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. Pd(PPh\(_3\))\(_4\) (4 mol %) and the aryl iodide (0.9 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time, the reaction mixture was quenched with saturated aqueous NH\(_4\)Cl solution, extracted three times with EtOAc, dried over Na\(_2\)SO\(_4\) and concentrated \emph{in vacuo}. The crude residue was purified by flash column chromatography on silica gel.

**Typical procedure 4 (TP4): Acylation reactions of heteroarylmagnesium reagents**

To the freshly prepared heteroarylmagnesium reagent was added ZnCl\(_2\) (1.0 M in THF, 1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. CuCN·2LiCl (1.0 M in THF, 20 mol %) and the acyl chloride (0.9 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time, the reaction mixture was quenched with saturated aqueous NH\(_4\)Cl/NH\(_3\) solution (10:1), extracted three times with EtOAc, dried over Na\(_2\)SO\(_4\) and concentrated \emph{in vacuo}. The crude residue was purified by flash column chromatography on silica gel.
Typical procedure 5 (TP5): Preparation of sulfoxides using heteroarylmagnesium reagents
A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-methoxybenzenesulfinyl chloride (0.9 equiv) and cooled to -20 °C. The freshly prepared heteroarylmagnesium reagent (1 equiv) in THF was added dropwise and the reaction mixture was warmed to 25 °C. After stirring for the indicated time, the reaction mixture was quenched with saturated aqueous NH₄Cl solution, extracted three times with EtOAc, dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel.

2.3 Preparation of Functionalized Thiophenes and Thienothiophenes of Type 5
Preparation of (5-bromo-4-(methylthio)thiophen-2-yl)(3-chloro-4-methoxyphenyl)-methanol (5a)

![Chemical structure of 5a]

Prepared according to TP1 from 2,5-dibromo-3-(methylthio)thiophene (2a; 576 mg, 2 mmol) and iPrMgCl-LiCl (1a; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to -20 °C and 3-chloro-4-methoxybenzaldehyde (4a; 307 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification (pentane/Et₂O, 1:1) furnished 5a as a yellow oil (504 mg, 74%).

¹H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.40 (d, J=2.1Hz, 1H), 7.29 (dd, J=8.5Hz, 2.1Hz, 1H), 7.08 (d, J=8.5Hz, 1H), 6.84 (s, 1H), 6.42 (d, J=4.4Hz, 1H), 5.81 (d, J=3.5Hz, 1H), 3.79 (s, 3H), 2.39 (s, 3H).

¹³C NMR (100 MHz, d6-DMSO) δ (ppm) = 154.2, 152.8, 137.6, 131.5, 127.8, 127.1, 126.4, 121.2, 113.4, 113.1, 69.8, 56.5, 20.1.
C. EXPERIMENTAL SECTION

**MS** (70 eV, EI), *m/z* (%) = 380 (M⁺, 100), 378 (M⁺, 78), 363 (42), 361 (27), 236 (21), 170 (38), 128 (15), 108 (14).

**HRMS** (EI), *m/z* calc. for C_{13}H_{12}BrClO_{2}S_{2} (377.9151): 377.9133 (M⁺).

**IR** (ATR) *ν* (cm⁻¹) = 3083, 3002, 2965, 2921, 2868, 2837, 1602, 1499, 1460, 1438, 1414, 1283, 1256, 1196, 1183, 1149, 1116, 1061, 1021, 968, 884, 821, 813, 794, 688.

**Preparation of 1-(5'-bromo-4'-(methylthio)-[2,2'-bithiophen]-5-yl)ethanone (5b)**

![Diagram of 1-(5'-bromo-4'-(methylthio)-[2,2'-bithiophen]-5-yl)ethanone](image)

Prepared according to TP1 from 2,5-dibromo-3-(methylthio)thiophene (2a; 576 mg, 2 mmol) and iPrMgCl-LiCl (1a; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (2.0 mL, 2.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (92 mg, 0.08 mmol) and 1-(5-iodothiophen-2-yl)ethanone (4b; 454 mg, 1.8 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 8:2) afforded 5b as a red-brown yellow solid (491 mg, 82%).

**m.p.:** 73.8-75.4 °C.

**¹H NMR** (300 MHz, CDCl₃) *δ* (ppm) = 7.58 (d, *J*=3.9Hz, 1H), 7.17 (s, 1H), 7.12 (d, *J*=3.9Hz, 1H), 2.55 (s, 3H), 2.52 (s, 3H).

**¹³C NMR** (75 MHz, CDCl₃) *δ* (ppm) = 190.3, 143.7, 143.2, 137.2, 134.4, 133.2, 128.3, 124.4, 115.5, 26.6, 20.2.

**MS** (70 eV, EI), *m/z* (%) = 334 (M⁺, 45), 332 (M⁺, 40), 319 (36), 317 (31), 263 (21), 262 (100), 183 (70), 108 (26), 44 (36), 43 (33).

**HRMS** (EI), *m/z* calc. for C_{11}H_{9}BrOS_{3} (333.8999): 333.8992 (M⁺).

**IR** (ATR) *ν* (cm⁻¹) = 3074, 3055, 2994, 2916, 1643, 1500, 1435, 1408, 1354, 1289, 1272, 1074, 1039, 1029, 966, 933, 882, 796, 744, 691, 662.

**Preparation of 1,4-bis(5-bromo-4-(methylthio)thiophen-2-yl)benzene (5c)**

![Diagram of 1,4-bis(5-bromo-4-(methylthio)thiophen-2-yl)benzene](image)

Prepared according to TP1 from 2,5-dibromo-3-(methylthio)thiophene (2a; 576 mg, 2 mmol) and iPrMgCl-LiCl (1a; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂...
(2.0 mL, 2.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (92 mg, 0.08 mmol) and 1,4-diodobenzene (4c; 314 mg, 0.95 mmol) in 1 h. Recrystallisation from EtOAc afforded 5c as a pale yellow solid (391 mg, 84%).

**m.p.:** 182.7-183.3 °C.

**1H NMR** (400 MHz, CD₂Cl₂) δ (ppm) = 7.55 (s, 4H), 7.25 (s, 2H), 2.52 (s, 6H).

**13C NMR** (100 MHz, CD₂Cl₂) δ (ppm) = 144.5, 132.8, 132.7, 126.5, 125.8, 115.8, 20.2.

**MS** (70 eV, El), m/z (%) = 494 (M⁺, 55), 492 (M⁺, 100), 490 (M⁺, 40), 479 (26), 477 (42), 475 (20), 383 (6), 246 (7), 242 (8), 236 (7).

**HRMS** (El), m/z calc. for C₁₆H₁₂Br₂S₄ (489.8189): 489.8171 (M⁺).

**IR** (ATR) ν (cm⁻¹) = 3085, 3068, 3034, 2991, 2917, 2846, 2822, 1484, 1434, 1418, 1408, 1335, 1319, 1289, 1272, 1169, 1120, 1104, 1020, 1008, 967, 951, 808.

**Preparation of tert-butyl 5-bromo-4-(methylthio)thiophene-2-carboxylate (5d)**

Prepared according to **TP1** from 2,5-dibromo-3-(methylthio)thiophene (2a; 576 mg, 2 mmol) and iPrMgCl·LiCl (1a; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −40 °C and di-tert-butyl dicarbonate (4d; 524 mg, 2.4 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 3 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 50:1) furnished 5d as a white solid (521 mg, 85%).

**m.p.:** 48.0-49.8 °C.

**1H NMR** (300 MHz, CDCl₃) δ (ppm) = 7.54 (s, 1H), 2.57 (s, 3H), 1.56 (s, 9H).

**13C NMR** (75 MHz, CDCl₃) δ (ppm) = 159.8, 142.1, 135.4, 134.3, 111.3, 82.5, 28.2, 19.0.

**MS** (70 eV, El), m/z (%) = 310 (M⁺, 32), 308 (M⁺, 29), 256 (26), 255 (25), 254 (16), 253 (24), 252 (19), 239 (56), 237 (100), 235 (36), 127 (20).

**HRMS** (El), m/z calc. for C₁₀H₁₃BrO₂S₂ (307.9540): 307.9532 (M⁺).

**IR** (ATR) ν (cm⁻¹) = 3098, 3008, 2979, 2931, 2920, 1691, 1514, 1391, 1368, 1330, 1266, 1252, 1166, 1152, 1134, 1076, 1031, 850, 835, 799, 746.
Preparation of (5-bromo-4-(phenylthio)thiophen-2-yl)(4-methoxyphenyl)methanol (5e)

Prepared according to TP1 from 2,5-dibromo-3-(phenylthio)thiophene (2b; 350 mg, 1 mmol) and iPrMgCl·LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 4-methoxybenzaldehyde (4e; 123 mg, 0.9 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification (pentane/Et₂O, 8.5:1.5) furnished 5e as a white solid (334 mg, 91%).

m.p.: 94.0-95.7 °C.

¹H NMR (400 MHz, d₆-DMSO) δ (ppm) = 7.27-7.33 (m, 3H), 7.20 (t, J=7.3Hz, 1H), 7.12 (d, J=7.2Hz, 2H), 6.81-6.98 (m, 3H), 6.39 (d, J=4.5Hz, 1H), 5.83 (d, J=4.5Hz, 1H), 3.70 (s, 3H).

¹³C NMR (100 MHz, d₆-DMSO) δ (ppm) = 159.1, 157.5, 136.2, 136.1, 129.9, 127.8, 127.7, 127.5, 127.2, 125.3, 119.7, 114.2, 70.6, 55.5.

MS (70 eV, EI), m/z (%) = 408 (M⁺, 58), 406 (M⁺, 60), 388 (21), 386 (18), 298 (12), 218 (19), 217 (30), 190 (13), 137 (11), 125 (100), 109 (15), 77 (31).

HRMS (EI), m/z calc. for C₁₈H₁₅BrO₂S₂ (405.9697): 405.9680 (M⁺).

IR (ATR) ν (cm⁻¹) = 3436, 3070, 3046, 3006, 2957, 2836, 2362, 2339, 1610, 1581, 1515, 1476, 1454, 1439, 1313, 1251, 1173, 1144, 1104, 1033, 1022, 996, 844, 820, 816, 741, 684.
Preparation of 2-bromo-5-(4-nitrophenyl)-3-(phenylthio)thiophene (5f)

Prepared according to TP1 from 2,5-dibromo-3-(phenylthio)thiophene (2b; 350 mg, 1 mmol) and iPrMgCl-LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and 1-iodo-4-nitrobenzene (4f; 224 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 100:3) afforded 5f as a yellow solid (302 mg, 86%).

m.p.: 129.0-130.9 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 8.21-8.29 (m, 2H), 7.62-7.69 (m, 2H), 7.42 (s, 1H), 7.25-7.39 (m, 5H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 147.3, 144.5, 138.7, 135.2, 132.1, 129.4, 129.3, 128.9, 127.5, 125.9, 124.5, 119.9.

MS (70 eV, EI), m/z (%) = 395 (M⁺, 10), 393 (M⁺, 100), 391 (95), 312 (13), 267 (15), 266 (72), 265 (24), 234 (14), 221 (36), 189 (13), 121 (11), 113 (15), 77 (14), 43 (14).

HRMS (EI), m/z calc. for C₁₆H₁₀BrNO₂S₂ (390.9336): 390.9333 (M⁺).

IR (ATR) ν (cm⁻¹) = 3092, 3076, 3061, 2932, 2842, 1591, 1578, 1516, 1506, 1477, 1341, 1332, 1108, 1022, 851, 819, 740, 726, 687.

Preparation of 2-bromo-5-(4-methoxyphenyl)-3-(phenylthio)thiophene (5g)

Prepared according to TP1 from 2,5-dibromo-3-(phenylthio)thiophene (2b; 5.25 g, 15 mmol) and iPrMgCl-LiCl (1a; 13.13 mL, 15.75 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (15 mL, 15.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (867 mg, 0.75 mmol) and 1-iodo-4-methoxybenzene (4g; 3.16 g, 13.5 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 50:1) afforded 5g as a pale yellow solid (4.9 g, 96%).
m.p.: 96.0-98.4 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.40-7.51 (m, 2H), 7.13-7.34 (m, 6H), 6.85-6.98 (m, 2H), 3.78-3.89 (m, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 160.1, 148.8, 136.7, 129.1, 127.7, 127.0, 126.5, 125.7, 125.6, 125.5, 121.1, 114.5, 55.4

MS (70 eV, EI), m/z (%) = 378 (M$^+$, 100), 376 (M$^+$, 100), 297 (47), 253 (23), 221 (30), 177 (19), 151 (19), 108 (19), 77 (45), 43 (24).

HRMS (EI), m/z calc. for C$_{17}$H$_{13}$BrOS$_2$ (377.9571): 377.9569 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3071, 3052, 2998, 2962, 2936, 2907, 2831, 1604, 1572, 1527, 1492, 1476, 1436, 1412, 1283, 1247, 1178, 1112, 1023, 813, 800, 738, 688.

Preparation of ethyl 4-(5-bromo-4-(pyridin-2-ylthio)thiophen-2-yl)benzoate (5h)

Prepared according to TP1 from 2-((2,5-dibromothiophen-3-yl)thio)pyridine (2c; 351 mg, 1 mmol) and iPrMgCl-LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl$_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh$_3$)$_4$ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (4h; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et$_2$O, 8.5:1.5 + 1% NEt$_3$) afforded 5h as a pale yellow solid (347 mg, 92%).

m.p.: 102.6-104.3 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.46 (dd, $J$=3.9Hz, 2.0Hz, 1H), 8.04-8.13 (m, 2H), 7.59-7.68 (m, 2H), 7.55 (td, $J$=7.7Hz, 2.0Hz, 1H), 7.45 (s, 1 H), 7.06 (ddd, $J$=7.5Hz, 5.0Hz, 1.1Hz, 1H), 6.92-7.02 (m, 1H), 4.40 (q, $J$=7.2Hz, 2H), 1.42 (t, $J$=7.1Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 165.9, 159.2, 149.7, 148.2, 137.1, 136.6, 130.5, 130.4, 128.0, 125.8, 125.4, 122.5, 120.5, 120.4, 61.2, 14.3.

MS (70 eV, EI), m/z (%) = 421 (M$^+$, 5), 419 (M$^+$, 5), 342 (12), 341 (25), 340 (100), 313 (12), 312 (64), 267 (11), 266 (10).

HRMS (EI), m/z calc. for C$_{18}$H$_{14}$BrNO$_2$S$_2$ (418.9649): 418.9617 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3087, 3068, 3046, 2982, 2957, 2935, 2896, 1704, 1605, 1569, 1562, 1444, 1418, 1276, 1180, 1117, 1107, 1088, 1019, 851, 834, 822, 815, 765, 719, 692.
Preparation of (5-bromo-4-(trimethylsilyl)thiophen-2-yl)(2,3-dichlorophenyl)-methanol (5i)

Prepared according to TP1 from (2,5-dibromothiophen-3-yl)trimethylsilane (2d; 628 mg, 2 mmol) and iPrMgCl-LiCl (1a; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 2,3-dichlorobenzaldehyde (4i; 315 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification (pentane/Et₂O, 8.5:1.5) furnished 5i as a colorless oil (635 mg, 86%).

**H NMR** (400 MHz, d6-DMSO) δ (ppm) = 7.65-7.69 (m, 1H), 7.59 (dd, J=8.0Hz, 1.8Hz, 1H), 7.44 (t, J=7.8Hz, 1H), 6.98 (d, J=0.8Hz, 1H), 6.65 (d, J=4.7Hz, 1H), 6.22 (d, J=4.3Hz, 1H), 0.32 (s, 9H).

**C NMR** (100 MHz, d6-DMSO) δ (ppm) = 153.6, 144.3, 133.5, 132.1, 130.1, 130.0, 129.3, 129.0, 126.7, 116.1, 67.5, -0.5.

**MS** (70 eV, EI), m/z (%) = 410 (M⁺, 35), 408 (M⁺, 40), 399 (11), 398 (12), 397 (56), 396 (22), 395 (100), 394 (15), 393 (64), 337 (16), 335 (18), 237 (25), 235 (25), 175 (25), 139 (46), 137 (39), 73 (100).

**HRMS** (EI), m/z calc. for C₁₄H₁₂BrCl₂OSSi (407.9173): 407.9172 (M⁺).

**IR** (ATR) ν (cm⁻¹) = 3332, 2957, 2897, 2873, 2361, 2349, 1515, 1450, 1419, 1330, 1298, 1264, 1249, 1179, 1154, 1102, 1052, 1027, 993, 837, 816, 788, 773, 754, 742, 731, 697, 655.
Preparation of (2-bromo-5-(4-methoxyphenyl)thiophen-3-yl)trimethylsilane (5j)

Prepared according to TP1 from (2,5-dibromothiophen-3-yl)trimethylsilane (2d; 3.14 g, 10 mmol) and iPrMgCl·LiCl (1a; 8.75 mL, 10.5 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (10 mL, 10 mmol, 1.0 M in THF), Pd(PPh₃)₄ (462 mg, 0.4 mmol) and 1-iodo-4-methoxybenzene (4g; 2.57 g, 11 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 100:1) afforded 5j as a pale yellow solid (3.0 g, 87%).

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.45-7.55 (m, 2H), 7.19 (s, 1H), 6.88-6.95 (m, 2H), 3.85 (s, 3H), 0.43 (s, 9H).
¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 159.6, 149.1, 132.7, 127.3, 127.1, 126.1, 117.6, 114.3, 55.4, -0.7.
MS (70 eV, EI), m/z (%) = 342 (M⁺, 70), 340 (M⁺, 42), 327 (35), 325 (21), 203 (52), 173 (27), 139 (31), 137 (28), 74 (22), 73 (30), 45 (68), 44 (100), 43 (32).
HRMS (EI), m/z calc. for C₁₄H₁₇BrOSSi (339.9953): 339.9939 (M⁺).
IR (ATR) ν (cm⁻¹) = 3090, 3054, 2997, 2955, 2935, 2899, 2831, 1878, 1606, 1532, 1490, 1456, 1422, 1308, 1288, 1249, 1179, 1108, 1035, 1001, 948, 835, 818, 808, 753, 698.

Preparation of (5-bromo-4-(trimethylsilyl)thiophen-2-yl)(furan-3-yl)methanone (5k)

(2,5-dibromothiophen-3-yl)trimethylsilane (2d; 628 mg, 2 mmol) and iPrMgCl·LiCl (1a; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the acylation reaction was accomplished according to TP4 with ZnCl₂ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and furan-2-carbonyl chloride (4j; 235 mg, 1.8 mmol) in 8 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 50:1) afforded 5k as a pale yellow solid (423 mg, 72%).
m.p.: 108.6-110.2 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 8.10 (s, 1H), 7.70 (dd, $J$=1.8Hz, 0.7Hz, 1H), 7.42 (dd, $J$=3.6Hz, 0.8Hz, 1H), 6.62 (dd, $J$=3.6Hz, 1.7Hz, 1H), 0.45 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 172.0, 152.1, 146.7, 145.5, 145.0, 137.6, 119.3, 117.6, 112.6, -1.0.

MS (70 eV, El), m/z (%) = 330 (M$^+$, 33), 328 (M$^+$, 31), 316 (12), 315 (72), 313 (68), 163 (28), 139 (17), 99 (16), 95 (100), 73 (16).

HRMS (El), m/z calc. for C$_{12}$H$_{13}$BrO$_2$SSi (327.9589): 327.9588 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3137, 3110, 2959, 2362, 2349, 1623, 1566, 1491, 1462, 1396, 1296, 1247, 1226, 1174, 1143, 1124, 1076, 998, 941, 844, 828, 788, 766, 742, 720.

Preparation of (5-bromo-6-(trimethylsilyl)thieno[3,2-b]thiophen-2-yl)(4-methoxyphenyl)methanol (5l)

Prepared according to TP1 from (2,5-dibromothieno[3,2-b]thiophen-3-yl)trimethylsilane (2e; 370 mg, 1 mmol) and iPrMgCl-LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 4-methoxybenzaldehyde (4e; 123 mg, 0.9 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 ºC and continuously stirred for 2 h. Subsequently, sat. aq. NH$_4$Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatographical purification (pentane/Et$_2$O, 8:2) furnished 5l as a colorless oil (311 mg, 81%).

$^1$H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.30-7.36 (m, 2H), 7.24 (d, $J$=1.0Hz, 1H), 6.87-6.90 (m, 2H), 6.38 (d, $J$=4.3 Hz, 1H), 5.92 (d, $J$=4.3 Hz, 1H), 3.71 (s, 3H), 0.36 (s, 9H).

$^{13}$C NMR (100 MHz, d6-DMSO) δ (ppm) = 159.0, 155.9, 141.9, 141.7, 136.8, 135.5, 127.9, 117.5, 114.0, 108.8, 71.0, 55.5, -0.5.

MS (70 eV, El), m/z (%) = 426 (M$^+$, 44), 424 (M$^+$, 22), 412 (60), 411 (74), 409 (51), 397 (19), 395 (22), 332 (11), 331 (14), 139 (12), 137 (13), 136 (12), 135 (100), 121 (14), 77 (21), 75 (24), 73 (39).
HRMS (EI), m/z calc. for C_{17}H_{17}BrO_S_2Si (423.9623): 423.9619 (M^+).

IR (ATR) ν (cm⁻¹) = 3393, 3075, 3034, 2999, 2954, 2896, 2865, 2835, 2060, 1610, 1586, 1510, 1328, 1304, 1246, 1171, 1110, 1032, 1002, 829, 757, 699, 664.

Preparation of (2-bromo-5-(4-methoxyphenyl)thieno[3,2-b]thiophen-3-yl)trimethylsilane (5m)

Prepared according to TP1 from (2,5-dibromothieno[3,2-b]thiophen-3-yl)trimethylsilane (2e; 370 mg, 1 mmol) and iPrMgCl·LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and 1-iodo-4-methoxybenzene (4g; 258 mg, 1.1 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 100:1) afforded 5m as white solid (381 mg, 96%).

m.p.: 133.7-135.5 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.53-7.60 (m, 2H), 7.37 (s, 1H), 6.92-6.98 (m, 2H), 3.86 (s, 3H), 0.41-0.53 (m, 9H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 159.7, 147.6, 143.0, 141.8, 135.7, 127.3, 127.2, 114.7, 114.4, 108.8, 55.4, -0.8.

MS (70 eV, EI), m/z (%) = 398 (M⁺, 100), 396 (M⁺, 86), 383 (40), 381 (36), 326 (33), 324 (32), 311 (16), 309 (17), 260 (12), 259 (66), 216 (12), 75 (16), 73 (19), 43 (19).

HRMS (EI), m/z calc. for C_{16}H_{17}BrOS₂Si (395.9673): 395.9662 (M⁺).

IR (ATR) ν (cm⁻¹) = 3080, 3000, 2955, 2940, 2895, 2834, 1603, 1523, 1488, 1438, 1425, 1291, 1247, 1185, 1030, 1007, 965, 874, 837, 828, 813, 802, 789, 756, 698, 681.

Preparation of 2-bromo-5-(4-methoxyphenyl)-3-(o-tolyl)thiophene (5n)

Prepared according to TP1 from 2,5-dibromo-3-(o-tolyl)thiophene (2f; 332 mg, 1 mmol) and iPrMgCl·LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently,
the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and 1-iodo-4-methoxybenzene (4g; 211 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 100:1) afforded 5n as a pale yellow oil (310 mg, 96%).

m.p.: 56.9-58.7 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.48-7.54 (m, 2H), 7.24-7.38 (m, 4H), 6.88-6.98 (m, 2H) 7.15 (s, 1H), 3.85 (s, 3H), 2.33 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 159.7, 143.8, 138.1, 136.1, 132.3, 131.2, 130.2, 129.0, 126.8, 126.1, 125.6, 124.8, 114.4, 110.2, 55.4, 20.2.

MS (70 eV, EI), m/z (%) = 360 (M⁺, 100), 358 (M⁺, 95), 345 (12), 338 (11), 279 (15), 277 (10), 263 (9), 235 (12), 203 (15), 171 (8), 115 (9).

HRMS (EI), m/z calc. for C₁₈H₁₅BrOS (358.0027): 358.0024 (M⁺).

IR (ATR) υ (cm⁻¹) = 3092, 3058, 3012, 2955, 2933, 2904, 2834, 1605, 1515, 1486, 1460, 1450, 1439, 1289, 1250, 1178, 1111, 1024, 972, 819, 808, 798, 756, 750, 720, 694, 663.

Preparation of 4-(5-bromo-4-(2-(dimethylamino)phenyl)thiophen-2-yl)benzonitrile (5o)

Prepared according to TP1 from 2-(2,5-dibromothiophen-3-yl)-N,N-dimethylaniline (2g; 361 mg, 1 mmol) and iPrMgCl-LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and 4-iodobenzonitrile (4k; 206 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 50:1 + 1% NEt₃) afforded 5o as a pale yellow solid (312 mg, 91%).

m.p.: 111.8-113.1 °C.

¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.68 (s, 4H), 7.43 (dd, J=7.7Hz, 1.7Hz, 1H), 7.31-7.40 (m, 2H), 7.08 (dd, J=8.2Hz, 1.1Hz, 1H), 7.03 (td, J=7.4Hz, 1.1Hz, 1H), 2.67 (s, 6H).

¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 152.3, 141.1, 139.5, 137.7, 132.8, 132.5, 129.9, 127.9, 125.6, 124.4, 121.1, 118.7, 118.1, 111.0, 110.2, 43.2.
**C. EXPERIMENTAL SECTION**

**MS** (70 eV, EI), \( m/z \) (\%) = 384 (M\(^+\), 20), 382 (M\(^+\), 19), 304 (23), 303 (100), 301 (29), 289 (13), 288 (60), 287 (11), 269 (10), 146 (13), 43 (26).

**HRMS** (EI), \( m/z \) calc. for C\(_{19}\)H\(_{15}\)BrN\(_2\)S (382.0139): 382.0132 (M\(^+\)).

**IR** (ATR) \( \nu \) (cm\(^{-1}\)) = 3063, 3044, 2969, 2934, 2858, 2830, 2784, 2223, 1602, 1594, 1484, 1451, 1440, 1330, 1176, 1159, 1049, 974, 946, 935, 837, 827, 817, 763, 742, 696.

**Preparation of 4-(5-bromo-4-(2-methoxyphenyl)thiophen-2-yl)benzonitrile (5p)**

Prepared according to **TP1** from 2,5-dibromo-3-(2-methoxyphenyl)thiophene (2h; 348 mg, 1 mmol) and iPrMgCl-LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with ZnCl\(_2\) (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh\(_3\))\(_4\) (46 mg, 0.04 mmol) and 4-iodobenzonitrile (4k; 206 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et\(_2\)O, 9:1) afforded 5p as a pale yellow solid (300 mg, 90%).

**m.p.**: 128.6-130.5 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 7.67 (s, 4H), 7.40-7.50 (m, 2H), 7.38 (s, 1H), 7.01-7.09 (m, 2H), 3.88 (s, 3H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 157.0, 141.2, 137.6, 136.3, 132.8, 132.0, 130.7, 128.2, 125.7, 120.9, 120.5, 118.6, 111.4, 111.1, 111.1, 55.7.

**MS** (70 eV, EI), \( m/z \) (\%) = 371 (M\(^+\), 100), 369 (M\(^+\), 95), 276 (19), 275 (99), 246 (16), 146 (9).

**HRMS** (EI), \( m/z \) calc. for C\(_{18}\)H\(_{12}\)BrNOS (368.9823): 368.9790 (M\(^+\)).

**IR** (ATR) \( \nu \) (cm\(^{-1}\)) = 3086, 3059, 3016, 2979, 2949, 2845, 2224, 1597, 1485, 1464, 1438, 1330, 1251, 1178, 1166, 1112, 1011, 971, 844, 828, 817, 790, 757, 738, 721, 701, 660.
Preparation of ethyl 4-(5-bromo-4-(pyridin-2-yl)thiophen-2-yl)benzoate (5q)

Prepared according to TP1 from 2-(2,5-dibromothiophen-3-yl)pyridine (2i; 319 mg, 1 mmol) and iPrMgCl-LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and ethyl 4-iodo-benzoate (4h; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 8.5:1.5 + 1% NEt₃) afforded 5q as a white solid (310 mg, 89%).

m.p.: 104.6-106.2 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 8.63 (dd, J=5.8Hz, 2.0Hz, 1H), 8.36 (dt, J=8.2Hz, 0.9Hz, 1H), 8.36 (dt, J=8.2Hz, 0.9Hz, 1H), 7.99-8.13 (m, 2H), 7.77 (td, J=7.8Hz, 1.8Hz, 1H), 7.63-7.72 (m, 2H), 7.37 (s, 1H), 7.24 (ddd, J=7.6Hz, 4.8Hz, 1.1Hz, 1H), 4.40 (q, J=7.2Hz, 2H), 1.41 (t, J=7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 166.0, 151.0, 149.6, 143.6, 139.3, 137.0, 136.5, 130.3, 130.0, 129.5, 125.2, 122.7, 120.6, 108.2, 61.1, 14.3.

MS (70 eV, EI), m/z (%) = 389 (M⁺, 100), 387 (M⁺, 96), 359 (21), 342 (24), 235 (25), 234 (12), 190 (5).

HRMS (EI), m/z calc. for C₁₈H₁₄BrNO₂S (386.9929): 386.9951 (M⁺).

IR (ATR) ν (cm⁻¹) = 3069, 2990, 2979, 2931, 2902, 2871, 1706, 1603, 1579, 1505, 1469, 1434, 1409, 1365, 1266, 1180, 1109, 1100, 1015, 855, 832, 781, 767, 742, 714, 694.

Preparation of 2'-bromo-5'-(3-methoxyphenyl)-2,3'-bithiophene (5r)

Prepared according to TP1 from 2',5'-dibromo-2,3'-bithiophene (2j; 324 mg, 1 mmol) and iPrMgCl-LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at -20 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and 1-iodo-3-
methoxybenzene (4l; 211 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 40:1) afforded 5r as a yellow oil (261 mg, 83%).

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.43-7.49 (m, 1H), 7.34-7.38 (m, 1H), 7.31 (t, J=7.9 Hz, 1H), 7.22 (bs, 1H), 7.13-7.18 (m, 1H), 7.06-7.12 (m, 2H), 6.88 (dd, J=8.0Hz, 2.5Hz, 1H), 3.86 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 160.1, 142.2, 134.4, 134.1, 131.5, 130.1, 127.6, 127.3, 126.6, 126.1, 118.0, 113.9, 111.1, 108.1, 55.4.

MS (70 eV, EI), m/z (%) = 352 (M⁺, 100), 350 (M⁺, 93), 309 (16), 307 (15), 240 (3), 228 (4), 176 (4), 175 (3), 108 (3).

HRMS (EI), m/z calc. for C₁₅H₁₁BrOS₂ (275.9820): 275.9817 (M⁺).

IR (ATR) ν (cm⁻¹) = 3101, 3068, 2999, 2955, 2934, 2832, 1597, 1578, 1480, 1462, 1429, 1288, 1272, 1260, 1201, 1166, 1045, 837, 824, 809, 770, 682.

Preparation of (5-bromo-4-(2-methoxyphenyl)thiophen-2-yl)(5-iodofuran-2-yl)-methanol (5s)

Prepared according to TP1 from 2,5-dibromo-3-(2-methoxyphenyl)thiophene (2h; 348 mg, 1 mmol) and iPrMgCl·LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to 0 °C and ZnCl₂ (0.5 mL, 0.5 mmol, 1.0 M in THF) was added. The reaction mixture was allowed to warm to 25 °C in 30 min. Then, 5-iodofuran-2-carbaldehyde (4m; 200 mg, 0.9 mmol) in THF was added and the reaction mixture was continuously stirred for 2 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification (pentane/Et₂O, 8:2) furnished 5s as a brown oil (266 mg, 60%).

¹H NMR (400 MHz, d₆-DMSO) δ (ppm) = 7.40 (ddd, J=15.6Hz, 7.4Hz, 1.8Hz, 1H), 7.31 (dd, J=7.6Hz, 1.8 Hz, 1H), 7.11 (dd, J=8.4Hz, 1.0Hz, 1H), 7.00 (dt, J=7.5Hz, 1.2Hz,
1H), 6.93 (d, J=1.0Hz, 1H), 6.64 (d, J=3.1Hz, 1H), 6.56 (d, J=5.3Hz, 1H), 6.30 (dd, J=3.2Hz, 0.7Hz, 1H), 5.94 (d, J=5.3Hz, 1H), 3.76 (s, 3H).

$^{13}$C NMR (100 MHz, d$_6$-DMSO) δ (ppm) = 161.1, 157.1, 146.9, 133.9, 132.1, 131.0, 127.4, 121.0, 121.0, 120.8, 112.2, 110.4, 108.6, 91.8, 64.6, 56.0.

MS (70 eV, EI), m/z (%) = 492 (M$^+$, 88), 490 (M$^+$, 100), 488 (17), 475 (40), 473 (37), 411 (17), 364 (14), 362 (12), 224 (16), 221 (25), 190 (27), 128 (15), 127 (12), 115 (10).

HRMS (EI), m/z calc. for C$_{16}$H$_{12}$BrIO$_3$S (489.8735): 489.8737 (M$^+$).

IR (ATR) υ (cm$^{-1}$) = 3070, 3051, 2960, 2930, 2894, 2362, 2337, 1775, 1699, 1641, 1596, 1458, 1430, 1394, 1328, 1248, 1174, 1148, 1119, 1045, 1019, 956, 927, 748.

**Preparation of 5-(5-bromo-4-(2-methoxyphenyl)thiophen-2-yl)furan-2-carb-aldehyde (5t)**

Prepared according to **TP1** from 2,5-dibromo-3-(2-methoxyphenyl)thiophene (2h; 348 mg, 1 mmol) and iPrMgCl·LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with ZnCl$_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh$_3$)$_4$ (46 mg, 0.04 mmol) and 5-iodofuran-2-carbaldehyde (4m; 200 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et$_2$O, 100:1) afforded 5t as a light brown solid (249 mg, 76%).

m.p.: 114.8-116.4 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 9.63 (s, 1H), 7.38-7.52 (m, 3H), 7.30 (d, J=3.6Hz, 1H), 6.99-7.08 (m, 2H), 6.69 (d, J=3.9Hz, 1H), 3.87 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 176.9, 156.9, 153.5, 151.7, 136.6, 132.0, 131.1, 130.7, 128.9, 120.6, 120.5, 111.4, 110.9, 107.9, 55.6.

MS (70 eV, EI), m/z (%) = 364 (M$^+$, 100), 362 (M$^+$, 99), 269 (12), 268 (74), 211 (33), 139 (11).

HRMS (EI), m/z calc. for C$_{16}$H$_{11}$BrO$_3$S (361.9612): 361.9604 (M$^+$).

IR (ATR) υ (cm$^{-1}$) = 3125, 3107, 3096, 2998, 2982, 2950, 2925, 2843, 1664, 1484, 1470, 1461, 1393, 1280, 1251, 1238, 1034, 1016, 961, 893, 794, 762.

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2.3.1 Further Functionalization of Monobromothiophene 5g

Preparation of (3,4-dichlorophenyl)(5-(4-methoxyphenyl)-3-(phenylthio)thiophen-2-yl)methanol (7a)

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with iPrMgCl-LiCl (1a; 0.92 ml, 1.1 mmol, 1.2 M in THF). 2-bromo-5-(4-methoxy-phenyl)-3-(phenylthio)thiophene (5g; 377 mg, 1.0 mmol) was added as a solution in THF (1.0 M) at 25 °C and continuously stirred for 1 h. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard. Subsequently, the reaction mixture was cooled to −20 °C and 3,4-dichlorobenzaldehyde (4n; 158 mg, 0.9 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification (pentane/Et₂O, 6:4) furnished 7a as a white solid (328 mg, 77%).

m.p.: 108.6-110.1 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.44-7.51 (m, 2H), 7.42 (dd, J=1.4 Hz, 0.8 Hz, 1H), 7.22-7.31 (m, 3H), 7.10-7.21 (m, 5H), 6.85-6.92 (m, 2H), 6.10 (d, J=3.0 Hz, 1H), 3.82 (s, 3H), 2.45 (d, J=3.6 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 159.9, 150.5, 149.3, 142.8, 137.8, 132.5, 131.3, 130.3, 129.2, 128.1, 127.1, 126.8, 126.3, 126.2, 125.4, 124.4, 121.4, 114.4, 69.4, 55.4.

MS (70 eV, EI), m/z (%) = 472 (M⁺, 100), 456 (11), 217 (13), 190 (15), 175 (36), 173 (42), 151 (15), 145 (20), 121 (11), 111 (19), 77 (30).

HRMS (EI), m/z calc. for C₂₄H₁₉Cl₂O₂S₂ (472.0125): 472.0114 (M⁺).

IR (ATR) ν (cm⁻¹) = 3533, 3466, 3070, 3049, 3003, 2955, 2928, 2897, 2836, 1603, 1581, 1571, 1505, 1478, 1463, 1417, 1291, 1251, 1177, 1031, 1024, 828, 822, 772, 739, 733, 687.
Preparation of ethyl 4-(5-(4-methoxyphenyl)-3-(phenylthio)thiophen-2-yl)benzoate (7b)

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with iPrMgCl·LiCl (1a; 0.92 ml, 1.1 mmol, 1.2 M in THF). 2-bromo-5-(4-methoxy-phenyl)-3-(phenylthio)thiophene (5g; 377 mg, 1.0 mmol) was added as a solution in THF (1.0 M) at 25 °C and continuously stirred for 1 h. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (58 mg, 0.05 mmol) and ethyl 4-iodobenzoate (4h; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 9:1) afforded 7b as a pale yellow solid (293 mg, 73%).

m.p.: 129.4-132.0 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 8.06 (d, J=8.6Hz, 2H), 7.50-7.69 (m, 4H), 7.36 (s, 1H), 7.12-7.28 (m, 5H), 6.94 (d, J=8.9 Hz, 2H), 4.39 (q, J=7.1 Hz, 2H), 3.84 (s, 3H), 1.40 (t, J=7.2 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 166.4, 159.9, 148.2, 147.6, 139.8, 138.6, 129.5, 129.1, 128.7, 127.1, 126.9, 126.2, 126.1, 126.1, 124.5, 124.2, 114.5, 61.0, 55.4, 14.3.

MS (70 eV, EI), m/z (%) = 446 (M⁺, 100), 403 (7), 296 (6), 281 (9), 221 (12), 200 (8), 77 (12).

HRMS (EI), m/z calc. for C₂₆H₂₂O₃S₂ (446.1010): 446.1004 (M⁺).

IR (ATR) ν (cm⁻¹) = 3071, 3050, 3000, 2983, 2928, 2904, 2852, 2830, 1709, 1607, 1581, 1517, 1499, 1428, 1269, 1250, 1183, 1176, 1101, 1024, 851, 824, 798, 773, 738, 702, 690.
Preparation of (4-chlorophenyl)(5-(4-methoxyphenyl)-3-(phenylthio)thiophen-2-yl)methanone (7c)

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with iPrMgCl-LiCl (1a; 0.92 ml, 1.1 mmol, 1.2 M in THF). 2-bromo-5-(4-methoxy-phenyl)-3-(phenylthio)thiophene (5g; 377 mg, 1.0 mmol) was added as a solution in THF (1.0 M) at 25 °C and continuously stirred for 1 h. Complete Br/Mg-exchange was monitored by GC-analysis of iodolized reaction aliquots using undecane as internal standard. Subsequently, the acylation reaction was accomplished according to TP4 with ZnCl₂ (1 mL, 1 mmol, 1.0 M in THF), CuCN·2LiCl (0.1 mL, 0.1 mmol, 1.0 M in THF) and 4-chlorobenzoyl chloride (4o; 158 mg, 0.9 mmol) in 8 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 9:1) afforded 7c as a pale yellow oil (274 mg, 70%).

\[ \text{1H NMR} (300 MHz, CDCl}_3 \delta (ppm) = 7.74-7.85 (m, 2H), 7.50-7.65 (m, 2H), 7.28-7.50 (m, 7H), 7.23-7.27 (m, 1H), 6.78-6.91 (m, 2H), 3.80 (s, 3 H). \]

\[ \text{13C NMR} (75 MHz, CDCl}_3 \delta (ppm) = 189.1, 159.7, 147.6, 142.9, 138.7, 137.4, 137.0, 134.2, 133.1, 130.7, 129.6, 129.2, 128.7, 126.9, 125.8, 123.6, 114.4, 55.4. \]

\[ \text{MS (70 eV, EI), } m/z \% = 436 (M^+, 100), 421 (12), 325 (5), 281 (5), 253 (5), 221 (8), 141 (14), 139 (42). \]

\[ \text{HRMS (EI), } m/z \text{ calc. for } \text{C}_{24}\text{H}_{17}\text{ClO}_2\text{S}_2 (436.0358): 436.0359 (M^+). \]

\[ \text{IR (ATR) } \nu (\text{cm}^{-1}) = 3054, 2998, 2953, 2926, 2869, 2845, 2834, 1630, 1607, 1585, 1536, 1500, 1421, 1407, 1292, 1248, 1172, 1087, 1031, 1007, 998, 823, 806, 788, 760, 746, 688. \]
2.4 Preparation of Functionalized Pyridines of Type 10

Preparation of ethyl 4-(5-bromo-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)benzoate (10a)

Prepared according to TP1 from 3,5-dibromo-2-(4-(trifluoromethyl)phenyl)pyridine (8a; 381 mg, 1 mmol) and iPrMgCl-LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at -55 °C in 2 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (4h; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 9:1 + 1% NEt₃) afforded 10a as a white solid (354 mg, 88%).

m.p.: 97.5-99.1 °C.

¹H NMR (600 MHz, CDCl₃) δ (ppm) = 8.80 (d, J=2.2Hz, 1H), 7.99-8.02 (m, 2H), 7.92 (d, J=2.2Hz, 1H), 7.51 (d, J=8.2Hz, 2H), 7.44 (d, J=8.2Hz, 2H), 7.23-7.26 (m, 2H), 4.39 (q, J=7.4Hz, 2H), 1.41 (t, J=7.4Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 166.0, 154.0, 150.0, 142.4, 142.2 (q, J=1.1Hz), 140.7, 136.8, 130.3 (q, J=32.8Hz), 130.2, 130.0, 129.9, 129.4, 125.1 (q, J=3.7Hz), 123.9 (q, J=272.4Hz), 119.9, 61.2, 14.3.

MS (70 eV, EI), m/z (%): 451 (M⁺, 97), 450 (M⁺, 100), 449 (M⁺, 95), 448 (M⁺, 85), 421 (32), 419 (35), 406 (21), 404 (21), 378 (15), 376 (17), 297 (31), 296 (15), 228 (11), 227 (11).

HRMS (EI), m/z calc. for C₂₁H₁₄BrF₃NO₂ (449.0238): 449.0231 (M⁺).

IR (ATR) ν (cm⁻¹) = 3055, 2982, 2940, 2904, 1705, 1608, 1426, 1368, 1323, 1310, 1288, 1273, 1166, 1120, 1111, 1101, 1068, 1024, 1009, 854, 783, 769, 715, 706
Preparation of ethyl 4-(5-bromo-2-(4-methoxyphenyl)pyridin-3-yl)benzoate (10b)

Prepared according to TP1 from 3,5-dibromo-2-(4-methoxyphenyl)pyridine (8b; 343 mg, 1 mmol) and iPrMgCl·LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at -78 °C in 2 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (4h; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 8.5:1.5 + 1% NEt₃) afforded 10b as a white solid (236 mg, 64%).

m.p.: 157.5-160.1 °C.

¹H NMR (600 MHz, CDCl₃) δ (ppm) = 8.71 (d, J=2.2Hz, 1H), 7.91-8.02 (m, 2H), 7.82 (d, J=2.2Hz, 1H), 7.14-7.32 (m, 4H), 6.68-6.79 (m, 2H), 4.36 (q, J=7.1Hz, 2H), 3.76 (s, 3H), 1.38 (t, J=7.1Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 166.2, 159.7, 155.3, 149.6, 143.4, 140.4, 136.1, 131.1, 131.0, 129.7, 129.7, 129.3, 118.4, 113.6, 61.1, 55.2, 14.3.

MS (70 eV, EI), m/z (%) = 413 (M⁺, 91), 411 (M⁺, 100), 410 (M⁺, 61), 384 (27), 382 (26), 340 (11), 339 (11), 338 (10).

HRMS (EI), m/z calc. for C21H₁₈BrNO₃ (411.0470): 411.0473 (M⁺).

IR (ATR) ν (cm⁻¹) = 3062, 3003, 2979, 2961, 2936, 2843, 1708, 1604, 1511, 1424, 1402, 1368, 1308, 1283, 1271, 1252, 1175, 1115, 1098, 1043, 1026, 1022, 1010, 1004, 909, 860, 841, 793, 782, 772, 706.

Preparation of 4-(5-bromo-2-(thiophen-2-yl)pyridin-3-yl)benzonitrile (10c)

Prepared according to TP1 from 3,5-dibromo-2-(thiophen-2-yl)pyridine (8c; 343 mg, 1 mmol) and iPrMgCl·LiCl (1a; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and 4-iodobenzonitrile
C. EXPERIMENTAL SECTION

(4k; 206 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 8.5:1.5 + 1% NEt₃) afforded 10c as a white solid (228 mg, 74%).

m.p.: 192.0-193.9 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 8.68 (d, J=2.2Hz, 1H), 7.66-7.81 (m, 3H), 7.39-7.51 (m, 2H), 7.34 (dd, J=5.3Hz, 1.1Hz, 1H), 6.84 (dd, J=5.1Hz, 3.7Hz, 1H), 6.54 (dd, J=3.9Hz, 1.1Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 150.0, 148.7, 143.3, 142.3, 140.4, 134.0, 132.7, 130.0, 128.5, 128.5, 127.7, 118.3, 118.1, 112.5.

MS (70 eV, EI), m/z (%) = 342 (M⁺, 100), 341 (M⁺, 79), 340 (M⁺, 100), 339 (M⁺, 60), 261 (13), 260 (36).

HRMS (EI), m/z calc. for C₁₆H₉BrN₂S (339.9670): 339.9667 (M⁺).

IR (ATR) ν (cm⁻¹) = 3096, 3092, 3064, 3027, 2956, 2924, 2851, 2238, 1606, 1536, 1505, 1436, 1397, 1268, 1188, 1180, 1107, 1015, 971, 909, 858, 841, 832, 823, 774, 704, 662.

Preparation of 5-bromo-3-(4-methoxyphenyl)-2-(phenylthio)pyridine (10d)

Prepared according to TP1 from 3,5-dibromo-2-(phenylthio)pyridine (8d; 343 mg, 1 mmol) and iPr₂Mg·LiCl (1a; 0.5 mL, 0.55 mmol, 1.1 M in THF) at -65 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and 1-iodo-4-methoxybenzene (4g; 211 mg, 0.9 mmol) in 12 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 100:3 + 1% NEt₃) afforded 10d as a white solid (199 mg, 60%).

m.p.: 107.8-109.8 °C.

¹H NMR (400 MHz, d6-DMSO) δ (ppm) = 8.36 (d, J=2.4Hz, 1H), 7.78 (d, J=2.4Hz, 1H), 7.35-7.44 (m, 7H), 7.01-7.05 (m, 2H), 3.79 (s, 3H).

¹³C NMR (100 MHz, d6-DMSO) δ (ppm) = 160.0, 156.0, 148.8, 139.6, 137.3, 135.2, 130.9, 130.7, 129.6, 129.1, 128.8, 117.2, 114.5, 55.7.

MS (70 eV, EI), m/z (%) = 374 (M⁺, 23), 373 (M⁺, 100), 371 (M⁺, 88), 328 (12), 140 (29), 88 (10), 61 (12), 44 (29), 43 (58).

HRMS (EI), m/z calc. for C₁₈H₁₄BrNOS (370.9979): 370.9971 (M⁺).
2.5 Preparation of Functionalized Heterocycles of Type 14 and 17

Preparation of tert-butyl 5-bromo-4-methylthiophene-2-carboxylate (14a)

Prepared according to TP2 from 2,5-dibromo-3-(methylthio)thiophene (11a; 512 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L^2; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the reaction mixture was cooled to −40 °C and di-tert-butyl dicarbonate (4d; 524 mg, 2.4 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 100: 1) furnished 14a as a yellow oil (460 mg, 83%).

^1H NMR (300 MHz, CDCl₃) δ (ppm) = 7.39 (s, 1H), 2.19 (s, 3H), 1.56 (s, 9H).

^13C NMR (75 MHz, CDCl₃) δ (ppm) = 160.6, 138.2, 134.5, 134.1, 116.7, 82.1, 28.2, 15.2.

MS (70 eV, EI), m/z (%) = 278 (M⁺, 14), 276 (M⁺, 15), 223 (10), 222 (100), 221 (12), 220 (100), 205 (43), 203 (44), 186 (26), 141 (60), 96 (24), 69 (10), 57 (60), 55 (21).

HRMS (EI), m/z calc. for C₁₀H₁₃BrO₂S (275.9820): 275.9817 (M⁺).

IR (ATR) ν (cm⁻¹) = 2978, 2932, 1702, 1426, 1368, 1296, 1254, 1156, 1074, 848, 818, 798, 748, 718.
Preparation of ethyl 4-(5-bromo-4-methylthiophen-2-yl)benzoate (14b)

Prepared according to TP2 from 2,5-dibromo-3-(methylthio)thiophene (11a; 512 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (2.0 mL, 2.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (92 mg, 0.04 mmol) and ethyl 4-iodobenzoate (4h; 498 mg, 1.8 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 95:5) afforded 14b as a pale yellow solid (556 mg, 83%).

\[ \text{m.p.: } 89.2-90.7 \, ^\circ C. \]

\[ ^1H \text{ NMR} \ (300 \text{ MHz, CDCl}_3) \delta \ (\text{ppm}) = \]
\[ 8.03 \ (d, J=8.8\text{Hz}, \ 2\text{H}), \ 7.54 \ (d, J=8.6\text{Hz}, \ 2\text{H}), \]
\[ 7.09 \ (s, \ 1\text{H}), \ 4.39 \ (q, J=7.1\text{Hz}, \ 2\text{H}), \ 2.22 \ (s, \ 3\text{H}), \ 1.4 \ (t, J=7.1\text{Hz}, \ 3\text{H}). \]

\[ ^{13}C \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \delta \ (\text{ppm}) = 166.1, \ 142.1, \ 138.6, \ 137.8, \ 130.3, \ 129.4, \ 126.2, \]
\[ 124.9, \ 110.4, \ 61.0, \ 15.3, \ 14.4. \]

\[ \text{MS} \ (70 \text{ eV, EI), } m/z \ (%)=327 \ (14), \ 326 \ (M^+, \ 100), \ 325 \ (14), \ 324 \ (M^+, \ 93), \ 298 \ (33), \]
\[ 296 \ (30), \ 281 \ (57), \ 279 \ (56), \ 217 \ (11), \ 172 \ (32), \ 171 \ (31). \]

\[ \text{HRMS} \ (\text{EI), } m/z \ \text{calc. for } C_{14}H_{13}BrO_2S \ (323.9820): \ 323.9807 (M^+). \]

\[ \text{IR (ATR) } \nu \ (\text{cm}^{-1}) = 3076, \ 2984, \ 2906, \ 1704, \ 1604, \ 1510, \ 1472, \ 1438, \ 1364, \ 1272, \ 1232, \]
\[ 1186, \ 1128, \ 1110, \ 1020, \ 850, \ 764, \ 690. \]

Preparation of (5-bromo-4-methylthiophen-2-yl)(thiophen-2-yl)methanone (14c)

Prepared according to TP2 from 2,5-dibromo-3-methylthiophene (11a; 512 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the acylation reaction was accomplished according to TP4 with ZnCl₂ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and thiophene-2-carbonyl chloride (4p; 352 mg, 2.4 mmol) in 4 h. Flash column
chromatographical purification on silica gel (pentane/Et₂O, 95:5) afforded 14c an off-white solid (488 mg, 85%).

m.p.: 100.2-101.4 °C.

^1^H NMR (300 MHz, CDCl₃) δ (ppm) = 7.85 (dd, J=3.8Hz, 1.1Hz, 1H), 7.69 (dd, J=4.9Hz, 1.1Hz, 1H), 7.57 (s, 1H), 7.17 (dd, J=5.0Hz, 3.8Hz, 1H), 2.25 (s, 3H).

^13^C NMR (75 MHz, CDCl₃) δ (ppm) = 177.6, 142.2, 141.8, 138.7, 134.6, 133.6, 133.0, 128.0, 120.0, 15.4.

MS (70 eV, EI), m/z (%) =289 (11), 288 (M⁺, 100), 287 (11), 286 (M⁺, 93), 207 (13), 205 (37), 203 (36), 111 (77), 96 (11).

HRMS (EI), m/z calc. for C₁₀H₇BrOS₂ (285.9122): 285.9117 (M⁺).

IR (ATR) υ (cm⁻¹) = 3004, 2362, 2340, 1740, 1658, 1582, 1522, 1432, 1366, 1228, 1222, 1204, 1098, 1056, 780, 706.

**Preparation of 5,5'-dibromo-4,4'-dimethyl-2,2'-bithiophene (14d)**

Prepared according to TP2 from 2,5-dibromo-3-methylthiophene (11a; 1.02 g, 4 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 6.0 mL, 4.2 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 672 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, at -40 °C, ZnCl₂ (2 mL, 2 mmol, 1 M in THF) and CuCN·2LiCl (2 mL, 2 mmol, 1 M in THF) were successively added and continuously stirred for 10 min. The reaction mixture was added dropwise to a solution of chloranil (1.47 g, 6 mmol) in THF (15 mL) at 0 °C. Then, the solution was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (5x 10 mL). The combined organic phases were washed with aq. NH₃ (2 M, 2x 30 mL), dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished 14d as a pale yellow solid (612 mg, 87%).

m.p.: 106.2-107.8 °C.

^1^H NMR (300 MHz, CDCl₃) δ (ppm) = 6.77 (s, 2H), 2.17 (s, 6H).

^13^C NMR (75 MHz, CDCl₃) δ (ppm) = 138.1, 135.9, 125.5, 108.4, 15.2.
**C. Experimental Section**

**MS** (70 eV, El), \( m/z\) (%) = 354 (\( \text{M}^+\), 51), 353 (10), 352 (\( \text{M}^+\), 100), 350 (\( \text{M}^+\), 43), 229 (10), 192 (19), 191 (11).

**HRMS** (El), \( m/z\) calc. for \( \text{C}_{10}\text{H}_{8}^{79}\text{Br}_2\text{S}_2 \) (349.8434): 349.8422 (\( \text{M}^+\)).

**IR** (ATR) \( \nu \) (cm\(^{-1}\)) = 3054, 2916, 1740, 1634, 1544, 1410, 1374, 1186, 1022, 994, 942, 834, 812, 734.

**Preparation of (5-bromo-4-hexylthiophen-2-yl)(4-methoxyphenyl)methanol (14e)**

Prepared according to **TP2** from 2,5-dibromo-3-hexylthiophene (11b; 652 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2’-oxy-bis(N,N-diethylethanamine) (**L**\(^2\); 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the reaction mixture was cooled to -20 °C and 4-methoxybenzaldehyde (4e; 245 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH\(_4\)Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Flash column chromatographical purification (pentane/Et\(_2\)O, 8.5:1.5) furnished **14e** as a pale yellow oil (487 mg, 71%).

**\(^1\)H NMR** (400 MHz, d\(_6\)-DMSO) \( \delta \) (ppm) = 7.27 (d, \( J=8.8\) Hz, 2H), 6.81-6.93 (m, 2H), 6.59 (d, \( J=0.8\) Hz, 1H), 6.19 (d, \( J=4.4\) Hz, 1H), 5.75 (d, \( J=4.4\) Hz, 1H), 3.71 (s, 3H), 2.33-2.43 (m, 2H), 1.35-1.49 (m, 2H), 1.13-1.28 (m, 6H), 0.72-0.90 (m, 3H).

**\(^{13}\)C NMR** (100 MHz, d\(_6\)-DMSO) \( \delta \) (ppm) = 158.9, 151.2, 141.4, 136.8, 127.8, 125.0, 114.0, 107.0, 70.7, 55.5, 31.4, 29.6, 29.3, 28.6, 22.5, 14.4.

**MS** (70 eV, El), \( m/z\) (%) = 384 (\( \text{M}^+\), 25), 382 (\( \text{M}^+\), 26), 367 (28), 365 (27), 304 (19), 303 (100), 287 (17), 233 (20), 137 (20), 135 (94), 109 (25), 77 (11).

**HRMS** (El), \( m/z\) calc. for \( \text{C}_{18}\text{H}_{23}\text{BrO}_2\text{S} \) (382.0602): 382.0593 (\( \text{M}^+\)).

**IR** (ATR) \( \nu \) (cm\(^{-1}\)) = 3063, 3035, 3000, 2954, 2926, 2855, 1610, 1510, 1457, 1441, 1303, 1245, 1170, 1135, 1109, 1032, 1008, 996, 833.
Preparation of 2-bromo-3-hexyl-5-((4-methoxyphenyl)sulfinyl)thiophene (14f)

Prepared according to TP2 from 2,5-dibromo-3-hexylthiophene (11b, 652 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the sulfoxide was prepared according to TP5 with 4-methoxybenzenesulfinyl chloride (4q; 343 mg, 1.8 mmol) in 4 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded 14f as colorless oil (503 mg, 70%).

\[ ^1H \text{ NMR} (300 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 7.56-7.69 (m, 2H), 7.25 (s, 1H), 6.97-7.09 (m, 2H), 3.86 (s, 3H), 2.47-2.58 (m, 2H), 1.47-1.64 (m, 2H), 1.20-1.38 (m, 6H), 0.72-0.98 (m, 3H). \]

\[ ^{13}C \text{ NMR} (75 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 162.3, 147.4, 142.8, 135.5, 131.6, 126.4, 116.6, 114.8, 55.5, 31.5, 29.5, 29.4, 28.8, 22.5, 14.0. \]

MS (70 eV, EI), \( m/z \) (%) = 400 (M⁺, 2), 354 (46), 352 (43), 204 (23), 203 (100), 139 (31), 123 (10), 77 (7), 41 (8).

HRMS (EI), \( m/z \) calc. for \( \text{C}_{17}\text{H}_{21}\text{BrO}_2\text{S}_2 \) (400.0166): 400.0166 (M⁺).

IR (ATR) \( \nu \) (cm⁻¹) = 3069, 3043, 3005, 2954, 2926, 2856, 1592, 1577, 1494, 1440, 1406, 1304, 1249, 1180, 1170, 1085, 1049, 1026, 989, 827, 796.

Preparation of (5-bromo-4-methylfuran-2-yl)(thiophen-2-yl)methanone (14g)

Prepared according to TP2 from 2,5-dibromo-3-methylfuran (11c; 480 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the acylation reaction was accomplished according to TP4 with ZnCl₂ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and thiophene-2-carbonyl chloride (4p; 352 mg, 2.4 mmol) in 4 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 95:5) afforded 14g as a pale yellow solid (428 mg, 79%).
m.p.: 80.6-81.9 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.14 (dd, $J$=3.8Hz, 1.1Hz, 1H), 7.70 (dd, $J$=5.0Hz, 1.2Hz, 1H), 7.24 (s, 1H), 7.19 (t, $J$=4.4Hz, 1H), 2.07 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 172.1, 152.9, 141.9, 134.1, 133.8, 128.3, 126.6, 123.0, 122.0, 10.5.

MS (70 eV, EI), $m/z$ (%) = 272 (M$^+$, 31), 270 (M$^+$, 31), 190 (11), 135 (26), 111 (100).

HRMS (EI), $m/z$ calc. for C$_{10}$H$_7$BrO$_2$S (269.9350): 269.9347 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3118, 3112, 2962, 2926, 2360, 2342, 1714, 1608, 1596, 1490, 1410, 1356, 1306, 1294, 1240, 1208, 1168, 1074, 1060, 964, 812, 744, 734, 616.

Preparation of 4-(5-bromo-4-methylfuran-2-yl)benzonitrile (14h)

![Chemical Structure](image)

Prepared according to TP2 from 2,5-dibromo-3-methylfuran (11c; 480 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L$_2$; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl$_2$ (2.0 mL, 2.0 mmol, 1.0 M in THF), Pd(PPh$_3$)$_4$ (92 mg, 0.08 mmol) and 4-iodobenzonitrile (4k; 550 mg, 2.4 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et$_2$O, 95:5) afforded 14h as a yellow solid (409 mg, 78%).

m.p.: 99.5-101.6 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.6-7.7 (m, 4H), 6.68 (s, 1H), 2.03 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 152.7, 133.7, 132.6, 124.9, 123.5, 122.3, 118.8, 112.0, 110.5, 10.6.

MS (70 eV, EI), $m/z$ (%) = 264 (9), 263 (M$^+$, 72), 262 (10), 261 (M$^+$, 73), 182 (22), 155 (13), 154 (100), 153 (24), 130 (19), 127 (45), 126 (11), 102 (13), 77 (11), 63 (13).

HRMS (EI), $m/z$ calc. for C$_{12}$H$_8$BrNO (260.9789): 260.9780 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3108, 2962, 2926, 2870, 2222, 1918, 1766, 1606, 1532, 1516, 1484, 1446, 1386, 1348, 1266, 1178, 1078, 924, 834, 814, 684, 660.
Preparation of 1-(5-bromo-4-methylfuran-2-yl)-2,2-dimethylpropan-1-ol (14i)

Prepared according to TP2 from 2,5-dibromo-3-methylfuran (11c; 480 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2’-oxy-bis(N,N-diethylethanamine) (L2; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the reaction mixture was cooled to -20 °C and pivaldehyde (4r; 206 mg, 2.4 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na2SO4 and concentrated in vacuo. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished 14i as a yellow oil (361 mg, 73%).

1H NMR (300 MHz, CDCl3) δ (ppm) = 6.11 (s, 1H), 4.21 (s, 1H), 1.94-2.01 (m, 4H), 0.96 (s, 9H).
13C NMR (75 MHz, CDCl3) δ (ppm) = 156.7, 119.6, 118.6, 111.5, 76.4, 35.6, 25.7, 10.5.
MS (70 eV, EI), m/z (%) = 248 (M+ 6), 246 (M+ 8), 231 (19), 229 (19), 192 (8), 191 (94), 190 (11), 189 (100), 57 (32), 55 (17), 53 (18).
HRMS (EI), m/z calc. for C10H15BrO2 (246.0255): 246.0242 (M+).
IR (ATR) ν (cm⁻¹) = 3426, 2956, 2870, 1542, 1396, 1366, 1206, 1158, 1074, 1048, 1034, 902, 814, 794, 734, 612.

Preparation of 4-(3,5-dibromo-4-methylthiophen-2-yl)benzonitrile (14j)

Prepared according to TP2 from 2,3,5-tribromo-4-methylthiophene (11e; 670 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2’-oxy-bis(N,N-diethylethanamine) (L2; 336 mg, 2.1 mmol) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl2 (2.0 mL, 2.0 mmol, 1.0 M in THF), Pd(PPh3)4 (92 mg, 0.08 mmol) and 4-iodobenzonitrile (4k; 550 mg, 2.4 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et2O, 50:1) afforded 14j as a white solid (545 mg, 77%).
m.p.: 160.8-162.3 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.72 (s, 4H), 2.29 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 138.3, 137.2, 135.8, 132.4, 129.4, 118.4, 112.0, 111.2, 110.0, 16.4.

MS (70 eV, EI), $m/z$ (%) = 357 (M$^+$, 87), 355 (M$^+$, 49), 278 (21), 276 (21), 197 (22), 196 (17), 152 (11), 70 (18), 61 (13), 45 (18), 44 (57), 43 (100).

HRMS (EI), $m/z$ calc. for C$_{12}$H$_7$Br$_2$NS (354.8666): 354.8657 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3085, 3070, 3056, 3035, 2957, 2919, 2852, 2359, 2228, 1920, 1605, 1504, 1454, 1407, 1393, 1386, 1380, 1334, 1328, 1308, 1180, 1110, 1044, 1019, 924, 842, 832, 807, 800, 755.

Preparation of (3,5-dibromo-4-methylthiophen-2-yl)(2,4-dichlorophenyl)methanone (14k)

Prepared according to TP2 from 2,3,5-tribromo-4-methylthiophene (11e; 670 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L$^2$; 336 mg, 2.1 mmol) at 0 °C in 1 h. Subsequently, the acylation reaction was accomplished according to TP4 with ZnCl$_2$ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and 2,4-dichlorobenzoyl chloride (4s; 377 mg, 1.8 mmol) in 8 h. Flash column chromatographical purification on silica gel (pentane/Et$_2$O, 50:1) afforded 14k as a pale yellow solid (662 mg, 86%).

m.p.: 133.6-134.8 °C.

$^1$H NMR (400 MHz, d$_6$-DMSO) $\delta$ (ppm) = 7.74-7.83 (m, 1H), 7.55-7.61 (m, 2H), 2.16 (s, 3H).

$^{13}$C NMR (100 MHz, d$_6$-DMSO) $\delta$ (ppm) = 184.6, 140.8, 137.3, 137.2, 136.6, 131.4, 130.7, 130.0, 128.5, 121.1, 119.7, 16.3.

MS (70 eV, EI), $m/z$ (%) = 429 (M$^+$, 79), 427 (M$^+$, 31), 177 (11), 175 (61), 173 (100), 147 (19), 145 (32), 44 (22).

HRMS (EI), $m/z$ calc. for C$_{12}$H$_6$Br$_2$Cl$_2$OS (427.7863): 427.7931 (M$^+$).
IR (ATR) $\nu$ (cm$^{-1}$) = 3066, 2915, 2362, 2339, 1614, 1379, 1323, 1289, 1241, 1138, 1102, 1053, 1020, 865, 844, 818, 776, 753, 706, 670.

**Preparation of (3,5-dibromo-4-methylthiophen-2-yl)(4-methoxyphenyl)methanol (14l)**

Prepared according to TP2 from 2,3,5-tribromo-4-methylthiophene (11e; 670 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2’-oxy-bis(N,N-diethylethanamine) (L$^2$; 336 mg, 2.1 mmol) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 4-methoxybenzaldehyde (4e; 245 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH$_4$Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatographical purification (pentane/Et$_2$O, 8:2) furnished 14l as a colorless oil (618 mg, 88%).

$^1$H NMR (400 MHz, d6-DMSO) $\delta$ (ppm) = 7.21-7.29 (m, 2H), 6.82-6.89 (m, 2H), 6.41 (d, $J$=4.1Hz, 1H), 5.79 (d, $J$=4.1Hz, 1H), 3.69 (s, 3H), 2.05 (s, 3H).

$^{13}$C NMR (100 MHz, d6-DMSO) $\delta$ (ppm) = 159.1, 146.0, 136.1, 135.1, 128.1, 114.1, 108.3, 107.4, 70.8, 55.5, 15.8.

**MS** (70 eV, EI), $m/z$ (%) = 392 (M$^+$, 57), 390 (M$^+$, 27), 377 (16), 375 (33), 311 (15), 283 (18), 136 (16), 135 (42), 109 (100), 108 (20), 92 (11), 77 (25).

**HRMS** (EI), $m/z$ calc. for C$_{13}$H$_{12}$Br$_2$O$_2$S (389.8925): 389.8917 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3334, 2999, 2953, 2922, 2834, 1609, 1586, 1510, 1462, 1440, 1379, 1328, 1304, 1246, 1173, 1148, 1110, 1030, 952, 831, 797, 760, 740, 685.
Preparation of 2,4-dibromo-5-((4-methoxyphenyl)sulfinyl)-3-methylthiophene (14m)

Prepared according to TP2 from 2,3,5-tribromo-4-methylthiophene (11e; 670 mg, 2 mmol), 2,4,6-trisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 336 mg, 2.1 mmol) at 0 °C in 1 h. Subsequently, the sulfoxide was prepared according to TP5 with 4-methoxybenzenesulfinyl chloride (4q; 496 mg, 2.6 mmol) in 4 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 6:4) afforded 14m as white solid (770 mg, 94%).

m.p.: 110.8-112.7 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.64-7.77 (m, 2H), 6.98-7.04 (m, 2H), 3.85 (s, 3H), 2.17 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 162.5, 144.1, 138.2, 134.6, 126.8, 115.6, 115.2, 114.8, 55.6, 15.5.

MS (70 eV, EI), $m/z$ (%) = 412 (M$^+$, 14), 410 (M$^+$, 15), 364 (49), 361 (100), 360 (47), 347 (23), 345 (11), 155 (32), 139 (38), 123 (14), 92 (12), 77 (12).

HRMS (EI), $m/z$ calc. for C$_{12}$H$_{10}$Br$_2$O$_2$S$_2$ (409.8468): 409.8503 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3088, 3067, 3002, 2963, 2933, 2904, 2842, 2361, 2339, 1590, 1574, 1494, 1452, 1446, 1388, 1324, 1301, 1255, 1184, 1176, 1081, 1062, 1045, 1024, 993, 932, 834, 822, 794, 780.

Preparation of (5-bromo-3-methoxythiophen-2-yl)(3-chloro-4-methoxyphenyl)-methanol (14n)

Prepared according to TP2 from 2,5-dibromo-3-methoxythiophene (11f; 544 mg, 2 mmol), 2,4,6-trisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF)
and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the reaction mixture was cooled to −20 °C and 3-chloro-4-methoxybenzaldehyde (4a; 307 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH₄Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification (pentane/Et₂O, 6:4) furnished 14n as a yellow oil (478 mg, 73%).

\[ 1^H \text{NMR} (400 MHz, d6-DMSO) \delta (ppm) = 7.29 (d, J=2.2Hz, 1H), 7.20 (dd, J=8.8Hz, 2.1Hz, 1H), 7.11 (s, 1H), 7.04 (d, J=8.6Hz, 1H), 6.17 (bs, 1H), 5.82 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H). \]

\[ 1^3C \text{NMR} (100 MHz, d6-DMSO) \delta (ppm) = 153.9, 151.8, 138.0, 127.9, 127.5, 126.1, 121.2, 121.0, 112.9, 109.2, 66.4, 59.4, 56.5. \]

\[ \text{MS} (70 eV, EI), m/z (%) = 364 (M^+, 49), 362 (M^+, 32), 347 (58), 345 (38), 285 (37), 283 (100), 223 (28), 219 (33), 171 (32), 155 (26), 111 (30), 108 (36), 85 (46), 77 (52), 63 (48), 42 (54). \]

\[ \text{HRMS (EI), m/z calc. for C}_{13}H_{12}BrClO_{3}S (361.9379): 361.9371 (M^+). \]

\[ \text{IR (ATR) } \nu (\text{cm}^{-1}) = 3094, 3004, 2962, 2935, 2905, 2840, 1697, 1595, 1580, 1558, 1498, 1459, 1438, 1366, 1309, 1282, 1255, 1207, 1196, 1183, 1150, 1090, 1061, 1020, 981, 914, 884, 809, 726, 692, 685. \]

**Preparation of 4-(5-bromo-3-methoxythiophen-2-yl)benzonitrile (14o)**

\[ \text{Prepared according to TP2 from 2,5-dibromo-3-methoxythiophene (11f; 544 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (2.0 mL, 2.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (92 mg, 0.08 mmol) and 4-iodobenzonitrile (4k 412 mg, 1.8 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 9:1) afforded 14o as a yellow solid (361 mg, 69%).} \]
m.p.: 162.1-164.0 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.67-7.80 (m, 2H), 7.54-7.64 (m, 2H), 6.95 (s, 1H), 3.93 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 154.5, 137.2, 132.4, 126.4, 120.6, 119.3, 119.1, 112.5, 109.2, 59.0.

MS (70 eV, EI), $m/z$ (%) = 295 (M$^+$, 84), 293 (M$^+$, 80), 201 (16), 200 (39), 147 (10), 146 (100), 139 (12), 127 (32), 125 (10), 114 (14), 102 (38), 75 (15), 63 (16), 62 (14), 45 (16), 43 (17).

HRMS (EI), $m/z$ calc. for $C_{12}H_8BrNOS$ (292.9510): 292.9511 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3099, 3082, 2980, 2940, 2852, 2223, 1601, 1556, 1543, 1508, 1433, 1369, 1313, 1204, 1181, 1165, 1079, 988, 911, 826, 800, 705, 660, 653.

**Preparation of 2(5-bromo-3-methoxythiophen-2-yl)(4-chlorophenyl)methanone (14p)**

Prepared according to TP2 from 2,5-dibromo-3-methoxythiophene (11f; 544 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L$^2$; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the acylation reaction was accomplished according to TP4 with ZnCl$_2$ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and 4-chlorobenzoyl chloride (4o; 315 mg, 1.8 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et$_2$O, 8.5:1.5) afforded 14p as a pale yellow solid (389 mg, 66%).

m.p.: 137.0-138.7 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.65-7.75 (m, 2H), 7.36-7.46 (m, 2H), 6.91 (s, 1H), 3.81 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 185.5, 159.0, 138.2, 137.1, 130.3, 128.1, 122.9, 122.4, 119.8, 59.0.

MS (70 eV, EI), $m/z$ (%) = 332 (M$^+$, 63), 330 (M$^+$, 44), 315 (20), 297 (23), 295 (24), 221 (59), 219 (58), 216 (20), 139 (100), 111 (97), 75 (37).
**C. Experimental Section**

**HRMS (El), m/z calc. for C₁₂H₃BrClO₂S (329.9117):** 329.9115 (M⁺).

**IR (ATR) v (cm⁻¹) =** 3108, 3098, 2980, 2945, 2862, 1604, 1532, 1422, 1380, 1290, 1277, 1211, 1088, 1014, 986, 871, 827, 805, 748, 701, 693.

**Preparation of 4-(5-bromo-6-(trimethylsilyl)pyridin-3-yl)benzonitrile (17a)**

![Chemical structure](attachment:17a.png)

Prepared according to TP2 from 3,5-dibromo-2-(trimethylsilyl)pyridine (15; 309 mg, 1 mmol), 2,4,6-triisopropylmagnesium bromide (1c; 1.5 mL, 1.05 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 168 mg, 2.1 mmol) at 25 °C in 2 h. Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and 4-iodobenzonitrile (4k; 206 mg, 0.9 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 9:1 + 1% NEt₃) afforded 17a as a pale yellow solid (179 mg, 60%).

**m.p.:** 126.5-128.4 °C.

**¹H NMR (400 MHz, d₆-DMSO) δ (ppm) =** 9.04 (d, J=2.0Hz, 1H), 8.29 (d, J=2.1Hz, 1H), 7.90-7.97 (m, 4H), 0.37 (s, 9H).

**¹³C NMR (100 MHz, d₆-DMSO) δ (ppm) =** 166.2, 146.7, 140.5, 136.7, 135.2, 133.4, 129.3, 128.5, 119.0, 111.8, -0.5.

**MS (70 eV, El), m/z (%) =** 332 (M⁺, 15), 330 (M⁺, 16), 318 (18), 317 (100), 316 (20), 315 (92), 271 (10), 251 (38), 194 (12), 139 (11), 137 (11), 73 (10), 72 (14).

**HRMS (El), m/z calc. for C₁₅H₁₅BrN₂Si (330.0188):** 330.0136 (M⁺).

**IR (ATR) v (cm⁻¹) =** 3095, 3049, 2966, 2949, 2896, 2227, 1609, 1577, 1505, 1430, 1358, 1348, 1247, 1147, 1047, 1024, 1012, 856, 836, 769, 757, 722.

**Preparation of ethyl 4-(5-bromo-6-(trimethylsilyl)pyridin-3-yl)benzoate (17b)**

![Chemical structure](attachment:17b.png)

Prepared according to TP2 from 3,5-dibromo-2-(trimethylsilyl)pyridine (15; 309 mg, 1 mmol), 2,4,6-triisopropylmagnesium bromide (1d; 1.5 mL, 1.05 mmol, 0.7 M in THF) and 2,2'-oxy-bis(N,N-diethylethanamine) (L²; 168 mg, 2.1 mmol) at 25 °C in 2 h.
Subsequently, the cross-coupling was accomplished according to TP3 with ZnCl₂ (1.0 mL, 1.0 mmol, 1.0 M in THF), Pd(PPh₃)₄ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (4h; 249 mg, 0.9 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et₂O, 95:5) afforded 17b as a pale yellow solid (208 mg, 61%).

**m.p.**: 88.2-89.8 °C.

**¹H NMR** (400 MHz, d₆-DMSO) δ (ppm) = 9.02 (d, J=2.0Hz, 1H), 8.25 (d, J=2.0Hz, 1H), 7.95-8.03 (m, 2H), 7.84-7.90 (m, 2H), 4.29 (q, J=7.1Hz, 2H), 1.29 (t, J=7.2Hz, 3H), 0.37 (s, 9H).

**¹³C NMR** (100 MHz, d₆-DMSO) δ (ppm) = 165.8, 165.7, 146.7, 140.4, 136.5, 135.8, 130.3, 130.2, 129.3, 127.9, 61.3, 14.6, -0.5.

**MS** (70 eV, EI), m/z (%) = 379 (M⁺, 44), 377 (M⁺, 44), 365 (22), 364 (100), 363 (20), 362 (94), 334 (31), 332 (17), 299 (47), 298 (79), 284 (30), 270 (12), 139 (11), 137 (11), 44 (32), 43 (30).

**HRMS** (EI), m/z calc. for C₁₇H₂₀BrNO₂Si (379.0426): 379.0417 (M⁺).

**IR** (ATR) ν (cm⁻¹) = 3045, 3041, 2976, 2953, 2899, 2899, 1701, 1608, 1573, 1479, 1410, 1365, 1355, 1288, 1274, 1244, 1226, 1184, 1115, 1103, 1046, 1022, 1012, 855, 838, 807, 724, 699.
3. ONE-POT PREPARATION OF MAGNESIUM DI(HETERO)ARYL- AND DIALKENYLBORONATES FOR SUZUKI-MIYURA CROSS-COUPlings

3.1 TYPICAL PROCEDURES

Typical procedure 1 (TP1): Preparation of magnesium diorganoboronates $R_2B(OBu)_2MgX$ via direct Mg insertion in the presence of B(OBu)$_3$

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with Mg turnings (78 mg, 3.2 mmol) and LiCl (93 mg, 2.2 mmol). LiCl was dried in vacuo using a heatgun (450 °C, 5 min). After addition of THF (2 mL), the Mg was activated with 1,2-dibromoethane (2 mol%) and Me$_3$SiCl (5 mol%). Then B(OBu)$_3$ (230 mg, 1 mmol) was added at 25 °C followed by a solution of the organic halide (2 mmol) in THF (2 mL) and stirred for the given time leading to a THF-solution of the magnesium diorganoboronate.

Typical procedure 2 (TP2): Preparation of magnesium organoboronates $RB(OBu)_3MgX$ via direct Mg insertion in the presence of B(OBu)$_3$

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with Mg turnings (78 mg, 3.2 mmol) and LiCl (93 mg, 2.2 mmol). LiCl was dried in vacuo using a heatgun (450 °C, 5 min). After addition of THF (2 mL), the Mg was activated with 1,2-dibromoethane (2 mol%) and Me$_3$SiCl (5 mol%). Then B(OBu)$_3$ (460 mg, 2 mmol) was added at 25 °C followed by a solution of the organic halide (2 mmol) in THF (2 mL) and stirred for the given time leading to a THF-solution of the magnesium organoboronate.

Typical procedure 3 (TP3): Suzuki-Miyaura cross-coupling reactions

A dry, argon-flushed Schlenk flask was charged with the electrophile E–X (1.6 mmol), PdCl$_2$ (44 mg, 4 mol%), dpff (14 mg, 4 mol%) and Cs$_2$CO$_3$ (1.3 g, 4 mmol) and suspended in EtOH (4 mL) and DMF (1 mL). Afterwards the magnesium (di-)organoboronate solution (2 mmol) was transferred to this mixture via cannula. The resulting suspension was stirred at 65 °C for the given time. Subsequently, the reaction mixture was diluted with EtOAc (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3x 15 mL). The combined organic phases were dried over Na$_2$SO$_4$ and the solvent was removed in vacuo. The crude product was purified by flash column chromatography to give the analytically pure product.
Typical procedure 4 (TP4): Suzuki-Miyaura cross-coupling reactions
A dry, argon-flushed Schlenk flask was charged with the electrophile E–X (1.6 mmol), Pd(PPh₃)₄ (93 mg, 4 mol%) and Cs₂CO₃ (1.3 g, 4 mmol) and suspended in EtOH (4 mL). Afterwards the magnesium (di-)organoborinate solution (2 mmol) was transferred to this mixture via cannula. The resulting suspension was stirred at 65 °C for the given time. Subsequently, the reaction mixture was diluted with EtOAc (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3x 15 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was removed in vacuo. The crude product was purified by flash column chromatography to give the analytically pure product.

Typical procedure 5 (TP5): Suzuki-Miyaura cross-coupling reactions
A dry, argon-flushed Schlenk flask was charged with the electrophile E–X (1.4 mmol), Pd(PPh₃)₄ (93 mg, 4 mol%) and Na₂CO₃·10H₂O (0.76 g, 2.66 mmol) and suspended in 1,4-dioxane (4 mL) and H₂O (1.5 mL). Afterwards the magnesium (di-)organoborinate solution (2 mmol) was transferred to this mixture via cannula. The resulting suspension was stirred at 110 °C for the given time. Subsequently, the reaction mixture was diluted with EtOAc (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3x 15 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was removed in vacuo. The crude product was purified by flash column chromatography to give the analytically pure product.

3.2 Preparation of Functionalized Magnesium (Di)arylboronates and Subsequent Suzuki-Miyaura Cross-Couplings

Preparation of methyl 4’-cyanobiphenyl-2-carboxylate (21a)

The magnesium organoborinate 19a was prepared according to TP2 from methyl 2-bromobenzoate (18a, 430 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromobenzonitrile (22a, 291 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et₂O = 7:3) furnished 21a as a brown oil (243 mg, 65%).
**C. Experimental Section**

**1H NMR** (300 MHz, CDCl₃) δ (ppm) = 7.95 (dd, J=7.7Hz, 1.1Hz, 1H), 7.70 (d, J=8.3Hz, 2H), 7.55-7.63 (m, 1H), 7.46-7.53 (m, 1H), 7.41 (d, J=8.3Hz, 2H), 7.32 (dd, J=7.5Hz, 0.8Hz, 1H), 3.68 (s, 3H).

**13C NMR** (75 MHz, CDCl₃) δ (ppm) = 167.9, 146.3, 141.0, 131.7, 131.7, 130.5, 130.4, 130.0, 129.1, 128.2, 118.8, 111.0, 52.0.

**MS** (70 eV, El), m/z (%) = 237 (M⁺, 43), 207 (15), 206 (100), 178 (22), 177 (18), 151 (17).

**HRMS** (El), m/z calc. for C₁₅H₁₁NO₂ (237.0790): 237.0780 (M⁺).

**IR** (ATR) υ (cm⁻¹) = 3062, 3000, 2951, 2855, 2227, 1720, 1608, 1598, 1482, 1446, 1432, 1288, 1276, 1254, 1190, 1126, 1089, 1028, 1006, 959, 842, 762, 734, 704.

**Preparation of tert-butyl (4'-(tert-butylcarbamoyl)-biphenyl-4-yl) carbonate (21b)**

The magnesium diorganoboronate 20a was prepared according to TP1 from 4-bromophenyl tert-butyl carbonate (18b, 546 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromo-N-(tert-butyl)benzamide (22b, 410 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et₂O = 5.5:4.5) furnished 21b as a white solid (539 mg, 91%).

m.p.: 166.0-168.8 °C.

**1H NMR** (300 MHz, CDCl₃) δ (ppm) = 7.79 (d, J=8.0Hz, 2H), 7.59 (d, J=8.8Hz, 4H), 7.26 (d, J=8.6Hz, 2H), 6.02 (br s, 1H), 1.58 (s, 9H), 1.50 (s, 9H).

**13C NMR** (75 MHz, CDCl₃) δ (ppm) = 151.7, 150.9, 142.9, 137.7, 134.7, 128.1, 127.2, 127.0, 121.7, 83.7, 51.6, 28.9, 27.7.

**MS** (70 eV, El), m/z (%) = 369 (M⁺, 1), 269 (37), 213 (56), 198 (11), 197 (100), 57 (20), 42 (27), 41 (10).

**HRMS** (El), m/z calc. for C₂₂H₂₇NO₄ (369.1940): 369.1943 (M⁺).

**IR** (ATR) υ (cm⁻¹) = 3253, 2973, 2925, 1750, 1630, 1609, 1544, 1487, 1455, 1368, 1273, 1256, 1218, 1143, 1006, 895, 881, 838, 824, 794, 777, 683.
Preparation of 6-hydroxy-5-methoxy-3',5'-bis(trifluoromethyl)-biphenyl-3-carb-aldehyde (21c)

The magnesium diorganoboronate 20b was prepared according to TP1 from 3,5-di(trifluoromethyl)bromobenzene (18c, 586 mg, 2 mmol) in 15 min at 25 °C. A cross-coupling reaction was performed according to TP3 with 5-bromovanillin (22c, 368 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 8:2) furnished 21c as a pale yellow solid (483 mg, 87%).

m.p.: >275 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 9.9 (s, 1H), 8.1 (s, 2H), 7.9 (s, 1H), 7.6 (s, 1H), 7.5 (s, 1H), 4.1 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 190.5, 157.5, 148.7, 147.6, 138.3, 131.7 (q, $J$=33.4Hz), 129.7, 129.1, 128.4, 127.5 (m), 121.5 (m), 108.8, 56.6.

MS (70 eV, EI), $m/z$ (%) = 364 (M$^+$, 5), 228 (8), 88 (4), 61 (12), 45 (13), 43 (100).

HRMS (EI), $m/z$ calc. for C$_{16}$H$_{10}$F$_6$O$_3$ (364.0534): 364.0522 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3294, 2970, 2360, 1740, 1672, 1500, 1382, 1362, 1294, 1272, 1180, 1152, 1118, 898, 864, 844, 750, 710, 682.

Preparation of 4'-acetyl-biphenyl-4-carbonitrile (21d)

The magnesium diorganoboronate 20c was prepared according to TP1 from 4-bromobenzonitrile (18d, 364 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromoacetophenone (22d, 318 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 9:1) furnished 21d as a white solid (290 mg, 82%).
m.p.: 106.2-107.8 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.08 (d, $J$=8.7Hz, 2H), 7.67-7.81 (m, 6H), 2.66 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 197.4, 144.3, 143.5, 136.9, 132.9, 129.1, 127.9, 27.4, 118.6, 111.9, 26.7.

MS (70 eV, EI), $m/z$ (%) = 222 (5), 221 (M$^+$, 19), 207 (14), 206 (100), 178 (30), 177 (18), 151(24).

HRMS (EI), $m/z$ calc. for C$_{15}$H$_{11}$NO (221.0841): 221.0826 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3050, 2226, 1682, 1602, 1396, 1358, 1266, 1178, 1116, 1004, 956, 862, 814, 742, 714, 622.

Preparation of 6-hydroxy-5-methoxy-4′-(methylthio)-biphenyl-3-carbaldehyde (21e)

The magnesium diorganoboronate 20d was prepared according to TP1 from 4-bromothioanisole (18e, 406 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 5-bromovanillin (22c, 370 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/EtOAc = 3:1) furnished 21e as a white solid (382 mg, 87%).

m.p.: 124.9-125.6 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 9.88 (s, 1H), 7.57 (d, $J$=8.2Hz, 2H), 7.52 (d, $J$=1.9Hz, 1H), 7.42 (d, $J$=1.9Hz, 1H), 7.35 (d, $J$=8.5Hz, 2H), 6.46 (br s, 1H), 4.03 (s, 3H), 2.54 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 190.9, 148.6, 147.5, 138.3, 132.9, 129.4, 128.3, 127.1, 126.4, 108.7, 107.4, 56.5, 15.7.

MS (70 eV, EI), $m/z$ (%) = 276 (5), 275 (14), 274 (M$^+$, 100), 212 (5), 184 (6).

HRMS (EI), $m/z$ calc. for C$_{15}$H$_{14}$O$_3$S (274.0664): 274.0655 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3198, 2978, 2922, 2848, 2362, 1732, 1666, 1588, 1498, 1454, 1428, 1388, 1366, 1304, 1246, 1150, 1124, 1090, 1044, 1014, 854, 822, 732, 706, 680.
Preparation of 5-(4-(methylthio)phenyl)-1H-indole (21f)

The magnesium diorganoboronate 20d was prepared according to TP1 from 4-bromothio-anisole (18e, 406 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 5-bromo-1H-indole (22e, 314 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/EtOAc = 8.5:1.5) furnished 21f as a pale yellow solid (352 mg, 92%).

m.p.: 82.6-83.9 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.16 (br s, 1H), 7.87 (s, 1H), 7.61 (d, $J=8.6$Hz, 2H), 7.43-7.48 (m, 2H), 7.37 (d, $J=8.4$Hz, 2H), 7.24 (t, $J=2.4$Hz, 1H), 6.59-6.65 (m, 1H), 2.55 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 139.6, 136.1, 135.2, 132.7, 128.4, 127.7, 127.2, 124.9, 121.6, 118.9, 111.2, 103.0, 16.2.

MS (70 eV, EI), $m/z$ (%) = 240 (15), 239 (M$^+$, 100), 224 (54), 57 (12).

HRMS (EI), $m/z$ calc. for C$_{15}$H$_{13}$NS (239.0769): 239.0764 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3402, 3022, 2920, 1738, 1594, 1578, 1464, 1412, 1342, 1230, 1210, 1096, 1066, 1008, 970, 954, 886, 800, 722.

Preparation of 4’-(tert-butylcarbamoyl)-biphenyl-3-yl diethylcarbamate (21g)

The magnesium diorganoboronate 20e was prepared according to TP1 from 3-bromo-phenyl diethylcarbamate (18f, 544 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromo-N-(tert-butyl)benzamide (22b, 410 mg, 1.6 mmol) in 7 h. Flash column chromatographical purification (pentane/Et$_2$O = 4:6) furnished 21g as a pale yellow solid (525 mg, 90%).
m.p.: 140.1-143.6 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.78 (d, $J=8.0$Hz, 2H), 7.62 (d, $J=8.0$Hz, 2H), 7.39-7.44 (m, 2H), 7.35-7.38 (m, 1H), 7.12-7.17 (m, 1H), 6.02 (br s, 1H), 3.44 (q, $J=6.9$Hz, 4H), 1.49 (s, 9H), 1.25 (t, $J=8.0$Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 166.5, 154.1, 151.9, 143.0, 141.4, 134.7, 129.6, 127.2, 127.1, 123.8, 121.2, 120.5, 51.6, 42.1 (d, $J=24.8$Hz), 28.9, 13.8 (d, $J=66.0$Hz).

MS (70 eV, EI), m/z (%) = 368 (M$^+$, 6), 100 (100), 72 (30).

HRMS (EI), m/z calc. for C$_{22}$H$_{28}$N$_2$O$_3$ (368.2100): 368.2092 (M$^+$).

IR (ATR) ν (cm$^{-1}$) = 3486, 3393, 3035, 2972, 2946, 2894, 2876, 1707, 1707, 1621, 1595, 1516, 1485, 1442, 1333, 1247, 1164, 1116, 1096, 1073, 1040, 877, 820, 796, 735, 692.

Preparation of ethyl 5-(2-fluorophenyl)nicotinate (21h)

The magnesium diorganoboronate 20f was prepared according to TP1 from 1-bromo-2-fluorobenzene (18g, 350 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with ethyl 5-bromonicotinate (22f, 368 mg, 1.6 mmol) in 3 h. Flash column chromatographical purification (pentane/EtOAc = 8:2) furnished 21h as a brown powder (307 mg, 79%).

m.p.: 80.2-81.0 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 9.18 (br s, 1H), 8.91 (br s, 1H), 8.42 (s, 1H), 7.32-7.45 (m, 2H), 7.12-7.24 (m, 2H), 4.39 (q, $J=7.1$Hz, 2H), 1.38 (t, $J=7.1$Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 165.2, 159.8 (d, $J=249.0$Hz), 153.1, 149.8, 137.1 (d, $J=3.1$Hz), 131.6, 130.6 (d, $J=1.7$Hz), 130.5 (d, $J=3.9$ Hz), 126.3, 124.9 (d, $J=3.9$Hz), 124.7, 116.5 (d, $J=22.1$Hz), 61.6, 14.4.

MS (70 eV, EI), m/z (%) = 246 (14), 245 (M$^+$, 100), 217 (71), 200 (94), 172 (93), 145 (26), 125 (23), 100 (7), 75 (7).

HRMS (EI), m/z calc. for C$_{14}$H$_{12}$FNO$_2$ (245.0852): 245.0848 (M$^+$).

IR (ATR) ν (cm$^{-1}$) = 3059, 2986, 1724, 1496, 1438, 1367, 1314, 1275, 1250, 1232, 1211, 1109, 1053, 1026, 916, 865, 819, 755, 728, 704, 662.
Preparation of ethyl 5-(4-(dimethylamino)phenyl)nicotinate (21i)

The magnesium diorganoboronate 20g was prepared according to TP1 from 4-bromo-N,N-dimethylaniline (18h, 400 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with ethyl 5-bromonicotinate (22f, 368 mg, 1.6 mmol) in 2 h. Flash column chromatographical purification (pentane/EtOAc = 7:3) furnished 21i as a brown solid (390 mg, 90%).

\[\text{m.p.: 100.8-102.2 °C.}\]

\(\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\) δ (ppm) = 9.05 (d, } J=1.9Hz, 1H), 8.94 (d, } J=2.3Hz, 1H), 8.41 (t, } J=2.1Hz, 1H), 7.50-7.53 (m, 2H), 6.78-6.81 (m, 2H), 4.41 (q, } J=7.1Hz, 2H), 2.99 (s, 6H), 1.41 (t, } J=6.9Hz, 3H).}

\(\text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3\) δ (ppm) = 165.8, 151.0, 150.8, 148.0, 136.5, 134.1, 127.9, 126.3, 124.2, 112.9, 61.5, 40.5, 14.5.}

\(\text{MS (70 eV, EI), } m/z (%) = 271 (16), 270 (M^+ 100), 242 (46), 225 (7), 154 (7), 98 (10).\)

\(\text{HRMS (EI), } m/z \text{ calc. for } C_{16}H_{18}N_2O_2 (270.1368): 270.1363 (M^+).}\)

\(\text{IR (ATR) } \nu (\text{cm}^{-1}) = 3788, 2980, 2900, 2814, 2361, 2341, 1716, 1607, 1529, 1434, 1362, 1306, 1290, 1255, 1230, 1119, 1006, 815, 768.}\)

Preparation of diethyl 2'-chloro-5'-methoxy-biphenyl-2,4-dicarboxylate (21j)

The magnesium diorganoboronate 20h was prepared according to TP1 from 2-bromo-1-chloro-4-methoxybenzene (18i, 443 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with diethyl 4-bromoisophthalate (22g, 482 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/Et\textsubscript{2}O = 8:2) furnished 21j as yellow oil (467 mg, 81%).

\(\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\) δ (ppm) = 8.67 (dd, } J=1.9Hz, 0.4Hz, 1H), 8.23 (dd, } J=7.9Hz, 1.8Hz, 1H), 7.37 (dd, } J=7.9Hz, 0.5Hz, 1H), 7.32 (dd, } J=8.8Hz, 0.4Hz, 1H),
6.87 (dd, J=8.8Hz, 3.0Hz, 1H), 6.79 (d, J=3.0Hz, 1H), 4.44 (q, J=7.1Hz, 2H), 4.17 (q, J=7.1Hz, 2H), 3.81 (s, 3H), 1.43 (t, J=7.2Hz, 3H), 1.10 (t, J=7.2Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 166.3, 165.5, 158.0, 144.3, 140.7, 132.4, 131.3, 131.2, 130.3, 129.7, 124.0, 115.4, 114.4, 61.4, 61.2, 55.6, 14.3, 13.7.

MS (70 eV, EI), m/z (%) = 362 (M$^+$, 2), 328 (21), 327 (100), 317 (13), 300 (18), 299 (99), 271 (40), 253 (10).

HRMS (EI), m/z calc. for C$_{19}$H$_{19}$ClO$_5$ (362.0921): 362.0916 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3487, 3392, 3018, 2964, 2953, 2924, 2885, 2861, 1699, 1621, 1485, 1442, 1333, 1260, 1161, 1118, 1040, 990, 879, 796, 692.

Preparation of 3-fluoro-4’-((triisopropylsilyl)oxy)-biphenyl-4-carbonitrile (21k)

The magnesium diorganoboronate 20i was prepared according to TP1 from (4-bromo-phenoxy)-triisopropylsilane (18j, 659 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromo-2-fluorobenzonitrile (22h, 320 mg, 1.6 mmol) in 4 h. Flash column chromatographical purification (pentane/Et$_2$O = 9.5:0.5) furnished 21k as a pale brown solid (411 mg, 70%).

m.p.: 56.2-57.9 °C.

$^1$H NMR (600 MHz, CDCl$_3$) δ (ppm) = 7.64 (dd, J=8.1Hz, 6.8Hz, 1H), 7.46-7.49 (m, 2H), 7.44 (dd, J=8.1Hz, 1.7Hz, 1H), 7.39 (dd, J=10.5Hz, 1.7Hz, 1H), 6.96-7.01 (m, 2H), 6.13 (spt, J=7.5Hz, 3H), 1.13 (d, J=7.5Hz, 18H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 163.5 (d, J=256.5Hz), 157.5, 148.2 (d, J=8.3Hz), 133.5, 130.5 (d, J=2.3Hz), 128.3, 122.7 (d, J=3.0Hz), 120.6, 114.2, 114.0 (d, J=19.5Hz), 98.9 (d, J=15.8Hz), 17.9, 12.7.

MS (70 eV, EI), m/z (%) = 269 (M$^+$, 20), 327 (19), 326 (66), 298 (36), 271 (20), 270 (100), 257 (11), 256 (54), 240 (13), 196 (11), 135 (31), 43(16).

HRMS (EI), m/z calc. for C$_{22}$H$_{28}$FNOSi (369.1924): 369.1921 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3488, 3392, 3048, 3036, 2958, 2935, 2878, 2857, 2243, 2222, 1623, 1514, 1484, 1442, 1333, 1310, 1253, 1160, 1115, 1096, 1073, 1041, 868, 796, 692.
Preparation of ethyl 2-(4-(methylthio)phenyl)-3-propylhex-2-enoate (21l)

The magnesium diorganoboronate 20d was prepared according to TP1 from 4-bromothioanisole (18e, 406 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with ethyl 2-bromo-3-propylhex-2-enoate (22i, 421 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et₂O = 9.5:0.5) furnished 21l as a colorless oil (365 mg, 75%).

\(^1\)H NMR (600 MHz, CDCl₃) \(\delta\) (ppm) = 7.22 (dt, \(J=8.5\)Hz, 1.9Hz, 2H), 7.11 (dt, \(J=8.5\)Hz, 2.2Hz, 2H), 4.15 (q, \(J=7.0\)Hz, 2H), 2.50 (s, 3H), 2.35-2.40 (m, 2H), 1.93-1.97 (m, 2H), 1.54-1.58 (m, 2H), 1.36-1.41 (m, 2H), 1.22 (t, \(J=7.1\)Hz, 3H), 0.98 (t, \(J=7.4\)Hz, 3H), 0.78 (t, \(J=7.4\)Hz, 3H).

\(^13\)C NMR (150 MHz, CDCl₃) \(\delta\) (ppm) = 168.9, 150.6, 136.9, 134.8, 130.3, 129.9, 126.1, 60.4, 34.9, 34.9, 22.1, 21.4, 15.7, 14.3, 14.2.

MS (70 eV, EI), \(m/\ell\) (%) = 307 (26), 306 (M⁺, 100), 260 (62), 245 (50), 231 (55), 203 (37), 189 (48), 143 (62), 129 (58), 128 (40), 115 (43).

HRMS (EI), \(m/\ell\) calc. for \(\text{C}_{18}\text{H}_{26}\text{O}_2\text{S}\) (306.1654): 306.1645 (M⁺).

IR (ATR) \(\nu\) (cm\(^{-1}\)) = 3487, 3392, 3072, 2981, 2946, 2887, 2845, 1735, 1695, 1621, 1515, 1485, 1444, 1333, 1260, 1215, 1161, 1120, 1097, 1073, 1046, 878, 796, 692.

Preparation of 2-(4-methoxyphenyl)nicotinonitrile (21m)

The magnesium diorganoboronate 20j was prepared according to TP1 from 4-bromoanisole (18k, 374 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 2-chloronicotinonitrile (23a, 222 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 7:3) furnished 21m as a yellow powder (260 mg, 78%).
m.p.: 138.0-139.7 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.79-8.81 (m, 1H), 7.99-8.01 (m, 1H), 7.89-7.93 (m, 2H), 7.26-7.29 (m, 1H), 6.99-7.03 (m, 2H), 3.85 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 159.7, 158.9, 150.9, 140.3, 128.8, 128.0, 119.3, 116.4, 112.5, 105.1, 53.8.

MS (70 eV, EI), $m/z$ (%) = 211 (17), 210 (M$^+$, 100), 195 (26), 167 (39), 140 (19).

HRMS (EI), $m/z$ calc. for C$_{13}$H$_{10}$N$_3$O (210.0793): 210.0776 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3070, 3010, 2967, 2838, 2224, 1882, 1607, 1582, 1574, 1553, 1516, 1458, 1431, 1416, 1308, 1247, 1183, 1108, 1040, 1021, 830, 804, 787, 772.

Preparation of dimethyl 3-(4-(trimethylsilyl)phenyl)pyridine-2,4-dicarboxylate (21n)

The magnesium diorganoborinate 20k was prepared according to TP1 from (4-bromo-phenyl)trimethylsilane (18l, 458 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with dimethyl 3-chloropyridine-2,4-dicarboxylate (23b, 368 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et$_2$O = 4:6) furnished 21n as a pale yellow oil (429 mg, 78%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 9.21 (d, $J$=1.7Hz, 1H), 8.38 (d, $J$=1.7Hz, 1H), 7.61 (d, $J$=8.0Hz, 2H), 7.36 (d, $J$=8.3Hz, 2H), 3.99 (s, 3H), 3.82 (s, 3H), 0.31 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 166.6, 164.8, 151.6, 148.7, 141.0, 139.6, 137.2, 137.0, 133.6, 127.4, 127.2, 52.8, 52.7, -1.2.

MS (70 eV, EI), $m/z$ (%) = 343 (M$^+$, 26), 329 (26), 328 (100), 208 (10), 180 (27), 106 (19), 89 (90), 59 (11).

HRMS (EI), $m/z$ calc. for C$_{18}$H$_{21}$NO$_4$Si (343.1240): 343.1232 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3488, 3392, 3062, 3040, 3012, 2981, 2925, 2868, 1713, 1621, 1515, 1485, 1441, 1333, 1274, 1162, 1113, 1095, 1073, 902, 877, 796, 692.
Preparation of tert-butyl (4-(2-methylquinolin-8-yl)phenyl) carbonate (21o)

The magnesium diorganoboronate 20a was prepared according to TP1 from 4-bromo-phenyl tert-butyl carbonate (18b, 546 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 2-methyl-8-(perfluorobutoxy)quinoline (24a, 706 mg, 1.6 mmol) in 3 h. Flash column chromatographical purification (pentane/EtOAc = 8.5:1.5) furnished 21o as a white solid (415 mg, 78%).

m.p.: 98.2-100.4 °C.

\( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 8.07 (d, \( J=8.4\)Hz, 1H), 7.63-7.91 (m, 4H), 7.53 (t, \( J=7.6\)Hz, 1H), 7.29 (dd, \( J=8.2\)Hz, 2.1Hz, 3H), 2.70 (s, 3H), 1.62 (s, 9H).

\( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 158.7, 152.0, 150.3, 145.3, 138.9, 137.1, 136.2, 131.9, 130.2, 127.3, 126.9, 125.3, 121.8, 120.4, 83.4, 27.7, 25.6.

MS (70 eV, El), \( m/z \) (%) = 335 (M\(^+\), 73), 235 (59), 234 (100), 218 (10), 57 (12), 43 (11).

HRMS (El), \( m/z \) calc. for C\(_{21}\)H\(_{21}\)NO\(_3\) (335.1521): 335.1524 (M\(^+\)).

IR (ATR) \( \nu \) (cm\(^{-1}\)) = 3005, 2982, 2933, 2359, 2333, 1749, 1601, 1500, 1370, 1274, 1258, 1218, 1145, 892, 831, 813, 783, 756.

Preparation of 2-methyl-4-(4-(trifluoromethyl)phenyl)quinoline (21p)

The magnesium diorganoboronate 20l was prepared according to TP1 from 1-bromo-4-(trifluoromethyl)benzene (18m, 450 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 2-methylquinolin-4-yl 4-methylbenzene-sulfonate (24b, 502 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et\(_2\)O = 6:4) furnished 21p as a pale yellow solid (314 mg, 70%).
m.p.: 111.2-112.9 °C.

\[ \text{H NMR (300 MHz, CDCl}_3) \delta (\text{ppm}) = 8.13 (d, J=8.3\text{Hz}, 1H), 7.67-7.85 (m, 4H), 7.62 (d, J=8.0\text{Hz}, 2H), 7.41-7.50 (m, 1H), 7.23 (s, 1H), 2.80 (s, 3H). \]

\[ \text{C NMR (75 MHz, CDCl}_3) \delta (\text{ppm}) = 158.5, 148.3, 147.0, 141.8, 130.5 (q, J=32.3\text{Hz}), 129.8, 129.6, 129.1, 126.1, 125.5 (q, J=3.8\text{Hz}), 125.1, 124.6, 124.1 (q, J=270.8\text{Hz}), 122.1, 25.3. \]

\[ \text{MS (70 eV, EI), m/z (%) = 288 (12), 287 (M}^+\text{, 73), 286 (15), 218 (11), 70 (11), 61 (14), 45 (12), 43 (100).} \]

\[ \text{HRMS (EI), m/z calc. for } \text{C}_{17}\text{H}_{12}\text{F}_3\text{N (287.0922): 287.0921 (M}^+\text{).} \]

\[ \text{IR (ATR) } \nu (\text{cm}^{-1}) = 3069, 2970, 2923, 1737, 1619, 1597, 1557, 1504, 1414, 1403, 1377, 1322, 1154, 1113, 1065, 1018, 852, 837, 766, 757. \]

**Preparation of (2'-methoxy-biphenyl-4-yl)(methyl)sulfane (21q)**

The magnesium diorganoboronate 20d was prepared according to TP1 from 4-bromothioanisole (18e, 406 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 2-methoxyphenyl trifluoromethanesulfonate (24c, 410 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et\(_2\)O = 9.5:0.5) furnished 21q as a pale yellow solid (298 mg, 81%).

m.p.: 78.0-81.1 °C.

\[ \text{H NMR (300 MHz, CDCl}_3) \delta (\text{ppm}) = 7.50 (d, J=8.3\text{Hz}, 2H), 7.29-7.40 (m, 4H), 7.04 (dd, J=15.5\text{Hz}, 7.2\text{Hz}, 2H), 3.84 (s, 3H), 2.54 (s, 3H). \]

\[ \text{C NMR (75 MHz, CDCl}_3) \delta (\text{ppm}) = 156.4, 137.0, 135.3, 130.6, 129.9, 128.6, 127.0, 126.3, 120.8, 111.2, 55.5, 15.9. \]

\[ \text{MS (70 eV, EI), m/z (%) = 230 (M}^+, 100), 168 (100).} \]

\[ \text{HRMS (EI), m/z calc. for } \text{C}_{14}\text{H}_{14}\text{OS (230.0765): 230.0749 (M}^+\text{).} \]

\[ \text{IR (ATR) } \nu (\text{cm}^{-1}) = 3052, 3024, 3000, 2964, 2937, 2919, 2836, 2361, 2337, 1739, 1593, 1576, 1478, 1465, 1434, 1256, 1228, 1182, 1089, 1050, 1025, 1002, 815, 803, 753, 719. \]
Preparation of 4'-amino-3'-chloro-biphenyl-2-ol (21r)

![Chemical Structure](image)

The magnesium organoboronate 19b was prepared according to TP2 from 2-bromophenyl tert-butyl carbonate (18n, 546 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromo-2-chloroaniline (22j, 330 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/Et₂O = 4:6) furnished 21r as a brown solid (301 mg, 86%) (Note: under the reaction conditions, the protecting group is cleaved and the free phenol is obtained).

**m.p.:** 119.9-122.0 °C.

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 7.41 (d, J=1.9Hz, 1H), 7.14-7.31 (m, 3H), 6.91-7.10 (m, 2H), 6.88 (d, J=8.3Hz, 1H), 4.28 (bs, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 152.5, 142.5, 130.1, 130.0, 128.8, 128.4, 127.7, 127.1, 120.8, 119.8, 116.2, 115.7.

**MS** (70 eV, El), m/z (%) = 221 (29), 220 (12), 219 (M⁺, 100), 184 (45), 183 (27), 156 (35), 109 (10), 78 (16), 77 (17).

**HRMS** (El), m/z calc. for C₁₂H₁₀ClNO (219.0451): 219.0447 (M⁺).

**IR** (ATR) ν (cm⁻¹) = 3365, 3275, 2957, 2923, 2853, 1745, 1605, 1589, 1495, 1486, 1448, 1369, 1293, 1272, 1203, 1158, 1112, 1050, 880, 857, 833, 803, 754, 717, 679.

Preparation of ethyl 4'-cyano-3'-fluoro-biphenyl-4-carboxylate (21s)

![Chemical Structure](image)

The magnesium organoboronate 19c was prepared according to TP2 from 4-bromo-2-fluorobenzonitrile (18o, 400 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with ethyl 4-bromobenzoate (22k, 367 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et₂O = 8:2) furnished 21s as a white solid (270 mg, 72%).
m.p.: 131.5-133.4 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.16 (dt, $J$=8.4Hz, $J$=2.1Hz, 2H), 7.72 (dd, $J$=8.1Hz, 6.6Hz, 1H), 7.65 (dt, $J$=8.6Hz, 1.9Hz, 2H), 7.49 (ddd, $J$=15.0Hz, 8.0Hz, 1.7Hz, 2H), 4.42 (q, $J$=7.1Hz, 2H), 1.43 (t, $J$=7.2Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 165.9, 163.4 (d, $J$=258.0Hz), 147.3 (d, $J$=7.5Hz), 142.0 (d, $J$=1.5Hz), 133.9, 131.1, 130.4, 127.1, 123.6 (d, $J$=3.8Hz), 115.1 (d, $J$=20.3Hz), 113.8, 100.7 (d, $J$=15.8Hz), 61.3, 14.3.

MS (70 eV, EI), $m/z$ (%) = 269 (M$^+$, 23), 241 (36), 225 (20), 224 (100), 196 (35), 195 (30), 176 (18), 169 (34), 168 (13), 112 (17), 85 (11), 84 (24), 45 (12).

HRMS (EI), $m/z$ calc. for C$_{16}$H$_{12}$FNO$_2$ (269.0852): 269.0845 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3392, 3208, 3065, 3034, 2924, 2234, 1703, 1622, 1515, 1485, 1443, 1333, 1161, 1117, 1096, 1073, 876.

Preparation of tert-butyl 4'-methoxy-biphenyl-4-carboxylate (21t)

The magnesium organoboronate 19d was prepared according to TP2 from tert-butyl 4-bromo-benzoate (18p, 514 mg, 1 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromoanisole (22l, 300 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et$_2$O = 9.5:0.5) furnished 21t as a white solid (402 mg, 89%).

m.p.: 101.3-103.9 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.05 (d, $J$=8.3Hz, 2H), 7.59 (t, $J$=8.8Hz, 4H), 7.01 (d, $J$=8.6Hz, 2H), 3.87 (s, 3H), 1.63 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 165.7, 159.7, 144.7, 132.6, 129.9, 128.3, 127.0, 126.3, 114.3, 80.9, 55.3, 28.2.

MS (70 eV, EI), $m/z$ (%) = 284 (M$^+$, 20), 241 (14), 228 (13), 227 (100), 212 (22), 210 (12), 184 (11), 43 (44).

HRMS (EI), $m/z$ calc. for C$_{18}$H$_{20}$O$_3$ (284.1412): 284.1408 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 2990, 2976, 2932, 2852, 2835, 1706, 1598, 1529, 1488, 1456, 1366, 1292, 1250, 1181, 1162, 1106, 1035, 1007, 848, 829, 772, 760, 698.
Preparation of 4'-tert-butyl 3-ethyl biphenyl-3,4'-dicarboxylate (21u)

The magnesium organoboronate 19d was prepared according to TP2 from tert-butyl 4-bromo-benzoate (18p, 514 mg, 1 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with ethyl 4-bromobenzoate (22m, 386 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et₂O = 9:1) furnished 21u as a colorless oil (402 mg, 78%).

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 8.31 (s, 1H), 7.99- 8.15 (m, 3H), 7.80 (d, J=7.7Hz, 1H), 7.67 (d, J=8.3Hz, 2H), 7.53 (t, J=7.7Hz, 1H), 4.43 (q, J=7.2Hz, 2H), 1.63 (s, 9H), 1.43 (t, J=7.2Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 166.3, 165.5, 144.0, 140.4, 131.4, 131.2, 131.2, 130.0, 129.0, 128.9, 128.3, 126.9, 81.1, 61.1, 28.2, 14.3.

MS (70 eV, EI), m/z (%) = 326 (M⁺, 2), 270 (10), 225 (12), 70 (13), 61 (15).

HRMS (EI), m/z calc. for C₁₈H₂₂O₄ (326.1518): 326.1519 (M⁺).

IR (ATR) ν (cm⁻¹) = 2977, 2932, 2906, 1708, 1608, 1477, 1439, 1392, 1366, 1291, 1237, 1162, 1103, 1083, 1042, 1015, 858, 848, 746, 691.

3.3 Preparation of Functionalized Magnesium Dialkenylboronates and Subsequent Suzuki-Miyaura Cross-Couplings

Preparation of 2',3',4',5'-tetrahydro-biphenyl-4-carbonitrile (26a)

The magnesium organoboronate 19e was prepared according to TP2 from 1-iodo-cyclohex-1-ene (25a, 416 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromo-benzonitrile (22a, 291 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et₂O = 9.5:0.5) furnished 26a as a pale yellow oil (206 mg, 71%).
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 7.58 (d, \(J=8.3\)Hz, 2H), 7.45 (d, \(J=8.3\)Hz, 2H), 6.21-6.32 (m, 1H), 2.34-2.47 (m, 2H), 2.19-2.33 (m, 2H), 1.74-1.86 (m, 2H), 1.61-1.74 (m, 2H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 147.0, 135.3, 132.0, 128.3, 125.3, 119.2, 109.8, 27.0, 25.9, 22.7, 21.8.

MS (70 eV, EI), \(m/z\) (%) = 184 (16), 183 (M\(^+\), 100), 182 (28), 169 (13), 168 (74), 167 (11), 155 (55), 154 (56), 153 (16), 142 (17), 141 (10), 140 (35), 129 (23), 128 (14), 127 (19), 116 (18), 115 (35).

HRMS (EI), \(m/z\) calc. for C\(_{13}\)H\(_{13}\)N (183.1048): 183.1038 (M\(^+\)).

IR (ATR) \(\nu\) (cm\(^{-1}\)) = 3057, 2928, 2863, 2833, 2226, 1727, 1692, 1602, 153, 1432, 1413, 1350, 1181, 1137, 1080, 918, 862, 821, 799, 712.

**Preparation of (E)-4-styrylbenzonitrile (26b)**

![Diagram](image)

The magnesium organoboronate 19f was prepared according to TP2 from (E)-(2-iodovinyl)benzene (25b, 460 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 4-bromo-benzonitrile (22a, 291 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et\(_2\)O = 8:2) furnished 26b as a pale yellow solid (310 mg, 95%).

m.p.: 118.0-119.2 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 7.48-7.73 (m, 6H), 7.30-7.44 (m, 3H), 7.23 (d, \(J=16.3\)Hz, 1H), 7.10 (d, \(J=16.3\)Hz, 1H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 141.8, 136.3, 132.4, 132.4, 128.8, 128.6, 126.9, 126.8, 126.7, 119.0, 110.5.

MS (70 eV, EI), \(m/z\) (%) = 206 (15), 205 (M\(^+\), 100), 204 (98), 203 (34), 190 (44), 178 (12), 177 (24), 176 (19), 165 (21), 102 (22), 89 (43), 88 (47).

HRMS (EI), \(m/z\) calc. for C\(_{15}\)H\(_{11}\)N (205.0891): 205.0883 (M\(^+\)).

IR (ATR) \(\nu\) (cm\(^{-1}\)) = 3082, 3023, 3001, 2954, 2921, 2224, 1739, 1600, 1575, 1502, 1449, 1412, 1174, 972, 956, 872, 823, 757, 718, 690.
Preparation of ethyl 4-(1-phenylvinyl)benzoate (26c)

The magnesium diorganoboronate 20m was prepared according to TP1 from (1-bromovinyl)-benzene (25c, 366 mg, 2 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to TP3 with ethyl 4-bromobenzoate (22k, 367 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/Et₂O = 9.5:0.5) furnished 26c as a colorless oil (383 mg, 95%).

\[\text{H NMR (300 MHz, CDCl}_3\text{)} \delta (\text{ppm}) = 8.01 (d, J=8.7\text{Hz}, 2\text{H}), 7.40 (d, J=8.7\text{Hz}, 2\text{H}), 7.28-7.37 (m, 5\text{H}), 5.55 (d, J=1.0\text{Hz}, 1\text{H}), 5.53 (d, J=1.0\text{Hz}, 1\text{H}), 4.39 (q, J=7.1\text{Hz}, 2\text{H}), 1.40 (t, J=7.1\text{Hz}, 3\text{H}).\]

\[\text{C NMR (75 MHz, CDCl}_3\text{)} \delta (\text{ppm}) = 166.4, 149.3, 145.9, 140.8, 129.7, 129.5, 128.3, 128.2, 128.0, 127.8, 115.8, 60.9, 14.3.\]

\[\text{MS (70 eV, EI), } m/z (\%) = 252 (M^+, 34), 207 (39), 179 (24), 178 (30), 155 (11), 141 (12), 127 (16), 113 (20), 111 (14), 99 (25), 96 (25), 85 (60), 84 (11), 83 (24), 71 (79), 70 (16), 69 (23), 57 (100), 56 (17), 55 (27), 43 (100), 41 (21).\]

\[\text{HRMS (EI), } m/z \text{ calc. for } C_{17}H_{16}O_2 (252.1150): 252.1150 (M^+).\]

\[\text{IR (ATR) } \nu (\text{cm}^{-1}) = 2982, 1714, 1608, 1494, 1446, 1404, 1366, 1268, 1176, 1102, 1018, 904, 864, 774, 700.\]

3.4 Preparation of Functionalized Magnesium Diheteroarylboronates and Subsequent Suzuki-Miyaura Cross-Couplings

Preparation of methyl 2-amino-5-(benzofuran-3-yl)benzoate (28a)

The magnesium diorganoboronate 20n was prepared according to TP1 from 3-bromo-1-benzofuran (27a, 394 mg, 2 mmol) in 30 min at 25 °C. A cross-coupling reaction was performed according to TP3 with methyl 2-amino-5-bromobenzoate (22n, 368 mg,
1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/EtOAc = 8:2 with 0.5% NEt₃) furnished 28a as a white solid (359 mg, 84%).

**m.p.:** 86.3-87.4 °C.

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 8.17 (d, J=2.2Hz, 1H), 7.81 (dd, J=4.7Hz, 2.2Hz, 1H), 7.74 (s, 1H), 7.51-7.59 (m, 2H), 7.28-7.40 (m, 2H), 6.81 (d, J=8.4Hz, 1H), 3.93 (s, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 168.4, 155.7, 149.5, 140.5, 133.4, 130.0, 126.6, 124.4, 122.8, 121.5, 120.2, 117.4, 111.7, 111.2, 51.7.

**HRMS (ESI) = m/z** calc. for C₁₆H₁₄NO₃ (268.0974): 268.0967 ([M+H]+).

**IR (ATR) υ (cm⁻¹) =** 3492, 3378, 2954, 1684, 1628, 1578, 1556, 1450, 1438, 1360, 1306, 1292, 1230, 1102, 1084, 826, 790, 746, 710.

**Preparation of 4-(benzofuran-3-yl)phenyl diethylcarbamate (28b)**

The magnesium diorganoboronate 20n was prepared according to TP1 from 3-bromo-1-benzofuran (27a, 394 mg, 2 mmol) in 30 min at 25 °C. A cross-coupling reaction was performed according to TP3 with 3-bromophenyl diethylcarbamate (22o, 436 mg, 1.6 mmol) in 3 h. Flash column chromatographical purification (pentane/Et₂O = 7.5:2.5) furnished 28b as a orange oil (428 mg, 86%).

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 7.84-7.91 (m, 1H), 7.82 (s, 1H), 7.45-7.61 (m, 3H), 7.41-7.45 (m, 1H), 7.28-7.41 (m, 2H), 7.16 (dt, J=6.7Hz, 2.5Hz, 1H), 3.20-3.64 (m, 4H), 1.10-1.37 (m, 6H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 155.7, 154.1, 152.0, 141.5, 133.2, 129.6, 126.3, 124.5, 124.1, 123.0, 121.7, 120.8, 120.3, 111.7, 42.1 (d, J=25.5Hz), 13.8 (d, J=65.3Hz).

**MS (70 eV, EI), m/z (%) =** 310 (12), 309 (M⁺, 65), 181 (14), 152 (19), 100 (47), 72 (100), 44 (15).

**HRMS (EI), m/z** calc. for C₁₉H₁₉NO₃ (309.1365): 309.1368 (M⁺).

**IR (ATR) υ (cm⁻¹) =** 3487, 3392, 3009, 2955, 2915, 2859, 1740, 1691, 1622, 1485, 1440, 1398, 1332, 1246, 1167, 1119, 1073, 975, 872, 796, 734.
Preparation of diethyl 4-(thiophen-3-yl)isophthalate (28c)

The magnesium diorganoboronate 20o was prepared according to TP1 from 3-bromo-thiophene (27b, 406 mg, 2 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to TP3 with diethyl 4-bromoisophthalate (22g, 482 mg, 1.6 mmol) in 4 h. Flash column chromatographical purification (pentane/Et₂O = 8.5:1.5) furnished 28c as a pale brown solid (346 mg, 72%).

**m.p.:** 48.8-50.5 °C.

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 8.42 (d, J=1.9Hz, 1H), 8.15 (dd, J=8.2Hz, 1.8Hz, 1H), 7.50 (d, J=8.0Hz, 1H), 7.34-7.40 (m, 1H), 7.32 (dd, J=3.0Hz, 1.4Hz, 1H), 7.12 (dd, J=5.0Hz, 1.4Hz, 1H), 4.42 (q, J=7.1Hz, 2H), 4.21 (q, J=7.2Hz, 2H), 1.42 (t, J=7.0Hz, 3H), 1.16 (t, J=7.2Hz, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 168.1, 165.6, 140.7, 140.5, 131.8, 131.7, 130.7, 130.5, 129.4, 128.2, 125.4, 123.1, 61.4, 61.3, 14.3, 13.8.

**MS** (70 eV, EI), m/z (%) = 305 (16), 304 (M⁺, 90), 259 (100), 232 (17).

**HRMS** (EI), m/z calc. for C₁₆H₁₆O₄S (304.0769): 304.0739 (M⁺).

**IR** (ATR) ν (cm⁻¹) = 3487, 3392, 3117, 3075, 3034, 2951, 2918, 2884, 1737, 1694, 1621, 1485, 1442, 1333, 1261, 1216, 1160, 1117, 1073, 981, 873, 795, 774, 751, 692.

Preparation of 2-(methylthio)-3-(thiophen-3-yl)pyrazine (28d)

The magnesium diorganoboronate 20o was prepared according to TP1 from 3-bromo-thiophene (27b, 406 mg, 2 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to TP3 with 2-bromo-3-(methylthio)pyrazine (22p, 328 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et₂O = 9:1) furnished 28d as a brown oil (262 mg, 79%).
1H NMR (300 MHz, CDCl3) δ (ppm) = 8.31 (d, J=2.4Hz, 1H), 8.26 (d, J=2.6Hz, 1H), 8.03 (dd, J=2.8Hz, 1.3Hz, 1H) 7.68 (dd, J=5.0Hz, 1.3Hz, 1H), 7.41 (dd, J=5.0Hz, 2.8Hz, 1H), 2.57 (s, 3H).

13C NMR (75 MHz, CDCl3) δ (ppm) = 155.0, 147.9, 141.2, 138.3, 138.0, 128.4, 126.8, 125.4, 13.6.

MS (70 eV, EI), m/z (%) = 209 (11), 208 (M+, 100), 207 (17), 193 (32), 175 (72), 134(10), 110 (16).

HRMS (EI), m/z calc. for C9H8N2S2 (208.0129): 208.0128 (M+).

IR (ATR) υ (cm⁻¹) = 3486, 3392, 3142, 3059, 2940, 2895, 1621, 1485, 1333, 1260, 1162, 1124, 1096, 1072, 1041, 880, 794, 736, 692.

Preparation of 4-(benzothiophen-3-yl)-N-(tert-butyl)benzamide (28e)

The magnesium diorganoboronate 20p was prepared according to TP1 from 3-bromo-benzothiophene (27c, 426 mg, 2 mmol) in 1 h at 0 °C. A cross-coupling reaction was performed according to TP3 with 4-bromo-N-(tert-butyl)benzamide (22b, 410 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et2O = 7:3) furnished 28e as a white solid (380 mg, 77%).

m.p.: 114.9-116.7 °C.

1H NMR (400 MHz, CDCl3) δ (ppm) = 7.91-7.96 (m, 1H), 7.82-7.91 (m, 3H), 7.64 (d, J=8.0Hz, 2H), 7.45 (s, 1H), 7.38-7.41 (m, 2H), 6.07 (br s, 1H), 1.52 (s, 9H).

13C NMR (100 MHz, CDCl3) δ (ppm) = 166.5, 140.7, 138.7, 137.5, 137.0, 134.8, 128.6, 127.2, 124.5, 124.5, 124.2, 122.9, 122.6, 51.7, 28.9.

MS (70 eV, EI), m/z (%) = 309 (M+, 38), 253 (60), 238 (15), 237 (100), 209 (17), 208 (30), 165 (19), 104 (10).

HRMS (EI), m/z calc. for C19H19NOS (309.1187): 309.1192 (M+).

IR (ATR) υ (cm⁻¹) = 3485, 3392, 3209, 3074, 3037, 1621, 1485, 1333, 1260, 1161, 1116, 1096, 1073, 1045, 879, 796, 692.
Preparation of ethyl 4-(3-methylisoxazol-4-yl)benzoate (28f)

The magnesium organoboronate 19g was prepared according to TP2 from 4-bromo-3,5-dimethylisoxazole (27d, 352 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with ethyl 4-bromobenzoate (22k, 367 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et2O = 7.5:2.5) furnished 28f as a pale brown solid (232 mg, 60%).

m.p.: 71.1-72.2 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.12 (dt, $J$=8.6Hz, 1.7Hz, 2H), 7.34 (dt, $J$=8.6Hz, 1.7Hz, 2H), 4.41 (q, $J$=7.1Hz, 2H), 2.43 (s, 3H), 2.29 (s, 3H), 1.41 (t, $J$=7.2Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 166.1, 165.7, 158.3, 135.1, 130.0, 129.5, 128.8, 116.0, 61.1, 14.3, 11.6, 10.8.

MS (70 eV, EI), $m/z$ (%) = 246 (10), 245 (M$^+$, 75), 217 (15), 202 (10), 201 (13), 200 (100), 172 (12), 131 (39), 103 (13), 77 (10).

HRMS (EI), $m/z$ calc. for C$_{14}$H$_{15}$NO$_3$ (245.1052): 245.1046 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3486, 3392, 3062, 3035, 2986, 2942, 1710, 1621, 1515, 1485, 1443, 1333, 1259, 1161, 1116, 1096, 1073, 1041, 878, 796, 692.

Preparation of dimethyl 3-(thiophen-2-yl)pyridine-2,5-dicarboxylate (28g)

The magnesium diorganoboronate 20q was prepared according to TP1 from 2-chlorothiophene (27e, 237 mg, 2 mmol) in 30 min at 25 °C. A cross-coupling reaction was performed according to TP3 with dimethyl 3-chloropyridine-2,5-dicarboxylate (23c, 367 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/EtOAc = 9:1) furnished 28g as a pale yellow solid (381 mg, 86%).

m.p.: 110.9-111.7 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 9.17 (d, $J$=1.9Hz, 1H), 8.46 (d, $J$= 1.9Hz, 1H), 7.48 (dd, $J$=5.1Hz, 1.2Hz, 1H), 7.21 (dd, $J$=3.6Hz, 1.2Hz, 1H), 7.13 (dd, $J$=5.0Hz, 3.6Hz, 1H), 4.01 (s, 3H), 3.90 (s, 3H).
\[^{13}\text{C} \text{NMR} \] (75 MHz, CDCl\textsubscript{3}) \( \delta \) (ppm) = 166.7, 164.7, 152.0, 148.8, 139.3, 137.3, 129.3, 128.0, 127.8, 127.7, 127.1, 53.0, 52.8.

\[\text{MS} \] (70 eV, EI), \( m/z \) (%) = 277 (M\textsuperscript{+}, 57), 246 (11), 219 (56), 218 (25), 171 (21), 161 (65), 70 (15), 61 (21), 45 (15), 43 (100).

\[\text{HRMS} \] (EI), \( m/z \) calc. for \( \text{C}_{13}\text{H}_{11}\text{NO}_4\text{S} \) (277.0409): 277.0405 (M\textsuperscript{+}).

\[\text{IR} \] (ATR) \( \nu \) (cm\textsuperscript{-1}) = 3074, 2956, 1736, 1724, 1594, 1556, 1450, 1424, 1300, 1256, 1198, 1130, 1106, 1012, 766, 734.

**Preparation of ethyl 5-(pyridin-3-yl)furan-2-carboxylate (28h)**

![Structure of ethyl 5-(pyridin-3-yl)furan-2-carboxylate](image)

The magnesium diorganoboronate 20r was prepared according to TP1 from 3-bromopyridine (27f, 316 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP5 with ethyl 5-bromofuran-2-carboxylate (22q, 307 mg, 1.4 mmol) in 24 h. Flash column chromatographical purification (pentane/EtOAc = 7:3 with 0.5% NEt\textsubscript{3}) furnished 28h as a white solid (248 mg, 82%).

\[\text{m.p.:} \] 44.5-45.7 °C.

\[^1\text{H} \text{NMR} \] (300 MHz, CDCl\textsubscript{3}) \( \delta \) (ppm) = 8.95 (d, \( J=1.5\text{Hz} \), 1H), 8.51 (dd, \( J=4.8\text{Hz} \), 1.6Hz, 1H), 7.99-8.02 (m, 1H), 7.29 (dd, \( J=8.0\text{Hz} \), 4.8Hz, 1H), 7.19 (d, \( J=3.6\text{Hz} \), 1H), 6.77 (d, \( J=3.6\text{Hz} \), 1H), 4.33 (q, \( J=7.1\text{Hz} \), 2H), 1.34 (t, \( J=7.1\text{Hz} \), 3H).

\[^{13}\text{C} \text{NMR} \] (75 MHz, CDCl\textsubscript{3}) \( \delta \) (ppm) = 158.6, 154.4, 149.6, 146.3, 144.9, 131.9, 125.8, 123.7, 119.6, 108.1, 61.2, 14.4.

\[\text{MS} \] (70 eV, EI), \( m/z \) (%) = 218 (11), 217 (M\textsuperscript{+}, 100), 189 (72), 172 (54), 145 (35), 116 (43), 89 (14), 44 (10).

\[\text{HRMS} \] (EI), \( m/z \) calc. for \( \text{C}_{12}\text{H}_{11}\text{NO}_3 \) (217.0739): 217.0728 (M\textsuperscript{+}).

\[\text{IR} \] (ATR) \( \nu \) (cm\textsuperscript{-1}) = 3120, 3085, 3049, 2982, 2928, 2904, 1716, 1566, 1524, 1516, 1470, 1415, 1371, 1334, 1301, 1279, 1226, 1149, 1113, 1017, 964, 920, 867, 821, 806, 758, 712, 675.
Preparation of 2-methoxy-5-(4-nitrophenyl)pyridine (28i)

The magnesium diorganoboronate 9h was prepared according to TP1 from 5-bromo-2-methoxypyridine (27g, 376 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP3 with 1-bromo-4-nitrobenzene (22r, 323 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 8.5:1.5) furnished 28i as a pale yellow solid (311 mg, 85%).

m.p.: 162.9-164.4 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.42 (d, $J=2.6$Hz, 1H), 8.26-8.30 (m, 2H), 7.81 (dd, $J=8.6$Hz, 2.6Hz, 1H), 7.64-7.68 (m, 2H), 6.85 (dd, $J=8.6$Hz, 0.6Hz, 1H), 3.98 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 164.8, 147.2, 145.8, 144.6, 137.5, 127.9, 127.3, 124.6, 111.5, 53.9.

MS (70 eV, EI), $m/z$ (%) = 231 (16), 230 (M$^+$, 100), 201 (56), 183 (29), 154 (52), 141 (34), 127 (31), 114 (24), 42 (17).

HRMS (EI), $m/z$ calc. for C$_{12}$H$_{10}$N$_2$0$_3$ (230.0691): 230.0669 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3075, 2949, 2440, 1596, 1564, 1505, 1477, 1442, 1415, 1395, 1375, 1341, 1309, 1297, 1257, 1179, 1139, 1106, 1042, 1019, 999, 923, 855, 834, 733. 695.

Preparation of ethyl 5-(6-chloropyridin-3-yl)thiophene-2-carboxylate (28j)

The magnesium diorganoboronate 20t was prepared according to TP1 from 5-bromo-2-chloropyridine (27h, 385 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to TP4 with 5-bromothiophene-2-carboxylate (22s, 329 mg, 1.4 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 9:1) furnished 28j as a white solid (270 mg, 72%).
m.p.: 81.8-83.3 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.64 (dd, $J=2.6$Hz, 0.7Hz, 1H), 7.83 (dd, $J=8.3$Hz, 2.6Hz, 1H), 7.75-7.77 (m, 1H), 7.30 (d, $J=3.9$Hz, 1H), 4.36 (q, $J=7.1$Hz, 1H), 1.38 (t, $J=7.1$Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 162.0, 151.5, 145.4, 136.1, 134.6, 134.4, 128.8, 125.2, 124.7, 61.7, 14.5.

MS (70 eV, EI), $m/z$ (%) = 268 (10), 267 (M$^+$, 64), 240 (20), 221 (100), 152 (17), 102 (6), 61 (10).

HRMS (EI), $m/z$ calc. for C$_{12}$H$_{10}$ClNO$_2$S (267.0121): 267.0119 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3394, 2993, 2340, 1710, 1532, 1443, 1363, 1288, 1275, 1098, 1008, 834, 814, 745.
4. Preparation of α-Substituted β,γ-Unsaturated Ketones and Esters via the Direct Addition of Substituted Allylic Zinc Reagents

4.1 Preparation of Starting Materials

All reagents were obtained from commercial sources. Compounds 29f\textsuperscript{176a}, 29g\textsuperscript{178b} as well as 29h\textsuperscript{274} and 29i\textsuperscript{274} were prepared according to literature known procedures.

4.2 Typical Procedures

Typical procedure 1 (TP1): Preparation of allylic zinc reagents RZnX·LiCl via direct zinc insertion in the presence of lithium chloride

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol). LiCl was dried in vacuo using a heatgun (450 °C, 5 min). After addition of THF (10 mL), the Zn powder was activated with 1,2-dibromoethane (2 mol%) and Me\textsubscript{3}SiCl (5 mol%). Then a solution of the allyl halide (10 mmol) in THF (10 mL) was added at 25 °C and stirred for 1 h until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, the remaining Zn powder was allowed to settle down or centrifuged (10 min, 2000 rpm). The yield of the insertion reaction was determined by iodometric titration.\textsuperscript{192}

Typical procedure 2 (TP2): Preparation of α-substituted β,γ-unsaturated ketones and esters via direct addition of allylic zinc reagents to acid chlorides and chloroformates

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding acid chloride or chloroformate (0.8 equiv) in THF (1.0 mL) and cooled down to the indicated temperature. Subsequently, the freshly prepared allylic zinc reagent in THF (1 equiv) was added dropwise and the reaction mixture was stirred at the indicated temperature for the given time. The reaction mixture was quenched at room temperature with sat. NH\textsubscript{4}Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

4.3 Preparation of Substituted Allylic Zinc Reagents

Preparation of but-2-en-1-ylzinc bromide (30a)

According to TP1, the allylic zinc reagent 30a was prepared from 1-bromobut-2-ene (29a, 1.35 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.42 M (83%).

Preparation of cinnamyldzinc chloride (30b)

According to TP1, the allylic zinc reagent 30b was prepared from cinnamyl chloride (29b, 1.53 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.43 M (86%).

Preparation of (3-methylbut-2-en-1-yl)zinc bromide (30c)

According to TP1, the allylic zinc reagent 30c was prepared from 1-bromo-3-methylbut-2-ene (29c, 1.49 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.46 M (92%).

Preparation of (2-(trimethylsilyl)but-2-en-1-yl)zinc chloride (30d)

According to TP1, the allylic zinc reagent 30d was prepared according a literature-known procedure2 from (1-chlorobut-2-en-2-yl)trimethylsilane (29d, 1.63 g, 10.0 mmol) using Zn powder (6.54 g, 100 mmol) and LiCl (1.27 g, 30 mmol) at 25 °C in 18 h. Titration with iodine indicates a concentration of 0.41 M (81%).
Preparation of (3,7-dimethylocta-2,6-dien-1-yl)zinc bromide (30e)

According to TP1, the allylic zinc reagent 30e was prepared from 1-bromo-3,7-dimethylocta-2,6-diene (29e, 2.17 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.42 M (83%).

Preparation of cyclohex-2-en-1-ylzinc bromide (30f)

According to TP1, the allylic zinc reagent 30f was prepared from 3-bromocyclohex-1-ene (29f, 1.61 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.45 M (89%).

Preparation of 2-methyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-enylzinc chloride (30g)

Zinc powder (1.60 g, 25.0 mmol) and dry LiCl (500 mg, 12.0 mmol) were covered with dry THF (10 mL) and activated by the addition of 1,2-dibromoethane (2 mol%) and Me₃SiCl (5 mol%). Subsequently, a solution of 2-chloromethyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene (29g, 1.71 g, 10.0 mmol) in THF (10 mL) was added in with a syringe pump at 25 °C within 2 h. The resulting mixture was stirred under nitrogen at 25 °C for 30 h. The remaining zinc powder was allowed to settle down. Titration with iodine indicates a concentration of 0.37 M (73%).
Preparation of 2-enecarboxylic acid ethyl ester-6-cyclohexenylzinc chloride (30h)

According to TP1, the allylic zinc reagent 30h was prepared from 6-chloro cyclohex-1-enecarboxylic acid ethyl ester (29h, 1.89 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.45 M (90%).

Preparation of 2-cyano-5-cyclopentenylzinc chloride (30i)

According to TP1, the allylic zinc reagent 30i was prepared from 5-chloro-cyclopent-1-enecarbonitrile (29i, 1.28 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.35 M (69%).

4.4 Preparation of α-Substituted β,γ-unsaturated ketones

Preparation of 1-(4-(tert-butyl)phenyl)-2-methylbut-3-en-1-one (32a)

According to TP2, the α-substituted β,γ-unsaturated ketone 32a was prepared from 30a (4.75 mL, 2.00 mmol, 0.42 M in THF) and 4-(tert-butyl)benzoyl chloride (31a, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et₂O 50:1) furnished 4a as a colorless oil (294 mg, 85%).

1H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.96 (d, J=8.6Hz, 2H), 7.50 (d, J=8.9Hz, 2H), 5.95-6.11 (m, 1H), 5.08-5.27 (m, 2H), 4.10-4.25 (m, 1H), 1.28-1.48 (m, 12H).

13C-NMR (75 MHz, CDCl₃) δ (ppm) = 200.8, 156.7, 138.4, 133.7, 128.5, 125.5, 116.3, 45.4, 35.1, 31.1, 17.1.

MS (70 eV, EI), m/z (%) = 216 (M⁺, 1), 162 (27), 161 (100), 160 (6), 146 (23), 118 (24), 115 (8), 91 (14).

HRMS (EI), m/z calc. for C₁₅H₂₀O (216.1514): 216.1501 (M⁺).
IR (ATR) $\nu$ (cm$^{-1}$) = 3080, 3055, 3039, 2964, 2933, 2905, 2870, 1678, 1634, 1604, 1455, 1408, 1364, 1268, 1220, 1191, 1109, 993, 974, 963, 916, 847, 790, 719.

Preparation of 2-methyl-1-(thiophen-2-yl)but-3-en-1-one (32b)

According to TP2, the $\alpha$-substituted $\beta,\gamma$-unsaturated ketone 32b was prepared from 30a (4.75 mL, 2.00 mmol, 0.42 M in THF) and thiophene-2-carbonyl chloride (31b, 235 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et$_2$O 30:1) furnished 32b as a colorless oil (226 mg, 85%).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.79 (dd, $J$=3.9Hz, 1.1Hz, 1H), 7.66 (dd, $J$=5.0Hz, 1.1Hz, 1H), 7.15 (dd, $J$=5.0Hz, 3.9Hz, 1H), 6.01 (ddd, $J$=17.5Hz, 10.0Hz, 7.9Hz, 1H), 5.11-5.30 (m, 2H), 3.93-4.07 (m, 1H), 1.37 (d, $J$=6.9Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 194.0, 143.6, 138.0, 133.8, 132.1, 128.1, 116.6, 47.4, 17.2.

MS (70 eV, EI), $m/z$ (%) = 166 (M$^+$, 21), 112 (39), 111 (100), 83 (37), 55 (13), 45 (7).

HRMS (EI), $m/z$ calc. C$_9$H$_{10}$OS (166.0452): 166.0447 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3081, 2976, 2932, 2873, 1655, 1632, 1517, 1412, 1354, 1234, 1212, 1056, 991, 918, 862, 830, 772, 719.

Preparation of 2-methyl-1-(3,4,5-trimethoxyphenyl)but-3-en-1-one (32c)

According to TP2, the $\alpha$-substituted $\beta,\gamma$-unsaturated ketone 32c was prepared from 30a (4.75 mL, 2.00 mmol, 0.42 M in THF) and 3,4,5-trimethoxybenzoyl chloride (31c, 369 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et$_2$O 7:3) furnished 32c as a white solid (260 mg, 65%).

m.p.: 60.4-61.3 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.27 (s, 2H), 5.92-6.09 (m, 1H), 5.15-5.23 (m, 2H), 4.07-4.21 (m, 1H), 3.78-4.03 (m, 9H), 1.35 (d, $J$=6.9Hz, 3H).


13C-NMR (75 MHz, CDCl3) δ (ppm) = 199.9, 153.0, 142.6, 138.4, 131.5, 116.4, 106.2, 60.9, 56.3, 45.5, 17.2.

**MS** (70 eV, EI), m/z (%) = 250 (M+, 55), 235 (13), 219 (28), 196 (62), 195 (100), 167 (19), 139 (16), 124 (15), 122 (27), 92 (12), 77 (26), 66 (17), 55 (20), 53 (16).

**HRMS** (EI), m/z calc. for C14H18O4 (250.1205): 250.1198 (M+).

**IR** (ATR) ν (cm⁻¹) = 3080, 3009, 2971, 2953, 2933, 2873, 2839, 1670, 1580, 1507, 1464, 1453, 1411, 1339, 1310, 1230, 1166, 1154, 1149, 1125, 990, 918, 867, 781, 771, 742.

**Preparation of 1-(4-(tert-butyl)phenyl)-2-phenylbut-3-en-1-one (32d)**

![Structure of 32d](image)

According to TP2, the α-substituted β,γ-unsaturated ketone 32d was prepared from 30b (4.65 mL, 2.00 mmol, 0.43 M in THF) and 4-(tert-butyl)benzoyl chloride (31a, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et2O 30:1) furnished 32d as a yellow oil (401 mg, 90%).

1H-NMR (300 MHz, CDCl3) δ (ppm) = 7.96 (d, J=8.9Hz, 2H), 7.45 (d, J=8.9Hz, 2H), 7.24-7.40 (m, 5 H), 6.32-6.47 (m, 1H), 5.20-5.34 (m, 2H), 5.07-5.17 (m, 1H), 1.32 (s, 9H).

13C-NMR (75 MHz, CDCl3) δ (ppm) = 198.1, 156.8, 138.6, 137.4, 133.8, 129.0, 128.9, 128.4, 127.1, 125.5, 117.0, 57.9, 35.1, 31.0.

**MS** (70 eV, EI), m/z (%) = 278 (M+, 6), 222 (21), 221 (24), 162 (11), 161 (100), 146 (10), 118 (17), 117 (15), 115 (15), 91 (17).

**HRMS** (EI), m/z calc. for C20H22O (278.1671): 278.1669 (M+).

**IR** (ATR) ν (cm⁻¹) = 3060, 3028, 2962, 2904, 2867, 1720, 1676, 1602, 1452, 1408, 1363, 1268, 1223, 1187, 1108, 844, 760, 698.

**Preparation of 2-phenyl-1-(thiophen-2-yl)but-3-en-1-one (32e)**

![Structure of 32e](image)

According to TP2, the α-substituted β,γ-unsaturated ketone 32e was prepared from 30b (4.65 mL, 2.00 mmol, 0.43 M in THF) and thiophene-2-carbonyl chloride (31b, 235 mg,
1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:EtO 30:1) furnished 32e as a yellow oil (281 mg, 77 %).

\[ \text{H-NMR (300 MHz, CDCl}_3 \text{)} \delta \text{ (ppm)} = 7.75 (\text{dd, } J=3.9\text{Hz, 1.1Hz, 1H}), 7.62 (\text{dd, } J=5.0\text{Hz, 1.1Hz, 1H}), 7.17-7.49 (\text{m, 5H}), 7.10 (\text{dd, } J=5.0\text{Hz, 3.9Hz, 1H}), 6.39 (\text{ddd, } J=17.0\text{Hz, 10.1Hz, 8.0Hz, 1H}), 5.02-5.43 (\text{m, 3H}). \]

\[ \text{C-NMR (75 MHz, CDCl}_3 \text{)} \delta \text{ (ppm)} = 191.3, 143.5, 138.4, 136.6, 134.0, 132.7, 129.0, 128.3, 128.1, 127.4, 117.5, 59.4. \]

\[ \text{MS (70 eV, EI), } m/z \text{ (%) } = 228 (M^+ , 37), 195 (14), 117 (21), 115 (32), 111 (100), 91 (14), 44 (16). \]

\[ \text{HRMS (EI), } m/z \text{ calc. for C}_{14}H_{12}OS (228.0609): 228.0601 (M^+ ). \]

\[ \text{IR (ATR) } \nu \text{ (cm}^{-1} \text{) } = 3104, 3087, 3060, 3025, 2977, 1643, 1634, 1515, 1454, 1410, 1357, 1316, 1249, 1204, 1069, 991, 921, 801, 752, 720, 696, 669, 652. \]

### Preparation of 1-(furan-2-yl)-2-phenylbut-3-en-1-one (32f)

![Chemical Structure](image)

According to TP2, the \( \alpha \)-substituted \( \beta,\gamma \)-unsaturated ketone 32f was prepared from 30b (4.65 mL, 2.00 mmol, 0.43 m in THF) and furan-2-carbonyl chloride (31d, 209 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:EtO 30:1) furnished 32f as an off-white solid (285 mg, 84 %).

\[ \text{m.p.: 42.0-43.1 °C.} \]

\[ \text{H-NMR (300 MHz, CDCl}_3 \text{)} \delta \text{ (ppm)} = 7.57 (\text{dd, } J=1.7\text{Hz, 0.8Hz, 1H}), 7.14-7.46 (\text{m, 6H}), 6.50 (\text{dd, } J=3.6\text{Hz, 1.7Hz, 1H}), 6.38 (\text{ddd, } J=17.1\text{Hz, 10.1Hz, 8.0Hz, 1H}), 5.08-5.31 (\text{m, 3 H}). \]

\[ \text{C-NMR (75 MHz, CDCl}_3 \text{)} \delta \text{ (ppm)} = 187.3, 152.0, 146.6, 138.1, 136.2, 128.8, 128.4, 127.3, 118.2, 117.7, 112.4, 58.0. \]

\[ \text{MS (70 eV, EI), } m/z \text{ (%) } = 212 (M^+ , 24), 170 (17), 118 (12), 117 (100), 116 (16), 115 (60), 91 (29). \]

\[ \text{HRMS (EI), } m/z \text{ calc. for C}_{14}H_{12}O_2 (212.0837): 212.0836 (M^+ ). \]

\[ \text{IR (ATR) } \nu \text{ (cm}^{-1} \text{) } = 3144, 3119, 3096, 3083, 3060, 3029, 3021, 1665, 1650, 1463, 1453, 1390, 1327, 1256, 1165, 1041, 1001, 993, 943, 928, 917, 905, 824, 770, 762, 751, 728, 695, 668. \]
Preparation of 7-chloro-3-phenylhept-1-en-4-one (32g)

According to TP2, the α-substituted β,γ-unsaturated ketone 32g was prepared from 30b (4.65 mL, 2.00 mmol, 0.43 M in THF) and 4-chlorobutanoyl chloride (31e, 226 mg, 1.6 mmol) at -20 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et₂O 9.5:0.5) furnished 32g as a yellow oil (257 mg, 72 %).

\( ^1H \)NMR (600 MHz, CDCl₃) \( \delta \) (ppm) = 7.18-7.36 (m, 5H), 6.13-6.35 (m, 1H), 5.03-5.26 (m, 2H), 4.39 (d, \( J=8.2 \) Hz, 1H), 3.24-3.69 (m, 2H), 2.51-2.75 (m, 2H), 1.59-2.26 (m, 2H).

\( ^13C \)NMR (150 MHz, CDCl₃) \( \delta \) (ppm) = 207.7, 137.7, 135.6, 129.0, 128.2, 127.5, 117.8, 63.2, 44.2, 38.1, 26.4.

MS (70 eV, EI), \( m/z \) (%) = 222 (M⁺, 5), 186 (10), 129 (5), 116 (18), 115 (63), 107 (28), 105 (100), 91 (22), 77 (16), 41 (28).

HRMS (EI), \( m/z \) calc. for C₁₃H₁₅ClO (222.0811): 222.0804 (M⁺).

IR (ATR) \( \nu \) (cm⁻¹) = 3080, 3056, 3025, 2961, 2925, 1711, 1687, 1671, 1620, 1598, 1494, 1441, 1311, 1296, 1241, 1216, 1124, 1072, 1030, 974, 942, 917, 762, 700.

Preparation of 1-(4-(tert-butyl)phenyl)-2,2-dimethylbut-3-en-1-one (32h)

According to TP2, the α-substituted β,γ-unsaturated ketone 32h was prepared from 30c (4.35 mL, 2.00 mmol, 0.46 M in THF) and 4-(tert-butyl)benzoyl chloride (31a, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et₂O 30:1) furnished 32h as a colorless oil (343 mg, 93 %).

\( ^1H \)NMR (300 MHz, CDCl₃) \( \delta \) (ppm) = 7.89 (d, \( J=8.3 \) Hz, 2H), 7.41 (d, \( J=8.6 \) Hz, 2H), 6.16-6.29 (m, 1H), 5.17-5.31 (m, 2H), 1.42 (s, 6H), 1.34 (s, 9H).

\( ^13C \)NMR (75 MHz, CDCl₃) \( \delta \) (ppm) = 203.8, 155.3, 144.2, 134.0, 129.5, 124.9, 113.8, 50.0, 34.9, 31.1, 26.2.

MS (70 eV, EI), \( m/z \) (%) = 230 (M⁺, 5), 162 (100), 161 (52), 146 (61), 145 (11), 118 (60), 117 (23), 115 (21), 105 (14), 91 (33), 77 (15), 41 (30).
HRMS (EI), m/z calc. for C_{16}H_{12}O (230.1671): 230.1663 (M^+).
IR (ATR) v (cm^{-1}) = 3084, 2964, 2905, 2868, 1674, 1632, 1604, 1463, 1411, 1363, 1260, 1173, 1109, 973, 917, 846, 773, 668.

Preparation of 1-(4-(tert-butyl)phenyl)-2-methyl-3-(trimethyl-silyl)but-3-en-1-one (32i)

According to TP2, the α-substituted β,γ-unsaturated ketone 32i was prepared from 30d (4.90 mL, 2.00 mmol, 0.41 M in THF) and 4-(tert-butyl)benzoyl chloride (31a, 315 mg, 1.6 mmol) at 25 °C over night. Flash column chromatography (silica, pentane:Et_{2}O 9.5:0.5) furnished 32i as a colorless oil (415 mg, 98 %).

\[ \text{1H-NMR (300 MHz, CDCl}_3 \text{)} \delta (ppm) = 7.87 (d, J=8.6Hz, 2H), 7.45 (d, J=8.6Hz, 2H), 5.57-5.74 (m, 1H), 5.50 (d, J=1.9Hz, 1H), 4.16-4.32 (m, 1H), 1.35 (s, 9H), 1.31 (d, J=6.6Hz, 3H), 0.18 (s, 9H).\]

\[ \text{13C-NMR (75 MHz, CDCl}_3 \text{)} \delta (ppm) = 201.0, 156.2, 151.9, 134.2, 128.5, 126.9, 125.3, 46.5, 35.0, 31.1, 18.1, -0.7.\]

MS (70 eV, EI), m/z (%) = 288 (M^+, 1), 274 (25), 162 (100), 161 (69), 146 (31), 118 (26), 115 (12), 91 (17), 73 (57), 57 (20).

HRMS (EI), m/z calc. for C_{18}H_{28}OSi (288.1909): 288.1906 (M^+).
IR (ATR) v (cm^{-1}) = 3081, 3074, 2965, 2940, 2871, 1667, 1517, 1419, 1369, 1358, 1254, 1232, 1059, 939, 856, 837, 729, 671.

Preparation of 2-methyl-1-(thiophen-2-yl)-3-(trimethylsilyl)-but-3-en-1-one (32j)

According to TP2, the α-substituted β,γ-unsaturated ketone 32j was prepared from 30d (4.90 mL, 2.00 mmol, 0.41 M in THF) and thiophene-2-carbonyl chloride (31b, 235 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_{2}O 25:1) furnished 32j as a colorless oil (378 mg, 99 %).

\[ \text{1H-NMR (300 MHz, CDCl}_3 \text{)} \delta (ppm) = 7.87 (d, J=8.6Hz, 2H), 7.45 (d, J=8.6Hz, 2H), 5.57-5.74 (m, 1H), 5.50 (d, J=1.9Hz, 1H), 4.16-4.32 (m, 1H), 1.35 (s, 9H), 1.31 (d, J=6.6Hz, 3H), 0.18 (s, 9H).\]

\[ \text{13C-NMR (75 MHz, CDCl}_3 \text{)} \delta (ppm) = 201.0, 156.2, 151.9, 134.2, 128.5, 126.9, 125.3, 46.5, 35.0, 31.1, 18.1, -0.7.\]

MS (70 eV, EI), m/z (%) = 288 (M^+, 1), 274 (25), 162 (100), 161 (69), 146 (31), 118 (26), 115 (12), 91 (17), 73 (57), 57 (20).

HRMS (EI), m/z calc. for C_{18}H_{28}OSi (288.1909): 288.1906 (M^+).
IR (ATR) v (cm^{-1}) = 3081, 3074, 2965, 2940, 2871, 1667, 1517, 1419, 1369, 1358, 1254, 1232, 1059, 939, 856, 837, 729, 671.
\[ {^{1}H-NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta \ (\text{ppm}) = 7.65-7.73 \ (m, \text{ 1H}), 7.55-7.63 \ (m, \text{ 1H}), 7.03-7.17 \ (m, \text{ 1H}), 5.70-5.79 \ (m, \text{ 1H}), 5.53 \ (d, J=1.7\text{Hz, 1H}), 4.03-4.19 \ (m, \text{ 1H}), 1.33 \ (d, J=6.4\text{Hz, 3H}), 0.16 \ (s, \text{ 9H}). \]

\[ {^{13}C-NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ (\text{ppm}) = 194.2, 151.6, 144.2, 133.1, 131.8, 127.9, 127.1, 48.5, 18.1, -0.7. \]

\[ \text{MS} \ (70 \text{ eV, Ei), } m/z \ (%) = 238 \ (M^+, 5), 224 \ (18), 223 \ (80), 149 \ (9), 111 \ (100), 75 \ (17), 73 \ (40), 45 \ (9). \]

\[ \text{HRMS} \ (\text{EI), } m/z \ \text{calc. for } C_{12}H_{18}OSSi \ (238.0848): 238.0853 \ (M^+). \]

\[ \text{IR} \ (\text{ATR}) \ \nu \ (\text{cm}^{-1}) = 3104, 3084, 3054, 2954, 2933, 2896, 2874, 1656, 1512, 1452, 1414, 1369, 1354, 1247, 1233, 1222, 1053, 931, 872, 832, 756, 716, 690. \]

**Preparation of 1-(4-(tert-butyl)phenyl)-6-methyl-2-vinylept-5-en-1-one (32k)**

According to TP2, the \( \alpha \)-substituted \( \beta,\gamma \)-unsaturated ketone 32k was prepared from 30e (4.75 mL, 2.00 mmol, 0.42 M in THF) and 4-(tert-butyl)benzoyl chloride (31a, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:EtO 50:1) furnished 32k as a colorless oil (319 mg, 70%).

\[ {^{1}H-NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta \ (\text{ppm}) = 7.86 \ (d, J=8.9\text{Hz, 2H}), 7.41 \ (d, J=8.9\text{Hz, 2H}), 6.13-6.28 \ (m, \text{ 1H}), 5.16-5.31 \ (m, \text{ 2H}), 5.00-5.10 \ (m, \text{ 1H}), 1.91-2.04 \ (m, \text{ 2H}), 1.74-1.85 \ (m, \text{ 2H}), 1.65 \ (s, \text{ 3H}), 1.26-1.53 \ (m, \text{ 15H}). \]

\[ {^{13}C-NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ (\text{ppm}) = 203.9, 155.1, 143.5, 134.7, 131.9, 129.2, 124.8, 124.1, 114.5, 53.5, 39.1, 34.9, 31.1, 25.6, 23.1, 23.0, 17.4. \]

\[ \text{MS} \ (70 \text{ eV, Ei), } m/z \ (%) = 298 \ (M^+, 17), 230 \ (44), 217 \ (16), 216 \ (100), 147 \ (11), 146 \ (88), 145 \ (18), 122 \ (16), 117 \ (34), 115 \ (19), 103 \ (12), 91 \ (44), 90 \ (11), 77 \ (16), 41 \ (31). \]

\[ \text{HRMS} \ (\text{EI), } m/z \ \text{calc. for } C_{21}H_{36}O \ (298.2297): 298.2283 \ (M^+). \]

\[ \text{IR} \ (\text{ATR}) \ \nu \ (\text{cm}^{-1}) = 3081, 3043, 2964, 2906, 2868, 1715, 1674, 1605, 1461, 1364, 1268, 1188, 1110, 1070, 1016, 972, 914, 843, 835, 775, 707. \]
Preparation of 1-(furan-2-yl)-6-methyl-2-vinylhept-5-en-1-one (32l)

According to TP2, the α-substituted β,γ-unsaturated ketone 32l was prepared from 30e (4.75 mL, 2.00 mmol, 0.42 M in THF) and furan-2-carbonyl chloride (31d, 209 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et₂O 50:1) furnished 32l as a yellow oil (276 mg, 79 %).

\[ ^1H\text{-NMR} (300 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 7.55 (\text{dd, } J=1.7\text{Hz, } 0.8\text{Hz, } 1\text{H}), 7.23 (\text{dd, } J=3.6\text{Hz, } 0.8\text{Hz, } 1\text{H}), 6.49 (\text{dd, } J=3.6\text{Hz, } 1.7\text{Hz, } 1\text{H}), 6.23 (\text{dd, } J=17.4\text{Hz, } 10.8\text{Hz, } 1\text{H}), 5.13-5.26 (\text{m, } 2\text{H}), 5.00-5.13 (\text{m, } 1\text{H}), 1.78-2.08 (\text{m, } 4\text{H}), 1.65 (\text{s, } 3\text{H}), 1.52 (\text{s, } 3\text{H}), 1.41 (\text{s, } 3\text{H}). \]

\[ ^{13}\text{C-NMR} (75 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 191.5, 152.1, 145.3, 142.1, 132.0, 124.0, 118.6, 114.7, 111.6, 52.7, 38.2, 25.6, 23.0, 21.2, 17.5. \]

\[ \text{MS (70 eV, EI), } m/z (\%) = 232 (\text{M}^+, 1), 150 (100), 122 (22), 121 (37), 81 (14), 73 (11), 70 (20), 69 (57), 67 (12), 61 (34), 55 (10), 43 (10), 42 (13), 41 (45). \]

\[ \text{HRMS (EI), } m/z \text{ calc. for C}_{15}\text{H}_{20}\text{O}_{2} (232.1483): 232.1472 (\text{M}^+). \]

\[ \text{IR (ATR) } \nu (\text{cm}^{-1}) = 3130, 3084, 2971, 2935, 2875, 1720, 1663, 1560, 1461, 1384, 1278, 1225, 1161, 1078, 1068, 1012, 979, 910, 884, 824, 762. \]

Preparation of 1-chloro-9-methyl-5-vinyldec-8-en-4-one (32m)

According to TP2, the α-substituted β,γ-unsaturated ketone 32m was prepared from 30e (4.75 mL, 2.00 mmol, 0.42 M in THF) and 4-chlorobutanoyl chloride (31e, 226 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et₂O 50:1) furnished 32m as a colorless oil (271 mg, 74 %).

\[ ^1\text{H-NMR} (300 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 5.94 (\text{dd, } J=17.6\text{Hz, } 10.6\text{Hz, } 1\text{H}), 4.97-5.36 (\text{m, } 3\text{H}), 3.57 (\text{t, } J=6.2\text{Hz, } 2\text{H}), 2.66 (\text{dt, } J=7.0\text{Hz, } 3.5\text{Hz, } 2\text{H}), 1.40-2.33 (\text{m, } 12\text{H}), 1.14-1.36 (\text{m, } 3\text{H}). \]
\textbf{13C-NMR} (75 MHz, CDCl$_3$) $\delta$ (ppm) = 211.7, 141.4, 132.0, 123.9, 115.2, 54.2, 44.6, 37.6, 34.6, 26.7, 25.7, 23.0, 19.6, 17.6.

\textbf{MS} (70 eV, EI), $m/z$ (%) = 242 (M$^+$, 1), 162 (13), 160 (41), 107 (18), 105 (57), 88 (29), 83 (34), 81 (24), 77 (14), 73 (35), 70 (70), 69 (96), 67 (17), 61 (100), 45 (94), 43 (67), 42 (41), 41 (68).

\textbf{HRMS} (EI), $m/z$ calc. for C$_{14}$H$_{23}$ClO (242.1437): 242.1432 (M$^+$).

\textbf{IR} (ATR) $\nu$ (cm$^{-1}$) = 3085, 3050, 2967, 2925, 2856, 1705, 1632, 1447, 1410, 1374, 1358, 1296, 1101, 1076, 1002, 919, 731.

\textbf{Preparation of 1-(cyclohex-2-en-1-yl)-2-phenoxyethanone (32n)}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

According to TP2, the $\alpha$-substituted $\beta$,\gamma-unsaturated ketone 32n was prepared from 30f (4.45 mL, 2.00 mmol, 0.45 M in THF) and 2-phenoxyacetyl chloride (31f, 273 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et$_2$O 9.5:0.5) furnished 32n as a yellow oil (260 mg, 75%).

\textbf{1H-NMR} (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.24-7.41 (m, 2H), 6.82-7.07 (m, 3H), 5.89-6.01 (m, 1H), 5.81 (ddd, $J$=10.2Hz, 5.3Hz, 2.2Hz, 1H), 4.61-4.81 (m, 2H), 3.50 (ddd, $J$=9.1Hz, 6.1Hz, 3.3Hz, 1H), 2.00-2.13 (m, 1H), 1.51-1.98 (m, 5H).

\textbf{13C-NMR} (75 MHz, CDCl$_3$) $\delta$ (ppm) = 207.9, 157.9, 131.0, 129.7, 122.9, 121.7, 114.6, 71.7, 45.5, 24.7, 24.3, 20.6.

\textbf{MS} (70 eV, EI), $m/z$ (%) = 216 (M$^+$, 29), 188 (11), 123 (25), 122 (11), 109 (46), 108 (16), 107 (58), 95 (28), 81 (100), 80 (14), 79 (50), 77 (64), 66 (10), 65 (13), 53 (11), 41 (10).

\textbf{HRMS} (EI), $m/z$ calc. for C$_{14}$H$_{16}$O$_2$ (216.1150): 216.1149 (M$^+$).

\textbf{IR} (ATR) $\nu$ (cm$^{-1}$) = 3097, 3060, 3041, 2936, 2867, 1707, 1681, 1598, 1588, 1494, 1432, 1198, 1173, 1085, 1072, 1049, 963, 885, 833, 751, 690.
Preparation of (4-(tert-butyl)phenyl)(cyclohex-2-en-1-yl)-methanone (32o)

According to TP2, the α-substituted β,γ-unsaturated ketone 32o was prepared from 30f (4.45 mL, 2.00 mmol, 0.45 M in THF) and 4-(tert-butyl)benzoyl chloride (31a, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et₂O 30:1) furnished 32o as a yellow oil (322 mg, 83 %).

\[ {^1}H\text{-NMR} \ (600 \text{ MHz, CDCl}_3) \ \delta (\text{ppm}) = 7.91 \ (d, J=8.8\text{Hz}, 2\text{H}), 7.47 \ (d, J=8.8\text{Hz}, 2\text{H}), 5.85-6.01 \ (m, 1\text{H}), 5.65-5.79 \ (m, 1\text{H}), 4.01-4.11 \ (m, 1\text{H}), 1.81-2.12 \ (m, 5\text{H}), 1.62-1.73 \ (m, 1\text{H}), 1.25-1.39 \ (m, 9\text{H}). \]

\[ {^{13}}C\text{-NMR} \ (150 \text{ MHz, CDCl}_3) \ \delta (\text{ppm}) = 201.5, 156.5, 133.6, 129.9, 128.5, 125.5, 124.9, 43.8, 35.1, 31.1, 25.9, 24.8, 20.9. \]

\[ \text{MS} \ (70 \text{ eV, EI}), \ m/z \ (\%) = 242 \ (M^+, 1), 238 \ (3), 227 \ (2), 223 \ (6), 185 \ (6), 162 \ (13), 161 \ (100), 146 \ (7), 117 \ (3), 115 \ (2), 91 \ (3), 77 \ (2). \]

\[ \text{HRMS} \ (\text{EI}), \ m/z \ \text{calc. for C}_{17}\text{H}_{22}\text{O} (242.1671): 242.1662 \ (M^+). \]

\[ \text{IR} \ (ATR) \ \nu \ (\text{cm}^{-1}) = 3087, 3062, 3032, 2958, 2905, 2876, 1675, 1650, 1603, 1461, 1407, 1363, 1267, 1233, 1187, 1116, 1110, 1102, 1015, 963, 845, 718, 700. \]

Preparation of (4-(tert-butyl)phenyl)((1S,5S)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl)methanone (32p)

According to TP2, the α-substituted β,γ-unsaturated ketone 32p was prepared from 30g (5.41 mL, 2.00 mmol, 0.37 M in THF) and 4-(tert-butyl)benzoyl chloride (31a, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et₂O 50:1) furnished 32p as a white solid (318 mg, 67 %).

\[ \text{m.p.: 122.8-124.8 °C.} \]

\[ {^1}H\text{-NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta (\text{ppm}) = 7.92 \ (d, J=8.6\text{Hz}, 2\text{H}), 7.48 \ (d, J=8.6\text{Hz}, 2\text{H}), 4.76-4.87 \ (m, 1\text{H}), 4.59 \ (s, 1\text{H}), 4.43-4.55 \ (m, 1\text{H}), 2.46-2.59 \ (m, 1\text{H}), 2.30-2.42 \ (m, 1\text{H}), 2.19-2.30 \ (m, 1\text{H}), 1.98-2.10 \ (m, 2\text{H}), 1.66 \ (d, J=10.2\text{Hz}, 1\text{H}), 1.34 \ (s, 9\text{H}), 1.28 \ (s, 3\text{H}), 0.85 \ (s, 3\text{H}). \]
13C-NMR (100 MHz, CDCl₃) δ (ppm) = 202.2, 156.4, 149.3, 134.7, 128.9, 125.5, 111.0, 51.7, 42.1, 40.3, 40.2, 35.0, 31.1, 28.6, 27.3, 25.8, 21.6.

MS (70 eV, EI), m/z (%) = 296 (M⁺, 3), 255 (11), 162 (26), 161 (100), 146 (12), 134 (16), 119 (12), 118 (17), 93 (11), 91 (15), 57 (11), 41 (10).

HRMS (EI), m/z calc. for C₂₁H₂₈O (296.2140): 296.2144 (M⁺).

IR (ATR) ν (cm⁻¹) = 3076, 3063, 2960, 2944, 2915, 2864, 1669, 1629, 1602, 1464, 1363, 1333, 1268, 1237, 1220, 1195, 1106, 1050, 1006, 938, 886, 861, 846, 838, 824, 800, 752, 711, 683.

Preparation of ((1S,5S)-6,6-dimethyl-2-methylenebicyclo-[3.1.1]heptan-3-yl)-(thiophen-2-yl)methanone (32q)

According to TP2, the α-substituted β,γ-unsaturated ketone 32q was prepared from 30g (5.41 mL, 2.00 mmol, 0.37 M in THF) and thiophene-2-carbonyl chloride (31b, 235 mg, 1.6 mmol) at -78 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et₂O 30:1) furnished 32q as a yellow oil (351 mg, 89%).

1H-NMR (400 MHz, CDCl₃) δ (ppm) = 7.75 (dd, J=3.8Hz, 1.1Hz, 1H), 7.66 (dd, J=4.9Hz, 1.2Hz, 1H), 7.16 (dd, J=5.0Hz, 3.8Hz, 1H), 4.83 (s, 1H), 4.64-4.74 (m, 1H), 4.28-4.40 (m, 1H), 2.52 (t, J=5. Hz, 1H), 2.32-2.44 (m, 1H), 1.99-2.15 (m, 2H), 1.75 (d, J=9.9Hz, 1H), 1.28 (s, 3H), 0.84 (s, 3H).

13C-NMR (100 MHz, CDCl₃) δ (ppm) = 195.5, 149.0, 145.3, 134.0, 132.3, 128.1, 111.2, 51.5, 43.6, 40.3, 39.9, 28.8, 27.3, 25.8, 21.6.

MS (70 eV, EI), m/z (%) = 246 (M⁺, 1), 177 (7), 135 (19), 134 (11), 119 (10), 111 (100), 93 (37), 91 (12), 69 (7), 43 (26), 41 (28).

HRMS (EI), m/z calc. for C₁₅H₁₈OS (246.1078): 246.1073 (M⁺).

IR (ATR) ν (cm⁻¹) = 3098, 3083, 2974, 2918, 2866, 1660, 1632, 1517, 1412, 1353, 1235, 1212, 1196, 1064, 1050, 938, 885, 833, 761, 718.
Preparation of ethyl 6-(furan-2-carbonyl)cyclohex-1-ene-carboxylate (32r)

According to TP2, the α-substituted β,γ-unsaturated ketone 32r was prepared from 30h (4.45 mL, 2.00 mmol, 0.45 M in THF) and furan-2-carbonyl chloride (31d, 209 mg, 1.6 mmol) at -78 °C → 25 °C over night. Flash column chromatography (silica, pentane:Et2O 1:1) furnished 32r as a white solid (223 mg, 90 %).

m.p.: 56.6-57.2 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.56-7.61 (m, 1H), 7.29 (dt, $J$=4.0Hz, 1.4Hz, 1H), 7.24 (dt, $J$=3.6Hz, 0 Hz, 1H), 6.53 (dd, $J$=3.6Hz, 1.7Hz, 1H), 4.23-4.33 (m, 1H), 4.02-4.16 (m, 2H), 2.18-2.40 (m, 2H), 1.81-2.01 (m, 2H), 1.56-1.71 (m, 2H), 1.14 (t, $J$=7.3Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 190.2, 166.4, 152.1, 146.2, 142.9, 128.6, 117.2, 112.2, 60.4, 42.7, 26.3, 25.4, 18.6, 14.0.

MS (70 eV, EI), $m/z$ (%) = 248 (M$^+$, 10), 203 (23), 202 (100), 174 (17), 95 (45), 79 (16).

HRMS (EI), $m/z$ calc. for C$_{14}$H$_{16}$O$_4$ (248.1049): 248.1046 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3139, 3123, 3096, 2984, 2968, 2957, 2907, 2869, 2827, 1696, 1657, 1646, 1470, 1395, 1374, 1285, 1267, 1253, 1233, 1201, 1171, 1142, 1094, 1080, 1071, 1055, 1034, 1020, 1007, 957, 943, 923, 789, 753, 730, 707.

Preparation of ethyl 6-(4-chlorobenzoyl)cyclohex-1-ene-carboxylate (32s)

According to TP2, the α-substituted β,γ-unsaturated ketone 32s was prepared from 30h (4.45 mL, 2.00 mmol, 0.45 M in THF) and 4-chlorobenzoyl chloride (31g, 280 mg, 1.6 mmol) at -78 °C → 25 °C over night. Flash column chromatography (silica, pentane:Et$_2$O 8:2) furnished 32s as a white solid (234 mg, 80 %).

m.p.: 59.4-60.3 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.89-8.01 (m, 2H), 7.37-7.50 (m, 2H), 7.26-7.37 (m, 1H), 4.39-4.51 (m, 1H), 4.09 (dq, $J$=7.1Hz, 1.7Hz, 2H), 2.15-2.40 (m, 2H), 1.89-2.02 (m, 1H), 1.74-1.87 (m, 1H), 1.50-1.71 (m, 2H), 1.15 (t, $J$=7.1Hz, 3H).
C. EXPERIMENTAL SECTION

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 200.2, 166.5, 142.6, 139.2, 134.6, 129.9, 129.2, 128.9, 60.5, 42.0, 26.1, 25.4, 18.5, 14.1.

MS (70 eV, EI), $m/z$ (%) = 292 (M$^+$, 2), 247 (4), 246 (8), 140 (7), 139 (100), 111 (11), 79 (4).

HRMS (EI), $m/z$ calc. for C$_{16}$H$_{17}$ClO$_3$ (292.0866): 292.0860 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3097, 3069, 2990, 2938, 2863, 2824, 1699, 1677, 1586, 1481, 1446, 1397, 1281, 1245, 1214, 1101, 1091, 1082, 1065, 1043, 1005, 947, 916, 834, 751, 737, 674.

Preparation of 5-(4-chlorobenzoyl)cyclopent-1-enecarbonitrile (32t)

According to TP2, the $\alpha$-substituted $\beta,\gamma$-unsaturated ketone 32t was prepared from 30i (5.70 mL, 2.00 mmol, 0.35 M in THF) and 4-chlorobenzoyl chloride (31g, 280 mg, 1.6 mmol) at -78 °C → 25 °C over night. Flash column chromatography (silica, pentane:Et$_2$O 1:1) furnished 32t as a white solid (162 mg, 70%).

m.p.: 77.3-79.5 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.86-7.97 (m, 2H), 7.42-7.53 (m, 2H), 6.88 (q, $J$=2.5Hz, 1H), 4.59-4.73 (m, 1H), 2.58-2.74 (m, 2H), 2.38-2.55 (m, 1H), 2.09-2.23 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 196.7, 152.0, 140.4, 133.6, 130.1, 129.2, 115.7, 113.7, 53.9, 33.1, 28.2.

MS (70 eV, EI), $m/z$ (%) = 231 (M$^+$, 1), 142 (2), 140 (6), 139 (100), 111 (21), 92 (2), 76 (3), 75 (7), 65 (2).

HRMS (EI), $m/z$ calc. for C$_{13}$H$_{10}$CINO (231.0451): 231.0443 (M$^+$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3091, 3066, 2976, 2921, 2848, 2220, 1675, 1587, 1573, 1486, 1434, 1399, 1345, 1319, 1282, 1222, 1209, 1086, 1006, 859, 844, 832, 818, 732, 720, 670.
4.4.1 Further Functionalization of \( \beta, \gamma \)-Unsaturated Ketone \( 32d \)

**Preparation of (3S,4S)-4-(4-(tert-butyl)phenyl)-3-phenylhepta-1,6-dien-4-ol (rac)(33)**

![ structure of compound 33 ]

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-(4-(tert-butyl)phenyl)-2-phenylbut-3-en-1-one (\( 32d \), 557 mg, 2.0 mmol) and cooled to 0 °C. Then, allyl Grignard reagent (1.80 mL, 2.2 mmol, 1.22 \text{ M} \text{ in THF}) was added dropwise and the reaction mixture was warmed to 25 °C. After stirring for 1.5 h, the reaction mixture was quenched with saturated aqueous NH\(_4\)Cl solution (10 mL), extracted with EtOAc (3x10 mL), dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The compound was used directly for the metathesis reaction without further purification since GC-analysis indicated >98 % purity.

**Preparation of (1S,2S)-1-(4-(tert-butyl)phenyl)-2-phenylcyclopent-3-enol (rac)(34)**

![ structure of compound 34 ]

The synthesis of 34 is following a literature-known procedure.\(^{275}\) A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with Grubbs II catalyst (85 mg, 0.10 mmol) and dissolved in dichloromethane (15 mL). The crude of 7 (641 mg, 2.0 mmol) was dissolved in dichloromethane (5 mL) and added dropwise to the reaction mixture. After heating to 40 °C for 4 h, the solvent was removed \textit{in vacuo} and the crude residue obtained was purified by flash column chromatography (silica, pentane:Et\(_2\)O 9:1) to give the analytically pure product 34 as an off-white solid (567 mg, 97 %).

**m.p.:** 67.9-69.3 °C.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \text{ (ppm)} = 7.37-7.48 \) (m, 4H), 7.26-7.36 (m, 3H), 7.02-7.15 (m, 2H), 6.04-6.16 (m, 1H), 5.82-5.98 (m, 1H), 4.37-4.50 (m, 1H), 3.01-3.13 (m, 1H), 2.82-2.96 (m, 1H), 1.53-1.65 (m, 1H), 1.40 (s, 9H).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \text{ (ppm)} = 149.4, 144.0, 137.2, 131.4, 130.3, 129.0, 128.5, 127.5, 124.9, 124.9, 83.0, 63.7, 50.6, 34.4, 31.4.

4.5 Preparation of α-substituted β,γ-unsaturated esters

Preparation of ethyl 2-phenylbut-3-enoate (36a)

According to TP2, the α-substituted β,γ-unsaturated ester 36a was prepared from 30b (4.65 mL, 2.00 mmol, 0.43 M in THF) and ethyl carbonochloridate (35a, 174 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et₂O 30:1) furnished 36a as a colorless oil (195 mg, 64%).

$^1$H-NMR (600 MHz, CDCl₃) δ (ppm) = 7.22-7.41 (m, 5H), 6.16-6.28 (m, 1H), 5.09-5.25 (m, 2H), 4.31 (d, $J=8.1$ Hz, 1H), 4.09-4.26 (m, 2H), 1.24 (t, $J=7.2$ Hz, 3H).

$^{13}$C-NMR (150 MHz, CDCl₃) δ (ppm) = 172.3, 138.1, 135.9, 128.7, 128.0, 127.3, 117.4, 61.0, 55.8, 14.1.

MS (70 eV, EI) m/z (%) = 190 (M⁺, 7), 117 (100), 116 (8), 115 (31), 91 (10).

HRMS (EI, m/z calc. for C₁₂H₁₄O₂ (190.0994): 190.0985 (M⁺).

IR (ATR) $\nu$ (cm⁻¹) = 3084, 3063, 3029, 2981, 2936, 2905, 2872, 1729, 1495, 1454, 1367, 1306, 1225, 1191, 1151, 1027, 990, 922, 728, 697.

Preparation of phenyl 2-phenylbut-3-enoate (36b)

According to TP2, the α-substituted β,γ-unsaturated ester 36b was prepared from 30b (4.65 mL, 2.00 mmol, 0.43 M in THF) and phenyl carbonochloridate (35b, 251 mg, 1.6 mmol) at -78 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et₂O 30:1) furnished 36b as a colorless oil (297 mg, 78%).
\( ^1H\)-NMR (400 MHz, CDCl\(_3\)) \( \delta (ppm) = 7.12-7.55 \) (m, 8H), 6.94-7.11 (m, 2H), 6.33 (ddd, \( J=17.1Hz, 10.2Hz, 7.9Hz, 1H \)), 5.21-5.36 (m, 2H), 4.56 (d, \( J=7.8Hz, 1H \)).

\( ^{13}C\)-NMR (100 MHz, CDCl\(_3\)) \( \delta (ppm) = 170.7, 150.7, 137.6, 135.2, 129.4, 128.9, 128.0, 127.6, 125.9, 121.3, 118.1, 55.7. \)

MS (70 eV, EI), \( m/z \) (%) = 238 (M\(^+\), 1), 145 (22), 144 (100), 116 (26), 115 (65), 91 (20), 65 (10).

HRMS (EI), \( m/z \) calc. for C\(_{16}\)H\(_{14}\)O\(_2\) (238.0994): 238.0993 (M\(^+\)).

IR (ATR) \( \nu (cm^{-1}) = 3081, 3067, 3025, 2983, 2925, 1743, 1590, 1490, 1453, 1304, 1290, 1186, 1161, 1144, 1119, 1069, 984, 979, 941, 821, 756, 729, 696, 687.

Preparation of allyl 2-phenylbut-3-enoate (36c)

\[ \begin{align*} \text{O} & \quad \text{Ph} \\ \text{CH} = \text{CH} & \quad \text{O} \\ \text{CH} = \text{CH} & \quad \text{O} \\ \text{CH} = \text{CH} & \quad \text{O} \end{align*} \]

According to TP2, the \( \alpha \)-substituted \( \beta,\gamma \)-unsaturated ester 36c was prepared from 30b (4.65 mL, 2.00 mmol, 0.43 m in THF) and allyl carbonochloridate (35c, 193 mg, 1.6 mmol) at \(-78 \, ^{\circ}C \rightarrow 25 \, ^{\circ}C \) in 2 h. Flash column chromatography (silica, pentane:Et\(_2\)O 30:1) furnished 36c as a colorless oil (265 mg, 82 %).

\( ^1H\)-NMR (600 MHz, CDCl\(_3\)) \( \delta (ppm) = 7.21-7.41 \) (m, 5H), 6.19-6.28 (m, 1H), 5.82-5.93 (m, 1H), 5.10-5.32 (m, 4H), 4.55-4.67 (m, 2H), 4.35 (d, \( J=8.2Hz, 1H \)).

\( ^{13}C\)-NMR (150 MHz, CDCl\(_3\)) \( \delta (ppm) = 172.0, 138.0, 135.7, 131.9, 128.7, 128.0, 127.4, 118.3, 117.6, 65.5, 55.8. \)

MS (70 eV, EI), \( m/z \) (%) = 202 (M\(^+\), 1), 118 (13), 117 (100), 116 (11), 115 (42), 91 (13), 41 (11).

HRMS (EI), \( m/z \) calc. for C\(_{13}\)H\(_{14}\)O\(_2\) (202.0994): 202.0985 (M\(^+\)).

IR (ATR) \( \nu (cm^{-1}) = 3084, 3063, 3029, 2983, 2941, 2882, 1732, 1495, 1453, 1306, 1220, 1190, 1149, 989, 921, 729, 697.

Preparation of phenyl 2,2-dimethylbut-3-enoate (36d)

\[ \begin{align*} \text{O} & \quad \text{Me} \\ \text{CH} = \text{CH} & \quad \text{O} \\ \text{CH} = \text{CH} & \quad \text{O} \end{align*} \]

According to TP2, the \( \alpha \)-substituted \( \beta,\gamma \)-unsaturated ester 36d was prepared from 30c (4.35 mL, 2.00 mmol, 0.46 m in THF) and phenyl carbonochloridate (35b, 251 mg,
1.6 mmol) at -20 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et₂O 30:1) furnished 36d as a colorless oil (213 mg, 70%).

**1H-NMR** (300 MHz, CDCl₃) δ (ppm) = 7.31-7.47 (m, 2H), 7.18-7.29 (m, 1H), 7.00-7.15 (m, 2H), 6.20 (dd, J=17.4Hz, 10.8Hz, 1H), 5.14-5.34 (m, 2H), 1.49 (s, 6H).

**13C-NMR** (75 MHz, CDCl₃) δ (ppm) = 174.8, 151.0, 142.0, 129.4, 125.7, 121.4, 113.6, 45.1, 24.6.

**MS** (70 eV, EI), m/z (%) = 190 (M⁺, 7), 97 (10), 95 (11), 94 (100), 69 (89), 41 (36).

**HRMS** (EI), m/z calc. for C₁₂H₁₄O₂ (190.0994): 190.0996 (M⁺).

**IR** (ATR) υ (cm⁻¹) = 3088, 3067, 3043, 2979, 2935, 2873, 1747, 1638, 1593, 1493, 1470, 1192, 1161, 1106, 1070, 1001, 915, 832, 738, 688, 670.
5. Preparation of Functionalized Alkenylzinc Reagents Bearing Carbonyl Groups via Direct Metal Insertion

5.1 Preparation of Starting Materials

All reagents were obtained from commercial sources. Compounds 37a, 37b, 37c, 37d, 37e and 42d, 37f, 37g and 37h, 37i, 42a and 42b, 42c as well as 42e were prepared according to literature-known procedures. Compound 42f was synthesized analogous a literature-known procedure employing PhSSO$_2$Ph as electrophile.

5.2 Typical Procedures

Typical procedure 1 (TP1): LiCl-mediated zinc insertion into activated alkenyl bromides

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

Typical procedure 2 (TP2): LiCl-mediated magnesium insertion in the presence of zinc chloride into less activated alkenyl bromides

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.5 equiv) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, magnesium turnings (2.5 equiv) were added, followed by THF (1 mL/mmol). The magnesium was activated using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then, ZnCl₂-solution (1.1 equiv, 1 M in THF) was added followed by the substrate (1 equiv). The reaction mixture was stirred at 25 °C until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, solids were allowed to settle or the reaction mixture was centrifuged (10 min, 2000 rpm). The yield of the insertion reaction was determined by iodometric titration of the supernatant solution.

Typical procedure 3 (TP3): Allylation or Acylation of alkenyl zinc reagents

The freshly prepared zinc reagent was cooled to -40 °C and the corresponding allyl bromide (0.8–0.9 equiv) was added, followed by CuCN·2LiCl (1 M in THF). The reaction mixture was allowed to warm to 0 °C. After stirring for the given time, the reaction mixture was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL), washed with sat. NH₄Cl/NH₃ solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 4 (TP4): Cross-coupling reactions of alkenyl zinc reagents

The desired aryl bromide or iodide (0.8 equiv) was added to the freshly prepared zinc reagent followed by Pd(PPh₃)₄ (2 mol%) and the mixture was stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 5 (TP5): Preparation of tetrahydrophthalazines of type 5

The freshly prepared zinc reagent was cooled to -40 °C and CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) was added followed by the corresponding acid chloride (0.6-
0.8 equiv). After stirring for the given time at -40 °C, the reaction mixture was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL), washed with sat. NH₄Cl/NH₃ solution (9:1, 2x10 mL) and extracted with Et₂O (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was dissolved in MeOH (20 mL) and hydrazine hydrate (3 equiv) was added at room temperature. After stirring for 14 h, the reaction mixture was concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

5.3 Preparation of Alkenyl Zinc Reagents from Activated Alkenyl Bromides

Preparation of (2-formylcyclohex-1-en-1-yl)zinc bromide (38a)

According to TP1, the zinc reagent 38a was prepared from 2-bromocyclohex-1-ene-1-carbaldehyde (37a, 1.89 g, 10.0 mmol) using Zn powder (1.31 g, 20.0 mmol) and LiCl (848 mg, 20.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.77 M (86%).

Preparation of (5-formyl-3,6-dihydro-2H-pyran-4-yl)zinc bromide (38b)

According to TP1, the zinc reagent 38b was prepared from 4-bromo-5,6-dihydro-2H-pyran-3-carbaldehyde (37b, 955 mg, 5.00 mmol) using Zn powder (490 mg, 7.50 mmol) and LiCl (318 mg, 7.5 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.72 M (77%).

Preparation of (3-oxocyclohex-1-en-1-yl)zinc bromide (38c)

According to TP1, the zinc reagent 38c was prepared from 3-bromocyclohex-2-enone (37c, 1.75 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.77 M (86%).
Preparation of (3-oxocyclohex-1-en-1-yl)zinc bromide (38d)

According to TP1, the zinc reagent 38d was prepared from 3-bromocyclopent-2-enone (37d, 1.50 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.99 M (94%).

Preparation of (2-benzoylcyclopent-1-en-1-yl)zinc bromide (38e)

According to TP1, the zinc reagent 38e was prepared from (2-bromocyclopent-1-en-1-yl)(phenyl)methanone (37e, 2.51 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.56 M (62%).

Preparation of (Z)-(4,4-dimethyl-1-oxopent-2-en-3-yl)zinc bromide (38f)

According to TP1, the zinc reagent 38f was prepared from (Z)-3-bromo-4,4-dimethylpent-2-enal (37f, 1.91 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.61 M (67%).

Preparation of (Z)-(1-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)zinc bromide (38g)

According to TP1, the zinc reagent 38g was prepared from (Z)-3-bromo-3-(4-fluorophenyl)acrylaldehyde (37g, 2.29 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.32 M (35%).
Preparation of (Z)-(1-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)zinc bromide (38h)

According to TP1, the zinc reagent 38h was prepared from (Z)-3-bromo-3-(4-methoxyphenyl)acrylaldehyde (37h, 2.41 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.37 M (41%).

Preparation of (Z)-(3-ethoxy-3-oxo-1-phenylprop-1-en-1-yl)zinc bromide (38i)

According to TP1, the zinc reagent 38i was prepared from (Z)-ethyl 3-bromo-3-phenylacrylate (37i, 2.55 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.56 M (62%).

5.4 Reactions of Alkenyl Zinc Reagents of Type 38 with Electrophiles

Preparation of 4-(2-formylcyclohex-1-en-1-yl)benzonitrile (40a)

The cross-coupling reaction of 38a (2.60 mL, 2.00 mmol, 0.77 M in THF) with 4-bromobenzonitrile (39a, 291 mg, 1.60 mmol) was performed according to TP4 in 1.5 h. Flash column chromatography (silica, pentane:Et₂O 8.5:1.5) furnished 40a as a yellow solid (276 mg, 82 %).

m.p.: 78.0-79.8 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 9.42 (s, 1 H), 7.68 (d, J=8.6Hz, 2H), 7.35 (d, J=8.6Hz, 2H), 2.57-2.47 (m, 2H), 2.43-2.11 (m, 2H), 1.89-1.65 (m, 4H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 192.2, 156.7, 144.3, 136.9, 132.0, 129.3, 118.3, 112.1, 33.6, 22.2, 22.2, 21.2.
**C. Experimental Section**

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

**HRMS** \( m/z \) calc. for \( \text{C}_{14}\text{H}_{13}\text{NO} \) (211.0997): 211.0992.

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

**Preparation of ethyl 2-[(2-formylcyclohex-1-en-1-yl)methyl]prop-2-enoate (40b)**

The allylation reaction of \( 38a \) (2.60 mL, 2.00 mmol, 0.77 M in THF) with CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (39b, 347 mg, 1.80 mmol) was performed according to TP3 in 1 h. Flash column chromatography (silica, pentane:Et\(_2\)O 9:1) furnished \( 40b \) as a colorless oil (377 mg, 94%).

**\(^1\)H-NMR** (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 10.07 (s, 1H), 6.27 (d, \( J=1.1\)Hz, 1H), 5.51 (d, \( J=1.1\)Hz, 1H), 4.21 (d, \( J=7.1\)Hz, 2H), 3.54 (s, 2H), 2.28-2.14 (m, 4H), 1.16 (dt, \( J=6.4\)Hz, 3.2Hz, 4H), 1.37 (t, \( J=7.1\)Hz, 3H).

**\(^1\)3C-NMR** (75 MHz, CDCl\(_3\)) \( \delta \) (ppm) = 191.2, 166.5, 154.8, 138.0, 135.5, 126.2, 61.0, 33.7, 31.6, 22.4, 22.0, 21.6, 14.1.

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

**HRMS** \( m/z \) calc. for \( \text{C}_{13}\text{H}_{18}\text{O}_3 \) (222.1256): 222.1258.

**IR** (ATR) \( \nu \) (cm\(^{-1}\)) = 2956, 2257, 1781, 1678, 1629, 1588, 1505, 1377, 1255, 1169, 1144, 1112, 1035, 934, 814, 762.

**Preparation of ethyl 3-(2-formylcyclohex-1-en-1-yl)prop-2-ynoate (40c)**

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenyl zinc reagent \( 38a \) (2.80 mL, 2.40 mmol, 0.85 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.24 mL, 0.24 mmol, 1.0 M in THF) was added, followed by ethyl 3-bromoprop-2-ynoate (39c, 354 mg, 2.00 mmol) and the reaction mixture was
stirred for 3 h at -78 °C. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et₂O 4:1) to give 40c as a colorless oil (331 mg, 80%).

**¹H-NMR** (300 MHz, CDCl₃) δ (ppm) = 10.15 (s, 1H), 4.28 (q, J=6.0Hz, 2H), 2.50-2.40 (m, 2H), 2.35-2.25 (m, 2H), 1.75-1.60 (m, 4H), 1.33 (t, J=6.0Hz, 3H).

**¹³C-NMR** (75 MHz, CDCl₃) δ (ppm) = 191.5, 153.3, 147.6, 135.8, 88.3, 81.8, 62.4, 31.2, 22.3, 21.5, 20.6, 14.0.

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

**HRMS** m/z calc. for C₁₂H₁₄O₃ (206.0943): 206.0946.

**IR** (ATR) v (cm⁻¹) = 2939, 2210, 1708, 1678, 1366, 1255, 1217, 1140, 1017, 747.

**Preparation of 2-[(2-bromophenyl)carbonyl]cyclohex-1-ene-1-carbaldehyde (40d)**

The acylation reaction of 38a (2.80 mL, 2.40 mmol, 0.85 M in THF) with CuCN·2LiCl (2.40 mL, 2.40 mmol, 1 M in THF) and 2-bromobenzoyl chloride (39d, 439 mg, 2.00 mmol) was performed according to TP3 in 4 h. Flash column chromatography (silica, pentane:Et₂O 10:1 then 4:1) furnished 40d as a colorless oil (297 mg, 51%).

**¹H-NMR** (300 MHz, CDCl₃) δ (ppm) = 9.74 (s, 1H), 7.70-7.55 (m, 2H), 7.45-7.35 (m, 2H), 2.50-2.35 (m, 4H), 1.80-1.70 (m, 4H).

**¹³C-NMR** (75 MHz, CDCl₃) δ (ppm) = 197.3, 191.2, 154.6, 141.7, 139.0, 134.3, 133.2, 131.2, 127.9, 120.7, 28.7, 22.5, 21.8, 20.8.

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

**HRMS** m/z calc. for C₁₄H₁₃BrO₂ (292.0099): 292.0092.

**IR** (ATR) v (cm⁻¹) = 2937, 1751, 1434, 1172, 1065, 1026, 1008, 911, 755, 734.
Preparation of 5-(2-formylcyclohex-1-en-1-yl)pyridine-3-carbonitrile (40e)

![Chemical structure of 40e]

The cross-coupling reaction of 38a (2.80 mL, 2.40 mmol, 0.85 M in THF) with 5-bromopyridine-3-carbonitrile (39e, 366 mg, 2.00 mmol) was performed according to TP4 in 3 h. Flash column chromatography (silica, hexanes:Et₂O 1:1) furnished 40e as a yellow oil (276 mg, 65%).

\[ ^1\text{H-NMR} \quad (300 \text{ MHz, CDCl}_3 \quad \delta (\text{ppm}) = 9.42 (\text{s, 1H}), 8.88-8.87 (\text{m, 1H}), 8.69-8.68 (\text{m, 1H}), 7.88-7.87 (\text{m, 1H}), 2.55-2.45 (\text{m, 2H}), 2.43-2.35 (\text{m, 2H}), 1.85-1.70 (\text{m, 4H}). \]

\[ ^{13}\text{C-NMR} \quad (75 \text{ MHz, CDCl}_3 \quad \delta (\text{ppm}) = 191.0, 152.2, 151.9, 151.7, 138.8, 138.6, 135.5, 115.9, 109.9, 33.8, 22.3, 22.1, 21.0. \]

\[ \text{MS} \quad (70 \text{ eV, EI}, \quad m/z \quad \% = 212 (M^+, 73), 211 (73), 183 (100), 169 (29), 155 (63). \]

\[ \text{HRMS} \quad m/z \quad \text{calc. for C}_{13}\text{H}_{12}\text{N}_2\text{O} \quad (212.0950): \quad 212.0939. \]

\[ \text{IR (ATR)} \quad \nu \quad (\text{cm}^{-1}) = 2934, 2860, 2234, 1667, 1625, 1418, 1223, 1024, 905, 707, 652. \]

Preparation of 2-[4-(trifluoromethyl)phenyl]cyclohex-1-ene-1-carbaldehyde (40f)

![Chemical structure of 40f]

The cross-coupling reaction of 38a (2.80 mL, 2.40 mmol, 0.85 M in THF) with 4-bromobenzotrifluoride (39f, 450 mg, 2.00 mmol) was performed according to TP4 in 4 h. Flash column chromatography (silica, hexanes:Et₂O 10:1 then 4:1) furnished 40f as a yellow oil (369 mg, 73%).

\[ ^1\text{H-NMR} \quad (300 \text{ MHz, CDCl}_3 \quad \delta (\text{ppm}) = 9.45 (\text{s, 1H}), 7.66 (\text{q, } J=9.0\text{Hz, 2H}), 7.37 (\text{q, } J=9.0\text{Hz, 2H}), 2.60-2.50 (\text{m, 2H}), 2.40-2.30 (\text{m, 2H}), 1.85-1.60 (\text{m, 4H}). \]

\[ ^{13}\text{C-NMR} \quad (75 \text{ MHz, CDCl}_3 \quad \delta (\text{ppm}) = 192.1, 157.4, 143.2, 136.7, 130.4 (\text{q, } J=33\text{Hz}), 128.9, 125.3 (\text{q, } J=4\text{Hz}), 123.9 (\text{q, } J=272\text{Hz}), 33.9, 22.3, 22.2, 21.3. \]

\[ \text{MS} \quad (70 \text{ eV, EI}, \quad m/z \quad \% = 254 (M^+, 25), 253 (22), 185 (50), 159 (19), 43 (100). \]

\[ \text{HRMS} \quad m/z \quad \text{calc. for C}_{14}\text{H}_{13}\text{F}_3\text{O} \quad (254.0918): \quad 254.0907. \]

\[ \text{IR (ATR)} \quad \nu \quad (\text{cm}^{-1}) = 2937, 1671, 1614, 1322, 1211, 1163, 1121, 1109, 1067, 1017, 840. \]
Preparation of 2-[(dimethylamino)methyl)cyclohex-1-ene-1-carbaldehyde (40g)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with CH₂Cl₂ (2 mL) and N,N,N',N'-tetramethyldiaminomethane (204 mg, 2.00 mmol) and was cooled to 0 °C. Then, trifluoroacetic anhydride (420 mg, 2 mmol) was added dropwise at 0 °C and the resulting clear solution was stirred for 15 min. Then, the alkenyl zinc reagent 38a (2.82 mL, 2.00 mmol, 0.71 M in THF) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with sat. NaCl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dissolved in EtOAc (30 mL) and washed with HCl (2x20 mL, 2 M). The aqueous solution was neutralized with NaHCO₃, NaOH (2 M, 10 mL) was added and subsequently extracted with EtOAc (3x10 mL). After drying over Na₂SO₄ and evaporation of solvents 40g was isolated as a yellow liquid (226 mg, 68%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 10.13 (s, 1H), 3.27 (s, 2H), 2.36-2.27 (m, 2H), 2.24 (s, 6H), 2.24-2.19 (m, 2H), 1.68-1.54 (m, 4H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 188.4, 155.1, 136.5, 59.7, 45.4, 30.8, 22.4, 22.0, 21.6.

MS (70 eV, EI), m/z (%) = 167 (M⁺, 20), 138 (100), 122 (22), 110 (22), 79 (23), 58 (34), 42 (57).

HRMS m/z calc. for C₁₀H₁₇NO (167.1310): 167.1307.

IR (ATR) ν (cm⁻¹) = 2945, 1675, 1604, 1454, 1319, 1277, 1256, 1169, 1104, 1033, 1012, 951, 843, 832, 762, 675.

Preparation of 4-[(dimethylamino)methyl]-5,6-dihydro-2H-pyran-3-carbaldehyde (40h)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with CH₂Cl₂ (2 mL) and N,N,N',N'-tetramethyldiaminomethane (163 mg, 1.6 mmol) and was cooled to 0 °C. Then, trifluoroacetic anhydride (336 mg, 1.6 mmol) was added dropwise at 0 °C and the resulting clear solution was stirred for 15 min. Then, the alkenylzinc reagent 38b (3.1 mL, 2.00 mmol, 0.65 M in THF) was added and the
reaction mixture was stirred for 30 min. The reaction was quenched with sat. NaCl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue obtained was dissolved in EtOAc (30 mL) and washed with HCl (2x 20 mL, 2 M). The aqueous solution was neutralized with NaHCO$_3$, NaOH (2 M, 10 mL) was added and subsequently extracted with EtOAc (3x10 mL). After drying over Na$_2$SO$_4$ and evaporation of solvents 40h was isolated as a yellow liquid (237 mg, 88 %).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 10.08 (s, 1H), 4.49-4.45 (m, 2H), 3.39 (t, $J$=5.5Hz, 2H), 2.67 (s, 2H), 2.01-1.95 (m, 2H), 1.83 (s, 6H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 188.1, 152.7, 136.1, 64.3, 64.0, 58.9, 45.4, 29.7.

MS (70 eV, EI), $m/z$ (%) = 169 (M$^+$, 19), 124 (100), 123 (16), 94 (25), 58 (87), 44 (15), 42 (16).

HRMS $m/z$ calc. for C$_9$H$_{15}$NO$_2$ (169.1103): 161.1108.

IR (ATR) $\nu$ (cm$^{-1}$) = 2944, 2822, 2768, 1663, 1461, 1387, 1290, 1252, 1165, 1115, 1041, 1016, 1002, 950, 855, 839, 758, 694, 675.

Preparation of 3-(4-Cyanophenyl)-2-cyclohexen-1-one (40i)

![Structure of 3-(4-Cyanophenyl)-2-cyclohexen-1-one (40i)](image)

The cross-coupling reaction of 38c (4.80 mL, 2.40 mmol, 0.50 M in THF) with 4-iodobenzonitrile (39a, 458 mg, 2.00 mmol) was performed according to TP4 in 3 h. Flash column chromatography (silica, hexanes:Et$_2$O 1:1 then 1:2) furnished 40i as a colorless solid (349 mg, 88 %).

m.p.: 95.8-97.4 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.70 (d, $J$=8.3Hz, 2 H), 7.61 (d, $J$=8.5Hz, 2 H), 6.41 (s, 1H), 2.75 (dt, $J$=6.0Hz, 1.2Hz, 2H), 2.50 (d, $J$=7.1Hz, 2H), 2.18 (quint, $J$=6.4Hz, 2H), 1.83 (s, 6H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 199.1, 157.2, 143.3, 132.5, 127.3, 126.6, 118.2, 113.2, 37.1, 27.9, 22.6.

MS (70 eV, EI), $m/z$ (%) = 197 (M$^+$, 44), 169 (100), 141 (69), 140 (90), 113 (24).

HRMS $m/z$ calc. for C$_{13}$H$_{11}$NO (197.0841): 197.0838.

IR (ATR) $\nu$ (cm$^{-1}$) = 2951, 2223, 1662, 1603, 1343, 1259, 1183, 1130, 889, 830, 816.
Preparation of 3-[4-(ethoxycarbonyl)phenyl]-2-cyclohexen-1-one (40j)

The cross-coupling reaction of 38c (4.80 mL, 2.40 mmol, 0.50 M in THF) with ethyl 4-iodobenzoate (39h, 552 mg, 2.00 mmol) was performed according to TP4 in 3 h. Flash column chromatography (silica, hexanes:E\textsubscript{2}O 2:1 then 1:1) furnished 40j as a colorless solid (373 mg, 76 %).

\textbf{m.p.:} 62.2-64.3 °C.

\textbf{H-NMR} (300 MHz, CDCl\textsubscript{3}) \textit{\delta} (ppm) = 8.07 (d, \textit{J} = 8.8 Hz, 2 H), 7.58 (d, \textit{J} = 8.8 Hz, 2 H), 6.44 (t, \textit{J} = 1.5 Hz, 1 H), 4.39 (q, \textit{J} = 7.1 Hz, 2 H), 2.78 (dt, \textit{J} = 6.1, 1.5 Hz, 2 H), 2.53-2.47 (m, 2 H), 2.17 (quint, \textit{J} = 6.4 Hz, 2 H), 1.40 (t, \textit{J} = 7.1 Hz, 3 H).

\textbf{C-NMR} (75 MHz, CDCl\textsubscript{3}) \textit{\delta} (ppm) = 199.5, 165.9, 158.4, 143.0, 131.5, 129.8, 126.7, 125.9, 61.2, 37.2, 28.0, 22.7, 14.3.

\textbf{MS} (70 eV, EI), \textit{m/z} (%) = 244 (M\textsuperscript{+}, 100), 216 (41), 199 (48), 171 (99), 144 (94).

\textbf{HRMS} \textit{m/z}: calc. for C\textsubscript{15}H\textsubscript{16}O\textsubscript{3} 244.1099, found 244.1099.

\textbf{IR} (ATR) \textit{\tilde{\nu}} (cm\textsuperscript{-1}) = 2944, 1704, 1665, 1602, 1287, 1269, 1184, 1110, 1021, 766, 698.

Preparation of ethyl 1,1'-bi(cyclohexane)-1,2'-dien-3-one (40k)

The allylation reaction of 38c (4.80 mL, 2.40 mmol, 0.50 M in THF) with CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and 3-bromocyclohexene (39i, 322 mg, 2.00 mmol) was performed according to TP3 in 1 h. Flash column chromatography (silica, pentane:E\textsubscript{2}O 4:5) furnished 40k as a colorless oil (269 mg, 76 %).

\textbf{H-NMR} (300 MHz, CDCl\textsubscript{3}) \textit{\delta} (ppm) = 5.90-5.80 (m, 2H), 5.55-5.48 (m, 1H), 2.95-2.85 (m, 1H), 2.40-2.20 (m, 4H), 2.15-1.80 (m, 5H), 1.75-1.40 (m, 3H).

\textbf{C-NMR} (75 MHz, CDCl\textsubscript{3}) \textit{\delta} (ppm) = 200.1, 169.4, 129.7, 126.9, 125.8, 43.22, 37.5, 28.3, 27.6, 24.9, 23.0, 20.6.

\textbf{MS} (70 eV, EI), \textit{m/z} (%) = 176 (M\textsuperscript{+}, 45), 120 (100), 105 (72), 92 (74), 91 (92).
HRMS $m/z$ calc. for C$_{12}$H$_{16}$O (176.1201): 176.1201.

IR (ATR) $\nu$ (cm$^{-1}$) = 2930, 1662, 1619, 1257, 1241, 1187, 1133, 965, 884, 725.

Preparation of 3-[2-(Ethoxycarbonyl)ethynyl]-2-cyclohexen-1-one (40l)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenyl zinc reagent 38c (4.80 mL, 2.40 mmol, 0.50 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.24 mL, 0.24 mmol, 1.0 M in THF) was added, followed by ethyl 3-bromoprop-2-ynoate (39c, 354 mg, 2.00 mmol) and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched with sat. NH$_4$Cl solution (10 mL) and extracted with Et$_2$O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et$_2$O 2:1) to give 40l as a colorless oil (273 mg, 71 %).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 6.35 (t, $J$=1.9Hz, 1H), 4.27 (q, $J$=7.1Hz, 2H), 2.50-2.40 (m, 4H), 2.11-2.01 (m, 2H), 1.33 (t, $J$=7.2Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 197.6, 153.1, 139.4, 135.7, 88.2, 83.1, 62.5, 37.2, 29.3, 22.3, 13.9.

MS (70 eV, EI), $m/z$ (%) = 192 (M$^+$, 41), 164 (85), 147 (85), 120 (99), 92 (100).

HRMS $m/z$ calc. for C$_{11}$H$_{12}$O$_3$ (192.0786): 192.0780.

IR (ATR) $\nu$ (cm$^{-1}$) = 2942, 2218, 1707, 1676, 1261, 1245, 1187, 1145, 1135, 1015, 747.

Preparation of 3-[4-(trifluoromethyl)phenyl]-2-cyclopenten-1-one (40m)

The cross-coupling reaction of 38d (3.43 mL, 2.40 mmol, 0.70 M in THF) with 4-iodobenzotrifluoride (39f, 544 mg, 2.00 mmol) was performed according to TP4 in 3 h. Flash column chromatography (silica, hexanes:Et$_2$O 1:1 then 1:2) furnished 40m as a colorless solid (333 mg, 74 %).
m.p.: 106.5-108.2 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.78-7.70 (m, 4H), 6.64 (t, $J$=1.5Hz, 1H), 3.09-3.06 (m, 2H), 2.65-2.62 (m, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm) = 208.7, 171.7, 137.4, 132.6 (q, $J$=32Hz), 129.4, 127.0, 125.9 (q, $J$=4Hz), 123.7 (q, $J$=272Hz), 35.3, 28.7.

MS (70 eV, EI), $m/z$ (%) = 226 (M$^+$, 95), 225 (33), 170 (28), 157 (100), 129 (38).

HRMS $m/z$ calc. for C$_{12}$H$_9$F$_3$O (226.0605): 226.0597.

IR (ATR) $\nu$ (cm$^{-1}$) = 2925, 1689, 1601, 1163, 1132, 1110, 1064, 1014, 829.

Preparation of ethyl 4-(2-benzoylcyclopent-1-en-1-yl)benzoate (40n)

![Chemical Structure](image)

The cross-coupling reaction of 38e (3.60 mL, 2.00 mmol, 0.56 M in THF) with ethyl 4-bromobenzoate (39j, 367 mg, 1.60 mmol) was performed according to TP4 over night. Flash column chromatography (silica, hexanes:Et$_2$O 9:1) furnished 40n as a white solid (359 mg, 70 %).

m.p.: 70.5-71.9 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.62-7.87 (m, 4H), 7.33-7.48 (m, 1H), 7.16-7.33 (m, 4H), 4.29 (q, $J$=7.2Hz, 2H), 2.84-3.14 (m, 4H), 2.15 (quin, $J$=7.6Hz, 2H), 1.32 (t, $J$=7.1Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm) = 198.1, 166.1, 144.2, 140.4, 139.7, 136.2, 133.1, 129.3, 129.3, 129.2, 128.4, 127.6, 60.9, 38.0, 37.7, 22.7, 14.2.

MS (70 eV, EI), $m/z$ (%) = 320 (M$^+$, 42), 319 (29), 292 (27), 291 (100), 275 (12), 247 (42), 141 (13), 105 (54), 77 (23).

HRMS $m/z$ calc. for C$_{21}$H$_{20}$O$_3$ (320.1412): 320.1407.

IR (ATR) $\nu$ (cm$^{-1}$) = 3061, 2981, 2961, 2930, 2901, 2868, 2836, 1709, 1645, 1606, 1592, 1578, 1447, 1406, 1365, 1342, 1309, 1266, 1176, 1172, 1104, 1022, 862, 844, 772, 715, 703, 692, 674.
Preparation of ethyl 2-((2-benzoylcyclopent-1-en-1-yl)methyl)acrylate (40)

The allylation reaction of 38e (3.60 mL, 2.00 mmol, 0.56 m in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 m in THF) and ethyl (2-bromomethyl)acrylate (39b, 347 mg, 1.80 mmol) was performed according to TP3 over night. Flash column chromatography (silica, pentane:Et₂O 9:1) furnished 40 as a colorless oil (404 mg, 79%).

\[ \text{H-NMR (300 MHz, CDCl₃) } \delta (ppm) = 7.70-7.85 (m, 2H), 7.47-7.56 (m, 1H), 7.35-7.47 (m, 2H), 6.16 (d, J=1.1Hz, 1H), 5.48 (q, J=1.4Hz, 1H), 4.11 (q, J=7.0Hz, 2H), 3.14 (s, 2H), 2.63-2.84 (m, 2H), 2.49 (t, J=7.6Hz, 2H), 1.77-2.05 (m, 2H), 1.21 (t, J=7.1Hz, 3 H).

\[ \text{C-NMR (75 MHz, CDCl₃) } \delta (ppm) = 197.0, 166.7, 148.5, 138.5, 138.2, 137.6, 132.5, 128.8, 128.4, 126.2, 60.7, 37.2, 36.2, 32.2, 22.4, 14.1.

\[ \text{MS (70 eV, EI), } m/z (%) = 284 (M⁺, 18), 211 (10), 184 (15), 105 (100), 77 (20).

\[ \text{HRMS m/z calc. for } C_{8}H_{20}O_{3} (284.1412): 284.1402.

\[ \text{IR (ATR) } \nu (\text{cm}^{-1}) = 3075, 3061, 3027, 2977, 2954, 2937, 2905, 2852, 1712, 1643, 1596, 1578, 1447, 1298, 1267, 1235, 1174, 1141, 1124, 1023, 947, 865, 817, 795, 712, 695.

Preparation of 2-[1-tert-butyl-3-oxoprop-1-en-1-yl]benzaldehyde (40p)

The cross-coupling reaction of 38f (3.80 mL, 2.00 mmol, 0.53 m in THF) with 2-bromobenzaldehyde (39k, 296 mg, 1.60 mmol) was performed according to TP4 in 2 h. Flash column chromatography (silica, hexanes:Et₂O 1:1) furnished 40p as a yellow wax (319 mg, 92%).

\[ \text{H-NMR (300 MHz, CDCl₃) } \delta (ppm) = 10.04 (s, 1H), 9.10 (d, J=8.0Hz, 1H), 8.02 (dd, J =8.0Hz, 1.4Hz, 1H), 7.65 (td, J =7.5Hz, 1.7Hz, 1H), 7.56 (dt, J=7.5Hz, 1.4Hz, 1H), 7.22 (dd, J=7.6Hz, 1.0Hz, 1H), 6.39 (d, J=8.0Hz, 1H), 1.18 (s, 9H).
C. Experimental Section

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 193.0, 190.9, 171.3, 139.3, 134.6, 133.3, 130.2, 129.3, 128.7, 128.7, 38.0, 29.3.

**MS** (70 eV, EI), $m/z$ (%) = 216 (M$^+$, >1), 187 (100), 160 (17), 131 (23), 103 (11), 77 (13), 57 (17), 41 (11).

**HRMS** $m/z$ calc. for C$_{14}$H$_{16}$O$_2$ (216.1150): 216.1158.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 2970, 2850, 2758 (vw), 1684, 1671, 1591, 1480, 1396, 1366, 1264, 1198, 1176, 1132, 878, 826, 803, 781, 754, 713, 702.

**Preparation of ethyl 2-[(2-formylcyclohex-1-en-1-yl)methyl]prop-2-enoate (40q)**

![Chemical Structure](image)

The allylation reaction of 38f (3.85 mL, 2.00 mmol, 0.52 M in THF) with 3-bromocyclohexene (39i, 258 mg, 1.60 mmol) was performed according to TP3 in 30 min. Flash column chromatography (silica, pentane:Et$_2$O 95:5) furnished 40q as a colorless oil (294 mg, 96%).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 10.36 (d, $J$=8.3Hz, 1H), 5.84 (dd, $J$=8.2Hz, 1.2Hz, 1H), 5.77-5.58 (m, 2H), 3.35-3.14 (m, 1H), 2.23-2.09 (m, 3H ), 2.00-1.81 (m, 1H), 1.79-1.51 (m, 2H), 1.14 (s, 9H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 191.2, 188.1, 152.7, 145.9, 136.1, 64.3, 64.0, 58.9, 45.4, 29.7, 26.5.

**MS** (70 eV, EI), $m/z$ (%) = 192 (M$^+$, 23), 163 (85), 135 (100), 108 (75), 79 (86), 57 (81), 41 (89).

**HRMS** $m/z$ calc. for C$_{13}$H$_{20}$O (192.1514): 192.1508.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 2938, 2868, 1668, 1614, 1449, 1394, 1366, 1208, 1152, 1134, 1030, 890, 855, 722, 664.
Preparation of \((E)\)-ethyl 4-(4-fluorophenyl)-2-methylene-6-oxohex-4-enoate (40r)

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CHO} \\
\text{F} & \\
\end{align*}
\]

The allylation reaction of 38g (6.30 mL, 2.00 mmol, 0.32 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (39b, 347 mg, 1.80 mmol) was performed according to TP3 in 1 h. Flash column chromatography (silica, pentane:Et₂O 7.5:2.5) furnished 40r as a yellow oil (466 mg, 95 %).

\[^1\text{H-NMR (300 MHz, CDCl}_3\text{)}\delta (\text{ppm}) = 10.05 (d, J=7.7\text{Hz}, 1H), 7.39-7.54 (m, 2H), 6.96-7.15 (m, 2H), 6.43 (d, J=7.7\text{Hz}, 1H), 6.27 (s, 1H), 5.49 (t, J=1.8\text{Hz}, 1H), 4.23 (q, J=7.0\text{Hz}, 2H), 4.02 (s, 2H) 1.30 (t, J=7.0\text{Hz}, 3H).
\]

\[^{13}\text{C-NMR (75 MHz, CDCl}_3\text{)}\delta (\text{ppm}) = 191.0, 166.1, 163.8 (d, J=251.3\text{Hz}), 156.2, 137.3, 135.0 (d, J=3.4\text{Hz}), 128.8, 128.7 (d, J=8.4\text{Hz}), 127.0, 116.0 (d, J=21.6\text{Hz}), 61.3, 31.6, 14.1.
\]

\[^\text{MS (70 eV, EI), } m/z (\%) = 262 (M^+, 9), 233 (22), 205 (20), 190 (12), 189 (100), 159 (13), 146 (22), 133 (9).
\]

\[^\text{HRMS } m/z \text{ calc. for C}_{15}\text{H}_{15}\text{FO}_3 (262.1005): 262.1003.
\]

\[^\text{IR (ATR) } \nu (\text{cm}^{-1}) = 3116, 3062, 2982, 2937, 2910, 2857, 2762, 2724, 1712, 1662, 1600, 1506, 1225, 1197, 1178, 1159, 1110, 1096, 1027, 1017, 855, 834, 769, 717, 654.
\]

Preparation of \((E)\)-ethyl 4-(4-methoxyphenyl)-2-methylene-6-oxohex-4-enoate (40s)

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CHO} \\
\text{MeO} & \\
\end{align*}
\]

The allylation reaction of 38h (5.40 mL, 2.00 mmol, 0.37 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (39b, 347 mg, 1.80 mmol) was performed according to TP3 in 1 h. Flash column chromatography (silica, pentane:Et₂O 6:4) furnished 40s as a yellow oil (439 mg, 89 %).

\[^1\text{H-NMR (300 MHz, CDCl}_3\text{)}\delta (\text{ppm}) = 10.02 (d, J=7.7 \text{Hz}, 1H), 7.35-7.59 (m, 2H), 6.80-7.00 (m, 2H), 6.47 (d, J=7.7\text{Hz}, 1H), 6.26 (s, 1H), 5.49 (s, 1H), 4.24 (q, J=7.2\text{Hz}, 2H), 4.01 (s, 2H), 3.82 (s, 3H), 1.30 (t, J=7.2\text{Hz}, 3H).
\]
$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 191.2, 166.3, 161.4, 156.9, 137.7, 130.8, 128.3, 127.2, 126.8, 114.2, 61.2, 55.3, 31.2, 14.1.

**MS** (70 eV, EI), $m/z$ (%) = 274 (M$^+$, 9), 246 (11), 245 (19), 228 (20), 217 (15), 202 (14), 201 (100), 199 (18), 173 (19), 171 (13), 161 (27), 158 (15), 133 (11), 128 (11).

**HRMS** $m/z$ calc. for C$_{16}$H$_{18}$O$_4$ (274.1205): 274.1198.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3093, 3037, 2978, 2961, 2936, 2905, 2839, 1710, 1661, 1600, 1567, 1510, 1462, 1442, 1291, 1246, 1177, 1140, 1115, 1027, 961, 828, 752.

### Preparation of (Z)-ethyl 4-(4-chlorophenyl)-4-oxo-3-phenylbut-2-enoate (40t)

![Chemical Structure](image)

The acylation reaction of 38i (3.60 mL, 2.00 mmol, 0.56 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (39l, 280 mg, 1.60 mmol) was performed according to TP3 in 3 h. Flash column chromatography (silica, pentane:Et$_2$O 8.5:1.5) furnished 40t as a white solid (427 mg, 85%).

**m.p.**: 126.6-129.3 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.82-7.95 (m, 2H), 7.29-7.54 (m, 7H), 6.50 (s, 1H), 4.09 (q, $J$=7.2Hz, 2H), 1.15 (t, $J$=7.1Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 195.2, 165.0, 155.0, 139.9, 134.5, 133.9, 130.6, 130.2, 129.2, 129.1, 126.9, 118.0, 61.0, 13.9.

**MS** (70 eV, EI), $m/z$ (%) = 314 (M$^+$, 36), 286 (14), 269 (10), 141 (25), 139 (100), 111 (12).

**HRMS** $m/z$ calc. for C$_{18}$H$_{15}$ClO$_3$ (314.0710): 314.0702.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3089, 3066, 3030, 2991, 2980, 2903, 1703, 1671, 1615, 1585, 1571, 1367, 1349, 1340, 1288, 1280, 1219, 1194, 1185, 1175, 1156, 1093, 1021, 1009, 971, 966, 914, 869, 845, 838, 776, 762, 736, 688.
Preparation of (E)-diethyl 5-methylene-3-phenylhex-2-enedioate (40u)

The allylation reaction of 38i (3.60 mL, 2.00 mmol, 0.56 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (39b, 307 mg, 1.60 mmol) was performed according to TP3 over night. Flash column chromatography (silica, pentane:Et₂O 9:1) furnished 40u as a yellow oil (364 mg, 79 %).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.28-7.52 (m, 5H), 6.31 (s, 1H), 6.17 (t, J=1.4Hz, 1H), 5.43 (t, J=1.5Hz, 1H), 4.07-4.31 (m, 6H), 1.18-1.40 (m, 6H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 166.8, 166.0, 155.3, 140.3, 137.7, 129.1, 128.5, 126.7, 125.2, 119.5, 60.8, 60.1, 32.4, 14.2, 14.1.

MS (70 eV, EI), m/z (%) = 288 (M⁺, 6), 243 (34), 242 (100), 214 (19), 213 (12), 185 (17), 170 (29), 169 (68), 142 (22), 141 (91), 115 (21).

HRMS m/z calc. for C₁₇H₂₀O₄ (288.1362): 288.1358.

IR (ATR) ν (cm⁻¹) = 3104, 3083, 3058, 2980, 2937, 2904, 2872, 1708, 1624, 1446, 1367, 1268, 1251, 1197, 1164, 1157, 1131, 1095, 1050, 1022, 941, 877, 816, 767, 696.

5.4.1 Preparation of 1-Substituted Tetrahydropthalazines

Preparation of 1-phenyl-5,6,7,8-tetrahydropthalazine (41a)

The acylation reaction of 38a (3.10 mL, 2.00 mmol, 0.65 M in THF) with benzoyl chloride (225 mg, 1.60 mmol) was performed in 14 h followed by the reaction hydrazine hydrate (300 mg, 6.00 mmol) according to TP5. Flash column chromatography (silica, CH₂Cl₂:EtOAc 9:1) furnished 41a as a colorless solid (166 mg, 54 %).

m.p.: 80.0-84.2 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 8.86 (s, 1H), 7.30-7.64 (m, 5H), 2.83 (t, J=6.3Hz, 2H), 2.65 (t, J=6.2Hz, 2H), 1.73-1.94 (m, 4H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 160.2, 151.5, 138.7, 137.7, 135.8, 134.3, 129.6, 127.3, 26.4, 26.1, 22.0, 21.3.
**Preparation of 1-(3-chlorophenyl)-5,6,7,8-tetrahydrophthalazine (41b)**

![Chemical Structure](image)

The acylation reaction of 38a (3.77 mL, 2.00 mmol, 0.53 M in THF) with 3-chlorobenzoyl chloride (210 mg, 1.20 mmol) was performed in 14 h followed by the reaction hydrazine hydrate (300 mg, 6.00 mmol) according to TP5. Flash column chromatography (silica, CH2Cl2:EtOAc 1:1) furnished 41b as a brown solid (160 mg, 54%).

**m.p.:** 110.3-112.0 °C.

**1H-NMR** (300 MHz, CDCl3) δ (ppm) = 8.85 (s, 1H), 7.56-7.51 (m, 1H), 7.46-7.36 (m, 3H), 2.81 (t, J=6.3Hz, 2H), 2.64 (t, J=6.2Hz, 2H), 1.93-1.72 (m, 4H).

**13C-NMR** (75 MHz, CDCl3) δ (ppm) = 160.1, 151.5, 138.7, 137.6, 135.7, 134.3, 129.6, 129.2, 128.9, 127.2, 26.4, 26.0, 22.0, 21.3.

**MS** (70 eV, EI), m/z (%): 244 (M⁺, 61), 243 (100), 229 (14), 109 (7), 165 (8), 153 (8), 152 (16).

**HRMS** (EI) m/z calc. for C_{14}H_{13}ClN_{2} (245.0846 [M⁺+H]): 245.0839.

**IR** (ATR) υ (cm⁻¹) = 2944, 2855, 1562, 1425, 1398, 1331, 1231, 1076, 1022, 1006, 956, 885, 860, 828, 800, 768, 728, 700.

**Preparation of 1-thiophen-2-yl-5,6,7,8-tetrahydrophthalazine (41c)**

![Chemical Structure](image)

The acylation reaction of 38a (4.00 mL, 3.00 mmol, 0.75 M in THF) with 2-thiophenecarbonyl chloride (264 mg, 1.80 mmol) was performed in 14 h followed by
the reaction hydrazine hydrate (450 mg, 9.00 mmol) according to TP5. Flash column chromatography (silica, CH₂Cl₂:EtOAc 9:1) furnished 41c as a yellow solid (164 mg, 49 %).

m.p.: 120.6-123.4 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 8.72 (s, 1H), 7.52 (dd, J=3.7Hz, 1.1Hz, 1H), 7.49 (dd, J=5.0Hz, 1.1Hz, 1H), 7.15 (dd, J=5.2Hz, 3.7Hz, 1H), 2.99-2.86 (m, 2H), 2.84-2.71 (m, 2H), 1.96-1.76 (m, 4H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 154.8, 150.6, 140.5, 137.2, 134.1, 128.6, 128.5, 127.4, 26.9, 26.3, 22.2, 21.1.

MS (70 eV, El), m/z (%): 216 (M⁺, 100), 215 (68), 160 (50), 91 (49), 77 (54), 44 (67), 41 (66).

HRMS (EI) m/z calc. for C₁₂H₁₂N₂S (216.0721): 216.0719.

IR (ATR): v (cm⁻¹) = 2940, 2860, 1559, 1542, 1437, 1414, 1365, 1300, 1114, 1053, 940, 928, 858, 836, 798, 708.

5.5 PREPARATION OF ALKENYL ZINC REAGENTS OF FROM LESS ACTIVATED ALKENYL BROMIDES

Preparation of (2-(ethoxycarbonyl)cyclohex-1-en-1-yl)zinc chloride (43a)

According to TP2, the zinc reagent 43a was prepared from ethyl 2-bromocyclohex-1-ene-1-carboxylate (42a, 2.33 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and ZnCl₂ (11.0 mL, 1 M in THF) in 14 h at 25 °C. Titration with iodine indicates a concentration of 0.33 M (70 %).

Preparation of (2-(ethoxycarbonyl)cyclopent-1-en-1-yl)zinc chloride (43b)

According to TP2, the zinc reagent 7c was prepared from ethyl 2-bromocyclopent-1-ene-1-carboxylate (42b, 438 mg, 2.00 mmol) using Mg turnings (122 mg, 5.00 mmol), LiCl (127 mg, 3.00 mmol) and ZnCl₂ (2.2 mL, 1 M in THF) in 14 h at 25 °C. Titration with iodine indicates a concentration of 0.42 M (84 %).
Preparation of \((\text{Z})-(1\text{-methoxy}-1\text{-oxohex}-2\text{-en-3-yl})\text{zinc chloride (43c)}\)

According to TP2, the zinc reagent 43c was prepared from \((\text{Z})\)-methyl 3-bromohex-2-enoate (42c, 2.07 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and ZnCl\(_2\) (11.0 mL, 1 M in THF) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.26 M (50%).

Preparation of 2-bromocyclopentenzinc chloride (43d)

According to TP2, the zinc reagent 43d was prepared from 1,2-dibromocyclopentene (42d, 2.26 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and ZnCl\(_2\) (11.0 mL, 1 M in THF) in 8 h at 25 °C. Titration with iodine indicates a concentration of 0.51 M (98%).

Preparation of ((1S,4R)-3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)zinc chloride (43e)

According to TP2, the zinc reagent 43e was prepared from 2,3-dibromobicyclo-[2.2.1]hepta-2,5-diene (43e, 2.50 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and ZnCl\(_2\) (11.0 mL, 1 M in THF) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.39 M (70%).

Preparation of (2-(phenylthio)cyclopent-1-en-1-yl)zinc chloride (43f)

According to TP2, the zinc reagent 43f was prepared from (2-bromocyclopent-1-en-1-yl)(phenyl)sulfane (42f, 2.55 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and ZnCl\(_2\) (11.0 mL, 1 M in THF) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.35 M (68%).
5.6 Reactions of Alkenyl Zinc Reagents of Type 43 with Electrophiles

Preparation of ethyl 2-(5-(trimethylsilyl)thiophen-2-yl)cyclohex-1-enecarboxylate (44a)

The cross-coupling reaction of 43a (4.00 mL, 2.00 mmol, 0.50 M in THF) with 2-bromo-5-trimethylsilylthiophene (39m, 470 mg, 2.00 mmol) was performed according to TP4 in 3 h. Flash column chromatography (silica, hexanes:EtO 1:1 then 9:1) furnished 44a as a colorless solid (436 mg, 71%).

m.p.: 106.5-108.2 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.07 (d, $J$=3.5Hz, 1H), 6.98 (d, $J$=3.3Hz, 1H), 4.03 (q, $J$=7.2Hz, 2H), 2.46-2.38 (m, 4H), 1.75-1.68 (m, 4H), 1.01 (t, $J$=7.2Hz, 3H), 0.28 (s, 9H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm) = 170.8, 149.3, 139.7, 134.9, 133.6, 129.7, 126.0, 60.5, 32.4, 27.2, 22.4, 21.6, 13.6, -0.1.

MS (70 eV, EI), m/z (%) = 308 (M$^+$, 100), 293 (41), 262 (18), 235 (43), 234 (30), 103 (20).

HRMS m/z calc. for C$_{16}$H$_{24}$O$_2$SSi (308.1266): 308.1246.

IR (ATR) $\nu$ (cm$^{-1}$) = 2936, 1709, 1277, 1247, 1218, 1046, 990, 836, 804, 755.

Preparation of ethyl 5-[2-(ethoxycarbonyl)cyclopent-1-en-1-yl]thiophene-2-carboxylate (44b)

The cross-coupling reaction of 43b (6.25 mL, 2.00 mmol, 0.32 M in THF) with ethyl 5-bromothiophene-2-carboxylate (39n, 376 mg, 1.60 mmol) was performed according to TP4 in 1.5 h. Flash column chromatography (silica, hexanes:EtO 9:1) furnished 44b as a colorless solid (373 mg, 79%).
C. EXPERIMENTAL SECTION

m.p.: 64.2-65.5 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.70 (d, $J$=3.9Hz, 1H), 7.46 (d, $J$=3.9Hz, 1H), 4.35 (q, $J$=7.1 Hz, 2H), 4.27 (q, $J$=7.1Hz, 2H), 3.00 (tt, $J$=7.7Hz, 2.3Hz, 2H), 2.91-2.83 (m, 2H), 1.98 (quint, $J$=7.7Hz, 2H), 1.38 (t, $J$=7.2Hz, 3H), 1.32 (t, $J$=7.2Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 165.9, 162.4, 143.8, 143.0, 134.7, 132.6, 129.9, 129.7, 61.1, 60.5, 39.7, 35.9, 21.5, 14.3, 14.2.

MS (70 eV, EI), $m/z$ (%) = 294 (M$^+$, 100), 265 (30), 251 (45), 223 (16), 222 (58), 221 (36), 193 (11), 147 (12).

HRMS $m/z$ calc. for C$_{15}$H$_{18}$O$_4$S (294.0926): 294.0920.

IR (ATR) $\nu$ (cm$^{-1}$) = 2982, 2961, 1695, 1599, 1519, 1474, 1440, 1366, 1328, 1216, 1098, 1040, 1022, 824, 752.

Preparation of ethyl 2-[2-(ethoxycarbonyl)prop-2-en-1-yl]cyclopent-1-ene-1-carboxylate (44c)

![Structure of 44c]

The allylation reaction of 43b (6.25 mL, 2.00 mmol, 0.32 M in THF) with CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (39b, 309 mg, 1.60 mmol) was performed according to TP3 in 1.5 h. Flash column chromatography (silica, pentane:Et$_2$O 9:1) furnished 44c as a colorless oil (348 mg, 86%).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 6.23-6.18 (m, 1H), 5.54-5.49 (m, 1H), 4.26-4.12 (m, 4H), 3.66-3.61 (m, 2H), 2.69-2.60 (m, 2H), 2.49-2.39 (m, 2H), 1.81 (quint, $J$=7.7 Hz, 2H), 1.33-1.21 (m, 6H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 167.0, 165.9, 155.1, 137.8, 129.4, 125.5, 60.7, 59.7, 37.9, 33.6, 31.9, 21.5, 14.3, 14.1.

MS (70 eV, EI), $m/z$ (%) = 252 (M$^+$, 2), 206 (100), 149 (56), 134 (35), 133 (75), 105 (68), 79 (31).

HRMS $m/z$ calc. for C$_{14}$H$_{20}$O$_4$ (252.1362): 252.1353.

IR (ATR) $\nu$ (cm$^{-1}$) = 2980, 1706, 1631, 1446, 1368, 1255, 1174, 1144, 1107, 1026, 946, 771.
Preparation of (Z)-methyl 3-(4-chlorobenzoyl)hex-2-enoate (44d)

The acylation reaction of 43c (7.70 mL, 2.00 mmol, 0.26 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (39l, 315 mg, 1.80 mmol) was performed according to TP3 in 1 h. Flash column chromatography (silica, pentane:Et2O 9:1) furnished 44d as a yellow oil (412 mg, 86%).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) = 7.75-7.90 (m, 2H), 7.35-7.51 (m, 2H), 5.99 (t, $J=1.6$Hz, 1H), 3.55 (s, 3H), 2.36 (dt, $J=7.8$Hz, 1.6Hz, 2H), 1.46-1.61 (m, 2H), 0.96 (t, $J=7.4$Hz, 3H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) = 196.9, 165.4, 159.0, 139.9, 133.5, 129.9, 129.1, 118.3, 51.7, 37.1, 20.3, 13.6.

MS (70 eV, EI), $m/z$ (%) = 266 (M$^+$, 3), 236 (10), 235 (16), 234 (23), 199 (23), 172 (10), 171 (30), 139 (100), 111 (36), 75 (14).

HRMS $m/z$ calc. for C$_{14}$H$_{15}$ClO$_3$ (266.0710): 266.0712.

IR (ATR) $\nu$ (cm$^{-1}$) = 3095, 3071, 3033, 2991, 2962, 2950, 2927, 2904, 2875, 1718, 1671, 1635, 1586, 1571, 1436, 1398, 1338, 1286, 1251, 1232, 1195, 1167, 1122, 1107, 1085, 1023, 1012, 960, 930, 894, 840, 829, 755, 742, 729, 680, 653.

Preparation of (Z)-6-ethyl 1-methyl 5-methylene-3-propylhex-2-enedioate (44e)

The allylation reaction of 43c (7.70 mL, 2.00 mmol, 0.26 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (39b, 348 mg, 1.80 mmol) was performed according to TP3 in 2 h. Flash column chromatography (silica, pentane:Et2O 9.5:0.5) furnished 44e as a colorless oil (368 mg, 77%).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 6.21 (q, $J=1.1$Hz, 1H), 5.81 (s, 1H), 5.48 (q, $J=1.7$Hz, 1H), 4.20 (q, $J=7.0$Hz, 2H), 3.52-3.83 (m, 5H), 1.97-2.18 (m, 2H), 1.39-1.55 (m, 2H), 1.28 (t, $J=7.1$Hz, 3H), 0.89 (t, $J=7.5$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 166.9, 166.6, 159.9, 137.5, 125.3, 117.2, 60.8, 50.9, 39.9, 33.2, 20.8, 14.1, 13.7.
**Preparation of 1-bromo-2-(3-cyclohexen-1-yl)cyclopentene (44f)**

![1-bromo-2-(3-cyclohexen-1-yl)cyclopentene structure]

The allylation reaction of 43d (4.30 mL, 2.40 mmol, 0.56 M in THF) with CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and 3-bromocyclohexene (39i, 322 mg, 2.00 mmol) was performed according to TP3 in 1 h. Flash column chromatography (silica, hexanes) furnished 44f as a colorless oil (392 mg, 86%).

**\( ^1H\)-NMR** (300 MHz, CDCl\( _3\)) \( \delta \) (ppm) = 5.85-5.70 (m, 1H), 5.45-5.35 (m, 1H), 3.40-3.30 (m, 1H), 2.70-2.55 (m, 2H), 2.35-2.20 (m, 2H), 2.20-1.40 (m, 8H).

**\( ^13C\)-NMR** (75 MHz, CDCl\( _3\)) \( \delta \) (ppm) = 143.9, 128.8, 128.2, 115.2, 39.8, 36.7, 31.1, 26.7, 24.7, 21.8, 21.7.

**MS** (70 eV, EI), \( m/z \) (%) = 226 (M\(^+\), 7), 147 (100), 119 (37), 91 (57), 91 (57).

**HRMS** \( m/z \) calc. for C\(_{14}\)H\(_{15}\)Br (226.0357): 226.0335.

**IR** (ATR) \( \nu \) (cm\(^{-1}\)) = 2930, 2855, 1708, 1652, 1445, 1316, 1044, 917, 881, 722.

**Preparation of (2-bromocyclopent-1-en-1-yl)(2-bromophenyl)methanone (44g)**

![2-bromocyclopent-1-en-1-yl)(2-bromophenyl)methanone structure]

The acylation reaction of 44d (3.51 mL, 2.00 mmol, 0.57 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.0 M in THF) and 2-bromobenzoyl chloride (39d, 527 mg, 2.40 mmol) was performed according to TP3 in 4 h. Flash column chromatography (silica, hexanes:CH\(_2\)Cl\(_2\) 4:1) furnished 44g as a colorless oil (421 mg, 64%).
**C. Experimental Section**

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.67-7.52 (m, 1H), 7.49-7.19 (m, 3H), 2.90 (tt, $J$=7.8Hz, 2.3Hz, 2H), 2.84-2.74 (m, 2H), 2.04 (quint, $J$=7.7Hz, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 193.4, 141.2, 139.5, 133.1, 133.0, 131.3, 128.9, 127.5, 119.5, 43.9, 33.4, 21.5.

**MS** (70 eV, EI), $m/z$ (%) = 330 (M$^+$, 14), 250 (96), 249 (100), 185 (51), 183 (51), 170 (50).

**HRMS** $m/z$ calc. for C$_{12}$H$_{10}$Br$_2$O (329.9255): 329.9074.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 2925, 1647, 1588, 1431, 1330, 1298, 1250, 1025, 744, 683.

**Preparation of 3-(2-bromocyclopent-1-en-1-yl)cyclohexanone (44h)**

![Image of 3-(2-bromocyclopent-1-en-1-yl)cyclohexanone](image)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenyl zinc reagent 43d (4.3 mL, 2.40 mmol, 0.56 M in THF) and cooled to -40 °C. CuCN·2LiCl (2.40 mL, 2.40 mmol, 1.0 M in THF) was added, followed by a solution of cyclohexenone (39o, 192 mg, 2.00 mmol) and chlorotrimethylsilane (0.8 mL, 5 mmol) in THF (1 mL) and the reaction mixture was stirred for 0.5 h at -40 °C and then 2 h at room temperature. The reaction was quenched with sat. NH$_4$Cl/NH$_3$ (9:1) solution (10 mL) and extracted with Et$_2$O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et$_2$O 9:1) to give 44h as a colorless oil (338 mg, 70%).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 3.04-2.91 (m, 1H), 2.68-2.58 (m, 2H), 2.47-2.20 (m, 5H), 2.19-2.05 (m, 1H), 2.01-1.88 (m, 2H), 1.85-1.53 (m, 4H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 210.5, 141.6, 116.0, 45.1, 41.1, 39.8, 39.5, 30.3, 29.0, 25.4, 21.5.

**MS** (70 eV, EI), $m/z$ (%) = 242 (M$^+$, >1), 163 (35), 91 (16), 70 (16), 61 (16), 43 (100).

**HRMS** $m/z$ calc. for C$_{11}$H$_{15}$BrO (242.0306): 242.0288.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 2935, 1699, 1652, 1446, 1319, 1261, 1221, 1061, 926, 755.
Preparation of 3-(2-bromocyclopent-1-en-1-yl)cyclohex-3-enone (44i)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenylzinc reagent 43d (4.3 mL, 2.40 mmol, 0.56 M in THF) and cooled to -40 °C. CuCN·2LiCl (2.40 mL, 2.40 mmol, 1.0 M in THF) was added, followed by 3-iodocyclohexenone (39p, 444 mg, 2.00 mmol) and the reaction mixture was stirred for 0.5 h at -40 °C and then 2 h at 0 °C. The reaction was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL) and extracted with Et₂O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et₂O 9:1) to give 44i as a colorless oil (314 mg, 65 %).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 6.10 (s, 1H), 2.85-2.70 (m, 4H), 2.65-2.50 (m, 2H), 2.45-2.35 (m, 2H), 2.20-1.90 (m, 4H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 200.1, 155.9, 137.9, 127.2, 123.7, 43.7, 37.4, 34.9, 28.3, 22.9, 21.7.

MS (70 eV, EI), m/z (%) = 242 (31), 240 (M⁺, 32), 161 (38), 133 (100), 105 (44).

HRMS m/z calc. for C₁₁H₁₃BrO (240.0150): 240.0146.

IR (ATR) ν (cm⁻¹) = 2945, 1658, 1589, 1325, 1254, 1188, 1133, 956, 884, 732.

Preparation of 1-bromo-2-(2-ethoxycarbonylthynyl)cyclopentene (44j)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenylzinc reagent 43d (3.80 mL, 2.00 mmol, 0.53 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.0 M in THF) was added, followed by a solution of ethyl 3-bromoprop-2-ynoate (39c, 425 mg, 2.40 mmol) in THF (2 mL) and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na₂SO₄ and
concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et₂O 10:1) to give 44j as a colorless oil (377 mg, 78 %).

\[ ^1H-NMR \quad (300 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 4.27 \text{ (q, } J=7.1\text{Hz, } 2\text{H}), \quad 2.78 \text{ (tt, } J=7.7\text{Hz, } 2.6\text{Hz, } 2\text{H}), \quad 2.61-2.51 \text{ (m, } 2\text{H}), \quad 2.11-1.97 \text{ (m, } 2\text{H}), \quad 1.33 \text{ (t, } J=7.1\text{Hz, } 3\text{H}). \]

\[ ^{13}C-NMR \quad (75 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 153.9, \quad 134.8, \quad 121.9, \quad 85.9, \quad 81.4, \quad 62.1, \quad 40.9, \quad 35.5, \quad 22.6, \quad 14.1. \]

**MS** (70 eV, EI), \( m/z \) (%) = 242 (M⁺, 4), 91 (100), 90 (53), 89 (57), 63 (62), 62 (53).

**HRMS** \( m/z \) calc. for C₁₀H₁₁BrO₂ (241.9942): 241.9936.

**IR** (ATR) \( \nu (\text{cm}^{-1}) \) = 2981, 2204, 1704, 1366, 1268, 1207, 1162, 1092, 1020, 746.

**Preparation of 5-(2-bromocyclopent-1-en-1-yl)pyridine-3-carbonitrile (44k)**

\[
\begin{align*}
\text{Br} & \quad \text{CN} \\
\text{C} & \quad \text{C}
\end{align*}
\]

The cross-coupling reaction of 43d (3.92 mL, 2.00 mmol, 0.51 M in THF) with 5-bromo-3-cyanopyridine (39e, 403 mg, 2.20 mmol) was performed according to **TP4** in 3 h. Flash column chromatography (silica, hexanes:Et₂O 3:1) furnished 44k as a brown solid (271 mg, 54 %).

**m.p.**: 74.8-76.7 °C.

\[ ^1H-NMR \quad (300 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 9.01 \text{ (d, } J=2.2\text{Hz, } 1\text{H}), \quad 8.77 \text{ (d, } J=1.9 \text{ Hz, } 1\text{H}), \quad 8.25 \text{ (t, } J=2.1\text{Hz, } 1\text{H}), \quad 2.97-2.86 \text{ (m, } 2\text{H}), \quad 2.86-2.75 \text{ (m, } 2\text{H}), \quad 2.18-2.04 \text{ (m, } 2\text{H}). \]

\[ ^{13}C-NMR \quad (75 \text{ MHz, CDCl}_3) \delta (\text{ppm}) = 151.5, \quad 150.4, \quad 137.5, \quad 133.3, \quad 132.2, \quad 122.2, \quad 116.4, \quad 109.5, \quad 42.5, \quad 35.4, \quad 21.8. \]

**MS** (70 eV, EI), \( m/z \) (%) = 248 (M⁺, 34), 169 (100), 168 (23), 142 (12), 115 (12), 63 (11).

**HRMS** \( m/z \) calc. for C₁₁H₉BrN₂ (247.9949): 247.9930.

**IR** (ATR) \( \nu (\text{cm}^{-1}) \) = 2943, 2844, 2231, 1620, 1559, 1431, 1423, 1308, 1289, 1186, 1158, 1092, 1026, 932, 904, 787, 701, 666.
Preparation of ethyl 4-((1S,4R)-3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)benzoate (44l)

The cross-coupling reaction of 43e (5.15 mL, 2.00 mmol, 0.39 M in THF) with ethyl 4-iodobenzoate (39h, 442 mg, 1.60 mmol) was performed according to TP4 in 5 h. Flash column chromatography (silica, pentane:EtO 50:1) furnished 44l as a yellow oil (306 mg, 60 %).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.96-8.08 (m, 2H), 7.51-7.76 (m, 2H), 6.77 -7.09 (m, 2H), 4.37 (q, $J$=7.0Hz, 2H), 3.86-4.02 (m, 1H), 3.60-3.78 (m, 1H), 2.36 (dt, $J$=6.4Hz, 1.7Hz, 1H), 2.16 (dt, $J$=6.4Hz, 1.8Hz, 1H), 1.39 (t, $J$=7.1Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 166.3, 147.6, 141.7, 141.4, 139.3, 132.7, 129.4, 128.9, 125.7, 70.3, 60.9, 60.8, 54.8, 14.3.

MS (70 eV, EI), m/z (%) = 320 (M$^+$, 70), 318 (M$^+$, 70), 240 (14), 239 (63), 213 (13), 211 (19), 168 (10), 167 (63), 166 (86), 165 (100), 152 (14), 66 (35).

HRMS m/z calc. for C$_{16}$H$_{15}$BrO$_2$ (318.0255): 318.0253.

IR (ATR) $\nu$ (cm$^{-1}$) = 3119, 3066, 2979, 2938, 2904, 2869, 1756, 1710, 1605, 1407, 1366, 1269, 1251, 1181, 1101, 1018, 854, 771, 761, 718, 701.

Preparation of ethyl 2-(((1S,4R)-3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)methyl)-acrylate (44m)

The allylation reaction of 43e (5.15 mL, 2.00 mmol, 0.39 M in THF) with CuCN-2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (39b, 348 mg, 1.80 mmol) was performed according to TP3 overnight. Flash column chromatography (silica, pentane:EtO 50:1) furnished 44m as a yellow oil (310 mg, 61 %).
C. EXPERIMENTAL SECTION

\[^{1}\text{H-NMR}\] (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 6.60-6.96 (m, 2H), 6.19 (d, \(J=1.1\)Hz, 1H), 4.20 (q, \(J=6.8\)Hz, 2H), 3.51 (bs, 1H), 3.40 (bs, 1H), 3.04-3.29 (m, 2H), 2.21 (dt, \(J=6.1\)Hz, 1.5Hz, 1H), 2.03 (dt, \(J=6.1\)Hz, 1.8Hz, 1H), 1.30 (t, \(J=7.2\)Hz, 3H), 0.03-0.22 (m, 1H).

\[^{13}\text{C-NMR}\] (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 166.9, 147.9, 142.0, 141.5, 136.5, 131.6, 126.0, 71.7, 60.8, 58.2, 53.7, 31.8, 14.2.

**MS** (70 eV, EI), \(m/z\) (%) = 284 (M\(^+\), 16), 282 (M\(^+\), 16), 218 (17), 216 (18), 214 (9), 213 (9), 175 (34), 157 (9), 131 (19), 130 (28), 129 (100), 128 (41), 127 (15), 115 (20), 103 (19), 91 (20), 66 (23), 43 (13).

**HRMS** \(m/z\) calc. for C\(_{13}\)H\(_{15}\)BrO\(_2\) (282.0255): 282.0250.

**IR** (ATR) \(\nu\) (cm\(^{-1}\)) = 3067, 2977, 2938, 2905, 2869, 1713, 1629, 1368, 1295, 1250, 1219, 1175, 1140, 1114, 1026, 945, 842, 812, 705.

**Preparation of ethyl 4-(2-(phenylthio)cyclopent-1-en-1-yl)benzoate (44n)**

\[
\text{SPh} \\
\text{CO}_2\text{Et}
\]

The cross-coupling reaction of 43f (5.70 mL, 2.00 mmol, 0.35 M in THF) with ethyl 4-iodobenzoate (39h, 442 mg, 1.60 mmol) was performed according to TP4 in 3 h. Flash column chromatography (silica, pentane:Et\(_2\)O 9:5:0,5) furnished 44n as a colorless oil (420 mg, 81%).

\[^{1}\text{H-NMR}\] (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 7.94-8.12 (m, 2H), 7.55-7.71 (m, 2H), 7.15-7.47 (m, 5H), 4.38 (q, \(J=7.2\)Hz, 2H), 2.84-2.99 (m, 2H), 2.46-2.62 (m, 2H), 1.96 (quin, \(J=7.3\)Hz, 2H), 1.39 (t, \(J=7.1\)Hz, 3H).

\[^{13}\text{C-NMR}\] (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 166.4, 141.3, 139.8, 133.7, 132.9, 131.7, 129.3, 128.9, 128.7, 127.5, 127.3, 60.8, 38.8, 37.4, 22.0, 14.3.

**MS** (70 eV, EI), \(m/z\) (%) = 324 (M\(^+\), 100), 279 (6), 218 (5), 173 (4), 141 (9), 128 (5), 115 (8).

**HRMS** \(m/z\) calc. for C\(_{20}\)H\(_{20}\)O\(_2\)S (324.1184): 324.1166.

**IR** (ATR) \(\nu\) (cm\(^{-1}\)) = 3070, 3056, 2976, 2952, 2934, 2903, 2843, 1709, 1605, 1575, 1474, 1439, 1405, 1365, 1269, 1181, 1105, 1097, 1022, 850, 771, 741, 700, 690.
Preparation of (4-chlorophenyl)(2-(phenylthio)cyclopent-1-en-1-yl)methanone (44o)

The acylation reaction of 43f (5.70 mL, 2.00 mmol, 0.35 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (39l, 280 mg, 1.60 mmol) was performed according to TP3 overnight. Flash column chromatography (silica, pentane:Et₂O 9.5:0.5) furnished 44o as a white solid (432 mg, 86%).

m.p.: 74.7-76.3 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.63-7.75 (m, 2H), 7.46-7.57 (m, 2H), 7.28-7.46 (m, 5H), 2.80-2.93 (m, 2H), 2.33-2.46 (m, 2H), 1.80-1.97 (m, 2H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 191.2, 159.0, 137.9, 137.7, 134.5, 132.3, 129.6, 129.0, 129.0, 128.5, 128.5, 38.7, 35.7, 23.6.

MS (70 eV, EI), m/z (%) = 314 (M⁺, 61), 236 (18), 203 (22), 175 (15), 147 (13), 142 (12), 141 (14), 139 (100), 111 (54), 110 (35), 109 (10), 77 (16), 75 (12), 65 (15).

HRMS m/z calc. for C₁₈H₁₅ClO₂S (314.0532): 314.0527.

IR (ATR) ν (cm⁻¹) = 3083, 3063, 3045, 2993, 2984, 2913, 1706, 1675, 1615, 1585, 1574, 1366, 1349, 1340, 1288, 1280, 1219, 1194, 1185, 1175, 1156, 1093, 1021, 1009, 971, 966, 914, 869, 846, 773, 764, 736, 688.
6. SYNTHESIS OF FUNCTIONALIZED ADAMANTYLZINC REAGENTS USING A Br/Mg-INSERTION IN THE PRESENCE OF ZnCl₂

6.1 PREPARATION OF STARTING MATERIALS

All reagents were obtained from commercial sources. Compound 45c²⁸⁷ was prepared according to a literature-known procedure.

**Preparation of ethyl 3-bromoadamantane-1-carboxylate (45b)**

![Chemical Structure](attachment:structure.png)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 3-bromoadamantane-1-carboxylic acid²⁸⁸ (5.2 g, 20 mmol) and dissolved in 100 mL EtOH. After cooling to 0 °C, SOCl₂ (3.57 g, 30 mmol) was added dropwise and the reaction mixture was stirred over night while slowly warming up to room temperature. The reaction was quenched with water (100 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The pure product was obtained without further purification as a colorless oil (5.69 g, 99%).

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 4.11 (q, J=7.2Hz, 2H), 2.47 (s, 2H), 2.23-2.39 (m, 4H), 2.14-2.24 (m, 2H), 1.88 (d, J=3.0Hz, 4H), 1.69 (d, J=1.4Hz, 2H), 1.24 (t, J=7.0Hz, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 175.4, 63.9, 60.5, 49.7, 48.1, 44.9, 37.1, 34.5, 31.7, 14.1.

**MS** (70 eV, EI), m/z (%) = 285 ([M-H]⁺, 2), 208 (13), 207 (100), 161 (16), 133 (45), 91 (14), 79 (13), 43 (18).

**HRMS** (EI), m/z calc. for C₁₃H₁₉BrO₂ (285.0490 ([M-H])): 285.0490 ([M-H]).

**IR** (ATR) ν (cm⁻¹) = 2979, 2935, 2911, 2859, 1724, 1476, 1453, 1365, 1332, 1310, 1244, 1219, 1171, 1149, 1103, 1075, 1020, 1004, 968, 945, 909, 863, 825, 744, 697, 672.

6.2 Typical Procedures

Typical procedure 1 (TP1): LiCl-mediated magnesium insertion in the presence of zinc chloride in adamantyl bromides

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.1 equiv) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, magnesium turnings (2 equiv) were added, followed by THF (1 mL/mmol). The magnesium was activated using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then, ZnCl₂-solution (1.1 equiv, 1 M in THF) was added followed by the substrate (1 equiv). The reaction mixture was stirred at 25 °C until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, solids were allowed to settle or the reaction mixture was centrifuged (10 min, 2000 rpm). The yield of the insertion reaction was determined by iodometric titration of the supernatant solution.

Typical procedure 2 (TP2): Cross-coupling reactions of adamantyl zinc reagents

The desired aryl halide (0.9 equiv) was added to the freshly prepared zinc reagent followed by Pd(OAc)₂ (1 mol%) and SPhos (2 mol%) and the mixture was stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 3 (TP3): Acylation of adamantyl zinc reagents

The freshly prepared zinc reagent was cooled to -40 °C and the corresponding acyl chloride (0.9 equiv) was added, followed by CuCN·2LiCl (1 M in THF). The reaction mixture was allowed to warm to room temperature. After stirring for the given time, the reaction mixture was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL), washed with sat. NH₄Cl/NH₃ solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.
Typical procedure 4 (TP4): Addition of adamantly zinc reagents to nitroso derivatives

To the freshly prepared adamantyl zinc reagent was added the nitroso derivative (0.9 equiv, 1.0M in THF) and the reaction mixture was stirred for the indicated time at room temperature. EtOH (1 ml/mmol), FeCl₂ (2 equiv) and NaBH₄ (1.1 equiv) were added and the reaction mixture was stirred at room temperature over night. After stirring for the given time, the reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

6.3 Preparation of Functionalized Adamantylzinc Reagents

Preparation of adamantan-1-ylzinc chloride (46a)

According to TP1, the zinc reagent 46a was prepared from 1-bromoadamantane (45a, 1.08 g, 5.0 mmol) using Mg turnings (241 mg, 10.0 mmol), LiCl (233 mg, 5.5 mmol) and ZnCl₂ (5.5 mL, 1 M in THF) in 2 h at 25 °C. Titration against iodine indicates a concentration of 0.32 M (85 %).

Preparation of 3-(ethoxycarbonyl)adamantan-1-ylzinc chloride (46b)

According to TP1, the zinc reagent 46b was prepared from ethyl 3-bromoadamantane-1-carboxylate (45b, 1.44 g, 5.0 mmol) using Mg turnings (241 mg, 10.0 mmol), LiCl (233 mg, 5.5 mmol) and ZnCl₂ (5.5 mL, 1 M in THF) in 2 h at 25 °C. Titration against iodine indicates a concentration of 0.24 M (63 %).

Preparation of spiro[adamantane-2,2′-[1,3]dioxolan]-5-ylzinc chloride (46c)

According to TP1, the zinc reagent 46c was prepared from 5-bromospiro[adamantane-2,2′-[1,3]dioxolane] (45c, 1.37 g, 5.0 mmol) using Mg turnings (241 mg, 10.0 mmol),
LiCl (233 mg, 5.5 mmol) and ZnCl₂ (5.5 mL, 1 M in THF) in 3 h at 25 °C. Titration against iodine indicates a concentration of 0.22 M (57 %).

6.4 FUNCTIONALIZATION OF ADAMANTYLZINC REAGENTS

Preparation of ethyl 4-(adamantan-1-yl)benzoate (48a)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)₂ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and ethyl 4-chlorobenzoate (47c, 166 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et₂O 50:1) furnished 48a as a white solid (222 mg, 87 %).

m.p.: 119.8-120.8 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.90-8.05 (m, 2H), 7.35-7.49 (m, 2H), 4.36 (q, J=7.2Hz, 2H), 2.11 (bs, 3H), 1.92 (d, J=2.8Hz, 6H), 1.70-1.86 (m, 6H), 1.38 (t, J=7.2Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 166.7, 156.5, 129.4, 127.7, 124.9, 60.7, 42.9, 36.7, 36.6, 28.8, 14.4.

MS (70 eV, EI), m/z (%) = 284 (M⁺, 2), 88 (5), 73 (6), 70 (11), 61 (16), 45 (15), 44 (6), 43 (100), 42 (6).

HRMS (EI), m/z calc. for C₁₉H₂₄O₂ (284.1776): 284.1771.

IR (ATR) ν (cm⁻¹) = 2908, 2849, 1712, 1609, 1447, 1408, 1368, 1309, 1275, 1188, 1179, 1102, 1042, 1015, 977, 960, 874, 860, 851, 814, 768, 714, 704.

Preparation of 4-(adamantan-1-yl)benzonitrile (48b)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)₂ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromobenzonitrile (47d, 164 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et₂O 20:1) furnished 48b as a white solid (187 mg, 88 %).
m.p.: 125.3-127.1 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.53-7.66 (m, 2H), 7.37-7.51 (m, 2H), 2.12 (bs, 3H), 1.89 (d, $J$=2.8Hz, 6H), 1.67-1.85 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 156.7, 132.0, 125.8, 119.2, 109.3, 42.7, 36.8, 36.5, 28.7.

MS (70 eV, EI), $m/z$ (%) = 237 (M$^+$, 56), 181 (27), 180 (75), 135 (20), 94 (25), 61 (17), 45 (15), 43 (100).

HRMS (EI), $m/z$ calc. for C$_{17}$H$_{19}$N (237.1517): 237.1503.

IR (ATR) $\nu$ (cm$^{-1}$) = 3069, 3045, 3041, 2915, 2897, 2847, 2233, 1607, 1505, 1448, 1408, 1398, 1343, 1318, 1289, 1260, 1175, 1100, 1067, 1040, 1031, 1019, 974, 850, 834, 805.

**Preparation of 1-(adamantan-1-yl)phenyl)ethanone (48c)**

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 1-(4-bromophenyl)ethanone (47e, 179 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 20:1) furnished 48e as a white solid (192 mg, 84 %).

m.p.: 115.6-116.8 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.91 (d, $J$=8.6Hz, 2H), 7.45 (d, $J$=8.8Hz, 2H), 2.58 (s, 3H), 2.11 (bs, 3H), 1.93 (d, $J$=2.8Hz, 6H), 1.67-1.88 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 197.9, 156.9, 134.6, 128.3, 125.1, 42.9, 36.7, 36.7, 28.8, 26.5.

MS (70 eV, EI), $m/z$ (%) = 254 (M$^+$, 2), 239 (8), 88 (5), 70 (10), 61 (16), 45 (14), 43 (100), 42 (6).

HRMS (EI), $m/z$ calc. for C$_{18}$H$_{22}$O (254.1671): 254.1665.

IR (ATR) $\nu$ (cm$^{-1}$) = 2908, 2848, 1714, 1679, 1602, 1562, 1406, 1359, 1345, 1269, 1244, 1191, 1177, 1104, 1077, 1058, 1041, 1032, 1012, 976, 963, 951, 847, 832, 804, 768, 678.
Preparation of (4-(adamantan-1-yl)phenyl)(methyl)sulfane (48d)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and (4-bromophenyl)-(methyl)sulfane (47f, 183 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 9:1) furnished 48d as a white solid (218 mg, 94%).

**m.p.:** 78.2-80.8 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.19-7.41 (m, 4H), 2.49 (s, 3H), 2.12 (bs, 3H), 1.91 (d, $J$=2.8Hz, 6H), 1.69-1.86 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 148.6, 134.8, 126.9, 125.5, 43.2, 36.8, 35.9, 28.9, 16.3.

**MS** (70 eV, EI), $m/z$ (%) = 258 (M$^+$, 100), 201 (47), 164 (13), 154 (28), 57 (14), 43 (11), 41 (10).

**HRMS** (EI), $m/z$ calc. for C$_{17}$H$_{22}$S (258.1442): 258.1448.

**IR** (ATR) υ (cm$^{-1}$) = 3074, 3055, 3024, 2906, 2897, 2846, 1495, 1446, 1433, 1398, 1342, 1246, 1175, 1101, 1092, 1033, 1010, 963, 824, 804, 796, 737, 718.

Preparation of 4-(adamantan-1-yl)-N,N-dimethylaniline (48e)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromo-N,N-dimethylaniline (47g, 180 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 9:1) furnished 48e as a white solid (142 mg, 62%).

**m.p.:** 118.2-119.8 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.23-7.35 (m, 2H), 6.72-6.86 (m, 2H), 2.86-3.07 (m, 6H), 2.12 (bs, 3H), 1.89-2.00 (m, 6H), 1.72-1.87 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 148.6, 140.0, 125.4, 112.8, 43.4, 40.9, 36.9, 35.3, 29.1.
**C. Experimental Section**

**MS** (70 eV, EI), *m/z* (%) = 255 (M⁺, 100), 199 (16), 198 (87), 184 (8), 161 (10), 135 (8), 134 (21), 43 (16).


**IR** (ATR) *υ* (cm⁻¹) = 3090, 3032, 2983, 2896, 2844, 1615, 1518, 1491, 1446, 1442, 1356, 1350, 1341, 1232, 1205, 1165, 1099, 1063, 975, 949, 822, 797.

**Preparation of (4-(adamantan-1-yl)phenyl)trimethylsilane (48f)**

![Structure of 48f]

The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)₂ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and (4-bromophenyl)trimethylsilane (**47h**, 206 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane pur) furnished 48f as a white solid (205 mg, 80 %).

**m.p.:** 126.2-127.9 °C.

**¹H NMR** (300 MHz, CDCl₃) *δ* (ppm) = 7.46-7.57 (m, 2H), 7.35-7.44 (m, 2H), 2.13 (bs, 3H), 1.96 (d, *J*=2.8Hz, 6H), 1.69-1.89 (m, 6H), 0.29 (s, 9H).

**¹³C NMR** (75 MHz, CDCl₃) *δ* (ppm) = 151.9, 137.0, 133.3, 124.3, 43.1, 36.8, 36.2, 29.0, -1.0.

**MS** (70 eV, EI), *m/z* (%) = 284 (M⁺, 9), 271 (8), 270 (23), 269 (100), 135 (4), 73 (8), 43 (11).


**IR** (ATR) *υ* (cm⁻¹) = 3070, 3015, 2954, 2905, 2847, 1596, 1448, 1396, 1342, 1250, 1244, 1115, 1102, 1031, 1017, 859, 835, 826, 798, 757, 722, 691, 668.

**Preparation of 4-(adamantan-1-yl)benzaldehyde (48g)**

![Structure of 48g]

The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)₂ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromobenzaldehyde (**47i**, 167 mg, 0.9 mmol) was performed according to **TP2** in 1 h. Flash column chromatography (silica, pentane:Et₂O 50:1) furnished 48g as a white solid (190 mg, 88 %).
**C. Experimental Section**

m.p.: 97.0-98.9 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 9.98 (s, 1H), 7.75-7.89 (m, 2H), 7.45-7.62 (m, 2H), 2.13 (bs, 3H), 1.94 (d, $J$=2.8Hz, 6H), 1.66-1.88 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 192.1, 158.5, 134.1, 129.7, 125.6, 42.9, 36.9, 36.6, 28.8.

**MS (70 eV, EI), m/z (%) = 240 (M$^+$, 100), 184 (18), 183 (39), 155 (54), 94 (16), 91 (12), 79 (9).**

**HRMS (EI), m/z calc. for C$_{17}$H$_{20}$O (240.1514): 240.1500.**

**IR (ATR) $\nu$ (cm$^{-1}$) = 3090, 3055, 2901, 2846, 1695, 1685, 1602, 1569, 1446, 1412, 1368, 1344, 1304, 1222, 1205, 1165, 1112, 1102, 1079, 1030, 1012, 977, 860, 825, 801, 654.**

**Preparation of 3-(adamantan-1-yl)phenyl diethylcarbamate (48h)**

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 3-bromophenyl diethylcarbamate (47j, 245 mg, 0.9 mmol) was performed according to TP2 in 1 h. Flash column chromatography (silica, pentane:Et$_2$O 9:1) furnished 48h as a white solid (206 mg, 70 %).

m.p.: 66.1-67.2 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.30 (t, $J$=7.9Hz, 3H), 7.16-7.22 (m, 2H), 7.10 (t, $J$=2.1Hz, 1H), 6.95 (ddd, $J$=7.9Hz, 2.3Hz, 1.1Hz, 1H), 3.23-3.57 (m, 4H), 2.10 (bs, 3H), 1.93 (d, $J$=3.0Hz, 6H), 1.68-1.86 (m, 6H), 1.09-1.36 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 154.4, 152.9, 151.5, 128.6, 121.6, 118.4, 118.8, 118.4, 43.1, 42.2, 41.9, 36.8, 36.2, 28.9, 14.3, 13.4.

**MS (70 eV, EI), m/z (%) = 327 (M$^+$, 7), 228 (2), 171 (3), 101 (5), 100 (100), 91 (2), 79 (2), 72 (18), 43 (2).**

**HRMS (EI), m/z calc. for C$_{21}$H$_{29}$NO$_2$ (327.2198): 327.2186.**

**IR (ATR) $\nu$ (cm$^{-1}$) = 3035, 2977, 2900, 2846, 1709, 1603, 1585, 1489, 1470, 1453, 1412, 1378, 1345, 1316, 1271, 1237, 1222, 1183, 1165, 1151, 1097, 1088, 1049, 980, 966, 876, 786, 774, 754, 695.**
Preparation of 1-(6-methoxynaphthalen-2-yl)adamantane (48i)

The cross-coupling reaction of 48a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 2-bromo-6-methoxynaphthalene (47k, 213 mg, 0.9 mmol) was performed according to TP2 in 3 h. Flash column chromatography (silica, pentane:Et$_2$O 7:3) furnished 48i as a white solid (250 mg, 95 %).

m.p.: 150.5-152.7 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.64-7.80 (m, 3H), 7.50-7.61 (m, 1H), 7.07-7.19 (m, 2H), 3.93 (s, 3H), 2.16 (bs, 3H), 2.04 (s, 6H), 1.73-1.96 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 157.3, 146.6, 132.7, 129.4, 129.0, 126.4, 124.6, 122.7, 118.4, 105.4, 55.3, 43.2, 36.9, 36.2, 29.0.

MS (70 eV, EI), m/z (%) = 292 (M$^+$, 100), 236 (13), 235 (52), 220 (12), 203 (6), 198 (14), 171 (14), 165 (6).

HRMS (EI), m/z calc. for C$_{21}$H$_{24}$O (292.1827): 292.1829.

IR (ATR) $\nu$ (cm$^{-1}$) = 3049, 3014, 2946, 2899, 2843, 1632, 1605, 1503, 1484, 1460, 1451, 1391, 1337, 1265, 1223, 1196, 1186, 1179, 1163, 1154, 1122, 1036, 1031, 923, 885, 849, 822, 814, 797, 726, 672.

Preparation of 2,7-di(adamantan-1-yl)-fluorene (48j)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 2,7-dibromo-fluorene (47l, 146 mg, 0.45 mmol) was performed according to TP2 in 3 h. Flash column chromatography (silica, pentane:Et$_2$O 9:1) furnished 48j as a white solid (206 mg, 70 %).

m.p.: 308.9-311.8 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.70 (d, $J$=8.0Hz, 2H), 7.57 (s, 2H), 7.39 (dd, $J$=8.0Hz, 1.7Hz, 2H), 3.88 (s, 2H), 2.16 (bs, 6H), 2.02 (d, $J$=3.0Hz, 12H), 1.74-1.95 (m, 12H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 149.8, 143.3, 139.3, 123.3, 121.4, 119.1, 43.5, 37.2, 36.9, 36.4, 29.1.
**Preparation of 4,4'-di(adamantan-1-yl)-1,1'-biphenyl (48k)**

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (4 mg, 0.02 mmol), SPhos (16 mg, 0.04 mmol) and 4,4'-dibromo-1,1'-biphenyl (47m, 125 mg, 0.4 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 98:2) furnished 48k as a white solid (206 mg, 70 %).

**m.p.: >250 °C.**

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.51-7.68 (m, 4H), 7.36-7.50 (m, 4H), 2.15 (bs, 6H), 1.99 (d, $J$=2.8Hz, 12H), 1.66-1.93 (m, 12H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 150.1, 138.3, 126.7, 125.2, 43.2, 36.9, 36.1, 29.0.

**MS** (70 eV, EI), $m/z$ (%) = 422 (M$^+$, 100), 365 (4), 328 (5), 301 (9), 136 (4), 135 (31), 93 (8), 79 (9).

**HRMS** (EI), $m/z$ calc. for C$_{32}$H$_{38}$ (422.2974): 422.2967.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3083, 3056, 3023, 2898, 2846, 1499, 1448, 1366, 1355, 1342, 1315, 1243, 1214, 1178, 1101, 1020, 1003, 977, 828, 810, 799, 761, 727, 703.

**Preparation of 3-(adamantan-1-yl)benzothiophene (48l)**

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 3-bromobenzothiophene (49a, 192 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane pur) furnished 48l as a white solid (188 mg, 84 %).
C. EXPERIMENTAL SECTION

m.p.: 150.3-151.9 °C.

\(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 8.11-8.31 (m, 1H), 7.78-7.97 (m, 1H), 7.19-7.44 (m, 2H), 7.08 (s, 1H), 1.99-2.45 (m, 9H), 1.62-1.99 (m, 6H).

\(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 146.1, 141.7, 137.5, 124.7, 123.4, 123.0, 119.8, 42.0, 37.1, 37.0, 28.8.

MS (70 eV, EI), \(m/z\) (%) = 268 (M\(^+\), 100), 225 (6), 212 (14), 211 (84), 185 (5), 184 (6), 174 (14), 147 (10), 115 (6).

HRMS (EI), \(m/z\) calc. for C\(_{18}\)H\(_{20}\)S (268.1286): 268.1279.

IR (ATR) \(\nu\) (cm\(^{-1}\)) = 3104, 3072, 2935, 2910, 2900, 2884, 2848, 1452, 1446, 1423, 1344, 1308, 1258, 1175, 1163, 1100, 1062, 1028, 994, 974, 932, 871, 846, 790, 757, 705, 652.

Preparation of 3-(adamantan-1-yl)benzofuran (48m)

![Chemical structure of 3-(adamantan-1-yl)benzofuran](image)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 3-bromobenzofuran (49b, 177 mg, 0.9 mmol) was performed according to TP2 in 3 h. Flash column chromatography (silica, pentane:Et\(_2\)O 100:1) furnished 48m as a white solid (129 mg, 57%).

m.p.: 69.7-71.5 °C.

\(^1H\) NMR (600 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 7.83 (d, \(J=8.0Hz\), 1H), 7.49 (d, \(J=8.2Hz\), 1H), 7.32 (s, 1H), 7.27 (d, \(J=8.2Hz\), 1H), 7.22 (t, \(J=7.4Hz\), 1H), 2.05-2.20 (m, 9H), 1.78-1.92 (m, 6H).

\(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 156.0, 139.4, 130.5, 126.5, 123.6, 121.9, 121.7, 111.7, 42.2, 37.0, 33.3, 28.5.

MS (70 eV, EI), \(m/z\) (%) = 252 (M\(^+\), 100), 196 (9), 195 (46), 167 (22), 158 (12), 131 (6).

HRMS (EI), \(m/z\) calc. for C\(_{18}\)H\(_{20}\)O (252.1514): 252.1511.

IR (ATR) \(\nu\) (cm\(^{-1}\)) = 3085, 3063, 3032, 2901, 2847, 1582, 1451, 1344, 1284, 1255, 1203, 1183, 1157, 1104, 1083, 1030, 1004, 976, 929, 867, 793, 766, 744, 684.
Preparation of 5-(adamantan-1-yl)-2-methylbenzothiazole (48n)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-2-methylbenzothiazole (49c, 205 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, EtOAc pur) furnished 48n as a brown solid (232 mg, 91%).

m.p.: 147.4-149.6 °C.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.89-8.00 (m, H), 7.73 (d, $J$=8.6Hz, 1H), 7.40 (dd, $J$=8.6Hz, 1.9Hz, 1H), 2.82 (s, 3H), 2.12 (bs, 3H), 1.93-2.03 (m, 6H), 1.68-1.87 (m, 6H).
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 166.8, 153.7, 149.9, 132.5, 122.3, 120.7, 118.6, 43.4, 36.8, 36.3, 29.0, 20.1.
MS (70 eV, El), m/z (%) = 283 (M$^+$, 83), 240 (10), 227 (19), 226 (100), 189 (18), 184 (5), 162 (10).
HRMS (El), m/z calc. for C$_{18}$H$_{21}$NS (283.1395): 283.1351.
IR (ATR) $\nu$ (cm$^{-1}$) = 3054, 3028, 2954, 2925, 2916, 2901, 2843, 1739, 1526, 1458, 1448, 1415, 1342, 1308, 1260, 1241, 1168, 1160, 1101, 1067, 980, 974, 923, 795, 728, 656.

Preparation of 5-(adamantan-1-yl)-1-methyl-indole (48o)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-1-methyl-indole (49d, 189 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 8:2) furnished 48o as a white solid (170 mg, 71%).

m.p.: 171.7-173.5 °C.
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm) = 7.64 (d, $J$=1.9Hz, 1H), 7.34-7.38 (m, 1H), 7.29-7.33 (m, 1H), 7.04 (d, $J$=3.0Hz, 1H), 6.49 (d, $J$=3.0Hz, 1H), 3.79 (s, 3H), 2.16 (bs, 3H), 2.05 (d, $J$=3.0Hz, 6H), 1.75-1.91 (m, 6H).
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) = 142.6, 135.0, 128.7, 128.4, 119.2, 116.5, 108.7, 100.9, 43.9, 37.0, 36.0, 32.8, 29.2.

**MS** (70 eV, EI), $m/z$ (%) = 265 (M$^+$, 100), 222 (6), 209 (17), 208 (90), 194 (5), 193 (11), 171 (16), 144 (15), 131 (5), 43 (24).

**HRMS** (EI), $m/z$ calc. for C$_{19}$H$_{23}$N (265.1830): 265.1823.

**IR** (ATR) $\nu$ ($\text{cm}^{-1}$) = 3112, 3061, 3037, 2925, 2901, 2843, 2818, 1514, 1489, 1448, 1421, 1368, 1342, 1333, 1287, 1244, 1167, 1104, 1081, 1030, 1008, 981, 974, 924, 875, 847, 791, 760, 724, 676.

**Preparation of 2-(adamantan-1-yl)thiophene (48p)**

![Diagram of 2-(adamantan-1-yl)thiophene (48p)]

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 2-bromothiophene (49e, 147 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 100:1) furnished 48p as a white solid (120 mg, 61%).

**m.p.:** 66.1-67.2 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.14 (dd, $J=5.0$Hz, 1.1Hz, 1H), 6.89-7.01 (m, 1H), 6.83 (dd, $J=3.5$Hz, 1.2Hz, 1H), 2.10 (bs, 3H), 2.00 (d, $J=2.8$Hz, 6H), 1.71-1.88 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 158.3, 126.3, 121.9, 120.1, 45.0, 36.7, 36.2, 28.9.

**MS** (70 eV, EI), $m/z$ (%) = 218 (M$^+$, 71), 175 (7), 162 (13), 161 (100), 128 (6), 124 (15), 97 (6).

**HRMS** (EI), $m/z$ calc. for C$_{14}$H$_{19}$S (218.1129): 218.1144.

**IR** (ATR) $\nu$ ($\text{cm}^{-1}$) = 3098, 3070, 2898, 2846, 1526, 1446, 1342, 1314, 1261, 1228, 1100, 1077, 1052, 1004, 966, 850, 823, 808, 703, 694, 686.
Preparation of ethyl 5-(adamantan-1-yl)thiophene-2-carboxylate (48q)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and ethyl 5-bromothiophene-2-carboxylate (49f, 212 mg, 0.9 mmol) was performed according to TP2 in 3 h. Flash column chromatography (silica, pentane:Et$_2$O 9.5:0.5) furnished 48q as a white solid (139 mg, 53 %).

m.p.: 85.9-88.2 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.65 (d, $J$=3.9Hz, 1H), 6.83 (d, $J$=3.9Hz, 1H), 4.33 (q, $J$=7.2Hz, 2H), 2.09 (bs, 3H), 1.97 (d, $J$=2.8Hz, 6H), 1.65-1.86 (m, 6H), 1.36 (t, $J$=7.2Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 165.9, 162.6, 133.2, 130.0, 121.4, 60.8, 44.6, 36.8, 36.4, 28.7, 14.4.

MS (70 eV, EI), m/z (%) = 290 (M$^+$, 100), 257 (23), 245 (26), 234 (12), 233 (51), 196 (15), 161 (31), 135 (45), 94 (10), 93 (13), 91 (10), 79 (16).

HRMS (EI), m/z calc. for C$_{17}$H$_{22}$O$_2$S (290.1341): 290.1336.

IR (ATR) $\nu$ (cm$^{-1}$) = 3077, 2983, 2960, 2918, 2851, 2842, 1707, 1536, 1455, 1366, 1335, 1317, 1254, 1212, 1192, 1086, 1048, 1036, 1010, 999, 976, 867, 820, 814, 805, 762, 747.

Preparation of 5-(adamantan-1-yl)-2,2'-bithiophene (48r)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-2,2'-bithiophene (49g, 221 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane pur) furnished 48r as a white solid (157 mg, 58 %).

m.p.: 69.9-70.7 °C.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm) = 7.17 (dd, $J$=5.1Hz, 1.2Hz, 1H), 7.11 (dd, $J$=3.6Hz, 1.1Hz, 1H), 6.96-7.05 (m, 2H), 6.72 (d, $J$=3.6Hz, 1H), 2.10 (bs, 3H), 1.93-2.06 (m, 6H), 1.71-1.87 (m, 6H).
\[^{13}\text{C} \text{NMR} \text{ (150 MHz, CDCl}\text{"}{3}\text{) } \delta \text{ (ppm) } = 157.6, 138.1, 133.9, 127.6, 123.7, 123.1, 122.9, 121.0, 44.8, 36.6, 36.6, 36.4, 28.9, 28.9.\]

\[
\text{MS (70 eV, EI), } m/z \text{ (%) } = 300 (M^+, 100), 257 (4), 245 (6), 244 (13), 243 (63), 210 (11), 209 (4), 206 (12), 121 (5), 61 (4), 45 (4), 43 (26).\]

\[
\text{HRMS (EI), } m/z \text{ calc. for } \text{C}_{18}\text{H}_{20}\text{S}_2 = 300.1006: 300.0996.\]

\[
\text{IR (ATR) } \nu \text{ (cm}^{-1}) = 3119, 3069, 2910, 2898, 2846, 1512, 1460, 1445, 1428, 1342, 1318, 1204, 1184, 1100, 1060, 1003, 976, 887, 876, 840, 823, 810, 797, 688, 684.\]

\[\text{Preparation of adamantan-1-yl(4-fluorophenyl)methanone (51a)}\]

![Image of molecular structure](image)

The acylation reaction of \(46a\) (3.2 mL, 1.0 mmol, 0.32 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 4-fluorobenzoyl chloride \(50a\), 143 mg, 0.9 mmol) was performed according to TP3 over night. Flash column chromatography (silica, pentane:Et\(_2\)O 50:1) furnished \(51a\) as a white solid (207 mg, 89%).

\[
\text{m.p.: 78.8-80.8 °C.}\]

\[
\text{\(^1\text{H NMR (300 MHz, CDCl}\text{"}{3}\text{) } \delta \text{ (ppm) } = 7.53-7.73 (m, 2H), 6.96-7.14 (m, 2H), 2.09 (bs, 3H), 2.01 (d, } J=2.8Hz, 6H), 1.67-1.85 (m, 6H).}\]

\[
\text{\(^{13}\text{C NMR (75 MHz, CDCl}\text{"}{3}\text{) } \delta \text{ (ppm) } = 208.1, 163.9 (d, } J=251.1Hz), 135.3 (d, } J=3.4Hz), 129.9 (d, } J=8.5Hz), 115.0 (d, } J=21.4Hz), 46.9, 39.2, 36.5, 28.1.}\]

\[
\text{MS (70 eV, EI), } m/z \text{ (%) } = 258 (M^+, 3), 136 (8), 135 (100), 123 (6), 107 (5), 93 (9), 81 (3), 79 (10), 77 (3), 67 (4).\]

\[
\text{HRMS (EI), } m/z \text{ calc. for } \text{C}_{17}\text{H}_{19}\text{FO} = 258.1420: 258.1416.\]

\[
\text{IR (ATR) } \nu \text{ (cm}^{-1}) = 3085, 2957, 2922, 2905, 2890, 2884, 2854, 1665, 1591, 1501, 1452, 1404, 1346, 1266, 1231, 1208, 1178, 1156, 1112, 1102, 1096, 1039, 1010, 986, 973, 956, 952, 929, 846, 815, 794, 746, 687, 678.\]
Preparation of adamantan-1-yl(4-chlorophenyl)methanone (51b)

![Chemical Structure]

The acylation reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (50b, 158 mg, 0.9 mmol) was performed according to TP3 over night. Flash column chromatography (silica, pentane:Et2O 92:8) furnished 51b as a pale yellow solid (173 mg, 70 %).

* m.p.: 92.4-95.7 °C.
* $^1$H NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) = 7.43-7.61 (m, 2H), 7.26-7.40 (m, 2H), 2.07 (bs, 3H), 1.98 (d, $J=2.8$Hz, 6H), 1.63-1.81 (m, 6H).
* $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 208.6, 137.6, 136.4, 128.8, 128.2, 47.0, 39.1, 36.5, 28.1.
* MS (70 eV, EI), $m/z$ (%) = 274 (M$^+$, 4), 139 (6), 136 (12), 135 (100), 111 (5), 107 (5), 93 (11), 79 (13), 67 (5), 42 (17).
* HRMS (EI), $m/z$ calc. for C$_{17}$H$_{19}$ClO (274.1124): 274.1111.
* IR (ATR) $\nu$ (cm$^{-1}$) = 2911, 2849, 1724, 1659, 1586, 1484, 1450, 1394, 1343, 1268, 1232, 1184, 1172, 1115, 1089, 1046, 1010, 989, 972, 957, 950, 927, 840, 816, 808, 768, 760, 742, 728, 686, 668.

Preparation of adamantan-1-yl(4-methoxyphenyl)methanone (51c)

![Chemical Structure]

The acylation reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 4-methoxybenzoyl chloride (50c, 154 mg, 0.9 mmol) was performed according to TP3 over night. Flash column chromatography (silica, pentane:Et2O 9:1) furnished 51c as a white solid (195 mg, 80 %).
m.p.: 61.5-63.9 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.61-7.85 (m, 2H), 6.56-7.03 (m, 2H), 3.84 (s, 3H), 1.88-2.21 (m, 9H), 1.57-1.91 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 207.1, 161.6, 131.1, 130.3, 113.1, 55.3, 46.8, 39.5, 36.7, 28.3.

MS (70 eV, EI), m/z (%) = 270 (M$^+$, 20), 136 (9), 135 (100), 107 (6), 93 (13).

HRMS (EI), m/z calc. for C$_{18}$H$_{22}$O$_2$ (270.1620): 270.1617.

IR (ATR) $\nu$ (cm$^{-1}$) = 3079, 3054, 3020, 3002, 2944, 2902, 2890, 2848, 1656, 1596, 1510, 1453, 1439, 1319, 1303, 1264, 1233, 1186, 1170, 1113, 1104, 1029, 1010, 986, 974, 952, 930, 835, 820, 809, 788, 766, 750, 697, 680.

**Preparation of adamantan-1-yl(6-chloropyridin-3-yl)methanone (51d)**

![Diagram](image)

The acylation reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 6-chloronicotinoyl chloride (50d, 159 mg, 0.9 mmol) was performed according to TP3 over night. Flash column chromatography (silica, pentane:Et$_2$O 9:1) furnished 51d as a yellow oil (109 mg, 44%).

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 8.66 (d, $J$=2.5Hz, 1H), 7.86 (dd, $J$=8.3Hz, 2.5Hz, 1H), 7.36 (d, $J$=8.3Hz, 1H), 2.09 (bs, 3H), 1.97 (d, $J$=2.8Hz, 6H), 1.64-1.84 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 206.4, 153.0, 148.4, 138.0, 133.4, 123.9, 47.2, 38.8, 36.3, 27.9.

MS (70 eV, EI), m/z (%) = 275 (M$^+$, 1), 136 (14), 135 (100), 107 (8), 93 (16), 81 (5), 79 (13).

HRMS (EI), m/z calc. for C$_{16}$H$_{18}$ClNO (275.1077): 275.1071.

IR (ATR) $\nu$ (cm$^{-1}$) = 2953, 2917, 2849, 1727, 1633, 1570, 1459, 1377, 1261, 1211, 1194, 1173, 1119, 1093, 1036, 1007, 972, 961, 950, 926, 832, 815, 809, 762, 751, 723, 687.
Preparation of ethyl 2-(adamantan-1-ylmethyl)acrylate (53a)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the adamantyl zinc reagent 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) and cooled to -40 °C. Ethyl 2-(bromomethyl)acrylate (52a, 174 mg, 0.9 mmol) was added, followed by CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF). The reaction mixture was allowed to warm to room temperature. After stirring over night, the reaction mixture was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL), washed with sat. NH₄Cl/NH₃ solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, pentane:Et₂O 100:1) to give the analytically pure product 53a as a colorless oil (203 mg, 91%).

^1H NMR (300 MHz, CDCl₃) δ (ppm) = 6.18 (d, J=1.9Hz, 1H), 5.40 (d, J=1.9Hz, 1H), 4.20 (q, J=7.2Hz, 2H), 2.16 (s, 2H), 1.93 (bs, 3H), 1.57-1.67 (m, 6H), 1.39-1.51 (m, 6H), 1.30 (t, J=7.0Hz, 3H).

^13C NMR (75 MHz, CDCl₃) δ (ppm) = 168.2, 137.6, 126.8, 60.6, 45.5, 42.1, 36.9, 33.2, 28.7, 14.2.

MS (70 eV, EI), m/z (%) = 248 (M⁺, 2), 177 (3), 136 (11), 135 (100), 107 (4), 93 (8), 81 (3), 79 (8), 67 (3).

HRMS (EI), m/z calc. for C₁₆H₂₄O₂ (248.1776): 248.1755.

IR (ATR) ν (cm⁻¹) = 2980, 2899, 2847, 1717, 1625, 1448, 1406, 1366, 1312, 1297, 1291, 1278, 1208, 1176, 1131, 1101, 1027, 982, 941, 875, 856, 819, 735, 690.

Preparation of ethyl 3-(adamantan-1-yl)propiolate (53b)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the adamantyl zinc reagent 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) and cooled to -40 °C. CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) was added, followed by ethyl 3-bromoprop-2-ynoate (52b, 159 mg, 0.9 mmol) and the reaction mixture was stirred over night slowly warming up to room temperature. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc dried over
Na₂SO₄ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:Et₂O 100:1) to give 53b as a white solid (138 mg, 66 %).

**m.p.:** 55.2-56.2 °C.

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 4.20 (q, J=7.2Hz, 2H), 1.97 (bs, 3H), 1.92 (d, J=2.8Hz, 6H), 1.58-1.78 (m, 6H), 1.29 (t, J=7.2Hz, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 154.2, 95.9, 72.1, 61.7, 41.5, 36.1, 29.6, 27.5, 14.1.

**MS** (70 eV, EI), *m/z* (%) = 232 (M⁺, 5), 205 (82), 204 (77), 187 (84), 148 (48), 135 (31), 119 (100), 93 (30), 91 (52), 79 (48), 77 (36), 43 (47).

**HRMS** (EI), *m/z* calc. for C₁₅H₂₀O₂ (232.1463): 232.1457.

**IR** (ATR) υ (cm⁻¹) = 2983, 2906, 2853, 2226, 1702, 1665, 1474, 1453, 1366, 1317, 1300, 1248, 1184, 1144, 1114, 1100, 1025, 989, 856, 812, 791, 752.

### Preparation of adamantan-1-yl(phenyl)sulfane (53c)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the adamantyl zinc reagent 46a (3.2 mL, 1.0 mmol, 0.32 m in THF) and cooled to 0 °C. S-phenyl benzenesulfonylthioate (52c, 225 mg, 0.9 mmol) was added and the reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane pur) to give 53c as a pale brown solid (216 mg, 98 %).

**m.p.:** 73.9-74.9 °C.

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 7.48-7.57 (m, 2H), 7.40-7.55 (m, 2H), 7.26-7.42 (m, 3H), 2.01 (bs, 3H), 1.82 (d, J=2.8Hz, 6H), 1.50-1.71 (m, 6H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 137.6, 130.5, 128.5, 128.2, 47.8, 43.6, 36.2, 30.0.

**MS** (70 eV, EI), *m/z* (%) = 244 (M⁺, 9), 136 (13), 135 (100), 107 (7), 93 (14), 79 (15), 61 (9), 43 (49).

**HRMS** (EI), *m/z* calc. for C₁₆H₂₆S (244.1286): 244.1292.
**Preparation of 3-(adamantan-1-yl)cyclohexanone (53d)**

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the adamanyl zinc reagent 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) and cooled to -40 °C. CuCN·2LiCl (1.0 mL, 1.0 mmol, 1.0 M in THF) was added, followed by a solution of cyclohexenone (52d, 87 mg, 0.9 mmol) and chlorotrimethylsilane (0.4 mL, 2.5 mmol) in THF (1 mL) and the reaction mixture was stirred overnight slowly warming up to room temperature. The reaction was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na₂SO₄ and concentrated _in vacuo_. The crude residue obtained was purified by flash column chromatography (silica, pentane:Et₂O 8:2) to give **53d** as a white solid (190 mg, 91%).

**m.p.**: 67.0-67.4 °C.

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 2.27-2.48 (m, 2H), 2.02-2.27 (m, 3H), 1.87-2.01 (m, 4H), 1.65-1.75 (m, 3H), 1.55-1.65 (m, 3H), 1.39-1.54 (m, 7H), 1.23-1.37 (m, 2H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 213.4, 49.7, 42.1, 41.5, 39.4, 37.2, 34.4, 28.6, 25.7, 24.6.

**MS** (70 eV, EI), _m/z_ (%) = 232 (M⁺, 3), 136 (10), 135 (100), 96 (6), 93 (9), 79 (10), 42 (32), 41 (6).

**HRMS** (EI), _m/z_ calc. for C₁₆H₂₄O (232.1827): 232.1821.

**IR** (ATR) ν (cm⁻¹) = 2965, 2942, 2896, 2862, 2844, 1709, 1449, 1424, 1418, 1360, 1347, 1322, 1316, 1304, 1277, 1268, 1238, 1228, 1216, 1168, 1102, 1058, 1034, 998, 967, 927, 899, 862, 814, 760, 722, 661.
Preparation of $N$-phenyladamantan-1-amine (55a)

The amine synthesis was performed according to TP4 in 2 h with 46a (3.2 mL, 1.0 mmol, 0.32 M in THF), nitrosobenzene (54a, 96 mg, 0.9 mmol), FeCl$_2$ (254 mg, 2 mmol) and NaBH$_4$ (42 mg, 1.1 mmol). Flash column chromatography (silica, pentane:EtOAc 7:1) furnished 55a as a pale yellow solid (182 mg, 89 %).

m.p.: 73.3-75.7 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.07-7.25 (m, 2H), 6.59-6.93 (m, 3H), 3.40 (bs, 1H), 2.12 (bs, 3H), 1.89 (d, $J$=2.8Hz, 6H), 1.58-1.82 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 145.9, 128.7, 119.3, 119.2, 52.3, 43.5, 36.5, 29.7.

MS (70 eV, EI), $m/z$ (%) = 227 (M$^+$, 33), 170 (50), 136 (10), 135 (100), 93 (24), 91 (9), 79 (21), 43 (39).

HRMS (EI), $m/z$ calc. for C$_{16}$H$_{21}$N (227.1674): 227.1664.

IR (ATR) $\nu$ (cm$^{-1}$) = 3414, 3089, 3050, 3014, 2902, 2847, 1597, 1503, 1494, 1472, 1448, 1432, 1356, 1344, 1324, 1306, 1286, 1270, 1236, 1181, 1131, 1096, 1081, 992, 978, 861, 818, 741, 690.

Preparation of $N^1$-(adamantan-1-yl)-$N^4$,$N^4$-dimethylbenzene-1,4-diamine (55b)

The amine synthesis was performed according to TP4 in 2 h with 46a (3.2 mL, 1.0 mmol, 0.32 M in THF), $N$,$N$-dimethyl-4-nitrosoaniline (54b, 135 mg, 0.9 mmol), FeCl$_2$ (254 mg, 2 mmol) and NaBH$_4$ (42 mg, 1.1 mmol). Flash column chromatography (silica, pentane:EtOAc 1:1) furnished 55b as a brown solid (172 mg, 71 %).

m.p.: 105.2-107.4 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 6.83 (d, $J$=8.3Hz, 2H), 6.66 (d, $J$=8.3Hz, 2H), 2.64-3.11 (m, 7H), 1.95-2.22 (m, 3H), 1.46-1.88 (m, 12H).
**C. EXPERIMENTAL SECTION**

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) = 146.6, 135.1, 125.0, 113.5, 52.6, 43.8, 41.3, 36.5, 29.8.

**MS** (70 eV, EI), $m/z$ (%) = 270 (M$^+$, 100), 213 (14), 136 (13), 135 (34), 121 (12), 93 (7), 79 (6).

**HRMS** (EI), $m/z$ calc. for C$_{18}$H$_{26}$N$_2$ (270.2096): 270.2090.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3296, 3036, 2985, 2901, 2842, 2790, 1616, 1511, 1479, 1443, 1354, 1340, 1326, 1309, 1282, 1243, 1212, 1177, 1163, 1124, 1107, 1101, 1094, 1054, 944, 934, 922, 818, 806, 788, 773, 722, 689.

**Preparation of ethyl 3-(4-(methylthio)phenyl)adamantane-1-carboxylate (56a)**

The cross-coupling reaction of 46b (4.2 mL, 1.0 mmol, 0.24 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and (4-bromophenyl)(methyl)-sulfane (47f, 183 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 7:3) furnished 56a as a colorless oil (259 mg, 87%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.17-7.35 (m, 4H), 4.12 (q, $J=7.2$Hz, 2H), 2.47 (s, 3H), 2.22 (bs, 2H), 2.00 (s, 2H), 1.83-1.97 (m, 8H), 1.73 (bs, 2H), 1.24 (t, $J=7.0$Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 177.3, 147.2, 135.4, 126.9, 125.4, 60.2, 44.2, 42.1, 41.7, 38.1, 36.2, 35.6, 28.7, 16.2, 14.2.

**MS** (70 eV, EI), $m/z$ (%) = 330 (M$^+$, 100), 257 (16), 201 (16), 164 (9), 137 (12).

**HRMS** (EI), $m/z$ calc. for C$_{20}$H$_{26}$O$_2$S (330.1654): 330.1653.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3079, 3024, 2979, 2904, 2853, 1720, 1569, 1497, 1448, 1400, 1364, 1343, 1320, 1242, 1200, 1173, 1149, 1104, 1097, 1067, 1022, 1013, 970, 958, 915, 824, 808, 736, 720, 690.
Preparation of ethyl 3-(4-(ethoxycarbonyl)phenyl)adamantane-1-carboxylate (56b)

\[
\text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}
\]

The cross-coupling reaction of \(46b\) (4.2 mL, 1.0 mmol, 0.24 M in THF) with Pd(OAc)_2 (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and ethyl 4-bromobenzoate \(47b\) (206 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et\(_2\)O 7:3) furnished \(56b\) as a colorless solid (269 mg, 84 %).

\[\text{m.p.: 27.1-28.3 °C.}\]

\[\text{H NMR (300 MHz, CDCl}_3\text{) } \delta \text{ (ppm) = 7.84-8.11 (m, 2H), 7.33-7.58 (m, 2H), 4.36 (q,} J=7.2Hz, 2H), 4.12 (q, J=7.1Hz, 2H), 2.15-2.34 (m, 2H), 2.03 (s, 2H), 1.83-1.97 (m, 7H), 1.74 (bs, 3H), 1.37 (t, J=7.2Hz, 3H), 1.24 (t, J=7.2Hz, 3H).\]

\[\text{C NMR (75 MHz, CDCl}_3\text{) } \delta \text{ (ppm) = 177.1, 166.6, 155.1, 129.5, 128.1, 124.9, 60.7, 60.3, 43.8, 41.9, 41.6, 38.0, 36.9, 35.5, 28.6, 14.3, 14.2.}\]

\[\text{MS (70 eV, EI), } m/z \text{ (%) = 356 (M}^+\text{, 37), 311 (13), 284 (20), 283 (100), 255 (6), 227 (8), 163 (6), 155 (12), 93 (10), 91 (6).}\]

\[\text{HRMS (EI), } m/z \text{ calc. for } \text{C}_{22}\text{H}_{28}\text{O}_4 \text{ (356.1988): 356.1981.}\]

\[\text{IR (ATR) } \nu \text{ (cm}^{-1}\text{) = 3092, 3053, 2986, 2927, 2903, 2855, 1710, 1608, 1447, 1409, 1389, 1365, 1271, 1250, 1241, 1197, 1172, 1103, 1067, 1017, 978, 912, 859, 842, 775, 766, 749, 730, 707.}\]

Preparation of ethyl 3-(2-methylbenzothiazol-5-yl)adamantane-1-carboxylate (56c)

\[
\text{CO}_2\text{Et}
\]

The cross-coupling reaction of \(46b\) (4.2 mL, 1.0 mmol, 0.24 M in THF) with Pd(OAc)_2 (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-2-methylbenzothiazole \(49c\) (205 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et\(_2\)O 6.5:3.5) furnished \(56c\) as a white solid (224 mg, 70 %).
m.p.: 83.6-84.5 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.95 (d, $J=1.9$Hz, 1H), 7.75 (d, $J=8.6$Hz, 1H), 7.40 (dd, $J=8.6$Hz, 1.9Hz, 1H), 4.11 (q, $J=7.2$Hz, 2H), 2.82 (s, 3H), 2.16-2.35 (m, 2H), 2.08 (s, 2H), 1.95 (d, $J=3.3$Hz, 8H), 1.65-1.81 (m, 2H), 1.24 (t, $J=7.0$Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 177.2, 167.1, 153.5, 148.7, 132.8, 122.3, 120.9, 118.6, 60.2, 44.4, 42.3, 41.7, 38.1, 36.6, 35.6, 28.7, 20.0, 14.2.

MS (70 eV, EI), $m/z$ (%) = 355 (M$^+$, 100), 283 (16), 282 (76), 240 (11), 227 (11), 226 (51), 190 (13), 189 (16), 162 (25), 93 (14), 61 (11), 45 (12), 44 (16), 43 (95).

HRMS (EI), $m/z$ calc. for C$_{21}$H$_{25}$NO$_2$S (355.1606): 355.1609.

IR (ATR) $\nu$ (cm$^{-1}$) = 3053, 3032, 2981, 2930, 2918, 2905, 2853, 1716, 1548, 1530, 1458, 1450, 1417, 1389, 1367, 1341, 1266, 1256, 1248, 1230, 1170, 1164, 1149, 1101, 1074, 1057, 1022, 1002, 974, 954, 935, 901, 878, 863, 815, 775, 734, 699, 681.

### Preparation of ethyl 3-(4-chlorobenzoyl)adamantane-1-carboxylate (57a)

![Chemical Structure](attachment:image.png)

The acylation reaction of 46b (4.2 mL, 1.0 mmol, 0.24 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (50b, 158 mg, 0.9 mmol) was performed according to TP3 over night. Flash column chromatography (silica, pentane:Et$_2$O 8:2) furnished 57a as a colorless oil (256 mg, 82 %).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.46-7.61 (m, 2H), 7.30-7.42 (m, 2H), 4.02-4.19 (m, 2H), 2.16-2.25 (m, 2H), 2.10 (s, 2H), 1.85-2.04 (m, 8H), 1.64-1.84 (m, 4H), 1.18-1.29 (m, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 207.4, 176.7, 137.1, 136.8, 128.9, 128.3, 60.4, 47.1, 41.0, 40.0, 38.3, 37.9, 35.4, 28.0, 14.2.

MS (70 eV, EI), $m/z$ (%) = 346 (M$^+$, 4), 273 (5), 208 (12), 207 (100), 161 (15), 139 (9), 134 (5), 133 (33), 91 (6), 79 (6).

HRMS (EI), $m/z$ calc. for C$_{20}$H$_{23}$ClO$_3$ (346.1336): 346.1326.
\textbf{IR (ATR)} \nu (\text{cm}^{-1}) = 3069, 2978, 2907, 2857, 1720, 1670, 1591, 1487, 1450, 1393, 1366, 1344, 1324, 1263, 1243, 1227, 1208, 1175, 1117, 1103, 1091, 1076, 1038, 1011, 952, 905, 839, 828, 740, 684, 670.

\textbf{Preparation of ethyl 3-(furan-2-carbonyl)adamantane-1-carboxylate (57b)}

![Chemical Structure](image)

The acylation reaction of \(46b\) (4.2 mL, 1.0 mmol, 0.24 M in THF) with CuCN\(\cdot\)2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and furan-2-carbonyl chloride (\(50e\), 118 mg, 0.9 mmol) was performed according to TP3 over night Flash column chromatography (silica, pentane:Et\(_2\)O 7:3) furnished 57b as a colorless oil (147 mg, 54%).

\textbf{\(^1H\) NMR} (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 7.53 (d, \(J=1.1\)Hz, 1H), 7.21 (d, \(J=3.6\)Hz, 1H), 6.48 (dd, \(J=3.6\)Hz, 1.7Hz, 1H), 4.10 (q, \(J=7.2\)Hz, 2H), 2.14-2.28 (m, 4H), 2.03 (bs, 4H), 1.91 (d, \(J=3.0\)Hz, 4H), 1.74 (bs, 2H), 1.23 (t, \(J=7.0\)Hz, 3H).

\textbf{\(^{13}C\) NMR} (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 193.4, 176.9, 152.7, 145.0, 118.3, 111.7, 60.3, 45.9, 41.0, 39.1, 38.1, 37.3, 35.6, 28.0, 14.2.

\textbf{MS} (70 eV, EI), \(m/z\) (%) = 302 (M\(^+\), 37), 229 (12), 208 (13), 207 (100), 161 (22), 133 (52), 91 (11), 91 (11), 79 (10).

\textbf{HRMS} (EI), \(m/z\) calc. for C\(_{18}\)H\(_{22}\)O\(_4\) (302.1518): 302.1513.

\textbf{IR (ATR)} \nu (\text{cm}^{-1}) = 3125, 2975, 2908, 2857, 1721, 1658, 1560, 1462, 1386, 1366, 1297, 1278, 1235, 1162, 1123, 1104, 1078, 1053, 1040, 1014, 956, 921, 883, 864, 815, 760, 732, 696, 673.

\textbf{Preparation of 5-(4-(methylthio)phenyl)spiro[adamantane-2,2'-[1,3]dioxolane] (58a)}

![Chemical Structure](image)

The cross-coupling reaction of \(46c\) (4.5 mL, 1.0 mmol, 0.22 M in THF) with Pd(OAc)\(_2\) (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and (4-bromophenyl)(methyl)-sulfane (\(47f\), 183 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et\(_2\)O 9:1) furnished 58a as a white solid (208 mg, 73%).
m.p.: 89.1-89.9 °C.

$^{1}$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.15-7.36 (m, 4H), 3.97 (s, 4H), 2.47 (s, 3H), 1.98-2.33 (m, 6H), 1.95 (bs, 2H), 1.88 (bs, 2H), 1.62-1.81 (m, 4H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 147.3, 135.0, 126.8, 125.5, 110.8, 64.3, 64.2, 42.4, 40.5, 36.9, 35.1, 34.0, 27.5, 16.2.

MS (70 eV, EI), m/z (%) = 316 (M$^+$, 100), 201 (7), 137 (7), 113 (17), 99 (15), 73 (8), 55 (8).

HRMS (EI), m/z calc. for C$_{19}$H$_{24}$O$_2$S (316.1497): 316.1483.

IR (ATR) $\nu$ (cm$^{-1}$) = 3075, 3017, 2991, 2921, 2906, 2856, 1718, 1594, 1495, 1443, 1393, 1384, 1245, 1223, 1181, 1123, 1096, 1063, 1036, 1006, 966, 952, 924, 904, 883, 816, 808, 796, 761, 738, 719, 677.

Preparation of 4-(spiro[adamantane-2,2'-[1,3]dioxolan]-5-yl)benzonitrile (58b)

The cross-coupling reaction of 46c (4.5 mL, 1.0 mmol, 0.22 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromobenzonitrile (47d, 164 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 6.5:3.5) furnished 58b as a white solid (204 mg, 77 %).

m.p.: 85.3-87.6 °C.

$^{1}$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.53-7.63 (m, 2H), 7.40-7.49 (m, 2H), 3.91-4.05 (m, 4H), 2.16-2.28 (m, 2H), 1.66-2.15 (m, 12H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 155.5, 132.0, 125.9, 119.1, 110.4, 109.5, 64.4, 42.0, 40.2, 36.7, 36.0, 33.8, 27.3.

MS (70 eV, EI), m/z (%) = 295 (M$^+$, 100), 252 (27), 193 (44), 180 (15), 113 (46), 99 (61), 73 (24), 55 (18), 45 (11), 43 (50).

HRMS (EI), m/z calc. for C$_{19}$H$_{21}$NO$_2$ (295.1572): 295.1569.

IR (ATR) $\nu$ (cm$^{-1}$) = 3066, 3042, 2975, 2928, 2907, 2857, 2223, 1726, 1503, 1469, 1446, 1385, 1252, 1228, 1188, 1137, 1123, 1097, 1091, 1064, 1038, 1018, 1004, 945, 924, 905, 832, 824, 797, 731, 682.
Preparation of 5-(3,4-dimethoxyphenyl)spiro[adamantane-2,2'-[1,3]dioxolane] (58c)

The cross-coupling reaction of 46c (4.5 mL, 1.0 mmol, 0.22 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromo-1,2-dimethoxybenzene (47n, 195 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 4:6) furnished 58c as a white solid (211 mg, 71 %).

m.p.: 94.6-96.1 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 6.84-6.94 (m, 2H), 6.75-6.84 (m, 1H), 3.97 (d, J=1.1Hz, 4H), 3.88 (s, 3H), 3.85 (s, 3H), 2.24-2.20 (m, 2H), 1.99-2.08 (m, 3H), 1.95 (bs, 2H), 1.88 (bs, 2H), 1.58-1.83 (m, 5H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 148.5, 147.0, 143.0, 116.9, 110.8, 108.8, 64.3, 64.2, 55.9, 55.8, 42.7, 40.8, 36.9, 35.1, 34.0, 27.6.

MS (70 eV, EI), m/z (%) = 330 ($M^+$, 100), 215 (6), 193 (5), 151 (4), 113 (13), 99 (9), 55 (4), 43 (8).

HRMS (EI), m/z calc. for C$_{20}$H$_{26}$O$_4$ (330.1831): 330.1831.

IR (ATR) $\nu$ (cm$^{-1}$) = 3074, 3002, 2992, 2932, 2906, 2852, 2838, 1602, 1585, 1517, 1462, 1444, 1408, 1385, 1364, 1323, 1255, 1238, 1224, 1186, 1163, 1155, 1135, 1123, 1095, 1053, 1027, 1005, 955, 932, 902, 843, 797, 767, 754.

6.5 Preparation of $\alpha,\alpha'$-Diadamantyl-Sexithiophene

Preparation of 5-(adamantan-1-yl)-2,2':5',2''-terthiophene (48s)

The cross-coupling reaction of 46a (3.2 mL, 1.0 mmol, 0.32 M in THF) with Pd(OAc)$_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-2,2':5',2''-terthiophene (49h, 295 mg, 0.9 mmol) was performed according to TP2 in 2 h. Flash column chromatography (silica, pentane:Et$_2$O 100:1) furnished 48s as a yellow solid (220 mg, 64 %).
m.p.: 171.0-173.0 °C.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm) = 7.13-7.25 (m, 2H), 6.96-7.10 (m, 4H), 6.67-6.76 (m, 1H), 2.10 (bs, 3H), 1.99 (d, $J$=2.7Hz, 6H), 1.70-1.84 (m, 6H).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ (ppm) = 157.9, 137.4, 137.0, 135.5, 133.6, 127.8, 124.3, 124.2, 123.4, 123.4, 123.1, 121.1, 44.8, 36.6, 36.5, 28.8.

MS (70 eV, EI), $m/z$ (%) = 382 (M$^+$, 100), 327 (5), 326 (6), 325 (27), 292 (5), 288 (6), 261 (5), 248 (22), 42 (5), 41 (6).

HRMS (EI), $m/z$ calc. for C$_{22}$H$_{22}$S$_3$ (382.0884): 382.0870.

IR (ATR) $\nu$ (cm$^{-1}$) = 3072, 3063, 2954, 2902, 2847, 1514, 1495, 1460, 1447, 1423, 1377, 1364, 1342, 1315, 1232, 1207, 1193, 1159, 1099, 1058, 1004, 965, 912, 831, 790, 675.

**Preparation of 5-(adamantan-1-yl)-5''-bromo-2,2':5',2''-terthiophene (59)**

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 48s (180 mg, 0.4 mmol) and dissolved in 2 mL CHCl$_3$. Then, N-bromo-succinimide (75 mg, 0.42 mmol) was added and the reaction mixture was stirred over night at room temperature. The reaction was quenched with water (5 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. The pure product 59 was obtained without further purification as a colorless solid (181 mg, 98 %).

m.p.: 154.6-157.3 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 6.81-7.14 (m, 5H), 6.72 (d, $J$=3.6Hz, 1H), 2.09 (bs, 3H), 1.89-2.04 (m, 6H), 1.67-1.89 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 192.4, 158.2, 138.8, 137.5, 134.3, 133.3, 130.6, 124.5, 123.4, 123.4, 121.2, 110.7, 44.8, 36.6, 36.5, 28.8.

MS (70 eV, EI), $m/z$ (%) = 461 (M$^+$, 100), 459 (M$^+$, 90), 406 (7), 405 (25), 404 (8), 403 (23), 368 (5), 366 (6), 203 (6).

HRMS (EI), $m/z$ calc. for C$_{22}$H$_{21}$BrS$_3$ (461.9968): 461.9951.

IR (ATR) $\nu$ (cm$^{-1}$) = 3079, 3063, 2900, 2846, 1506, 1445, 1426, 1343, 1315, 1248, 1225, 1194, 1101, 1064, 1052, 1003, 969, 892, 853, 788, 692, 684, 654.
Preparation of 5,5'''''-diadamantan-1-yl)-2,2':5',2'':5'',2''':5'''',2''''':5''''''-sexithiophene (60)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (24 mg, 1 mmol), LiCl (22 mg, 0.5 mmol) and 59 (153 mg, 0.39 mmol) and dissolved in 2 mL THF. Then, the reaction mixture was cold to 0 °C and the reaction was initiated by adding a catalytic amount of iodine. The reaction mixture was stirred for 1 h slowly warming up to room temperature. After addition of Ni(dppp)Cl₂ (22 mg, 0.04 mmol) in 1 mL THF, the reaction mixture was refluxed over night. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, pentane:Et₂O 97:3) to give 60 as a yellow solid (229 mg, 77%).

m.p.: 115.3-117.0 °C.

¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.15-7.22 (m, 2H), 6.92-7.12 (m, 8H), 6.64-6.77 (m, 2H), 2.09 (bs, 6H), 1.98 (d, J=2.7Hz, 12H), 1.72-1.85 (m, 12H).

¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 157.9, 137.3, 137.0, 135.4, 133.6, 127.8, 124.3, 124.2, 123.4, 123.1, 121.1, 44.8, 36.6, 36.5, 28.8.

MS (70 eV, EI), m/z (%) = 762 (M⁺, 1), 518 (12), 517 (22), 516 (51), 384 (17), 383 (26), 382 (100), 326 (7), 325 (28), 292 (5), 288 (6).

HRMS (EI), m/z calc. for C₄₄H₄₂S₆ (762.1611): 762.1599.

IR (ATR) ν (cm⁻¹) = 3064, 2901, 2846, 1738, 1714, 1506, 1446, 1425, 1343, 1315, 1256, 1225, 1195, 1100, 1063, 1051, 1003, 969, 892, 868, 837, 790, 689, 683, 654.
7. **FULL FUNCTIONALIZATION OF THE IMIDAZOLE SCAFFOLD BY SELECTIVE METALATION AND SULFOXIDE/MAGNESIUM EXCHANGE**

### 7.1 PREPARATION OF STARTING MATERIALS

All reagents were obtained from commercial sources. Compounds $61^{259}$ and $68a^{254}$ were prepared according to literature-known procedures.

**Preparation of 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-*$N$,*$N$-dimethyl-imidazole-1-sulfonamide (67)**

![Chemical structure of 67]

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with $61$ (5.79 g, 20 mmol) and dissolved in 20 mL THF. TMPMgCl·LiCl ($62$, 20 mL, 22 mmol, 1.1 m in THF) was added and the resulting mixture was stirred for 2 h at room temperature. After cooling to -20 °C, a solution of $68a$ (3.94 g, 18 mmol) in 20 mL THF was added dropwise and stirred for 4 h while slowly warming up to room temperature. The reaction was quenched with sat. NH$_4$Cl solution (50 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 6.5:3.5) to give $67$ as a white solid (7.30 g, 86 %).

**m.p.**: 116.3-117.2 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.37 (s, 2H), 7.02 (s, 1H), 3.74 (s, 3H), 3.04 (s, 6H), 2.31 (s, 6H), 0.97 (s, 9H), 0.38 (d, $J$=1.11Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 159.9, 159.5, 138.2, 136.1, 135.9, 132.5, 125.6, 59.8, 37.9, 27.0, 18.3, 16.3, -4.0, -4.0.

**MS** (70 eV, EI), $m/z$ (%) = 456 ([M-CH$_3$]$^+$, 3), 416 (14), 415 (24), 414 (100), 168 (11), 167 (26), 166 (87), 102 (21), 73 (20).

**HRMS** (EI), $m/z$ calc. for $C_{19}H_{36}N_3O_4S_2Si$ (456.1447 ([M-CH$_3$])): 456.1442 ([M-CH$_3$]).
IR (ATR) ν (cm⁻¹) = 3124, 2981, 2953, 2930, 2885, 2853, 1472, 1457, 1364, 1250, 1178, 1146, 1138, 1095, 1058, 1005, 976, 930, 834, 823, 814, 775, 736, 667.

7.2 Typical Procedures

Typical procedure 1 (TP1): Deprotonation at position 4 with TMPMgCl-LiCl
A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 67 and dissolved in THF (1 mL/mmol). After cooling to -30 °C, TMPMgCl-LiCl (62, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 1 h at -30 °C until GC-analysis of iodolyzed reaction aliquot showed full consumption of the starting material.

Typical procedure 2 (TP2): Sulfoxide-Magnesium Exchange at position 5
A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the sulfoxide and dissolved in THF (1 mL/mmol). After cooling to -78 °C, iPrMgCl-LiCl (63, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 1 h at -78 °C until GC-analysis of iodolyzed reaction aliquot showed full consumption of the starting material.

Typical procedure 3 (TP3): Deprotonation at position 2 with TMP₂Zn·2MgCl·2LiCl
A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the imidazol derivative and dissolved in THF (1 mL/mmol). After cooling to -20 °C, TMP₂Zn·2MgCl·2LiCl (65, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 1 h at -20 °C until GC-analysis of iodolyzed reaction aliquot showed full consumption of the starting material.

Typical procedure 4 (TP4): Deprotonation at position 2 with TMPMgCl-LiCl
A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the imidazol derivative and dissolved in THF (1 mL/mmol). After cooling to -78 °C, TMPMgCl-LiCl (62, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 1 h at -78 °C until GC-analysis of iodolyzed reaction aliquot showed full consumption of the starting material.

Typical procedure 5 (TP5): Deprotection at position 2 with TBAF
A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the protected imidazol derivative and dissolved in THF (10 mL/mmol).
After cooling down to 0 °C, TBAF·3H₂O (64, 1 equiv, 0.1 M in THF) was added dropwise and the reaction mixture was stirred for 5 min. The reaction mixture was quenched with sat. NH₄Cl solution and extracted with EtOAc (3x). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

**Typical procedure 6 (TP6): Cross-coupling reactions of imidazol zinc reagents**

To the freshly prepared imidazol magnesium reagent was added ZnCl₂ (1.0M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. Pd(PPh₃)₄ (5 mol %) and the aryl iodide (0.9 or 1.1 equiv) were added and the reaction mixture was stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

**Typical procedure 7 (TP7): Allylation of imidazol zinc reagents**

To the freshly prepared imidazol magnesium reagent was added ZnCl₂ (1.0M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. CuCN·2LiCl (1.0M in THF, 1.1 equiv) and the allyl bromide (0.9 or 1.1 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the given time, the reaction mixture was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

**Typical procedure 8 (TP8): Acylation of imidazol zinc reagents**

To the freshly prepared imidazol magnesium reagent was added ZnCl₂ (1.0M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. CuCN·2LiCl (1.0M in THF, 1.1 equiv) and the acyl chloride (0.9 or 1.1 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the given time, the reaction mixture was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.
**Typical procedure 9 (TP9): Pd-catalyzed acylation of imidazol zinc reagents**

To the freshly prepared imidazol magnesium reagent was added ZnCl$_2$ (1.0M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. Pd(PPh$_3$)$_4$ (5 mol %) and the acyl chloride (0.9 or 1.1 equiv) were added and the reaction mixture was stirred for the given time at room temperature. The reaction mixture was quenched with sat. NH$_4$Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

**Typical procedure 10 (TP10): Deprotection/Reprotection**

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the protected imidazol derivative and dissolved in DCM (2 mL/mmol). Trimethyloxonium tetrafluoroborate (1 equiv) was added at room temperature and the reaction mixture was stirred over night. After removing the solvent in high vacuum, the remaining solid was dissolved in EtOH (10 mL/mmol), conc. HCl (5 ml/mmol) was added and the reaction mixture was stirred at 60 ºC for 30 min. The reaction was quenched with sat. NaHCO$_3$ solution and extracted with EtOAc (3x). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

7.3 **Selective Functionalization on Position 4 of the Imidazole Ring**

**Preparation of ethyl 4-(2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)imidazol-4-yl)benzoate (70a)**

![Chemical Structure](image)

Prepared according to **TP1** from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl-LiCl (62, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 ºC in 1 h.
Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and ethyl 4-iodobenzoate (68b, 124 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded 70a as a orange solid (234 mg, 84%).

m.p.: 132.7-133.9 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.84 (d, J=8.0Hz, 2H), 7.66 (d, J=8.0 Hz, 2H), 6.92 (s, 2H), 4.27-4.43 (m, 2H), 1.37 (t, J=7.2Hz, 3 H), 1.08 (s, 9H), 0.46 (d, J=11.9Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 166.2, 158.4, 157.7, 147.8, 136.4, 133.7, 132.9, 131.2, 130.2, 130.0, 128.3, 125.4, 60.9, 59.4, 37.9, 27.1, 18.7, 15.8, 14.3, -4.1, -4.2.

MS (70 eV, EI), m/z (%) = 604 ([M-CH₃]⁺, 3), 564 (22), 563 (40), 562 (100), 328 (18), 183 (15), 167 (25), 166 (20), 102 (17), 92 (11), 73 (49).


IR (ATR) υ (cm⁻¹) = 3056, 2980, 2936, 2853, 1716, 1474, 1376, 1282, 1272, 1171, 1130, 1109, 1097, 1050, 1012, 964, 843, 822, 779, 726, 669.

Preparation of 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (70b)

Prepared according to TP1 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (62, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.55 mL, 0.55 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and 1-iodo-4-(trifluoromethyl)benzene (68c, 122 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded 70b as a pale orange solid (201 mg, 72%).
C. EXPERIMENTAL SECTION

m.p.: 149.5-151.9 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.72 (d, $J$=8.6Hz, 2H), 7.43 (d, $J$=8.9Hz, 2H), 6.91 (s, 2H), 3.50 (s, 3H), 3.15 (s, 6H), 2.08 (s, 6H), 1.08 (s, 9H), 0.48 (s, 3H), 0.45 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 158.5, 157.7, 147.4, 135.6, 133.6, 133.1, 131.2, 130.4, 130.3 (q, $J$=32.3Hz), 125.4, 124.0 (q, $J$=3.7Hz), 124.0 (q, $J$=272.1Hz), 59.4, 37.9, 27.0, 18.6, 15.8, -4.1, -4.1.

MS (70 eV, EI), m/z (%) = 614 ([M-H]$^+$, 3), 560 (17), 559 (31), 558 (100), 167 (10), 73 (11).

HRMS (EI), m/z calc. for C$_{27}$H$_{35}$F$_3$N$_3$O$_4$S$_2$Si (614.1790 ([M-H])): 614.1781 ([M-H]).

IR (ATR) $\nu$ (cm$^{-1}$) = 3061, 2954, 2926, 2888, 2853, 1737, 1620, 1474, 1380, 1322, 1224, 1172, 1159, 1118, 1093, 1072, 1054, 1011, 959, 857, 841, 823, 817, 780, 722, 716, 668.

Preparation of 2-(tert-butyldimethylsilyl)-4-(4-chlorophenyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (70c)

Prepared according to TP1 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl-LiCl (62, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl$_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), Pd(PPh$_3$)$_4$ (29 mg, 0.025 mmol) and 1-chloro-4-iodobenzene (68d, 107 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8.5:1.5) afforded 70c as a pale yellow solid (186 mg, 71%).

m.p.: 144.8-146.1 °C.

$^1$H NMR (600 MHz, CDCl$_3$) δ (ppm) = 7.51 (d, $J$=8.5Hz, 2H), 7.12 (d, $J$=8.5Hz, 2H), 6.90 (s, 2H), 3.55 (s, 3H), 3.12 (s, 6H), 2.10 (s, 6H), 1.06 (s, 9H), 0.46 (s, 3H), 0.42 (s, 3H).
C. EXPERIMENTAL SECTION

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ (ppm) = 158.4, 157.6, 147.8, 134.5, 133.7, 132.1, 131.4, 131.2, 130.6, 127.3, 125.4, 59.5, 37.9, 27.1, 18.6, 15.9, -4.1, -4.2.

MS (70 eV, EI), $m/z$ (%) = 566 ([M-CH$_3$$]$+, 3), 527 (14), 526 (49), 525 (31), 524 (100), 290 (18), 232 (12), 193 (10), 183 (13), 167 (25), 166 (20), 102 (19), 92 (11), 73 (44).

HRMS (EI), $m/z$ calc. for C$_{25}$H$_{33}$ClN$_3$O$_4$S$_2$Si (566.1370 ([M-CH$_3$$]$]): 566.1368 ([M-CH$_3$$]$).

IR (ATR) $\nu$ (cm$^{-1}$) = 3074, 3052, 2956, 2932, 2888, 2856, 1740, 1603, 1533, 1473, 1417, 1380, 1290, 1254, 1218, 1193, 1170, 1131, 1097, 1088, 1053, 1012, 976, 965, 934, 854, 838, 822, 813, 779, 738, 726, 710, 668.

Preparation of 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-4-(4-methoxyphenyl)-N,N-dimethyl-imidazole-1-sulfonamide (70d)

Prepared according to TP1 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl-LiCl (62, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl$_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), Pd(PPh$_3$)$_4$ (29 mg, 0.025 mmol) and 1-iodo-4-methoxybenzene (68e, 105 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded 70d as a orange solid (157 mg, 60%).

m.p.: 124.4-126.3 °C.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm) = 7.57 (d, $J$=8.78Hz, 2H), 6.94 (s, 2H), 6.71 (d, $J$=8.78Hz, 2H), 3.76 (s, 3H), 3.55 (s, 3H), 3.11 (s, 6H), 2.10 (s, 6H), 1.08 (s, 9H), 0.47 (s, 3H), 0.43 (s, 3H).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ (ppm) = 160.0, 158.3, 157.5, 149.1, 134.1, 131.4, 131.0, 130.5, 125.4, 124.7, 112.6, 59.5, 55.1, 37.9, 27.1, 18.7, 15.9, -4.1, -4.1.
**Preparation of 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-4-(pyridin-4-yl)imidazole-1-sulfonamide (70e)**

Prepared according to TP1 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (62, 0.5 mL, 0.55 mmol, 1.1 M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.55 mL, 0.55 mmol, 1.0 M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and 4-iodopyridine (68f, 92 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 3:7) afforded 70e as a yellow oil (147 mg, 60%).

**1H NMR** (400 MHz, CDCl₃) δ (ppm) = 8.34-8.50 (m, 2H), 7.52-7.67 (m, 2H), 6.97 (s, 2H), 3.55 (s, 3H), 3.13 (s, 6H), 2.12 (s, 6H), 1.08 (s, 9H), 0.47 (s, 3H), 0.44 (s, 3H).

**13C NMR** (100 MHz, CDCl₃) δ (ppm) = 158.7, 157.9, 149.6, 148.9, 146.0, 133.9, 133.7, 128.5, 128.4, 124.1, 59.6, 38.0, 27.0, 18.7, 16.0, -4.2, -4.2.

**MS** (70 eV, EI), m/z (%) = 548 (M⁺, 1), 493 (15), 492 (25), 491 (100), 311 (10), 310 (19), 309 (94), 278 (21), 277 (47), 201 (11), 183 (17), 167 (13), 166 (11), 102 (11), 92 (16), 43 (27).

**HRMS** (EI), m/z calc. for C₂₇H₃₉N₃O₅S₂Si (577.2100): 577.2093.

**IR** (ATR) ν (cm⁻¹) = 3117, 2981, 2952, 2936, 2910, 2857, 1707, 1634, 1616, 1474, 1373, 1292, 1271, 1249, 1182, 1171, 1154, 1128, 1110, 1097, 1022, 975, 951, 864, 838, 820, 813, 775, 734, 725, 710, 696, 673.

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**Preparation of 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-4-(pyridin-4-yl)imidazole-1-sulfonamide (70e)**

Prepared according to TP1 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (62, 0.5 mL, 0.55 mmol, 1.1 M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.55 mL, 0.55 mmol, 1.0 M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and 4-iodopyridine (68f, 92 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 3:7) afforded 70e as a yellow oil (147 mg, 60%).

**1H NMR** (400 MHz, CDCl₃) δ (ppm) = 8.34-8.50 (m, 2H), 7.52-7.67 (m, 2H), 6.97 (s, 2H), 3.55 (s, 3H), 3.13 (s, 6H), 2.12 (s, 6H), 1.08 (s, 9H), 0.47 (s, 3H), 0.44 (s, 3H).

**13C NMR** (100 MHz, CDCl₃) δ (ppm) = 158.7, 157.9, 149.6, 148.9, 146.0, 133.9, 133.7, 128.5, 128.4, 124.1, 59.6, 38.0, 27.0, 18.7, 16.0, -4.2, -4.2.

**MS** (70 eV, EI), m/z (%) = 548 (M⁺, 1), 493 (15), 492 (25), 491 (100), 311 (10), 310 (19), 309 (94), 278 (21), 277 (47), 201 (11), 183 (17), 167 (13), 166 (11), 102 (11), 92 (16), 43 (27).

**HRMS** (EI), m/z calc. for C₂₇H₃₉N₃O₅S₂Si (577.2100): 577.2093.

**IR** (ATR) ν (cm⁻¹) = 3117, 2981, 2952, 2936, 2910, 2857, 1707, 1634, 1616, 1474, 1373, 1292, 1271, 1249, 1182, 1171, 1154, 1128, 1110, 1097, 1022, 975, 951, 864, 838, 820, 813, 775, 734, 725, 710, 696, 673.

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Preparation of \((E)-2-\text{(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-4-(oct-1-en-1-yl)-imidazole-1-sulfonamide} (70f)\)

Prepared according to \textbf{TP1} from \(2-\text{(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol)}\) and \(\text{TMPMgCl-LiCl (62, 0.5 mL, 0.55 mmol, 1.1M in THF)}\) at \(-30\,^\circ\text{C}\) in 1 h. Subsequently, the cross-coupling was accomplished according to \textbf{TP6} with \(\text{ZnCl}_2 (0.55 mL, 0.55 mmol, 1.0M in THF)}), \(\text{Pd(PPh}_3)_4 (29 mg, 0.025 mmol)\) and \((E)-1\text{-ido-oct-1-ene (68g, 107 mg, 0.45 mmol)}\) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded \(70f\) as a brown solid (216 mg, 83%).

\textbf{m.p.}: 98.9-101.2 °C.

\(\text{\textsuperscript{1}H NMR} (300 \text{ MHz, CDCl}_3 \delta (ppm) = 7.31 (s, 2H), 6.57-6.77 (m, 1H), 6.26-6.39 (m, 1H), 3.72 (s, 3H), 3.01 (s, 6H), 2.31 (s, 6H), 2.00-2.15 (m, 2H), 1.21-1.32 (m, 8H), 1.05 (s, 9H), 0.82-0.93 (m, 3H), 0.40 (s, 3H), 0.39 (s, 3H).}

\(\text{\textsuperscript{13}C NMR} (75 \text{ MHz, CDCl}_3 \delta (ppm) = 166.2, 158.4, 157.7, 147.8, 136.4, 133.7, 132.9, 131.2, 130.2, 130.0, 128.3, 125.4, 60.9, 59.4, 37.9, 27.1, 18.7, 15.8, 14.3, -4.1, -4.2.}

\(\text{MS (70 eV, EI), } m/z \% = 581 (M^+, 2), 547 (10), 526 (18), 525 (31), 524 (96), 474 (15), 473 (38), 398 (17), 291 (27), 290 (100), 257 (10), 193 (28), 183 (11), 167 (43), 166 (18).\)

\(\text{HRMS (EI), } m/z \text{ calc. for } \text{C}_{28}\text{H}_{47}\text{N}_{3}\text{O}_{4}\text{S}_{2}\text{Si (581.2777)}: 581.2766.\)

\(\text{IR (ATR) } \nu (\text{cm}^{-1}) = 3062, 2992, 2959, 2923, 2902, 2858, 1741, 1654, 1458, 1372, 1359, 1248, 1220, 1178, 1157, 1091, 1049, 1010, 944, 841, 824, 779, 725, 673, 660.\)
Preparation of ethyl 2-((2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)methyl)acrylate (70g)

Prepared according to TP1 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (62, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the allylation reaction was accomplished according to TP7 with ZnCl₂ (0.55 mL, 0.55 mmol, 1.0M in THF), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.0M in THF) and ethyl 2-(bromomethyl)acrylate (68h, 235 mg, 0.45 mmol) over night. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded 70g as a colorless solid (256 mg, 98%).

m.p.: 97.7-99.9 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.24 (s, 2H), 5.88 (d, J=1.1Hz, 1H), 4.85 (d, J=1.4Hz, 1H), 4.08-4.16 (m, 2H), 3.71 (s, 3H), 3.04 (s, 6H), 2.26 (s, 6H), 1.22-1.26 (m, 3H), 0.98 (s, 9H), 0.27-0.47 (m, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 166.4, 158.9, 156.9, 146.4, 136.7, 136.1, 132.3, 131.0, 124.9, 124.8, 60.6, 59.7, 37.9, 29.5, 26.9, 18.5, 16.2, 14.1, -4.1, -4.2.

MS (70 eV, EI), m/z (%) = 583 (M⁺, 1), 528 (16), 527 (29), 526 (100), 345 (16), 344 (11), 183 (21), 168 (10), 167 (30), 166 (33), 102 (14), 73 (29).

HRMS (EI), m/z calc. for C₃₂H₄₁N₆O₆S₂Si (583.2206): 583.2212.

IR (ATR) ν (cm⁻¹) = 3112, 2983, 2950, 2928, 2911, 2888, 2855, 1717, 1636, 1474, 1376, 1272, 1244, 1220, 1180, 1152, 1119, 1094, 1054, 1040, 1020, 1006, 960, 842, 823, 780, 726.
Preparation of 2-(tert-butyldimethylsilyl)-4-(4-chlorobenzoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (70h)

Prepared according to TP1 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (62, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the acylation reaction was accomplished according to TP8 with ZnCl₂ (0.55 mL, 0.55 mmol, 1.0M in THF), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.0M in THF) and 4-chlorobenzoyl chloride (68i, 79 mg, 0.45 mmol) over night. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded 70h as a pale yellow solid (225 mg, 82%).

**m.p.**: 139.0-140.6 °C.

**¹H NMR** (300 MHz, CDCl₃) δ (ppm) = 7.68 (d, J=8.9Hz, 2H), 7.30 (d, J=8.9Hz, 2H), 7.16 (s, 2H), 3.53 (s, 3H), 3.07 (s, 6H), 2.14 (s, 6H), 1.00 (s, 9H), 0.38-0.47 (m, 6H).

**¹³C NMR** (75 MHz, CDCl₃) δ (ppm) = 186.7, 159.0, 157.5, 144.2, 139.7, 137.9, 134.8, 134.3, 131.8, 131.4, 128.2, 125.9, 59.6, 38.1, 26.9, 18.6, 16.1, -4.0, -4.1.

**MS** (70 eV, EI), m/z (%) = 594 ([M-CH₃]+, 4), 555 (20), 554 (66), 553 (43), 552 (100), 454 (21), 183 (46), 168 (28), 167 (100), 166 (78), 139 (78), 111 (25), 108 (37), 102 (46), 75 (35), 73 (74), 43 (29).

**HRMS** (EI), m/z calc. for C₂₆H₃₃ClN₃O₅S₂Si (594.1319 ([M-CH₃])): 594.1329 ([M-CH₃]).

**IR** (ATR) ν (cm⁻¹) = 3125, 2952, 2931, 2900, 2857, 1730, 1676, 1586, 1473, 1417, 1381, 1274, 1250, 1217, 1176, 1156, 1091, 1065, 1022, 1011, 971, 902, 844, 822, 814, 781, 762, 726, 686, 670.
Preparation of ethyl 3-(2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)propiolate (70i)

Prepared according to TP1 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (67, 236 mg, 0.5 mmol) and TMPMgCl-LiCl (62, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, ZnCl₂ (0.55 mL, 0.55 mmol, 1.0M in THF) was added and stirred for 15 min at -30 °C. CuCN-2LiCl (0.55 mL, 0.55 mmol, 1.0M in THF) and ethyl 3-bromopropiolate (68j, 80 mg, 0.45 mmol) were added and the reaction mixture was stirred over night while warming up to room temperature. The reaction was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 7:3) to give 70i as a yellow oil (133 mg, 53%).

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.42 (s, 2H), 4.24 (q, J=6.8Hz, 2H), 3.73 (s, 3H), 3.09 (s, 6H), 2.32 (s, 6H), 1.31 (t, J=6.8Hz, 3H), 1.00 (s, 9H), 0.33-0.45 (m, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 159.6, 158.2, 153.0, 141.6, 134.3, 132.4, 125.4, 125.0, 86.7, 76.3, 62.1, 59.7, 38.1, 27.0, 18.4, 16.3, 14.1, -4.0, -4.0.

MS (70 eV, EI), m/z (%) = 552 ([M-CH₃]⁺, 1), 412 (38), 356 (32), 334 (36), 298 (57), 269 (58), 189 (27), 183 (44), 182 (65), 167 (91), 147 (71), 102 (87), 75 (37), 73 (100).

HRMS (EI), m/z calc. for C₂₄H₃₄N₃O₅S₂Si (552.1658 ([M-CH₃])): 552.1654 ([M-CH₃]).

IR (ATR) ν (cm⁻¹) = 3114, 2954, 2931, 2906, 2858, 2232, 1710, 1472, 1418, 1383, 1288, 1275, 1245, 1217, 1176, 1165, 1096, 1066, 1033, 1010, 971, 844, 822, 813, 781, 748, 725.
7.4 Selective Functionalization on Position 5 of the Imidazole Ring

Preparation of ethyl 4-(2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-4-(2-(ethoxycarbonyl)allyl)-imidazol-5-yl)benzoate (72a)

Prepared according to TP2 from ethyl 2-((2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)methyl)-acrylate (70g, 292 mg, 0.5 mmol) and iPrMgCl·LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and ethyl 4-iodobenzoate (68b, 124 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8.5:1.5) afforded 72a as a pale yellow solid (173 mg, 71%).

m.p.: 83.8-85.1 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 8.10 (d, J=8.0Hz, 2 H), 7.47 (d, J=8.0Hz, 2H), 6.18 (s, 1H), 5.41 (s, 1H), 4.39 (q, J=7.2Hz, 2H), 4.13 (q, J=7.0Hz, 2H), 3.37 (s, 2H), 2.28 (s, 6H), 1.40 (t, J=6.9Hz, 3H), 1.23 (t, J=7.1Hz, 3H), 1.06 (s, 6H), 0.39 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 166.8, 166.0, 155.0, 140.1, 138.4, 134.0, 131.0, 130.7, 129.2, 128.4, 125.8, 61.2, 60.6, 36.6, 29.1, 27.0, 18.6, 14.3, 14.1, -4.0.

MS (70 eV, EI), m/z (%) = 548 ([M-H]+, 1), 534 (4), 504 (5), 494 (15), 493 (30), 492 (100), 344 (6), 103 (8).

HRMS (EI), m/z calc. for C₂₆H₃₈N₃O₆SSi (548.2251 ([M-H])): 548.2239 ([M-H]).

IR (ATR) μ (cm⁻¹) = 3118, 2981, 2947, 2937, 2910, 2857, 1708, 1634, 1617, 1474, 1373, 1293, 1271, 1254, 1249, 1183, 1153, 1128, 1111, 1099, 1022, 976, 951, 864, 826, 821, 776, 735, 724, 710, 697, 673.
Preparation of ethyl 2-((2-(tert-butyldimethylsilyl)-5-(4-cyanophenyl)-1-(N,N-dimethyl-sulfamoyl)-imidazol-4-yl)methyl)acrylate (72b)

Prepared according to TP2 from ethyl 2-((2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)methyl)-acrylate (70g, 292 mg, 0.5 mmol) and iPrMgCl·LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and 4-iodobenzonitrile (68k, 103 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded 72b as a brown solid (202 mg, 90%).

m.p.: 98.3-99.7 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.72 (d, J=8.6Hz, 2H), 7.54 (d, J=8.6Hz, 2H), 6.21 (d, J=1.1Hz, 1H), 5.46 (d, J=1.4Hz, 1H), 4.14 (q, J=7.0Hz, 2H), 3.36 (s, 2H), 2.31 (s, 6H), 1.24 (t, J=7.2Hz, 3H), 1.05 (s, 9H), 0.39 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 166.6, 155.7, 140.6, 138.1, 134.4, 131.7, 131.7, 127.5, 126.1, 118.3, 112.6, 60.7, 36.7, 29.2, 27.0, 18.6, 14.1, 4.1.

MS (70 eV, EI), m/z (%) = 501 ([M-H]+, 1), 447 (11), 446 (28), 445 (100), 103 (17), 92 (19), 76 (10), 75 (28), 73 (14).

HRMS (EI), m/z calc. for C₂₄H₃₃N₄O₄Si (501.1992 ([M-H])): 501.1992 ([M-H]).

IR (ATR) ν (cm⁻¹) = 3060, 2978, 2956, 2929, 2908, 2854, 2229, 1715, 1640, 1612, 1466, 1372, 1302, 1250, 1190, 1179, 1152, 1135, 1108, 1096, 1043, 1020, 972, 848, 838, 823, 813, 776, 729, 694, 665.
Preparation of 2-(\(\text{tert}\)-butyldimethylsilyl)-\(N\),\(N\)-dimethyl-4,5-di((\(E\))-oct-1-en-1-yl)-imidazole-1-sulfonamide (72c)

Prepared according to TP2 from (\(E\))-2-(\(\text{tert}\)-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-\(N\),\(N\)-dimethyl-4-(oct-1-en-1-yl)-imidazole-1-sulfonamide (70f, 291 mg, 0.5 mmol) and \(i\)PrMgCl·LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and (\(E\))-1-iodooct-1-ene (68g, 107 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 75:1) afforded 72c as a colorless oil (202 mg, 88%).

\(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) (ppm) = 6.56-6.71 (m, 1H), 6.21-6.46 (m, 2H), 5.85-5.98 (m, 1H), 2.79 (s, 6H), 2.13-2.31 (m, 4H), 1.23-1.40 (m, 16H), 1.08 (s, 9H), 0.82-0.96 (m, 6H), 0.37 (s, 6H).

\(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) (ppm) = 153.6, 139.2, 138.1, 132.8, 126.9, 120.1, 117.5, 37.8, 33.4, 33.0, 31.7, 31.7, 29.2, 29.2, 29.0, 28.9, 27.1, 22.6, 22.6, 18.6, 14.1, 14.0, -4.2.

MS (70 eV, EI), \(m/z\) (%) = 509 (M⁺, 1), 454 (15), 453 (36), 452 (100), 389 (12), 388 (31), 377 (33), 287 (22), 262 (33), 76 (12), 73 (25), 57 (14), 43 (20), 41 (11).

HRMS (EI), \(m/z\) calc. for \(\text{C}_{27}\text{H}_{51}\text{N}_{3}\text{O}_{2}\text{SSi}\) (509.3471): 509.3456.

IR (ATR) \(\nu\) (cm⁻¹) = 3037, 2955, 2926, 2855, 1646, 1463, 1376, 1286, 1248, 1183, 1162, 1143, 1123, 1022, 962, 840, 823, 813, 777, 763, 749, 722, 668.

Preparation of (\(E\))-2-(\(\text{tert}\)-butyldimethylsilyl)-\(N\),\(N\)-dimethyl-5-((4-nitrophenyl)-4-(oct-1-en-1-yl)-imidazole-1-sulfonamide (72d)

Prepared according to TP2 from (\(E\))-2-(\(\text{tert}\)-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-\(N\),\(N\)-dimethyl-4-(oct-1-en-1-yl)-imidazole-1-sulfonamide (70f, 291 mg, 0.5 mmol) and \(i\)PrMgCl·LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and (\(E\))-1-iodooct-1-ene (68g, 107 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 75:1) afforded 72d as a colorless oil (202 mg, 88%).
291 mg, 0.5 mmol) and iPrMgCl-LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and 1-iodo-4-nitrobenzene (68l, 112 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded 72d as a yellow solid (232 mg, 100%).

m.p.: 120.2-123.1 °C.

\(^1\)H NMR (300 MHz, CDCl₃) δ (ppm) = 8.31 (d, J=8.8Hz, 2H), 7.61 (d, J=8.8Hz, 2H), 6.60-6.73 (m, 1H), 5.82-5.95 (m, 1H), 2.33 (s, 6H), 2.04-2.18 (m, 2H), 1.22-1.40 (m, 8H), 1.13 (s, 9H), 0.81-0.92 (m, 3H), 0.42 (s, 6H).

\(^{13}\)C NMR (75 MHz, CDCl₃) δ (ppm) = 156.4, 147.7, 141.2, 136.3, 135.1, 132.2, 125.2, 123.1, 118.4, 36.7, 33.0, 31.6, 29.1, 28.9, 27.1, 22.6, 18.7, 14.0, -4.3.

MS (70 eV, EI), m/z (%) = 505 ([M-CH₃]⁺, 3), 465 (14), 464 (31), 463 (100), 420 (7), 399 (9), 388 (19), 298 (8), 277 (13), 274 (9).

HRMS (EI), m/z calc. for C₂₄H₃₇N₄O₄S: 505.2305 ([M-CH₃]).

IR (ATR) ν (cm\(^{-1}\)) = 3106, 2953, 2928, 2857, 1700, 1662, 1602, 1515, 1468, 1377, 1341, 1249, 1156, 1103, 1045, 1014, 969, 862, 854, 836, 822, 812, 776, 731, 713, 668.

Preparation of (E)-ethyl 4-(2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-(oct-1-en-1-yl)-imidazol-4-yl)benzoate (72e)

Prepared according to TP2 from ethyl 4-(2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)benzoate (70a, 310 mg, 0.5 mmol) and iPrMgCl-LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and (E)-1-iodooct-1-ene (68g; 107 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded 72e as a pale yellow solid (147 mg, 60%).
m.p.: 68.9-70.4 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) = 8.01 (d, $J$=8.7Hz, 2H), 7.90 (d, $J$=8.7Hz, 2H), 6.38-6.50 (m, 1H), 5.89-6.03 (m, 1H), 4.37 (q, $J$=7.1Hz, 2H), 2.85 (s, 6H), 2.14-2.23 (m, 2H), 1.19-1.48 (m, 11H), 1.09 (s, 6H), 0.84-0.94 (m, 3H), 0.40 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) = 166.6, 154.0, 140.5, 139.1, 139.0, 129.4, 128.7, 128.5, 127.6, 117.0, 60.8, 37.8, 33.4, 31.7, 29.0, 28.5, 27.1, 22.6, 18.7, 14.3, 14.1, -4.2.

MS (70 eV, EI), $m/z$ (%) = 546 ([M-H]$^+$, 1), 504 (11), 492 (14), 491 (33), 490 (100), 426 (7), 416 (5), 415 (16), 330 (5).

HRMS (EI), $m/z$ calc. for C$_{28}$H$_{44}$N$_3$O$_4$SSi (546.2822 ([M-H])): 546.2835 ([M-H]).

IR (ATR) $\nu$ (cm$^{-1}$) = 3084, 3058, 2981, 2950, 2856, 1715, 1608, 1470, 1455, 1375, 1270, 1246, 1222, 1176, 1146, 1121, 1106, 1072, 998, 977, 862, 822, 776, 731, 713, 694, 666.

**Preparation of ethyl 4-(2-(tert-butylidimethylsilyl)-5-(4-chlorophenyl)-1-(N,N-dimethyl-sulfamoyl)-imidazol-4-yl)benzoate (72f)**

Prepared according to TP2 from ethyl 4-(2-(tert-butylidimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)benzoate (70a, 310 mg, 0.5 mmol) and iPrMgCl·LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl$_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh$_3$)$_4$ (29 mg, 0.025 mmol) and 1-chloro-4-iodobenzene (68d, 131 mg, 0.55 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded 72f as a white solid (191 mg, 70%).

m.p.: 197.7-199.3 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.88 (d, $J$=8.3Hz, 2H), 7.33-7.52 (m, 6H), 4.33 (q, $J$=7.2Hz, 2H), 2.38 (s, 6H), 1.35 (t, $J$=7.2Hz, 3H), 1.17 (s, 9H), 0.45 (s, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 166.4, 155.0, 139.9, 137.6, 135.7, 132.8, 129.4, 129.1, 128.8, 128.4, 127.9, 126.6, 60.8, 36.5, 27.1, 18.8, 14.3, -4.2.
MS (70 eV, El), m/z (%) = 546 ([M-H]+, 1), 504 (7), 493 (13), 492 (42), 491 (30), 490 (100), 398 (11), 372 (7), 107 (9), 102 (8), 76 (17).

HRMS (El), m/z calc. for C_{28}H_{33}ClN_{3}O_{4}S_{2}Si (546.1650 ([M-H])): 546.1634 ([M-H]).

IR (ATR) υ (cm⁻¹) = 3092, 2991, 2976, 2956, 2934, 2904, 2886, 2854, 1707, 1612, 1472, 1384, 1272, 1246, 1162, 1108, 1084, 1044, 1015, 981, 844, 823, 816, 779, 731, 724, 669.

**Preparation of ethyl 4-(2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-4-(4-(trifluoromethyl)phenyl)-imidazol-5-yl)benzoate (72g)**

![Chemical Structure](image)

Prepared according to TP2 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (70b, 308 mg, 0.5 mmol) and iPrMgCl·LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and ethyl 4-iodobenzoate (68b, 124 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded 72g as a brown solid (223 mg, 80%).

m.p.: 110.8-112.4 °C.

^1H NMR (300 MHz, CDCl₃) δ (ppm) = 8.17 (d, J=8.0Hz, 2H), 7.53 (d, J=8.0Hz, 2H), 7.37-7.49 (m, 4H), 4.43 (q, J=7.2Hz, 2H), 2.33 (s, 6H), 1.17 (s, 9H), 0.45 (s, 6H).

^13C NMR (75 MHz, CDCl₃) δ (ppm) = 165.9, 155.1, 139.6, 136.7, 134.6, 131.5, 131.4, 129.9 (q, J=32.3Hz), 128.8, 128.0, 127.0, 125.1 (q, J=3.7Hz), 124.2 (q, J=271.8Hz), 61.4, 36.5, 27.1, 18.8, 14.3, -4.2.

MS (70 eV, El), m/z (%) = 580 ([M-H]+, 2), 538 (9), 526 (11), 525 (31), 524 (100), 107 (13), 92 (20), 76 (20).

HRMS (El), m/z calc. for C_{28}H_{38}N_{3}O_{6}S_{2}Si (580.1913 ([M-H])): 580.1905 ([M-H]).

IR (ATR) υ (cm⁻¹) = 2954, 2935, 2901, 2857, 1718, 1619, 1475, 1464, 1378, 1323, 1284, 1273, 1250, 1160, 1119, 1107, 1086, 1064, 1043, 1017, 973, 847, 823, 814, 782, 776, 733, 725, 712, 697, 669.
Preparation of 2-(tert-butyldimethylsilyl)-5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (72h)

Prepared according to TP2 from 2-(tert-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (70b, 308 mg, 0.5 mmol) and iPrMgCl·LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and 1-chloro-4-iodobenzene (68d, 131 mg, 0.55 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded 72h as a white solid (217 mg, 80%).

m.p.: 175.5-177.0 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.42-7.55 (m, 6H), 7.34-7.41 (m, 2H), 2.39 (s, 6H), 1.17 (s, 9H), 0.45 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 155.0, 139.5, 136.8, 135.8, 132.8, 129.2, 128.9 (q, J=32.3Hz), 128.3, 127.8, 126.9, 125.1 (q, J=3.9Hz), 124.2 (q, J=272.1Hz), 36.5, 27.1, 18.8, -4.2.

MS (70 eV, EI), m/z (%) = 543 (M⁺, 1), 489 (11), 488 (40), 487 (26), 486 (100), 379 (6), 107 (10), 92 (14), 76 (12).

HRMS (EI), m/z calc. for C₂₄H₂₉ClF₃N₃O₂Si (543.1390): 543.1399.

IR (ATR) ν (cm⁻¹) = 3060, 2978, 2959, 2937, 2890, 2855, 1620, 1486, 1377, 1325, 1248, 1159, 1126, 1108, 1086, 1065, 1043, 1016, 977, 844, 837, 822, 815, 779, 746, 728, 719.
Preparation of 2-(tert-butyldimethylsilyl)-4-(4-chlorophenyl)-N,N-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (72i)

Prepared according to TP2 from 2-(tert-butyldimethylsilyl)-4-(4-chlorophenyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-N,N-dimethyl-imidazole-1-sulfonamide (70c, 291 mg, 0.5 mmol) and iPrMgCl-LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and 1-iodo-4-(trifluoromethyl)benzene (68c, 123 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded 72i as a white solid (166 mg, 68%).

m.p.: 199.3-200.5 °C.

¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.75 (d, J=8.1Hz, 2H), 7.58 (d, J=8.2Hz, 2H), 7.23-7.33 (m, 2H), 7.09-7.21 (m, 2H), 2.33 (s, 6H), 1.17 (s, 9H), 0.45 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 155.1, 140.1, 134.1, 133.1, 132.0, 131.5, 131.4 (q, J=33.0Hz), 128.4, 128.2, 126.5, 125.6 (q, J=3.8Hz), 123.8 (q, J=272.6Hz), 36.4, 27.1, 18.8, -4.2.

MS (70 eV, EI), m/z (%) = 528 ([M-CH₃]+, 4), 489 (12), 488 (51), 487 (33), 486 (100), 394 (11), 107 (15), 102 (11), 92 (21), 43 (12).

HRMS (EI), m/z calc. for C₂₃H₂₆ClF₃N₃O₂SSi 528.1156 ([M-CH₃]): 528.1155 ([M-CH₃]).

IR (ATR) v (cm⁻¹) = 3087, 3056, 2982, 2958, 2937, 2910, 2895, 2858, 1621, 1516, 1486, 1408, 1374, 1327, 1295, 1263, 1249, 1204, 1190, 1156, 1120, 1107, 1092, 1080, 1068, 1041, 1016, 976, 956, 935, 854, 847, 837, 828, 819, 778, 732, 698, 674.
Preparation of ethyl 4-(2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-fluorophenyl)(hydroxy)methyl)-imidazol-4-yl)benzoate (72j)

Prepared according to TP2 from ethyl 4-(2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)benzoate (70a, 310 mg, 0.5 mmol) and iPrMgCl-LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, 4-fluorobenzaldehyde (68m, 56 mg, 0.45 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred over night. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 7:3) to give 72j as a yellow solid (250 mg, 100%).

m.p.: 143.4-146.0 °C.

¹H NMR (400 MHz, d₆-DMSO) δ (ppm) = 7.79-7.91 (m, 2H), 7.74 (d, J=8.5Hz, 2H), 7.08-7.21 (m, 2H), 6.87-7.04 (m, 2H), 6.57 (d, J=4.4Hz, 1H), 6.34 (d, J=4.4Hz, 1H), 4.23 (q, J=7.1Hz, 2H), 2.80 (s, 6H), 1.26 (t, J=7.1Hz, 3H), 1.05 (s, 9H), 0.23-0.50 (m, 6H).

¹³C NMR (100 MHz, d₆-DMSO) δ (ppm) = 165.9, 161.4 (d, J=242.7Hz), 153.6, 141.2, 138.3, 138.1 (d, J=2.9Hz), 133.5, 129.0, 128.7, 128.6, 128.1 (d, J=8.2Hz), 114.9 (d, J=21.4Hz), 63.7, 61.0, 37.6, 27.6, 18.9, 14.5, -3.5, -3.6.

MS (70 eV, EI), m/z (%) = 561 (M⁺, 1), 506 (15), 505 (32), 504 (100), 123 (11), 102 (12), 92 (35), 75 (24), 73 (20).

HRMS (EI), m/z calc. for C₂₇H₃₆FN₃O₅S₂Si (561.2129): 561.2122.

IR (ATR) ν (cm⁻¹) = 3408, 3068, 2987, 2951, 2933, 2909, 2856, 1683, 1609, 1510, 1474, 1417, 1380, 1366, 1278, 1256, 1250, 1220, 1178, 1164, 1148, 1133, 1110, 1069, 1032, 1019, 968, 858, 835, 821, 812, 794, 778, 721, 696, 670.
Preparation of \((E)-2-(\text{tert-butyl}d\text{imethyl}silyl)-5-(4\text{-chlorobenzoyl})-N,N\text{-dimethyl}-4-(\text{oct}-1\text{-en}-1\text{-yl})\text{-imidazole-1-sulfonamide (72k)}

Prepared according to TP2 from \((E)-2-(\text{tert-butyl}d\text{imethyl}silyl)-5-((4\text{-methoxy-3,5-dimethylphenyl)-sulfinyl})-N,N\text{-dimethyl}-4-(\text{oct}-1\text{-en}-1\text{-yl})\text{-imidazole-1-sulfonamide (70f, 291 mg, 0.5 mmol) and }\text{iPrMgCl·LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the Pd-catalyzed acylation was accomplished according to TP9 with ZnCl\(_2\) (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh\(_3\))\(_4\) (29 mg, 0.025 mmol) and 4-chlorobenzoyl chloride (68i, 96 mg, 0.55 mmol) over night at room temperature. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded 72k as a yellow oil (212 mg, 79%).

\(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta (\text{ppm) = 7.76 (d, } J=8.3Hz, \text{ 2H), 7.45 (d, } J=8.6Hz, \text{ 2H), 6.56-6.74 (m, 1H), 5.77-5.92 (m, 1H), 2.72 (s, 6H), 1.94-2.14 (m, 2H), 1.18-1.37 (m, 8H), 1.10 (s, 9H), 0.81-0.93 (m, 3H), 0.44 (s, 6H).}

\(^13\text{C NMR (75 MHz, CDCl}_3\) \(\delta (\text{ppm) = 186.4, 157.7, 143.8, 140.4, 136.8, 136.2, 131.2, 129.0, 125.5, 118.9, 37.9, 32.8, 31.6, 28.8, 28.7, 27.1, 22.5, 18.6, 14.0, -4.2.}

\text{MS (70 eV, EI, } m/z (\%) = 522 ([M-CH}_3]+, 3), 483 (12), 482 (46), 481 (28), 480 (100), 389 (17), 287 (11), 140 (13), 139 (35), 92 (43), 76 (16), 75 (13), 73 (45), 56 (10), 41 (11).

\text{HRMS (EI, } m/z \text{ calc. for } C_{25}H_{37}ClN_3O_3SSi 522.2013 ([M-CH}_3]): 522.2131 ([M-CH}_3]).

\text{IR (ATR) } \nu (\text{cm}^{-1}) = 3031, 2955, 2928, 2856, 1659, 1587, 1464, 1373, 1250, 1218, 1169, 1157, 1090, 1014, 967, 924, 842, 823, 814, 780, 762, 736, 724, 683, 670.
Preparation of ethyl 4-(2-(tert-butyldimethylsilyl)-5-(4-chlorobenzoyl)-1-\((N,N\)-dimethyl-sulfamoyl)-imidazol-4-yl)benzoate (72l)

Prepared according to TP2 from ethyl 4-(2-(tert-butyldimethylsilyl)-1-(\(N\),\(N\)-dimethyl-sulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)benzoate (70a, 310 mg, 0.5 mmol) and \(i\)PrMgCl-LiCl (63, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the Pd-catalyzed acylation was accomplished according to TP9 with ZnCl\(_2\) (0.6 mL, 0.6 mmol, 1.0M in THF), Pd(PPh\(_3\))\(_4\) (29 mg, 0.025 mmol) and 4-chlorobenzoyl chloride (68i, 96 mg, 0.55 mmol) over night at room temperature. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9:1) afforded 72l as a white solid (190 mg, 66%).

\textbf{m.p.:} 143.4-146.0 °C.

\(\text{\(^1\)H NMR}\ (400\ MHz, CDCl}\_3\) \(\delta\) (ppm) = 7.90 (d, \(J=8.8\)Hz, 2H), 7.71 (d, \(J=9.0\)Hz, 2H), 7.62 (d, \(J=8.8\)Hz, 2H), 7.36 (d, \(J=8.8\)Hz, 2H), 4.32 (q, \(J=7.0\)Hz, 2H), 2.73 (s, 6H), 1.34 (t, \(J=7.1\)Hz, 3H), 1.13 (s, 9H), 0.47 (s, 6H).

\(\text{\(^{13}\)C NMR}\ (100\ MHz, CDCl}\_3\) \(\delta\) (ppm) = 188.3, 166.2, 155.8, 141.5, 141.1, 136.3, 135.1, 131.0, 129.8, 129.7, 129.3, 127.1, 126.2, 61.0, 37.9, 27.1, 18.6, 14.3, -4.1.

\(\text{MS}\ (70\ eV, \text{EI}), \ m/z\) (%): 560 ([M-CH\(_3\)]\(^+\), 1), 463 (20), 461 (51), 354 (43), 325 (18), 309 (33), 138 (62), 111 (28), 108 (100), 44 (28), 43 (31).

\(\text{HRMS}\ (\text{EI}), \ m/z\) calc. for C\(_{26}\)H\(_{31}\)ClN\(_3\)O\(_5\)SSi (560.1442 ([M-CH\(_3\)])): 560.1459 ([M-CH\(_3\)]).

\(\text{IR}\ (\text{ATR})\ \nu\) (cm\(^{-1}\)) = 3085, 3066, 2978, 2954, 2928, 2852, 1784, 1720, 1659, 1586, 1379, 1355, 1273, 1245, 1231, 1183, 1167, 1140, 1100, 1092, 1073, 1019, 995, 976, 902, 841, 822, 780, 771, 743, 733, 726, 698, 671.
7.5 Selective Functionalization on Position 2 of the Imidazole Ring

7.5.1 Selective Deprotection on Position 2

Preparation of ethyl 4-(5-(4-chlorophenyl)-1-(N,N-dimethylsulfamoyl)-imidazol-4-yl)-benzoate (73a)

Prepared according to TP5 from ethyl 4-(2-(tert-butyldimethylsilyl)-5-(4-chlorophenyl)-1-(N,N-dimethyl-sulfamoyl)-imidazol-4-yl)benzoate (72f, 619 mg, 1.13 mmol) and TBAF·3H2O (64, 357 mg, 1.13 mmol, 0.1M in THF) at 0 °C in 5 min. Flash column chromatographical purification on silica gel (pentane/EtOAc, 1:1) afforded 73a as a pale yellow solid (456 mg, 93%).

m.p.: 165.4-167.3 °C.

1H NMR (300 MHz, CDCl3) δ (ppm) = 8.13 (s, 1H), 7.90 (d, J=8.3Hz, 2H), 7.35-7.50 (m, 6H), 4.33 (q, J=7.2Hz, 2H), 2.52 (s, 6H), 1.36 (t, J=7.0Hz, 3H).

13C NMR (75 MHz, CDCl3) δ (ppm) = 166.3, 140.0, 139.1, 137.0, 136.2, 133.2, 129.6, 129.3, 129.2, 127.1, 126.8, 126.0, 60.9, 37.2, 14.3.

MS (70 eV, El), m/z (%) = 433 (M⁺, 100), 325 (42), 253 (18), 252 (26), 218 (22), 133 (17), 123 (40), 108 (28), 57 (19).

HRMS (El), m/z calc. for C20H20ClN3O4S (433.0863): 433.0856.

IR (ATR) ν (cm⁻¹) = 3147, 3088, 3071, 2957, 2923, 2866, 2854, 1707, 1612, 1484, 1474, 1382, 1364, 1268, 1254, 1246, 1185, 1169, 1135, 1100, 1092, 1081, 1018, 1005, 977, 966, 938, 863, 835, 780, 742, 722, 696.
Preparation of 5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73b)

Prepared according to TP5 from 2-(tert-butyldimethylsilyl)-5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(tri-fluoromethyl)phenyl)-imidazole-1-sulfonamide (72h, 1.43 g, 2.63 mmol) and TBAF·3H₂O (64, 829 mg, 2.63 mmol, 0.1M in THF) at 0 °C in 5 min. Flash column chromatographical purification on silica gel (pentane/EtOAc, 6.5:3.5) afforded 73b as a white solid (1.06 g, 94%).

m.p.: 157.7-159.2 °C.

^1H NMR (300 MHz, CDCl₃) δ (ppm) = 8.13 (s, 1H), 7.43-7.52 (m, 6H), 7.36-7.43 (m, 2H), 2.53 (s, 6H).

^13C NMR (75 MHz, CDCl₃) δ (ppm) = 139.6, 139.1, 136.3, 136.2, 133.1, 129.3 (q, J=32.5Hz), 129.2, 127.2, 127.0, 126.0, 125.3 (q, J=3.7Hz), 124.1 (q, J=272.1Hz), 37.2.  

MS (70 eV, EI), m/z (%) = 429 (M⁺, 100), 323 (28), 322 (21), 321 (75), 286 (46), 157 (27), 152 (12), 150 (27), 137 (11), 123 (57), 108 (72), 57 (19), 44 (12).

HRMS (EI), m/z calc. for C₁₈H₁₅ClF₃N₃O₂S (429.0526): 429.0522.

IR (ATR) υ (cm⁻¹) = 3138, 3122, 2956, 2930, 2856, 1618, 1479, 1390, 1325, 1240, 1206, 1166, 1141, 1117, 1106, 1084, 1062, 1022, 1014, 1003, 960, 940, 846, 832, 742, 725, 715.

Preparation of 4-(4-chlorophenyl)-N,N-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73c)

Prepared according to TP5 from 2-(tert-butyldimethylsilyl)-4-(4-chlorophenyl)-N,N-dimethyl-5-(4-(tri-fluoromethyl)phenyl)-imidazole-1-sulfonamide (72i, 544 mg, 1.0 mmol) and TBAF-3H₂O (64, 316 mg, 1.0 mmol, 0.1M in THF) at 0 °C in 5 min.
Flash column chromatographical purification on silica gel (pentane/EtOAc, 6.5:3.5) afforded 73c as a white solid (430 mg, 100%).

**m.p.:** 201.7-203.2 °C.

**$^1$H NMR** (400 MHz, CDCl$_3$) δ (ppm) = 8.13 (s, 1H), 7.72 (d, $J$=8.0Hz, 2H), 7.59 (d, $J$=8.0Hz, 2H), 7.23-7.32 (m, 2H), 7.16-7.23 (m, 2H), 2.50 (s, 6H).

**$^{13}$C NMR** (150 MHz, CDCl$_3$) δ (ppm) = 140.3, 139.2, 133.6, 132.7, 132.4, 131.8 (q, $J$=33.0Hz), 130.9, 128.6, 128.5, 125.6 (q, $J$=3.5Hz), 124.7, 123.7 (q, $J$=272.6Hz), 37.2.

**MS** (70 eV, El), $m/z$ (%) = 429 (M$^+$, 100), 323 (25), 322 (19), 321 (67), 286 (41), 122 (59), 108 (73), 57 (17), 44 (13), 43 (19).

**HRMS** (EI), $m/z$ calc. for C$_{18}$H$_{15}$ClF$_3$N$_3$O$_2$S (429.0526): 429.0520.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3150, 3127, 3066, 2976, 2937, 2937, 1701, 1622, 1493, 1461, 1412, 1392, 1330, 1270, 1240, 1207, 1171, 1161, 1140, 1118, 1106, 1094, 1081, 1070, 1052, 1024, 1014, 1004, 959, 940, 859, 844, 836, 827, 754, 737, 726, 696, 656.

### 7.5.2 Selective Functionalization on Position 2

**Preparation of ethyl 4-(5-(4-chlorophenyl)-1-(N,N-dimethylsulfamoyl)-2-(2-(ethoxy-carbonyl)allyl)-imidazol-4-yl)benzoate (76a)**

Prepared according to TP3 from ethyl 4-(5-(4-chlorophenyl)-1-(N,N-dimethylsulfamoyl)-imidazol-4-yl)benzoate (73a, 109 mg, 0.25 mmol) and TMP$_2$Zn·2MgCl·2LiCl (65, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the allylation reaction was accomplished according to TP7 with CuCN·2LiCl (0.25 mL, 0.25 mmol, 1.0M in THF) and ethyl 2-(bromomethyl)acrylate (68h, 53 mg, 0.275 mmol) in 1.5 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7.5:2.5) afforded 76a as a yellow oil (121 mg, 81%).

**$^1$H NMR** (300 MHz, CDCl$_3$) δ (ppm) = 7.84 (d, $J$=8.8Hz, 2H), 7.38-7.51 (m, 2H), 7.29-7.38 (m, 4H), 6.33 (s, 1H), 5.60 (s, 1H), 4.19-4.37 (m, 4H), 4.11 (s, 2H), 2.49 (s, 6H), 1.27-1.37 (m, 6H).
\[^{13}\text{C NMR}\] (75 MHz, CDCl\(_3\)) \(\delta\) ppm = 166.7, 166.4, 148.8, 137.4, 137.2, 137.1, 135.8, 133.3, 129.4, 129.4, 129.0, 128.9, 128.2, 127.0, 126.9, 126.0, 60.9, 60.9, 37.0, 14.3, 14.3.

\[^{\text{MS}}\] (70 eV, EI), \(m/z\) (%) = 545 (M\(^+\), 9), 440 (18), 439 (45), 438 (51), 437 (100), 409 (14), 366 (17), 365 (14), 364 (19), 43 (42).

\[^{\text{HRMS}}\] (EI), \(m/z\) calc. for \(\text{C}_{26}\text{H}_{28}\text{ClN}_{4}\text{O}_{6}\text{S}\) (545.1387): 545.1374.

\[^{\text{IR}}\] (ATR) \(\nu\) (cm\(^{-1}\)) = 2979, 2935, 2912, 2873, 1712, 1611, 1482, 1450, 1380, 1273, 1168, 1124, 1092, 1079, 1017, 975, 838, 825, 780, 722.

**Preparation of ethyl 4-(5-(4-chlorophenyl)-1-(N,N-dimethylsulfamoyl)-2-(4-nitrophenyl)imidazol-4-yl)benzoate (76b)**

![Chemical Structure]

Prepared according to TP3 from ethyl 4-(5-(4-chlorophenyl)-1-(N,N-dimethylsulfamoyl)-imidazol-4-yl)-benzoate (73a, 109 mg, 0.25 mmol) and TMP\(_2\)Zn·2MgCl·2LiCl (65, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with \(\text{Pd(PPh}_3)_4\) (14 mg, 0.0125 mmol) and 1-iodo-4-nitrobenzene (68l, 56 mg, 0.225 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:5:2:5) afforded 76b as a yellow solid (91 mg, 76%).

\[^{\text{m.p.}}\]: 131.0-133.6 °C.

\[^{1}\text{H NMR}\] (300 MHz, CDCl\(_3\)) \(\delta\) ppm = 8.27-8.37 (m, 2H), 7.84-7.98 (m, 4H), 7.37-7.56 (m, 6H), 4.34 (q, \(J=7.2\text{Hz}\), 2H), 2.39 (s, 6H), 1.36 (t, \(J=7.2\text{Hz}\), 3H).

\[^{13}\text{C NMR}\] (75 MHz, CDCl\(_3\)) \(\delta\) ppm = 166.2, 148.5, 148.3, 138.7, 138.7, 138.8, 136.6, 136.1, 132.6, 130.9, 129.6, 129.6, 129.3, 129.1, 127.6, 127.2, 123.0, 61.0, 37.1, 14.3.

\[^{\text{MS}}\] (70 eV, EI), \(m/z\) (%) = 554 (M\(^+\), 2), 449 (44), 448 (33), 447 (100), 419 (17), 417 (25), 402 (15), 373 (11), 340 (22), 177 (18), 150 (11), 139 (16).

\[^{\text{HRMS}}\] (EI), \(m/z\) calc. for \(\text{C}_{26}\text{H}_{23}\text{ClN}_{4}\text{O}_{6}\text{S}\) (554.1027): 554.1015.

\[^{\text{IR}}\] (ATR) \(\nu\) (cm\(^{-1}\)) = 3095, 2983, 2947, 2924, 2911, 2860, 1719, 1604, 1519, 1483, 1383, 1351, 1267, 1240, 1168, 1134, 1125, 1107, 1098, 1091, 1078, 1018, 1006, 974, 953, 856, 832, 780, 760, 737, 728, 718, 696.
Preparation of ethyl 2-((5-(4-chlorophenyl)-1-(N,N-dimethylsulfamoyl)-4-(4-(trifluoromethyl)phenyl)-imidazol-2-yl)methyl)acrylate (76c)

Prepared according to TP3 from 5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73b, 109 mg, 0.25 mmol) and TMP₂Zn·2MgCl·2LiCl (65, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the allylation reaction was accomplished according to TP7 with CuCN·2LiCl (0.25 mL, 0.25 mmol, 1.0M in THF) and ethyl 2-(bromomethyl)acrylate (68h, 44 mg, 0.225 mmol) over night. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded 76c as a white solid (105 mg, 86%).

m.p.: 86.3-89.3 °C.

$^1$H NMR (300 MHz, CDCl₃) δ (ppm) = 7.28-7.55 (m, 8H), 6.34 (s, 1H), 5.61 (s, 1H), 4.26 (q, $J=7.2$ Hz, 2H), 4.11 (s, 2H), 2.51 (s, 6H), 1.31 (t, $J=7.0$Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl₃) δ (ppm) = 166.7, 148.8, 137.1, 137.0, 136.3, 135.9, 133.3, 129.0 (q, $J=32.5$Hz), 129.0, 128.1, 127.1, 126.9, 126.0, 125.0 (q, $J=3.7$Hz), 124.1 (q, $J=272.1$Hz), 60.9, 37.0, 33.4, 14.2.

MS (70 eV, EI), m/z (%) = 541 (M⁺, 5), 436 (13), 435 (40), 434 (38), 433 (100), 405 (15), 389 (14), 388 (14), 387 (19), 362 (20), 361 (22), 360 (24), 359 (20), 108 (14), 43 (27).

HRMS (EI), m/z calc. for C₂₄H₂₃ClF₃N₃O₄S (541.1050): 541.1043.

IR (ATR) ν (cm⁻¹) = 3096, 3003, 2984, 2928, 2882, 2855, 1724, 1618, 1423, 1391, 1324, 1306, 1204, 1169, 1155, 1118, 1108, 1091, 1079, 1064, 1017, 969, 960, 948, 850, 832, 822, 808, 744, 724, 714.
Preparation of ethyl 4-(5-(4-chlorophenyl)-1-\((N,N\text{-dimethylsulfamoyl})\)-4-(4-(trifluoromethyl)phenyl)-imidazol-2-yl)benzoate (76d)

Prepared according to TP3 from 5-(4-chlorophenyl)-\(N,N\text{-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73b, 109 mg, 0.25 mmol) and TMP\textsubscript{2}Zn·2MgCl·2LiCl (65, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with Pd(PPh\textsubscript{3})\textsubscript{4} (14 mg, 0.0125 mmol) and ethyl 4-iodobenzoate (68b, 76 mg, 0.275 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded 76d as a pale yellow solid (104 mg, 72%).

\textbf{m.p.:} 157.8-159.3 °C.

\textbf{\(^1\text{H NMR}\)} (300 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) = 8.10-8.22 (m, 2H), 7.77-7.88 (m, 2H), 7.40-7.54 (m, 8H), 4.41 (q, \(J=7.2Hz\), 2H), 2.38 (s, 6H), 1.42 (t, \(J=7.0Hz\), 3H).

\textbf{\(^{13}\text{C NMR}\)} (75 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) = 166.0, 149.4, 137.8, 136.1, 136.1, 135.8, 135.6, 132.6, 131.5, 129.9, 129.4 (q, \(J=32.5Hz\)), 129.2, 129.1, 128.1, 127.5, 125.2 (q, \(J=3.9Hz\)), 124.1 (q, \(J=271.8Hz\)), 61.3, 37.1, 14.3.

\textbf{MS} (70 eV, EI), \(m/z\) (%) = 577 (M\textsuperscript{+}, 5), 472 (29), 471 (52), 470 (92), 469 (100), 161 (13), 157 (12), 133 (12), 122 (12).

\textbf{HRMS} (EI), \(m/z\) calc. for \(\text{C}_{27}\text{H}_{23}\text{ClF}_{3}\text{N}_{3}\text{O}_{4}\text{S}\) (577.1050): 577.1043.

\textbf{IR} (ATR) \(\nu\) (cm\textsuperscript{-1}) = 3087, 3062, 2984, 2972, 2956, 2934, 2904, 2872, 2855, 1721, 1618, 1489, 1389, 1326, 1288, 1277, 1167, 1125, 1106, 1090, 1081, 1064, 1018, 1005, 971, 850, 833, 778, 740, 729, 718.
Preparation of 5-(4-chlorophenyl)-2-(4-cyanophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76e)

Prepared according to TP3 from 5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73b, 109 mg, 0.25 mmol) and TMP₂Zn·2MgCl·2LiCl (65, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with Pd(PPh₃)₄ (14 mg, 0.0125 mmol) and 4-iodobenzonitrile (68k, 52 mg, 0.225 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded 76e as a pale brown solid (113 mg, 95%).

m.p.: 142.4-144.3 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.82-7.91 (m, 2H), 7.71-7.81 (m, 2H), 7.45-7.52 (m, 8H), 2.38 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 148.7, 138.2, 136.2, 136.0, 135.9, 132.6, 131.6, 130.6, 129.8 (q, J=32.3Hz), 129.4, 128.9, 127.6, 127.5, 125.2 (q, J=3.9Hz), 124.0 (q, J=271.8Hz), 118.4, 113.3, 37.1.

MS (70 eV, EI), m/z (%) = 530 (M⁺, 8), 425 (33), 424 (58), 423 (86), 422 (100), 267 (15), 157 (17), 123 (22), 114 (42), 108 (16), 43 (12).

HRMS (EI), m/z calc. for C₂₅H₁₈ClF₃N₄O₂S (530.0791): 530.0785.

IR (ATR) ν (cm⁻¹) = 3094, 3056, 2983, 2955, 2929, 2858, 2229, 1926, 1720, 1612, 1605, 1520, 1384, 1351, 1324, 1312, 1297, 1270, 1203, 1169, 1135, 1118, 1109, 1096, 1082, 1063, 1017, 1008, 974, 956, 853, 848, 832, 748, 729, 722, 696.
Preparation of 5-(4-chlorophenyl)-2-((4-fluorophenyl)(hydroxy)methyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76f)

Prepared according to TP4 from 5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73b, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (62, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, 4-fluorobenzaldehyde (68m, 34 mg, 0.275 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 6 h. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 7:3) to give 76f as a white solid (127 mg, 92%).

**m.p.:** 155.1-157.8 °C.

**¹H NMR** (600 MHz, CDCl₃) δ (ppm) = 7.44-7.52 (m, 6H), 7.33-7.44 (m, 4H), 7.06 (t, J=8.6Hz, 2H), 6.28 (d, J=6.7Hz, 1H), 4.47 (d, J=7.9Hz, 1H), 2.23 (s, 6H).

**¹³C NMR** (150 MHz, CDCl₃) δ (ppm) = 162.5 (d, J=246.8Hz), 152.4, 137.3 (d, J=3.1Hz), 136.7, 136.4, 135.7, 133.3, 133.3, 129.5 (d, J=8.1Hz), 129.4 (q, J=32.5Hz), 129.2, 127.6, 127.1, 125.2 (q, J=3.9Hz), 124.0 (q, J=271.5Hz), 115.4 (d, J=21.3Hz), 70.1, 36.6.

**MS** (70 eV, EI), m/z (%) = 553 (M⁺, 12), 431 (35), 430 (48), 429 (100), 428 (71), 417 (21), 323 (17), 321 (41), 286 (24), 156 (17), 123 (64), 120 (24), 108 (56), 61 (15), 57 (21), 44 (18), 43 (31).

**HRMS** (EI), m/z calc. for C₂₅H₂₀ClF₄N₃O₃S (553.0850): 553.0841.

**IR** (ATR) ν (cm⁻¹) = 3387, 3003, 2960, 2929, 2857, 1619, 1604, 1508, 1382, 1327, 1222, 1170, 1120, 1111, 1086, 1064, 1016, 977, 962, 854, 838, 747, 724.
Preparation of 5-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76g)

Prepared according to TP4 from 5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73b, 109 mg, 0.25 mmol) and TMPMgCl-LiCl (62, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, S-(3,4-dichlorophenyl) benzenesulfonothioate (68n, 72 mg, 0.225 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred over night. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 8.5:1.5) to give 76g as a white solid (127 mg, 93%).

m.p.: 131.1-133.0 °C.

¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.83 (d, J=1.7Hz, 1H), 7.32-7.53 (m, 8H), 7.23-7.31 (m, 2H), 2.65 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 145.5, 138.4, 136.2, 136.0, 135.8, 133.8, 133.7, 133.3, 132.9, 130.8, 129.9, 129.4 (q, J=32.5Hz), 129.1, 128.6, 127.6, 126.9, 125.1 (q, J=3.7Hz), 124.0 (q, J=272.1Hz), 37.5.

MS (70 eV, EI), m/z (%) = 605 (M⁺, 23), 502 (21), 501 (47), 500 (67), 498 (57), 497 (100), 465 (17), 464 (61), 462 (82), 461 (23), 439 (46), 191 (17), 189 (24), 154 (17), 43 (49).

HRMS (EI), m/z calc. for C₂₄H₁₇Cl₂F₃N₃O₂S₂ (604.9780): 604.9778.

IR (ATR) ν (cm⁻¹) = 3092, 2994, 2956, 2920, 2851, 1618, 1487, 1455, 1410, 1379, 1322, 1250, 1223, 1190, 1165, 1122, 1108, 1094, 1082, 1062, 1045, 1033, 1016, 972, 951, 851, 834, 815, 747, 728, 710.
Preparation of 2-(4-chlorobenzoyl)-5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)imidazole-1-sulfonamide (76h)

Prepared according to TP4 from 5-(4-chlorophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)imidazole-1-sulfonamide (73b, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (62, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, the Pd-catalyzed acylation was accomplished according to TP9 with ZnCl₂ (0.3 mL, 0.3 mmol, 1.0M in THF), Pd(PPh₃)₄ (14 mg, 0.0125 mmol) and 4-chlorobenzoyl chloride (68i, 48 mg, 0.275 mmol) over night at room temperature. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8.5:1.5) afforded 76h as a pale yellow solid (83 mg, 58%).

m.p.: 245.4-246.2 °C.

¹H NMR (400 MHz, d8-THF) δ (ppm) = 8.03 (d, J=8.4Hz, 2H), 7.51-7.60 (m, 10H), 2.65 (s, 6H).

¹³C NMR (100 MHz, d8-THF) δ (ppm) = 185.5, 146.9, 141.2, 138.6, 137.6, 137.1, 135.6, 134.9, 132.6, 130.1 (q, J=32.1Hz), 130.0, 129.8, 129.5, 128.6, 128.2, 126.0 (q, J=3.9Hz), 125.4 (q, J=271.7Hz).

MS (70 eV, EI), m/z (%) = 567 (M⁺, 39), 460 (15), 433 (20), 431 (32), 146 (22), 139 (60), 122 (36), 111 (45), 108 (100), 44 (18), 42 (16).

HRMS (EI), m/z calc. for C₂₅H₁₉Cl₂F₃N₃O₃S (567.0398): 567.0384.

IR (ATR) ν (cm⁻¹) = 3088, 2961, 2920, 2852, 1678, 1617, 1583, 1482, 1380, 1324, 1211, 1204, 1164, 1126, 1109, 1096, 1083, 1063, 1014, 981, 962, 912, 856, 846, 836, 764, 734, 720.
Preparation of 4-(4-chlorophenyl)-2-(4-cyanophenyl)-N,N-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76i)

Prepared according to TP4 from 4-(4-chlorophenyl)-N,N-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73c, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (62, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to TP6 with ZnCl₂ (0.3 mL, 0.3 mmol, 1.0M in THF), Pd(PPh₃)₄ (14 mg, 0.0125 mmol) and 4-iodobenzonitrile (68k, 52 mg, 0.225 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded 76i as a white solid (90 mg, 75%).

m.p.: 208.3-209.5 °C.

¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.82-7.91 (m, 2H), 7.71-7.79 (m, 4H), 7.63 (d, J=8.0Hz, 2H), 7.23-7.29 (m, 2H), 7.16-7.23 (m, 2H), 2.34 (s, 6H).

¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 148.8, 138.9, 135.8, 133.9, 133.2, 131.7, 131.6, 131.6 (q, J=32.8Hz), 130.6, 130.5, 128.7, 128.6, 127.9, 125.7 (q, J=3.7Hz), 124.6 (q, J=272.4Hz), 118.3, 113.3, 37.0.

MS (70 eV, EI), m/z (%) = 530 (M⁺, 6), 425 (37), 424 (49), 423 (100), 422 (81), 267 (13), 123 (13), 114 (28), 108 (10), 43 (11).

HRMS (EI), m/z calc. for C₂₅H₁₉ClF₃N₄O₂S (530.0791): 530.0790.

IR (ATR) ν (cm⁻¹) = 3098, 3071, 2982, 2948, 2238, 1620, 1544, 1490, 1403, 1383, 1330, 1315, 1294, 1240, 1200, 1172, 1161, 1136, 1122, 1106, 1091, 1078, 1068, 1022, 1008, 977, 852, 838, 733, 696, 658.
Preparation of 4-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-N,N-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76j)

Prepared according to TP4 from 4-(4-chlorophenyl)-N,N-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73c, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (62, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, S-(3,4-dichlorophenyl) benzenesulfonothioate (68n, 72 mg, 0.225 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred over night. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 8.5:1.5) to give 76j as a white solid (96 mg, 70%).

m.p.: 155.4-156.4 °C.

¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.82 (d, J=1.9Hz, 1H), 7.73 (d, J=8.1Hz, 2H), 7.49-7.57 (m, 4H), 7.09-7.14 (m, 2H), 7.02-7.08 (m, 2H), 2.64 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 145.4, 139.1, 135.8, 133.7, 133.6, 133.6, 133.4, 132.9, 132.5, 131.7 (q, J=32.6Hz), 130.8, 130.5, 129.9, 128.5, 128.2, 127.4, 125.5 (q, J=3.8Hz), 123.7 (q, J=272.9Hz), 37.5.

MS (70 eV, EI), m/z (%) = 605 (M⁺, 23), 502 (22), 501 (51), 500 (54), 497 (100), 466 (14), 465 (20), 464 (56), 463 (34), 462 (78), 461 (19), 440 (11), 439 (43), 191 (11), 189 (15), 154 (11), 108 (10), 43 (10).

HRMS (EI), m/z calc. for C₂₄H₁₇Cl₂F₃N₃O₂S₂ (604.9780): 604.9767.

IR (ATR) ν (cm⁻¹) = 3099, 3068, 2986, 2927, 2859, 1487, 1452, 1421, 1394, 1363, 1330, 1283, 1244, 1225, 1185, 1173, 1161, 1124, 1106, 1091, 1080, 1067, 1035, 1014, 969, 952, 858, 844, 832, 810, 725, 698, 676.
7.6 **Selective N-3-Alkylation and Subsequent N-1 De-protection**

Preparation of 4-(4-(4-chlorophenyl)-1-methyl-5-(4-(trifluoromethyl)phenyl)-imidazol-2-yl)benzonitrile (78a)

The reaction was performed according to TP10 with 5-(4-chlorophenyl)-2-(4-cyanophenyl)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76e, 265 mg, 0.5 mmol), trimethyloxonium tetrafluoroborate (66, 74 mg, 0.5 mmol) and conc. HCl (2.5 mL). Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded 78a as a white solid (158 mg, 72%).

**m.p.**: 204.4-207.3 °C.

**$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$ (ppm) = 7.88 (d, $J=7.8$Hz, 2H), 7.76 (dd, $J=11.1$Hz, 8.1Hz, 4H), 7.51 (d, $J=7.8$Hz, 2H), 7.39 (d, $J=7.8$Hz, 2H), 7.20 (d, $J=7.8$Hz, 2H), 3.55 (s, 3H).

**$^{13}$C NMR** (100 MHz, CDCl$_3$) $\delta$ (ppm) = 146.5, 138.3, 134.4, 133.8, 133.0, 132.4, 132.0, 131.1 (q, $J=32.9$Hz), 131.0, 130.2, 129.3, 128.6, 128.3, 126.2 (q, $J=3.7$Hz), 123.8 (q, $J=272.3$Hz), 118.3, 112.6, 33.6.

**MS** (70 eV, EI), $m/z$ (%) = 437 (M$^+$, 100), 436 (35), 421 (6), 401 (3), 267 (3), 190 (4), 186 (3), 123 (3).

**HRMS** (EI), $m/z$ calc. for C$_{24}$H$_{15}$ClF$_3$N$_3$ (437.0907): 437.0902.

**IR** (ATR) $\nu$ (cm$^{-1}$) = 3097, 3072, 2956, 2925, 2872, 2856, 2226, 1730, 1608, 1513, 1486, 1465, 1407, 1381, 1326, 1294, 1284, 1275, 1244, 1167, 1130, 1106, 1092, 1069, 1032, 1018, 1010, 959, 848, 837, 825, 792, 739, 716, 705, 690, 652.
Preparation of 4-(5-(4-chlorophenyl)-1-methyl-4-(4-(trifluoromethyl)phenyl)-imidazol-2-yl)benzonitrile (78b)

The reaction was performed according to TP10 with 4-(4-chlorophenyl)-2-(4-cyanophenyl)-N,N-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76i, 265 mg, 0.5 mmol), trimethyloxonium tetrafluoroborate (66, 74 mg, 0.5 mmol) and conc. HCl (2.5 mL). Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded 78b as a white solid (162 mg, 72%).

m.p.: 176.1-178.0 °C.

$^1$H NMR (600 MHz, CDCl$_3$) = 7.88 (d, J=8.5Hz, 2H), 7.74-7.82 (m, 2H), 7.60 (d, J=8.0Hz, 2H), 7.42-7.53 (m, 4H), 7.29-7.38 (m, 2H), 3.54 (s, 3H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ (ppm) = 146.3, 137.5, 137.2, 135.7, 134.5, 132.5, 132.0, 131.4, 129.8, 129.3, 128.7 (q, J=32.3Hz), 128.4, 126.9, 125.2 (q, J=3.9Hz), 123.3 (q, J=271.8Hz), 118.4, 112.6, 33.4.

MS (70 eV, EI), m/z (%) = 437 (M$^+$, 100), 436 (36), 425 (5), 424 (5), 423 (16), 422 (5), 421 (7), 267 (5), 190 (6).

HRMS (EI), m/z calc. for C$_{24}$H$_{15}$ClF$_3$N$_3$ (437.0907): 437.0903.

IR (ATR) ν (cm$^{-1}$) = 3067, 2959, 2928, 2871, 2228, 1739, 1608, 1515, 1484, 1412, 1378, 1321, 1246, 1162, 1132, 1108, 1090, 1064, 1035, 1014, 960, 852, 837, 737, 716, 699, 676.
Preparation of 4-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-1-methyl-5-(4-(trifluoro-methyl)phenyl)-imidazole (78c)

The reaction was performed according to TP10 with 5-(4-chlorophenyl)-2-((3,4-dichloro-phenyl)thio)-N,N-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76g, 303 mg, 0.5 mmol), trimethyloxonium tetrafluoroborate (66, 74 mg, 0.5 mmol) and conc. HCl (2.5 mL). Flash column chromatographical purification on silica gel (pentane/EtOAc, 8.5:1.5) afforded 78c as a white solid (167 mg, 65%).

m.p.: 158.4-160.9 °C.

$^1$H NMR (600 MHz, CDCl$_3$) δ (ppm) = 7.73 (d, $J=8.3$Hz, 6H), 7.41-7.47 (m, 3H), 7.33-7.39 (m, 3H), 7.18-7.22 (m, 2H), 7.15 (dd, $J=8.5$Hz, 2.1Hz, 1H), 3.48 (s, 3H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ (ppm) = 139.3, 137.8, 134.0, 133.8, 133.5, 133.1, 131.6, 131.5, 131.3 (q, $J=32.8$Hz), 131.1, 131.0, 130.9, 129.9, 128.6, 128.3, 127.7, 126.3 (q, $J=3.7$Hz), 124.6 (q, $J=272.4$Hz), 32.6.

MS (70 eV, EI), $m/z$ (%) = 512 (M$^+$, 100), 511 (41), 479 (11), 295 (14), 246 (11), 186 (29), 145 (10), 43 (32).

HRMS (EI), $m/z$ calc. for C$_{23}$H$_{14}$Cl$_3$F$_3$N$_2$S (511.9895): 511.9890.

IR (ATR) $\nu$ (cm$^{-1}$) = 3080, 3060, 2925, 2852, 1738, 1617, 1569, 1513, 1484, 1458, 1406, 1367, 1322, 1297, 1263, 1164, 1121, 1107, 1090, 1068, 1030, 1014, 960, 875, 851, 836, 816, 807, 776, 735, 713, 692, 674.
Preparation of 5-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-1-methyl-4-(4-(trifluoro-methyl)phenyl)-imidazole (78d)

The reaction was performed according to TP10 with 4-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-N,N-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76j, 303 mg, 0.5 mmol), trimethylxonium tetrafluoroborate (66, 74 mg, 0.5 mmol) and conc. HCl (2.5 mL). Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded 78d as a white solid (185 mg, 72%).

\[ \text{m.p.: } 168.3-169.6 \, ^\circ \text{C.} \]

\[ \text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3 \delta (\text{ppm}) = 7.58 \, (d, J=8.2Hz, 2H), 7.47 \, (d, J=8.5Hz, 4H), 7.42 \, (d, J=2.2Hz, 1H), 7.36 \, (d, J=8.5Hz, 1H), 7.26 \, (d, J=8.5Hz, 2H), 7.14 \, (dd, J=8.2Hz, 2.2Hz, 1H), 3.46 \, (s, 3H).} \]

\[ \text{\textsuperscript{13}C NMR (150 MHz, CDCl}_3 \delta (\text{ppm}) = 138.5, 137.6, 136.9, 135.8, 134.1, 133.4, 132.3, 131.7, 131.4, 131.1, 129.8, 129.8, 128.8 \, (q, J=32.5Hz), 128.3, 127.6, 126.8, 125.2 \, (q, J=3.9Hz), 124.2 \, (q, J=271.8Hz), 32.4.} \]

\[ \text{MS (70 eV, EI), m/z (\%) = 512 (M^+, 98), 511 (51), 479 (12), 295 (13), 152 (29), 61 (11), 45 (11), 44 (15), 43 (51).} \]

\[ \text{HRMS (EI), m/z calc. for C}_{23}\text{H}_{14}\text{Cl}_3\text{F}_3\text{N}_2\text{S (511.9895): 511.9904.} \]

\[ \text{IR (ATR) } \nu (\text{cm}^{-1}) = 3078, 3056, 2956, 2925, 2854, 1617, 1515, 1482, 1450, 1366, 1325, 1305, 1246, 1166, 1134, 1112, 1104, 1093, 1066, 1032, 1015, 961, 881, 847, 835, 821, 808, 753, 746, 700, 675.} \]
D. APPENDIX
1. **List of Abbreviations**

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
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<td>Ad</td>
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<td>ATR</td>
<td>attenuated total reflection (IR)</td>
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<td>9-BBN</td>
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<td>4-(dimethylamino)pyridine</td>
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</table>
Hex    hexyl
HRMS  high resolution mass spectroscopy
Hz     Hertz
iPr    iso-propyl
IR     infrared
isityl 2,4,6-triisopropylphenyl
J      coupling constant (NMR)
L      ligand
LDA    lithium N,N-diisopropylamide
m      mol/L
m      meta
Me     methyl
min    minute
mp.    melting point
MS     mass spectroscopy
MHz    Megahertz
nBu    n-butyl
nPr    n-propyl
NBS    N-bromosuccinimide
NCS    N-chlorosuccinimide
Nf     nonaflate
NHC    N-heterocyclic carbene
NIS    N-iodosuccinimide
NMR    nuclear magnetic resonance
NMP    N-methylpyrrolidin-2-one
NP     naphthalide
o      ortho
p      para
PEPPSI-IPr  [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
PG     protecting group
Ph     phenyl
Piv    pivalyl
ppm    parts per million
Py     pyridyl
D. APPENDIX

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>organic substituent</td>
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