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LiCl-Mediated Direct Insertion of Magnesium Into
Aryl, Heteroaryl and Benzylic Halides.
Regio- and Chemoselective Synthesis of 5-Membered
Ring Heterocycles.

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aus

Paris, Frankreich

München 2010
Erklärung


Ehrenwörtliche Versicherung

Diese Dissertation wurde selbstständig, ohne unerlaubte Hilfe erarbeitet.

München, am 1. März 2010

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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>dba</td>
<td>trans,trans-dibenzylideneacetone</td>
</tr>
<tr>
<td>DCE</td>
<td>dichloroethane</td>
</tr>
<tr>
<td>dest.</td>
<td>distilled</td>
</tr>
<tr>
<td>DMAP</td>
<td>dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>E</td>
<td>electrophile</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionization</td>
</tr>
<tr>
<td>EN</td>
<td>electronegativity</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FG</td>
<td>functional group</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>iPr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR)</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>molar</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>M.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidine</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>R</td>
<td>organic substituent</td>
</tr>
<tr>
<td>SPhos</td>
<td>2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tfp</td>
<td>tris-(2-furyl)phosphine</td>
</tr>
<tr>
<td>TMP</td>
<td>2,2,6,6-tetramethylpiperidyl</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>4-toluenesulfonyl</td>
</tr>
<tr>
<td>TP</td>
<td>typical procedure</td>
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A. INTRODUCTION
Introduction

1. Overview

Chemistry’s future will rely on the development of new environmentally benign and inexpensive methods for the synthesis of complex structures. Since Frankland’s revolutionary discovery of \( \text{Et}_2\text{Zn} \) over 150 years ago,¹ organometallic chemistry has constantly been developed to a versatile toolbox for synthetic, medicinal and industrial chemists. A plethora of reactions have been designed for the formation of carbon-carbon and carbon-heteroatom bonds.

Due to the fact that organometallic reagents are known for many different main group and transition metals they offer a wide range of different applications. Transition metals such as Pd, Ni, Ru or Fe are often used as catalysts for cross-coupling or metathesis reactions.² Main-group organometallic reagents containing metals such as Li, Mg, Zn³ or B on the other hand are mostly used as nucleophiles.⁴ The reactivity of these nucleophiles greatly depends on the polarity of the carbon-metal bond and therefore on the electronegativity of the metal.⁵ Organolithium reagents for example (electronegativity of Li: 1.0) display a very high reactivity towards electrophiles but therefore have a low tolerance towards many functional groups. In contrast, organoboron reagents (electronegativity of B: 2.0) show a very low reactivity towards electrophiles but tolerate a wide range of functional groups. Organomagnesium reagents (electronegativity of Mg: 1.2) play a special role in this series because they react easily with electrophiles but also are indifferent towards many important functional groups. Their convenient method of preparation and their low toxicity make organomagnesium reagents widely used reagents for organic synthesis and industrial applications.

In 1995 Overman and coworkers published an enantioselective total synthesis of \((-\)-Ptilomycalin A which is a guanidine alkaloid isolated from the Caribbean sponge *Ptilocaulis*.

³ In chemistry text books, zinc can be found classified both as a transition-element and as a main-group element. The IUPAC defines a transition-element as “an element whose atom has an incomplete d sub-shell, or which can give rise to cations with an incomplete d sub-shell.” (A. D. McNaught, A. Wilkinson (Eds.), Compendium of Chemical Terminology, Blackwell Scientific Publications, Oxford, 1997). According to this rule, zinc has to be classified as a main-group element since both elemental zinc ([Ar]3d¹⁰4s²) and the Zn²⁺ ion ([Ar]3d¹⁰) have a complete d-shell. For a thorough investigation, see: W. B. Jensen, J. Chem. Educ. 2003, 80, 952.
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*spiculifer* and the Red Sea sponge *Hemimycale sp.* In a key step of the synthesis, the alkylmagnesium reagent 1 is added to the highly functionalized aldehyde 2 and the resulting alcohol is directly oxidized to the ketone 3 in 58% yield (Scheme 1).

![Scheme 1](image)

**Scheme 1:** Use of an alkylmagnesium reagent in the total synthesis of (−)-Ptilomycalin A according to *Overman*

More recently, in 2007 process chemists at *Johnson & Johnson* have developed an improved multi-kilogram synthesis of the tryptase inhibitor RWJ-56423 which has potential for the treatment of allergic and inflammatory disorders. In this case, benzothiazol-2-yl magnesium chloride (4) was added to the imidazolidine 5 to produce the ketone 6 in 80% yield on a 10 kg scale (Scheme 2).

![Scheme 2](image)

**Scheme 2:** *Johnson & Johnson’s* synthesis of an intermediate towards RWJ-56423 on a 10 kg scale

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2. Preparation of Magnesium Reagents

2.1. Magnesium Insertion Into Carbon-Halogen Bonds

The first preparation of an organomagnesium reagent was performed in the year 1900 when Victor Grignard made the observation that methyl iodide reacted with magnesium turnings to yield a clear and colorless solution in the presence of diethyl ether.9 He could show that this solution and similar reagents were able to attack aldehydes and ketones to give the corresponding alcohols in approximately 70 % yield (Scheme 3).

\[
\begin{align*}
\text{MeI} & \xrightarrow{\text{Mg, Et}_2\text{O}} \text{MeMgI} \\
\text{PhCHO} & \xrightarrow{\text{HO}} \text{Ph} \\
\end{align*}
\]

Scheme 3: First experiments conducted by Victor Grignard in 1900

Subsequently, Grignard investigated the behavior of organomagnesium reagents towards different electrophiles such as esters and CO\textsubscript{2} and explored occurring side reactions such as homo-couplings.10 For his pioneering work in this field he was awarded the Nobel Prize in Chemistry in 1912.

The exact mechanism of the magnesium insertion into organic halides is not yet completely elucidated. According to Garst and Ungváry the mechanism “remains rich in speculation and short on discriminating fact, a disturbing status for what may be the most-often-used non-trivial reaction.”11 A radical mechanism is generally accepted but there is much controversy concerning possible reaction pathways. While M. S. Kharasch and H. M. Walborsky support

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the hypothesis that the formed radicals stay on the metal surface (A Model); J. F. Garst strongly believes in the theory that the formed radicals can freely diffuse into the solvent (D Model).

A major limitation of the insertion reaction is that it is usually conducted at high temperatures, which strongly limits the scope of functional groups that can be used. In a ground-breaking series of publications, Rieke and co-workers showed that using highly reactive magnesium powder (Mg*), prepared by the reduction of MgCl₂ with lithium and naphthalene, it is possible to lower the temperature of the insertion to up to –78 °C. For the first time functionalized magnesium compounds bearing functional groups such as an ester or a nitrile became available via insertion reactions (Scheme 4).

**Scheme 4**: Preparation a functionalized magnesium reagent using highly reactive magnesium powder (Mg*)

### 2.2. The Halogen-Magnesium Exchange Reaction

An alternative preparation of organomagnesium reagents lies in the halogen-magnesium exchange reaction. It was first described by Prévost in 1931 when reacting cinnamyl bromide (7) with ethylmagnesium bromide (8) furnishing cinnamylmagnesium bromide (9) in low yield (Scheme 5).

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The requirement of the halogen-magnesium exchange reaction is that the generated magnesium reagent has to be more stable than the exchange reagent. Knochel and coworkers could demonstrate the significance of the iodine-magnesium exchange reaction using iPrMgBr (10). Since the reaction proceeds at low temperatures down to –80 °C, sensitive heterocycles such as the polyhalogenated pyrimidine 11 and the iodoalkene 12 can be magnesiated using iPrMgBr (10) and quenched with typical electrophiles (Scheme 6).

An extension of this work was published in 2004 and 2006 when Knochel reported the preparation of the mixed lithium and magnesium reagents iPrMgCl·LiCl (13) and sBu2Mg·LiCl (14). These reagents are a tremendous improvement compared to earlier methods because they allow even electron-rich organic bromides to be used in halogen-magnesium exchange reactions compared to the usually more expensive and less stable iodides. Experimental as well as theoretical considerations support the proposed mechanism

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which involves the break-up of polymeric $i\text{PrMgCl}$ by LiCl and formation of the magnesium-lithium ate complex 15 (Scheme 7).

![Scheme 7: Rate acceleration of the bromine-magnesium exchange reaction by LiCl](image)

The halogen-magnesium exchange reaction is also an excellent method for the stereoselective preparation of alkenylmagnesium reagents.\textsuperscript{22} With the use of $i\text{PrMgCl-LiCl}$ (13) it is now possible to stereoselectively prepare functionalized alkenylmagnesium reagents at low temperatures (Scheme 8).\textsuperscript{23}

![Scheme 8: Preparation of alkenylmagnesium reagents using $i\text{PrMgCl-LiCl}$ (13)](image)


2.3. Directed Deprotonation Using Magnesium Amide Bases

Yet another approach for the preparation of organomagnesium compounds is the directed metalation reaction using magnesium amide bases. Diethyl- and diisopropylaminomagnesium bromides were first used by Hauser for the self condensation of esters. Eaton then demonstrated their synthetic utility by preparing various ortho-magnesiated aromatics using TMPMgBr and TMP$_2$Mg. In 1995 Mulzer and coworkers used for the first time TMPMgCl for the directed metalation of various pyridine derivatives. However, the limited solubility of such bases in common organic solvents as well as the requirement for an excess of the magnesium bases (2-7 equiv) to achieve high conversions has precluded their general use. Recently, Knochel et al. have developed the mixed lithium and magnesium amide base TMPMgCl-LiCl (16) which has many advantages compared to earlier magnesium amide bases or lithium amide bases. It is easily prepared, offers long term stability at ambient temperatures and is compatible with sensitive functional groups even in non-cryogenic conditions (Scheme 9).

In an extension from this work, the mixed magnesium and lithium bisamide TMP₂Mg·2 LiCl (17) was prepared by the reaction of TMPMgCl·LiCl (16) with TMPLi. It features an improved kinetic basicity compared to TMPMgCl·LiCl (16) and is able to metatalte even inactivated substrates such as unsubstituted benzoates (Scheme 10).

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3. Preparation of Zinc Reagents

Similarly to organomagnesium compounds, multiple methods for the generation of organozinc reagents are known. The classical insertion of zinc dust or foil into organic halides is the most common method for the preparation of functionalized organozinc halides. This method offers a great tolerance towards functional groups such as esters, ketones and nitriles. A drawback of the classical zinc insertion is that it requires long reaction times and that expensive organic iodides have to be used almost exclusively. Improvements came with the development of highly active zinc powder (Zn*) pioneered by Rieke and most recently in 2007 with the LiCl-mediated insertion of zinc powder by Knochel and co-workers. They could show that the simple addition of LiCl considerably increases reaction rates for the insertion into organic iodides and bromides (Scheme 11).

Scheme 11: LiCl accelerated insertion of zinc dust to 2-iodobenzotrifluoride

The iodine-zinc exchange is a convenient method for the preparation of diorganozinc compounds. A wide range of alkyl iodides undergo a iodine-zinc exchange using diethylzinc and catalytic amounts of a Cu(I) salt. In 2004, it was shown that iPr₂Zn (18) combined with catalytic amounts of Li(acac) enabled for the first time to perform an iodine-zinc exchange on aromatic substrates such as the functionalized aldehyde 19 (Scheme 12).
Directed metalations offer another method for the synthesis of organozinc reagents. This interesting field was first explored by Kondo who developed highly active zincate bases for the directed ortho metalation. More recently, the group of Knochel developed highly chemoselective and sensitive TMP-derived zinc bases for the deprotonation of functionalized aromatics and heteroaromatics. These bases tolerate very sensitive heterocycles and functional groups such as the oxadiazole or the nitroarene (Scheme 13).

**Scheme 12**: Li(acac) catalyzed iodine-zinc exchange reaction on the functionalized aldehyde 19

**Scheme 13**: TMP-derived zinc bases for the deprotonation of sensitive substrates

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4. Objectives

In a first project, the influence of LiCl towards the insertion of magnesium into aromatic bromides and chlorides will be investigated. The goal of this project is to enable the preparation of functionalized organomagnesium reagents by a simple magnesium insertion under very mild reaction conditions (Scheme 14).

\[
\begin{array}{c}
\text{FG} \quad \begin{array}{c}
\text{Mg, LiCl} \\
\text{THF}
\end{array} \quad \begin{array}{c}
\text{MgX·LiCl}
\end{array} \\
\text{X = Halogen}
\end{array}
\]

Scheme 14: Magnesium insertion in the presence of LiCl

In an extension of this method, the functionalization of very sensitive substrates such as aromatic esters and heterocycles will be explored using a magnesium insertion in the presence of ZnCl₂ (Scheme 15).

\[
\begin{array}{c}
\text{FG} \quad \begin{array}{c}
\text{Mg, LiCl, ZnCl}_2 \\
\text{THF}
\end{array} \quad \begin{array}{c}
\text{ZnX·LiCl}
\end{array} \\
\text{X = Halogen}
\end{array}
\]

Scheme 15: Preparation of functionalized zinc reagents by a magnesium insertion in the presence of ZnCl₂

It is then planned to apply the above mentioned reaction sequence for the convenient and expedient preparation of highly functionalized benzylic and alkylzinc reagents (Scheme 16).

\[
\begin{array}{c}
\text{FG} \quad \begin{array}{c}
\text{Mg, LiCl, ZnCl}_2 \\
\text{THF}
\end{array} \quad \begin{array}{c}
\text{ZnX·LiCl}
\end{array} \\
\text{Alkyl-X} \\
\text{X = Halogen}
\end{array}
\]

Scheme 16: Proposed synthesis of functionalized benzylic and alkylzinc reagents

Based on the results of the regioselective Zn-insertion into polyhalogenated aromatics, the behavior of the magnesium insertion into similar substrates bearing a directing group (DG) will be ascertained (Scheme 17).
Introduction

Due to the relevance of organometallic reagents for industrial applications, the preparation of organomagnesium and organozinc compounds will be studied on a larger scale using the above mentioned methodologies.

The second project will involve the use of magnesium amide bases such as TMPMgCl·LiCl (16) for the preparation of functionalized 5-membered ring heterocycles. Starting from substrates bearing an ester group at the 2-position the full functionalization of these heterocycles will be attempted (Scheme 18).

Furthermore, starting from readily available 2,5-dichlorothiophene, the synthesis of fully substituted thiophenes will be investigated using deprotonation and insertion reactions (Scheme 19).

A third topic will be the metalation of enol phosphates based on D(+)-camphor derivatives. Employing bromine-magnesium exchange and deprotonation reactions the functionalization of this important framework will be probed (Scheme 20).
Introduction

Scheme 20: Functionalization of enol phosphates

The fourth project will be devoted to the preparation of 1-aryliminozinc reagents as acyl anion equivalents. The role of MgCl₂ in the α-addition of several organozinc reagents to various arylisonitriles will be explored (Scheme 21).

Scheme 21: MgCl₂ mediated α-addition of zinc reagents to isonitriles
B. RESULTS AND DISCUSSION
1. LiCl-Mediated Direct Insertion of Magnesium Into Aryl, Heteroaryl and Benzylic Halides

1.1. Magnesium Insertion in the Presence of LiCl Into Aryl and Heteroaryl Bromides

As mentioned above, organomagnesium compounds are frequently used reagents in organic synthesis. The insertion of magnesium metal into carbon-halogen bonds is the most commonly used method of preparation for these reagents. Due to the harsh reaction conditions however, the magnesium insertion cannot be used for the synthesis of functionalized magnesium reagents. Based on the observation that lithium salts such as Li(acac)\textsuperscript{35} and LiCl greatly enhance the halogen-metal exchange reaction\textsuperscript{21} as well as the insertion reaction of zinc dust into organic halides,\textsuperscript{33} the influence of LiCl on the traditional magnesium insertion was investigated (Scheme 22).

![Scheme 22: LiCl-mediated preparation of functionalized magnesium reagents](image)

The presence of LiCl (ca. 1.2 equiv) strongly facilitates the magnesium insertion into various aryl bromides. Because of these mild conditions, some additional functional groups can be present in the aromatic bromide. Thus, the Boc-protected bromophenols 22a and 22b reacted readily with magnesium turnings (2.5 equiv) in the presence of LiCl (1.25 equiv) at –10 °C in THF. The magnesium turnings were treated with iBu\textsubscript{2}AlH (1 mol%) which ensures a smooth reaction start.\textsuperscript{38} In case of the meta-substituted aryl bromide 22a, the insertion was completed within 60 min, whereas for the para-substituted substrate 22b the insertion required only 20 min. In the absence of LiCl, no reaction was observed under these reaction conditions. The resulting magnesium reagent 23a and 23b reacted cleanly with electrophiles. In the presence of CuCN·2 LiCl (20 mol%),\textsuperscript{31} an acylation with 4-chlorobenzoyl chloride (0.7 equiv) produced the ketone 24a in 95 % yield. Alternatively, the reaction of the Grignard reagent

**Results and Discussion**

23b with MeSO₂SMe (0.7 equiv) furnished the functionalized thioether 24b in 92% yield (Scheme 23). The Boc-group is perfectly tolerated during the organometallic reaction step.

\[ \text{Br} \quad \text{Mg (2.5 equiv)} \quad \text{LiCl (1.25 equiv)} \quad \text{THF, -10 °C, 1 h} \]

\[ \text{Br} \quad \text{MgBr-LiCl} \quad \text{THF, -10 °C, 1 h} \]

\[ \text{O} \quad \text{Cl} \quad \text{O} \quad \text{Cl} \]

\[ \text{O} \quad \text{Boc} \quad \text{O} \quad \text{Boc} \]

**Scheme 23:** Magnesium insertion into Boc-protected bromophenols with magnesium turnings in the presence of LiCl

Similarly, a tosylxy group is also compatible with the Mg insertion conditions. Thus, the treatment of 1-tosylxy-3-bromobenzene (22c) with Mg (2.5 equiv) and LiCl (1.25 equiv) at 0 °C for 2 h provided the corresponding Grignard reagent 23c which reacted with DMF (0.7 equiv) to give the aldehyde 24c in 77% yield (Table 1, entry 1). Even a sensitive pivalate protection group for the dibromophenol 22d could be used. The magnesium reagent 23d was regioselectively prepared within 1 h at –20 °C and underwent addition to benzaldehyde to yield the alcohol 24d in 86% (entry 2). Various bromochlorobenzenes such as 22e-f undergo a selective insertion in the carbon-bromine bond leading to the magnesium reagents 23e-f. Pd-catalyzed Negishi cross-coupling reaction of the corresponding zinc reagent derived from 23e using Pd(dbai)₂ (3 mol%), tris(2-furyl)phosphine (tfp; 6 mol%) and ethyl 4-iodobenzoate as electrophile furnished the biphenyl 24e in 94% yield (entry 3). A copper(I)-catalyzed acylation of 23e with pivaloyl chloride (0.7 equiv) gave the ketone 24f in 69% yield (entry 39).


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4). Also, the Grignard reagent 23f derived from 1-bromo-4-chlorobenzene (22f) added readily to benzaldehyde giving the benzhydryl alcohol 24g in 89 % yield (entry 5). The bromofluorobiphenyl 22g reacts with Mg/LiCl within 30 min at 25 °C. The reaction of the resulting magnesium reagent with MeSO2SMe led to the expected thioether 24h in 84 % yield (entry 6).

The formation of magnesium reagents containing a trifluoromethyl group is dangerous and difficult to perform especially at temperatures between 30 and 50 °C due to the exothermic reaction of magnesium with the trifluoromethyl moiety.41 By using magnesium turnings in the presence of LiCl, Grignard reagents from ortho, meta, para or meta,meta-substituted benzotrifluorides 22h-k can safely be prepared at 0 °C within 30 min. After transmetallation to the corresponding zinc reagents and Negishi cross-coupling reactions39 with ethyl 4-iodobenzoate, the desired trifluoromethyl-substituted biphenyls 24i-l were obtained in 83-97 % yield (entries 7-10). Remarkably, the yield remains excellent regardless of the substitution pattern. Alternatively, the Grignard reagent 23l derived from 2-bromo-1-chloro-4-(trifluoromethyl)benzene (22l) could be prepared and subsequently reacted with 4-chlorobenzaldehyde which gave the alcohol 24m in 88 % yield (entry 11).

Electron-rich bromobenzenes such as 22m-o containing either a dimethylamino group or a methylene-dioxy group reacted also within 30 min with Mg/LiCl providing the corresponding magnesium reagents 23m-o. Addition to an aldehyde or reaction with a sulfonothioate afforded the polyfunctionalized anilines 24n-o in 65-91 % yield (entries 12-13). The reaction of magnesium reagents with ketones is often accompanied by several side reactions. Nevertheless, the magnesium reagent 23o adds to the α-acidic methyl benzyl ketone in the presence of LaCl3·2 LiCl42 yielding the tertiary alcohol 24p in 91 % yield (entry 14).

The expeditious preparation of heterocyclic organometallics is of central importance in modern pharmaceutical and agrochemical research.43 The LiCl-mediated magnesium insertion is suitable for the preparation of polyfunctional heteroaryl magnesium reagents. Heterocyclic halides like 5-bromo-2-chloro-pyridine 22p reacted rapidly with Mg/LiCl (0 °C, 30 min) and the resulting magnesium compound 23p underwent a Negishi cross-coupling reaction or a

Results and Discussion

copper(i)-catalyzed allylation reaction leading to the pyridines \(24q-r\) in 62-84 % yield (entries 15-16).

Finally, the LiCl-mediated insertion of Mg turnings to bromobenzonitrile derivatives was examined. Despite the presence of the electronegative cyano substituent, the insertion reaction requires 35-45 min at 25 °C. The formation of the Grignard reagents \(23q-s\) is accompanied by reduction products in variable amounts, showing a possible limitation for this direct insertion. Nevertheless, the magnesium reagents \(23q-s\) could be prepared and reacted with typical electrophiles such as 1-bromo-4-(trifluoromethyl)benzene via a cross-coupling reaction using \(\text{Pd(OAc)}_2\) (1 mol%) and S-Phos (2 mol%) as a catalytic system. The resulting biphenyl \(24s\) is then obtained in 68 % yield (entry 17). Copper(i)-catalyzed acylation of \(23r-s\) with various acid chlorides provided the expected ketones \(24t-u\) in 57-60 % yield (entries 18-19).

Table 1: Preparation of functionalized aromatics and heterocycles of type \(24\) by the reaction of magnesium in the presence of LiCl with aryl bromides of type \(22\) followed by quenching with an electrophile

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>(T [^\circ C]), (t [\text{min}])</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%](^{a})</th>
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<tbody>
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<td>(\text{PhBr} \quad \text{OTs}) (22c)</td>
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<td>(\text{PhCHO} \quad \text{OTs}) (24c)</td>
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<td>2</td>
<td>(\text{Br} \quad \text{Br} \quad \text{PivO}) (22d)</td>
<td>-20, 60</td>
<td>PhCHO</td>
<td>(\text{Br} \quad \text{OH} \quad \text{Ph}) (24d)</td>
<td>86</td>
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<tr>
<td>3</td>
<td>(\text{Br} \quad \text{Cl}) (22e)</td>
<td>25, 10</td>
<td>(\text{CO}_2\text{Et})</td>
<td>(\text{Cl}) (24e)</td>
<td>94(^{b})</td>
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<tr>
<td>4</td>
<td>(\text{Br} \quad \text{Cl}) (22e)</td>
<td>25, 10</td>
<td>(\text{Cl}) (\text{O}) (\text{Cl})</td>
<td>(\text{Cl}) (24f)</td>
<td>69(^{c})</td>
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### Results and Discussion

**Table 1 (continued)**

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<tr>
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<td>0, 30 PhCO₂Et</td>
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### Results and Discussion

Table 1 (continued)

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<th>Product</th>
<th>Yield [%]$^a$</th>
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<td>[22p]</td>
<td>0, 30</td>
<td>Me$_2$C</td>
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<tr>
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<td>Br</td>
<td>[24s]</td>
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<td>[22r]</td>
<td>25, 45</td>
<td>CO</td>
<td>[24t]</td>
<td>57$^d$</td>
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$^a$ Values for yield are estimated.

$^b$ Additional experiments were conducted.

$^c$ Independently confirmed.

$^d$ Reported in previous studies.
Results and Discussion

Table 1 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>T [°C], t [min]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][a]</th>
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<td><img src="image2" alt="Electrophile Image" /></td>
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<td>60%[d]</td>
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</table>

[a] Yield of analytically pure product; [b] Obtained after a Pd-catalyzed cross-coupling reaction; [c] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20-100 mol%); [d] Obtained in the presence of LaCl₃·2 LiCl (100 mol%).

1.2. Preparation of Aryl- and Heteroarylzinc Reagents by Magnesium Insertion in the Presence of LiCl and ZnCl₂

The previously described LiCl-mediated magnesium insertion displays a remarkable tolerance towards functional groups but fails in the case of ester-containing substrates or highly sensitive heterocycles. Bromo-substituted aromatic esters also underwent a magnesium insertion in the presence of LiCl, but the resulting arylmagnesium compounds decomposed rapidly. However, in the presence of ZnCl₂ (1.1 equiv), the generated arylmagnesium species was transmetalated in situ to the corresponding stable organozinc reagent.

Thus, ethyl 2-bromobenzoate (25, 1.0 equiv) was readily converted to the arylzinc reagent 26 using magnesium powder (2.5 equiv), LiCl (2.5 equiv) and ZnCl₂ (1.1 equiv) within 3 h at 25 °C. After a Cu(I)-catalyzed reaction with allyl bromide, the expected product 27 was isolated in 88 % yield (Scheme 24). Magnesium powder was used in these experiments preferentially over Mg turnings since shorter reaction times can be achieved in this way.

![Scheme 24](image)

**Scheme 24:** LiCl-promoted insertion of magnesium into ethyl 2-bromobenzoate 25 and direct transmetalation with ZnCl₂

This method was successfully used for the preparation of various interesting zincated heterocycles. The zincation of the 3-position of benzofuran is of special interest since the bromide does not directly react with Zn and LiCl. The strong reduction potential of Mg
compared to Zn ensures, however, a rapid formation of the organometallic species. Thus, 3-bromobenzofuran (28) was converted by the treatment with Mg/LiCl/ZnCl$_2$ within 2 h at 25 °C into the corresponding zinc reagent 29. A Negishi cross-coupling$^{39}$ with 2-iodocyclohexenone$^{45}$ using Pd(OAc)$_2$ (1 mol%) and S-Phos (2 mol%) as ligand provided the cyclohexenone 30 in 91 % yield. The metalation of 5-membered ring heterocycles often requires mild conditions since these metalated ring systems often have the tendency to undergo fragmentation reactions.$^{46}$ Still, their functionalization is a desirable task, because they are often found in natural products and frequently display important pharmaceutical properties. The isoxazole framework for example is found in ibotenic acid which is a strong neurotoxin.$^{47}$ 3,5-Dimethyl-4-bromoisoxazole (31) was smoothly converted to the corresponding zinc reagent 32 within 15 min at 25 °C by the treatment with Mg/LiCl/ZnCl$_2$. After a Negishi cross-coupling reaction with 3-bromoanisole, the arylated isoxazole 33 was isolated in 90 % yield (Scheme 25).

![Scheme 25: Preparation and reaction of zincated heterocycles using Mg/LiCl/ZnCl$_2$](image)

Pyrazoles are important heterocyclic structures that have attracted considerable interest in medicinal chemistry.$^{48}$ Surprisingly, in the case of 5-chloro-3-methyl-1-phenyl-1$H$-pyrazole 34 even the less reactive heterocyclic chloride could be used for the insertion to give the

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Results and Discussion

Zincated pyrazole 35. A CuCN·2 LiCl-mediated acylation with 4-chlorobenzoyl chloride provided the ketone 36 in 91% yield. More functionalized substrates such as the chloropyrimidine 37 also reacted with Mg/LiCl/ZnCl₂ (25 °C, 9 h) and led after a copper(I)-catalyzed allylation to the allylated uracil derivative 39 in 68% yield (Scheme 26).

Scheme 26: Magnesium insertion into heterocyclic chlorides in the presence of LiCl and ZnCl₂

1.3. Regioselectivity of Zinc and Magnesium Insertions into Polybrominated Arenes

In the case of di- or tribromo-aromatics, the question of regioselective metal insertion arises. As shown above, the magnesium insertion into the 2,4-disubstituted dibromide 22d is highly selective and only metalation in the para-position is observed (Table 1, entry 2). This is consistent with the results obtained by Rieke who observed the same selectivity using Rieke magnesium (Mg*). This is surprising, given the fact that in 2007, Knochel have shown that the LiCl-mediated zinc insertion into polyhalogenated aromatics bearing a directing group (DG) was entirely ortho-selective (Scheme 27).³³b

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**Results and Discussion**

Further investigations revealed that zinc reagents obtained by in situ transmetalation from the corresponding magnesium reagents with ZnCl\(_2\) showed the same selectivity as the regular magnesium insertion. This means that the insertion metal is responsible for the regioselectivity and not the resulting metal species. This behavior can be explained by assuming that the zinc insertion requires a coordination to the directing group (DG) of 40, whereas magnesium metal which has a much stronger reducing power does not need this ortho-coordination site and preferably inserts to the least sterically hindered carbon-bromine bond (Scheme 28).

The reaction of tert-butyl 2,4-dibromophenyl carbonate (40a) with Zn/LiCl led only to the ortho-insertion zinc reagent.\(^{50}\) After cross-coupling with 3-iodo-trifluoromethylbenzene the biphenyl 43a was isolated in 60 % yield. However, by treating 40a with Mg/LiCl (THF, –20 °C) the insertion of magnesium occurred only in para-position providing, after a Pd-catalyzed cross-coupling\(^{39}\) with ethyl 4-iodobenzoate, the biphenyl derivative 44a in 97 % isolated yield.

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\(^{50}\) All regioselective zinc insertions in this chapter were performed by M. A. Schade and are given here for the sake of completeness.
Results and Discussion

A similar reaction was observed with 2,4,6-tribromo-1-pivaloyloxybenzene (40b) as the insertion with Zn/LiCl provided the corresponding ortho-inserted zinc reagent. After transmetalation with CuCN·2 LiCl and acylation with 2-fluorobenzoyl chloride, the polyfunctional ketone 43b was isolated in 81 % yield. Alternatively, the reaction of 40b with Mg/LiCl/ZnCl₂ leads only to an insertion in para-position and the resulting intermediate can be converted to the ketone 44b via a Cu(I)-mediated acylation in 85 % yield (Scheme 29).

Scheme 29: Ortho- and para-functionalization of polybrominated aromatics using zinc or magnesium insertions

This method can also be applied advantageously to substrates bearing sensitive functionalities like triazenes, which are a synthetic equivalent of diazonium salts. Thus, the treatment of the 2,4-dibromoaryltriazene derivative 40c with Mg/LiCl (THF, 0 °C, 30 min) provided regioselectively the para-inserted magnesium derivative 42c. After the addition of pivaldehyde, the functionalized benzylic alcohol 44c was obtained in 76 % yield (Scheme 30).

This regioselective insertion is triggered by several directing groups. Whereas the zinc insertion was always selective in the tested substrates, the magnesium insertion sometimes gave product mixtures. The di- and tri-brominated tosyl-protected phenols 40d-e for example inserted zinc smoothly and selectively in the presence of LiCl. The magnesium insertion, on the other hand, produced the two possible magnesium reagents 42d-e in 80:20 ratios (Scheme 31).

Even a slight variation of the directing group sometimes decreased the selectivity of the magnesium insertion. As described above, the pivaloyloxy directing group induces selectivity for both the zinc and the magnesium insertion. Thus, when treating the dibromopivaloyloxybenzene derivative 40f with Zn/LiCl or Mg/LiCl the expected insertion products 41f and 42f were obtained. Quenching of these organometallic reagents with 4-chlorobenzoyl chloride in the presence of CuCN·2 LiCl provided the benzophenone derivatives 43f and 44f in 75 % and 78 % yield respectively. The tribrominated derivative 40g reacted similarly. After LiCl-mediated insertions and Pd-catalyzed cross-coupling reactions with ethyl 4-iodobenzoate or 4-iodotoluene the ortho- or para-substituted biaryls 42g and 44g were obtained in 78-90 % yield.

Scheme 30: Regioselective magnesium insertion into a functionalized triazene derivative

Scheme 31: Regioselectivity of the zinc and magnesium insertion into tosyl-protected polybrominated phenols

52 The selectivity and the product ratio were determined by 1H-NMR measurement of the hydrolyzed magnesium or zinc reagents.
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When changing the directing group to an acetyl group, the selectivity of the magnesium insertion surprisingly dropped to a ratio of 85:15 for both the di- and the tribrominated aromatics 40h-i. Then again, the selectivity of the zinc insertion still remained excellent (Scheme 32).

Scheme 32: Regioselective zinc and magnesium insertions using a pivalate or acetate as a directing group

1.4. Preparation of Benzylic Zinc Reagents by the Insertion of Magnesium in the Presence of LiCl and ZnCl₂

Benzylic organometallics are valuable synthetic intermediates. Because of the more ionic nature of the carbon-metal bond, these organometallics have especially high reactivity. Benzylic zinc compounds are of particular interest since, in contrast to benzylic lithium and magnesium reagents, they tolerate numerous functional groups.

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Results and Discussion

These reagents can be prepared by the direct zinc insertion into benzylic bromides but often require elevated temperatures and polar co-solvents.\textsuperscript{55} In 2008, the group of Knochel reported the LiCl-mediated zinc insertion into commercially available benzylic chlorides.\textsuperscript{56} This mild method allowed for the preparation of a vast variety of functionalized benzylic zinc reagents bearing functional groups such as ketones, esters or nitriles (Scheme 33).

Scheme 33: LiCl-mediated zinc insertion into benzylic chlorides

The new procedure using magnesium turnings in the presence of ZnCl\textsubscript{2} and LiCl as described above, was successfully used to prepare a range of functionalized benzylic zinc reagents of type 46 starting from the corresponding benzylic chlorides 45 via an intermediate benzylic magnesium compound which was transmetalated in situ to 46.

In a typical experiment, the addition of 2-chlorobenzyl chloride (45a) to magnesium turnings (2.5 equiv), LiCl (1.25 equiv) and ZnCl\textsubscript{2} (1.1 equiv) in THF led to the benzylic zinc chloride 46a within 45 min at 25 °C as indicated by iodometric titration. Prior activation of the magnesium turnings was not required. The intermediate benzylic magnesium reagent was transmetalated in situ to the corresponding zinc organometallic. In the absence of ZnCl\textsubscript{2} the resulting magnesium reagent decomposes rapidly and a considerable amount of homo-coupling product 48 is observed. Interestingly, in the presence of ZnCl\textsubscript{2} the amount of homo-coupling formed is below 5 % (Scheme 34).


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Although Zn in the presence of LiCl also led to a smooth reaction with various benzylic chlorides, the use of a stronger reducing metal such as magnesium allows shorter insertion times. Thus, the treatment of 4-fluorobenzyl chloride (45b) with Zn powder (2.0 equiv) in the presence of LiCl (2.0 equiv) provided the corresponding zinc reagent 46b with a reaction time of 24 h at 25 °C. On the other hand, the reaction of 45b with Mg turnings (2.5 equiv), ZnCl₂ (1.1 equiv) and LiCl (1.25 equiv) in THF leads to a complete conversion within 45 min (Scheme 35).

The Pd-catalyzed cross-coupling of 46b with 4-bromobenzonitrile (0.7 equiv) provided the expected diarylmethane 47b in 75 % yield (Table 2, entry 1). Functional groups such as an ester were also tolerated. Thus, the reaction of ethyl 3-chloromethyl benzoate (45c) with Mg/LiCl/ZnCl₂ at 25 °C for 2 h provided the corresponding zinc reagent 46c. Its copper(I)-mediated reaction with an allylic bromide, such as ethyl (2-bromomethyl)acrylate led to the diester 47c in 67 % yield (entry 2).

Other halogen atoms on the aromatic ring are readily tolerated. 3-Trifluoromethylbenzyl chloride (45d) was converted to the benzylic zinc organometallic 46d within 30 min at 25 °C. The reaction with 4-chlorobenzoyl chloride (after transmetalation with CuCN·2LiCl) gave the desired ketone 47d in 91 % yield (entry 3). Similarly, the chloro-substituted benzylic chlorides 45a and 45e reacted smoothly with magnesium turnings in the presence of LiCl and ZnCl₂ within 15 to 45 min at 25 °C. The resulting zinc reagents 46a and 46e were treated with
Results and Discussion

A sulfonothioate or acetyl chloride and the expected products 47a and 47e were obtained in 76-89% yield (entries 4-5).

Also, electron-rich benzylic chlorides were converted to the corresponding zinc reagents without the formation of significant amounts of homo-coupling products. The methoxy-substituted benzylic zinc chlorides 46f-g were obtained after 1 h of stirring at 25 °C. After a Cu(I)-mediated treatment with 4-bromobenzoyl chloride or 3,3-dimethylbutanoyl chloride the products 47f-g were isolated in 81-82% yield (entries 6-7).

Secondary benzylic chlorides can be converted to their corresponding organozinc reagents as well. Thus, 1,1-diphenylchloromethane (45h) reacted cleanly with Mg/LiCl/ZnCl₂ to the secondary benzylic zinc compound 46h and could subsequently be reacted with an acid chloride to give the expected ketone 47h in 81% yield (entry 8). However, the treatment of a tertiary benzylic chloride such as cumyl chloride or trityl chloride with Mg, LiCl and ZnCl₂ only led to decomposition products.

Table 2: Preparation and reactions of benzylic zinc reagents 46 from the corresponding benzylic chlorides 45 using Mg, LiCl and ZnCl₂ at 25 °C

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<thead>
<tr>
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<th>Substrate</th>
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<th>Product</th>
<th>Yield [%]</th>
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<td>47b</td>
<td>75&lt;sup&gt;H&lt;/sup&gt;</td>
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<tr>
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<tr>
<td>3</td>
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<tr>
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<td>45</td>
<td>MeSO₂SMe</td>
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Results and Discussion

Table 2 (continued)

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<td>81(^{[b]})</td>
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[a] Yield of analytically pure product; [b] Obtained after a Pd-catalyzed cross-coupling reaction; [c] The organozinc reagent was transmetalated with CuCN·2 LiCl (20-100 mol%).

This in situ method (Mg, LiCl, ZnCl\(_2\)) has two important advantages:

1. By adding just 0.5 equivalents of ZnCl\(_2\) it is possible to prepare highly reactive dibenzylic zinc reagents.
2. The in situ method produces more reactive benzylic zinc reagents due to the presence of MgCl\(_2\) generated during the reaction which accelerates the addition reaction to carbonyl derivatives.

Thus, the addition of benzylzinc chloride (46i) generated by using Zn/LiCl leads to less than 20 % conversion in the case of the addition to 4-dimethylaminobenzaldehyde after 20 h reaction time at 25 °C. In contrast, by generating benzylzinc chloride (46i) using
Results and Discussion

Mg/LiCl/ZnCl₂, the desired benzylic alcohol 47i was obtained in 98 % isolated yield after a reaction time of only 1 h at 25 °C (Scheme 36).57

Scheme 36: Reactivity of benzylzinc chloride (47i) depending on its preparation method

1.5. Preparation of Alkylzinc Reagents by the Insertion of Magnesium in the Presence of LiCl and ZnCl₂

The insertion of zinc dust into alkyl iodides is a well known and often used reaction.30 The corresponding alkyl bromides react much slower and require harsh reaction conditions for their formation such as Rieke zinc (Zn*)32, 58 or zinc dust in the presence of LiCl at elevated temperatures.33a In many cases this precludes the presence of sensitive functional groups. Based on the results of the magnesium insertion in the presence of LiCl and ZnCl₂ into benzylic chlorides described above, these reaction conditions were also investigated using alkyl bromides as insertion substrates.

Thus, the reaction of 6-bromo-2,2-dimethylhexanenitrile (49) with Mg turnings (2.5 equiv) in the presence of dry ZnCl₂ (1.1 equiv) and dry LiCl (1.25 equiv) in THF (~ 0.28 M solution) was complete within 2.5 h at 25 °C providing the desired zinc reagent 50 in approximately 70 % yield. Alternatively, the treatment of 6-bromo-2,2-dimethylhexanenitrile (49) with zinc dust (2.5 equiv) in the presence of LiCl (1.25 equiv) required a reaction time of 50 h at 50 °C to reach completion59 (Scheme 37).

57 This experiment was performed by A. Metzger and is given here for the sake of completeness.
Results and Discussion

Scheme 37: Comparison of reaction rates using Mg/LiCl/ZnCl₂ and Zn/LiCl

The amide function is an important structural motif present in many natural products. Therefore, 5-bromo-N,N-diethylpentanamide (51) was chosen as a substrate. Its treatment with Mg turnings (2.5 equiv), ZnCl₂ (1.1 equiv) and LiCl (2.5 equiv) provided the functionalized Zn-reagent 52, which reacted well in a Cu(I)-mediated allylation reaction with 3-bromocyclohexene (0.7 equiv) yielding the unsaturated amide 53 in 70 % yield (Scheme 38).

Scheme 38: Magnesium insertion in the presence of LiCl and ZnCl₂ into 5-bromo-N,N-diethylpentanamide

Interestingly, in the presence of an aromatic ketone, the corresponding zinc reagent 55 was obtained from [3-(3-bromopropyl)phenyl] (phenyl)methanone (54). It reacted cleanly with S-benzyl benzenesulfonothioate to afford the thioether 56a in 58 % yield. Also, treatment of 55 with 3-bromocyclohexene (0.7 equiv) in the presence of CuCN·2 LiCl (20 mol%) led to the allylated ketone 56b in 61 % yield (Scheme 39).
Results and Discussion

Scheme 39: Preparation of alkylzinc reagent 55 bearing a keto group

The preparation of secondary alkylzinc compounds was also investigated. Thus, the reaction of the secondary cyclic alkyl bromide 57 with magnesium powder (2.5 equiv), LiCl (2.5 equiv) and ZnCl₂ (1.1 equiv) afforded the cyclohexylzinc reagent 58 after 2 h at 25 °C. A subsequent Cu(i)-catalyzed allylation with ethyl (2-bromomethyl)acrylate led to the unsaturated ester derivative 59 in 68 % yield (Scheme 40).

Scheme 40: Magnesium insertion in the presence of LiCl and ZnCl₂ into the cyclohexyl derivative 59

1.6. Larger Scale Preparations of Organomagnesium and Organozinc Reagents

The larger scale preparation of organomagnesium and organozinc reagents is an important task for industrial process chemists. One of the problems of the large scale magnesium insertion into organic halides is the often uncontrollable reaction start which is accompanied by a large evolution of heat. As the addition of LiCl allows the use of lower temperatures for the magnesium insertion, the larger scale preparation of magnesium and zinc compounds was studied for potential industrial applications.
Thus, 2-bromo-1-pivaloyloxybenzene (22v, 40 mmol) was treated with Mg (2.5 equiv) and LiCl (1.25 equiv) in THF at –20 °C. After slow addition and stirring for 30 min at –20 °C the conversion of the starting bromide 22v was complete and the magnesium reagent 23v was obtained in 93 % yield as indicated by titration (Table 3, entry 1). The insertion started promptly and the internal temperature never exceeded –14 °C. Similarly, 3-bromo-1-pivaloyloxybenzene (22w, 40 mmol) could be inserted using the same protocol and the corresponding magnesium reagent 23w was furnished in 86 % yield (entry 2). The Boc protecting group was also compatible with the magnesium insertion on an 86 mmol scale at –20 °C. When maintaining a slow addition rate, the internal temperature did not rise above –16 °C and led to the Boc-protected organometallic 23b reagent in 91 % yield (entry 3).

Electron-rich or sterically demanding substrates such as 4-bromoanisole (22x) or bromomesitylene (22y) were smoothly converted to their respective magnesium reagents 23x-y at 0 °C and a yield of 93-97 % could be obtained within 30 min, as indicated by iodometric titrations (entries 4 and 5).

As an example of a heterocyclic bromide, 3-bromopyridine (22z) was converted to the corresponding Grignard reagent 23z in 90 % yield on a 100 mol scale (entry 6). When performing the reaction at ambient temperatures, the inside temperature ranged between 20 °C and 38 °C. When cooling the reaction mixture in an ice/water-bath, the inside temperature could be maintained between 1 °C and 7 °C.

The magnesium reagent of a typical alkyl bromide such as (3-bromopropyl)benzene (60) could conveniently be prepared at 0 °C in 91 % yield without the formation of homo-coupling by-products (entry 7).

Additionally, benzylic zinc reagents could be prepared on a larger scale. Using the system consisting of Mg/LiCl/ZnCl₂ 2-chlorobenzyl chloride (45a) was smoothly converted to the corresponding benzylic zinc reagent 46a in excellent yield (entry 8).

---

### Results and Discussion

Table 3: Scale-up experiments for the preparation of functionalized magnesium and zinc reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>T [°C]</th>
<th>Scale [mmol]</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22v</td>
<td>-20</td>
<td>40</td>
<td>23v</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>22w</td>
<td>-20</td>
<td>40</td>
<td>23w</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>22b</td>
<td>-20</td>
<td>86</td>
<td>23b</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>22x</td>
<td>0</td>
<td>50</td>
<td>23x</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>22y</td>
<td>0</td>
<td>50</td>
<td>23y</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>22z</td>
<td>0</td>
<td>100</td>
<td>23z</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>0</td>
<td>50</td>
<td>61</td>
<td>91</td>
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</table>
Results and Discussion

Table 3 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>T [°C]</th>
<th>Scale [mmol]</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><img src="image" alt="Image" /></td>
<td>0</td>
<td>50</td>
<td><img src="image" alt="Image" /></td>
<td>90</td>
</tr>
</tbody>
</table>

In order to show that the reactivity of magnesium reagents prepared on a larger scale was equal to the smaller scale experiments, 10 mmol aliquots of selected Grignard reagents were reacted with electrophiles. Addition of freshly titrated 2-pivaloyloxyphenylmagnesium bromide (22v) to a solution of DMF (1.2 equiv) in THF at –20 °C furnished the benzaldehyde 24v in 83 % yield (Table 4, entry 1). Similarly, the Grignard reagent derived from Boc-protected 4-bromophenol 23b could be reacted with 4-chlorobenzaldehyde to give the diarylmethane 24w in 90 % yield (entry 2). A 10 mmol aliquot of the heterocyclic 3-pyridylmagnesium bromide (23z) was added to anisaldehyde and the resulting benzylic alcohol 24x could be isolated in 94 % yield (entry 3).

Finally, the magnesium compounds prepared in a large scale from 4-bromoanisole and bromomesitylene 23x-y showed the same reactivity as their smaller scale counterparts. Their reaction with 4-isopropylbenzaldehyde or a Cu(I)-catalyzed acylation with 4-anisoyl chloride afforded the expected products 24y-z in 89-96 % yield (entries 4-5).

Table 4: Reactions of functionalized magnesium reagents of type 23 prepared on a big scale with typical electrophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Magnesium Reagent</th>
<th>T [°C]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image" /></td>
<td>-20</td>
<td>DMF</td>
<td><img src="image" alt="Image" /></td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td>-20</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>90</td>
</tr>
</tbody>
</table>

[a] Isolated yield.
### Results and Discussion

Table 4 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Magnesium Reagent</th>
<th>( T [^\circ C] )</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>( \text{MgBr\cdot LiCl} ) &amp; 23z &amp; 0 &amp; ( \text{H} ) &amp; ( \text{CH} ) &amp; ( \text{24x} ) &amp; 94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>( \text{MgBr\cdot LiCl} ) &amp; 23x &amp; 0 &amp; ( \text{H} ) &amp; ( \text{O} ) &amp; ( \text{OH} ) &amp; ( \text{24y} ) &amp; 96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>( \text{MgBr\cdot LiCl} ) &amp; 23y &amp; 0 &amp; ( \text{Cl} ) &amp; ( \text{O} ) &amp; ( \text{O} ) &amp; ( \text{24z} ) &amp; 89[b]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure product. [b] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20 mol%).
2. Regio- and Chemoselective Synthesis of Functionalized 5-Membered-Ring Heterocycles

2.1. Preparation of Polyfunctional Furan, Thiophene, Indole and Pyrrole Derivatives

The quest for new biologically active molecules is probably the most important task in synthetic organic chemistry today. As these molecules are mostly manufactured in chemical laboratories, the development of new methods for their synthesis is an incredibly important mission. Heteroatoms play a large role in most biologically active compounds because of their ability to interact with enzymatic centers or receptors through H-bonding or their lone electron pairs. Important classes of molecules bearing heteroatoms are heterocycles, which are found in many natural products. Six of seven of America’s top-selling drugs in the year 2008 all included at least one heterocycle, and therefore their selective synthesis and functionalization is of great chemical, biological and medicinal interest.61

Directed lithiations of 5-membered ring heterocycles are well known reactions, but they often require low temperatures or have a poor functional group tolerance.62 Magnesiations or zincations using amide bases or ate-complexes are compatible with some functional groups, but can only be performed at the activated 2- or 5-positions.63

With the recent development of new and mild magnesium amide bases such as TMPMgCl·LiCl (16)27 the metalation of functionalized furans and thiophenes was investigated.

In first experiments, the regioselectivity of the deprotonation of ethyl thiophene-2- and furan-2-carboxylate (62a-b) with TMPMgCl·LiCl (16) was determined. Thus, ethyl thiophene-2-carboxylate 62a was treated with TMPMgCl·LiCl (16, 1.1 equiv) at –40 °C. Complete and selective metatlation in the 5-position was achieved within 30 min and the resulting

magnesium reagent 63a was reacted with TMS-CN furnishing the silylated thiophene 65a in 72 % yield. Additionally, the magnesium compound 63a could be reacted with 1,2-dibromo-1,1,2,2-tetrachloroethane or with allyl bromide in a copper-(I)-catalyzed allylation reaction, to give the expected products 65b-c in 66-89 % yield. The diester 65d could be prepared in 63 % yield by the reaction of 63a with ethyl cyanoformate (Scheme 41).

The reaction of ethyl furan-2-carboxylate 62b with TMPMgCl·LiCl (16) did not lead to a selective metalation. Contrary to the thiophene analogue, deprotonation is favored in the 3-position but a product ratio of 80:20 is obtained (Scheme 41).

A further functionalization of 5-membered ring heterocycles could be achieved. Using TMPMgCl·LiCl (16), 2,5-disubstituted furans and thiophenes could be metalated in the 3-position for the first time. Thus, treatment of the diester 66a with TMPMgCl·LiCl (16, 1.1 equiv) at −78 °C furnished the corresponding magnesium reagent within 10 min. The subsequent reaction with MeSO2SMe afforded the thioether 67a in 93 % yield (Table 5, entry 1). After a transmetalation with ZnCl2 and a subsequent Pd-catalyzed cross-coupling reaction with 3-iodobenzotrifluoride the arylated furan 67b could be obtained in 79 % yield (entry 2). Similarly, a copper(I)-catalyzed reaction with an acid chloride yielded the expected ketone 67c in 85 % (entry 3) Furthermore, the addition of TsCN to this magnesium reagent produced the nitrile 67d in 66 % yield (entry 4). The corresponding thiophene derivative 67e could also be prepared in 58 % yield by deprotonation of the diester 65d with TMPMgCl·LiCl (−60 °C, 30 min) and quenching with TsCN (entry 5).

The furan 66b and the thiophene 65a bearing a trimethylsilyl group in the 5-position could both be selectively metalated in the 3-position at −30 °C within 1 h. Reaction of the furan-
Results and Discussion

derived magnesium reagent with hexachloroethane furnished the chlorinated product $67f$ in 48 % yield (entry 6). Both magnesium reagents could be reacted with TsCN and the polyfunctional heterocycles $65g-h$ were obtained in 52-69 % yield (entries 7-8). The corresponding thiophene derivative was reacted in a Cu(1)-catalyzed allylation$^{31}$ reaction yielding the tri-substituted thiophene $67i$ in 54 % (entry 9).

Treatment of the brominated furan derivative $66c$ with TMPMgCl·LiCl (16) at –78 °C leads to the magnesiated furan within 30 min. After copper-catalyzed acylation reactions with benzoyl chloride the expected ketone ($67j$) could be isolated in 75% yield (entries 10). Additionally, the reaction with benzenesulfonyl chloride or TsCN led to the expected products $67k-l$ in 59-63 % yield (entries 11-12). After a transmetalation with ZnCl$_2$ the resulting zinc reagent could be used in a Negishi cross-coupling reaction$^{39}$ with ethyl 4-iodobenzoate and the diester $67m$ was obtained in 86 % yield (entry 13). Treatment of the zinc reagent with chloranil as an oxidizing agent$^{64}$ afforded the corresponding homo-coupling product $67n$ in 80 % yield (entry 14). The magnesium reagent derived from the brominated thiophene 65b was also obtained by deprotonation with TMPMgCl·LiCl (16, 1.1 equiv, -50 °C, 30 min). Subsequent reactions with a sulfonothioate or TsCN gave the 2,3,5-trisubstituted thiophenes $67o-p$ in 50-68 % yield (entries 15-16).

Table 5: Preparation of 2,3,5-trisubstituted furans and thiophenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>$T$ [°C], $t$ [min]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%]$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$66a$</td>
<td>-78, 10</td>
<td>MeSO$_2$SMe</td>
<td>$67a$</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>$66a$</td>
<td>-78, 10</td>
<td>I$_{2}$CF$_3$</td>
<td>$67b$</td>
<td>79$^b$</td>
</tr>
</tbody>
</table>

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### Results and Discussion

Table 5 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>T [°C], t [min]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{F}}-\text{CO}_2\text{Et} ) (66a)</td>
<td>-78, 10</td>
<td>( \text{O} \text{Cl} )</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{F}}-\text{CO}_2\text{Et} ) (67c)</td>
<td>85[a]</td>
</tr>
<tr>
<td>4</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{F}}-\text{CO}_2\text{Et} ) (66a)</td>
<td>-78, 10</td>
<td>( \text{TscN} )</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{F}}-\text{CO}_2\text{Et} ) (67d)</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{F}}-\text{CO}_2\text{Et} ) (65d)</td>
<td>-60, 30</td>
<td>( \text{TscN} )</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{F}}-\text{CO}_2\text{Et} ) (67e)</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{TMS}} ) (66b)</td>
<td>-30, 60</td>
<td>( \text{C}_2\text{Cl}_6 )</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{TMS}} ) (67f)</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{TMS}} ) (66b)</td>
<td>-30, 60</td>
<td>( \text{TscN} )</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{TMS}} ) (67g)</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{TMS}} ) (65a)</td>
<td>-35, 60</td>
<td>( \text{TscN} )</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{TMS}} ) (67h)</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{TMS}} ) (65a)</td>
<td>-35, 60</td>
<td>( \text{BrCH} = \text{CH}_2 )</td>
<td>( \text{EtO}<em>2\text{C-C}</em>{\text{TMS}} ) (67i)</td>
<td>54[b]</td>
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</table>
## Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>T [°C], t [min]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>EtO₂C–[66c]–Br</td>
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<td>PhCH₂Cl</td>
<td>67j</td>
<td>75[b]</td>
</tr>
<tr>
<td>11</td>
<td>EtO₂C–[66c]–Br</td>
<td>-78, 30</td>
<td>PhSO₂Cl</td>
<td>67k</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>EtO₂C–[66c]–Br</td>
<td>-78, 30</td>
<td>TsCN</td>
<td>67l</td>
<td>63</td>
</tr>
<tr>
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<td>I-PhCO₂Et</td>
<td>67m</td>
<td>86[b]</td>
</tr>
<tr>
<td>14</td>
<td>EtO₂C–[66c]–Br</td>
<td>-78, 30</td>
<td>Cl₂Ph</td>
<td>67n</td>
<td>80[b]</td>
</tr>
<tr>
<td>15</td>
<td>EtO₂C–[65b]–Br</td>
<td>-50, 30</td>
<td>PhSO₂SPh</td>
<td>67o</td>
<td>68</td>
</tr>
<tr>
<td>16</td>
<td>EtO₂C–[65b]–Br</td>
<td>-50, 30</td>
<td>TsCN</td>
<td>67p</td>
<td>50</td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure product; [b] Obtained after transmetalation with ZnCl₂ (1.1 equiv) and a Pd-catalyzed cross-coupling reaction; [c] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20-100 mol%); [d] Obtained after transmetalation with ZnCl₂ (1.1 equiv).
Results and Discussion

A further functionalization of the 4-position could also be achieved. Thus, the thiomethyl-substituted furan 67a could be deprotonated using TMPMgCl·LiCl (16, 1.1 equiv) within 45 min at −78 °C. A subsequent reaction with 4-cyanobenzaldehyde furnished the alcohol 69a in 67 % yield. On the other hand, when metalating the nitrile 67d with TMPMgCl·LiCl (1.1 equiv) the resulting magnesium reagent was not stable even at −78 °C. However, when performing the reaction in the presence of 1.1 equiv of ZnCl2 the magnesium reagent could be transmetalated in situ to the more stable zinc compound 68b. After a Pd-catalyzed cross-coupling reaction39 with 4-iodobenzonitrile the fully substituted furan 69b was isolated in 71 % yield (Scheme 42).

![Chemical Structures and Reactions]

Scheme 42: Preparation of fully substituted furan derivatives

When trying to deprotonate the 5-brominated furans 67k-l two metalation products were formed. The 4-metalated products of type 68 partly rearranged in a halogen dance reaction and gave the two magnesiated furans of type 68 and 70 in 80:20 ratios.65 This problem can be avoided when first functionalizing the 5-position. Thus, the brominated furan 67k was subjected to a halogen-magnesium exchange reaction with iPrMgCl·LiCl (13, 1.1 equiv) and the magnesium reagent was obtained after 30 min at −50 °C. Reaction with TsCN then afforded the 2,3,5-trisubstituted furan 71 in 73 % yield. Subsequent deprotonation proceeds smoothly (16, −78 °C, 25 min) and the allylated product 72 could be isolated in 74 % yield after a Cu(I)-catalyzed reaction with allyl bromide (Scheme 43).

Results and Discussion

Nitrogen-containing heterocycles are an important substance class in pharmaceutical and medicinal chemistry. The tosyl-protected indole 73, bearing an ester group in the 2-position could be metalated selectively in the 3-position using TMPCl·LiCl (16, 1.1 equiv, –25 °C, 2.5 h). Subsequent reaction with benzaldehyde furnished the benzhydryl alcohol 75a in 91 % yield. The magnesium reagent 74 could also be trapped with allyl bromide in a Cu(i)-catalyzed reaction,31 to yield the allylated indole 75b in 95 %.

The Boc-protected pyrrole 76 could not be metalated with TMPCl·LiCl (16). At temperatures below 0 °C no reaction was observed, and above 0 °C the resulting magnesium reagent decomposed rapidly. Using the more reactive base TMP2Mg·2 LiCl (17)29 76 could be deprotonated at –30 °C within 1.5 h. A Negishi cross-coupling reaction39 using Pd(PPh3)4 and 4-chloriodobenzene then provided the arylated pyrrole 78 in 95 % yield (Scheme 44).
Results and Discussion

2.2. Regio- and Chemoselective Synthesis of Fully Substituted Thiophenes

The thiophene moiety is an important building block for various new materials\(^{66}\) and modern drug design.\(^{67}\) Therefore, the selective functionalization of every position of the thiophene ring is of particular interest. Based upon the results of the functionalization of 5-membered ring heterocycles mentioned above, a general reaction scheme was developed for the selective preparation of fully substituted thiophenes (Scheme 45).


Results and Discussion

Thus, it was envisioned to start from 2,5-dichlorothiophene 79. The use of chlorine atoms as protecting groups was chosen because of the following requirements:

- It needed to possess directing ability in order to enable the metalation in the 3- and 4-position
- It needed to be easily cleft to give access to the 2- and 5-positions

After deprotonation and functionalization of the 3- and 4-positions using TMPMgCl·LiCl and subsequent quenching with an electrophile (E¹ and E²) both Cl atoms are cleft, furnishing 3,4-disubstituted thiophenes of type 84. Selective magnesation and quenching with electrophiles (E³ and E⁴) on the remaining 2- and 5-position then lead to fully substituted thiophenes of type 86.

The use of chlorine atoms as a protecting group for the 2- and 5-position turned out to be the method of choice. They have a suitable directing ability and can easily be cleft reductively.

Thus, the reaction of 2,5-dichlorothiophene (79) with TMPMgCl·LiCl (16; 1.1 equiv, 25 °C, 30 min) led to the corresponding 3-magnesiated thiophene 80, which could be trapped with PhSO₂SMe giving the thiomethylated compound 81a in 92 % yield. The subsequent deprotonation of 81a using TMPMgCl·LiCl (16) also proceeded smoothly (−10 °C, 30 min) and the resulting magnesiated intermediate was reacted with DMF, yielding the aldehyde 83a in 95 % (Table 6, entry 1).

Treatment of the magnesiated intermediate 80 with ethyl cyanoformate yielded the ester 81b in 76% yield. A subsequent deprotonation of 81b, proceeded smoothly (−30 °C, 30 min) and the expected products 83b-d were isolated in 76-95 % yield after a Pd-catalyzed cross-
Results and Discussion

coupling reaction, a reaction with an acid cyanide or a Cu(I)-catalyzed allylation (entries 2-4). Similarly, the 3-magnesiated thiophene reacted directly with Boc₂O affording the ester 81e in 82% yield. Subsequent metalation and again trapping with Boc₂O provided the diester 83e in 79% yield (entry 5). Ketones are sensitive functional groups and often react with polar organometallics. However, the Cu(I)-catalyzed quenching of the 3-thienylmagnesium reagent 80 with acid chlorides afforded the ketones 81f and 81g. These ketones readily underwent metalation using (–78 to –50 °C, 30 to 45 min) and, after Negishi cross-coupling reactions with 4-iodobenzonitrile or 4-chloroiodobenzene, the arylated products 83f and 83g were obtained in 77-86% yield (entries 6-7). Similarly, a cyano function is tolerated as well. Thus, the treatment of the magnesium reagent 80 with TsCN furnished the nitrile 81h in 73% yield. After a subsequent metalation of 81h (–30 °C, 15 min) and trapping of the resulting magnesium reagent with DMF, the functionalized aldehyde 83h was obtained in 86% yield (entry 8).

The synthesis of 3,4-substituted chlorothiophenes of type 5 is also possible using the crude intermediate products of type 81. Thus, the reaction of the magnesium compound 80 with ethyl cyanoformate gave the corresponding 3-substituted dichlorothiophene. After an aqueous workup, the crude mixture was again treated with TMPMgCl-LiCl (1; –30 °C, 30 min) and quenched with NCCO₂Et, yielding the diester 83i in 87% overall yield (entry 9). Similarly, PhSO₂SMe or an acid chloride could be used as a second electrophile (E₂) leading to the 3,4-substituted thiophenes 83j and 83k in 67-73% overall yield (entries 10-11). When quenching the thienylmagnesium reagent 80 with PhSO₂SMe, the subsequent deprotonation of the crude reaction mixture proceeded smoothly (–10 °C, 30 min) and the resulting magnesium reagent could be used in a Pd-catalyzed cross-coupling reaction to give the expected product 83l in 84% overall yield (entry 12).

Table 6: Synthesis of 3,4-difunctionalized dichlorothiophenes of type 83

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product of type 4 (yield[a])</th>
<th>Product of type 5 (yield[b])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeSO₂SMe</td>
<td>DMF 83a: 95%</td>
</tr>
<tr>
<td>2</td>
<td>Cl-SMe</td>
<td>DMF 83a: 92%</td>
</tr>
</tbody>
</table>

**Results and Discussion**

Table 6 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>E&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Product of type 4 (yield&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>E&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Product of type 5 (yield&lt;sup&gt;b&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NC&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>81b: 76 %</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
</tr>
<tr>
<td>3</td>
<td>NC&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>81b: 76 %</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
</tr>
<tr>
<td>4</td>
<td>NC&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>81b: 76 %</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
</tr>
<tr>
<td>5</td>
<td>Boc&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>81c: 82 %</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
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<tr>
<td>6</td>
<td>PhCl</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>81e: 78 %&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
</tr>
<tr>
<td>7</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>81f: 75 %&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
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<tr>
<td>8</td>
<td>TsCN</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>81f: 73 %</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
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**Results and Discussion**

Table 6 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>E&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Product of type 4 (yield&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>E&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Product of type 5 (yield&lt;sup&gt;d&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>O(\text{NC} \text{CO}_2\text{Et})</td>
<td>O(\text{NC} \text{CO}_2\text{Et})</td>
<td>E\text{to}_2 \text{Cl}_2 \text{CO}_2\text{Et}</td>
<td>83i: 87 %&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>O(\text{NC} \text{CO}_2\text{Et})</td>
<td>Me\text{SO}_2\text{Me}</td>
<td>Me\text{S} \text{CO}_2\text{Et}</td>
<td>83j: 73 %&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>11</td>
<td>O(\text{NC} \text{CO}_2\text{Et})</td>
<td>O(\text{Cl} \text{C}_6\text{H}_4\text{Me})</td>
<td>O(\text{Cl} \text{C}_6\text{H}_4\text{Me})</td>
<td>83k: 67 %&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Me\text{SO}_2\text{Me}</td>
<td>O(\text{O}_2\text{Me})</td>
<td>O(\text{O}_2\text{Me})</td>
<td>83l: 84 %&lt;sup&gt;[b, d]&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure product; [b] Obtained after transmetalation with ZnCl\(_2\) (1.1 equiv) and a Pd-catalyzed cross-coupling reaction; [c] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20 mol%); [d] Overall yield over two steps.

The reductive cleavage of a carbon-chlorine bond can be achieved by various metal-catalyzed reactions.<sup>69</sup> The method developed by Schlosser using Pd/C and ammonium formate as a reductive system was chosen.<sup>70</sup> However, it was observed that conventional heating led to a sluggish reaction. For example, the reduction of the dichlorothiophene 83g in EtOH at 80 °C using a sealed tube required 5 days to achieve completion. However, by using microwave irradiation (100 W, 70 °C, open vessel), the reduction was complete within 5 h and the dechlorinated thiophene 84a was isolated in 76 % yield.

Remarkably, this reduction was completely selective, and only reduced the carbon-chlorine bonds at the thiophene ring without affecting other aromatic C-Cl-bonds (see Scheme 46, compound 84a). The same procedure was used for the chlorothiophenes 83f, 83j and 83k (5-6

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h, 100 W, 70 °C, open vessel) furnishing the dechlorinated products **84b-d** in 77-95 % yield (Scheme 46).

![Scheme 46: Reduction of dichlorothiophenes of type 83 using Pd/C and HCO2NH4 under microwave irradiation](image)

A further deprotonation of the dechlorinated thiophenes of type **84** was achieved with complete regioselectivity. When treating the thiophene **84b** and **84c** with TMPMgCl-LiCl (16; 1.1 equiv, –40 to –30 °C, 30-60 min) the ester moiety is acting as a directing group\(^\text{71}\) and magnesiation occurs regioselectively next to this ester group. Cu(I)-catalyzed alkylation\(^\text{31}\) or Pd-catalyzed cross-coupling reactions afforded the expected products **85a-85d** in 57-93 % yield. Similarly, a ketone can also play the role of an efficient directing group and the product **85e** was isolated in 92 % yield after deprotonation of **84a** and quenching with NCCO2Et.

The remaining 5-position could be metalated as well between –50 and –20 °C with TMPMgCl-LiCl (1; 1.1 equiv, 30-45 min). The resulting magnesiated intermediates were trapped with aldehydes and DMF or can be used in allylations or cross-coupling reactions\(^\text{39}\) furnishing the fully substituted thiophene derivatives **86a-86f** in 70-87% yield. Moreover, the magnesiated thiophene derived from thiophene **85b** could be subjected to a transition metal-free homo-coupling reaction using chloranil\(^\text{64}\) and the highly functionalized dithiophene **86g** was obtained in 63 % yield (Scheme 47).

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Dichlorothiophenes of type 83 could also be magnesiated directly at the 2- and 5-positions using a LiCl-mediated magnesium insertion. Thus, the addition of the dichlorothiophene 83j to Mg-turnings (2.5 equiv), LiCl (1.25 equiv) and ZnCl₂ (1.1 equiv) in THF regioselectively gave the zinicated intermediate 87 (25 °C, 3 h) which could be arylated in a Pd-catalyzed reaction with 4-iodoanisole leading to the arylated product 88 in 91 % yield. Repeated treatment of 88 with magnesium turnings, LiCl and ZnCl₂ (25 °C, 4 h) afforded the zinc compound 89 and following an allylation reaction catalyzed by CuCN·2 LiCl (20 mol%) the fully functionalized thiophene 90 was isolated 71 % yield. Additionally, the magnesium insertion into the dichlorothiophene 83e could be conducted at –50 °C within 3 h. A subsequent Negishi cross-coupling reaction with iodobenzene furnished the arylated thiophene 92 in 82 % yield. The second insertion also proceeded smoothly at –50 °C within 3 h and after a Cu(I)-catalyzed allylation reaction the fully substituted thiophene 94 could be isolated in 88 % yield (Scheme 48).
As an application, a thiophene analogue of Atorvastatin (95; Lipitor®, HMG-CoA reductase inhibitor, anti-cholesterol agent) was prepared starting from 2,5-dichlorothiophene (79). Using the procedure described above, selective deprotonations and successive quenching with ethyl cyanoformate and iodobenzene in a Negishi cross-coupling reaction furnished the 3,4-disubstituted dichlorothiophene 96 in 69% yield. Regioselective magnesium insertion in the presence of LiCl and ZnCl₂ (25 °C, 3 h) and subsequent Pd-catalyzed cross-coupling with 2-bromopropene (using Pd(OAc)₂ and SPhos as a catalytic system) afforded the alkene 97 in 94% yield. The Mg-insertion into the remaining C-Cl bond of 97 proceeded smoothly (25 °C, 3 h). A Negishi cross-coupling reaction with 4-bromofluorobenzene, then yielded the arylated product 98 in 66% yield. After hydrogenation of the double-bond and amide formation using Weinreb’s method (PhNH₂, AlMe₃) the thiophene analogue 99 of the Atorvastatin core (95) was obtained in 85% yield (36% overall yield, Scheme 49).

Scheme 48: Magnesium insertion in the presence of LiCl into dichlorothiophenes of type 83

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Scheme 49: Application to the synthesis of a thiophene-based Atorvastatin (Lipitor®) derivative
3. Preparation of Functionalized Enol Phosphates by Halogen-Magnesium Exchange and Directed Deprotonation Reactions

Enol phosphates are an important class of organic compounds that have found applications as insecticides and phosphatase inactivators. Additionally, they can be used as versatile intermediates for the regioselective preparation of substituted double bonds. Several methods have been developed allowing efficient transition metal-catalyzed cross-coupling reactions with this kind of substrates. In fact, enol phosphates are a useful synthetic alternative to the corresponding triflates since they are generally less expensive and more stable. Their preparation is conveniently performed starting either from enolizable ketones or α-halo carbonyl compounds.

The synthesis of lithiated enol phosphates of type 100 via halogen-lithium exchange or deprotonation using LDA has already been described by Wiemer. However, these lithium reagents do not react with electrophiles (E⁺) but rearrange to the corresponding β-keto phosphonates 101 in good yields (Scheme 50).

![Scheme 50: Rearrangement of lithiated enol phosphates to the corresponding β-keto phosphonate](image)

As organomagnesium reagents are less reactive than organolithium reagents it is expected that the corresponding magnesium reagents are more stable. Hence, the preparation of magnesiated enol phosphates derived from D(+) camphor was investigated using halogen-magnesium exchange and directed deprotonation reactions. Camphor derivatives are often

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Results and Discussion

used as chiral auxiliaries in stereoselective reactions. Developing a functionalization of the camphor skeleton would therefore be a highly desirable process.

Starting from commercially available D(+)-bromocamphor (102) the enol phosphate 103 was prepared by deprotonation with LDA (1.1 equiv, −78 °C, 1.5 h) and quenching of the resulting enolate with diethyl chlorophosphate in 82 % yield.

The corresponding magnesium reagent 104a was smoothly generated by treatment of 103 with iPrMgCl·LiCl (13, 1.1 equiv, 25 °C, 2 h). No rearrangement to the β-keto phosphonate was observed (Scheme 51).

The magnesium reagent 104 reacted well with electrophiles (E⁺). Thus, treatment of 104 with allyl bromide using copper(I)-catalysis gave the allylated product 105a in 62 % yield (Table 7, entry 1). Similarly, the cycloalkenylmagnesium reagent 104a could be used in an acylation reaction with benzoyl chloride using CuCN·2 LiCl³¹ (20 mol%) and the expected ketone 105b was obtained in 67 % yield (entry 2). Additionally, the use of ethyl cyanoformate allowed the synthesis of the ester 105c in 72 % yield (entry 3). Thioethers are easily prepared by quenching the Grignard reagents with sulfonothioates. Using PhSO₂SPh as an electrophile, the corresponding phenyl thioether 105d was obtained in 65 % yield (entry 4). After a transmetalation with ZnCl₂ (1.1 equiv), the resulting organozinc reagent underwent a Negishi cross-coupling reaction.³⁹ The electron rich 3-bromoanisole could be used as an electrophile by using Buchwald’s S-Phos ligand (4 mol%) and Pd(OAc)₂ (2 mol%) yielding the arylated camphor derivative 105e in 69 % yield (entry 5).

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**Results and Discussion**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Magnesium Reagent</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>Br vinyl</td>
<td><img src="image2" alt="Image" /></td>
<td>62[b]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td>Ph Cl</td>
<td><img src="image4" alt="Image" /></td>
<td>67[b]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td>NC CO2Et</td>
<td><img src="image6" alt="Image" /></td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td>PhSO2SPh</td>
<td><img src="image8" alt="Image" /></td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Image" /></td>
<td>Br OMe</td>
<td><img src="image10" alt="Image" /></td>
<td>68[c]</td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure product; [b] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20 mol%); [c] Obtained after transmetalation with ZnCl₂ (1.1 equiv) and a Pd-catalyzed cross-coupling reaction.

Starting from the enol phosphate 107 (prepared from D(+)-camphor 106) the magnesium reagent 104a could be prepared by a deprotonation reaction. Treatment of 104b with TMPMgCl·LiCl (16, 1.1 equiv, 25 °C) furnished the corresponding magnesium reagent in reasonable yield (~80 %) but required 12 h to reach completion. Using the more reactive bisamide TMP₂Mg·2 LiCl (17, 1.1 equiv) full conversion to the Grignard reagent 104b could be achieved with in 30 min at 25 °C. The magnesium reagent 104b had a similar reactivity, regardless of its preparation method. Thus, the Grignard reagent 104b generated by deprotonation with TMP₂MgCl·2 LiCl (17) could be trapped with allyl bromide using
copper(I) catalysis (20 mol %) and led to the expected product 105a in 77 % yield (Scheme 52).

An unexpected reaction pathway was observed when reacting the Grignard reagent 104 with aldehydes. Instead of giving the expected allylic alcohols of type 108 the products underwent a spontaneous elimination to give the α,β-unsaturated ketones 109a-c with an excellent E/Z-selectivity as shown by NMR analysis. Thus, after reaction of 104 with 4-cyanobenzaldehyde the ketone 109a was obtained in 72 % yield and >99:1 E/Z-selectivity. Similarly, 4-bromobenzaldehyde gave a similar elimination and yielded the unsaturated ketone 109b in 68 % yield and 98:2 E/Z-selectivity. Aliphatic aldehydes reacted as well, and after the treatment of cyclohexanecarbaldehyde with the magnesium reagent 104 the elimination product 109c was isolated in 70 % yield and 96:4 E/Z-selectivity (Scheme 53).
4. 1-Aryliminozinc Reagents as Acyl Anion Equivalents

Acyl anion equivalents are valuable synthetic intermediates in organic chemistry. One member of this class of compounds are iminozinc reagents. They were first prepared in 1904 by Sachs and Loevy by the reaction of phenylmagnesium bromide and methyl isocyanide. Since then, the α-addition of organometallic reagents to isonitriles has attracted considerable attention for example by Gilman and Ugi. A breakthrough was accomplished by Walborsky who showed in a series of papers that organolithium reagents could be added to isonitriles. Later, Ito and co-workers prepared [1-(arylimino)alkyl]zinc reagents by the reaction of diorganozinc compounds with aromatic isonitriles (Scheme 54).

Drawbacks of this reaction are a low functional group tolerance due harsh reaction conditions (95 °C in toluene) and the need to use diorganozinc compounds. Recently, Knochel and co-workers reported an accelerated attack of functionalized organozinc reagents to carbonyl compounds by the addition of MgCl₂. Reagents of such kind are conveniently prepared by a direct insertion of magnesium in the presence of LiCl and ZnCl₂ as described earlier. Based on this report, the addition of organozinc reagents to aryl isonitriles was reinvestigated.

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Results and Discussion

In preliminary experiments, various zinc reagents were reacted with commercially available 2,6-dimethylphenyl isonitrile (110) in the presence of MgCl₂. While alkyl and aromatic zinc reagents did not show any reactivity towards the isonitrile 110, the benzylic zinc reagent 111 added to 2,6-dimethylphenyl isonitrile (110) within 15 min at 0 °C. The resulting aryliminozinc reagent 112 could be trapped with allyl bromide under Cu(i)-catalysis 31 (20 mol%) and the resulting imine 113 could be isolated in moderate yield (Scheme 55).

During the reaction, it was observed that the aryliminozinc reagent 112 decomposed slowly, even at 0 °C. When lowering the temperature below 0 °C however, the reaction did not proceed to completion. It was envisioned that with the use of a more electron-poor isonitrile, the reaction could be performed at lower temperatures. Thus, 2,6-dichlorophenyl isonitrile (114) reacted with 4-methoxybenzylzinc chloride (111) in the presence of MgCl₂ at –78 °C within 30 min. Without MgCl₂ no reaction was observed under these reaction conditions. The resulting zinc reagent 115 was allylated in a Cu(i)-catalyzed reaction with allyl bromide and the resulting imine 116 could be isolated in 61 % yield (Scheme 56).
5. **Summary and Outlook**

This work was focused on the preparation of organomagnesium and organozinc reagents by magnesium insertion reactions and directed deprotonations. Furthermore, functionalized enol phosphates derived from D(+)-camphor were synthesized and preliminary experiments towards the MgCl₂-mediated reaction of zinc reagents with aryl isonitriles were conducted.

5.1. **LiCl-Mediated Direct Insertion of Magnesium Into Aryl, Heteroaryl and Benzylic Halides**

The insertion of readily available magnesium turnings into aryl bromides in the presence of LiCl was described. This method allowed the preparation of various functionalized magnesium reagents using a practical and economical procedure (Scheme 57).

Sensitive substrates such as aromatic esters or sophisticated heterocycles could also be converted by transmetalation with ZnCl₂ in situ to the corresponding organozinc reagents which then underwent reactions with various electrophiles (Scheme 58).
Results and Discussion

![Scheme 58: Preparation of functionalized zinc reagents](image)

This methodology was then successfully transferred to the preparation of benzylic zinc chlorides and alkylzinc bromides. In both cases, the reaction times using Mg/LiCl/ZnCl₂ were greatly accelerated compared to the corresponding zinc insertion (Scheme 59).

![Scheme 59: Preparation of functionalized benzylic and alkylzinc reagents](image)

Additionally, the magnesium and zinc insertion into 2,4-dibrominated and 2,4,6-tribrominated arenes was investigated. A highly useful regioselective insertion procedure was developed giving access to selectively metalated bromoarenes (Scheme 60).
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Scheme 60: Orthogonal regioselectivity pattern of zinc and magnesium insertions

Due to the relevance of organometallic reagents for industrial applications, all of the procedures described above were performed on a larger scale. Functionalized organomagnesium and organozinc reagents were prepared by insertion of magnesium in the presence of LiCl on a 25-100 mmol scale (Scheme 61).

Scheme 61: Magnesium reagents obtained after larger-scale experiments

Since the LiCl-mediated magnesium insertion allows the use of low temperatures, it might be possible to insert into alkenyl bromides without isomerisation of the double bond. Furthermore, the direct transmetalation with metal halides such as AlCl₃ or LaCl₃ would open an easy access to new interesting organometallics.

5.2. Regio- and Chemoselective Synthesis of Functionalized 5-Membered-Ring Heterocycles
The synthesis of various furan, thiophene, pyrrole and indole derivatives bearing an ester group in the 2-position was described. Using the magnesium amide bases TMPMgCl·LiCl and TMP₂Mg·2 LiCl all positions of the heterocyclic core could be functionalized (Scheme 62).

Furthermore, a practical method for the preparation of fully substituted thiophenes was developed. Starting from commercially available 2,5-dichlorothiophene, a sequence of directed deprotonations using TMPMgCl·LiCl or magnesium insertions in the presence of LiCl afforded a broad range of fully substituted thiophenes (Scheme 63).

Extensions of this work could include the preparation of functionalized materials such as organic conductors or organic solar cells based on thiophene and other heterocycles.
5.3. Preparation of Functionalized Enol Phosphates by Halogen-Magnesium Exchange and Directed Deprotonation Reactions

The functionalization of cyclic enol phosphates based on D(+)-camphor was achieved by either halogen/magnesium exchange reactions or directed deprotonations using TMP-derived magnesium amide bases (Scheme 64).

Furthermore, the reaction of a camphor derived magnesium reagent with aldehydes furnished, after elimination, the corresponding \( \alpha,\beta \)-unsaturated enones in excellent \( E/Z \)-selectivity (Scheme 65).
**Results and Discussion**

Scheme 65: Reaction of aldehydes with a D(+)-camphor-derived magnesium reagent

As an application of this work, this method could be used for the convenient preparation of chiral $P,N$-ligands based on the camphor-core.

**5.4. 1-Aryliminozinc Reagents as Acyl Anion Equivalents**

Finally, preliminary experiments were conducted concerning the role of MgCl$_2$ towards the addition of organozinc reagents to aryl isonitriles. It was found that in the presence of MgCl$_2$ monoorganozinc reagents were able to attack 2,6-dichlorophenyl isonitrile even at $-78$ °C (Scheme 66).

Scheme 66: Influence of MgCl$_2$ on the addition of zinc reagents to isonitriles

Further investigations regarding the nature of the aryl isonitrile will need to be conducted. Possible targets could include CF$_3$-containing isonitriles. Moreover, due to their electronic similarity to $N$-heterocyclic carbenes, the use of isonitriles as ligands in palladium-catalyzed reactions could be investigated.
C. EXPERIMENTAL SECTION
1. General Considerations

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

Solvents

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

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

**Et₂O** was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

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

**DMF** was heated to reflux for 14 h over CaH₂ and distilled from CaH₂.

Solvents for column chromatography were distilled prior to use.

Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use. Following compounds were prepared according to literature procedures:

- O-Boc-Protected phenols,²⁷b tosyl-protected phenols,⁸⁶ aromatic pivalates,¹⁵ enol phosphates,⁷⁷ 2-iodocyclohex-2-en-1-one,⁸⁷ sulfonothioate derivatives,⁵⁴ 1-[(2,4-dibromophenyl)-diazenyl]-pyrrolidine,⁸⁸ ethyl 1-[(4-methylphenyl)sulfonyl]-1H-indole-2-

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Experimental Section

carboxylate, 89 1-tert-butyl 2,5-diethyl pyrrole-1,2,5-tricarboxylate,90 ethyl 5-bromo-2-furoate.91

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

*nBuLi* solution in hexane was purchased from Chemetall.

TMPMgCl·LiCl was prepared by slowly adding TMPH (105 mmol, 14.8 g) to an *iPrMgCl·LiCl* solution in THF (100 mmol, 1.4 M, 71.4 mL) and stirring of the resulting mixture at ambient temperature for 3 days.

TMP2Mg·2 LiCl was prepared according to a literature procedure.29

CuCN·2 LiCl solution (1 M) was prepared by drying CuCN (80 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a *Schlenk*-tube under vacuum at 140 °C for 5 h. After cooling, 80 mL dry THF were added and stirring was continued until the salt was dissolved.

ZnCl2 solution (1 M) was prepared by drying ZnCl2 (100 mmol, 136.3 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.

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

Content Determination of Organometallic Reagents

**Organzinc and organomagnesium** reagents were titrated against I2 in a 0.5 M LiCl solution in THF.60

**Organolithium** reagents were titrated against menthol using 1,10-phenanthroline as indicator in THF.92

**TMPMgCl·LiCl and TMP2Mg·2 LiCl** were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

Chromatography

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**Experimental Section**

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

**Thin layer chromatography** was performed using SiO₂ pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:

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

**Analytical Data**

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of CHCl₃ (δ_H : 7.25, δ_C : 77.0). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) as well as br (broad).

**Mass spectroscopy**: High resolution (HR-MS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an electron energy of 70 eV. For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890 / MSD 5973 was used.

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

**Melting points** (M.p.:) were determined on a BÜCHI B-540 apparatus and are uncorrected.
2. LiCl-Mediated Magnesium Insertions into Organic Halides

2.1. Magnesium Insertion in the Presence of LiCl into Aryl and Heteroaryl Bromides

2.1.1. Typical Procedure for the Magnesium Insertion in the Presence of LiCl (TP1)
A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with magnesium turnings (122 mg, 5 mmol). LiCl (5.0 mL, 0.5 M in THF, 2.5 mmol) was added and the magnesium was activated with \( i\text{Bu}_2\text{AlH} \) (0.2 mL, 0.1 M in THF, 0.02 mmol). After 5 min of stirring the aryl chloride or bromide (2.0 mmol) was added in one portion at the given temperature. The reaction mixture was stirred for the indicated time and then cannulated to a new Schlenk-flask for the reaction with an electrophile.

2.1.2. Typical Procedure for Cross-Coupling Reactions (TP2)
\( \text{ZnCl}_2 \) (2.0 mL, 1.0 M in THF, 2.0 mmol) was added to the freshly prepared magnesium reagent and the reaction mixture was stirred for 15 min. \( \text{Pd(dba)}_2 \) (23 mg, 2 mol%) and tfp (19 mg, 4 mol%) were added, followed by the addition of the corresponding aryl iodide or bromide (1.4 mmol), and the reaction mixture was stirred for the given time at 25 °C. The reaction mixture was quenched with sat. NH\(_4\)Cl solution (10 mL) and extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude residue was purified by flash column chromatography.

2.1.3. Typical Procedure for Acylations and Allylations (TP3)
\( \text{CuCN}_2\text{LiCl} \) (0.4 mL, 1.0 M in THF, 20 mol%) was added to the freshly prepared magnesium or zinc reagent and the reaction mixture was stirred for 15 min. After the addition of the corresponding acid chloride or allyl bromide (1.4 mmol) the reaction mixture was stirred for the given time at 25 °C. The reaction mixture was quenched with sat. NH\(_4\)Cl solution (10 mL) and extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude residue was purified by flash column chromatography.
2.1.4. Preparation of Title Compounds

Preparation of tert-butyl 3-(4-chlorobenzoyl)phenyl carbonate (24a):

The magnesium reagent 23a was prepared according to TP1 from 3-bromophenyl tert-butyl carbonate (22a, 546 mg, 2.0 mmol) in 1 h at -10 °C. An acylation reaction was performed according to TP3 with 4-chlorobenzoyl chloride (245 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH2Cl2 = 3:2) furnished 24a as a colorless solid (440 mg, 95%).

M.p.: 83-84 °C.

1H-NMR (400 MHz, CDCl3) δ (ppm): 7.75 (d, J = 8.6 Hz, 2H), 7.62 (td, J = 2.3 Hz, J = 8.6 Hz, 1H), 7.59-7.58 (m, 1H), 7.51-7.45 (m, 3H), 7.42-7.39 (m, 1H), 1.55 (s, 9H).

13C-NMR (100 MHz, CDCl3) δ (ppm): 194.1, 151.5, 151.0, 139.1, 138.5, 135.4, 131.4, 129.4, 128.7, 127.2, 125.6, 122.8, 84.1, 27.7.

IR (ATR) ν (cm⁻¹): 2985, 1749, 1653, 1580, 1439, 1369, 1248, 1138, 1085, 1004, 906, 824, 778.

MS (70 eV, EI) m/z (%): 232 (45) [M⁺-Boc], 139 (52), 57 (100).

HRMS (EI) for C13H9O2Cl (232.0291 [M⁺-Boc]): 232.0275.

Preparation of tert-butyl 4-(methylthio)phenyl carbonate (24b):

The magnesium reagent 23b was prepared according to TP1 from 4-bromophenyl tert-butyl carbonate (22b, 546 mg, 2.0 mmol) in 20 min at -10 °C. MeSO2SMe (177 mg, 1.4 mmol) was
added at -10 °C, the mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/CH₂Cl₂ = 4:1) furnished 24b as a colorless solid (309 mg, 92 %).

**M.p.:** 58-60 °C.

**¹H-NMR (300 MHz, CDCl₃) δ (ppm):** 7.26 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 2.46 (s, 3H), 1.54 (s, 9H).

**IR (ATR) ~ (cm⁻¹):** 2985, 1749, 1493, 1430, 1368, 1277, 1218, 1135, 1013, 890, 816, 779, 745.

**¹³C-NMR (75 MHz, CDCl₃) δ (ppm):** 151.8, 148.9, 135.5, 128.0, 121.7, 83.6, 27.7, 16.6.

**MS (70 eV, EI) m/z (%):** 240 (2) [M⁺], 207 (5), 140 (100), 125 (27), 69 (10), 57 (84).

**HRMS (EI) for C₁₂H₁₆O₃S (240.0820):** 240.0817.

**Preparation of 3-formylphenyl 4-methylbenzenesulfonate (24c):**

![Chemical structure of 3-formylphenyl 4-methylbenzenesulfonate](attachment:image.png)

The magnesium reagent 23c was prepared according to TP1 from 3-bromophenyl 4-methylbenzenesulfonate (22c, 654 mg, 2.0 mmol) in 2 h at 0 °C. DMF (102 mg, 1.4 mmol) was added at 0 °C, the mixture warmed to 25 °C and stirred for 30 min. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (CH₂Cl₂) furnished 24c as a colorless solid (299 mg, 77 %).

**M.p.:** 64-66 °C.

**¹H-NMR (300 MHz, CDCl₃) δ (ppm):** 9.91 (s, 1H), 7.77 (td, J = 1.3 Hz, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.50-7.45 (m, 2H), 7.33 (m, 3H), 2.44 (s, 3H).

**¹³C-NMR (75 MHz, CDCl₃) δ (ppm):** 190.5, 150.2, 145.8, 137.8, 132.0, 129.9, 128.4, 128.3, 128.2, 123.0, 21.7.

**IR (ATR) ~ (cm⁻¹):** 3092, 3056, 2846, 2740, 1691, 1579, 1482, 1439, 1364, 1282, 1220, 1188, 1178, 1126, 1090, 933, 802, 736.

**MS (70 eV, EI) m/z (%):** 276 (21) [M⁺], 155 (74), 91 (100), 65 (21).
**Experimental Section**

HRMS (EI) for C_{14}H_{12}O_{4}S (276.0456): 276.0447.

**Preparation of 2-bromo-4-[hydroxy(phenyl)methyl]phenyl pivalate (24d):**

![Chemical Structure](image)

The magnesium reagent 23d was prepared according to TP1 from 2,4-dibromophenyl pivalate (22d, 672 mg, 2.0 mmol) in 1 h at -20 °C. Benzaldehyde (149 mg, 1.4 mmol) was added at -20 °C and the mixture stirred for 30 min at this temperature. The reaction was quenched with sat. NH4Cl solution (10 mL) and extracted with Et2O (3x 10 mL). The combined organic layers were dried over Na2SO4 and concentrated in vacuo. Flash column chromatography (pentane/CH2Cl2 = 2:1 to CH2Cl2) furnished 24d as a pale yellow oil (435 mg, 86%).

1H-NMR (400 MHz, CDCl3) δ (ppm): 7.66 (d, J = 2.1 Hz, 1H), 7.37-7.30 (m, 6H), 7.06 (d, J = 8.6 Hz, 1H), 5.81 (s, 1H), 2.25 (brs, 1H) 1.40 (s, 9H).

13C-NMR (100 MHz, CDCl3) δ (ppm): 176.0, 147.6, 143.0, 142.9, 131.2, 128.7, 128.0, 126.6, 126.5, 123.5, 116.1, 75.2, 39.3, 27.2.

IR (ATR) ν (cm⁻¹): 3433, 2971, 1755, 1477, 1215, 1099, 1041, 892, 697.

MS (70 eV, EI) m/z (%): 362 (6) [M⁺], 280 (25), 201 (20), 105 (100), 57 (95).

HRMS (EI) for C_{18}H_{19}BrO_{3} (362.0518): 362.0508.

**Preparation of ethyl 3'-chlorobiphenyl-4-carboxylate (24e):**

![Chemical Structure](image)

The magnesium reagent 23e was prepared according to TP1 from 3-chlorobromobenzene (22e, 383 mg, 2.0 mmol) in 10 min at 25 °C. A cross-coupling reaction was performed according to TP2 with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 2 h. Flash column chromatography (pentane/CH2Cl2 = 4:1) furnished 24e as a colorless solid (341 mg, 94%).

M.p.: 67-69 °C.
Experimental Section

\[^1\text{H-NMR (300 MHz, CDCl}_3\text{)}\, \delta (\text{ppm}): 8.11 (d, J = 8.7 \text{ Hz}, 2\text{H}), 7.63-7.59 (m, 3\text{H}), 7.50-7.47 (m, 1\text{H}), 7.41-7.34 (m, 2\text{H}), 4.40 (q, J = 7.1 \text{ Hz}, 2\text{H}), 1.41 (t, J = 7.1 \text{ Hz}, 3\text{H}).\]

\[^{13}\text{C-NMR (75 MHz, CDCl}_3\text{)}\, \delta (\text{ppm}): 166.3, 144.0, 141.9, 134.8, 130.1, 130.1, 129.8, 128.1, 127.4, 127.0, 125.4, 61.0, 14.3.\]

\[\text{IR (ATR)}\, \tilde{\nu} (\text{cm}^{-1}): 3061, 2977, 1703, 1608, 1595, 1559, 1471, 1393, 1364, 1274, 1183, 1099, 1018, 851, 761, 704, 690.\]

\[\text{MS (70 eV, EI)}\, m/z (\%): 260 (49) [M^+], 232 (29), 215 (100), 152 (63), 76 (16).\]

\[\text{HRMS (EI) for C}_{15}\text{H}_{13}\text{ClO}_2 (260.0604): 260.0601.}\]

Preparation of 1-(3-chlorophenyl)-2,2-dimethylpropan-1-one (24f):

\[
\begin{array}{c}
\text{Cl} \\
\text{C} \\
\text{O} \\
\text{Me}
\end{array}
\]

The magnesium reagent 23e was prepared according to TP1 from 3-chlorobromobenzene (23e, 383 mg, 2.0 mmol) in 10 min at 25 °C. An acylation reaction was performed according to TP3 with pivaloyl chloride (169 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH\(_2\)Cl\(_2\) = 4:1) furnished 24f as a colorless oil (190 mg, 69%).

\[^{1}\text{H-NMR (400 MHz, CDCl}_3\text{)}\, \delta (\text{ppm}): 7.62-7.61 (m, 1\text{H}), 7.54-7.52 (m, 1\text{H}), 7.44-7.41 (m, 1\text{H}), 7.35-7.31 (m, 1\text{H}), 1.33 (s, 9\text{H}).\]

\[^{13}\text{C-NMR (100 MHz, CDCl}_3\text{)}\, \delta (\text{ppm}): 207.9, 140.2, 134.3, 130.7, 129.4, 127.9, 125.7, 44.3, 27.8.\]

\[\text{IR (ATR)}\, \tilde{\nu} (\text{cm}^{-1}): 2970, 2872, 1676, 1567, 1476, 1462, 1411, 1395, 1366, 1279, 1265, 1180, 1098, 1081, 984, 970, 884, 826, 798, 765, 739, 680, 663.\]

\[\text{MS (70 eV, EI)}\, m/z (\%): 196 (8) [M^+], 139 (100), 111 (19), 75 (11), 57 (48).\]

\[\text{HRMS (EI) for C}_{11}\text{H}_{13}\text{ClO} (196.0655): 196.0644.}\]

Preparation of 1-(4-chlorophenyl)-1-phenylmethanol (24g):

\[
\begin{array}{c}
\text{Cl} \\
\text{C} \\
\text{O} \\
\text{Ph}
\end{array}
\]

The magnesium reagent 23e was prepared according to TP1 from 3-chlorobromobenzene (23e, 383 mg, 2.0 mmol) in 10 min at 25 °C. An acylation reaction was performed according to TP3 with pivaloyl chloride (169 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH\(_2\)Cl\(_2\) = 4:1) furnished 24f as a colorless oil (190 mg, 69%).

\[^{1}\text{H-NMR (400 MHz, CDCl}_3\text{)}\, \delta (\text{ppm}): 7.62-7.61 (m, 1\text{H}), 7.54-7.52 (m, 1\text{H}), 7.44-7.41 (m, 1\text{H}), 7.35-7.31 (m, 1\text{H}), 1.33 (s, 9\text{H}).\]

\[^{13}\text{C-NMR (100 MHz, CDCl}_3\text{)}\, \delta (\text{ppm}): 207.9, 140.2, 134.3, 130.7, 129.4, 127.9, 125.7, 44.3, 27.8.\]

\[\text{IR (ATR)}\, \tilde{\nu} (\text{cm}^{-1}): 2970, 2872, 1676, 1567, 1476, 1462, 1411, 1395, 1366, 1279, 1265, 1180, 1098, 1081, 984, 970, 884, 826, 798, 765, 739, 680, 663.\]

\[\text{MS (70 eV, EI)}\, m/z (\%): 196 (8) [M^+], 139 (100), 111 (19), 75 (11), 57 (48).\]

\[\text{HRMS (EI) for C}_{11}\text{H}_{13}\text{ClO} (196.0655): 196.0644.}\]
The magnesium reagent 23f was prepared according to TP1 from 1-bromo-4-chlorobenzene (22f, 383 mg, 2.0 mmol) in 10 min at 25 °C. Benzaldehyde (149 mg, 1.4 mmol) was added and the mixture stirred for 15 min at 25 °C. The reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (CH₂Cl₂) furnished 24g as a colorless solid (271 mg, 89 %).

M.p.: 69-71 °C.

¹H-NMR (400 MHz, CDCl₃) δ (ppm): 7.32-7.21 (m, 9H), 5.71 (s, 1H), 2.45 (brs, 1H).

¹³C-NMR (100 MHz, CDCl₃) δ (ppm): 143.4, 142.1, 133.2, 128.6, 128.5, 127.8, 127.7, 126.5, 75.5.

IR (ATR) ν (cm⁻¹): 3351, 1588, 1485, 1453, 1402, 1191, 1086, 1011, 847, 791, 759.

MS (70 eV, EI) m/z (%): 218 (41) [M⁺], 165 (30), 139 (100), 105 (66), 78 (36).

HRMS (EI) for C₁₃H₁₁OCl(218.0498): 218.0491.

Preparation of 2-fluoro-4-(methylthio)biphenyl (24h):

The magnesium reagent 23g was prepared according to TP1 from 4-bromo-2-fluorobiphenyl (22g, 502 mg, 2.0 mmol) in 30 min at 25 °C. MeSO₂SMe (177 mg, 1.4 mmol) was added at 0 °C and the reaction mixture was warmed to 25 °C. The reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane) furnished 24h as a colorless solid (257 mg, 84 %).

M.p.: 70-72 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.55-7.51 (m, 2H), 7.46-7.41 (m, 2H), 7.38-7.33 (m, 2H), 7.10-7.01 (m, 2H), 2.51 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 159.8 (d, J = 249.3 Hz), 140.0 (d, J = 8.3 Hz), 135.4, 130.7 (d, J = 4.4 Hz), 128.8 (d, J = 3.1 Hz), 128.5, 127.5, 125.5 (d, J = 13.7 Hz), 122.2 (d, J = 3.4 Hz), 113.6 (d, J = 25.8 Hz), 15.6.
Experimental Section

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 1610, 1578, 1552, 1542, 1508, 1444, 1418, 1401, 1391, 1338, 1321, 1282, 1260, 1211, 1192, 1186, 1152, 1140, 1113, 1085, 1078, 1034, 1006, 994, 972, 963, 950, 915, 894, 850, 817, 764, 725, 713, 698, 660, 640.

MS (70 eV, EI) m/z (%): 218 (100) [M$^+$], 203 (51), 170 (24), 42 (47).

HRMS (EI) for C$_{13}$H$_{11}$FS (218.0565): 218.0578.

**Preparation of ethyl 2'-((trifluoromethyl)biphenyl-4-carboxylate (24i):**

![Ethyl 2'-((trifluoromethyl)biphenyl-4-carboxylate](image)

The magnesium reagent $23h$ was prepared according to TP1 from 1-bromo-2-(trifluoromethyl)benzene ($22h$, 450 mg, 2.0 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to TP2 with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 2 h at 25 °C. Flash column chromatography (pentane/CH$_2$Cl$_2$ = 4:1) furnished $24i$ as a colorless oil (400 mg, 97 %).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 8.08 (d, $J = 7.9$ Hz, 2H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.59-7.47 (m, 2H), 7.40 (d, $J = 7.9$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 1H), 4.40 (q, $J = 7.0$ Hz, 2H), 1.41 (t, $J = 7.0$ Hz, 3H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 166.4, 144.6, 140.3, 131.6, 131.4, 129.8, 129.0, 128.3 (q, $J = 30.2$ Hz), 127.8, 126.2 (q, $J = 5.3$ Hz), 124.0 (q, $J = 274.0$ Hz), 61.0, 14.3. (1 quarternary carbon not detected)

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2983, 1713, 1611, 1604, 1579, 1486, 1479, 1465, 1448, 1405, 1367, 1312, 1299, 1270, 1168, 1124, 1107, 1099, 1069, 1034, 1026, 1006, 957, 881, 859, 767, 753, 739, 707, 664.

MS (70 eV, EI) m/z (%): 249 (100) [M$^+$], 201 (41), 97 (13), 83 (12), 69 (13).

HRMS (EI) for C$_{16}$H$_{13}$F$_3$O$_2$ (294.0868): 294.0855.

**Preparation of ethyl 3'-((trifluoromethyl)biphenyl-4-carboxylate (24j):**
The magnesium reagent 23i was prepared according to TP1 from 1-bromo-3-(trifluoromethyl)benzene (22i, 450 mg, 2.0 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to TP2 with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 1.5 h at 25 °C. Flash column chromatography (pentane/CH₂Cl₂ = 4:1) furnished 24j as a colorless solid (375 mg, 91 %).

M.p.: 85-87 °C.

¹H-NMR (400 MHz, CDCl₃) δ (ppm): 8.14 (d, J = 8.0 Hz, 2H), 7.85 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.66-7.63 (m, 3H), 7.59-7.56 (m, 1H), 4.41 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃) δ (ppm): 166.3, 143.9, 140.9, 131.4 (q, J = 32.3 Hz), 130.5, 130.2, 130.0, 129.4, 124.7 (q, J = 3.7 Hz), 124.0 (q, J = 272 Hz), 124.0 (q, J = 3.7 Hz), 61.1, 14.3.

IR (ATR) ν (cm⁻¹): 3065, 2982, 2943, 2909, 2873, 1704, 1664, 1609, 1595, 1571, 1491, 1475, 1456, 1440, 1401, 1368, 1332, 1309, 1300, 1274, 1264, 1188, 1178, 1157, 1119, 1105, 1099, 1076, 1034, 1017, 976, 962, 928, 920, 875, 853, 840, 825, 816, 806, 766, 737, 701, 669.

MS (70 eV, EI) m/z (%): 249 (100) [M⁺], 266 (82), 250 (45), 201 (81), 152 (52).

HRMS (EI) for C₁₆H₁₃F₃O₂ (294.0868): 294.0877.

Preparation of ethyl 4'- (trifluoromethyl)biphenyl-4-carboxylate (24k):

The magnesium reagent 23j was prepared according to TP1 from 4-bromo benzotrifluoride (22j, 450 mg, 2.0 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to TP2 with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH₂Cl₂ = 4:1) furnished 24k as a colorless solid (398 mg, 97 %).
M.p.: 91-93 °C.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.14 (d, \(J = 8.8\) Hz, 2H), 7.71 (s, 4H), 7.65 (d, \(J = 8.8\) Hz, 2H), 4.41 (q, \(J = 7.0\) Hz, 2H), 1.41 (t, \(J = 7.0\) Hz, 3H).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\): 166.2, 143.9, 143.6, 130.2, 130.2, 130.1 (q, \(J = 33\) Hz), 127.6, 127.2, 125.8 (q, \(J = 4\) Hz), 124.1 (q, \(J = 272\) Hz), 61.1, 14.3.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2984, 1708, 1608, 1481, 1395, 1280, 1110, 838.

MS (70 eV, EI) \(m/z\) (%): 294 (38) [M\(^+\)], 249 (100), 201 (29), 152 (27), 71 (33), 57 (54).

HRMS (EI) for C\(_{16}\)H\(_{13}\)F\(_3\)O\(_2\) (294.0868): 294.0864.

Preparation of ethyl 3',5'-bis(trifluoromethyl)biphenyl-4-carboxylate (24l):

The magnesium reagent 23k was prepared according to TP1 from 1-bromo-3,5-bis(trifluoromethyl)benzene (22k, 586 mg, 2.0 mmol) in 30 min at 0 °C at 25 °C. A cross-coupling reaction was performed according to TP2 with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH\(_2\)Cl\(_2\) = 4:1) furnished 24l as a colorless solid (420 mg, 83%).

M.p.: 98-100 °C.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm): 8.17 (d, \(J = 8.2\) Hz, 2H), 8.03 (s, 2H), 7.90 (s, 1H), 7.67 (d, \(J = 8.2\) Hz, H), 4.42 (q, \(J = 7.2\) Hz, 2H), 1.42 (t, \(J = 7.2\) Hz, 3H).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm): 166.0, 142.3, 142.2, 132.3 (q, \(J = 33.3\) Hz), 130.9, 130.5, 127.4, 127.2, 123.2 (q, \(J = 273\) Hz), 121.7 (sept., \(J = 3.7\) Hz), 61.3, 14.3.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 1714, 1670, 1610, 1572, 1515, 1478, 1465, 1453, 1402, 1382, 1370, 1327, 1309, 1286, 1278, 1258, 1180, 1169, 1123, 1114, 1104, 1053, 1026, 1016, 964, 941, 919, 895, 874, 859, 845, 837, 828, 792, 780, 772, 727, 703, 682, 667.

MS (70 eV, EI) \(m/z\) (%): 362 (25) [M\(^+\)], 334 (44), 317 (100), 269 (29), 220 (11).

HRMS (EI) for C\(_{18}\)H\(_{19}\)BrO\(_3\) (362.0741): 362.0740

Preparation of (4-chlorophenyl)[2-chloro-5-(trifluoromethyl) phenyl]methanol (24m):
The magnesium reagent 23i was prepared according to TP1 from 2-bromo-1-chloro-4-(trifluoromethyl)benzene (22i, 519 mg, 2.0 mmol) in 30 min at 25 °C. 4-Chlorobenzaldehyde (197 mg, 1.4 mmol) was added at 0 °C and the mixture warmed to 25 °C. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (CH₂Cl₂) furnished 24m as a colorless solid (395 mg, 88%).

**M.p.:** 121-122 °C.

**1H-NMR (300 MHz, CDCl₃) δ (ppm):** 7.98-7.97 (m, 1H), 7.51-7.43 (m, 2H), 7.33-7.27 (m, 4H), 6.16 (s, 1H), 2.43 (brs, 1H).

**13C-NMR (75 MHz, CDCl₃) δ (ppm):** 141.6, 139.8, 135.9, 134.1, 130.2, 129.7 (q, \(J = 33\) Hz), 128.9, 128.4, 125.7 (q, \(J = 4\) Hz), 124.7 (q, \(J = 4\) Hz), 123.7 (q, \(J = 272\) Hz), 71.9.

**IR (ATR) \(\tilde{\nu}\) (cm⁻¹):** 3256, 1608, 1596, 1582, 1490, 1475, 1412, 1324, 1286, 1254, 1231, 1181, 1163, 1122, 1104, 1079, 1060, 1032, 1016, 966, 953, 946, 920, 908, 831, 825, 768, 731, 713, 699, 660, 636, 621, 606.

**MS (70 eV, EI) m/z (%):** 319 (23) [M⁺], 207 (100), 179 (31), 141 (23), 111 (33).

**HRMS (EI) for C₁₄H₉Cl₂F₃O (319.9983):** 319.9958.

**Preparation of 1-[2-(dimethylamino)phenyl]-2,2-dimethylpropan-1-ol (24n):**

The magnesium reagent 23m was prepared according to TP1 from 2-bromo-\(N,N\)-dimethylaniline (22m, 400 mg, 2.0 mmol) in 30 min at 25 °C. Pivaldehyde (121 mg, 1.4 mmol) was added at 0 °C and the mixture warmed to 25 °C. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic
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layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 9:1) furnished 24n as a colorless oil (263 mg, 91 %).

$^1$H-NMR (300 MHz, CDCl₃) δ (ppm): 7.34-7.22 (m, 2H), 7.14-7.07 (m, 2H), 4.56 (s, 1H), 2.68 (s, 6H), 0.93 (s, 9H).

$^{13}$C-NMR (75 MHz, CDCl₃) δ (ppm): 152.6, 136.2, 130.3, 127.7, 124.9, 122.7, 83.2, 46.8, 37.4, 26.5.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3408, 3156, 3062, 3024, 2950, 2905, 2866, 2826, 2786, 1597, 1578, 1481, 1459, 1450, 1406, 1391, 1361, 1301, 1276, 1237, 1214, 1178, 1162, 1154, 1146, 1098, 1066, 1040, 1009, 945, 935, 903, 870, 827, 769, 750, 734, 714, 648, 636.

MS (70 eV, EI) m/z (%): 207 (9) [M$^+$], 150 (100), 120 (20).

HRMS (EI) for C$_{13}$H$_{21}$NO (207.1623): 207.1618.

Preparation of 4-(benzylthio)-N,N-dimethylaniline (24o):

The magnesium reagent 23n was prepared according to TP1 from 4-bromo-N,N-dimethylaniline (22n, 400 mg, 2.0 mmol) in 30 min at 25 °C. S-benzyl benzenesulfonothioate (370 mg, 1.4 mmol) was added at 0 °C and the mixture warmed to 25 °C. The reaction was quenched with sat. NH$_4$Cl solution (10 mL) and extracted with Et$_2$O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/Et$_2$O = 9:1) furnished 24o as a pale orange solid (221 mg, 65 %).

M.p.: 93-94 °C.

$^1$H-NMR (300 MHz, CDCl₃) δ (ppm): 7.30-7.18 (m, 7H), 6.63 (d, J = 8.6 Hz, 2H), 3.96 (s, 2H), 2.95 (s, 6H).

$^{13}$C-NMR (75 MHz, CDCl₃) δ (ppm): 149.8, 138.5, 134.5, 128.9, 128.2, 126.8, 120.6, 112.7, 41.9, 40.5.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3060, 3029, 2923, 2852, 2799, 1860, 1595, 1501, 1446, 1353, 1227, 1204, 1167, 1068, 1025, 947, 806, 715, 695, 611.

MS (70 eV, EI) m/z (%): 243 (41) [M$^+$], 152 (100), 136 (7), 108 (3).

HRMS (EI) for C$_{15}$H$_{17}$NS (243.1082s): 243.1080.
Preparation of 2-(1,3-benzodioxol-5-yl)-1-phenylpropan-2-ol (24p):

The magnesium reagent 23o was prepared according to TP1 from 5-bromo-1,3-benzodioxole (22o, 402 mg, 2.0 mmol) in 30 min at 25 °C. In a second flask, 1-phenylacetone (188 mg, 1.4 mmol) and LaCl3·2 LiCl (2.7 mL, 1.4 mmol, 0.52 M in THF) were stirred at 25 °C for 30 min. 2m was then slowly added at 0 °C, the reaction mixture warmed to 25 °C and stirred for 2h. The reaction was quenched with sat. NH4Cl solution (10 mL) and extracted with Et2O (3x 10 mL). The combined organic layers were dried over Na2SO4 and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 9:1 → 4:1) furnished 24p as a colorless solid (326 mg, 91 %).

M.p.: 45-48 °C.

1H-NMR (300 MHz, C6D6) δ (ppm): 7.10-6.94 (m, 6H), 6.69-6.62 (m, 2H), 5.35-5.33 (m, 2H), 2.93-2.78 (m, 2H), 1.60 (s, H), 1.29 (s, 3H).

13C-NMR (75 MHz, C6D6) δ (ppm): 147.6, 146.2, 142.2, 137.2, 130.6, 127.8, 127.7, 127.4, 126.4, 118.3, 107.4, 106.3, 100.5, 74.0, 50.5, 29.2.

IR (ATR) ʋ (cm⁻¹): 3550, 3318, 3027, 2980, 2891, 2773, 1603, 1582, 1502, 1487, 1453, 1435, 1394, 1374, 1351, 1273, 1239, 1228, 1183, 1155, 1135, 1122, 1103, 1091, 1072, 1035, 971, 931, 910, 897, 878, 848, 833, 809, 801, 753, 728, 698, 650, 622, 609.

MS (70 eV, EI) m/z (%): 256 (1) [M⁺], 238 (8), 165 (100).

HRMS (EI) for C16H16O3 (256.1099): 256.1093.

Preparation of 2-chloro-5-(4-methoxyphenyl)pyridine (24q):
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The magnesium reagent 23p was prepared according to TP1 from 5-bromo-2-chloropyridine (22p, 385 mg, 2.0 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to TP2 with 4-iodoanisole (328 mg, 1.4 mmol) in 6 h at 25 °C. Flash column chromatography (CH₂Cl₂) furnished 24q as a colorless solid (258 mg, 84 %).

M.p.: 127-128 °C

\[ ^1H-NMR \ (300 \ MHz, \ CDCl_3) \ \delta (ppm): 8.55 (d, J = 2.2 Hz, 1H), 7.78 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H), 7.49-7.46 (m, 2H), 7.35 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H). \]

\[ ^13C-NMR \ (75 \ MHz, \ CDCl_3) \ \delta (ppm): 160.0, 149.6, 147.5, 136.7, 135.3, 128.8, 128.1, 124.1, 114.7, 55.4. \]

IR (ATR) $\nu$ (cm⁻¹): 3015, 2963, 2935, 2838, 1607, 1584, 1516, 1451, 1366, 1288, 1253, 1186, 1039, 814.

MS (70 eV, EI) m/z (%): 219 (100) [M⁺], 204 (50), 176 (39), 140 (21).

HRMS (EI) for C₁₂H₁₀ONCl (219.0451): 219.0428.

Preparation of 5-allyl-2-chloropyridine (24r):

The magnesium reagent 23p was prepared according to TP1 from 5-bromo-2-chloropyridine (22p, 385 mg, 2.0 mmol) in 30 min at 0 °C. An allylation reaction was performed according to TP3 with allyl bromide (169 mg, 1.4 mmol) in 15 min. Flash column chromatography (CH₂Cl₂) furnished 24r as a colorless oil (134 mg, 62 %).

\[ ^1H-NMR \ (300 \ MHz, \ CDCl_3) \ \delta (ppm): 8.20 (d, J = 2.4 Hz, 1H), 7.48-7.44 (m, 1H), 7.26-7.23 (m, 1H), 5.97-5.83 (m, 1H), 5.15-5.04 (m, 2H), 3.35 (d, J = 6.6 Hz, 2H). \]

\[ ^13C-NMR \ (75 \ MHz, \ CDCl_3) \ \delta (ppm): 149.7, 149.3, 139.0, 135.5, 134.2, 123.9, 117. 3, 36.3. \]

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3082, 3045, 2980, 2908, 1640, 1584, 1564, 1457, 1433, 1414, 1380, 1289, 1210, 1136, 1100, 1023, 992, 917, 841, 813, 742, 700, 684, 654.

MS (70 eV, EI) m/z (%): 153 (100) [M⁺], 118 (63), 91 (35).

HRMS (EI) for C₈H₆ClN (153.0345): 153.0339.

Preparation of 4′-(trifluoromethyl)biphenyl-2-carbonitrile (24s):
The magnesium reagent 23q was prepared according to TP1 from 2-bromobenzonitrile (22q, 364 mg, 2.0 mmol) in 35 min at 25 °C. A cross-coupling reaction was performed according to TP2 with 1-bromo-4-(trifluoromethyl)benzene (315 mg, 1.4 mmol) using Pd(OAc)$_2$ (5 mg, 1 mol%) and S-Phos (16 mg, 2 mol%) in 16 h. Flash column chromatography (pentane/CH$_2$Cl$_2$ = 2:1) furnished 24s as a colorless solid (235 mg, 68%).

M.p.: 103-104 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.82-7.65 (m, 6H), 7.53-7.48 (m, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 143.9, 141.5, 133.9, 133.0, 131.3 (q, $J$ = 33 Hz), 130.0, 129.2, 128.4, 125.7 (q, $J$ = 3 Hz), 124.0 (q, $J$ = 272 Hz), 118.2, 111.3.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2226, 1619, 1596, 1566, 1481, 1408, 1328, 1270, 1260, 1245, 1198, 1182, 1165, 1116, 1104, 1070, 1048, 1020, 1007, 974, 964, 958, 886, 844, 799, 766, 733, 708, 668, 660, 641, 636, 626, 611.

MS (70 eV, EI) $m/z$ (%): 247 (100) [M$^+$], 218 (34), 203 (19), 177 (11).

HRMS (EI) for C$_{14}$H$_8$F$_3$N (247.0609): 247.0620.

Preparation of 4-(3,3-dimethylbutanoyl)benzonitrile (24t):

The magnesium reagent 23r was prepared according to TP1 from 4-bromobenzonitrile (22r, 362 mg, 2.0 mmol) in 45 min at 25 °C. The freshly prepared magnesium reagent was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 m in THF, 2.0 mmol) was added. After stirring for 30 min, 3,3-dimethylbutanoyl chloride (188 mg, 1.4 mmol) was added and the reaction mixture was warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution (20 mL) followed by 25% aq. NH$_3$ solution (5 mL) and extracted with Et$_2$O (3x 30 mL). The
combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatography (pentane/CH$_2$Cl$_2$ = 2:1) furnished 24t as a colorless oil (161 mg, 57%).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 8.01 (d, $J$ = 8.3 Hz, 2H), 7.75 (d, $J$ = 8.3 Hz, 2H), 2.86 (s, 2H), 1.05 (s, 9H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 198.9, 141.1, 132.4, 128.5, 118.0, 116.0, 50.3, 31.5, 29.9.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3067, 2956, 2906, 2869, 2232, 1759, 1695, 1679, 1606, 1566, 1500, 1466, 1446, 1404, 1390, 1364, 1318, 1290, 1248, 1229, 1198, 1186, 1172, 1146, 1109, 1074, 1055, 1036, 1009, 931, 909, 855, 826, 794, 778, 736, 718, 698, 644, 618.

MS (70 eV, EI) $m/z$ (%): 201 (9) [M$^+$], 145 (98), 130 (100), 102 (31), 99 (19).

HRMS (EI) for C$_{13}$H$_{15}$NO (201.1154): 201.1154.

Preparation of 4-(3-bromobenzoyl)-2-fluorobenzonitrile (24u):

The magnesium reagent 23s was prepared according to TP1 from 4-bromo-2-fluorobenzonitrile (22s, 400 mg, 2.0 mmol) in 45 min at 25 °C. An acylation reaction was performed according to TP3 with 3-bromobenzoyl chloride (307 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH$_2$Cl$_2$ = 1:1) furnished 24u as a colorless solid (254 mg, 60%).

M.p.: 89-91 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.91-7.90 (m, 1H), 7.81-7.76 (m, 2H), 7.69-7.59 (m, 3H), 7.43-7.38 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 192.1, 162.4 (d, $J$ = 261 Hz), 142.9 (d, $J$ = 6.2 Hz), 137.6, 136.5, 133.8, 132.7, 130.3, 128.7, 125.7 (d, $J$ = 4 Hz), 123.1, 117.4 (d, $J$ = 21 Hz), 113.0, 105.3 (d, $J$ = 16 Hz).
2.2. Preparation of Aryl- and Heteroarylzinc Reagents by Magnesium Insertion in the Presence of LiCl and ZnCl₂

2.2.1. Typical Procedure for the Magnesium Insertion in the Presence of ZnCl₂ (TP4)

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (212 mg, 5.0 mmol) and was heated under high vacuum for 5 min. ZnCl₂ (300 mg, 2.2 mmol) was added and was similarly heated under high vacuum. Magnesium powder (122 mg, 5.0 mmol) and 5 mL THF were added and the magnesium powder was activated with iBu₂AlH (0.2 mL, 0.1 m in THF, 0.02 mmol). After 5 min of stirring the aryl or alkyl bromide (2.0 mmol) was added in one portion at the given temperature. The reaction mixture was stirred for the given time and then cannulated to a new Schlenk-flask for the reaction with an electrophile.

2.2.2. Typical Procedure for Cross-Coupling Reactions of Arylzinc Reagents (TP5)

Pd(dba)₂ (32 mg, 2 mol%), P(2-furyl)₃ (26 mg, 4 mol%) were added to the freshly prepared zinc reagent followed by the aryliodide (1.4 mmol) and the mixture was stirred for the given time at 25 °C. The reaction mixture was quenched with sat. NH₄Cl solution (10 mL) extracted with EtOAc (3x 10 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.
2.2.3. Typical Procedure for Acylation Reactions of Arylzinc Reagents (TP6)

The freshly prepared zinc reagent was cooled to -20 °C, CuCN·2 LiCl (2 mL, 2.0 mmol, 1 M in THF) was added and the reaction mixture was stirred for 15 min. After the addition of the acid chloride, the reaction mixture was allowed to warm to 25 °C and stirred for the given time. The reaction mixture was quenched with sat. NH₄Cl/NH₃ (9:1) solution (10 mL), washed with sat. NH₄Cl/NH₃ solution (9:1, 2x 10 mL) extracted with EtOAc (3x 10 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.

2.2.4. Preparation of Title Compounds

Preparation of ethyl 2-allylbenzoate (27):

[Chemical structure image]

The zinc reagent 26 was prepared according to TP4 from ethyl 2-bromobenzoate (25, 458 mg, 2.0 mmol) in 3 h at 25 °C. An allylation reaction was performed according to TP3 with allyl bromide (169 mg, 1.4 mmol) in 30 min. Flash column chromatography (pentane/Et₂O = 3:1) furnished 27 as a colorless oil (232 mg, 88 %).

^1^H-NMR (300 MHz, CDCl₃) δ: 7.90 (dd, J = 1.3 Hz, J = 8.2 Hz, 1H), 7.47-7.25 (m, 1H), 7.23 (t, J = 8.2 Hz, 2H), 6.11-5.98 (m, 1H), 5.07-5.01 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.79 (d, J = 5.4 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

^1^C-NMR (75 MHz, CDCl₃) δ: 167.6, 141.3, 137.4, 131.8, 130.8, 130.4, 130.1, 126.1, 115.4, 60.7, 38.3, 14.2.

IR (ATR) ν (cm⁻¹): 3056, 2982, 1423, 1266.

MS (70 eV, EI) m/z (%): 190 (53) [M⁺], 175 (63), 147 (74), 145 (73), 144 (37), 117 (81), 116 (45), 115 (100).

HRMS (EI) for C₁₂H₁₄O₂ (190.0994): 190.0996.
Preparation of 2-(1-benzofuran-3-yl)cyclohex-2-en-1-one (30):

\[
\text{Cyclohex-2-en-1-one (30)}
\]

According to TP4, the zinc reagent 29 was prepared from 3-bromo-1-benzofuran (28, 394 mg, 2.0 mmol) in 2 h at 25 °C. The Palladium-catalyzed cross-coupling reaction with 2-iodocyclohex-2-en-1-one (31, 1.4 mmol) using Pd(OAc)\(_2\) (5 mg, 1 mol%) and S-Phos (16 mg, 2 mol%) was performed according to TP5 in 30 min at 25 °C. Flash column chromatography (pentane/CH\(_2\)Cl\(_2\) = 1:1) furnished 30 as a pale yellow oil (271 mg, 91%).

**\(^1\)H-NMR (300 MHz, CDCl\(_3\))** \(\delta\) (ppm): 8.09 (s, 1H), 7.66-7.63 (m, 1H), 7.52-7.49 (m, 1H), 7.44-7.41 (m, 1H), 7.33-7.23 (m, 2H), 2.65-2.57 (m, 4H), 2.17-2.08 (m, 2H).

**\(^{13}\)C-NMR (75 MHz, CDCl\(_3\))** \(\delta\) (ppm): 197.4, 154.8, 146.5, 144.5, 131.5, 126.2, 124.1, 122.6, 120.3, 114.8, 111.6, 39.0, 26.4, 22.6.

**IR (ATR)** \(\tilde{\nu}\) (cm\(^{-1}\)): 3344, 3150, 2942, 2865, 1674, 1544, 1451, 1377, 1306, 1240, 1193, 1156, 1106, 1086, 1070, 958, 905, 856, 801, 714.

**MS (70 eV, EI)** \(m/z\) (%): 212 (100) [M\(^+\)], 184 (49), 167 (23), 156 (28), 149 (69), 128 (21).

**HRMS (EI)** for C\(_{16}\)H\(_{15}\)ClO\(_2\)S (212.0837): 212.0828.

Preparation of 4-(3-methoxyphenyl)-3,5-dimethylisoxazole (33):

\[
\text{4-(3-methoxyphenyl)-3,5-dimethylisoxazole (33)}
\]

According to TP4, the zinc reagent 32 was prepared from 4-bromo-3,5-dimethylisoxazole (31, 352 mg, 2.00 mmol) in 15 min at 25 °C. The Pd-catalyzed cross-coupling reaction with 1-bromo-3-methoxybenzene (212 mg, 1.4 mmol) using Pd(OAc)\(_2\) (5 mg, 1 mol%) and S-Phos (16 mg, 2 mol%) was performed according to TP5 in 1 h at 25 °C. Flash column chromatography (pentane/EtOAc = 9:1) furnished 33 as colorless oil (257 mg, 90%).
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$^{1}$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.37-7.32 (m, 1H), 6.91-6.87 (m, 1H), 6.85-6.81 (m, 1H), 6.78-6.77 (m, 1H), 3.83 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 165.2, 159.7, 158.7, 131.8, 19.8, 121.5, 116.5, 115.1, 112.6, 55.3, 11.6, 10.8.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2998, 2934, 2836, 1630, 1600, 1577, 1502, 1483, 1464, 1420, 1408, 1382, 1369, 1317, 1296, 1283, 1247, 1210, 1180, 1170, 1095, 1055, 1025, 1009, 995, 982, 875, 859, 844, 834, 784, 761, 705, 694, 677, 616.

MS (70 eV, EI) $m/z$ (%): 203 (100) [M$^+$.], 188 (50), 160 (37), 146 (16), 134 (22), 119 (30), 91 (20).

HRMS (EI) for C$_{12}$H$_{13}$NO$_2$ (203.0946): 203.0935.

Preparation of (4-toluoyl)(3-methyl-1-phenyl-1H-pyrazol-5-yl)methanone (36):

According to TP4, the zinc reagent 35 was prepared from 5-chloro-3-methyl-1-phenyl-1H-pyrazole (34, 385 mg, 2.0 mmol) in 3.5 h at 25 °C. The acylation reaction with 4-toluoyl chloride (216 mg, 1.4 mmol) was performed according to TP6 in 1 h at 25 °C. Flash column chromatography (pentane/EtOAc = 9:1) furnished 36 as colorless solid (352 mg, 91%).

M.p.: 131-132 °C.

$^{1}$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.83 (d, $J = 8.3$ Hz, 2H), 7.38-7.25 (m, 7H), 6.55 (s, 1H), 2.42 (s, 3H), 2.39 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 185.4, 148.7, 144.5, 140.1, 139.9, 134.7, 129.9, 129.2, 128.8, 127.7, 124.6, 113.1, 21.7, 13.4.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3056, 3034, 2928, 2854, 2360, 2342, 1738, 1650, 1598, 1502, 1462, 1434, 1360, 1288, 1240, 1148, 1134, 902, 832, 810, 794, 768, 752, 694, 668, 656, 638, 612.

MS (70 eV, EI) $m/z$ (%): 276 (100) [M$^+$.], 247 (30), 185 (13), 119 (26), 91 (20).

HRMS (EI) for C$_{18}$H$_{16}$N$_2$O (276.1263): 276.1256.
Preparation of ethyl 4-allyl-2,6-dimethylpyrimidine-5-carboxylate (39):

According to TP4, the zinc reagent 38 was prepared from ethyl 4-chloro-2,6-dimethylpyrimidine-5-carboxylate (37, 437 mg, 2.0 mmol) in 9 h at 25 °C. The allylic substitution reaction with allyl bromide (170 mg, 1.4 mmol) was performed according to TP3 in 1 h at 25 °C. Flash column chromatography (pentane/Et₂O = 6:1) furnished 39 as colorless oil (240 mg, 68 %).

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{) } \delta (ppm): 6.05-5.91 \text{ (m, 1H), 5.16-5.06 \text{ (m, 2H), 4.34 \text{ (q, } J = 7.1 Hz, \text{ 2H), 3.99 \text{ (s, 6H), 3.50 \text{ (td, } J = 1.5, J = 6.6 Hz, \text{ 2H), 1.35 \text{ (t, } J = 7.1 Hz, \text{ 3H).}}) \]

\[ \text{13C-NMR (75 MHz, CDCl}_3\text{) } \delta (ppm): 169.4, 169.2, 165.7, 164.6, 133.7, 117.4, 107.9, 61.5, 54.9, 54.5, 40.1, 14.1. \]

\[ \text{IR (ATR) } \tilde{\nu} \text{ (cm}^{-1}\text{): 2984, 2958, 2904, 2876, 2362, 2342, 1726, 1638, 1558, 1482, 1458, 1374, 1360, 1298, 1256, 1244, 1206, 1196, 1120, 1106, 1078, 1058, 996, 974, 944, 916, 868, 848, 814, 780, 746, 728, 684, 668, 652, 616.} \]

\[ \text{MS (70 eV, EI) } m/z \text{ (%): 252 (47) [M⁺], 223 (100), 205 (28), 179 (9).} \]

\[ \text{HRMS (EI) for } C_{12}H_{16}N_2O_4 \text{ (252.1110): 252.1104} \]

2.3. Regioselectivity of Zinc and Magnesium Insertions into Polybrominated Arenes

2.3.1. Preparation of Title Compounds

Preparation of ethyl 3'-bromo-4'-[(tert-butoxycarbonyl)oxy]biphenyl-4-carboxylate (44a):
The magnesium reagent 42a was prepared according to TP1 from tert-butyl 2,4-dibromophenyl carbonate (40a, 704 mg, 2.0 mmol) in 30 min at -10 °C. A cross-coupling reaction was performed according to TP2 with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 3 h. Flash column chromatography (pentane/CH₂Cl₂ = 2:1) furnished 44a as a pale brown solid (572 mg, 97 %).

**M.p.:** 59-61 °C.

**¹H-NMR (300 MHz, CDCl₃)** δ (ppm): 8.10 (d, J = 8.6 Hz 2H), 7.83 (d, J = 2.1 Hz, 1H), 7.60-7.53 (m, 3H), 7.29 (d, J = 8.3 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.58 (s, 9H), 1.41 (t, J = 7.2 Hz, 3H).

**¹³C-NMR (75 MHz, CDCl₃)** δ (ppm): 166.3, 150.8, 148.3, 143.2, 139.6, 132.1, 130.2, 129.9, 127.4, 127.0, 123.8, 116.9, 84.5, 61.1, 27.7, 14.3.

**IR (ATR)** \(~\nu\) (cm⁻¹): 2982, 2938, 2906, 1756, 1704, 1656, 1610, 1580, 1564, 1478, 1458, 1418, 1394, 1370, 1340, 1276, 1252, 1230, 1144, 1126, 1108, 1052, 1042, 1034, 1016, 956, 896, 854, 832, 770, 752, 726, 696, 678.

**MS (70 eV, EI)** m/z (%): 420 (<1) [M⁺], 320 (100), 294 (20), 277 (71), 168 (47), 139 (33).

**HRMS (EI)** for C₂₀H₂₁BrO₅ (420.0572): 420.0573.

**Preparation of 2,6-dibromo-4-(2,2-dimethylpropanoyl)phenyl pivalate (44b):**

The zinc reagent 42b was prepared according to TP4 from 2,4,6-dibromophenyl pivalate (40b, 4.15 g, 10.0 mmol) in 45 min at 25 °C. An acylation reaction was performed according...
Experimental Section

to TP6 with pivaloyl chloride (844 mg, 7.0 mmol) in 6 h. Flash column chromatography (pentane/CH₂Cl₂ = 4:1 → 1:1) furnished 44b as a colorless solid (2.50 g, 85%).

M.p.: 84-86 °C.

\(^1\)H-NMR (600 MHz, CDCl₃) \(\delta\) (ppm): 7.88 (s, 2H), 1.43 (s, 9H), 1.33 (s, 9H).

\(^1\)C-NMR (150 MHz, CDCl₃) \(\delta\) (ppm): 205.0, 174.2, 148.4, 137.6, 132.1, 117.1, 44.4, 39.5, 27.9, 27.2.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2968, 2934, 2910, 2872, 1764, 1684, 1550, 1478, 1456, 1396, 1380, 1366, 1286, 1270, 1236, 1226, 1194, 1158, 1078, 1046, 1026, 990, 946, 886, 852, 784, 750, 732, 714, 702, 680, 602, 584.

MS (70 eV, EI) \(m/z\) (%): 418 (<1) [M⁺], 336 (9), 279 (65), 192 (17), 165 (9), 84 (58), 57 (100).

HRMS (EI) for C\(_{16}\)H\(_{20}\)Br\(_2\)O\(_3\) (417.9779): 417.9768.

Preparation of 1-{3-bromo-4-[pyrrolidin-1-yldiazenyl]phenyl}-2,2-dimethylpropan-1-ol (44c):

\[\text{The magnesium reagent 42c was prepared according to TP1 from 1-[(2,4-dibromophenyl)diazenyl]pyrrolidine (40c, 666 mg, 2.0 mmol) in 30 min at 0 °C. Pivaldehyde (121 mg, 1.4 mmol) was added at 0 °C and the mixture was warmed to 25 °C. The reaction was quenched with sat. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (CH₂Cl₂) furnished 44c as a light brown solid (364 mg, 76%).}

M.p.: 164-166 °C.

\(^1\)H-NMR (600 MHz, CDCl₃) \(\delta\) (ppm): 7.51 (d, \(J = 1.8\) Hz, 1H), 7.31 (d, \(J = 8.3\) Hz, 1H), 7.15 (dd, \(J = 1.8\) Hz, \(J = 8.3\) Hz, 1H), 4.32 (s, 1H), 3.93-3.73 (brm, 4H), 2.03 (brs, 4H), 1.89 (s, 1H), 0.9 (s, 9H).
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\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\) (ppm): 147.8, 140.3, 131.9, 127.1, 118.6, 117.5, 81.5, 51.1, 46.8, 35.7, 25.9, 23.9, 23.6.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 3352, 2978, 2964, 2952, 2930, 2868, 2830, 2360, 1908, 1748, 1728, 1682, 1598, 1554, 1476, 1464, 1452, 1446, 1410, 1394, 1360, 1342, 1310, 1290, 1268, 1236, 1224, 1210, 1188, 1176, 1160, 1134, 1102, 1066, 1040, 1010, 972, 934, 908, 894, 876, 856, 830, 792, 766, 726, 710, 664, 638, 606, 580, 570, 556.

MS (70 eV, EI) \(m/z\) (%): 339 (7) [M\(^+\)], 282 (100), 185 (18), 77 (25).

HRMS (EI) for C\(_{15}\)H\(_{22}\)BrN\(_3\)O (339.0946): 339.0940.

Preparation of 2-bromo-4-(4-chlorobenzoyl)phenyl pivalate (44f):

The magnesium reagent 42f was prepared according to TP1 from 2,4-dibromophenyl pivalate (40f, 672 mg, 2.0 mmol) in 1 h at -20 °C. An acylation reaction was performed according to TP3 with 4-chlorobenzoyl chloride (245 mg, 1.4 mmol) in 1 h at 25 °C. Flash column chromatography (pentane/CH\(_2\)Cl\(_2\) = 3:1) furnished 44f as a colorless solid (430 mg, 78%).

M.p.: 54-56 °C.

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) (ppm): 8.02 (d, \(J = 2.0\) Hz, 1H), 7.74-7.71 (m, 3H), 7.47 (d, \(J = 8.3\) Hz, 2H), 7.22 (d, \(J = 8.3\) Hz, 1H), 1.41 (s, 9H).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\) (ppm): 193.0, 175.6, 151.9, 139.3, 136.0, 135.2, 135.0, 131.3, 130.1, 128.8, 123.7, 116.6, 39.4, 27.2.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2972, 2934, 2908, 2874, 1760, 1652, 1586, 1566, 1476, 1460, 1396, 1382, 1366, 1300, 1276, 1254, 1234, 1216, 1174, 1152, 1088, 1044, 1028, 1012, 958, 942, 898, 888, 852, 840, 800, 754, 704, 678, 658, 648, 628, 604, 590, 582.

MS (70 eV, EI) \(m/z\) (%): 394 (2) [M\(^+\)], 312 (100), 199 (58), 139 (88), 85 (62).

HRMS (EI) for C\(_{18}\)H\(_{16}\)BrClO\(_3\) (393.9971): 393.9980.

3,5-dibromo-4'-methylbiphenyl-4-yl pivalate (44g):
Experimental Section

The zinc reagent 42g was prepared according to TP4 from 2,4,6-tribromophenyl pivalate (40g, 830 mg, 2.0 mmol) in 45 min at 25 °C. A cross-coupling reaction was performed according to TP5 with 4-iodotoluene (305 mg, 1.4 mmol) in 3 h at 25 °C. Flash column chromatography (pentane/CH₂Cl₂ = 7:1) furnished 44g as a colorless solid (535 mg, 90 %).

M.p.: 84-86 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.72 (s, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 2.39 (s, 3H), 1.46 (s, 9H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 174.7, 145.1, 141.5, 138.3, 135.0, 130.7, 129.7, 126.9, 117.8, 39.5, 27.2, 21.1.

IR (ATR) ν (cm⁻¹): 2978, 2934, 2908, 2872, 1758, 1700, 1588, 1574, 1542, 1520, 1476, 1452, 1414, 1396, 1380, 1368, 1310, 1286, 1272, 1256, 1234, 1222, 1212, 1188, 1078, 1026, 962, 944, 884, 874, 860, 836, 814, 772, 750, 726, 692, 660, 644, 628, 614, 586, 572, 554.

MS (70 eV, EI) m/z (%): 423 (5) [M⁺], 340 (100), 153 (25).

HRMS (EI) for C₁₈H₁₈Br₂O₂ (423.9674): 423.9678.

2.4. Preparation of Benzylic Zinc Reagents by the Insertion of Magnesium in the Presence of LiCl and ZnCl₂

2.4.1. Typical Procedure for the Magnesium Insertion in the Presence of ZnCl₂ into Benzylic Chlorides (TP7)

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (122 mg, 5.0 mmol). LiCl (5.0 mL, 0.5 M in THF, 2.5 mmol) and ZnCl₂ (2.2 mL, 1.0 M in THF, 2.2 mmol) were added. The benzylic chloride (2.0 mmol) was added in one portion at the given temperature. The reaction mixture was
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stirred for the given time and then cannulated to a new Schlenk-flask for the reaction with an electrophile.

2.4.2. Preparation of Title Compounds

Preparation of 4-(4-fluorobenzyl)benzonitrile (47b):

![Chemical structure of 4-(4-fluorobenzyl)benzonitrile (47b)](image)

The zinc reagent 46b was prepared according to TP7 from 4-fluorobenzyl chloride (45b, 289 mg, 2.0 mmol) in 45 min at 25 °C. A dry and argon-fushed Schlenk-flask was charged with 4-bromobenzonitrile (255 mg, 1.4 mmol), Pd(OAc)₂ (5 mg, 1 mol%) and S-Phos (16 mg, 2 mol%). THF (2.0 mL) was added. The mixture was stirred for 15 min and cooled to 0 °C. The freshly prepared zinc reagent 46b was added, the reaction mixture warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/CH₂Cl₂ = 4:1) furnished 47b as a colorless solid (222 mg, 75%).

M.p.: 67-69 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.57 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.13-7.08 (m, 2H), 7.02-6.96 (m, 2H), 4.00 (s, 2H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 163.3, 160.1, 146.5, 135.0 (d, J = 3 Hz), 132.3, 130.3 (d, J = 8 Hz), 118.9, 115.5 (d, J = 21 Hz), 110.2, 41.1.

IR (ATR) ν (cm⁻¹): 3040, 2934, 2222, 1920, 1884, 1606, 1500, 1470, 1446, 1428, 1412, 1310, 1302, 1290, 1258, 1214, 1178, 1154, 1116, 1104, 1088, 1016, 984, 968, 954, 938, 922, 868, 844, 814, 796, 764, 734, 708, 682, 648, 624, 564.

MS (70 eV, EI) m/z (%): 211 (100) [M⁺], 183 (15), 109 (16).

HRMS (EI) for C₁₄H₁₀NF (211.0797): 211.0771.

Preparation of ethyl 3-[3-(ethoxycarbonyl)but-3-en-1-yl]benzoate (47c):
The zinc reagent 46c was prepared according to TP7 from 3-ethoxycarbonylbenzyl chloride (45c, 397 mg, 2.0 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent 46c was added to ethyl (2-bromomethyl)acrylate (270 mg, 1.4 mmol) in 1.0 mL THF at 25 °C. CuCN·2 LiCl (0.4 mL, 1.0 M in THF, 0.4 mmol) was added and the mixture was stirred for 15 min. The reaction mixture was quenched with sat. aq. NH₄Cl solution (45 mL) followed by 25% aq. NH₃ solution (5 mL) and extracted with CH₂Cl₂ (3x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash column chromatography (pentane/CH₂Cl₂ = 1:1) furnished 16c as a colorless oil (290 mg, 75 %).

\[1^H\text{-NMR (600 MHz, CDCl}_3\] \[\delta\text{ (ppm): 7.87-7.86 (m, 2H), 7.37-7.32 (m, 2H), 6.15 (s, 1H), 5.48 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 2.85-2.82 (m, 2H), 2.64-2.61 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H).}

\[1^3C\text{-NMR (150 MHz, CDCl}_3\] \[\delta\text{ (ppm): 167.0, 166.7, 141.7, 139.8, 133.0, 130.6, 129.5, 128.3, 127.3, 125.4, 60.9, 60.7, 34.7, 33.8, 14.3, 14.2.}

\[\text{IR (ATR) } \tilde{\nu}\text{ (cm}^{-1}\]): 2980, 2936, 2906, 2872, 1712, 1630, 1608, 1588, 1478, 1464, 1444, 1410, 1392, 1368, 1278, 1186, 1134, 1104, 1082, 1024, 944, 906, 862, 818, 750, 696, 668, 630, 624, 618, 582, 576, 568, 558.

\[\text{MS (70 eV, EI) } m/z\text{ (%): 276 (13) [M}^+\], 230 (55), 202 (100), 184 (25), 163 (56), 129 (32), 84 (96).}

\[\text{HRMS (EI) for C}_{16}\text{H}_{20}\text{O}_4\text{ (276.1362): 276.1356}

Preparation of 1-(4-chlorophenyl)-2-[3-(trifluoromethyl)phenyl]ethanone (47d):
The zinc reagent 46d was prepared according to TP7 from 3-(trifluoromethyl)benzyl chloride (45d, 389 mg, 2.0 mmol) in 30 min at 25 °C. The freshly prepared zinc reagent 46d was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, 4-chlorobenzoyl chloride (245 mg, 1.4 mmol) was added, the mixture warmed to 25 °C and was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (10 mL) followed by 25% aq. NH₃ solution (2 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/CH₂Cl₂ = 3:1) furnished 47d as a colorless solid (382 mg, 91%).

M.p.: 54-56 °C.

\[ \text{1H-NMR (300 MHz, CDCl₃)} \; \delta \text{ (ppm): 7.96-7.92 (m, 2H), 7.55-7.41 (m, 6H), 4.32 (s, 2H).} \]

\[ \text{13C-NMR (75 MHz, CDCl₃)} \; \delta \text{ (ppm): 195.4, 140.0, 135.0, 134.6, 133.0, 131.0 (q, } J = 32.2 \text{ Hz), 129.8, 129.1, 129.1, 126.3 (q, } J = 4 \text{ Hz) 124.0 (q, } J = 4 \text{ Hz), 124.0 (q, } J = 272 \text{ Hz), 44.9.} \]

\[ \text{IR (ATR)} \; \tilde{\nu} \text{ (cm}^{-1}) : 1694, 1682, 1588, 1572, 1488, 1454, 1400, 1334, 1302, 1284, 1210, 1186, 1176, 1156, 1118, 1106, 1092, 1074, 1014, 1004, 990, 960, 942, 922, 904, 878, 852, 832, 818, 812, 792, 784, 762, 754, 720, 700, 656, 628, 620, 598, 584, 562. \]

\[ \text{MS (70 eV, EI)} \; m/z \%: 279 (2), 139 (100), 111 (18), 75 (6). \]

\[ \text{HRMS (EI) for C}_{15}\text{H}_{10}\text{OClF}_3 \; (298.0372): 298.0352.} \]

**Preparation of 2-chlorobenzyl methyl sulphide (47a):**

\[
\begin{align*}
\text{Cl} & \quad \text{SMe} \\
\end{align*}
\]

The zinc reagent 46a was prepared according to TP7 from 2-chlorobenzyl chloride (45a, 322 mg, 2.0 mmol) in 45 min at 25 °C. MeSO₂SMe (177 mg, 1.4 mmol) was added to the freshly prepared zinc reagent 46a and the mixture was stirred for 16 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (10 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane) furnished 47b as a colorless oil (214 mg, 89%).

\[ \text{1H-NMR (300 MHz, CDCl₃)} \; \delta \text{ (ppm): 7.38-7.32 (m, 2H), 7.24-7.15 (m, 2H), 3.80 (s, 2H), 2.05 (s, 3H).} \]
Preparation of 1-(6-chloro-1,3-benzodioxol-5-yl)acetone (47e):

The zinc reagent 46e was prepared according to TP7 from 5-chloro-6-(chloromethyl)-1,3-benzodioxole (45e, 410 mg, 2.0 mmol) in 15 min at 25 °C. The freshly prepared zinc reagent 46e was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, acetyl chloride (110 mg, 1.4 mmol) was added, the mixture warmed to 25 °C and was stirred for 3 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (10 mL) followed by 25% aq. NH₃ solution (2 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Flash column chromatography (pentane/CH₂Cl₂ = 1:1) furnished 47e as a colorless solid (227 mg, 76%).

m.p.: 79-80 °C.

1H-NMR (300 MHz, CDCl₃) δ (ppm): 6.85 (s, 1H), 6.65 (s, 1H), 5.96 (s, 2H), 3.72 (s, 2H), 2.18 (s, 3H).

13C-NMR (75 MHz, CDCl₃) δ (ppm): 205.1, 147.5, 146.8, 126.0, 125.6, 110.8, 109.9, 101.8, 48.1, 29.5.

IR (ATR) ν (cm⁻¹): 2912, 1718, 1504, 1488, 1422, 1406, 1394, 1356, 1320, 1256, 110.8, 109.9, 101.8, 48.1, 29.5.

MS (70 eV, EI) m/z (%): 212 (23) [M⁺], 169 (100), 111 (6), 75 (9).

HRMS (EI) for C₁₀H₉O₃Cl (212.0240): 212.0225.

Preparation of 1-(4-bromophenyl)-2-(4-methoxyphenyl)ethanone (47f):
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The zinc reagent 46f was prepared according to TP7 from 4-methoxybenzyl chloride (45f, 276 mg, 1.8 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent 46f was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, 4-bromobenzoyl chloride (285 mg, 1.3 mmol) was added, the mixture warmed to 25 °C and was stirred for 2 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (10 mL) followed by 25% aq. NH₃ solution (2 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/CH₂Cl₂ = 3:1) furnished 4g as a colorless solid (323 mg, 81%).

**M.p.**: 117-118 °C.

**1H-NMR (300 MHz, CDCl₃)** \( \delta \) (ppm): 7.85 (d, \( J = 8.6 \) Hz, 2H), 7.58 (d, \( J = 8.4 \) Hz, 2H), 7.15 (d, \( J = 8.6 \) Hz, 2H), 6.85 (d, \( J = 8.4 \) Hz, 2H), 4.17 (s, 2H), 3.77 (s, 3H).

**13C-NMR (75 MHz, CDCl₃)** \( \delta \) (ppm): 196.9, 158.6, 135.3, 131.9, 130.4, 130.1, 128.3, 126.1, 114.2, 55.2, 44.7.

**IR (ATR)** \( \tilde{\nu} \) (cm⁻¹): 3310, 2914, 1754, 1494, 1488, 1434, 1424, 1404, 1092, 1058, 1008, 1000, 882, 822, 792, 716.

**MS (70 eV, EI)** \( m/z \) (%): 304 (6) [M⁺], 183 (19), 121 (100).

**HRMS (EI)** for C₁₅H₁₃BrO₂ (304.0099): 304.0085.

**Preparation of 4,4-dimethyl-1-(3,4,5-trimethoxyphenyl)pentan-2-one (47g):**

The zinc reagent 46g was prepared according to TP7 from 3,4,5-trimethoxybenzyl chloride (45g, 433 mg, 2.0 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent 46g was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, 3,3-dimethylbutanoyl chloride (188 mg, 1.4 mmol) was added, the mixture warmed to 25 °C and was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution.
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(10 mL) followed by 25% aq. NH₃ solution (2 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (CH₂Cl₂) furnished 47g as a colorless solid (323 mg, 82 %).

M.p.: 65-66 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 6.37 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H), 2.35 (s, 2H), 1.00 (s, 9H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 207.9, 153.3, 137.0, 129.8, 106.5, 60.8, 56.1, 53.9, 52.2, 31.0, 29.7.

IR (ATR) ν (cm⁻¹): 2984, 2954, 2902, 2868, 1708, 1586, 1508, 1463, 1438, 1422, 1384, 1360, 1350, 1328, 1268, 1240, 1188, 1148, 1124, 1072, 1030, 994, 970, 922, 834, 822, 780, 678, 618.

MS (70 eV, EI) m/z (%): 280 (15) [M⁺], 181 (100), 99 (4), 57 (12).

HRMS (EI) for C₁₆H₂₄O₄ (280.1675): 280.1675.

Preparation of 4,4-dimethyl-1,1-diphenylpentan-2-one (47h):

The zinc reagent 46h was prepared according to TP7 from 1,1’-(chloromethylene)dibenzene (45h, 405 mg, 2.0 mmol) in 30 min at 0 °C. The freshly prepared zinc reagent 46h was cooled to -20 °C and CuCN·2LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, 3,3-dimethylbutanoyl chloride (188 mg, 1.4 mmol) was added, the mixture warmed to 25 °C and was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution (10 mL) followed by 25% aq. NH₃ solution (2 mL) and extracted with Et₂O (3x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane → pentane/CH₂Cl₂ = 3:2) furnished 47h as a colorless solid (302 mg, 81 %).

M.p.: 45-47 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.35-7.20 (m, 10H), 5.09 (s, 1H), 2.44 (s, 2H), 1.01 (s, 9H).
13C-NMR (75 MHz, CDCl3) δ (ppm): 207.8, 138.4, 129.0, 128.6, 127.1, 65.7, 54.9, 31.3, 29.6.

IR (ATR) ʋ (cm⁻¹): 3060, 3028, 2980, 2956, 2904, 2868, 1714, 1596, 1582, 1492, 1464, 1452, 1398, 1388, 1360, 1348, 1306, 1294, 1272, 1252, 1230, 1190, 1154, 1126, 1084, 1060, 1032, 1004, 990, 948, 916, 902, 758, 746, 720, 702, 692, 628, 616, 604.

MS (70 eV, EI) m/z (%): 183 (1), 167 (100), 152 (10), 99 (18).

HRMS (EI) for C19H22O (266.1671): 266.1659.

2.5. Preparation of Alkylzinc Reagents by the Insertion of Magnesium in the Presence of LiCl and ZnCl₂

2.5.1. Preparation of Title Compounds

Preparation of 5-cyclohex-2-en-1-yl-N,N-diethylpentanamide (53):

The zinc reagent 52 was prepared according to TP4 from 5-bromo-N,N-diethylpentanamide (51, 472 mg, 2 mmol) in 1 h at 25 °C. CuCN·2 LiCl (0.4 mL, 1 M in THF, 20 mol%) was added at -20 °C and the mixture stirred for 30 min. 3-Bromocyclohexene (225 mg, 1.4 mmol, 0.7 equiv) was added at -20 °C under argon. The mixture was stirred for 1 h and allowed to warm up slowly to 20 °C before being quenched with sat. aqueous NH₄Cl solution (20 mL) and conc. ammonia (20 mL). The aqueous layer was extracted with diethyl ether three times. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (EtOAc/pentane = 1:4) to yield compound 53 (232 mg, 70 %) as colorless liquid.

1H-NMR (300 MHz, CDCl₃) δ (ppm): 5.64-5.51 (m, 2H), 3.37-3.23 (m, 4H), 2.28-2.23 (m, 2H) 2.03-1.09 (m, 21H).
Experimental Section

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 172.2, 132.1, 126.7, 41.9, 40.0 36.1, 35.0, 33.1, 29.0, 26.8, 25.7, 25.3, 21.5, 14.4, 13.1.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2967, 2931, 2861, 1616, 1480, 1430, 1380, 1362, 1264, 1221.

MS (EI, 70 eV) m/z (%): 237 (9), 156 (15), 115 (100), 100 (59), 58 (38).

HRMS (EI) for C$_{15}$H$_{27}$NO (237.2093): 237.2097.

Preparation of \{3-[3-(benzylthio)propyl]phenyl\}(phenyl)methanone (56a):

![Structure of 56a]

The zinc reagent 55 was prepared according to TP4 from [3-(3-bromopropyl)phenyl] (phenyl)methanone (54, 606 mg, 2 mmol) in 1.5 h at 25 °C. S-benzyl benzenesulfonothioate (370 mg, 1.4 mmol, 0.7 equiv) was added at -20 °C and the mixture stirred for 1 h. The solution was allowed to warm up slowly to 20 °C before being quenched with sat. aqueous NH$_4$Cl solution (20 mL). The aqueous layer was extracted with diethyl ether three times. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (Et$_2$O/pentane = 1:19) to yield compound 56a (254 mg, 58 %) as colorless liquid.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.79-7.70 (m, 4H), 7.60-7.44 (m, 3H), 7.31-7.22 (m, 7H), 3.70 (s, H), 2.75 (t, $J = 7.3$ Hz, 2H), 2.44 (t, $J = 7.0$ Hz, 2H), 1.95-1.85 (m, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 196.4, 146.7, 138.4, 137.9, 137.5, 137.5, 135.4, 132.2, 130.4, 129.9, 128.8, 128.5, 128.4, 128.2, 127.0, 36.6, 34.7, 30.6, 30.4.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3059, 3027, 2922, 2857, 1653, 1604, 1578, 1568, 1494, 1446, 1412, 1315, 1310, 1276, 1202, 1176, 1148, 1072, 1028, 1020, 1000, 938, 922, 847, 787, 768, 740, 697, 680.

MS (EI, 70 eV) m/z (%): 346 (52) [M$^+$] 255 (12), 222 (21), 209 (100), 196 (18), 145 (28), 105 (55), 91 (79).

HRMS (EI) for C$_{23}$H$_{22}$OS (346.1391): found 346.1394.

Preparation of [3-(3-cyclohex-2-en-1-ylpropyl)phenyl](phenyl)methanone (56b):
The zinc reagent 55 was prepared according to TP4 from [3-(3-bromopropyl)phenyl](phenyl)methanone (54, 606 mg, 2 mmol) in 1.5 h at 25 °C. CuCN·2 LiCl (0.4 mL, 1 M in THF, 20 mol%) was added at -20 °C and the mixture stirred for 30 min. 3-Bromocyclohexene (225 mg, 1.4 mmol, 0.7 equiv) was added at -20 °C under argon. The mixture was stirred for 1 h and allowed to warm up slowly to 20 °C before being quenched with sat. aqueous NH₄Cl solution (20 mL) and conc. ammonia (20 mL). The aqueous layer was extracted with diethyl ether three times. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (Et₂O/pentane = 1:9) to yield compound 56b (261 mg, 61 %) as colorless liquid.

**1H-NMR (300 MHz, CDCl₃) δ (ppm):** 7.43-6.97 (m, 9H), 5.70-5.56 (m, 2H), 3.02 (s, 1H) 2.60-2.53 (m, 2H), 2.10 (brs, 1H), 1.79-1.17 (m, 9H).

**13C-NMR (75 MHz, CDCl₃) δ (ppm):** 144.5, 141.5, 141.3, 132.1, 128.6, 128.4, 127.3, 127.2, 126.8, 126.8, 126.7, 35.9, 35.6, 35.0, 29.0, 28.5, 25.4, 21.5.

**IR (ATR) ν (cm⁻¹):** 2971, 2941, 2859, 1659, 1610, 1582, 1560, 1493, 1314, 1321, 1275, 1243, 1153, 1144, 1111, 1022, 1020, 998, 846, 787, 768, 740, 690, 680.

**MS (EI, 70 eV) m/z (%):** 304 (59) [M⁺], 209 (100), 196 (42), 183 (22), 118 (18), 105 (92), 77 (75).

**HRMS (EI) for C₂₂H₂₄O (304.1827):** 304.1804.

**Preparation of ethyl 2-(1,4-dioxaspiro[4.5]dec-8-ylmethyl)acrylate (59):**

The zinc reagent 58 was prepared according to TP4 from 8-bromo-1,4-dioxaspiro[4.5]decane (57, 442 mg, 2 mmol) in 2 h at 25 °C. CuCN·2 LiCl (1 M solution in THF, 0.4 mL, 0.2 equiv)
Experimental Section

was added at -20 °C and the mixture stirred for 30 min. ethyl 2-(bromomethyl)acrylate (270 mg, 1.4 mmol, 0.7 equiv) was added at -20 °C under argon. The mixture was stirred for 1 h and allowed to warm up slowly to 20 °C before being quenched with sat. aqueous NH₄Cl solution (20 mL) and 25% NH₃ (20 mL). The aqueous layer was extracted with diethyl ether three times. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (EtOAc/pentane = 1:9) to yield compound 59 (245 mg, 68 %) as colorless liquid.

\[ ^1H\text{-NMR (300 MHz, CDCl}_3 \] \( \delta \) (ppm): 6.13 (d, \( J = 1.7 \) Hz, 1H), 5.46-5.45 (m, 1H), 4.18 (q, \( J = 7.3 \) Hz, 2H), 3.90 (s, 4H), 2.21 (d, \( J = 6.8 \) Hz, 2H), 1.74-1.64 (m, 4H), 1.53-1.43 (m, 3H), 1.27 (t, \( J = 7.3 \) Hz, 3H), 1.23-1.21 (m, 1H).

\[ ^13C\text{-NMR (75 MHz, CDCl}_3 \] \( \delta \) (ppm): 167.3, 139.3, 125.8, 109.0, 64.2, 60.5, 38.8, 35.1, 34.3, 29.9, 14.2.

IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)): 2980, 2930, 2879, 2860, 1713, 1629, 1477, 1446, 1410, 1371, 1329, 1301, 1284, 1200, 1174, 1156, 1133, 1104, 1076, 1067, 1033, 1001, 982, 929, 884, 857, 820, 768, 661.

MS (EI, 70 eV) m/z (%): 254 (<1) [M\(^+\)], 198 (3), 181 (5), 99 (100), 86 (13).

HRMS (EI) for C\(_{14}\)H\(_{22}\)O\(_4\) (254.1518): 254.1494.

2.6. Larger Scale Preparations of Organomagnesium and Organozinc Reagents

2.6.1. Preparation of Title Compounds

Preparation of 2-[(2,2-dimethylpropanoyl)oxy]phenylmagnesium bromide (23v):

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.12 g, 50 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (2.43 g, 100 mmol) and THF (100 mL) were added and the
magnesium was activated with $i$Bu$_2$AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to –20 °C and 2-bromo-1-pivaloyloxybenzene (22v, 10.3 g, 40 mmol) was added slowly, so that the reaction temperature is kept below –15 °C. After complete addition, the reaction mixture was stirred for additional 30 min at –20 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk-flask and the yield of the magnesium reagent was determined by iodometric titration (106 mL, 0.35 M, 37.1 mmol, 93 %).

Preparation of 3-[(2,2-dimethylpropanoyl)oxy]phenylmagnesium bromide (23w):

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.12 g, 50 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (2.43 g, 100 mmol) and THF (100 mL) were added and the magnesium was activated with $i$Bu$_2$AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to –20 °C and 3-bromo-1-pivaloyloxybenzene (22w, 10.3 g, 40 mmol) was added slowly, so that the reaction temperature is kept below –15 °C. After complete addition, the reaction mixture was stirred for additional 30 min at –20 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk-flask and the yield of the magnesium reagent was determined by iodometric titration (108 mL, 0.32 M, 34.6 mmol, 86 %).

Preparation of 4-[(tert-butoxycarbonyl)oxy]phenylmagnesium bromide (23b):
A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (4.58 g, 108 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (5.23 g, 215 mmol) and THF (215 mL) were added and the magnesium was activated with iBu₂AlH (0.14 mL, 114 mg, 0.8 mmol). After 5 min of stirring, the suspension was cooled to –20 °C and 4-bromophenyl tert-butyl carbonate (22b, 23.49 g, 86 mmol) was added slowly, so that the reaction temperature is kept below –15 °C. After complete addition, the reaction mixture was stirred for additional 30 min at –20 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk-flask and the yield of the magnesium reagent was determined by iodometric titration (270 mL, 0.29 M, 78.3 mmol, 91 %).

Preparation of 4-methoxyphenylmagnesium bromide (23x):

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.67 g, 63 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (3.04 g, 125 mmol) and THF (125 mL) were added and the magnesium was activated with iBu₂AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to 0 °C and 4-bromoanisole (22x, 9.35 g, 50 mmol) was added slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk-flask and the yield of the magnesium reagent was determined by iodometric titration (126 mL, 0.38 M, 47.9 mmol, 97 %).

Preparation of mesitylmagnesium bromide (23y):

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A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.67 g, 63 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (22y, 3.04 g, 125 mmol) and THF (125 mL) were added and the magnesium was activated with iBu₂AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to 0 °C and 2-bromo-1,3,5-trimethylbenzene (9.95 g, 50 mmol) was added slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk-flask and the yield of the magnesium reagent was determined by iodometric titration (129 mL, 0.36 M, 46.3 mmol, 93 %).

Preparation of pyridine-3-ylmagnesium bromide (23z):

\[
\text{MgBr-LiCl}
\]

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (5.30 g, 125 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (6.08 g, 250 mmol) and THF (250 mL) were added and the magnesium was activated with iBu₂AlH (0.14 mL, 114 mg, 0.8 mmol). After 5 min of stirring, the suspension was cooled to 0 °C and 3-bromopyridine (22z, 15.80 g, 100 mmol) was added slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk-flask and the yield of the magnesium reagent was determined by iodometric titration (266 mL, 0.34 M, 90.4 mmol, 90 %).

Preparation of 3-phenylpropyl-1-magnesium bromide (61):

\[
\text{Ph-MgBr-LiCl}
\]
A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.67 g, 63 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (3.04 g, 125 mmol) and THF (125 mL) were added and the magnesium was activated with iBu₂AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to 0 °C and (3-bromopropyl)benzene (60, 9.95 g, 50 mmol) was added slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk-flask and the yield of the magnesium reagent was determined by iodometric titration (124 mL, 0.37 M, 45.7 mmol, 91 %).

Preparation of 2-chlorobenzylzinc chloride (46a):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (2.65 g, 62.5 mmol) and was heated under high vacuum for 20 min. ZnCl₂ (3.60 g, 55.0 mmol) was added and was similarly heated under high vacuum. Magnesium turnings (3.04 g, 125 mmol) and THF (125 mL) were added. The suspension was cooled to 0 °C and 2-chlorobenzyl chloride (45a, 8.05 g, 50 mmol) was slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed Schlenk-flask and the yield of the zinc reagent was determined by iodometric titration (132 mL, 0.34 M, 44.9 mmol, 90 %).

Preparation of 2-formylphenyl pivalate (24v):
Freshly prepared and titrated 3-[(2,2-dimethylpropanoyl)oxy]phenylmagnesium bromide (23v, 28.6 mL, 0.35 M, 10.0 mmol) was added to a solution of DMF (886 mg, 12 mmol) in THF (5 mL) at -20 °C. The reaction mixture was stirred for 15 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH₄Cl solution and extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/CH₂Cl₂ = 2:1) furnished 24v as colorless oil (1.71 g, 83 %).

$^1$H-NMR (300 MHz, CDCl₃) δ (ppm): 9.99 (s, 1H), 7.73 (d, $J = 7.5$ Hz, 1H), 7.59-7.52 (m, 2H), 7.34-7.31 (m, 1H), 1.36 (s, 9H).

$^{13}$C-NMR (75 MHz, CDCl₃) δ (ppm): 191.3, 176.8, 151.7, 137.7, 130.0, 127.8, 127.2, 122.1, 39.1, 27.1.

IR (ATR):  $\tilde{\nu}$ (cm$^{-1}$): 2976, 2937, 2909, 2874, 2730, 1752, 1697, 1606, 1589, 1480, 1449, 1397, 1388, 1368, 1272, 1235, 1162, 1135, 1101, 1030, 1001, 922, 897, 867, 820, 779, 756, 680, 645, 619.

MS (70 eV, EI) m/z (%): 206 (1) [M$^+$], 122 (45), 57 (66), 48 (100).

HRMS (EI) for C₁₂H₁₄O₃ (206.0943): 206.0917.

Preparation of tert-butyl 4-[(4-chlorophenyl)(hydroxy)methyl]phenyl carbonate (24w):

Freshly prepared and titrated 4-[(tert-butoxycarbonyl)oxy]phenylmagnesium bromide (23b, 35.5 mL, 0.29 M, 10.0 mmol) was added to a solution of 4-chlorobenzaldehyde (1.69 g, 12 mmol) in THF (5 mL) at -20 °C. The reaction mixture was stirred for 15 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH₄Cl solution and extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 4:1) furnished 24w as colorless oil (3.01 g, 90 %).

$^1$H-NMR (300 MHz, CDCl₃) δ (ppm): 7.33 (d, $J = 8.5$ Hz, 2H), 7.29 (s, 4H), 7.13 (d, $J = 8.5$ Hz, 2H), 5.80 (s, 1H), 2.01 (brs, 1H), 1.54 (s, 9H).
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$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 151.8, 150.5, 141.9, 140.9, 133.4, 128.6, 127.9, 127.6, 121.4, 83.7, 75.0, 27.7.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3493, 1728, 1526, 1508, 1496, 1380, 1303, 1294, 1261, 1219, 1150, 1086, 1040, 1013, 898, 824, 814, 806, 784, 614.

MS (70 eV, EI) $m/z$ (%): 334 (1) [M$^+$], 276 (12), 234 (77), 215 (52), 153 (67), 139 (66), 57 (100).

HRMS (EI) for C$_{18}$H$_{19}$ClO$_4$ (334.0972): 334.0980.

Preparation of (4-methoxyphenyl)(pyridin-3-yl)methanol (24x):

Freshly prepared and titrated pyridine-3-ylmagnesium bromide (23z, 29.4 mL, 0.34 M, 10.0 mmol) was added to a solution of 4-methoxybenzaldehyde (1.63 g, 12 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 15 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH$_4$Cl solution and extracted with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 1:1) furnished 24x as a pale brown solid (2.02 g, 94 %).

M.p.: 92-93 °C

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 8.45 (s, 1H), 8.31 (d, $J = 3.6$ Hz, 1H), 7.69 (td, $J = 1.7$ Hz, $J = 7.8$ Hz, 1H), 7.27-7.19 (m, 3H), 6.85 (d, $J = 8.8$ Hz, 2H), 5.77 (s, 1H), 4.56 (s, 1H), 3.77 s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 159.1, 147.8, 147.7, 140.1, 135.5, 134.4, 127.8, 123.4, 113.9, 73.3, 55.2.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3184, 3086, 3067, 3050, 3036, 2993, 2966, 2935, 2837, 1511, 1426, 1250, 1171, 1053, 1029, 805, 715.

MS (70 eV, EI) $m/z$ (%): 215 (100) [M$^+$], 198 (17), 137 (51), 109 (99).

HRMS (EI) for C$_{13}$H$_{13}$NO$_2$ (215.0946): 215.0935.

Preparation of (4-isopropylphenyl)(4-methoxyphenyl)methanol (24y):

Preparation of (4-isopropylphenyl)(4-methoxyphenyl)methanol (24y):
Experimental Section

Freshly prepared and titrated 4-methoxyphenylmagnesium bromide (23x, 29.4 mL, 0.34 M, 10.0 mmol) was added to a solution of 4-isopropylbenzaldehyde (1.78 g, 12 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 15 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH₄Cl solution and extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 2:1) furnished 24y as a colorless oil (2.46 g, 96 %).

**1H-NMR (300 MHz, CDCl₃)** $\delta$ (ppm): 7.32-7.14 (m, 6H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.77 (s, 1H) 3.79 (s, 3H), 2.90 (sept, $J = 7.0$ Hz, 1H), 2.29 (brs, 1H), 1.25 (d, $J = 7.0$ Hz, 6H).

**13C-NMR (75 MHz, CDCl₃)** $\delta$ (ppm): 158.9, 148.0, 141.5, 136.2, 127.8, 126.4, 126.4, 113.7, 75.6, 55.2, 33.7, 23.9.

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$)**: 2966, 2921, 1665, 1602, 1574, 1415, 1272, 1260, 1161, 1024, 909, 845.

**MS (70 eV, EI) m/z (%):** 256 (88) [M$^+$], 239 (42), 213 (20), 147 (61), 135 (100), 109 (40).

**HRMS (EI) for C₁₇H₂₀O₂ (256.1463):** 256.1458.

**Preparation of mesityl(4-methoxyphenyl)methanone (24z):**

Freshly prepared and titrated mesitylmagnesium bromide (23y, 27.8 mL, 0.36 M, 10.0 mmol) was slowly added to a solution of 4-methoxybenzoyl chloride (2.05 g, 12 mmol) and CuCN·2 LiCl (2 mL, 1 M in THF, 2 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 30 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH₄Cl/NH₃ (9:1) solution and extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 4:1) furnished 24z as a colorless oil (2.26 g, 89%).
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$\text{H-NMR (300 MHz, CDCl}_3) \, \delta \text{ (ppm): 7.76 (d, } J = 8.5 \text{ Hz, 2H), 6.90 (d, } J = 8.5 \text{ Hz, 2H), 6.87 (s, 2H), 3.85 (s, 3H), 2.32 (s, 3H), 2.08 (s, 6H).}$

$\text{C-NMR (75 MHz, CDCl}_3) \, \delta \text{ (ppm): 199.2, 163.9, 138.2, 137.2, 134.1, 1318, 130.5, 128.2, 114.0, 55.5, 21.1, 19.3.}$

$\text{MS (70 eV, EI) m/z (%): 254 (71) [M^+]}, 239 (33), 223 (100), 147 (23), 135 (40).$

$\text{HRMS (EI) for C}_{13}\text{H}_{15}\text{NO (201.1154): 201.1154.}$

3. Regio- and Chemoselective Synthesis of 5-Membered Ring Heterocycles

3.1. Preparation of Polyfunctional Furan, Thiophene, Indole and Pyrrole Derivatives

3.1.1. Typical Procedure for the Deprotonation of Heterocycles (TP8)

A dry and argon flushed Schlenk-flask, equipped with a magnetic stirrer and a septum was charged with the starting thiophene in THF (approx. 1 M solution) and cooled to the appropriate temperature. TMPMgCl-LiCl was added dropwise and the reaction mixture stirred for the indicated time (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of I$_2$ in THF).

3.1.2. Typical Procedure for Cross-Coupling Reactions (TP9)

To the freshly prepared magnesium reagent was added ZnCl$_2$ (1 M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. The catalytic system and the aryl iodide or bromide (1.5 equiv) were added and the reaction mixture was warmed to 25 $^\circ$C. After stirring for the indicated time the reaction mixture was quenched with half concentrated aqueous NH$_4$Cl solution, extracted three times with Et$_2$O, dried over Na$_2$SO$_4$ and
concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel.

3.1.3. Typical Procedure for Allylation or Acylation Reactions (TP10)

To the freshly prepared magnesium reagent was added CuCN·2 LiCl (1 M in THF, 20 mol %) and the reaction mixture was stirred for 15 min at the indicated temperature. The allyl bromide or acyl chloride was added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time the reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel.

3.1.4. Preparation of Title Compounds

Preparation of ethyl 5-(trimethylsilyl)thiophene-2-carboxylate (65a):

Prepared according to TP8 from ethyl thiophene-2-carboxylate (62a, 5.0 mmol, 781 mg) in 5 mL THF and trimethylsilylcyanide (6.0 mmol, 595 mg). Deprotonation time: 30 min at –40 °C. Reaction time with electrophile: 2 h at –40 °C. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 4:1) yielding 65a (821 mg, 72 %) as a colorless oil.

\[
\begin{array}{c}
\text{EtO}_2\text{C} \hline \text{S} \\
\text{TMS}
\end{array}
\]

\(^1\)H-NMR (300 MHz, CDCl₃) \(\delta (ppm): 7.81 (d, J = 3.7 Hz, 1H), 7.19 (d, J = 3.7 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H), 1.36 (t, J = 7.0 Hz, 3H), 0.32 (s, 9H).

\(^13\)C-NMR (75 MHz, CDCl₃) \(\delta (ppm): 162.2, 149.2, 138.6, 134.1, 134.0, 61.0, 14.4, -0.3.

IR (ATR) \(\tilde{\nu} \) (cm\(^{-1}\)): 1426, 1366, 1310, 1274, 1238, 1088, 986, 836, 824, 750.

MS (70 eV, EI) \(m/z \) (%): 228 (18) [M⁺], 213 (100), 185 (22), 84 (7), 75 (10).

HRMS (EI) for C₁₀H₁₆O₂SSi (228.0640): 228.0624.
Preparation of ethyl 5-bromothiophene-2-carboxylate (65b):

Prepared according to TP8 from ethyl thiophene-2-carboxylate (62a, 1.0 mmol, 156 mg) in 1 mL THF and 1,2-dibromo-1,1,2,2-tetrachloroethane (1.1 mmol, 358 mg) in 1 mL THF. Deprotonation time: 30 min at -40 °C. Reaction time with electrophile: 30 min at -40 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 10:1) 65b (209 mg, 89 %) as a colorless oil.

\( ^1H \text{-NMR (400 MHz, CDCl}_3 \) \( \delta \) (ppm): 7.54 (d, \( J = 3.9 \) Hz, 1H), 7.06 (d, \( J = 3.9 \) Hz, 1H), 4.32 (q, \( J = 7.2 \) Hz, 2H), 1.35 (t, \( J = 7.2 \) Hz, 3H).

\( ^{13}C \text{-NMR (100 MHz, CDCl}_3 \) \( \delta \) (ppm): 161.1, 135.2, 133.5, 130.8, 120.0, 61.4, 14.3.

IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)): 2982, 1706, 1532, 1414, 1366, 1278, 1246, 1172, 1084, 1048, 808, 742.

MS (70 eV, EI) \( m/z \) (%): 236 (43) [M\(^+\), \(^{81}\)Br], 234 (42) [M\(^+\), \(^{79}\)Br], 208 (39), 206 (37), 191 (100), 189 (98), 82 (18).

HRMS (EI) for C\(_7\)H\(_7\)BrO\(_2\)S (233.9350): 233.9324.

Preparation of ethyl 5-allylthiophene-2-carboxylate (65c):

Prepared according to TP8 from ethyl thiophene-2-carboxylate (62a, 1.0 mmol, 156 mg) in 1 mL THF and ally bromide (1.1 mmol, 133 mg). Deprotonation time: 30 min at -40 °C. An allylation reaction was performed according to TP10 using allyl bromide (1.1 mmol, 133 mg) at -40 °C during 1 h. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 7:1) yielding 65c (130 mg, 66%) as a colorless oil.

\( ^1H \text{-NMR (600 MHz, CDCl}_3 \) \( \delta \) (ppm): 7.63 (d, \( J = 3.6 \) Hz, 1H), 6.80 (d, \( J = 3.6 \) Hz, 1H), 5.99-5.92 (m, 1H), 5.18-5.13 (m, 2H), 4.31 (q, \( J = 7.2 \) Hz, 2H), 3.57 (d, \( J = 7.7 \) Hz, 2H), 1.34 (t, \( J = 7.2 \) Hz, 3H).
Experimental Section

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 162.3, 150.8, 135.3, 133.6, 131.9, 125.6, 117.2, 61.0, 34.6, 14.4.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2982, 1704, 1640, 1540, 1456, 1368, 1278, 1256, 1086, 990, 918, 816, 748.

MS (70 eV, EI) $m/z$ (%): 196 (89) [M$^+$], 168 (13), 151 (100), 123 (75), 79 (12).

HRMS (EI) for C$_{10}$H$_{12}$O$_2$S (196.0558): 196.0567.

Preparation of diethyl thiophene-2,5-dicarboxylate (65d):

Prepared according to TP8 from ethyl thiophene-2-carboxylate (62a, 5.0 mmol, 781 mg) in 5 mL THF and ethyl cyanoformate (5.5 mmol, 545 mg). Deprotonation time: 30 min at –40 °C. Reaction time with electrophile: 30 min at –40 °C and warming to 25 °C. The crude residue was purified by recrystallization (heptane) yielding 65d (714 mg, 63 %) as a slightly yellow solid

M.p.: 49-50 °C.

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.72 (s, 2H), 4.37 (q, $J = 7.2$ Hz, 4H), 1.38 (t, $J = 7.2$ Hz, 6H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 161.6, 139.2, 132.9, 61.7, 14.2.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2982, 2938, 1700, 1536, 1464, 1366, 1246, 1088, 1012, 746.

MS (70 eV, EI) $m/z$ (%): 228 (34) [M$^+$], 213 (7), 200 (18), 183 (100), 172 (26), 155 (65), 111 (9).

HRMS (EI) for C$_{10}$H$_{12}$O$_4$S (228.0456): 228.0460.

Preparation of diethyl 3-(methylthio)furan-2,5-dicarboxylate (67a):

Prepared according to TP8 from ethyl thiophene-2-carboxylate (62a, 5.0 mmol, 781 mg) in 5 mL THF and ethyl cyanofomate (5.5 mmol, 545 mg). Deprotonation time: 30 min at –40 °C. Reaction time with electrophile: 30 min at –40 °C and warming to 25 °C. The crude residue was purified by recrystallization (heptane) yielding 65d (714 mg, 63 %) as a slightly yellow solid

M.p.: 49-50 °C.

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.72 (s, 2H), 4.37 (q, $J = 7.2$ Hz, 4H), 1.38 (t, $J = 7.2$ Hz, 6H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 161.6, 139.2, 132.9, 61.7, 14.2.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2982, 2938, 1700, 1536, 1464, 1366, 1246, 1088, 1012, 746.

MS (70 eV, EI) $m/z$ (%): 228 (34) [M$^+$], 213 (7), 200 (18), 183 (100), 172 (26), 155 (65), 111 (9).

HRMS (EI) for C$_{10}$H$_{12}$O$_4$S (228.0456): 228.0460.
Prepared according to TP8 from diethyl furan-2,5-dicarboxylate (66a, 2.0 mmol, 424 mg) in 2 mL THF and PhSO₂SMe (2.5 mmol, 471 mg). Deprotonation time: 10 min at -78 °C. Reaction time with electrophile: 3 h min at –50 °C The crude residue was purified by flash column chromatography (CH₂Cl₂) yielding 67a (481 mg, 93 %) as a pale yellow solid.

**M.p.:** 69-70 °C.

**¹H-NMR (300 MHz, CDCl₃) δ (ppm):** 7.14 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 2.47 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).

**¹³C-NMR (75 MHz, CDCl₃) δ (ppm):** 158.4, 157.8, 145.9, 139.3, 133.6, 118.2, 116.5, 61.8, 61.4, 15.6, 14.3.

**IR (ATR) ν (cm⁻¹):** 2988, 2940, 2908, 2872, 1728, 1696, 1560, 1508, 1476, 1432, 1392, 1368, 1296, 1192, 1168, 1116, 1100, 1028, 1012, 972, 876, 860, 836, 768, 716.

**MS (70 eV, EI) m/z (%):** 258 (100) [M⁺], 228 (7) 212 (17), 196 (20).

**HRMS (EI) for C₁₁H₁₄N₅S (258.0562):** 258.0555.

**Preparation of diethyl 3-[3-(trifluoromethyl)phenyl]furan-2,5-dicarboxylate (67b):**

Prepared according to TP8 from diethyl furan-2,5-dicarboxylate (66a, 1.0 mmol, 212 mg) in 1 mL THF. Deprotonation time: 10 min at -78 °C. A cross-coupling reaction was performed according to TP9 using 3-iodobenzotrofluoride (1.1 mmol, 299 mg) and Pd(PPh₃)₄ (1 mol%, 12 mg) at 25 °C for 3 h. The crude residue was purified by flash column chromatography (CH₂Cl₂) yielding 67b (281 mg, 79 %) as a colorless solid.

**M.p.:** 78-79 °C.

**¹H-NMR (600 MHz, CDCl₃) δ (ppm):** 7.82 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 8.6, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.30 (s, 1H), 4.42 (q, J = 7.3 Hz, 2H), 4.34 (q, J = 7.3 Hz, 2H), 1.41 (t, J = 7.3 Hz, 3H), 1.30 (t, J = 7.3 Hz, 3H).

**¹³C-NMR (100 MHz, CDCl₃) δ (ppm):** 158.3, 157.9, 145.8, 141.4, 133.2, 132.6, 131.7, 10.6, 128.7, 126.3, 125.4, 123.0, 119.8, 61.8, 61.7, 14.3, 14.0.
**Experimental Section**

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2988, 1712, 1672, 1604, 1588, 1484, 1456, 1380, 1368, 1332, 1292, 1272, 1224, 1188, 1164, 1144, 1104, 1076, 1020, 972, 924, 900, 872, 848, 824, 796, 776, 760, 692.

**MS (70 eV, EI) m/z (%):** 356 (100) [M$^+$], 311 (32), 283 (34), 256 (17).

**HRMS (EI) for C$_{17}$H$_{15}$O$_5$F$_3$ (356.0872):** 356.0862.

**Preparation of diethyl 3-(3-fluorobenzoyl)furan-2,5-dicarboxylate (67c):**

Prepared according to TP8 from diethyl furan-2,5-dicarboxylate (66a, 1.0 mmol, 212 mg) in 1 mL THF. Deprotonation time: 10 min at -78 °C. An acylation reaction was performed according to TP10 using 3-fluorobenzoyl chloride (1.1 mmol, 174 mg) at -20 °C for 1 h. The crude residue was purified by flash column chromatography (pentane/Et$_2$O = 4:1) yielding 67c (285 mg, 85 %) as a colorless solid.

**M.p.:** 73-75 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.59-7.53 (m, 2H), 7.48-7.41 (m, 1H), 7.34-7.27 (m, 2H), 4.42 (q, $J = 7.1$ Hz, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 1.40 (t, $J = 7.1$ Hz, 3H), 1.07 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 188.3, 164.5, 161.2, 157.2 (d, $J = 36$ Hz), 146.5, 143.9, 138.7 (d, $J = 7$ Hz), 130.8, 130.4 (d, $J = 8$ Hz), 125.4, 121.0 (d, $J = 22$ Hz), 118.2, 115.7 (d, $J = 23$ Hz), 62.1, 62.1, 14.2, 13.7.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3144, 3108, 3088, 2988, 2944, 2908, 2880, 1796, 1712, 1668, 1588, 1540, 1480, 1444, 1404, 1384, 1364, 1312, 1260, 1220, 1192, 1168, 1148, 1084, 1008, 968, 900, 856, 808, 780, 752, 684, 672.

MS (70 eV, EI) m/z (%): 334 (100) [M$^+$], 289 (34), 262 (34), 239 (30), 210 (79), 187 (37), 122 (76).

HRMS (EI) for C$_{17}$H$_{15}$O$_6$F (334.0853): 334.0857.
Experimental Section

Preparation of diethyl 3-cyanofuran-2,5-dicarboxylate (67d):

Prepared according to TP8 from diethyl furan-2,5-dicarboxylate (66a, 5.0 mmol, 1.06 g) in 5 mL THF and tosylcyanide (6.0 mmol, 1.09 g). Deprotonation time: 10 min at –78 °C. Reaction time with electrophile: 30 min at –78 °C. The crude residue was purified by flash column chromatography (pentane/Et2O = 5:1) yielding 67d (781 mg, 66 %) as a colorless solid.

M.p.: 93-95 °C.

1H-NMR (300 MHz, CDCl3) δ (ppm): 7.37 (s, 1H), 4.48 (q, J = 7.3 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.3 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl3) δ (ppm): 156.6, 155.6, 150.2, 147.0, 119.2, 110.8, 104.1, 63.0, 62.4, 14.1, 14.0.

IR (ATR) ν (cm⁻¹): 3112, 3092, 3000, 2968, 2948, 2904, 2248, 1744, 1724, 1584, 1524, 1496, 1472, 1452, 1412, 1388, 1364, 1308, 1288, 1216, 1196, 1156, 1132, 1112, 1088, 1008, 964, 888, 872, 848, 820, 780, 764, 736, 704, 680.

MS (70 eV, EI) m/z (%): 237 (36) [M⁺], 209 (37), 192 (59), 181 (100), 164 (53), 137 (23).

HRMS (EI) for C11H11NO5 (237.0637): 237.0624.

Preparation of diethyl 3-cyanothiophene-2,5-dicarboxylate (67e):

Prepared according to TP8 from diethyl thiophene-2,5-dicarboxylate (65d, 1.7 mmol, 380 mg) in 2 mL THF and toslycyanide (2.0 mmol, 362 mg). Deprotonation time: 30 min at –60 °C. Reaction time with electrophile: 30 min at –50 °C. The crude residue was purified by flash column chromatography (pentane/Et2O = 3:1) yielding 67e (249 mg, 58 %) as a colorless solid.

M.p.: 78-80 °C.
**Experimental Section**

\[^{1}H-NMR\ (300\ \text{MHz, CDCl}_{3})\ \delta\ (\text{ppm}):\ 7.91\ (s,\ 1H),\ 4.45\ (q,\ J = 7.1\ \text{Hz, 2H}),\ 4.40\ (q,\ J = 7.4\ \text{Hz, 2H}),\ 1.43\ (t,\ J = 7.1\ \text{Hz, 3H}),\ 1.39\ (t,\ J = 7.4\ \text{Hz, 3H}).\]

\[^{13}C-NMR\ (75\ \text{MHz, CDCl}_{3})\ \delta\ (\text{ppm}):\ 160.0,\ 159.1,\ 144.6,\ 139.2,\ 135.3,\ 114.1,\ 112.8,\ 63.0,\ 62.6,\ 14.2,\ 14.0.\]

\[\text{IR (ATR) } \tilde{\nu}\ (\text{cm}^{-1}):\ 3092,\ 2984,\ 2940,\ 2236,\ 1732,\ 1700,\ 1536,\ 1476,\ 1452,\ 1400,\ 1368,\ 1300,\ 1284,\ 1260,\ 1204,\ 1160,\ 1120,\ 1088,\ 1012,\ 900,\ 860,\ 832,\ 804,\ 764,\ 716.\]

\[\text{MS (70 eV, EI) } m/z\ (%):\ 253\ (53)\ [M^{+}],\ 225\ (46),\ 208\ (100),\ 197\ (91),\ 180\ (82).\]

HRMS (EI) for C\(_{11}H_{11}NO_{4}S\) (253.0409): 253.0409.

**Preparation of ethyl 3-chloro-5-(trimethylsilyl)furan-2-carboxylate (67f):**

![Diagram](image)

Prepared according to TP8 from ethyl 5-(trimethylsilyl)furan-2-carboxylate (66b, 2.0 mmol, 414 mg) in 2 mL THF and hexachloroethane (3 mmol, 710 mg) in 3 mL THF. Deprotonation time: 4 h at –50 °C. Reaction time with electrophile: 15 h at –50 °C. The crude residue was purified by flash column chromatography (pentane/CH\(_2\)Cl\(_2\) = 2:1) yielding (67f) (237 mg, 48 %) as a colorless oil.

\[^{1}H-NMR\ (300\ \text{MHz, CDCl}_{3})\ \delta\ (\text{ppm}):\ 6.64\ (s,\ 1H),\ 4.38\ (q,\ J = 7.1\ \text{Hz, 2H}),\ 1.38\ (t,\ J = 7.1\ \text{Hz, 3H}),\ 0.29\ (s,\ 9H).\]

\[^{13}C-NMR\ (75\ \text{MHz, CDCl}_{3})\ \delta\ (\text{ppm}):\ 165.3,\ 158.2,\ 143.0,\ 123.6,\ 123.1,\ 61.0,\ 14.3,\ -2.0.\]

\[\text{IR (ATR) } \tilde{\nu}\ (\text{cm}^{-1}):\ 2962,\ 1720,\ 1570,\ 1482,\ 1370,\ 1342,\ 1276,\ 1252,\ 1176,\ 1142,\ 1094,\ 1038,\ 932,\ 838,\ 758.\]

\[\text{MS (70 eV, EI) } m/z\ (%):\ 246\ (53)\ [M^{+}],\ 231\ (100),\ 203\ (33),\ 174\ (6),\ 103\ (28),\ 75\ (41).\]

HRMS (EI) for C\(_{10}H_{15}ClO_{3}Si\) (246.0479): 246.0454.

**Preparation of ethyl 3-cyano-5-(trimethylsilyl)furan-2-carboxylate (67g):**

![Diagram](image)

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Prepared according to TP8 from ethyl 5-(trimethylsilyl)furan-2-carboxylate (66b, 1.0 mmol, 212 mg) in 1 mL THF and tosyl cyanide (1.2 mmol, 217 mg) in 1 mL THF. Deprotonation time: 1 h at –30 °C. Reaction time with electrophile: 15 min at –30 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 1:1) yielding 67g (141 mg, 52 %) as a colorless solid.

M.p.: 100-102 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 6.84 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H), 0.32 (s, 9H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 167.3, 156.7, 152.4, 122.3, 112.3, 103.0, 62.2, 14.1, -2.1.

IR (ATR) ν (cm⁻¹): 3118, 2962, 2904, 2246, 1722, 1576, 1476, 1376, 1296, 1248, 1200, 1106, 1074, 1016, 932, 838.

MS (70 eV, EI) m/z (%): 237 (21) [M⁺], 222 (100), 194 (47), 43 (9).

HRMS (EI) for C₁₁H₁₅NO₃Si (237.0821): 237.0828.

Preparation of ethyl 3-cyano-5-(trimethylsilyl)thiophene-2-carboxylate (67h):

Prepared according to TP8 from ethyl 5-(trimethylsilyl)thiophene-2-carboxylate (65a, 1.0 mmol, 228 mg) in 1 mL THF and tosyl cyanide (1.2 mmol, 218 mg) in 1 mL THF. Deprotonation time: 1 h at –35 °C. Reaction time with electrophile: 30 min at –35 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 1:1) yielding 67h (174 mg, 69 %) as a colorless solid.

M.p.: 61-62 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.40 (s, 1H), 4.42 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H), 0.35 (s, 9H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 159.9, 150.0, 145.0, 137.3, 115.4, 114.1, 62.6, 14.4, -0.3.
**Experimental Section**

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)):** 3082, 2956, 2940, 2898, 2234, 1694, 1520, 1420, 1328, 1282, 1248, 1100, 1028, 952, 836, 758.

**MS (70 eV, EI) \textit{m/z} (%)**: 253 (13) [M\(^+\)], 238 (100), 210 (25), 97 (4), 83 (7).

**HRMS (EI) for C\(_{11}\)H\(_{15}\)NO\(_2\)SSi (253.0593)**: 253.0576.

**Preparation of ethyl 3-allyl-5-(trimethylsilyl)thiophene-2-carboxylate (67i):**

![Chemical structure](image)

Prepared according to TP8 from ethyl 5-(trimethylsilyl)thiophene-2-carboxylate (65a, 0.5 mmol, 114 mg) in 0.5 mL THF. Deprotonation time: 1 h at -35 °C. An allylation reaction was performed according to TP10 using allyl bromide (0.6 mmol, 73 mg) at -35 °C for 15 min. The crude residue was purified by flash column chromatography (pentane/CH\(_2\)Cl\(_2\) = 6:1) yielding 67i (72 mg, 54 %) as a colorless oil.

**\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm):** 7.04 (s, 1H), 6.02-5.95 (m, 1H), 5.09-5.04 (m, 2H), 4.32 (q, \( J = 7.2 \text{ Hz} \), 2H), 3.77 (d, \( J = 6.5 \text{ Hz} \), 2H), 1.36 (t, \( J = 7.2 \text{ Hz} \), 3H), 0.31 (s, 9H).

**\(^13\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \) (ppm):** 162.5, 148.5, 146.7, 137.0, 136.3, 131.5, 115.8, 60.7, 33.8, 14.4, -0.4.

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)):** 2958, 1706, 1638, 1532, 1426, 1248, 1210, 1172, 1078, 1012, 972, 912, 834, 756.

**MS (70 eV, EI) \textit{m/z} (%)**: 268 (27) [M\(^+\)], 251 (100), 225 (28), 207 (9), 179 (5), 149 (13), 73 (45).

**HRMS (EI) for C\(_{13}\)H\(_{20}\)O\(_2\)SSi (268.0953)**: 268.0981.

**Preparation of ethyl 3-benzoyl-5-bromofuran-2-carboxylate (67j):**
Prepared according to TP8 from ethyl 5-bromofuran-2-carboxylate (66c, 1.0 mmol, 219 mg) in 1 mL THF. Deprotonation time: 30 min at -40 °C. An acylation reaction was performed according to TP10 using benzoyl chloride (1.2 mmol, 169 mg) at -40 °C for 15 h. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 5:4) yielding 67j (242 mg, 75 %) as a colorless solid.

M.p.: 95-96 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.85 (d, J = 7.0 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 2H), 6.61 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 0.96 (t, J = 7.1 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 189.5, 156.7, 143.3, 136.7, 134.0, 132.8, 129.5, 128.6, 127.8, 114.4, 61.6, 13.5.

IR (ATR) ʋ (cm⁻¹): 3116, 3066, 2982, 2360, 1720, 1668, 1574, 1478, 1400, 1304, 1250, 1176, 1100, 934, 830, 716, 686.

MS (70 eV, EI) m/z (%): 324 (98) [M⁺, ⁸¹Br], 322 (100) [M⁺, ⁷⁹Br], 278 (25), 250 (45), 219 (37), 217 (36), 170 (18), 143 (15), 105 (46), 77 (36).

HRMS (EI) for C₁₄H₁₁BrO₄ (321.9841): 321.9834.

Preparation of ethyl 5-bromo-3-chlorofuran-2-carboxylate (67k):

Prepared according to TP8 from ethyl 5-bromofuran-2-carboxylate (66c, 5.0 mmol, 1.095 g) in 5 mL THF and benzenesulfonyl chloride (7.5 mmol, 1.325 g). Deprotonation time: 30 min at -78 °C. Reaction time with electrophile: 3 h at -78 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 8:1) yielding 67k (748 mg, 59 %) as a colorless solid.

M.p.: 98-100 °C.
Experimental Section

1H-NMR (300 MHz, CDCl3) δ (ppm): 6.48 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl3) δ (ppm): 156.8, 141.7, 127.2, 125.3, 116.1, 61.5, 14.3.

IR (ATR) ~ ν (cm⁻¹): 3108, 2984, 2360, 1698, 1564, 1478, 1466, 1376, 1354, 1290, 1170, 1098, 932, 834, 764.

MS (70 eV, EI) m/z (%): 256 (14) [M +, 37Cl 81Br], 254 (53) [M +, 37Cl 79Br, 35Cl 81Br], 252 (43) [M+, 35Cl 79Br], 226 (93), 209 (100), 182 (64), 153 (24), 129 (23), 72 (21).

HRMS (EI) for C7H6BrClO3 (251.9189): 251.9185.

Preparation of ethyl 5-bromo-3-cyanofuran-2-carboxylate (67l):

Prepared according to TP8 from ethyl 5-bromofuran-2-carboxylate (66c, 5.0 mmol, 1.095 g) in 5 mL THF and tosyl cyanide (5.5 mmol, 997 mg) in 6 mL THF. Deprotonation time: 30 min at –78 °C. Reaction time with electrophile: 30 min at –78 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH2Cl2 = 3:1) yielding 67l (765 mg, 63 %) as a colorless solid.

M.p.: 103-105 °C.

1H-NMR (300 MHz, CDCl3) δ (ppm): 6.69 (s, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl3) δ (ppm): 155.3, 150.2, 128.7, 115.3, 110.6, 105.2, 62.7, 14.1.

IR (ATR) ~ ν (cm⁻¹): 3116, 3066, 2982, 1720, 1668, 1596, 1574, 1478, 1400, 1304, 1250, 1176, 1100, 1016, 934, 830, 716.

MS (70 eV, EI) m/z (%): 245 (30), [M+, 81Br], 243 (34) [M+, 79Br], 217 (96), 215 (100), 200 (54), 198 (55), 173 (34), 171 (34), 144 (16), 142 (18), 108 (9), 63 (18).

HRMS (EI) for C8H6BrNO3 (242.9531): 242.9521.

Preparation of ethyl 5-bromo-3-[4-(ethoxycarbonyl)phenyl]-2-furoate (67m):
Prepared according to TP8 from ethyl 5-bromofuran-2-carboxylate (66c, 1.0 mmol, 219 mg) in 1 mL THF. Deprotonation time: 10 min at -78 °C. A cross-coupling reaction was performed according to TP9 using ethyl 4-iodobenzoate (1.1 mmol, 304 mg) and Pd(PPh3)4 (1 mol%, 12 mg) at 25 °C for 6 h. The crude residue was purified by flash column chromatography (pentane/Et2O = 8:1) yielding 67m (314 mg, 86 %) as a colorless solid.

**M.p.:** 71-72 °C.

**1H-NMR (300 MHz, CDCl3)** \(\delta\) (ppm): 8.06 (d, \(J = 8.4\) Hz, 2H), 7.60 (d, \(J = 8.4\) Hz, 2H), 6.57 (s, 1H), 4.39 (q, \(J = 7.1\) Hz, 2H), 4.30 (q, \(J = 7.1\) Hz, 2H), 1.39 (t, \(J = 7.1\) Hz, 3H), 1.28 (t, \(J = 7.1\) Hz, 3H).

**13C-NMR (75 MHz, CDCl3)** \(\delta\) (ppm): 166.1, 157.8, 142.2, 135.5, 135.3, 130.6, 129.3, 129.2, 127.0, 115.9, 61.3, 61.1, 14.3, 14.1.

**IR (ATR)** \(\tilde{\nu}\) (cm\(^{-1}\)): 3744, 3392, 3112, 2988, 2936, 2876, 2532, 2400, 2244, 2188, 1980, 1940, 1704, 1664, 1612, 1584, 1568, 1536, 1516, 1476, 1444, 1420, 1392, 1368, 1312, 1280, 1260, 1236, 1184, 1164, 1124, 1108, 1080, 1020, 980, 936, 876, 860, 828, 764, 704, 668.

**MS (70 eV, EI)** \(m/z\) (%): 368 (100), [M\(^+\), \(^{81}\)Br], 366 (99) [M\(^+\), \(^{79}\)Br], 233 (54), 295 (33).

**HRMS (EI)** for C\(_{16}\)H\(_{15}\)BrO\(_5\) (368.0082): 368.0062.

### Preparation of diethyl 5,5'-dibromo-3,3'-bifuran-2,2'-dicarboxylate (67n):

Prepared according to TP8 from ethyl 5-bromofuran-2-carboxylate (66c, 1.0 mmol, 219 mg) in 1 mL THF. Deprotonation time: 10 min at -78 °C. ZnCl\(_2\) (1.1 mmol, 1 M in THF, 1.1 mL) was added and the mixture stirred for 15 min. Chloranil (1.5 mmol, 369 mmol) in 7 mL THF
Experimental Section

was slowly added and the solution stirred for 2 h at -40 °C. The reaction mixture was quenched with sat. NH₄Cl solution and extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (CH₂Cl₂) furnished 67n (174 mg, 80 %) as a pale brown solid.

M.p.: 168-170 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 6.61 (s, 2H), 4.29 (q, J = 7.1 Hz, 4H), 1.30 (t, J = 7.1 Hz, 6H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 157.8, 142.8, 126.7, 125.6, 116.9, 61.6, 14.4.


MS (70 eV, EI) m/z (%): 438 (26) [M⁺, ⁸¹Br, ⁸¹Br], 436 (53) [M⁺, ⁷⁹Br, ⁸¹Br], 434 ([M⁺, ⁷⁹Br, ⁷⁹Br], 357 (83), 327 (100), 299 (30), 227 (27).

HRMS (EI) for C₁₄H₁₂Br₂O₆ (435.8980): 435.8980.

Preparation of ethyl 5-bromo-3-(phenylthio)thiophene-2-carboxylate (67o):

Prepared according to TP8 from ethyl 5-bromothiophene-2-carboxylate (65b, 2.9 mmol, 671 mg) in 3.0 mL THF and phenyl benzenesulfonothioate (3.2 mmol, 801 mg) in 3.5 mL THF. Deprotonation time: 30 min at –50 °C. Reaction time with electrophile: 1 h at –50 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 5:1) yielding 67o (674 mg, 68 %) as a colorless solid.

M.p.: 56-58 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.60-7.57 (m, 2H), 7.46-7.41 (m, 3H), 6.26 (s, 1H), 4.36 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 161.1, 145.6, 135.0, 131.8, 130.4, 129.8, 129.6, 122.6, 118.9, 61.4, 14.4.
Experimental Section

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)):** 2970, 2360, 2340, 1696, 1502, 1422, 1310, 1266, 1152, 1086, 1018, 986, 816, 744, 690.

**MS (70 eV, EI) m/z (%):** 344 (100) [M\(^+\), \(^{81}\)Br], 342 (93) [M\(^+\), \(^{79}\)Br], 299 (33), 197 (30), 272 (14), 270 (16), 223 (41), 199 (36).

**HRMS (EI)** for C\(_{13}\)H\(_{11}\)BrO\(_2\)S\(_2\) (341.9384): 341.9362.

**Preparation of ethyl 5-bromo-3-cyanothiophene-2-carboxylate (67p):**

![Chemical Structure]

Prepared according to TP8 from ethyl 5-bromothiophene-2-carboxylate (65b, 1.0 mmol, 235 mg) in 1 mL THF and tosyl cyanide (1.1 mmol, 199 mg) in 3 mL THF. Deprotonation time: 30 min at –50 °C. Reaction time with electrophile: 50 min at –50 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/Et\(_2\)O = 10:1) yielding 67p (130 mg, 50 %) as a colorless solid.

**M.p.:** 94-96 °C.

**\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm):** 7.30 (s, 1H), 4.42 (q, \( J = 7.1 \) Hz, 2H), 1.41 (t, \( J = 7.1 \) Hz, 3H).

**\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \) (ppm):** 158.6, 141.8, 133.3, 120.2, 114.5, 112.3, 62.8, 14.1.

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)):** 3852, 3788, 3584, 3376, 3128, 3096, 3036, 3008, 2980, 2936, 2904, 2868, 2760, 2728, 2700, 2592, 2528, 2384, 2360, 2288, 2236, 2168, 2148, 2044, 2024, 1956, 1792, 1692, 1552, 1524, 1468, 1412, 1368, 1348, 1292, 1180, 1152, 1120, 1100, 1028, 1000, 940, 880, 860, 820, 760, 692.

**MS (70 eV, EI) m/z (%):** 261 (52) [M\(^+\), \(^{81}\)Br], 259 (53) [M\(^+\), \(^{79}\)Br], 216 (100), 189 (41), 107 (55).

**HRMS (EI)** for C\(_8\)H\(_6\)BrNO\(_2\)S (258.9303): 258.9307.

**Preparation of diethyl 3-[(4-cyanophenyl)(hydroxy)methyl]-4-(methylthio)furan-2,5-dicarboxylate (69a):**
Prepared according to TP8 from diethyl 3-(methylthio)furan-2,5-dicarboxylate (76a, 1.0 mmol, 253 mg) in 4 mL THF and 4-cyanobenzaldehyde (1.5 mmol, 197 mg) in 3 mL THF. Deprotonation time: 45 min at -78 °C. Reaction time with electrophile: 3 h at -78 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (CH$_2$Cl$_2$) yielding 69a (262 mg, 67 %) as a pale yellow oil.

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.59 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 2H), 6.26 (d, $J = 11.9$ Hz, 1H), 5.50 (d, $J = 11.9$ Hz, 1H), 4.48-4.36 (m, 4H), 2.39 (s, 3H), 1.43 (t, $J = 7.3$ Hz, 3H), 1.38 (t, $J = 7.2$ Hz, 3H).

$^{13}$C-NMR (150 MHz, CDCl$_3$) $\delta$ (ppm): 160.1, 157.5, 147.9, 146.2, 140.7, 140.5, 132.5, 128.0, 126.8, 118.9, 111.7, 67.7, 63.1, 62.3, 19.6, 14.5, 14.3.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3416, 2984, 2932, 2908, 2872, 2228, 1780, 1712, 1688, 1608, 1580, 1520, 1504, 1468, 1444, 1396, 1380, 1368, 1284, 1236, 1180, 1128, 1028, 1016, 976, 904, 856, 828, 776, 696.

MS (70 eV, EI) m/z (%): 389 (98) [M$^+$], 360 (52), 341 (37), 313 (100), 297 (20), 131 (55).
HRMS (EI) for C$_{19}$H$_{19}$NO$_6$S (389.0933): 389.0934.

Preparation of diethyl 3-cyano-4-(4-cyanophenyl)furan-2,5-dicarboxylate (69b):

Diethyl 3-cyanofuran-2,5-dicarboxylate (67d, 1 mmol, 237 mg) was dissolved in 4 mL THF and ZnCl$_2$ (1.1 mmol, 1 M in THF, 1.1 mL) and cooled to -78 °C. TMPMgCL-LiCl (1.2 mmol, 1.1 M in THF, 1.1 mL) was added and the reaction mixture stirred for 20 min. Pd(PPh$_3$)$_4$ (1 mol%, 12 mg) and 4-iodobenzonitrile (1.2 mmol, 275 mg) were added and the mixture warmed to 25 °C. After stirring for 3 h, the reaction was quenched with sat. NH$_4$Cl.
solution and extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (CH₂Cl₂) furnished 69b (239 mg, 71%) as a pale brown solid.

**M.p.**: 156-158 °C.

**1H-NMR (300 MHz, CDCl₃) δ (ppm)**: 7.79 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 4.52 (q, J = 7.1 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃) δ (ppm)**: 156.8, 155.5, 149.6, 142.1, 133.1, 132.1, 130.5, 118.0, 113.8, 110.2, 105.3, 63.3, 62.6, 14.1, 14.0.

**IR (ATR) ~ (cm⁻¹):** 2988, 2232, 1720, 1612, 1592, 1552, 1504, 1472, 1452, 1388, 1368, 1324, 1240, 1216, 1180, 1108, 1080, 1012, 984, 916, 888, 856, 844, 808, 776, 736, 704, 672.

**MS (70 eV, EI) m/z (%):** 338 (100) [M⁺], 310 (34), 293 (24), 281 (34), 264 (33).

**HRMS (EI) for C₁₈H₁₄N₂O₅ (338.0903):** 338.0888.

**Preparation of ethyl 3-chloro-5-cyanofuran-2-carboxylate (71):**

![Diagram of ethyl 3-chloro-5-cyanofuran-2-carboxylate](image)

Ethyl 5-bromo-3-chlorofuran-2-carboxylate (67k, 3.0 mmol, 748 mg) in 5 mL THF was cooled to -50 °C, and iPrMgCl·LiCl (3.3 mmol, 1.36 M in THF, 2.4 mL) was added. The reaction mixture was stirred for 30 min and tosyl cyanide was added. The reaction mixture was warmed to 25 °C and after stirring for 3 h was quenched with sat. NH₄Cl solution and extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/CH₂Cl₂ = 1:1) furnished 71 (440 mg, 73%) as a colorless solid.

**M.p.**: 80-81 °C.

**1H-NMR (300 MHz, CDCl₃) δ (ppm)**: 7.12 (s, 1H), 4.42 (q, J = 7.0 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃) δ (ppm)**: 156.2, 142.9, 127.3, 124.0, 123.4, 109.5, 62.3, 14.1.

**IR (ATR) ~ (cm⁻¹):** 3148, 3132, 2986, 2238, 1718, 1547, 1516, 1374, 1280, 1236, 1190, 1114, 1052, 1012, 972, 856, 768.
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MS (70 eV, EI) m/z (%): 199 (25) [M⁺], 171 (82), 154 (100), 127 (20), 98 (15).

HRMS (EI) for C₈H₆ClNO₃ (199.0036): 199.0020.

Synthesis of ethyl 4-allyl-3-chloro-5-cyanofuran-2-carboxylate (72):

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Cl} \\
\text{Cl} & \quad \text{C} \\
\text{C} & \quad \text{O}
\end{align*}
\]

Prepared according to TP8 from ethyl 3-chloro-5-cyanofuran-2-carboxylate (71, 0.68 mmol, 136 mg) in 1.4 mL THF. An allylation reaction was performed according to TP10 using allyl bromide (1.0 mmol, 121 mg) at -78 °C for 15 min. The crude residue was purified by flash column chromatography (pentane/CH₂Cl₂ = 1:1) yielding 72 (120 mg, 74 %) as a colorless oil.

\[
\begin{align*}
^1\text{H-NMR (300 MHz, CDCl}_3) & \delta \text{ (ppm): 5.93-5.80 (m, 1H), 5.22-5.13 (m, 2H), 4.42} \\
& \quad \text{(q, } J = 7.1 \text{ Hz, 2H), 3.37-3.34 (m, 2H), 1.40 (t, } J = 7.1 \text{ Hz, 3H).}
\end{align*}
\]

\[
\begin{align*}
{^1}\text{C-NMR (75 MHz, CDCl}_3) & \delta \text{ (ppm): 156.4, 142.8, 136.1, 131.3, 125.6, 124.4, 119.0, 109.9,} \\
& \quad \text{62.4, 27.9, 14.4.}
\end{align*}
\]

IR (ATR) \tilde{\nu} (cm⁻¹): 2986, 2234, 1726, 1532, 1406, 1286, 1184, 1032, 992, 924, 848, 768.

MS (70 eV, EI) m/z (%): 239 (68) [M⁺], 211 (30), 194 (100), 167 (21), 136 (27), 102 (29).

HRMS (EI) for C₁₁H₁₀ClNO₃ (239.0349): 239.0357.

Preparation of ethyl 3-(hydroxy(phenyl)methyl)-1-tosylindole-2-carboxylate (75a):

\[
\begin{align*}
\text{HO} & \quad \text{Ph} \\
\text{N} & \quad \text{CO}_2\text{Et} \\
\text{Ts} & \quad \text{Et}
\end{align*}
\]

Prepared according to TP8 from ethyl 1-tosylindole-2-carboxylate (73, 0.5 mol, 172 mg) in 2.5 mL THF and benzaldehyde (0.6 mmol, 64 mg). Deprotonation time: 30 min at -45 °C.
Reaction time with electrophile: 30 min at -45 °C. The crude residue was purified by flash column chromatography (CH₂Cl₂) yielding **75a** (205 mg, 91 %) as a colorless solid.

**M.p.:** 51-52 °C.

**¹H-NMR (300 MHz, CDCl₃) δ (ppm):** 8.00 (d, J = 8.7, 1H), 7.75 (d, J = 8.4, 2H), 7.44-7.12 (m, 10H), 6.15 (d, J = 5.2 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 2.82 (d, J = 5.2, 1H), 2.32 (s, 3H) 1.37 (t, J = 7.0 Hz, 3H).

**¹³C-NMR (75 MHz, CDCl₃) δ (ppm):** 163.2, 145.1, 141.5, 136.9, 134.2, 129.9, 129.6, 128.7, 128.3, 127.9, 127.6, 127.2, 126.7, 126.1, 124.3, 121.9, 115.4, 68.9, 62.7, 21.6, 13.9.

**IR (ATR) ν (cm⁻¹):** 3526 (w, br), 2984, 1716, 1596, 1448, 1368, 1258, 1174, 1016, 748, 668.

**MS (70 eV, EI) m/z (%):** 449 (4) [M⁺], 294 (54), 248 (100), 220 (14), 204 (9), 165 (6), 105 (12), 91 (13), 77 (6).

**HRMS (EI) for C₂₅H₂₃NO₅S (449.1297):** 449.1281.

**Synthesis of ethyl 3-allyl-1-tosylindole-2-carboxylate (75b):**

![Chemical Structure]

Prepared according to **TP8** from ethyl 1-tosylindole-2-carboxylate (**73**, 0.5 mol, 172 mg) in 2.5 mL THF. Deprotonation time: 30 min at -45 °C. An allylation reaction was performed according to **TP10** using allyl bromide (0.6 mmol, 73 mg) at -45 °C for 30 min. The crude residue was purified by flash column chromatography (CH₂Cl₂/pentane = 5:4) yielding **75b** (182 mg, 95 %) as a colorless solid.

**M.p.:** 66-68 °C.

**¹H-NMR (300 MHz, CDCl₃) δ (ppm):** 8.02 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 6.6 Hz, 2H), 7.47 (d, J = 7.9 Hz, 1H), 7.37 (t, J = 5.9 Hz, 1H), 7.23 (t, J = 7.0 Hz, 1H), 7.17 (d, J = 6.8 Hz, 2H), 5.93-5.80 (m, 1H), 5.03-4.93 (m, 2H), 4.45 (q, J = 7.1 Hz, 2H), 3.51 (td, J = 6.2 Hz, J = 1.7 Hz, 2H), 2.31 (s, 3H), 1.41 (t, J = 7.1 Hz, 3 H).

**¹³C-NMR (75 MHz, CDCl₃) δ (ppm):** 162.4, 144.8, 137.1, 134.6, 134.5, 129.8, 129.4, 128.8, 127.2, 126.7, 126.5, 124.0, 120.7, 116.3, 115.6, 62.1, 28.7, 21.6, 14.1.
IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2978, 1712, 1640, 1598, 1440, 1366, 1308, 1260, 1180, 1146, 1104, 1088, 1020, 810, 750, 666.

MS (70 eV, EI) $m/z$ (%): 383 (33) [M$^+$], 338 (8), 228 (100), 200 (16), 183 (27), 154 (77), 128 (28), 91 (34).

HRMS (EI) for C$_{21}$H$_{21}$NO$_4$S (383.1191): 383.1186.

Preparation of 1-\textit{tert}-butyl 2,5-diethyl 3-(4-chlorophenyl)pyrrole-1,2,5-tricarboxylate (78):

Prepared according to TP8 from 1-\textit{tert}-butyl 2,5-diethylpyrrole-1,2,5-tricarboxylate (76, 1.0 mmol, 311 mg) in 1 mL THF and TMP$_2$Mg·2 LiCl (1.1 mmol, 0.58 M in THF, 1.9 mL). Deprotonation time: 1.5 h at -30 °C. A cross-coupling reaction was performed according to TP9 using 4-iodochlorobenzene (1.5 mmol, 358 mg) and Pd(PPh$_3$)$_4$ (1 mol%, 12 mg) at 25 °C for 1.5 h. The crude residue was purified by flash column chromatography (CH$_2$Cl$_2$) yielding 78 (339 mg, 95%) as a colorless solid.

M.p.: 80-81 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 7.35-7.31 (m, 4H), 6.82 (s, 1H), 4.34 (q, $J$ = 7.1 Hz, 2H), 4.21 (q, $J$ = 7.1 Hz, 2H), 1.65 (s, 9H), 1.35 (t, $J$ = 7.1 Hz, 3H), 1.13 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm): 160.1, 159.5, 148.5, 133.5, 132.6, 130.9, 129.9, 127.9, 125.9, 123.2, 117.3, 86.3, 61.2, 61.2, 27.4, 14.3, 13.9.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2984, 2944, 2900, 1780, 1724, 1704, 1600, 1572, 1548, 1496, 1472, 1440, 1384, 1372, 1344, 1296, 1264, 1228, 1152, 1124, 1084, 1032, 1012, 984, 928, 896, 824, 784, 772, 756, 732, 680.

MS (70 eV, EI) $m/z$ (%): 421 (4) [M$^+$], 321 (100), 274 (14), 202 (13).

HRMS (EI) for C$_{21}$H$_{24}$ClNO$_6$ (421.1292): 421.1270.
3.2. Regio- and Chemoselective Synthesis of Fully Substituted Thiophenes

3.2.1. Typical Procedure for Dechlorination Reactions (TP11)

A round bottom flask equipped with a stirring bar and a reflux condenser was charged with the dichlorothiophene in EtOH. Pd/C and NH₄CO₂ were added and the reaction mixture was heated by using a Discover BenchMate® system (100 W, 70 °C) for 1 h. The mixture was allowed to cool to 25 °C, another portion of Pd/C was added and the mixture was again heated for 1 h in the microwave (100 W, 70 °C). This procedure was repeated for the indicated time. After the last reaction cycle the mixture was allowed to cool to 25 °C and filtered through Celite®. The crude residue was purified by flash column chromatography on silica gel if necessary.

3.2.2. Preparation of Title Compounds

Preparation of 2,5-dichloro-3-(methylthio)thiophene (81a):

Prepared according to TP8 from 79 (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. PhSO₂SMe (4.70 g, 25.0 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane) afforded 81a (3.66 g, 92 %) as a colorless oil.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 6.75 (s, 1H), 2.42 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 131.3, 127.2, 126.5, 124.0, 17.7.

IR (ATR) ν (cm⁻¹): 3090, 2921, 1510, 1429, 1411, 1308, 1151, 1032, 1014, 970, 849, 806, 695, 686.

MS (70 eV, EI) m/z (%): 198 (100) [M⁺], 183 (74), 163 (21), 139 (24).

HRMS (EI) for C₅H₄Cl₂S₂ (197.9131): 197.9124.
Preparation of ethyl 2,5-dichlorothiophene-3-carboxylate (81b): 

Prepared according to TP8 from 79 (3.06 g, 20.0 mmol) and TMPMgCl-LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (2.97 g, 30.0 mmol) was added at 0 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography on silica gel (pentane/CH₂Cl₂ = 6:1) afforded 81b (3.41 g, 76 %) as a colorless oil.

1H-NMR (600 MHz, CDCl₃) δ (ppm): 7.18 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 4.0 Hz, 3H).
13C-NMR (150 MHz, CDCl₃) δ (ppm): 160.8, 134.2, 128.6, 127.3, 126.2, 61.2, 14.2.
IR (ATR) ν (cm⁻¹): 3108, 2984, 1728, 1712, 1536, 1440, 1376, 1344, 1220, 1148, 1048, 1020, 932, 840, 768, 684.
MS (70 eV, EI) m/z (%): 224 (67) [M⁺], 196 (40), 181 (100), 107 (13).
HRMS (EI) for C₇H₆Cl₂O₂S (223.9466): 223.9474.

Preparation of tert-butyl 2,5-dichlorothiophene-3-carboxylate (81e):

Prepared according to TP8 from 79 (3.06 g, 20.0 mmol) and TMPMgCl-LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Boc₂O (6.55 g, 30 mmol) was added at -20 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded 81e (4.14 g, 82 %) as a colorless oil.

1H-NMR (300 MHz, CDCl₃) δ (ppm): 7.11 (s, 1H), 1.55 (s, 9H).
Experimental Section

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 159.9, 133.3, 130.0, 127.5, 125.7, 82.3, 28.2.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2978, 2931, 1708, 1534, 1475, 1456, 1439, 1393, 1366, 1346, 1241, 1163, 1145, 1046, 1035, 1002, 935, 919, 846, 790, 770, 744, 733, 685.

MS (70 eV, EI) $m/z$ (%): 252 (17) [M$^+$], 196 (100), 179 (59), 107 (8).

HRMS (EI) for C$_9$H$_{10}$Cl$_2$O$_2$S (251.9779): 251.9774.

Preparation of (2,5-dichloro-3-thienyl)(phenyl)methanone (81f):

Prepared according to TP8 from 79 (3.06 g, 20.0 mmol) and TMPMgCl-LiCl (19.6 mL, 1.15 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. An acylation reaction was performed according to TP10 using benzoyl chloride (3.51 g, 25.0 mmol) at -30 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH$_2$Cl$_2$ = 4:1) afforded 81f (4.01 g, 78 %) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.83-7.80 (m, 2H), 7.63-7.57 (m, 1H), 7.51-7.45 (m, 2H), 6.97 (s, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 188.7, 136.9, 136.5, 133.5, 130.8, 129.7, 128.6, 127.4, 127.0.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 4062, 4058, 4052, 3309, 3191, 3093, 3059, 3033, 2981, 2932, 2842, 1714, 1659, 1596, 1578, 1524, 1488, 1447, 1429, 1420, 1354, 1335, 1315, 1306, 1275, 1237, 1177, 1168, 1103, 1075, 1057, 1049, 1026, 1001, 989, 973, 932, 838, 821, 804, 789, 715, 692, 672, 661.

MS (70 eV, EI) $m/z$ (%): 256 (24) [M$^+$], 179 (32), 105 (100).

HRMS (EI) for C$_{11}$H$_6$Cl$_2$OS (255.9516): 255.9515.

Preparation of 1-(2,5-dichloro-3-thienyl)-2,2-dimethylpropan-1-one (81g):

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Prepared according to TP8 from 79 (3.06 g, 20.0 mmol) and TMPMgCl-LiCl (19.6 mL, 1.15 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. An acylation reaction was performed according to TP10 using pivaloyl chloride (3.02 g, 25.0 mmol) at -20 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded 81g (3.54 g, 75 %) as a pale yellow oil.

\(^1\text{H-NMR (300 MHz, CDCl}_3\) \(\delta\) (ppm): 6.85 (s, 1H), 1.24 (s, 9H).

\(^{13}\text{C-NMR (75 MHz, CDCl}_3\) \(\delta\) (ppm): 204.2, 137.3, 127.0, 126.9, 124.7, 45.0, 26.6.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2968, 2903, 2870, 1725, 1687, 1602, 1528, 1476, 1461, 1420, 1394, 1365, 1330, 1278, 1259, 1241, 1225, 1200, 1175, 1119, 1071, 1031, 997, 937, 917, 909, 905, 901, 894, 883, 869, 843, 824, 783, 753, 733, 728, 725, 718, 710, 700, 690, 667, 657.

MS (70 eV, EI) \(m/z\) (%): 236 (26) [M\(^+\)], 179 (100), 57 (19).

HRMS (EI) for C\(_9\)H\(_{10}\)Cl\(_2\)OS (235.9829): 235.9819.

Preparation of 2,5-dichlorothiophene-3-carbonitrile (81h):

\[\text{Prepared according to TP8 from 79 (3.06 g, 20.0 mmol) and TMPMgCl-LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. TsCN (3.81 g, 21.0 mmol) was added at -20 °C and the reaction mixture stirred for 18 h. The reaction mixture was quenched with half concentrated aqueous NH\(_4\)Cl solution, extracted three times with Et\(_2\)O, dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH\(_2\)Cl\(_2\) = 4:1) afforded 81h (2.60 g, 73 %) as a colorless solid.}

M.p.: 51-53 °C.

\(^1\text{H-NMR (300 MHz, CDCl}_3\) \(\delta\) (ppm): 6.95 (s, 1H).

\(^{13}\text{C-NMR (75 MHz, CDCl}_3\) \(\delta\) (ppm): 137.9, 129.0, 126.2, 111.9, 110.3.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 3098, 2231, 1671, 1525, 1427, 1344, 1174, 1053, 1019, 923, 836, 828, 686.

MS (70 eV, EI) \(m/z\) (%): 177 (100) [M\(^+\)], 142 (8), 98 (13), 79 (12).

HRMS (EI) for C\(_5\)H\(_2\)Cl\(_2\)NS (176.9207): 176.9211.
Preparation of 2,5-dichloro-4-(methylthio)thiophene-3-carbaldehyde (83a):

Prepared according to TP8 from 81a (1.99 g, 10.0 mmol) and TMPMgCl·LiCl (10.3 mL, 1.17 M in THF, 12.0 mmol). Deprotonation time: 30 min at -10 °C. DMF (1.10 g, 15.0 mmol) was added at -10 °C and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded 83a (2.15 g, 95 %) as a yellow oil.

\(^1\)H-NMR (300 MHz, CDCl₃) \(\delta\) (ppm): 10.09 (s, 1H), 2.38 (s, 3H).

\(^13\)C-NMR (75 MHz, CDCl₃) \(\delta\) (ppm): 184.2, 137.6, 133.8, 131.4, 131.2, 19.2.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)):
\begin{align*}
3970, 3343, 2933, 2881, 2779, 2588, 2093, 1699, 1677, 1645, 1489, 1415, 1400, 1313, 1290, 1095, 970, 839, 713.
\end{align*}

MS (70 eV, EI) \(m/z\) (%): 226 (100) [M⁺], 183 (25), 163 (15), 103 (26).

HRMS (EI) for C₆H₄Cl₂OS₂ (225.9081): 225.9067.

Preparation of ethyl 2,5-dichloro-4-[4-(ethoxycarbonyl)phenyl]thiophene-3-carboxylate (83b):

Prepared according to TP8 from 81b (675 mg, 3.0 mmol) and TMPMgCl·LiCl (3.4 mL, 1.15 M in THF, 3.9 mmol). Deprotonation time: 30 min at -30 °C. A cross-coupling reaction was performed according to TP9 using ethyl 4-iodobenzoate (1.24 g, 4.5 mmol) and Pd(PPh₃)₄ (36 mg, 1 mol %) at -30 °C during 16 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 1:1) afforded 83b (1.06 g, 95 %) as a pale yellow oil.
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\[ ^1H\text{-NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta \ (ppm): \ 8.08 \ (d, \ J = 8.6 \text{ Hz, 2H}), \ 7.34 \ (d, \ J = 8.6 \text{ Hz, 2H}), \ 4.39 \ (q, \ J = 7.0 \text{ Hz, 2H}), \ 4.09 \ (q, \ J = 7.4 \text{ Hz, 2H}), \ 1.40 \ (t, \ J = 7.0 \text{ Hz, 3H}), \ 1.00 \ (t, \ J = 7.4 \text{ Hz, 3H}). \]

\[ ^13C\text{-NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ (ppm): \ 166.2, \ 161.5, \ 138.0, \ 137.8, \ 131.6, \ 130.2, \ 130.1, \ 129.4, \ 129.4, \ 124.1, \ 61.4, \ 61.1, \ 14.3, \ 13.7. \]

\[ \text{IR (ATR) } \tilde{\nu} \ (\text{cm}^{-1}): \ 2979, \ 2935, \ 2904, \ 1712, \ 1610, \ 1577, \ 1571, \ 1540, \ 1505, \ 1443, \ 1406, \ 1389, \ 1366, \ 1268, \ 1243, \ 1174, \ 1154, \ 1100, \ 1052, \ 1016, \ 935, \ 864, \ 834, \ 772, \ 741, \ 710. \]

\[ \text{MS (70 eV, EI) } m/z \ (%): \ 372 (93) [M^+] \text{,} \ 327 (100), \ 299 (28), \ 255 (49). \]

\[ \text{HRMS (EI) for C}_{16}\text{H}_{15}\text{Cl}_{2}\text{O}_{4}\text{S} [M^+ + H^+] (373.0063): 373.0057. \]

**Preparation of ethyl 2,5-dichloro-4-(4-chlorobenzoyl)thiophene-3-carboxylate (83c):**

![Chemical Structure](image)

Prepared according to TP8 from 81b (225 mg, 1.0 mmol) and TMPMgCl·LiCl (1.0 mL, 1.15 M in THF, 1.2 mmol). Deprotonation time: 30 min at -30 °C. (4-Chlorophenyl)(oxo)acetonitrile (248 mg, 1.5 mmol) and Fe(acac)\textsubscript{3} (18 mg, 5 mol %) were added at -30 °C and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH\textsubscript{4}Cl solution, extracted three times with Et\textsubscript{2}O, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. Flash column chromatographical purification on silica gel (pentane/CH\textsubscript{2}Cl\textsubscript{2} = 3:2) afforded 83c (276 mg, 76 %) as a colorless solid.

**M.p.:** 67-69 °C.

\[ ^1H\text{-NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta \ (ppm): \ 7.76 \ (d, \ J = 8.8 \text{ Hz, 2H}), \ 7.44 \ (d, \ J = 8.8 \text{ Hz, 2H}), \ 4.07 \ (q, \ J = 7.28 \text{ Hz, 2H}), \ 1.03 \ (t, \ J = 7.28 \text{ Hz, 3H}). \]

\[ ^13C\text{-NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ (ppm): \ 188.3, \ 159.9, \ 140.5, \ 140.5, \ 137.9, \ 134.7, \ 130.6, \ 129.2, \ 128.4, \ 125.4, \ 61.7, \ 13.5. \]

\[ \text{IR (ATR) } \tilde{\nu} \ (\text{cm}^{-1}): \ 3088, \ 3057, \ 2989, \ 1706, \ 1698, \ 1676, \ 1585, \ 1571, \ 1475, \ 1455, \ 1445, \ 1378, \ 1270, \ 1241, \ 1221, \ 1177, \ 1097, \ 1088, \ 1012, \ 980, \ 930, \ 868, \ 848, \ 822, \ 815, \ 782, \ 774, \ 750, \ 719. \]
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MS (70 eV, EI) m/z (%): 362 (64) [M⁺], 317 (27), 223 (34), 141 (32), 139 (100).
HRMS (EI) for C_{14}H_{9}Cl_{3}O_{3}S 361.9338: 361.9322.

Preparation of ethyl 4-allyl-2,5-dichlorothiophene-3-carboxylate (83d):

![Chemical structure](image)

Prepared according to TP8 from 81b (712 mg, 3.2 mmol) and TMPMgCl·LiCl (3.2 mL, 1.17 M in THF, 3.8 mmol). Deprotonation time: 30 min at -30 °C. An allylation reaction was performed according to TP10 using allyl bromide (581 mg, 4.8 mmol) at -30 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded 83d (724 mg, 85 %) as a colorless oil.

M.p.: 51-53 °C.

^1^H-NMR (300 MHz, CDCl₃) δ (ppm): 5.89-5.76 (m, 1H), 5.03-4.94 (m, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.53 (td, J = 1.7 Hz, J = 5.9 Hz, 2 H), 1.36 (t, J = 7.2 Hz, 3H).

^1^3^C-NMR (75 MHz, CDCl₃) δ (ppm): 161.8, 136.6, 134.4, 131.9, 129.0, 123.2, 116.0, 61.3, 31.6, 14.1.

IR (ATR) ν (cm⁻¹): 3080, 2980, 1714, 1639, 1536, 1439, 1377, 1249, 1237, 1202, 1097, 1014, 991, 968, 910, 858, 784, 774, 742, 709, 674, 667, 658.

MS (70 eV, EI) m/z (%): 264 (100) [M⁺], 219 (51), 183 (58), 157 (20)
HRMS (EI) for C_{10}H_{10}Cl_{2}O_{2}S (263.9779): 263.9801.

Preparation of di-tert-butyl 2,5-dichlorothiophene-3,4-dicarboxylate (83e):

![Chemical structure](image)

Prepared according to TP8 from 81e (3.72 g, 14.7 mmol) and TMPMgCl·LiCl (12.1 mL, 1.32 M in THF, 16.0 mmol). Deprotonation time: 30 min at -20 °C. Boc₂O (4.80 g, 22.0 mmol) was added at -20 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with
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Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded **83e** (4.09 g, 79 %) as a colorless solid.

**M.p.:** 82-84 °C.

**¹H-NMR (300 MHz, CDCl₃) δ (ppm):** 1.54 (s, 18H).

**¹³C-NMR (75 MHz, CDCl₃) δ (ppm):** 160.1, 132.0, 128.9, 83.1, 28.0.

**IR (ATR) ν ~ (cm⁻¹):** 2978, 2934, 1728, 1707, 1669, 1536, 1472, 1455, 1391, 1385, 1365, 1286, 1257, 1230, 1153, 1088, 1038, 1028, 1015, 948, 928, 910, 845, 820, 789, 782, 773, 732, 714, 691, 687, 670, 662.

**MS (70 eV, EI) m/z (%):** 352 (6) [M⁺], 240 (100), 223 (41), 196 (22).

**HRMS (EI) for C₁₄H₁₈Cl₂O₄S (352.0303):** 352.0294.

**Preparation of 4-(4-benzoyl-2,5-dichloro-3-thienyl)benzonitrile (83f):**

![Chemical Structure](image)

Prepared according to **TP8** from **81f** (452 mg, 1.8 mmol) and TMPMgCl-LiCl (1.7 mL, 1.17 M in THF, 2.0 mmol). Deprotonation time: 45 min at -78 °C. A cross-coupling reaction was performed according to **TP9** using 4-iodo benzonitrile (618 mg, 2.7 mmol), Pd(dba)₂ (22 mg, 2 mol %) and P(o-furyl)₃ (18 mg, 4 mol %) at -78 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 13:7) afforded **83f** (543 mg, 84 %) as a colorless oil.

**¹H-NMR (300 MHz, CDCl₃) δ (ppm):** 7.77-7.74 (m, 2H), 7.59-7.53 (m, 3H), 7.44-7.32 (m, 4H).

**¹³C-NMR (75 MHz, CDCl₃) δ (ppm):** 190.1, 137.7, 136.7, 136.7, 136.2, 134.3, 132.1, 130.1, 129.7, 128.8, 127.4, 125.1, 118.3, 112.2.

**IR (ATR) ν ~ (cm⁻¹):** 3058, 2917, 2849, 2227, 1655, 1594, 1502, 1449, 1442, 1351, 1299, 1274, 1261, 1169, 1059, 1023, 973, 937, 867, 846, 838, 824, 794, 754, 726, 695, 683, 654.

**MS (70 eV, EI) m/z (%):** 357 (68) [M⁺], 280 (30), 217 (14), 105 (76), 77 (34), 44 (100).

**HRMS (EI) for C₁₈H₁₈Cl₂NOS (356.9782):** 356.9776.
Preparation of 1-[2,5-dichloro-4-(4-chlorophenyl)-3-thienyl]-2,2-dimethylpropan-1-one (83g):

![Structural formula of 83g]

Prepared according to TP8 from 81g (2.92 g, 12.3 mmol) and TMPMgCl·LiCl (12.1 mL, 1.17 M in THF, 14.2 mmol). Deprotonation time: 30 min at -50 °C. A cross-coupling reaction was performed according to TP9 using 4-chloroiodobenzene (4.29 g, 18.0 mmol) and Pd(PPh3)4 (142 mg, 1 mol %) at -50 °C during 8 h. Flash column chromatographical purification on silica gel (pentane/CH2Cl2 = 7:1) afforded 83g (3.28 g, 77 %) as a colorless solid.

M.p.: 77-78 °C.

1H-NMR (600 MHz, CDCl3) δ (ppm): 7.36 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 0.89 (s, 9H).

13C-NMR (75 MHz, CDCl3) δ (ppm): 209.1, 140.2, 135.3, 134.8, 134.8, 131.1, 128.9, 124.0, 121.6, 45.3, 26.7.

IR (ATR) ν (cm⁻¹): 2973, 2930, 2902, 2867, 1685, 1595, 1491, 1475, 1433, 1363, 1341, 1266, 1204, 1187, 1092, 1076, 1034, 1013, 999, 870, 847, 825, 819, 798, 758, 724, 704, 694.

MS (70 eV, EI) m/z (%): 346 (13) [M+], 291 (93), 262 (100), 226 (21), 183 (90), 108 (33).

HRMS (EI) for C15H13Cl3OS (345.9753): 345.9767.

Preparation of 2,5-dichloro-4-formylthiophene-3-carbonitrile (83h):

![Structural formula of 83h]

Prepared according to TP8 from 81h (196 mg, 1.1 mmol) and TMPMgCl·LiCl (1.0 mL, 1.20 M in THF, 1.2 mmol). Deprotonation time: 15 min at -30 °C. DMF (110 mg, 1.5 mmol)
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was added at -30 °C the reaction mixture warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (CH₂Cl₂) afforded 83h (195 mg, 86 %) as a colorless solid.

M.p.: 128-130 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 9.97 (s, 1H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 179.8, 139.8, 139.6, 134.4, 110.4, 109.4.

IR (ATR) ν (cm⁻¹): 2857, 2814, 2230, 1678, 1651, 1446, 1392, 1384, 1378, 1200, 1169, 964, 959, 889, 872, 805.

MS (70 eV, EI) m/z (%): 205 (16) [M⁺], 177 (10), 132 (6), 57 (100).

HRMS (EI) for C₆HCl₂NOS (204.9156): 204.9138.

Preparation of diethyl 2,5-dichlorothiophene-3,4-dicarboxylate (83i):

Prepared according to TP8 from 79 (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (2.38 g, 24.0 mmol) was added at 0 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. The crude residue was solved in THF and deprotonated according to TP8 using TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at -30 °C. Ethyl cyanoformate (2.38 g, 24.0 mmol) was added at -30 °C, the reaction mixture warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded 83i (5.17 g, 87 %) as a colorless oil.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 4.33 (q, J = 7.0 Hz, 4H), 1.34 (t, J = 7.0 Hz, 6H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 161.1, 130.4, 130.2, 62.0, 14.0.

IR (ATR) ν (cm⁻¹): 2982, 2937, 2904, 1726, 1535, 1451, 1378, 1367, 1354, 1298, 1260, 1201, 1170, 1113, 1085, 1014, 944, 910, 862, 794, 779, 751, 727, 667.
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**MS (70 eV, EI) m/z (%):** 296 (24) [M⁺], 251 (23), 223 (100).

**HRMS (EI) for C₁₀H₁₀Cl₂O₄S (295.9677):** 295.9675.

**Preparation of diethyl ethyl 2,5-dichloro-4-(methylthio)thiophene-3-carboxylate (83j):**

![Chemical structure](image)

Prepared according to **TP8** from 79 (3.06 g, 20.0 mmol) and TMPMgCl-LiCl (20.0 mL, 1.11 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (2.38 g, 24.0 mmol) was added at 0 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. The crude residue was solved in THF and deprotonated according to **TP8** using TMPMgCl-LiCl (20.0 mL, 1.11 M in THF, 22.0 mmol). Deprotonation time: 30 min at -30 °C. PhSO₂SMe (4.14 g, 22.0 mmol) was added at -30 °C, the reaction mixture warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 7:1) afforded 83j (3.95 g, 73 %) as a colorless oil.

**¹H-NMR (300 MHz, CDCl₃) δ (ppm):** 4.39 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.39 (t, J = 4.2 Hz, 3H).

**¹³C-NMR (75 MHz, CDCl₃) δ (ppm):** 161.9, 133.2, 131.2, 130.3, 129.2, 61.9, 19.1, 14.1.

**IR (ATR) ν (cm⁻¹):** 2981, 2925, 1721, 1592, 1509, 1474, 1464, 1442, 1419, 1389, 1367, 1331, 1202, 1113, 1094, 1073, 1014, 973, 959, 937, 931, 863, 838, 787, 732, 693, 674.

**MS (70 eV, EI) m/z (%):** 270 (100) [M⁺], 225 (76), 209 (30), 196 (30), 115 (22).

**HRMS (EI) for C₈H₈Cl₂O₂S₂ (269.9343):** 269.9330.

**Preparation of ethyl 2,5-dichloro-4-(2,2-dimethylpropanoyl)thiophene-3-carboxylate (83k):**

![Chemical structure](image)
Experimental Section

Prepared according to TP8 from 79 (3.06 g, 20.0 mmol) and TMPMgCl-LiCl (18.3 mL, 1.20 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (2.38 g, 24.0 mmol) was added at 0 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. The crude residue was solved in THF and deprotonated according to TP8 using TMPMgCl-LiCl (18.3 mL, 1.20 M in THF, 22.0 mmol). Deprotonation time: 30 min at -30 °C. An acylation reaction was performed according to TP10 using pivaloyl chloride (3.62 g, 30.0 mmol) at -30 °C during 18 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded 83k (4.41 g, 67 %) as a colorless solid.

M.p.: 44-46 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 4.30 (q, J = 4.2 Hz, 2H), 1.33 (t, J = 4.2 Hz, 3H), 1.23 (s, 9H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 206.7, 160.6, 140.1, 134.4, 127.9, 121.6, 61.9, 45.5, 27.2, 14.1.

IR (ATR) ν (cm⁻¹): 2986, 2970, 2940, 2871, 1706, 1696, 1666, 1478, 1462, 1456, 1439, 1391, 1379, 1363, 1350, 1267, 1239, 1193, 1162, 1113, 1040, 1018, 998, 932, 874, 847, 806, 789, 755, 751, 704, 691, 687, 668, 657.

MS (70 eV, EI) m/z (%): 308 (2) [M⁺], 251 (78), 223 (94), 57 (100).

HRMS (EI) for C₁₂H₁₄Cl₂O₃S (308.0041): 308.0027.

Preparation of 2,5-dichloro-3-(4-methoxyphenyl)-4-(methylthio)thiophene (83l):

Prepared according to TP8 from 79 (3.12 g, 20.4 mmol) and TMPMgCl-LiCl (19.7 mL, 1.14 M in THF, 22.5 mmol). Deprotonation time: 30 min at 25 °C. PhSO₂SMe (4.70 g, 25.0 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over
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Na₂SO₄ and concentrated in vacuo. The crude residue was solved in THF and deprotonated according to TP8 using TMPMgCl·LiCl (19.7 mL, 1.14 M in THF, 22.5 mmol). A cross-coupling reaction was performed according to TP9 using 4-iodo anisole (5.85 g, 25.0 mmol), Pd(dba)₂ (235 mg, 2 mol%) and P(2-furyl)₃ (189 mg, 4 mol%) at -30 °C during 2 h. Flash column chromatographical purification on silica gel (pentane) afforded 83l (5.23 g, 84 %) as a pale yellow solid.
M.p.: 86-87 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.32 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.03 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 159.5, 140.4, 131.1, 131.0, 129.0, 125.5, 122.5, 113.6, 55.2, 18.1.

IR (ATR) ν (cm⁻¹): 3017, 2962, 2919, 2837, 1607, 1571, 1534, 1495, 1460, 1450, 1441, 1431, 1422, 1309, 1300, 1283, 1248, 1174, 1165, 1108, 1041, 1024, 1009, 971, 886, 835, 807, 762, 665.

MS (70 eV, EI) m/z (%): 304 (100) [M⁺], 254 (31), 239 (12), 211 (11).

HRMS (EI) for C₁₂H₁₀Cl₂OS₂ (303.9550): 303.9556.

Preparation of 1-[4-(4-chlorophenyl)-3-thienyl]-2,2-dimethylpropan-1-one (84a):

Prepared according to TP11 from 83g (836 mg, 2.4 mmol) in 20 mL EtOH, NH₄CO₂ (630 mg, 10 mmol), and Pd/C (128 mg, 5 mol %). Total reaction time: 5 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 17:3) afforded 84a (507 mg, 76 %) as a colorless solid.
M.p.: 83-85 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.41 (d, J = 3.0 Hz, 1H), 7.33-7.29 (m, 2H), 7.26-7.23 (m, 2H), 7.21 (d, J = 3.0 Hz, 1H), 1.10 (s, 9H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 209.4, 141.0, 140.5, 134.8, 133.5, 129.7, 128.6, 125.0, 123.5, 45.0, 27.1.
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IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3116, 3089, 2968, 2953, 2927, 2864, 1670, 1523, 1485, 1471, 1459, 1431, 1395, 1360, 1269, 1224, 1176, 1155, 1087, 1014, 998, 907, 865, 838, 822, 807, 801, 771, 754, 723, 694.

MS (70 eV, EI) $m/z$ (%): 278 (37) [M$^+$], 223 (100).

HRMS (EI) for C$_{15}$H$_{15}$ClO$_5$: 278.0525.

Preparation of ethyl 4-(methylthio)thiophene-3-carboxylate (84b):

Prepared according to TP11 from 83j (3.58 g, 13.0 mmol) in 50 mL EtOH, NH$_4$CO$_2$ (2.46 g, 39.0 mmol) and Pd/C (415 mg, 3 mol %). Total reaction time: 5 h. 84b (2.42 g, 92 %) was afforded as a colorless solid without further purification.

M.p.: 40-41 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 8.17 (d, $J = 3.3$ Hz, 1H), 6.68 (d, $J = 3.3$ Hz, 1H), 4.33 (q, $J = 7.0$ Hz, 2H), 2.46 (s, 3H), 1.36 (t, $J = 7.0$, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 162.2, 137.7, 134.6, 130.7, 115.2, 60.8, 16.2, 14.3.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3108, 2987, 2969, 2917, 1694, 1656, 1498, 1458, 1440, 1432, 1412, 1375, 1354, 1246, 1172, 1161, 1128, 1118, 1032, 998, 950, 861, 821, 772, 722.

MS (70 eV, EI) $m/z$ (%): 202 (9) [M$^+$], 157 (10), 45 (100).

HRMS (EI) for C$_8$H$_{10}$O$_2$S$_2$: 202.0122: 202.0105.

Preparation of ethyl 4-(2,2-dimethylpropanoyl)thiophene-3-carboxylate (84c):

Prepared according to TP11 from 83k (3.47 g, 11.0 mmol) in 50 mL EtOH, NH$_4$CO$_2$ (3.15 g, 50.0 mmol) and Pd/C (351 mg, 3 mol %). Total reaction time: 5 h. 84c (2.43 g, 95 %) was afforded as a colorless oil without further purification.
Experimental Section

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 8.06 (d, $J = 3.2$ Hz, 1H), 7.13 (d, $J = 3.2$ Hz, 1H), 4.27 (q, $J = 7.0$ Hz, 2H), 1.32 (t, $J = 7.0$ Hz, 3H), 1.23 (s, 9H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 209.2, 161.9, 142.0, 133.2, 132.6, 122.5, 61.1, 45.0, 26.6, 14.2.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3106, 2973, 2907, 2904, 1711, 1692, 1512, 1479, 1462, 1439, 1390, 1381, 1363, 1298, 1242, 1196, 1166, 1159, 1079, 1030, 937, 928, 880, 867, 829, 805, 778, 748, 729, 693.

MS (70 eV, EI) m/z (%): 240 (2) [M$^+$], 183 (65), 155 (100).

HRMS (EI) for C$_{12}$H$_{16}$O$_3$S (240.0820): 240.0806.

Preparation of 4-(4-benzoyl-3-thienyl)benzonitrile (84d):

![Chemical Structure]

Prepared according to TP11 from 83f (520 mg, 1.5 mmol) in 7 mL EtOH, NH$_4$CO$_2$ (504 mg, 8 mmol) and Pd/C (80 mg, 5 mol %). Total reaction time: 6 h. Flash column chromatographical purification on silica gel (CH$_2$Cl$_2$) afforded 84d (333 mg, 77 %) as a colorless solid.

M.p.: 108-109 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.84-7.79 (m, 3H), 7.58-7.53 (m, 3H), 7.45-7.39 (m, 5H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 191.1, 141.9, 140.3, 139.6, 137.7, 133.6, 133.3, 132.1, 129.9, 129.2, 128.5, 125.8, 118.8, 111.0.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3081, 2224, 1644, 1606, 1598, 1579, 1526, 1492, 1448, 1421, 1410, 1260, 1165, 1128, 1081, 1001, 993, 910, 870, 855, 835, 829, 798, 763, 728, 721, 697, 661.

MS (70 eV, EI) m/z (%): 289 (100) [M$^+$], 260 (18), 212 (68), 140 (22), 105 (21).

HRMS (EI) for C$_{18}$H$_{11}$NOS (289.0561): 289.0531.

Preparation of ethyl 2-allyl-4-(methylthio)thiophene-3-carboxylate (85a):

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Prepared according to **TP8** from **84b** (990 mg, 4.9 mmol) and TMPMgCl\cdotLiCl (4.9 mL, 1.10 M in THF, 5.4 mmol). Deprotonation time: 30 min at -30 °C. An allylation reaction was performed according to **TP10** using allyl bromide (714 mg, 5.9 mmol) at -30 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded **85a** (1103 mg, 93 %) as a colorless oil.

**1H-NMR (300 MHz, CDCl₃)** δ (ppm): 6.49 (s, 1H), 6.04 – 5.91 (m, 1H), 5.17-5.09 (m, 2H), 4.35 (q, J = 7.0 Hz, 2H), 3.86 (td, J = 1.3 Hz, J = 6.6 Hz, 2H), 2.41 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H).

**13C-NMR (75 MHz, CDCl₃)** δ (ppm): 163.2, 153.2, 138.1, 135.3, 126.2, 117.3, 112.0, 60.7, 34.7, 16.4, 14.3.

**IR (ATR)** ν ~ (cm⁻¹): 3112, 3079, 2978, 2916, 1701, 1639, 1573, 1475, 1463, 1441, 1426, 1393, 1374, 1348, 1298, 1281, 1238, 1171, 1133, 1112, 1095, 1058, 1023, 992, 971, 859, 830, 784, 768, 745, 710, 657.

**MS (70 eV, EI)** m/z (%): 242 (54) [M⁺], 196 (62), 163 (100), 122 (29).


Preparation of ethyl 4-(methylthio)-2-[2-(trifluoromethyl)phenyl]thiophene-3-carboxylate (85b):

Prepared according to **TP8** from **84b** (1.96 g, 9.7 mmol) and TMPMgCl\cdotLiCl (8.9 mL, 1.20 M in THF, 10.7 mmol). Deprotonation time: 30 min at -30 °C. A cross-coupling reaction was performed according to **TP9** using 2-iodobenzotrifluoride (3.54 g, 13.0 mmol), Pd(dba)₂ (224 mg, 4 mol %) and P(o-furyl)₃ (180 mg, 8 mol %) at -30 °C. The reaction mixture was then heated to 50 °C for 6 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 3:1) afforded **85b** (2.36 g, 70 %) as a colorless solid.
**Experimental Section**

M.p.: 87-70 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.74-7.70 (m, 1H), 7.56-7.50 (m, 2H), 7.37-7.34 (m, 1H), 6.75 (s, 1H), 3.98 (q, $J = 7.0$ Hz, 2H), 2.49 (s, 3H), 0.81 (t, $J = 7.0$, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 162.3, 147.2, 137.8, 134.6, 133.2, 132.2, 130.8, 129.4 (q, $J = 30.4$ Hz), 128.4, 125.9 (q, $J = 5.2$ Hz), 120.0 (q, $J = 273.7$ Hz), 114.6, 60.3, 16.3, 13.3.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3099, 2989, 2901, 1705, 1604, 1580, 1524, 1482, 1376, 1347, 1313, 1265, 1249, 1218, 1173, 1166, 1138, 1124, 1105, 1063, 1034, 1026, 998, 966, 765, 733.

MS (70 eV, EI) m/z (%): 346 (100) [M$^+$], 301 (44), 271 (15), 231 (15).

HRMS (EI) for C$_{15}$H$_{13}$F$_3$O$_2$S$_2$ (346.0309): 346.0285.

**Preparation of ethyl 2-(4-chlorophenyl)-4-(2,2-dimethylpropanoyl)thiophene-3-carboxylate (85c):**

![chemical structure](image)

Prepared according to TP8 from 84c (712 mg, 3.0 mmol) and TMPMgCl-LiCl (3.1 mL, 1.18 M in THF, 3.6 mmol). Deprotonation time: 1 h at -40 °C. A cross-coupling reaction was performed according to TP9 using 4-chloroiodobenzene (1.07 g, 4.5 mmol), Pd(dba)$_2$ (35 mg, 2 mol %) and P(o-furyl)$_3$ (28 mg, 4 mol %) at -40 °C during 16 h. Flash column chromatographical purification on silica gel (pentane/CH$_2$Cl$_2$ = 2:1) afforded 85c (852 mg, 81 %) as a pale orange solid.

M.p.: 78-80 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.42-7.33 (m, 5H), 4.17 (q, $J = 7.2$ Hz, 2H), 1.32 (s, 9H), 1.14 (t, $J = 7.2$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 205.9, 164.1, 146.7, 142.5, 135.3, 131.2, 130.9, 130.3, 128.7, 124.2, 61.6, 44.8, 27.5, 14.1.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3111, 3072, 2980, 2972, 2934, 2915, 2867, 1687, 1651, 1591, 1565, 1552, 1522, 1492, 1476, 1462, 1453, 1444, 1398, 1389, 1381, 1361, 1357, 1280, 1265, 1230, 1211, 1192, 1168, 1154, 1134, 1094, 1089, 1046, 1028, 1012, 964, 958, 950, 937, 930, 910, 881, 858, 834, 824, 812, 797, 764, 739, 715, 700, 667.
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**MS (70 eV, EI)** \(m/z\) (%): 350 (28) [M\(^+\)], 294 (100), 266 (95), 149 (34).

**HRMS (EI)** for \(C_{18}H_{19}ClO_3S\) (350.0743): 350.0734.

**Preparation of ethyl 2-[3,5-bis(trifluoromethyl)phenyl]-4-(2,2-dimethylpropanoyl)thiophene-3-carboxylate (85d):**

![Chemical Structure](image)

Prepared according to **TP8** from \(84c\) (1.45 g, 6.0 mmol) and TMPMgCl-LiCl (6.3 mL, 1.12 M in THF, 7.0 mmol). Deprotonation time: 1 h at -40 °C. A cross-coupling reaction was performed according to **TP9** using 1-bromo-3,5-bis(trifluoromethyl)benzene (2.34 g, 8.0 mmol) and Pd(PPh\(_3\))\(_4\) at -40 °C. The reaction mixture was then heated to 50 °C for 16 h. Flash column chromatographical purification on silica gel (pentane/CH\(_2\)Cl\(_2\) = 4:1) afforded 85d (1.55 g, 57 %) as a colorless solid.

**M.p.:** 100-103 °C.

**\(^1H\)-NMR (300 MHz, CDCl\(_3\))** \(\delta\) (ppm): 7.92-7.90 (m, 3H), 7.45 (s, 1H), 4.15 (q, \(J = 7.2\) Hz, 2H), 1.33 (s, 9H), 1.10 (t, \(J = 7.2\) Hz, 3H).

**\(^13C\)-NMR (75 MHz, CDCl\(_3\))** \(\delta\) (ppm): 205.8, 162.9, 144.1, 143.0, 134.8, 131.6 (q, \(J = 33.7\) Hz), 131.1, 129.7, 127.4, 123.0 (q, \(J = 273.1\) Hz), 122.5, 61.6, 44.7, 27.1, 13.6.

**IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)):** 3123, 2969, 1718, 1685, 1618, 1525, 1478, 1456, 1449, 1439, 1399, 1384, 1361, 1320, 1276, 1272, 1254, 1209, 1197, 1175, 1154, 1127, 1104, 1096, 1037, 1018, 1002, 947, 911, 896, 867, 843, 808, 791, 779, 748, 734, 702, 683, 666, 652.

**MS (70 eV, EI)** \(m/z\) (%): 452 (0.3) [M\(^-\)], 395 (63), 367 (100), 347 (22), 303 (11), 125 (11).

**HRMS (EI)** for \(C_{20}H_{18}F_6O_3S\) (452.0881): 452.0870.

**Preparation of ethyl 4-(4-chlorophenyl)-3-(2,2-dimethylpropanoyl)thiophene-2-carboxylate (85e):**
Experimental Section

Prepared according to TP8 from 84a (460 mg, 1.6 mmol) and TMPMgCl·LiCl (1.5 mL, 1.17 M in THF, 1.8 mmol). Deprotonation time: 3 h at -50 °C. Ethyl cyanoformate (198 mg, 2.0 mmol) was added at -50 °C, the reaction mixture was stirred for 1 h and then warmed to 25 °C. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 1:1) afforded 85e (515 mg, 92 %) as a colorless solid.

M.p.: 92-93 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.41 (s, 1H), 7.34-7.26 (m, 4H), 4.32 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 211.9, 161.3, 146.5, 140.1, 134.4, 134.0, 130.2, 130.0, 129.4, 128.8, 61.8, 45.4, 27.1, 14.3.

IR (ATR) ν (cm⁻¹): 2967, 2934, 2869, 1701, 1685, 1526, 1500, 1479, 1462, 1444, 1436, 1362, 1265, 1246, 1232, 1214, 1173, 1163, 1093, 1076, 1053, 1018, 1006, 906, 891, 835, 823, 806, 793, 757, 732, 681.

MS (70 eV, EI) m/z (%): 350 (10) [M⁺], 293 (91), 265 (100).

HRMS (EI) for C₁₈H₁₉ClO₃S (350.0743): 350.0733.

Preparation of ethyl 5-allyl-2-[3,5-bis(trifluoromethyl)phenyl]-4-(2,2-dimethylpropanoyl) thiophene-3-carboxylate (86a):

Prepared according to TP8 from 58d (452 mg, 1.0 mmol) and TMPMgCl·LiCl (0.92 mL, 1.20 M in THF, 1.1 mmol). Deprotonation time: 45 min at -50 °C. An allylation reaction was
Experimental Section

performed according to TP10 using allyl bromide (145 mg, 1.2 mmol) at -50 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 4:1) afforded 86a (421 mg, 85 %) as a colorless oil.

H-NMR (300 MHz, CDCl₃) δ (ppm): 7.89-7.86 (m, 3H), 5.97-5.90 (m, 1H), 5.24-5.18 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.45 (td, J = 1.2 Hz, J = 6.6 Hz, 2H), 1.24 (s, 9H), 1.02 (t, J = 7.1 Hz, 3H).

C-NMR (75 MHz, CDCl₃) δ (ppm): 210.1, 162.3, 144.3, 140.6, 140.5, 135.4, 134.8, 131.3 (q, J = 34 Hz), 130.2, 128.4, 123.1 (q, J = 272 Hz), 122.2, 118.3, 61.4, 45.5, 33.1, 27.4, 13.5.

IR (ATR) ʋ (cm⁻¹): 2979, 1710, 1693, 1641, 1536, 1481, 1458, 1447, 1404, 1392, 1370, 1275, 1171, 1157, 1129, 1108, 1034, 1018, 1004, 936, 897, 872, 847, 834, 798, 781, 737, 703, 683.

MS (70 eV, EI) m/z (%): 492 (3) [M⁺], 435 (95), 407 (100), 257 (43).

HRMS (EI) for C₂₃H₂₂F₆O₃S (492.1194): 492.1187.

Preparation of ethyl 2-(4-chlorophenyl)-4-(2,2-dimethylpropanoyl)-5-formylthiophene-3-carboxylate (86b):

Prepared according to TP8 from 85c (351 mg, 1.0 mmol) and TMPMgCl·LiCl (0.93 mL, 1.18 M in THF, 1.1 mmol). Deprotonation time: 30 min at -40 °C. DMF (110 mg, 1.5 mmol) was added at -40 °C and the reaction mixture was warmed to 25 °C. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 1:1) afforded 86b (300 mg, 79 %) as a colorless solid.

M.p.: 105-107 °C.

H-NMR (300 MHz, CDCl₃) δ (ppm): 9.67 (s, 1H), 7.43-7.36 (m, 4H), 4.14 (q, J = 7.0, 2H), 1.27 (s, 9H), 1.10 (t, J = 7.0 Hz, 3H).

C-NMR (75 MHz, CDCl₃) δ (ppm): 208.3, 181.8, 161.9, 156.4, 150.5, 138.0, 136.2, 130.9, 130.4, 128.6, 128.5, 61.7, 45.3, 27.1, 13.7.
**Experimental Section**

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2976, 2935, 2894, 2869, 2839, 1699, 1681, 1674, 1593, 1520, 1471, 1446, 1405, 1383, 1362, 1356, 1290, 1268, 1201, 1159, 1117, 1090, 1013, 968, 874, 856, 846, 836, 825, 811, 800, 766, 715, 707, 670, 660.

**MS (70 eV, EI) m/z (%):** 378 (2) [M$^+$], 322 (68), 293 (100), 276 (39), 249 (17), 149 (16).

**HRMS (EI) for C$_{19}$H$_{19}$ClO$_4$S (378.0693):** 378.0690.

**Preparation of ethyl 4-(4-chlorophenyl)-3-(2,2-dimethylpropanoyl)-5-[2-(ethoxycarbonyl) prop-2-en-1-yl]thiophene-2-carboxylate (86c):**

![Chemical Structure of 86c](image)

Prepared according to TP8 from 85e (379 mg, 1.1 mmol) and TMPMgCl·LiCl (1.03 mL, 1.17 M in THF, 1.2 mmol). Deprotonation time: 30 min at -50 °C. An allylation reaction was performed according to TP10 using ethyl 2-(bromomethyl)acrylate (290 mg, 1.5 mmol) at -50 °C during 30 min. Flash column chromatographical purification on silica gel (pentane/CH$_2$Cl$_2$ = 1:1) afforded 86c (441 mg, 87 %) as a colorless solid.

**M.p.:** 74-76 °C.

**$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ (ppm):** 7.34 (d, $J = 7.6$ Hz, 2H), 7.19 (d, $J = 7.6$ Hz, 2H), 6.25 (s, 1H), 5.45 (s, 1H), 4.29 (q, $J = 7.6$ Hz, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.69 (brs, 2H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 0.84 (s, 9H).

**$^{13}$C-NMR (150 MHz, CDCl$_3$) $\delta$ (ppm):** 211.8, 165.8, 161.3, 148.3, 145.2, 138.3, 136.9, 134.3, 132.6, 131.5, 128.8, 127.3, 126.0, 61.6, 61.6, 44.7, 31.0, 27.1, 14.3, 14.1.

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2978, 2905, 1703, 1691, 1629, 1529, 1497, 1479, 1463, 1444, 1413, 1405, 1390, 1367, 1362, 1328, 1292, 1278, 1252, 1231, 1215, 1193, 1182, 1174, 1153, 1113, 1105, 1083, 1069, 1027, 1016, 977, 969, 942, 895, 879, 843, 834, 816, 778, 759, 739, 721, 706, 699.

**MS (70 eV, EI) m/z (%):** 462 (2) [M$^+$], 405 (100), 377 (28), 331 (22).

**HRMS (EI) for C$_{24}$H$_{31}$ClO$_5$NS [M$^+$ + NH$_4^+$] (480.1611):** 480.1614.
Preparation of ethyl 5-[(4-bromophenyl)(hydroxy)methyl]-4-(methylthio)-2-[2-(trifluoromethyl)phenyl]thiophene-3-carboxylate (86d):

Prepared according to TP8 from 85b (346 mg, 1.0 mmol) and TMPMgCl·LiCl (0.94 mL, 1.17 M in THF, 1.1 mmol). Deprotonation time: 1 h at -30 °C. 4-bromobenzaldehyde (222 mg, 1.2 mmol) was added at -30 °C, the reaction mixture was warmed to 25 °C and stirred for 16 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (CH₂Cl₂) afforded 86d (374 mg, 70 %) as a colorless oil.

¹H-NMR (600 MHz, CDCl₃) δ (ppm): 7.71-7.70 (m, 1H), 7.54-7.47 (m, 4H), 7.39-7.35 (m, 3H), 6.45 (d, 1H), 3.97 (q, J = 7.1 Hz, 2H), 2.95 (brs, 1H), 2.32 (s, 3H), 0.79 (t, J = 7.1 Hz, 3H).

¹³C-NMR (150 MHz, CDCl₃) δ (ppm): 162.6, 151.7, 144.0, 141.2, 134.0, 132.6, 132.4, 131.7, 131.0, 129.3 (q, J = 29 Hz), 128.8, 128.6, 128.4, 126.0 (q, 5 Hz), 123.6 (q, 274 Hz), 122.1, 70.7, 60.4, 20.3, 13.3.

IR (ATR) v (cm⁻¹): 3380, 2982, 2924, 1769, 1703, 1604, 1578, 1575, 1486, 1441, 1421, 1396, 1374, 1344, 1312, 1279, 1265, 1250, 1193, 1169, 1125, 1108, 1065, 1022, 1009, 972, 962, 949, 899, 858, 834, 824, 766, 736, 707, 696, 689, 683, 658.

MS (70 eV, EI) m/z (%): 530 (10) [M⁺], 517 (10), 486 (53), 471 (50), 441 (35), 344 (100).

HRMS (EI) for C₂₂H₁₈BrF₃O₃S₂ (529.9833): 529.9828.

Preparation of ethyl 5-cyclohex-2-en-1-yl-4-(methylthio)-2-[2-(trifluoromethyl)phenyl]thiophene-3-carboxylate (86e):
Prepared according to TP8 from 85b (346 mg, 1.0 mmol) and TMPMgCl-LiCl (0.94 mL, 1.17 M in THF, 1.1 mmol). Deprotonation time: 1 h at -30 °C. An allylation reaction was performed according to TP10 using 3-bromo-1-cyclohexene (209 mg, 1.3 mmol) at -30 °C during 2 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 3:2) afforded 86e (367 mg, 86 %) as a colorless oil.

1H-NMR (600 MHz, CDCl₃) δ (ppm): 7.71-7.69 (m, 1H), 7.53-7.47 (m, 2H), 7.39-7.37 (m, 1H), 5.91-5.87 (m, 1H), 5.74-5.72 (m, 1H), 4.29-4.27 (m, 1H), 3.98 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 2.13-2.07 (m, 3H), 1.83-1.78 (m, 1H), 1.72-1.63 (m, 2H), 0.81 (t, J = 7.1 Hz, 3H).

13C-NMR (150 MHz, CDCl₃) δ (ppm): 163.2, 155.1, 141.5, 134.0, 133.4, 132.6, 130.9, 129.6, 129.5 (q, J = 29 Hz), 129.1, 128.5, 127.3, 125.9 (q, J = 5 Hz), 123.7 (q, J = 274 Hz), 60.3, 36.0, 31.9, 24.8, 20.9, 20.8, 13.4.

IR (ATR) ν (cm⁻¹): 3021, 2982, 2925, 2860, 1720, 1604, 1578, 1527, 1485, 1453, 1441, 1394, 1372, 1341, 1312, 1276, 1264, 1239, 1187, 1164, 1127, 1108, 1065, 1032, 997, 970, 960, 948, 899, 888, 865, 837, 828, 802, 766, 733, 723, 704, 680, 672.

MS (70 eV, EI) m/z (%): 426 (10) [M⁺], 380 (98), 337 (100).

HRMS (EI) for C₂₁H₂₁F₃O₂S₂ (426.0935): 426.0923.

Preparation of ethyl 5-formyl-4-(methylthio)-2-[2-(trifluoromethyl)phenyl]thiophene-3-carboxylate (86f):

Prepared according to TP8 from 85b (260 mg, 0.75 mmol) and TMPMgCl-LiCl (0.71 mL, 1.17 M in THF, 0.83 mmol). Deprotonation time: 1 h at -30 °C. DMF (73 mg, 1.0 mmol) was added at -30 °C, the reaction mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical
Experimental Section

purification on silica gel (pentane/CH₂Cl₂ = 13:7) afforded 86f (238 mg, 85 %) as a colorless solid.

M.p.: 81-82 °C.

\(^{1}\)H-NMR (600 MHz, CDCl₃) \(\delta\) (ppm): 10.36 (s, 1H), 7.76-7.75 (m, 1H), 7.60-7.56 (m, 2H), 7.38-7.37 (m, 1H), 4.01 (q, \(J = 4.1\) Hz, 2H), 2.58 (s, 3H), 0.83 (t, \(J = 4.1\) Hz, 3H).

\(^{13}\)C-NMR (150 MHz, CDCl₃) \(\delta\) (ppm): 184.2, 161.7, 152.2, 143.8, 142.7, 135.5, 131.8, 131.6, 131.2, 129.5, 129.1 (q, \(J = 30\) Hz), 126.2 (q, \(J = 4\) Hz), 123.5 (q, \(J = 273\) Hz), 60.9, 21.3, 13.3.

IR (ATR) \(\tilde{\nu}\) (cm⁻¹): 2988, 2942, 2900, 1713, 1638, 1604, 1581, 1521, 1484, 1427, 1375, 1334, 1314, 1296, 1269, 1209, 1175, 1160, 1123, 1105, 1063, 1037, 1025, 992, 987, 966, 948, 763, 740, 712, 662, 657.

MS (70 eV, EI) m/z (%): 374 (100) [M⁺], 300 (20), 271 (14).

HRMS (EI) for C₁₆H₁₃F₃O₃S₂ (374.0258): 374.0246.

Preparation of diethyl 3,3'-bis(methylthio)-5,5'-bis[2-(trifluoromethyl)phenyl]-2,2'-bithiophene-4,4'-dicarboxylate (86g):

Prepared according to TP8 from 85b (260 mg, 0.75 mmol) and TMPMgCl-LiCl (0.71 mL, 1.17 m in THF, 0.83 mmol). Deprotonation time: 1 h at -30 °C. ZnCl₂ (0.83 mL, 1 m in THF, 1.1 equiv) was added at -30 °C and the reaction mixture stirred for 15 min. Chloranil (101 mg, 0.41 mmol) was added, the reaction mixture was warmed to 25 °C and stirred for 7 h. The reaction mixture was quenched with half concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane) afforded 86g (162 mg, 63 %) as a brown solid.

M.p.: 139-141 °C.

\(^{1}\)H-NMR (600 MHz, CDCl₃) \(\delta\) (ppm): 7.76-7.75 (m, 2H), 7.60-7.53 (m, 4H), 7.49-7.48 (m, 2H), 4.02 (q, \(J = 7.1\) Hz, 4H), 2.38 (s, 6H), 0.85 (t, \(J = 7.1\) Hz, 6H).
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$^{13}$C-NMR (150 MHz, CDCl$_3$) $\delta$ (ppm): 162.8, 145.1, 135.5, 134.2, 132.8, 132.6, 132.2, 131.1, 129.5 (q, $J$ = 30 Hz), 129.0, 126.1 (q, $J$ = 5 Hz), 123.7 (q, $J$ = 273), 60.6, 20.0, 13.4.


MS (70 eV, EI) m/z (%): 690 (100) [M$^+$], 673 (7), 271 (18).

HRMS (EI) for C$_{30}$H$_{28}$F$_6$NO$_4$S$_4$ [M$^+$ + NH$_4^+$] (708.0805): 708.0810.

Preparation of ethyl 5-chloro-2-(4-methoxyphenyl)-4-(methylthio)thiophene-3-carboxylate (88):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (286 mg, 11.8 mmol), LiCl (12.0 mL, 0.5 M in THF, 6.0 mmol) and ZnCl$_2$ (5.2 mL, 1.0 M in THF, 5.2 mmol). 83j (1.29 g, 4.7 mmol) was added in one portion at 25 °C and the mixture was stirred for 3 h. The reaction mixture was cannulated to a new dry and argon-flushed Schlenk-flask and Pd(dba)$_2$ (54 mg, 2 mol%), P(2-furyl)$_3$ (43 mg, 4 mol%) and 4-iodoanisole (772 mg, 3.3 mmol) were added. The mixture was stirred for 3 h and then quenched with concentrated aqueous NH$_4$Cl solution, extracted three times with Et$_2$O, dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH$_2$Cl$_2$ = 13:7) afforded 88 (1.03 g, 91%) as a colorless oil.

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.33 (d, $J$ = 8.5 Hz, 2H), 6.90 (d, $J$ = 8.5 Hz, 2H), 4.24 (q, $J$ = 4.1 Hz, 2H), 3.82 (s, 3H), 2.41 (s, 3H), 1.19 (t, $J$ = 4.1 Hz, 3H).

$^{13}$C-NMR (150 MHz, CDCl$_3$) $\delta$ (ppm): 164.8, 160.2, 142.0, 132.8, 132.2, 130.2, 129.8, 124.6, 114.1, 61.5, 55.4, 19.0, 13.9.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2980, 2926, 2904, 2836, 1720, 1606, 1574, 1534, 1498, 1462, 1440, 1428, 1392, 1370, 1338, 1310, 1292, 1246, 1192, 1176, 1112, 1094, 1060, 1030, 1018, 972, 942, 926, 864, 830, 810, 790, 778, 736, 718, 702, 636, 618, 572.

MS (70 eV, EI) m/z (%): 342 (100) [M$^+$], 297 (33).
HRMS (EI) for C_{15}H_{15}ClO_{3}S_{2} (342.0151): 342.0144.

Synthesis of ethyl 2-(4-methoxyphenyl)-5-(2-methylprop-2-en-1-yl)-4-(methylthio) thiophene-3-carboxylate (90):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (122 mg, 5.0 mmol), LiCl (5.0 mL, 0.5 M in THF, 2.5 mmol) and ZnCl\(_2\) (2.2 mL, 1.0 M in THF, 2.2 mmol). 88 (685 mg, 2 mmol) was added in one portion at 25 °C and the mixture was stirred for 4 h. The reaction mixture was cannulated to a new dry and argon-flushed Schlenk-flask and CuCN·2 LiCl (0.40 mL, 20 mol%) was added and the reaction mixture was stirred for 15 min. 3-Bromo-2-methylprop-1-ene (189 mg, 1.4 mmol) was added, the mixture was stirred for 3 h and then quenched with concentrated aqueous NH\(_4\)Cl solution, extracted three times with Et\(_2\)O, dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH\(_2\)Cl\(_2\) = 7:3) afforded 90 (358 mg, 71%) as a colorless oil.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm): 7.35 (d, \(J = 8.92\) Hz, 2H), 6.88 (d, \(J = 8.92\) Hz, 2H), 4.87 – 4.82 (m, 2H), 4.26 (q, \(J = 7.19\) Hz, 2H), 3.82 (s, 3H), 3.69 (brs, 2H), 2.33 (s, 3H), 1.78 (brs, 3H), 1.19 (t, \(J = 7.19\) Hz, 3H).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm): 166.0, 159.8, 145.9, 143.9, 142.4, 133.0, 129.6, 129.0, 125.8, 113.9, 112.8, 61.2, 55.3, 37.0, 22.2, 20.4, 14.0.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2978, 2924, 2836, 2360, 2342, 1718, 1652, 1608, 1574, 1536, 1502, 1462, 1440, 1418, 1392, 1372, 1342, 1292, 1248, 1176, 1132, 1112, 1094, 1024, 986, 972, 948, 932, 894, 864, 830, 810, 778, 742, 716, 668, 654, 636.

MS (70 eV, EI) \(m/z\) (%): 362 (100) [M\(^+\)], 301 (75), 260 (42), 247 (25), 175 (10).

HRMS (EI) for C\(_{10}\)H\(_{22}\)O\(_3\)S\(_2\) (362.1010): 362.1011.

Preparation of di-tert-butyl 2-chloro-5-phenylthiophene-3,4-dicarboxylate (92):
A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (292 mg, 12 mmol). LiCl (12.5 mL, 0.5 M in THF, 6.3 mmol) was added and the magnesium was activated with DIBAL-H (0.5 mL, 0.1 M in THF, 0.05 mmol). Di-tert-butyl 2,5-dichlorothiophene-3,4-dicarboxylate (83e, 1.77 g, 5.0 mmol) was added in one portion at -50 °C. The reaction mixture was stirred for 3 h and then cannulated to a new Schlenk-flask. ZnCl₂ (5.0 mL, 1 M in THF, 5.0 mmol) was added to the freshly prepared magnesium reagent and the reaction mixture was stirred for 15 min. Pd(dba)₂ (86 mg, 3 mol%) and tfp (69 mg, 6 mol%) were added, followed by the addition of iodobenzene (714 mg, 3.5 mmol), and the reaction mixture was stirred for 3 h at 25 °C. The reaction mixture was quenched with sat. NH₄Cl solution (15 mL) and extracted with Et₂O (3 x 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography (pentane/CH₂Cl₂ = 4:1 to 1:1) furnished 92 as a colorless solid (1.13 g, 82 %).

M.p.: 84-86 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 7.42-7.35 (m, 5H), 1.59 (s, 9H), 1.34 (s, 9H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 162.3, 161.1, 142.4, 132.5, 131.9, 131.3, 131.2, 129.2, 128.9, 128.3, 82.7, 82.2, 28.1, 27.7.

IR (ATR) v (cm⁻¹): 2976, 1727, 1708, 1365, 1233, 1149, 765.

MS (70 eV, EI) m/z (%): 394 (9) [M⁺], 282 (100), 265 (30), 238 (21), 57 (18).

HRMS (EI) for C₂₀H₂₃ClO₄S (394.1006): 394.0992.

Preparation of di-tert-butyl 2-[2-(ethoxycarbonyl)prop-2-en-1-yl]-5-phenylthiophene-3,4-dicarboxylate (94):
The magnesium insertion was performed according to **TP1** from **92** (790 mg, 2.0 mmol) in 3 h at -50 °C. A allylation reaction was performed according to **TP3** with ethyl (2-bromomethyl)acrylate (270 mg, 1.4 mmol) in 30 min. Flash column chromatography (CH$_2$Cl$_2$) furnished **94** as a colorless oil (580 mg, 88%).

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.42-7.40 (m, 2H), 7.37-7.33 (m, 3H), 6.30 (d, $J = 1.1$ Hz, 1H), 5.60 (d, $J = 1.1$ Hz, 1H), 4.23 (q, $J = 7.1$ Hz, 2H), 4.00 (m, 2H), 1.53 (s, 9H), 1.36 (s, 9H), 1.30 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (150 MHz, CDCl$_3$) $\delta$ (ppm): 166.3, 163.7, 162.6, 144.4, 142.2, 138.5, 132.8, 132.5, 132.1, 129.1, 128.4, 128.2, 126.9, 81.9, 81.8, 61.0, 30.8, 28.1, 27.8, 14.2.

**MS (70 eV, EI)** $m/z$ (%): 472 (1) [M$^+$], 360 (31), 342 (100), 270 (27), 57 (16).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 2977, 1707, 1631, 1475, 1392, 1365, 1244, 1150, 1122, 950, 847, 696.

**HRMS (EI)** for C$_{26}$H$_{32}$O$_6$S (472.1920): 472.1929.

**Preparation of ethyl 2,5-dichloro-4-phenylthiophene-3-carboxylate (96):**

Prepared according to **TP8** from **79** (2.14 g, 14.0 mmol) and TMPMgCl·LiCl (14.0 mL, 1.10 M in THF, 15.4 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (1.59 g, 16.0 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH$_4$Cl solution, extracted three times with Et$_2$O, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was solved in THF and deprotonated according to **TP8** using TMPMgCl·LiCl (14.0 mL, 1.10 M in THF, 15.4 mmol). A cross-coupling reaction was performed according to **TP9** using iodobenzene (4.08 g, 21.0 mmol), Pd(dba)$_2$ (161 mg, 2 mol%) and P(o-furyl)$_3$ (129 mg, 4 mol%) at -30 °C during 6 h. Flash column chromatographical purification on silica gel (pentane/CH$_2$Cl$_2$ = 4:1) afforded **96** (2.93 g, 69 %) as a colorless solid.

**M.p.:** 55-56 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.44-7.37 (m, 3H), 7.29 – 7.26 (m, 2H), 4.09 (q, $J = 7.1$ Hz, 2H), 0.99 (t, $J = 7.1$ Hz, 3H).
**Experimental Section**

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm): 161.9, 138.9, 133.2, 130.7, 130.6, 120.2, 128.2, 128.1, 123.5, 61.3, 13.6.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2982, 2932, 1722, 1544, 1498, 1482, 1464, 1446, 1384, 1366, 1280, 1246, 1176, 1156, 1098, 1072, 1054, 932, 862, 842, 806, 766, 702, 656, 630.

MS (70 eV, EI) m/z (%): 300 (40) [M$^+$], 255 (43), 207 (32), 192 (20), 44 (100).

HRMS (EI) for C$_{13}$H$_{10}$Cl$_2$O$_2$S (299.9779): 299.9774.

**Preparation of ethyl 5-chloro-2-isopropenyl-4-phenylthiophene-3-carboxylate (97):**

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (462 mg, 19.0 mmol), LiCl (19.0 mL, 0.5 M in THF, 9.5 mmol) and ZnCl$_2$ (8.4 mL, 1.0 M in THF, 8.4 mmol). 96 (2.30 g, 7.6 mmol) was added in one portion at 25 °C and the mixture was stirred for 3 h. The reaction mixture was cannulated to a new dry and argon-flushed Schlenk-flask and Pd(OAc)$_2$ (36 mg, 1 mol %), SPhos (62 mg, 2 mol %) and 2-bromopropene (641 mg, 5.3 mmol) were added. The mixture was stirred for 2 h and then quenched with concentrated aqueous NH$_4$Cl solution, extracted three times with Et$_2$O, dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH$_2$Cl$_2$ = 3:1) afforded 97 (1.53 g, 94 %) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 7.42-7.28 (m, 5H), 5.26 (brs, 1H), 5.20-5.18 (m, 1H), 4.03 (q, $J$ = 7.0 Hz, 2H), 2.11-2.10 (m, 3H), 0.97 (t, $J$ =7.0 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm): 164.8, 144.4, 138.8, 136.6, 133.6, 129.4, 129.2, 128.1, 127.9, 124.5, 117.5, 61.2, 23.3, 13.5.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2980, 2936, 2164, 2030, 1974, 1720, 1498, 1442, 1368, 1282, 1232, 1174, 1152, 1094, 1072, 1018, 902, 698.

MS (70 eV, EI) m/z (%): 306 (100) [M$^+$], 277 (87), 249 (56), 197 (33).

HRMS (EI) for C$_{16}$H$_{15}$ClO$_2$S (306.0481): 306.0475.

**Preparation of ethyl 5-(4-fluorophenyl)-2-isopropenyl-4-phenylthiophene-3-carboxylate (98):**

![Chemical Structure Image]
A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (182 mg, 7.5 mmol), LiCl (7.5 mL, 0.5 M in THF, 3.8 mmol) and ZnCl₂ (3.3 mL, 1.0 M in THF, 3.3 mmol). 97 (918 mg, 3.0 mmol) was added in one portion at 25 °C and the mixture was stirred for 3 h. The reaction mixture was cannulated to a new dry and argon-flushed Schlenk-flask and Pd(OAc)₂ (14 mg, 1 mol%), SPhos (25 mg, 2 mol%) and 4-bromofluorobenzene (368 mg, 2.1 mmol) were added. The mixture was stirred for 1 h and then quenched with concentrated aqueous NH₄Cl solution, extracted three times with Et₂O, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (toluene) afforded 98 (426 mg, 66 %) as a pale yellow solid.

M.p.: 55-57 °C.

¹H-NMR (600 MHz, CDCl₃) δ (ppm): 7.27-7.26 (m, 3H), 7.18-7.16 (m, 2H), 7.12 – 7.10 (m, 2H), 6.88 (t, J = 8.5 Hz, 2H), 5.33 (s, 1H), 5.19 (s, 1H), 4.03 (q, J = 7.1 Hz, 2H), 2.16 (s, 3H), 0.98 (t, J = 7.1, 3H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 166.0, 162.2 (d, J = 248), 144.9, 137.7, 136.9, 136.7, 135.4, 131.5, 130.8 (d, J = 8 Hz), 129.8, 129.4 (d, J = 3 Hz), 128.2, 127.4, 116.6, 115.3 (d, J = 21 Hz), 61.1, 23.5, 13.6.

IR (ATR) ̅ν (cm⁻¹): 2976, 2936, 2352, 1714, 1536, 1504, 1462, 1454, 1442, 1390, 1374, 1366, 1306, 1220, 1208, 1170, 1158, 1136, 1090, 1076, 1024, 1016, 900, 832, 812, 792, 754, 726, 712, 700.

MS (70 eV, EI) m/z (%): 366 (100) [M⁺], 337 (65), 309 (38), 139 (8), 91 (35).

HRMS (EI) for C₂₂H₁₉FO₂S (366.1090): 360.1080.

Preparation of 5-(4-fluorophenyl)-2-isopropyl-N,4-diphenylthiophene-3-carboxamide (99):
To a solution of 98 (117 mg, 0.32 mmol) in EtOH (10 mL) Pd/C (17 mg, 5 mol %) was added. The mixture was hydrogenated at 25 °C under 1 atm of H₂ for 18 h. The catalyst was removed by filtration through Celite® by using a short-pad column. The solvents were evaporated in vacuo and the crude material was used in the next step without purification.

In a dry and argon-flushed Schlenk-flask AlMe₃ (1.0 mL, 1 M in heptane, 1.0 mmol) was added slowly to a solution of aniline (93 mg, 1.0 mmol) in CH₂Cl₂ (3 mL) and the mixture was stirred for 15 min at 25 °C. The crude hydrogenated product was added, the reaction mixture was warmed to 40 °C and stirred for 48 h. After cooling, the mixture was transferred to an Erlenmeyer-flask and carefully quenched by the addition of 1 M HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3x 20 mL), the organic layer dried over MgSO₄ and concentrated in vacuo. Flash column chromatographical purification on silica gel (pentane/CH₂Cl₂ = 1:1) afforded 99 (113 mg, 85 %) as a colorless solid.

M.p.: 231-232 °C.

**1H-NMR (300 MHz, CDCl₃)** δ (ppm): 7.33-7.00 (m, 12H), 6.90 (t, \(J = 8.7\) Hz, 2H), 6.70 (brs, 1H), 3.89 (sept, \(J = 6.8\) Hz, 1H), 1.42 (d, \(J = 6.8\) Hz, 6H).

**13C-NMR (75 MHz, CDCl₃)** δ (ppm): 163.3, 162.1 (d, \(J = 247\) Hz), 156.5, 137.4, 135.6, 135.3, 135.2, 133.4, 130.8 (d, \(J = 8\) Hz), 130.0, 129.8 (d, \(J = 3\) Hz), 129.0, 128.8, 127.9, 124.3, 119.9, 115.3 (d, \(J = 21\) Hz), 29.0, 25.2.

**IR (ATR)** \(\tilde{\nu}\) (cm⁻¹): 3234, 2978, 2166, 1998, 1750, 1716, 1640, 1596, 1552, 1534, 1514, 1500, 1456, 1442, 1368, 1332, 1252, 1234, 1158, 1096, 1004, 828, 798, 758, 742, 722, 700.

**MS (70 eV, EI)** \(m/z\) (%): 415 (24) [M⁺], 323 (100), 281 (21), 139 (13).

**HRMS (EI)** for C₂₆H₂₂FNOS (415.1406): 415.1393.

### 4. Preparation of Functionalyzed Enol Phosphates by Halogen-Magnesium Exchange and Directed Deprotonation Reactions
4.1. Typical Procedure for the Br-Mg-Exchange on Enol Phosphates (TP12)

To neat 21 (367 mg, 1.0 mmol) was added iPrMgCl·LiCl (0.96 mL, 1.1 mmol, 1.14 M in THF) at 25 °C and the resulting mixture was stirred for 2 h at this temperature. Further functionalizations were performed as described.

4.2. Preparation of Title Compounds

Preparation of 3-allyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl diethyl phosphate (105a):

103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to TP12. CuCN·2 LiCl (1 M solution in THF, 0.2 mL) and allyl bromide (132 mg, 1.1 mmol) were then added dropwise and the reaction mixture was stirred for 1 h at 25 °C. The resulting mixture was then quenched with a sat. aq. NH₄Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/EtOAc = 6:1) furnished the compound 105a (203 mg, 62 %) as a colourless oil.

Preparation by deprotonation:

107 (1.0 mmol) in THF (2.0 mL) was reacted with freshly titrated TMP₂Mg·2 LiCl (1.3 mmol, 0.55 M in THF, 2.36 mL) at 25 °C and stirred for 30 min. CuCN·2 LiCl (1 M solution in THF, 0.2 mL) and allyl bromide (132 mg, 1.1 mmol) were then added dropwise and the reaction mixture was stirred for 1 h at 25 °C. The resulting mixture was then quenched with a sat. aq. NH₄Cl solution (30 mL) extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash
chromatography (pentane/EtOAc = 6:1) furnished the compound 105a (252 mg, 77 %) as a colourless oil.

$^{1}$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 5.83-5.69 (m, 1 H), 5.10-4.97 (m, 2 H), 4.20-4.10 (m, 4 H), 3.07-2.99 (m, 1 H), 2.79-2.69 (m, 1 H), 2.18 (d, $J$ = 3.7 Hz, 1 H), 1.85-1.74 (m, 1 H), 1.62-1.53 (m, 1 H), 1.47-1.39 (m, 1 H), 1.34 (tq, $J$ = 7.1 Hz, $J$ = 1.0 Hz, $J$ = 0.51 Hz, 6 H), 1.11-1.03 (m, 1 H), 1.00 (s, 3 H), 0.89 (s, 3 H), 0.72 (s, 3 H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 135.4, 124.6 (d, $J$ = 6 Hz), 115.8, 64.2, 55.1, 54.4, 52.4 (d, $J$ = 1 Hz), 32.5 (d, $J$ = 1 Hz), 30.2 (d, $J$ = 1 Hz), 25.4 (d, $J$ = 5 Hz), 19.7 (d, $J$ = 28 Hz), 16.2 (d, $J$ = 6 Hz), 10.2.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2954, 2873, 1672, 1639, 1476, 1444, 1388, 1368, 1319, 1271, 1211, 1167, 1133, 1054, 1028, 1008, 977, 928, 858, 820, 756, 647, 603.

MS (70 eV, EI) $m/z$ (%): 328 (2) [M$^+$], 111 (54), 97 (70), 85 (44), 83 (67), 71 (65), 69 (69), 57 (100), 55 (55), 43 (50).

HRMS (EI) for C$_{17}$H$_{29}$O$_4$P (328.1803): 328.1784.

Preparation of 3-benzoyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl diethyl phosphate (105b):

103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to TP12. The reaction mixture was cooled to –20 °C and CuCN·2 LiCl (1 M solution in THF, 0.2 mL) was added and the reaction mixture was stirred at this temperature for 30 min. Benzoyl chloride (155 mg, 1.1 mmol) was then added and the mixture was allowed to warm up to 25 °C over night. The resulting mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/EtOAc = 2:1) furnished the compound 105b (263 mg, 67 %) as a yellow oil.
**Experimental Section**

$^{1}$$H$-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.83-7.79 (m, 2 H), 7.50-7.37 (m, 3 H), 3.76-3.53 (m, 4 H), 2.82 (d, $J = 3.4$ Hz, 1 H), 2.06-1.95 (m, 1 H), 1.77-1.62 (m, 2 H), 1.49-1.41 (m, 1 H), 1.09 (m, 12 H), 0.83 (s, 3 H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 191.8 (d, $J = 2$ Hz), 158.5 (d, $J = 12$ Hz), 139.0, 132.0, 129.1, 128.0, 64.3 (t, $J = 6$ Hz), 56.8, 55.1, 52.8, 31.5 (d, $J = 2$ Hz), 26.0 (d, $J = 3$ Hz), 19.4 (d, $J = 6$ Hz), 15.9 (q, $J = 3$ Hz), 9.8.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2964, 2879, 1638, 1614, 1578, 1478, 1450, 1341, 1317, 1283, 1276, 1251, 1204, 1168, 1127, 1032, 1010, 977, 921, 894, 880, 827, 723, 703, 694, 657, 621.

MS (70 eV, EI) m/z (%): 392 (32) [M$^+$], 238 (23), 223 (34), 210 (33), 195 (38), 167 (13), 155 (13), 105 (100), 91 (9), 77 (34).

HRMS (EI) for C$_{21}$H$_{29}$O$_5$P: (392.1753): 392.1746.

**Preparation of ethyl 3-[(diethoxyphosphoryl)oxy]-4,7,7-trimethylbicyclo[2.2.1]hept-2-ene-2-carboxylate (105c):**

103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to TP12. The reaction mixture was cooled to −20 °C and ethyl cyanoformate (109 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/EtOAc = 3:1) furnished the compound 105c (260 mg, 72 %) as a yellow oil.

$^{1}$$H$-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 4.26-4.14 (m, 6H), 2.70 (d, $J = 3.5$ Hz, 1H), 1.95-1.90 (m, 1H), 1.68-1.64 (m, 1H), 1.53-1.49 (m, 1H), 1.34 (td, $J = 7.1$ Hz, $J = 1.1$ Hz, 6H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.26-1.22 (m, 1H), 1.07 (s, 3H), 0.91 (s, 3H), 0.77 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 163.6, 162.6 (d, $J = 11$ Hz), 120.0 (d, $J = 6$ Hz), 64.6, 59.9, 56.6, 55.3, 50.9, 31.3 (d, $J = 2$ Hz), 25.6, 19.4, 19.1, 16.1 (d, $J = 7$ Hz), 14.3, 9.8.
IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2978, 1703, 1635, 1392, 13709, 1339, 1275, 1246, 1186, 1025, 921.

MS (70 eV, EI) m/z (%): 360 (10) [M$^+$], 332 (14), 314 (95), 286 (82), 258 (37), 230 (38), 178 (100).

HRMS (EI) for C$_{17}$H$_{29}$O$_6$P (360.1702): 360.1708.

Preparation of diethyl 1,7,7-trimethyl-3-(phenylthio)bicyclo[2.2.1]hept-2-en-2-yl phosphate (105d):

103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to TP12. The reaction mixture was cooled to –20 °C and benzenethiosulfonic acid S-phenyl ester (275 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/Et$_2$O = 3:1) furnished the compound 105d (257 mg, 65 %) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.40-7.37 (m, 2H), 7.28-7.15 (m, 3H), 4.26-4.16 (m, 4H), 2.19 (d, $J = 3.5$ Hz, 1H), 1.81-1.71 (m, 1H), 1.67-1.59 (m, 1H), 1.53-1.45 (m, 1H), 1.36-1.30 (m, 6H), 1.25-1.16 (m, 1H), 1.07 (s, 3H), 0.99 (s, 3H), 0.70 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 155.1 (d, $J = 11$ Hz), 134.9, 130.7, 128.7, 126.5, 117.7 (d, $J = 7$ Hz), 64.5, 55.99, 54.2, 53.2, 32.9, 25.8, 19.4, 16.0 (d, $J = 7$ Hz), 10.0.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2958, 16919, 1477, 1440, 1280, 1133, 1034, 965, 823.

MS (70 eV, EI) m/z (%): 396 (75) [M$^+$], 368 (71), 319 (80), 287 (87), 214 (93), 105 (100).

HRMS (EI) for C$_{20}$H$_{29}$O$_4$PS (396.1524): 396.1532.

Preparation of diethyl 3-(3-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl phosphate (105e):
**Experimental Section**

103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to TP12 and then transmetallated with ZnCl₂ (1.1 equiv) at 0 °C. Pd(OAc)₂ (4.5 mg, 2 mol%), S-Phos (16.5 mg, 4 mol%) and 3-bromoanisole (281 mg, 1.5 mmol) were then added to the reaction mixture. The resulting mixture was stirred at 25 °C overnight and then quenched with a sat. aq. NH₄Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/EtOAc = 3:1) furnished the compound 105e (273 mg, 69 %) as a yellowish oil.

**1H-NMR (300 MHz, CDCl₃) δ (ppm):** 7.21 (t, J = 7.9 Hz, 1H), 7.07-7.02 (m, 2H), 6.73 (dd, J = 7.9 Hz, J = 2.2 Hz, 1H), 4.11-3.90 (m, 4H), 3.81 (s, 3H), 2.65 (d, J = 3.7 Hz, 1H), 2.13 (brs, 1H), 1.99-1.94 (m, 1H), 1.70 (t, J = 6.3 Hz, 2H), 1.35-1.27 (m, 1H), 1.22 (td, J = 7.2 Hz, J = 1.0 Hz, 3H), 1.15 (td, J = 7.2 Hz, J = 1.0 Hz, 3H), 1.13 (s, 3H), 0.97 (s, 3H), 0.81 (s, 3H).

**13C-NMR (75 MHz, CDCl₃) δ (ppm):** 159.4, 150.7 (d, J = 12 Hz), 135.7 (d, J = 2), 129.0, 126.3 (d, J = 7 Hz), 119.4, 112.4, 112.2, 64.2, 55.7, 55.5, 55.2, 53.5, 32.4, 25.8 (d, J = 3 Hz), 19.5 (d, J = 43 Hz), 15.9, 10.3.

**IR (ATR) ν (cm⁻¹):** 2953, 1636, 1597, 1483, 1271, 1161, 1129, 1025, 1003, 960, 922, 875, 784, 686.

**MS (70 eV, EI) m/z (%):** 394 (22) [M⁺], 240 (30), 225 (33), 212 (100), 197 (17).


**Preparation of 4-[(E)-(4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-ylidene)methyl]benzonitrile (109a):**
103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to TP12. The reaction mixture was cooled to –20 °C and 4-cyanobenzaldehyde (144 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH₄Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/Et₂O = 3:1) furnished the compound 109a (191 mg, 72%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃) δ (ppm): 7.65 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.18 (s, 1H), 3.03 (d, J = 4.5 Hz, 2H), 2.25-2.13 (m, 1H), 1.86-1.76 (m, 1H), 1.63-1.47 (m, 2H), 1.02 (s, 3H), 1.00 (s, 3H), 0.76 (s, 3H).

13C-NMR (75 MHz, CDCl₃) δ (ppm): 207.4, 145.1, 140.3, 132.3, 130.09, 125.1, 118.6, 111.8, 57.1, 49.2, 46.6, 30.4, 25.9, 20.6, 18.2, 9.2.

IR (ATR) ν (cm⁻¹): 3436, 2959, 2228, 1724, 1648, 1504, 1324, 1295, 1064, 1016, 837.

MS (70 eV, EI) m/z (%): 265 (100) [M⁺], 250 (58), 222 (57), 183 (59), 154 (54).

HRMS (EI) for C₁₈H₁₇NO (265.1467): 265.1492.

Preparation of (3E)-3-(4-bromobenzylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (109b):

103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to TP12. The reaction mixture was cooled to –20 °C and 4-bromobenzaldehyde (204 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH₄Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/Et₂O = 4:1) furnished the compound 109b (220 mg, 68%) as a colorless oil.
Experimental Section

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 7.50 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.14 (s, 1H), 3.03 (d, $J = 4.0$ Hz, 1H), 2.22-2.09 (m, 1H), 1.84-1.73 (m, 1H), 1.59-1.46 (m, 2H), 1.02 (s, 3H), 0.99 (s, 3H), 0.76 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 207.9, 142.8, 134.6, 131.9, 131.1, 126.2, 122.8, 57.1, 49.2, 46.7, 30.6, 25.9, 20.6, 18.3, 9.2.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3420, 2957, 1720, 1641, 1586, 1491, 1323, 1071, 1064, 1008, 796.

MS (70 eV, EI) $m/z$ (%): 320 (100) [M$^+$], 318 (98) [M$^+$], 303 (37), 275 (22), 249 (19), 236 (38), 196 (21), 128 (37).

HRMS (EI) for C$_{17}$H$_{19}$OBr (318.0619): 318.0621.

(3E)-3-(Cyclohexylmethylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (109c):

![Chemical Structure](image)

103 (367 mg, 1.0 mmol) was reacted at 25°C for 2 h according to TP12. The reaction mixture was cooled to –20°C and cyclohexanecarbaldehyde (123 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25°C. The resulting mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/Et$_2$O = 4:1) furnished the compound 109c (173 mg, 70%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 6.18 (d, $J = 8.9$ Hz, 1H), 2.67 (d, $J = 4.4$ Hz, 1H), 2.22-2.10 (m, 1H), 2.03-1.93 (m, 1H), 1.72-1.56 (m, 6H), 1.42-1.07 (m, 7H), 0.93 (s, 3H), 0.92 (s, 3H), 0.75 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 208.0, 141.0, 135.5, 57.7, 47.7, 46.0, 37.99, 32.3, 32.2, 30.09, 26.8, 25.8, 25.5, 20.5, 18.3, 9.2.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2848, 1725, 1662, 1446, 1257, 1109, 1065, 940.

MS (70 eV, EI) $m/z$ (%): 246 (95) [M$^+$], 231 (98), 218 (81), 203 (100), 95 (94).

HRMS (EI) for C$_{17}$H$_{26}$O (246.1984): 246.1963.
5. 1-Aryliminozinc Reagents as Acyl Anion Equivalents

Preparation of (2,6-dichlorophenyl)[1-(4-methoxybenzyl)but-3-en-1-ylidene]amine (116):

A flame-dried and argon-flushed Schlenk-flask was charged with 2,6-dichlorophenyl isonitrile (114, 1.1 mmol, 189 mg) in 3 mL THF and cooled to –78 °C. 4-Methoxybenzylzinc chloride (111, 1.0 mmol, 0.44 M in THF, 2.3 mL) was added slowly and the reaction mixture stirred for 30 min. CuCN·2 LiCl (0.2 mmol, 1 M in THF, 0.2 mmol) and allyl bromide (1.2 mmol, 145 mg) were added and the solution stirred for 15 min. The reaction mixture was quenched with sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Flash chromatographical purification (pentane/EtOAc = 4:1) furnished 116 (202 mg, 61 %) as a yellow oil.
D. APPENDIX
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Education:


10/2004-09/2006 Graduate studies (M.Sc.) at the Department of Chemistry, Ludwig-Maximilians-Universität Munich, Grade: sehr gut (very good)

10/2001-10/2004 Undergraduate studies (B.Sc.) at the Department of Chemistry, Ludwig-Maximilians-Universität Munich

Average Grade: 1.4 (A)
Research and Work Experience:

12/2006-02/2010 Research Associate in the Group of Prof. Dr. Paul Knochel, Ludwig-Maximilians-Universität Munich
Tasks included: Supervision of two Master’s Theses and one Bachelor’s Thesis, Teaching and supervising students in their sophomore organic chemistry course

03/2006-09/2006 Master’s Thesis in the group of Prof. Dr. Paul Knochel, Ludwig-Maximilians-Universität Munich
Topic: Regioselective Synthesis of Highly Functionalized Heterocycles

07/2005-09/2005 Visiting student in the group of Prof. Dr. Victor Snieckus, Queen’s University, Kingston, ON, Canada

11/2004-07/2005 Student Internship in the group of Prof. Dr. Paul Knochel, Ludwig-Maximilians-Universität Munich

Awards:

2008 Award of the Dr. Klaus Römer-Foundation for excellence during the Ph.D. thesis

2000 FCI-Award (Fund of the Chemical Industry, Germany) for the best Chemistry-Diploma in High School

Extracurricular Activities:

2002-2004 Elected student representative in the council of the Faculty of Chemistry and Pharmacy, Ludwig-Maximilians-Universität Munich

2002-2004 President of the Chemistry Students’ Association, Ludwig-Maximilians-Universität Munich

Interests: Music, playing the guitar, traveling, reading, cooking
Communications and Full Papers:


F. M. Piller, P. Knochel, Functionalization of Furan, Thiophene, Pyrrole and Indol Derivatives via Ortho-Magnesiation Reactions, *manuscript in preparation*.
Reviews:


Poster Presentations:


F. M. Piller, P. Knochel, Preparation of Polyfunctional Aryl, Heteroaryl and Benzylic Mg- and Zn-Reagents using Magnesium in the Presence of LiCl, Synthesefest, Munich, Germany, March 2009.


Oral Presentations:


Magnesium Insertions in the Presence of LiCl, Ludwig-Maximilians-Universität Munich, February 2009.