Preparation and Reactions of Polymagnesiated Aromatics and Heteroaromatics, Functionalized Cyclopropane Carbenoids and Soluble Lanthanide Reagents

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Erklärung


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“...manchmal bestätigt uns das, was wir versuchen nicht weniger als das, was wir erreichen.”

Siegfried Lenz

in „Die Auflehnung“
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A

GENERAL INTRODUCTION
1. Overview

The needs of the pharmaceutical and agrochemical industry have tremendously driven the research on new methodologies throughout the recent years. The requirements to be addressed by new synthetic approaches have thereby become more and more sophisticated. New reagents should display excellent properties in terms of reactivity, selectivity and functional group tolerance. At the same time, they should be as inexpensive as possible, and finally are expected to be environmentally acceptable, too.

Organometallic chemistry has proven an excellent tool to address this complex set of requirements. Beginning more than 150 years ago with the pioneering work of Frankland, it has been intensively developed ever since. In our times, it offers a highly diverse toolkit for the formation of new carbon-carbon and carbon-heteroatom bonds and there is an ongoing effort to increase this diversity. The palette of metals that can be used spans a wide range and nearly every metal in the periodic system has found some useful application in synthetic organic chemistry up to now.

The origin of the diversity in the properties of organometallic reagents lays mainly in the very different polarity of the carbon-metal bond. Thus, very polar carbon-metal bonds, as, for instance, in lithium-organic reagents, display an excellent reactivity towards many electrophiles, even at low temperatures. However, this drastically diminishes the tolerance towards functional groups. On the other hand, carbon-metal bonds with more covalent character, as found, for example, in organozinc reagents, react with suitable electrophiles in a highly selective manner, tolerating a multitude of functional groups. Nevertheless, the range of appropriate electrophiles is very limited due to the comparably low reactivity of the organozinc reagents. This lack in activity can be overcome using transition metals (like Cu, Ni or Pd) as catalysts. Organomagnesium reagents, in this context, are holding a privileged position. Showing a good to excellent reactivity to a broad number of electrophiles, they exhibit, at the same time, a remarkable tolerance to a broad range of functional groups at low temperature. They are also easily transmetallated to access other organometallic species (e.g. Zn, B, Cu), displaying a different reactivity pattern. Therefore, organomagnesium reagents represent impressively flexible tools in organic synthesis.

2. Preparation and Use of Organomagnesium Compounds

2.1. Conventional Preparation Methods

In 1901, Victor Grignard for the first time published the preparation of etheric solutions of organomagnesium reagents.\(^4\) Up to now, the oxidative addition of magnesium to the halogen-carbon bond of an organic halide in polar aprotic solvents (like diethyl ether or THF) is the most commonly used method for the preparation of organomagnesium or so-called Grignard-reagents (Scheme 1).\(^5\)

\[
\begin{align*}
RX & \xrightarrow{\text{ether or THF}} \text{Mg} \quad \text{RMgX} \\
R: \text{organic rest} & \quad X: \text{Cl, Br, I}
\end{align*}
\]

**Scheme 1**: Oxidative addition of Mg to an organic halide.

Since Grignard’s first contribution, the mechanism of this reaction was an intensively discussed issue.\(^6\) Kharasch and Reinmuth in 1954 established a basis for a mechanism that proposes the participation of surface bound radicals.\(^7\) More recent investigations support this hypothesis and the insertion reaction thus can be assumed to be an at least partly radical process that takes place at the surface of the magnesium metal.\(^8\)

The resulting reagents 1 are in solution in equilibrium with their corresponding diorgano-magnesium compounds 2 and the respective magnesium salt 3 as depicted in Scheme 2. This equilibrium reaction, known as Schlenk-equilibrium, is, as a first approximation, dependent on the solvent, the temperature and the counterion X (Scheme 2).

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Further influence on the behaviour of organomagnesium reagents in solution is exerted by the aggregation of the molecules, which is dependent on the solvent and the dilution.\(^9\) Thus, in ether, aggregates of 2-4 molecules exist, with the exception of highly diluted solutions. In THF, Grignard reagents are assumed to be monomeric.

As the insertion reaction normally takes place at ambient or higher temperature (in many cases, reflux in diethyl ether or THF), the possibilities for tolerating further functional groups in the substrate are strongly limited. This limitation can be partly overcome for example using activated magnesium according to the protocol developed by Rieke. It allows conducting the insertion reaction at lower temperatures, giving thereby access to organomagnesium reagents bearing comparatively robust functional groups like a tert-butyl ester or a nitrile.\(^{10}\)

Alternatively, also a Barbier-reaction can, in some cases, make an insertion reaction possible in the presence of functional groups.\(^{11}\)

Besides the “classical” insertion reaction, many other methods have been established to access organomagnesium species. For example, the transmetallation of lithium- or mercury-organometallics has found application in synthesis.\(^{12}\) Also, the magnesiation of acetylenes and olefins was reported. The treatment of the TMS-acetylene 4 with \textit{i}-BuMgCl in the presence of dicyclopentadienyltitanium dichloride in ether leads stereoselectively to the vinylic Grignard reagent 5, which can be trapped with acetophenone to afford the desired product 6 in 78 % yield (Scheme 3).\(^{13}\) Rieke found, that activated magnesium reacts with 1,4-dienes like 7 to


Scheme 3: Examples for the magnesiation of acetylenes and olefins.

give the corresponding cyclic magnesium reagent 8 which can be trapped with ethyl butyrate at reflux conditions to afford 9 in 96 % yield. A further possibility constitutes the deprotonation using magnesium bases which has recently become a very active research field.

2.2. The Halogen/Magnesium Exchange Reaction

Even though the methods described above give access to a variety of Grignard reagents, the tolerance towards functional groups is comparatively low. Moreover, the insertion reactions frequently require activation of the magnesium surface by iodine, dibromoethane or similar additives. The activated metals as described by Rieke have first to be freshly prepared from lithium naphtalenide and the corresponding magnesium halide and the active surface, in some cases, can be deactivated by polar functional groups. Besides that, all insertion reactions have in common to be heterogeneous which can cause the reaction control to be difficult, especially, as many of these reactions are strongly exothermic and the initiation period of the reaction is often not easily estimated.

The method of choice to circumvent these problems is the halogen-magnesium exchange reaction. The bromine/magnesium exchange reaction on cinnamyl bromide (10) was the first

---

reaction of this type to be reported. In 1931, Prévost described the formation of cinnamylmagnesium bromide (11) upon treatment of 10 with EtMgBr (Scheme 4).\textsuperscript{16} Urion some years later, observed a similar reaction for cyclohexyl bromide and ethylmagnesium bromide.\textsuperscript{17}

Scheme 4: First example of a bromine/magnesium exchange.

The mechanism of this exchange is still not elucidated. However, a halogen ate complex is assumed to be an intermediate in this process.\textsuperscript{18} Similar complexes have also been proposed for the halogen-lithium exchange.\textsuperscript{19} As schematically shown in Scheme 4, the halogen/magnesium exchange is an equilibrium reaction. Thereby, the equilibrium distribution is mainly depending on the stability of the reagent, which means that always the more stable reagent is formed.

The halogen/magnesium exchange furthermore did prove a useful tool for the generation of magnesium carbenoids. Villiéras found that treatment of bromoform (12) with $i$-PrMgCl at -78 °C furnishes the magnesium carbenoid 13 which can be trapped with an electrophile like TMSCl, to afford 14 in 90 % yield (Scheme 5).\textsuperscript{20} The high activity of electron-poor substrates in the halogen/magnesium exchange reaction was also observed by Tamborski and Moore, who were able to show that 1,4-dibromo-2,3,5,6-tetrafluorobenzene (15) reacts with EtMgBr at -78 °C in only 15 min to afford the double magnesiated reagent 16 (Scheme 5).\textsuperscript{21}

\textsuperscript{17} E. Urion, Comptes rendus de l'Académie des Sciences, Paris 1934, 198, 1244.
\textsuperscript{18} (a) R. W. Hoffmann, M. Bönstrup, M. Müller, Org. Lett. 2003, 5, 313; (b) V. P. W. Böhm, V. Schulze, M. Bönstrup, M. Müller, R. W. Hoffmann, Organometallics 2003, 22, 2925.
Scheme 5: Halogen/magnesium exchange on polyhalogenated substrates.

Throughout the following years, several contributions appeared reporting about iodine/magnesium-exchange reactions. However, the real breakthrough for the halogen/magnesium exchange came in 1998, when Knochel and Cahiez reported for the first time a low-temperature iodine/magnesium exchange, giving access to Grignard reagents bearing sensitive functionalities. Since this contribution, the kind and variety of available aryl- and heteroaryl magnesium reagents has dramatically increased. Scheme 6 gives an overview on some polyfunctional organomagnesium halides prepared from the corresponding iodides. An ester or nitrile function as seen in 17a and 17b can be easily tolerated and the mild and homogeneous conditions of the halogen/magnesium exchange also allowed transferring this protocol to the solid phase. More recently, highly functionalized aniline-derived Grignard reagents like 17d were synthesized and used in the synthesis of functionalized heterocycles. Finally, using PhMgCl as the exchange reagent, even a nitro

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Scheme 6: Highly functionalized aromatic organomagnesium halides prepared from the corresponding iodides.

and a keto group can be tolerated in the same molecule (17e), as shown by Knochel and Sapountzis.\textsuperscript{27} Also, numerous heterocyclic magnesium organometallics have become easily accessible. Some examples are given in Scheme 7, including a functionalized pyridine (18a) as well as an indol (18b). Using activated heterocycles, also organic bromides can be used as substrates. By that way, for example magnesiated thiazole (18c) or pyridine (18d) derivatives can be synthesized. Using 2,3,4,5-tetrachlorothiophene, even a chlorine/magnesium exchange is possible (18e; Scheme 7).\textsuperscript{28}

Scheme 7: Heteroaromatic Grignard reagents prepared via halogen/magnesium exchange reactions using \textit{i}-PrMgBr (starting from the corresponding: \textsuperscript{a}iodide, \textsuperscript{b}bromide, \textsuperscript{c}chloride).


However, the halogen/magnesium exchange in less active systems was for a long time restricted to the corresponding iodides. The exchange reactions on aromatic bromides mostly were too slow to be useful. In some cases, the use of trialkyl magnesiate reagents (R₃MgLi) according to the work of Oshima allowed the magnesiation of less active systems.²⁹

Quite recently then, Knochel and Krasovskiy found that by addition of LiCl, a catalysis of the bromine/magnesium exchange is possible.³⁰ Thus, 4-bromoanisole (19) reacts smoothly with the mixed reagent i-PrMgCl·LiCl to give the corresponding organomagnesium species 20 in 84 % conversion after 3 d at rt. Noteworthy, without the additive, only 17 % conversion can be obtained, even after 5 d at rt (Scheme 8).

![Scheme 8: Bromine/magnesium exchange in the presence of LiCl.](image)

The aromatic Grignard reagents obtained display a higher reactivity than the respective reagents without LiCl, giving good yields in their reactions with electrophiles. To explain this behaviour, a mechanism was proposed in which an ate-like intermediate of type 21 holds the central position. Thus, the addition of LiCl breaks aggregates of the respective reagent forming this highly reactive intermediate (21). After the exchange reaction did take place, the newly formed organometallic reagent 22 also has an ate like character and

---

displays an increased reactivity. Further experimental as well as theoretical effort supports this mechanistic explanation.\textsuperscript{31}

\[
\text{\textit{i-Pr-MgCl} \rightarrow \text{LiCl} \rightarrow \text{Mg-i-Pr}}  \\
2 \rightarrow 2 \text{\textit{i-Pr-MgCl} \rightarrow \text{LiCl}}  \\
\]

\textbf{Scheme 9:} Supposed mechanism of the LiCl-catalyzed bromine/magnesium exchange.

The LiCl catalysis has already found many applications. The use of the cheaper and more stable bromoarenes instead of the corresponding iodides makes this method a big improvement in organomagnesium chemistry. An overview of some organomagnesium reagents generated \textit{via} this new method is depicted in Scheme 10. Thus, the \textit{ortho}-chloroanisole and bromopyridinol derivatives \textbf{23a} and \textbf{23b} can be easily prepared starting from the corresponding bromides, as well as the triazine-functionalized reagent \textbf{23c}.\textsuperscript{30, 32}

Acyclic alkenylmagnesium reagents like \textbf{23d} are accessible \textit{via} a LiCl-catalyzed iodine/magnesium exchange.\textsuperscript{33}

\[
\text{\textbf{23a}} \quad \text{\textbf{23b}} \quad \text{\textbf{23c}} \quad \text{\textbf{23d}}
\]

\textbf{Scheme 10:} Grignard reagents synthesized \textit{via} the LiCl-catalyzed Br/Mg exchange.

Besides halide atoms, also sulfoxide and sulfide groups can undergo exchange reactions to yield organomagnesium reagents.\textsuperscript{34} The convenience and usefulness of the halogen/magnesium exchange reaction have led to applications in industrial processes\textsuperscript{35} as well as in natural product synthesis. Two recent examples for the latter one are given below.

In 2001, Smith reported the total synthesis of Phorboxazole A, a natural product isolated from the sponge Phorbas sp., displaying antifungal, antibiotic, an especially antiproliferative activity.\textsuperscript{36} In a key step of this synthesis, a Grignard reagent derived from bromomethyl-oxazole 24 is added diastereoselectively to the lactone 25, yielding the hemiacetal 26 in 76 % yield (Scheme 11).

![Scheme 11: Bromine/magnesium exchange in the synthesis of Phorboxazole A according to Smith.](image)

A further application of the iodine/magnesium exchange reaction was recently presented by Schmalz. In the course of studies on the total synthesis of (-)-Colchicine, the iodoarene 27 was treated at -25 °C with i-PrMgCl to afford the corresponding Grignard reagent.\textsuperscript{37} Subsequent reaction with succinic anhydride, followed by the deprotection of the acetylene, furnished the intermediate 28 in 73 % yield over three steps (Scheme 12).


Scheme 12: Iodine/magnesium exchange in the total synthesis of \((-\)-Colchicine) according to Schmalz.
3. Objectives

In a first project, the iodine/magnesium exchange should be transferred on aromatic substrates bearing unprotected alcohol or acid groups, as well as on heterocyclic substrates bearing the acidic protons on the ring. This should be accomplished by the stepwise reaction with 2 Grignard reagents, one acting selectively as a base, and one as a exchange reagent (Scheme 13). Besides finding the right exchange conditions, it was envisioned, to investigate the tolerance towards functional groups in the substrate as well as in the electrophiles. Further, to apply (for the alcohols and the acids) the method to aromatic and heteroaromatic substrates. And finally, to explore which classes of electrophiles are suitable for which Grignard reagents.

![Scheme 13](image)

Scheme 13: Exchange in the presence of acidic groups.

A second project should be devoted to the synthesis of new cyclopropane carbenoids from geminal cyclopropane dibromides. Different functional groups should be studied, depending on their electronic and complexing properties as well as the reactivity towards different electrophiles (Scheme 14). Both bromine atoms should be functionalized.

![Scheme 14](image)

Scheme 14: Supposed synthesis of new cyclopropane carbenoids.
In a third project, the solubilising effect of LiCl should be applied to trivalent lanthanide salts and a possible application of such a solution as promoter for the addition of organomagnesium reagents to carbonyl compounds should be developed (Scheme 15).

**Scheme 15**: Development and use of a soluble lanthanide (III) source.
B

RESULTS AND DISCUSSION
1. Halogen/Magnesium Exchange Reactions in the Presence of Unprotected Acidic Groups

1.1. Introduction

Functional groups bearing acidic protons are contained in numerous bioactive compounds. They play a fundamental role in biochemistry, as they can interact with enzymes and receptor systems through H-bonding or lone pair donation. Furthermore, the same abilities make them valuable parts of building blocks used in materials science.

As already mentioned, organometallic reagents are among the most powerful intermediates for the construction of complex molecules. Nevertheless, the use of these species practically always requires the protection of groups containing acidic protons.

To avoid tedious protection and deprotection cycles, a method using the unprotected substrates would be highly desirable. Mase has presented a protocol using stepwise treatment with Bu₂Mg and BuLi. It allows to functionalize benzoic acid derivatives (Scheme 16) as well as the corresponding amides or benzylic alcohols. More recently, Mortier reported the metallation of unprotected benzoic acids employing strong lithium bases (Scheme 16).

![Scheme 16: Metallation protocols according to Mase and Mortier.](image)

---

The use of organolithiums, however, in both cases precludes the presence of sensitive functional groups in the substrate. The use of organomagnesium reagents for both, the deprotonation and the exchange reaction, at low temperatures should facilitate a better functional group tolerance. A first, very prominent example of such a strategy is the exchange reaction on an aryl iodide that was performed by Nicolaou in course of his synthesis of the antibiotic Vancomycin (Scheme 17).40

Scheme 17: Iodine/magnesium exchange in the synthesis of Vancomycin.

However, huge excess of the organomagnesium reagents (30 equiv each) and the electrophile (100 equiv) has to be used. A first stoichiometric protocol has recently been presented by Knochel, who double-magnesiated functionalized iodoanilines by successive treatment with PhMgCl and i-PrMgCl (Scheme 18).41

Scheme 18: Double-magnesiation of iodoanilines according to Knochel.

In both examples cited above, the first magnesium reagent (MeMgCl or PhMgCl, respectively) displays a comparatively low activity in exchange reactions. This is necessary to avoid the formation of the Grignard reagent before the complete deprotonation of the acidic moieties has occurred. Otherwise, proton transfer from remaining acidic groups can result in quenching the desired organometallic species. The second reagent (i-PrMgCl) then is used to accomplish the iodine/magnesium exchange reaction.

1.2. Iodine/Magnesium Exchange Reactions on Unprotected Aromatic and Heteroaromatic Alcohols

Aromatic alcohols are important structural elements in materials science as well as in medicinal chemistry. Due to their comparatively high acidity, they are protected in almost all cases, when used together with organometallic reagents. Therefore, we did consider this class of compounds being interesting targets for our protection free strategy outlined above.

1.2.1. Starting Material Synthesis

Starting from the corresponding commercially available 4-substituted phenols (29), iodinated phenol derivatives of type 30 are easily accessible. Treatment of the alcohols of type 29 with silver (I) sulphate and elemental iodine (2.0 equiv each) in ethanol at ambient temperature results in the rapid formation of the diiodophenols of type 30, which are isolated in good to excellent yields (86-92 %; Scheme 19). Treatment with only one equivalent of the reagents

Scheme 19: Synthesis of mono- and diiodinated phenol derivatives of type 29 and 30.

leads to a mixture of the mono-(30e,f) and diiodinated products (30a-c), as well as remaining starting material (29). However, the main products are the desired mono-iodophenols (30e,
which are isolated in 59 and 62 % yield. All other starting materials were either commercially available or were synthesized according to literature procedures.\textsuperscript{43, 44}

1.2.2. Preliminary Studies and Optimization of the Reaction Conditions

Preliminary experiments had shown that PhMgCl and MeMgCl are superior deprotonating agents compared to heterogeneous bases like NaH or Na\textsubscript{2}CO\textsubscript{3}. The reactions proceed much cleaner and the handling of the homogeneous systems is by far easier.

MeMgCl and PhMgCl did give comparable results. However, commercial PhMgCl contains impurities like biphenyl and phenolate. Especially the latter one can cause difficulties in course of the purification of the products. Furthermore, the reaction product (CH\textsubscript{4}), in case of MeMgCl, is volatile which on one hand allows an optical monitoring of the reaction and on the other hand avoids the pollution of the reaction mixture by remaining byproducts. Finally, the concentration of the commercially available solutions of PhMgCl is maximally about 2.0 M, whereas the MeMgCl-solutions have a concentration of up to 3.0 M. This allows to reduce the amount of solvents used and keeps the concentration of the reaction solution on a comparatively high level (the subsequent exchange reaction is strongly dependent on the concentration).

With this information on hands, we started our investigation on the exchange reaction. We have found that the exchange reaction on 4-hydroxy-3,5-diiodobenzonitrile (30d) was com-

![Scheme 20: Optimization of the exchange conditions.](image)

\textsuperscript{44} V. Koch, S. Schnatterer, \textit{Synthesis} \textbf{1990}, \textit{499}.
Table 1: Optimization of the conditions for the exchange on functionalized diiodophenols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>substrate</th>
<th>FG</th>
<th>equiv LiCl</th>
<th>t [min]</th>
<th>Product</th>
<th>isol. Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30d</td>
<td>CN</td>
<td>0</td>
<td>20</td>
<td>32a</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>30d</td>
<td>CN</td>
<td>1</td>
<td>20</td>
<td>32a</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>30a</td>
<td>Br</td>
<td>0</td>
<td>120</td>
<td>32b</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>30a</td>
<td>Br</td>
<td>0.5</td>
<td>35</td>
<td>32b</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>30a</td>
<td>Br</td>
<td>1</td>
<td>20</td>
<td>32b</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>30b</td>
<td>CO₂Et</td>
<td>0</td>
<td>120 (incomplete)</td>
<td>32c</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>30b</td>
<td>CO₂Et</td>
<td>1</td>
<td>60</td>
<td>32c</td>
<td>73</td>
</tr>
</tbody>
</table>

The reaction with benzaldehyde as a test electrophile afforded the desired product 32a in 80 % yield (Scheme 20 and Table 1, entry 1). However, changing the incorporated functional group to bromine, the exchange reaction needed 3 h for completion; the reaction product with benzaldehyde (32b) was only obtained in 69 % yield (Table 1, entry 3). The exchange reaction on the corresponding 4-hydroxybenzoate 30b even did not become complete, quenching with benzaldehyde after 3 h afforded the product 32c in only 55 % yield. Besides the lower reaction rates, the solubility, especially of the double magnesiated reagents, was drastically diminished.

To overcome these problems, we investigated the effect of LiCl as additive on the exchange reactions. As already mentioned earlier, Krasovskiy and Knochel had found that this salt enhances the reactivity of Grignard reagents, furthermore the solubilizing effect of LiCl was already reported in the literature. By addition of 0.5 equiv LiCl, the exchange reaction on 4-bromo-2,6-diiodo-phenol (30a) was already much faster (35 min) and the yield of the reaction product with benzaldehyde (32b) was improved to 79 % (Table 1, entry 4). Using 1.0 equivalents LiCl, the exchange reaction was complete after 20 min and the isolated yield of 32b was 84 % (Table 1, entry 5). Also, the solubility was drastically improved and the organomagnesium reagent was obtained as slightly opalescent solution. Similarly, the exchange reaction on 4-hydroxy-3,5-diiodo-benzoic acid ethyl ester (30b) was now also completed in 1 h and the desired product (32c) was isolated in 73 % yield (Table 1, entry 6). Experiments with a higher loading of LiCl resulted in less clean reactions and lower yields.

It should be mentioned that in all cases a mono-exchange was exclusively observed. This can be expected since the exchange rate is inversely proportional on the electron density of the aromatic ring. After the first exchange, the formed C-Mg bond increases the ring electron-density and therefore the second exchange is disfavoured.
1.2.3. Exchange on Aromatic Substrates

Using the optimized reaction conditions, various functionalized phenols were subjected to
double metallation and reacted with a variety of electrophiles (Scheme 21 and Table 2).

As already partly shown above, a broad range of functional groups like a bromo- (entry 1),
trifluoromethyl- (entries 2 and 3), cyano- (entries 4-9) and ester group (entries 10-12) are
perfectly tolerated. After transmetallation to copper (CuCN·2LiCl, 1.1 equiv), the allylation of

![Scheme 21 and Table 2: Exchange on functionalized iodophenol derivatives of type 30.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate of Type 30</th>
<th>Electrophile</th>
<th>Product of Type 32</th>
<th>Yield[^a] [^b] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30a</td>
<td>Br·BrCH₂</td>
<td>32d</td>
<td>62[^b]</td>
</tr>
<tr>
<td>2</td>
<td>30c</td>
<td>PhCHO</td>
<td>32e: R = Ph</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>30d</td>
<td>CyCHO</td>
<td>32f: R = Cy</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>30e</td>
<td>t-BuCHO</td>
<td>32g</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>30d</td>
<td>allyl bromide</td>
<td>32h</td>
<td>82[^c]</td>
</tr>
<tr>
<td>Entry</td>
<td>Reactants</td>
<td>Products</td>
<td>Yield (%)</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>----------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>30d</td>
<td>32i</td>
<td>71d</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>30d</td>
<td>32j</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>32h</td>
<td>t-BuCHO</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>30e</td>
<td>PhCHO</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>30b allyl bromide</td>
<td>32m</td>
<td>74c</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>30f PhCHO</td>
<td>32n</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>30g allyl bromide</td>
<td>32o</td>
<td>70c</td>
<td></td>
</tr>
</tbody>
</table>

* Yield of analytically pure products.
* A transmetallation to copper was performed (CuCN·2LiCl, 1.1 equiv).
* Carried out in the presence of CuCN·2LiCl (5.0 mol%).
* Obtained by palladium-catalyzed cross-coupling after transmetallation with ZnCl₂ using Pd(dba)₂ (5.0 mol%) and tri-2-furylphosphine (10 mol%) as a catalyst system.

31a with ethyl (2-bromomethyl) acrylate furnished the unsaturated ester 32d in 62 % yield (entry 1). Both aliphatic and aromatic aldehydes react with similar yields (entries 2 and 3). Sterically hindered aldehydes like pivaldehyde furnish the corresponding alcohols in good

---

yields (entries 4 and 8). After transmetallation using ZnCl₂ (1.1 equiv), the Grignard reagent 31d can also be successfully used in a palladium-catalyzed cross-coupling reaction⁴⁶ with ethyl 4-iodobenzoate to give the functionalized biaryl 32i in 71 % yield (entry 6). Successive treatment of the Grignard reagent 31d with B(Oi-Pr)₃ and 2,2-dimethyl-1,3-propane diol afforded the boronic ester 32j in 66 % yield (entry 7).

This method also allows to functionalize selectively 2,6-diiodophenols with two different electrophiles in 2- and 6-position. Thus, the phenol 30d was first converted to 32h employing a copper catalyzed allylation (entry 5).⁴⁷ Subsequent conversion of 32h to the corresponding Grignard reagent and reaction with pivaldehyde provided the 2,6-difunctionalized phenol derivative 32k (entry 8).

Acylation reactions can be problematic due to competitive acylation of the phenolate. Thus, the acylation of the Grignard reagent derived from 30d with benzoil chloride in the presence of substoichiometric amounts of CuCN·2LiCl (0.3 equiv) affords the desired product 32p only in 27 % yield. The product of O-acylation, benzoic acid 4-cyano-2-iodo-phenyl ester (32q) is

![Scheme 22: Tuning the selectivity of the acylation reaction (LiCl is omitted in the structures of 31h and 31i for the sake of simplicity).](image)

also isolated in 25% yield (Scheme 22). This selectivity problem can be overcome by transmetallating the organomagnesium reagent to Zn (using 1.0 equiv ZnCl₂ in THF) before applying the copper-mediated acylation protocol. This changed procedure in combination with an improved workup (removing the sideproduct 32q by saponification) gives rise to the desired product 32p in 63% yield (traces of 32q were also detected, but not isolated).

1.2.4. Exchange on Heteroaromatic Substrates

Our method can also be successfully extended to heterocyclic systems. Thus, 3-hydroxy-2-iodopyridine (33a) was converted under similar conditions (-20 °C to rt, 2 h) to the corresponding dimagnesiated species 34a (Scheme 23). The resulting reagents display a lower reactivity towards electrophiles compared to the examples discussed above. Therefore, in the case of aldehydes, an excess of the Grignard reagent of type 34 with respect to the electrophile had to be employed. The reactions with benzaldehyde and butyraldehyde (0.9 equiv each) gave the expected secondary pyridyl alcohols 35a and 35b in 70% yield each (Table 3, entries 1 and 2). Allylation with allyl bromide (1.2 equiv) provided 35c in 74% yield (entry 3).

\[ \text{Scheme 23: Exchange on iodopyridinols of type 33.} \]

48 A similar improvement by a stepwise transmetallation through Zn was recently reported, see 34e
Table 3: Exchange on iodopyridinols of type 33.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate of Type 33</th>
<th>Electrophile</th>
<th>Product of Type 35</th>
<th>Yield(a) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33a</td>
<td>PhCHO</td>
<td>35a: R = Ph</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>33a</td>
<td>n-BuCHO</td>
<td>35b: R = n-Bu</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>33a</td>
<td>allyl bromide</td>
<td>35c</td>
<td>74(^b)</td>
</tr>
<tr>
<td>4</td>
<td>33a</td>
<td>MeSSO(_2)Me</td>
<td>35d</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>33b</td>
<td>H(^+)</td>
<td>1:3</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\(^a\)Yield of analytically pure products. \(^b\)The reaction was carried out in the presence of CuCN·2LiCl (1.0 mol%).

The reaction of 34a with MeSSO\(_2\)Me (1.2 equiv) afforded the thioether 35d in 42 % yield (entry 4). The reaction of 3-hydroxy-2,6-diiodopyridine resulted in a mixture of the 2- and 6-magnesiated species in a ratio of 1:3 (determined by \(^1\)H-NMR of a sample quenched with H\(^+\); entry 5). Tries to improve the selectivity of this exchange reaction to reach a synthetically useful ratio, however, failed.

5,7-Diiodo-8-hydroxy-quinoline (36) represents another interesting heterocyclic system. On the one hand, the pharmaceutical activity against Alzheimer’s disease is well documented, especially for the 5,7-dihalogenated compounds.\(^{49}\) On the other hand, as well known complex ligand for magnesium this substrate constitutes a benchmark example for the strength of this new methodology. We were pleased to find that, upon exposure to the reaction conditions, 5,7-diiodo-8-hydroxy-quinoline was regioselectively converted to the 5-magnesiated species 37 (Scheme 24). It afforded after Cu-catalyzed allylation only the 5-allylated product (38a) in 75 % isolated yield (Table 4, entry 1). The regioselectivity was proven by 2D NMR analyses of the allylated product 38a. The corresponding correlations are depicted in Figure 1. The selectivity can be rationalized assuming that on the one hand, the alcoholate in ortho position

Scheme 24 and Table 4: Exchange on 5,7-diiodo-8-hydroxy-quinoline (36).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product of Type 38</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>allyl bromide</td>
<td>38a</td>
<td>75&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>MeSSO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>38b</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>FG = NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>38c: FG = NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>70&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>FG = Br</td>
<td>38d: FG = Br</td>
<td>60&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of analytically pure products. <sup>b</sup> Carried out in the presence of CuCN·2LiCl (5.0 mol%). <sup>c</sup> Obtained by palladium-catalyzed cross-coupling after transmetallation with ZnCl<sub>2</sub> (1.1 equiv) using Pd(dbu)<sub>2</sub> (5.0 mol%) and tri-2-furylphosphine (10 mol%) as catalyst system.

is a strong donor for electron density and thus deactivates the position 7 for the exchange reaction. On the other hand, the oxophilicity of magnesium may cause the formation of complex aggregates that make the position also sterically less accessible. The reaction with MeSSO<sub>2</sub>Me leads to the 5-thiomethyl-quinoline 38b in 76% yield (entry 2). After transmetallation to Zn, a Pd-catalyzed cross-coupling with functionalized iodoarenes opens...
access to functionalized biphenyls.\textsuperscript{46} Thus, the reactions with 4-iodo-nitrobenzene and 4-bromo-1-iodobenzene afford the desired products 38c and 38d in 70 and 60 % (entries 3 and 4).

![Diagram](image)

**Fig. 1:** HMBC-correlations observed for 38a.
1.3. Halogen/Magnesium Exchange Reactions on Unprotected Aromatic and Heteroaromatic Carboxylic Acids

As a second interesting class of substrates, we investigated the exchange reactions on benzoic acid derivatives. This is especially useful, as common protecting groups are often removed under conditions not applicable for complex functionalized substrates. Thus, alkylamides, which are frequently used in organolithium chemistry, are hydrolyzed under strongly acidic conditions and at high temperatures. The selective removal of an ester in the presence of further groups that are sensitive to basic hydrolysis can be also problematic.

1.3.1. Starting Material Synthesis

Although many iodobenzoic acid derivatives are commercially available, some substrates had to be synthesized applying standard procedures. Starting from cheap 3,5-diaminobenzoic acid (39), a literature known Sandmeyer reaction gives access to 3,5-diiodobenzoic acid (40a). Treatment with SOCl₂ and EtOH afforded the diiodinated ester (41) in 71 % yield. An iodine/magnesium-exchange reaction occurs rapidly (15 min, GC analysis) at –50 °C and subsequent reaction of the formed Grignard reagent with CO₂ gives rise to the functionalized carboxylic acid 40b in 63 % isolated yield (Scheme 25).

Scheme 25: Synthesis of the 3,5-difunctionalized benzoic acids 40a and 40b.

The pivalate protected iodosalicylic acid ester 40c was synthesized by boiling commercial 5-iodosalicylic acid ester in pivalic anhydride for 2 h. Upon cooling and treatment with water, the desired product precipitates and can be easily isolated by filtration in 76 % yield (Scheme 26). 5-Cyano-2-hydroxy-3-iodobenzoic acid (43) was synthesized according to the methodology described above (chapter 1.2). Thus, deprotonation with MeMgCl in the presence of LiCl and subsequent exchange reaction using i-PrMgCl gave access to the double magnesiated species, which was trapped with an excess of CO\textsubscript{2}. Under these conditions, the functionalized benzoic acid 43 was obtained in 79 % yield (Scheme 26).

**Scheme 26**: Synthesis of 2-[(2,2-dimethylpropanoyl)oxy]-5-iodobenzoic acid (40c) and 5-cyano-2-hydroxy-3-iodobenzoic acid (43).
1.3.2. Exchange on Aromatic Substrates

In a first experiment, we reacted 4-iodobenzoic acid (40d) in the presence of LiCl (1.0 equiv) with MeMgCl (1.0 equiv) at -20 °C, and subsequently added i-PrMgCl. After warming up to rt and stirring for 3 h, a nearly full conversion to the desired Grignard reagent (44d) was observed. However, when benzaldehyde was added (1.2 equiv, at -20 °C, then warming up to rt), the reaction did not become complete and the desired product 45a was isolated in only 44 %. The reaction was sluggish and the solubility of the reagents obviously was worse than in the case of the phenols. Thus, we tried again with allover 2.0 equiv of LiCl by using i-PrMgCl-LiCl (1.1 equiv) as the exchange reagent. After warming up to rt and stirring for 0.5 h, a full conversion to the desired magnesium reagent was observed. Also the reaction with benzaldehyde, in this case, was readily completed after 0.5 at -20 °C to rt and the desired alcohol 45a was isolated in 95 % yield (Table 5, entry 1).

With these optimum conditions in hands, we applied this protocol to various electrophiles and substrates. The copper(I)-mediated acylation reaction with benzoyl chloride afforded the desired product 45b and 71 % isolated yield (Table 5, entry 2). Applying a mild acidic workup using citric acid, even a sensitive boronic ester can be installed by sequential reaction with B(Oi-Pr)₃ and 2,2-dimethyl-propane-1,3-diol, yielding 50 % of the desired product (45c) after recrystallization (entry 3). As shown in entry 4-6 of Table 5, also meta- (40e) and ortho- (40f) positions can be easily metallated using this protocol. The desired products from the reactions with pivaldehyde and cyclohexane carbaldehyde (45d and 45f) are obtained in 72 and 87 %, respectively (entries 4 and 6, Table 5). Remarkably, even using a functionalized electrophile like ethyl 2-(bromomethyl) acrylate the ester group is not affected and the allylated product 45e is obtained in 78 % yield (entry 5).

Several functionalized substrates can be used. Halides like a bromide (40g) or an additional iodide (40a) can be present. Whereas 3-bromo-5-iodobenzoic acid (40g) is cleanly converted to the corresponding Grignard reagent at -20 °C, the use of the (more reactive) diiodobenzoic acid 40a requires lower temperatures to afford a clean exchange reaction (-50 °C). The resulting Grignard reagents, in both cases, show good reactivity towards electrophiles and the products from their reactions with cyclohexane carbaldehyde, 4-bromo benzaldehyde or allyl bromide (45f, 45g, 45i) are isolated in 69-91 % yield (entries 7, 8 and 10). The reactions of these organomagnesium reagents with TsCN give rise to the corresponding benzonitriles 45h.
Scheme 27 and Table 5: Iodine/magnesium exchange on functionalized benzoic acid derivatives of type 40.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate of Type 40</th>
<th>Electrophile</th>
<th>Product of Type 45</th>
<th>Yielda [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40d</td>
<td>PhCHO</td>
<td>45a</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>-20 °C to rt, 45 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40d</td>
<td>PhCOCl</td>
<td>45b</td>
<td>71b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40d</td>
<td>B(Oi-Pr)_3</td>
<td>45c</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>1) B(Oi-Pr)_3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2) OH OH OH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40e</td>
<td>t-BuCHO</td>
<td>45d</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>-20 °C to rt, 45 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>40e</td>
<td>Br-CO_2Et</td>
<td>45e</td>
<td>78c</td>
</tr>
<tr>
<td>6</td>
<td>40f</td>
<td>CyCHO</td>
<td>45f</td>
<td>87</td>
</tr>
</tbody>
</table>

-20 °C to rt, 45 min
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td><img src="image1" alt="Reaction 7" /></td>
<td>-20 °C, 60 min</td>
</tr>
<tr>
<td>8</td>
<td><img src="image2" alt="Reaction 8" /></td>
<td>-50 °C, 60 min</td>
</tr>
<tr>
<td>9</td>
<td><img src="image3" alt="Reaction 9" /></td>
<td>-50 °C, 60 min</td>
</tr>
<tr>
<td>10</td>
<td><img src="image4" alt="Reaction 10" /></td>
<td>-50 °C, 60 min</td>
</tr>
<tr>
<td>11</td>
<td><img src="image5" alt="Reaction 11" /></td>
<td>-50 °C, 60 min</td>
</tr>
<tr>
<td>12</td>
<td><img src="image6" alt="Reaction 12" /></td>
<td>-20 °C, 60 min</td>
</tr>
<tr>
<td>13</td>
<td><img src="image7" alt="Reaction 13" /></td>
<td>-20 °C, 40 min</td>
</tr>
</tbody>
</table>
and 45j in only moderate yields of 40 % and 55 % (entries 9 and 11). Impurities contained in
the electrophile (commercially available TsCN is purchased in a technical purity of about
95 %) as well as the side product of the reaction with electrophile (tosyl sulfonic acid) are
not easily separable and complicate the purification.

Ester groups are perfectly tolerated, too. Thus, the ethyl ester 40h is smoothly metallated and
after reaction with pivaldehyde, the desired product (45k) is isolated in 70 % yield (entry 12).
Even a very sensitive pivaloate like 40i is an appropriate substrate and the reaction with
4-Br-C₆H₄SSO₂Ph proceeds smoothly. However, chromatographical purification on silica
results in the cleavage of the pivalate group and the corresponding 5-thiolated salicylic acid
45l is isolated in 54 % (entry 13). This shows the instability of this pivalate protecting
group. To demonstrate the stability of this group towards the reaction and workup conditions,
a bulky anthracene group was installed by reaction with anthraldehyde. By that way, it was
possible, to avoid chromatographical purification, as the crude product was a solid that was
precipitated. The desired pivalate 45m was isolated in 67 % yield (entry 14).

Finally, a sterically hindered substrate like 40j reacts smoothly under the usual reaction
conditions, quenching with p-bromobenzoyl chloride affords the ketoacid 45n in 81 % yield
(entry 15).

Finally, we were interested, if this protocol can also be used for substrates bearing two acidic
protons. Thus, we treated 5-cyano-2-hydroxy-3-iodobenzoic acid (43) first at -20 °C with two

\[ \text{Yield of analytically pure products.}^{\text{b}} \text{ The reaction was carried out in the presence of CuCN·2LiCl (20 mol%).} \]
\[ \text{c A transmetallation to copper with CuCN·2LiCl (1.15 equiv) was performed.}^{\text{b}} \text{ The reaction was carried out in the presence of (1.0 mol%).} \]

\[ \text{14} \quad 40i \quad \text{anthraldehyde} \quad 45m \quad 67 \]

\[ \text{15} \quad 40j \quad 4-\text{Br-} \quad 45n \quad 81^{\text{b}} \]

-20 °C to rt, 45 min

\[ \text{a} \]

51 It should be noted, that a purification by recrystallization could not be achieved, as the crude reaction product
was a viscous oil.
equivalents of MeMgCl (in the presence of an equimolar amount of LiCl), then with \textit{i-PrMgCl-LiCl} (1.05 equiv, -20 °C, 2 h) to get the triple-magnesiated benzonitrile 46, which reacted with PhSSO\textsubscript{2}Ph to give the highly functionalized product 47\textit{a} in 55 % yield (Scheme 28). 46 can also be transmetallated to Zn and used in a \textit{Negishi}-cross-coupling with 4-iodoethyl benzoate even though the yield is drastically lower and the desired biphenyl 47\textit{b} is isolated in only 26 % (Scheme 28).

\begin{center}
\begin{tikzpicture}
 \node at (0,0) {43};
 \node at (4,0) {46};
 \node at (8,0) {47\textit{a}: 55 \%};
 \node at (8,-4) {47\textit{b}: 26 \%};
 \node at (0,-8) {41};
 \node at (-3,-8) {40};
 \draw[->] (0,0) -- (4,0) node[midway,above] {1) MeMgCl, LiCl (2.0 equiv) THF, -30 °C};
 \draw[->] (4,0) -- (4,-4) node[midway,above] {2) \textit{i-PrMgCl-LiCl} (1.1 equiv) THF, -30 °C};
 \draw[->] (0,0) -- (8,0) node[midway,above] {PhSSO\textsubscript{2}Ph (1.1 equiv) -20 °C to rt};
 \draw[->] (0,-4) -- (8,-4) node[midway,above] {1) ZnCl\textsubscript{2}, THF, -20 °C to rt};
 \draw[->] (8,-4) -- (8,-8) node[midway,above] {2) Pd(dba)\textsubscript{2}, tfp 50 °C, 3 h};
 \end{tikzpicture}
\end{center}

\textbf{Scheme 28:} Generation and reactions of the triple magnesiated intermediate 46.

Attempts to use bromobenzoic acid derivatives as substrates failed. The exchange reaction is very slow and the attack of the exchange reagent to the carboxylate was observed as a side reaction.
1.3.2. Exchange on Heteroaromatic Substrates

Even though aromatic bromides did prove not suitable as substrate for our exchange protocol, we found, that highly activated heteroaromatic substrates like 5-bromo-2-furoic acid (48a), 5-bromothiophene-2-carboxylic acid (48b), or 4,5-dibromothiophene-2-carboxylic acid (48c) react rapidly in a bromine/magnesium exchange reaction at -20 to rt (Scheme 29 and Table 6). Thus, 5-bromo-2-furoic acid (48a) is magnesiated in only 30 minutes and its reactions with allyl bromide and 4-(trifluoromethyl)benzaldehyde lead to the expected products 49a and 49b in 92 and 88 % yields (entries 1 and 2). Analogously, the corresponding thiophene carboxylic acid 48b was smoothly metallated and reacted with benzaldehyde or MeSSO₂Me to afford the alcohol 49c as well as the thioether 49d in 72 and 93 % yield, respectively (entries 3 and 4). Transmetallation of the same Grignard reagent with ZnCl₂ followed by a Pd-catalyzed cross-coupling⁴⁶ with 4-iodo-N,N-dimethylaniline using Pd(dbca)₂ (5.0 mol%) and tri-2-furylphosphine (10 mol%) as a catalyst system, affords the functionalized biaryl 49e in 95 % yield (entry 5). 4,5-Dibromothiophene-2-carboxylic acid (48c) can be selectively magnesiated in the 5-position (-20 °C, 1 h). The resulting organometallic was quenched with water and the corresponding product 49f was isolated in 99 % yield (entry 6). The magnesium reagent was also reacted with allyl bromide to give the desired product 49g in 97 % yield (entry 7). Both compounds, 49f and 49g are known in the literature and were identified by comparison of the NMR data (see experimental section). The reaction with ethyl chloroformate gives, after recrystallization, 56 % of the desired product 49h. Attempts, to subject this molecule to a second Br/Mg-exchange, unfortunately failed.

\[
\text{Scheme 29: Exchange on furane and thiophene carboxylic acid derivatives.}
\]
Table 6: Exchange on furane and thiophene carboxylic acid derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate of Type 48</th>
<th>Electrophile</th>
<th>Product of Type 49</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br-O CO₂H</td>
<td>48a</td>
<td>allyl bromide</td>
<td>49a 92&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>-20 °C to rt, 30 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>48a</td>
<td>p-FCC₆H₄CHO</td>
<td>49b</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Br-S CO₂H</td>
<td>48b</td>
<td>PhCHO</td>
<td>49c 72</td>
</tr>
<tr>
<td></td>
<td>-20 °C to rt, 30 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>48b</td>
<td>MeSSO₂Me</td>
<td>49d</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>48b</td>
<td>p-NMe₂C₆H₄I</td>
<td>49e</td>
<td>95&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Br-S CO₂H</td>
<td>48c</td>
<td>H⁺</td>
<td>49f 99</td>
</tr>
<tr>
<td></td>
<td>-20 °C, 60 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>48c</td>
<td>allyl bromide</td>
<td>49g</td>
<td>97&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>48c</td>
<td>ClCO₂Et</td>
<td>49h</td>
<td>56</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of analytically pure products. <sup>b</sup> The reaction was carried out in the presence of CuCN·2LiCl (1.0 mol%). <sup>c</sup> Obtained by palladium-catalyzed cross-coupling after transmetallation with ZnCl₂.
We also were interested to use an N-heterocyclic substrate like 5-bromonicotinic acid (50). Even though the exchange reaction becomes nearly complete (TLC monitoring), the reactions of the Grignard reagent 51 with electrophiles like allyl bromide or PhSSO₂Ph proceed sluggishly, giving complex mixtures which could not be separated (Scheme 30).

**Scheme 30**: Attempted functionalization of 5-bromonicotinic acid (50).
1.4. Iodine/Magnesium-Exchange Reactions on Unprotected Imidazole Derivatives

The imidazole core is an important structural unit in the field of natural products and bioactive compounds. The functionalization of this basic structure using a halogen-metal exchange reaction has been intensively investigated as the halogenated starting materials are easily accessible. However, in almost all cases the acidic NH-group should be protected and the protecting group has to be removed after the reaction. A recent method using the unprotected substrate requires large excess of all reagents and gives only modest yields of the desired products.

Thus, we have reacted iodoimidazoles of type 52 with one equivalent of MeMgCl in the presence of LiCl (1.0 equiv) followed by the addition of i-PrMgCl·LiCl affording the corresponding Grignard reagent 53 which was trapped with different electrophiles. Trapping the organomagnesium reagent 53a with pivaldehyde affords the expected alcohol 54a in 98 % yield (entry 1, Table 7). The installation of a thioether group is realized by reacting 53a with MeSSO₂Me, affording the desired product 54b in 71 % yield (entry 2). The diiodinated substrate 52b can be transformed into the organomagnesium species 53b using the same set of conditions. The reaction with a sterically hindered aliphatic or an aromatic aldehyde proceeds smoothly and the products 54c and 54d were isolated in 85 and 86 % yield (entries 3 and 4).

Scheme 31: Exchange on mono- and diiodoimidazoles of type 52.

---


Table 7: Exchange on mono- and diiodoimidazoles of type 52.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate of Type 52</th>
<th>Electrophile</th>
<th>Product of Type 54</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="52a" /></td>
<td>t-BuCHO</td>
<td><img src="image" alt="54a" /></td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>52a</td>
<td>MeSSO₂Me</td>
<td><img src="image" alt="54b" /></td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="52b" /></td>
<td>t-BuCHO</td>
<td><img src="image" alt="54c" />: R = t-Bu</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="52b" /></td>
<td>PhCHO</td>
<td><img src="image" alt="54d" />: R = Ph</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>52b</td>
<td>allyl bromide</td>
<td><img src="image" alt="54e" /></td>
<td>97&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>52b</td>
<td><img src="image" alt="CO₂Et" /></td>
<td><img src="image" alt="54f" /></td>
<td>42&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="52b" /></td>
<td><img src="image" alt="EtO₂C" /></td>
<td><img src="image" alt="54f" /></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="52b" /></td>
<td>PhSSO₂Ph</td>
<td><img src="image" alt="54g" />: R' = Ph</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="52b" /></td>
<td>MeSSO₂Me</td>
<td><img src="image" alt="54h" />: R' = Me</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="52b" /></td>
<td><img src="image" alt="Br" /></td>
<td><img src="image" alt="54i" /></td>
<td>54&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="52b" /></td>
<td><img src="image" alt="NC" /></td>
<td><img src="image" alt="54j" /></td>
<td>61&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields of analytically pure products. <sup>b</sup> The reaction was performed in the presence of CuCN·2LiCl (1.0 mol%). <sup>c</sup> A transmetallation to copper using CuCN·2LiCl was performed. <sup>d</sup> The reaction was performed in the presence of CuCN·2LiCl (20 mol%). <sup>e</sup> Pd-catalyzed cross-coupling after transmetallation using ZnCl₂, Pd(dba)₂ (5.0 mol%) and tfp (10 mol%) were used as catalyst system.
The reaction of 53b with allyl bromide in the presence of a catalytic amount of CuCN·2LiCl affords the product 54e in 97 % yield (entry 5). However, using ethyl (2-bromomethyl)acrylate after transmetallation to copper, the yield drops dramatically and the allylation product 54f is obtained in 42 % (entry 6). The reaction of the magnesiated imidazole 53b with thiosulfonates proceeds cleanly providing the desired thioethers 54g and 54h in 64 and 73 % isolated yields (entries 7, 8). The introduction of a benzyl group is often accomplished by multistep processes in imidazole derived systems. Thus, the heterocyclic reagent 53b was reacted directly with a benzylic bromide to afford the expected product 54i in 54 % yield (entry 9). The organomagnesium species can also be transmetallated to Zn (ZnCl₂, 1.1 equiv) and used in a Pd-catalyzed cross-coupling reaction with 4-iodobenzonitrile. The expected product 54j is obtained in 61 % yield (entry 10).

Furthermore, we have subjected the thioether 54g to the previously used conditions and found that the exchange was smoothly completed in 45 min at -20 °C to give the dimagnesiated species 55 (Scheme 32). A copper-catalyzed allylation affords the desired product 56a in 63 % yield. Reacting 55 with (2E)-hex-2-enal gives the allylic alcohol 56b in 58 % yield.

![Scheme 32](image_url)

Scheme 32: Second exchange in the imidazole system.
1.5. Halogen/Magnesium-Exchange Reactions on Unprotected Uracil Derivatives

The functionalization of uracil and related nucleobase derivatives has been extensively investigated, as these systems represent core structural elements in a broad variety of pharmaceutically active compounds.\textsuperscript{56} Using organometallic methods, at least one of the two acidic protons in the uracil moiety has to be protected.\textsuperscript{57} The use of a completely unprotected halouracil as a substrate would thus complement the organometallic methodology known up to now. Furthermore, the generation of a triple anionic intermediate appears highly challenging, as this system should be highly prone to aggregate (e.g., 5-iodouracil (57a) itself is nearly insoluble in THF) and by this way give us the opportunity to prove the capability of our method in terms of reactivity and solubility.

1.5.1. Exchange on 5- and 6-Iodouracil

It turned out that 5-iodouracil (57a) is readily soluble in THF in the presence of LiCl (2.0 equiv; 0.5 M solution). After the addition of MeMgCl (2.0 equiv), the reaction mixture is still a clear solution. After adding i-PrMgCl (1.2 equiv), the magnesiated species 58a finally precipitates to give a thick, but still stirrable slurry. The use of three equivalents of LiCl is essential, experiments with less equivalents resulted in lower conversions. The magnesium reagent 58a can be easily trapped by the reaction with different electrophiles. Thus, the reaction with sterically demanding, aliphatic, aromatic or heteroaromatic aldehydes (1.3 equiv) affords the desired products 59a-d in 55 to 78 % yield (table 8, entries 1, 3-5). The reagent 58a can also be reacted with TMSCl. In this case, a larger excess of the electrophile (3.3 equiv) has to be used. After acidic aqueous workup, the desired product 59e, bearing only one TMS group, is isolated in 72 % yield (entry 6). The reaction with allyl bromide in the presence of catalytic amounts of CuCN-2LiCl (1.0 mol%) proceeds smoothly, giving the product 59f in 84 % yield (entry 7). The introduction of a sulfur functionality is conveniently accomplished by reacting 58a with thiosulfonates of the type R^2SSO_R^2. The corresponding thioethers 59h and 59i are prepared in 77 % and 64 % yield (entries 9 and 10). The installation of an ester group by the reaction with ethyl chloroformate is problematic, the


Scheme 32 and Table 8: Exchange reactions on 5- and 6-halouracils and reactions with electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate of Type 57</th>
<th>Electrophile</th>
<th>Product of Type 59</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57a</td>
<td>t-BuCHO</td>
<td>59a</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>57b</td>
<td>t-BuCHO</td>
<td>59a</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>57a</td>
<td>PhCHO</td>
<td>59b</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>57a</td>
<td>CyCHO</td>
<td>59c</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>57a</td>
<td>S</td>
<td>59d</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>57a</td>
<td>TMSCl</td>
<td>59e</td>
<td>61&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of isolated product.

<sup>e</sup> Yield after chromatography.

57a: X = I; Y = H
57b: X = Br; Y = H
57c: X = H; Y = I

59a-k: X = E, Y = H; 14-84 %
59l-m: X = H, Y = E; 64-69 %
isolated yields of analytically pure products. The reaction was performed in the presence of CuCN·2LiCl (1.0 mol%). A transmetallation to copper using CuCN·2LiCl was performed. The reaction was performed in the presence of CuCN·2LiCl (20 mol%). Pd-catalyzed cross-coupling after transmetallation using ZnCl₂· Pd(dba)₂ (5.0 mol%) and tfp (10 mol%) were used as catalyst system.

desired product 59j can only be isolated in 14 % yield (entry 11). The reaction with benzoyl chloride (not listed) did even run worse, giving a complex mixture which suggests that acid chlorides in general are no suitable electrophiles for this type of Grignard reagents. Also a lanthanide promoted addition to diphenyl acetone (see chapter 3) did not prove successful and the desired product 59k was isolated in only 20 % yield (entry 12).
The cheaper 5-bromouracil (57b) can be magnesiated using i-Pr₂Mg·LiCl (1.1 equiv). The reactions with standard electrophiles like t-BuCHO or methallyl bromide require a larger excess of the electrophiles (2.8 equiv) and provide lower yields than using 5-iodouracil (57a) as a substrate (compare to entries 2 and 8).

Similarly to 5-iodouracil, 6-Iodouracil (57c) can be smoothly metallated using the same reaction sequence. To receive a clean exchange reaction, the temperature should be kept at -20 °C. The reactions with allyl bromide and t-BuCHO proceed smoothly and give access to the expected products 59l and 59m in 64 % and 69 % yield, respectively (entries 13 and 14).

![Scheme 33: Functionalization of 6-iodopurine (60).](image)

Finally, we have applied our protocol to the purine core. An elegant magnesiation of purine derivatives with functionalization of the 6-position has been recently developed by Dvořák. Using the “LiCl-effect” it is now possible to achieve the magnesiation in position 6 without the need for a protecting group. Thus, 6-iodopurine (60) is, after deprotonation, subjected to an iodine/magnesium-exchange to produce the magnesium reagent 61, which reacts with PhSSO₂Ph to give the desired product 62 in 55 % yield (Scheme 33).

---

58 For the synthesis of 6-iodouracil, see: W. Pfleiderer, H. Deiss, Israel J. Chem. 1968, 6, 603.
1.5.2. Synthesis of Precursors for HEPT (69) and Emivirine (70)

Artificial nucleobase derivatives have found important applications as drugs, especially for the treatment of HIV and a broad variety of uracil derivatives has been tested for their activity. Many active compounds bear an alkyl substituent in 5-position and variable groups in the adjacent position 6. Encouraged by our results with 6-iodouracil (57c) as a substrate, we investigated the magnesiation of unprotected 5-alkyl-6-iodouracil derivatives of type 63. Generally, substrates of type 64 are readily accessible via a tricomponent reaction starting from urea, a malonic acid diester (most commonly, the ethyl ester is used) and the corresponding alkyl halide in presence of a base (usually NaOEt). Isopropylbarbituric acid (64b) is commercially available. The chlorination of these alkylbarbituric acids using POCl₃ and catalytic amounts of H₃PO₄ at reflux gives access to the 5-alkyl-chlorouracils of type 65 in good yields (Scheme 34). The conversion of chloropyrimidines into the corresponding iodides is well documented and is, in most of the cases, achieved by treating the chloropyrimidine in DMF with sodium iodide at elevated temperature. However, using the sterically hindered substrate 65b as a test system, subjecting it to these conditions, we found that a dechlorination cleanly took place, without installing the iodine in the molecule. Therefore, we had to choose a milder method. We were pleased to find, that treatment of the chlorides 65a and 65b with sodium iodide in 54 % HI at room temperature affords, after 1 to 3 days, the desired iodides 63a-b in 71 to 74 % yield. However, it should be noted, that the efficiency of this reaction is strongly dependent on the purity of the HI used, even though it always proceeds in a spot-to spot manner (as seen by TLC). Elemental iodine and other impurities can drastically decrease the purity of the crude product and by that way lower the yields, due to more complicated purification. The magnesiation according to our protocol occurs smoothly in case of both, the methyl (63a) and isopropyl (63b) derivatives, affording the triple magnesiated species of type 66. The introduction of a thio ether moiety by treating 66a with PhSSO₂Ph affords 67 in only 40 % yield. The reaction obviously does not go to completion and the main side product is the protolysis product of the Grignard reagent. This lents to assume that the reagent is quite sensitive and possibly unstable. Variations in the con-

Table 9: Optimization for the benzylation of the Grignard reagent 66b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BnBr, CuCN·2LiCl (20 mol%), TBAI, -20 °C to rt</td>
<td>~30&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1) Cul·2LiCl (1.3 equiv), -30 °C, 30 min</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>2) BnBr (2.0 equiv), -30 °C to rt</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1) CuI·2LiCl (1.3 equiv), -30 °C to rt, 30 min</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>2) BnBr (2.0 equiv), -30 °C to rt</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>BnI, CuCN·2LiCl (20 mol%), -30 °C to rt</td>
<td>25&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1) ZnCl₂ (1.5 equiv), -30 °C to rt</td>
<td>traces</td>
</tr>
<tr>
<td></td>
<td>2) BnBr, CuCN·2LiCl (20 mol%), -30 °C to rt</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1) Cul·2LiCl (1.5 equiv), -30 °C to rt, 30 min</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>2) BnBr (2.0 equiv), -30 °C to rt</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1) Cul·2LiCl (1.3 equiv), -30 °C, 5 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2) BnBr (2.0 equiv), -30 °C, 5 min, then to rt</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>1) Cul·2LiCl (1.5 equiv), -30 °C to rt, 30 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2) BnCl (2.0 equiv), -30 °C to rt</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

* Isolated yields of analytically pure products. <sup>b</sup> Not separable from TBAI. <sup>c</sup> BnI was generated <em>in situ</em> by a Finkelstein reaction in THF.

Conditions and the use of diphenyl disulfide as an electrophile did not significantly change the yield (max 38 %). Several conditions were tried for the benzylation reaction, the results of the optimization experiments are given in Table 9. Benzyl bromide turned out to be the superior electrophile, whereas benzyl iodide and benzyl chloride give worse results (compare with entries 4, 8). Using Cul·2LiCl as copper(I)-source and warming up to rt proved to be the most successful conditions. Thus, the reaction of 66b with benzyl bromide after transmetallation using Cul·2LiCl furnishes the uracil derivative 68 in 57 % yield.

The resulting products 67 and 68 are precursors of <em>HEPT</em> (69) and <em>Emivirine</em> (70), both highly potent agents for the treatment of HIV (Scheme 34).<sup>63</sup>

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Scheme 34: Synthesis of precursors for HEPT (69) and Emivirine (70).
2. Diastereoselective Synthesis of Cyclopropane Carbenoids Bearing a Nitrile Function

2.1. Introduction

The cyclopropane ring is a structural subunit of numerous bioactive compounds. Therefore, cyclopropane derivatives can be frequently found as targets in natural product and pharmacological chemistry.\(^\text{64}\) Thus, for instance, the taxoid 71, containing 2 cyclopropane units, displays an extremely high potency (2.95 nM) against drug resistant human breast cancer (Scheme 35).\(^\text{64b}\) Moreover, the cyclopropane moiety is also important in agrochemistry and constitutes the core structural unit of highly successful pyrethroid insecticides like Deltamethrin (72, Scheme 35).\(^\text{65}\) Thus, not surprisingly, the functionalization of cyclopropane derivatives has been extensively investigated.\(^\text{66}\)

\[\text{Scheme 35: Bioactive substances containing cyclopropane subunits.}\]

Carbenoids constitute compounds bearing a metal and a leaving group on the same carbon atom. Such derivatives are known for a multitude of metals, like, for example, zinc,\(^\text{67}\)


manganese or magnesium. The historical provenience of the latter ones was already mentioned above. In preceding studies, Knochel examined especially the generation of magnesium carbenoids using a halogen-magnesium exchange reaction. In the same group, the cyclopropane core was recently used for the generation of cyclopropylmagnesium carbenoid starting from the geminal dibromide (Scheme 36). This methodology proves to be especially useful, as it allows the stereoselective manipulation of one of the geminal halogen atoms and by that way the highly diastereoselective synthesis of functionalized cyclopropane derivatives of type 75.

2.2. Starting Material Synthesis and Preliminary Experiments

In this project, we intended to expand this methodology to further functionalized cyclopropane substrates. In the literature, a large number of geminal cyclopropane dihalides are known. Many of them are easily accessible via the reaction of the corresponding haloform with an olefin in the presence of a strong base under phase transfer catalysis (PTC) conditions. For the use in a diastereoselective exchange reaction a functional group in position to the dibromide, able to direct the exchange reagent by complexation, was regarded to be useful.

Scheme 36: Diastereoselective Br/Mg-exchange on the functionalized dibromopropane 73.

\[
\begin{align*}
\text{Me}_{n}, \text{O}_{2} \text{C} \quad \text{Br} & \xrightarrow{i-\text{PrMgCl}} \quad \text{EtO} \quad \text{Br} \\
\text{EtO} & \xrightarrow{-40 ^\circ \text{C}, 15 \text{ min}} \quad \text{Me}_{n}, \text{O}_{2} \text{C} \quad \text{E} \\
\text{E}^+ & \xrightarrow{} \quad \text{Me}_{n}, \text{O}_{2} \text{C} \quad \text{E}
\end{align*}
\]

Scheme 36: Diastereoselective Br/Mg-exchange on the functionalized dibromopropane 73.

For further recent work on cyclopropane magnesium derivatives, see: (b) M.S. Baird, A. V. Nizovtsev, I. G. Bolesov, Tetrahedron 2002, 58, 1581.

Scheme 37: Access to 76 and 77 following literature procedures.

With this objective in mind, the starting materials 76 and 77 were chosen and synthesized according to literature procedures (Scheme 37). Whereas the nitrile function of 76 should, due to the geometry of the molecule, display a lower ability to stabilize a magnesium reagent in β-position than the respective ester (no 5-membered ring through coordination, compare to 74 above), the electronic situation should be comparable in both molecules. Conversely, the benzylic ether 77 should have good coordination properties but lacks an electron withdrawing

Scheme 38: Attempted Br/Mg-exchange on the ether-functionalized substrate 77.

---

group in α-position to the dibromide. Test reactions using the starting dibromide 77 showed that a diastereoselective exchange reaction with i-PrMgCl (1.1 equiv) took place to give the magnesium reagent 78a. Unfortunately, even at -78 °C, the reaction cannot be stopped at this stage and 78a reacts with a further molecule of i-PrMgCl to give the magnesium derivative 78b. Therefore, trapping with an electrophile always results in mixtures of products of type 79a and 79b. As similar reactions are known in the literature 67b,69a and a clean monoexchange was not possible, we did focus our attention to the second substrate. We were pleased to find that using 2,2-dibromo-1-methyl-cyclopropanecarbonitrile (76), different results are obtained. In this case, the magnesium reagent 80 is formed in a diastereoselective manner and can be trapped with an electrophile (Scheme 39).

Despite the fact that this reaction is proceeding very cleanly according to GC analysis, the isolated yields for an allylation reaction in the first experiments were quite low (30-34 %). Polymeric fragments of 80 detected by GC-MS lent us to assume that some of the Grignard reagent is lost due to polymerization. We further supposed that the use of solvents which are less complexing than diethyl ether or THF should lead to a less reactive and therefore more stable magnesium reagent (as complexing solvents increase the reactivity by breaking aggregates of the magnesium reagent to yield the more reactive, monomeric species).

2.3. Functionalization of 2,2-Dibromo-1-methyl-cyclopropane-carbonitrile (76) via Halogen/Magnesium and Sulfoxide/Magnesium Exchange Reactions

Indeed, further investigations showed that the reaction of 76 with i-PrMgCl in a mixture of diethyl ether and dichloromethane (1:4) at -50 °C leads within 5 min to the clean formation of
the cis-cyclopropylmagnesium reagent 80. Dichloromethane proved to be superior to other solvents tested like toluene or t-BuOMe, as it gives clean reactions and at the same time, keeps all components in solution, even at -50 °C. Quenching 80 with aqueous ammonium chloride affords only the trans-2-bromocyclopropanecarbonitrile (81b) in 76 % yield with a diastereomeric ratio of >99:1 (Table 10, entry 1). The relative configuration was proven by 2D NMR spectroscopy (Fig. 2). The selectivity of this reaction could be explained assuming a precoordination of the exchange reagent by the nitrile function rather than by intramolecular stabilization through chelation. Considering the geometry of the system, only a side-on coordination of the magnesium to the nitrile would be possible.

The reaction of magnesium reagent 80 with iodine provides the desired iodobromocyclopropane 81c with a diastereoselectivity of 91:9 and a yield of 77 % (entry 2). The reactions of the cyclopropylmagnesium derivative 80 with MeSSO₂Me and PhSSO₂Ph provide the corresponding thioethers 81d (72 %; dr = 93:7) and 81e (86%; dr = 95:5; entries 3 and 4). G. Sklute was able to prove the cis-configuration of the cyano and thiophenyl groups by X-ray analysis of the thioether 81e.

![Fig. 2: Interactions observed in a NOESY experiment on 81b.](image)

The reaction of 80 with N,N-diethylaminomethylbenzotriazolate⁷⁴ provides the aminomethylated product 81f in 79 % yield (dr = 96:4; entry 5). The reaction of the magnesium carbenoid 80 with allyl bromide in the presence of CuCN·2LiCl (0.5 mol%) furnishes the allylated cyclopropane 81a in 78 % yield (dr > 99:1; entry 6). However, electrophiles requiring a larger amount of copper seem not to be suitable. Different loadings (5 %-100 %) of CuCN·2LiCl were tried for the acylation with benzoyl chloride, always leading to complex mixtures, the desired product 81g was not detected by GC-MS (entry 7).

Scheme 40 and Table 10: Exchange on 76 and the reactions with various electrophiles.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product of type 81</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield&lt;sup&gt;b&lt;/sup&gt; [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;C=CHBr</td>
<td>&gt;99:1</td>
<td>76</td>
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<td>2</td>
<td>I&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;C=CHBr</td>
<td>91:9</td>
<td>77&lt;sup&gt;c,e&lt;/sup&gt;</td>
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<tr>
<td>3</td>
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<td>93:7</td>
<td>72&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
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<td>79</td>
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<td>PhCOCl</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;C=CHBr</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

<sup>a</sup> Diastereomeric ratio determined by GC-MS analysis of the reaction mixture.

<sup>b</sup> Isolated yields of analytically pure compounds. Yields refer to the pure main diastereoisomer.

<sup>c</sup> The yield refers to the mixture of two diastereoisomers.

<sup>d</sup> The reaction was performed in the presence of CuCN·2LiCl (0.5 mol%).

<sup>e</sup> These experiments were performed by G. Sklute and are given here for the sake of completeness.
Various benzaldehydes undergo the addition of reagent 80 leading to the cis-configured benzylic alcoholates of type 82 as 1:1 mixture of diastereoisomers with respect to the newly formed carbinol centers. Interestingly, one of the diastereoisomers cyclizes to give, after workup and purification, the corresponding lactone of type 83, whereas the other one is isolated as the alcohol of type 84 (Scheme 41). The configuration of 83a was confirmed by X-ray analysis (Fig. 3).

Scheme 41: Reactions with different benzaldehydes.

The preparation of cyclopropanenitriles with stereochemically defined quaternary centers can be achieved by successive bromine/magnesium- and sulfoxide/magnesium-exchange. Thus, the bromine/magnesium-exchange on the thioether 81e (i-PrMgCl, 1.1 equiv, -50 °C, 5 min) followed by an allylation in the presence of CuCN-2LiCl with allyl bromide or methallyl...
bromide, respectively, furnishes the allylated products \(85a\) and \(85b\) in 70 and 71 % yield (Scheme 42). These thioethers were converted to the corresponding sulfoxides \(86a\)-\(86b\) using MCPBA (1.0 equiv, CH\(_2\)Cl\(_2\), -50 °C to rt, 0.5 h, 77-78 %). The sulfoxide/magnesium exchange\(^7\) was complete within 10 min at -50 °C. Treatment with either methallyl or allyl bromide in the presence of CuCN·2LiCl (0.5 mol%) provides the two diastereomeric cyclopropanenitriles \(87a\) (73 %) and \(87b\) (69 %) as single diastereoisomers (Scheme 42).

![Diagram of compounds 85a, 85b, 86a, 86b, 87a, and 87b](image)

**Fig. 4:** Correlations observed in NOE and NOESY experiments on the cyclopropane derivatives 85-87 (For NOE experiments, the white arrow indicates the signal that was irradiated).
Scheme 42: Diastereoselective generation of quaternary centers (MCPBA = 3-chloro-perbenzoic acid).
3. Preparation of Soluble Lanthanide Salts and Their Applications in Organomagnesium Chemistry

3.1. Introduction

The use of lanthanide reagents in organic synthesis has tremendously increased throughout the last 30 years. The growing importance of this field is impressively reflected by a recent Chemical Reviews special issue on lanthanide chemistry. Lanthanide derivatives have found applications in redox chemistry, like ceric ammonium nitrate (CAN) as an oxidant or SmI$_2$ as a reducing agent. Also, the synthesis of organolanthanides is a growing field. A further important property of the lanthanides is their commonly known lewis acidity, which is utilized in different stoichiometric as well as catalytic reactions. The latter ones are often performed in an asymmetric manner using chiral lanthanide complexes as catalysts. For the purpose of an introduction, of course, only just a few examples can be mentioned here, and the focus should be set now on two reactions that use the lewis acidic lanthanide species for the activation of a carbonyl compound for a 1,2-addition.

The first ‘classic’ to be mentioned is the Luche-reduction, which means the 1,2-reduction of a carbonyl moiety with NaBH$_4$ in the presence of CeCl$_3$. This method allows the selective 1,2-reduction of Michael systems, as well as the reduction of ketones in the presence of aldehydes. Normally, this reaction is performed using CeCl$_3$·7H$_2$O in alcoholic or aqueous solvent mixtures. A recent example is given in Scheme 43. The diastereoselective 1,2-reduction of the $\alpha,\beta,\gamma,\delta$-unsaturated ketone to the alcohol was used in course of the total synthesis of Antillatoxin, a marine neurotoxin (Scheme 43).
**Scheme 43**: Luche-reduction in the synthesis of Antillatoxin.

The second important reaction is the 1,2-addition of organometallics to carbonyl compounds,\(^{84}\) which mainly goes back to the pioneering work of Imamoto.\(^{85}\)

The presence of cerium chloride favors the 1,2-addition reaction comparatively to competitive reactions such as enolization or reduction (by β-hydride transfer). To explain this behaviour, one may first hark back on the lewis acidic and oxophilic nature of lanthanide salts (similarly to the Luche-reduction). A second explanation, that should not be underestimated, is a transmetallation to the lanthanide as first step, as organolanthanides are known to be less basic than, for example, lithium and magnesium organometallics and thus cause less enolization in α-acidic systems. Scheme 44 gives an overview on the addition of organometallics to carbonyl compounds and shows the usual side-products, including the products of the β-hydride reduction and the enolization. The latter one can react with a further molecule of the ketone to give the aldol product, depending on the reactivity of the carbonyl

\[ \text{R}^1\text{MX}_n + \text{R}^2\text{C}=\text{O} \rightarrow \text{R}^2\text{OMX}_n + \text{R}^1\text{R}^3 + \text{OMX}_n \]

- Addition product
- Reduction
- Enolization

**Scheme 44**: Addition of an organometallic reagent to a ketone.

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compound. In contrast to the Luche reduction, due to the sensitivity of the organometallics to moisture, anhydrous CeCl₃ has to be used. The activity of the lanthanide is thereby strongly dependent on the method used for drying. Dimitrov was able to show that drying the hydrate in vacuum using a stepwise increase of temperature more active cerium chloride is obtained than by simply heating to high temperatures immediately, which may cause the formation of unreactive polymeric species. However, the solubility of the respective salt has a huge impact on the reactivity, too. Only few lanthanide salts are soluble in appreciable amounts in organic solvents. Thus, a soluble lanthanide source would be highly appreciable.

3.2. Preparation of Soluble Lanthanide Salts of the Type LnCl₃·2LiCl

As already mentioned above, the addition of LiCl has proven to have a beneficial effect on the solubility and has been used for the synthesis of various organometallic complexes. We found that using this effect, THF soluble lanthanide halides of the type LnCl₃·2LiCl (Ln = La, Ce, Nd) can be readily obtained as 0.3-0.5 M solutions in THF (Scheme 45). Thus, the treatment of commercially available LaCl₃·6H₂O, CeCl₃·7H₂O or NdCl₃·6H₂O with LiCl (2.0 equiv) in water led to a slurry which was stirred 4 h at 25 °C under high vacuum. The dissolving of the salts in water turned out essential. Probably, this process enables chloride ions (from LiCl) to replace water molecules in the inner coordination sphere of the lanthanide. This might effect an easier removal of the water, at the same time avoiding the

\[
\text{LnCl}_3·6\text{H}_2\text{O} + 2 \text{LiCl} \rightarrow \text{LnCl}_3·2\text{LiCl}
\]

\[
\text{1. H}_2\text{O} \quad \text{2. stepwise drying} \quad \text{3. THF, MS 4Å} \quad 0.3-0.5 \text{ M solution in THF}
\]

Ln = La (90), Ce (91), Nd (92)

Scheme 45: Generation of soluble lanthanide salts of the type LnCl₃·2LiCl.

polycondensation reaction leading to the less reactive polymeric species. The resulting white powder was stirred with gradual increase of temperature (20 °C/4 h to 160 °C) for 28 h. The solid was dissolved in THF and stirred for 1 d in the presence of molecular sieves (4 Å). In preliminary experiments, molecular sieves had proven superior agents for the removal of remaining water, as illustrated in Fig. 5. However, it turned out that long-time storage (more than some days) should be avoided, as it leads to the deactivation of the solution, possibly by ion exchange.

![Graph](image_url)

**Fig 5**: Content of remaining protic impurities in a LaCl$_3$·2LiCl-solution after storage over molecular sieves (4Å).

After filtration through a combined filter system (filter paper / fresh molecular sieves), transparent, ca 0.33 M solutions of LnCl$_3$·2LiCl (Ln = La(90), Ce(91), Nd(92)) were obtained which can be stored indefinitely at 25 °C under argon. The content of remaining protic impurities was in the end less than 5 %, as shown by titration. In collaboration with researchers at Chemetall (Frankfurt) it could be proven that these impurities are different from water (as a Karl-Fischer-Titration indicated only traces of water). It seems to be likely that the detected protons come from some remaining lanthanide hydroxide species.

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90 This observation was done by Dr. Ralf Klötzing and is herewith gratefully acknowledged.
91 The content of remaining protic impurities was determined by titration with $n$-BuLi using ortho-phenanthroline as indicator, similarly to the method for concentration determination for Li- and Mg-reagents described by Paquette: H.-S. Lin, L. Paquette, *Synth. Commun.* **1994**, 24, 2503.
Furthermore, we investigated the long-time stability of several Grignard reagents in the presence of LaCl₃·2LiCl (Fig. 6, next page). As shown in the diagram, the most stable reagents were the aromatic ones, as well as allyl magnesium bromide (all ≥ 80 % of the starting activity after 24 h). The biggest decrease in activity (determined by titration) was found for the reactive secondary alkylmagnesium halides, especially i-PrMgCl, showing only 50 % of the starting activity after 24 h. Allover, however, the Grignard reagents display sufficient stability, as most reactions are complete in a few minutes (see below).

**Fig. 6**: Stability of several Grignard reagents in the presence of LaCl₃·2LiCl.
3.3. Addition Reactions to Carbonyl Functions

The solutions prepared above were subsequently tested in the reactions of Grignard reagents with carbonyl compounds. We were pleased to find, that these convenient solutions are superior promoters for the addition of various Grignard reagents to hindered and enolizable ketones (Scheme 46, Table 11). Thus, the reaction of the secondary alkylmagnesium chloride 93a with cyclopentanone (94a) leads in the absence of lanthanide salts to enolization and formation of aldol products and only 3-5 % of the addition product is obtained (entry 1, Table 10). By adding CeCl₃ (1.5 equiv) according to the procedure of Imamoto the desired alcohol 95a is isolated in 72 % yield whereas using the procedure of Dimitrov (CeCl₃, 1.0 equiv), the alcohol 95a is isolated in 80 % yield. By adding LnCl₃·2LiCl (Ln = La, Ce, Nd; 90-92) in THF (1.0 equiv) to cyclopentanone (94a) and stirring the mixture for 1 h, we have obtained after addition of i-PrMgCl (93a) at 0 °C (10 min) the alcohol 95a in 92-94 % isolated yield. Readily enolizable ketones such as diphenylacetone (94b) react with the sterically hindered Grignard reagent i-PrMgCl (93a) only under formation of the corresponding magnesium enolate (only 3 % of the addition product is produced), whereas in the presence of LnCl₃·2LiCl a yield of 95-97 % of the tertiary alcohol 95b is obtained (entry 2). A similar behaviour is observed for less reactive Grignard reagents such as functionalized arylmagnesium chlorides 93c-f, prepared via a halogen-magnesium exchange reaction. Due to the low reactivity of this type of reagents the use of i-PrMgCl·LiCl for the exchange reaction is essential to get the arylmagnesium chlorides as reagents of the more reactive type ArMgCl·LiCl. Thus, the reaction of these relatively unreactive magnesium reagents with various ketones proceeds in only moderate yields in the absence of lanthanide salts, whereas excellent yields are obtained in the presence of LnCl₃·2LiCl (73-95 % yield; entries 3-7).

Scheme 46: Addition of Grignard reagents to hindered and enolizable ketones.
Remarkably, even the Grignard reagent $93f$ bearing a sensitive nitro function reacts cleanly with the ketone $94d$ in the presence of LaCl$_3$·2LiCl, whereas in the absence of lanthanide salts as well as using Imamoto’s procedure no product $95g$ was obtained.

Sterically very hindered ketones such as the mesityl methyl ketone ($94e$) and hindered Grignard reagents such as mesitylmagnesium bromide ($93h$) or tert-butylmagnesium chloride ($93i$) react in moderate yields. A significant improvement is achieved by performing these reactions in the presence of LaCl$_3$·2LiCl (entries 8, 11, 12). It should be stressed that in the case of mesitylmagnesium bromide ($93h$), the standard procedure did not prove successful ($95h$ was isolated in only 48-56 %). Only transmetallating the Grignard reagent via treatment with LaCl$_3$·2LiCl for 4 h did result in significantly better yields. This observation can be explained assuming that, at least in this case, the transmetallation is mechanistically the first step. Due to the steric hindrance in the Grignard it becomes very slow and, if incomplete, the remaining magnesiumorganic reacts as a base. Treating sterically even more hindered di-tert-butyl ketone ($94f$) or dimesityl ketone ($94g$) with the comparatively small MeMgCl ($93g$) does nor lead to the formation of any addition product and thus represents the limit of this method in terms of steric hindrance (entries 9,10).

The addition of PhMgCl ($93j$) to camphor ($94j$) is highly diastereoselective, leading to the alcohol $95j$ in 93 % yield (entry 13). Reetz showed that the Grignard reagent’s counterion can influence its reactivity in an addition reaction to a carbonyl compound. We used camphor as a test substrate and found that in this case, the counterion shows only a low influence on the addition reaction. Thus, the magnesium reagents obtained via insertion from phenyl bromide or iodide, respectively, also lead to the clean formation of the desired product $95j$ in good yields (92 and 89 %, entries 14 and 15). Even a catalytic amount of LaCl$_3$·2LiCl promotes this addition reaction and the desired product can be still obtained as one diastereoisomer in 65 % isolated yield using only 10 % LaCl$_3$·2LiCl (entry 14, value in brackets).

It should be underlined, that the Nd ($92$) and Ce ($91$) derivatives show identical reactivity like the La species ($90$) mentioned above.$^{93}$

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93 Additionally, ErCl$_3$·6H$_2$O, PrCl$_3$·6H$_2$O, YCl$_3$·6H$_2$O and DyCl$_3$·6H$_2$O were used analogously to prepare solutions of type LnCl$_3$·2LiCl. Whereas PrCl$_3$·2LiCl shows similar behaviour as the La, Ce or Nd derivatives ($90$-$92$), ErCl$_3$·2LiCl, YCl$_3$·2LiCl and DyCl$_3$·2LiCl display lower catalytic activities and give mediocre results in the addition reactions.
Table 11: Addition of various Grignard reagents to hindered and enolizable ketones.

<table>
<thead>
<tr>
<th>entry</th>
<th>Grignard reagent 93</th>
<th>ketone of type 94</th>
<th>product of type 95</th>
<th>without additive (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CeCl₃ (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>LnCl₃&lt;sup&gt;c&lt;/sup&gt; 2LiCl (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>i-PrMgCl</td>
<td>93a</td>
<td>94a</td>
<td>3-5</td>
<td>72 (80)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>92&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95a</td>
<td></td>
<td></td>
<td>94&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>94b</td>
<td>95b</td>
<td>3</td>
<td>-</td>
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<tr>
<td></td>
<td>MgCl₂·LiCl</td>
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<td></td>
<td></td>
<td></td>
<td>95&lt;sup&gt;e&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Isolated Yield obtained by the direct reaction of the ketone with the Grignard reagent.<br><sup>b</sup> Isolated yield obtained in the presence of CeCl<sub>3</sub> (1.5 equiv) according to the method of Imamoto.<br><sup>c</sup> Isolated yield obtained in the presence of CeCl<sub>3</sub> (1.0 equiv) according to the method of Dimitrov.<br><sup>d</sup> The reaction was performed using LaCl<sub>3</sub>·2LiCl (1.0 equiv).<br><sup>e</sup> The reaction was performed using CeCl<sub>3</sub>·2LiCl (1.0 equiv).<br><sup>f</sup> The reaction was performed using NdCl<sub>3</sub>·2LiCl (1.0 equiv).<br><sup>g</sup> The Grignard reagent was first transmetallated by addition of LnCl<sub>3</sub>·2LiCl (1.0 equiv) and stirring for 4 h at room temperature, then the ketone was added at 0 °C.<br><sup>h</sup> The reaction was performed in the presence of 10 mol% LaCl<sub>3</sub>·2LiCl.
In the case of cyclic $\alpha,\beta$-unsaturated ketones such as cyclohex-2-enone (96), the addition of secondary alkylmagnesium compounds like cyclopentylmagnesium chloride proceeds exclusively in the presence of LaCl$_3$·2LiCl leading to the desired tertiary allylic alcohol 97 in 93 % yield (Scheme 47). Similarly, naphtylmagnesium bromide in the presence of LaCl$_3$·2LiCl adds smoothly to cyclopent-2-enone (98), giving the desired product 99 in 60 % (Scheme 46). The comparably low yield is due to the high propensity to eliminate water on silica. A control experiment did show, that in the absence of the lanthanide salt, the only product observed from the reaction of cyclohex-2-enone (96) and cyclopentylmagnesium chloride is the allylic alcohol 100 which can be isolated in 77 % yield (Scheme 48).

Scheme 47: Additions to cyclic $\alpha,\beta$-unsaturated ketones in the presence of LaCl$_3$·2LiCl.

Scheme 48: Control experiment without LaCl$_3$·2LiCl.
We also investigated the addition to an acyclic $\alpha, \beta$-unsaturated ketone. Unfortunately, the reactions of ($2E$)-1,3-diphenylprop-2-en-1-one (101) with phenylmagnesium chloride or isopropylmagnesium chloride in the presence of LaCl$_3$.2LiCl lead to roughly 2:1-mixtures of the corresponding 1,2- and 1,4-addition products (Scheme 49). Variations of the conditions could not change these ratios significantly.

Scheme 49: Attempted additions to acyclic $\alpha,\beta$-unsaturated ketones.
3.4. Solutions of the Second Generation

Even though the solutions described above turned out very practical, the concentrations of 0.3 M to 0.5 M are still comparatively low. Especially for industrial applications in a larger scale, a higher concentration would be desirable. Thus, we did prepare solutions of several lanthanide salts with different counter ions and also varying the anion in the lithium component. Partly, the solutions were generated using the above mentioned methodology (Method A). Another part was prepared by mixing the anhydrous lanthanide salt with the anhydrous lithium species under an inert atmosphere, subsequently adding dry THF (Method B). The mixtures then were heated at 50 °C for 12 h (except entry 1). After removal of insoluble parts by cannulisation or filtration, the lanthanide content of the solutions was determined by complexometric titration with EDTA (ethylenediamine tetraacetate). Table 12

Table 12: Solubility screening for lanthanide/lithium salt mixtures.

<table>
<thead>
<tr>
<th>entry</th>
<th>lanthanide source</th>
<th>lithium salt (equiv)</th>
<th>method</th>
<th>molarity $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LaCl$_3$</td>
<td>LiCl (2)</td>
<td>A</td>
<td>0.40$^c$</td>
</tr>
<tr>
<td>2</td>
<td>LaCl$_3$</td>
<td>LiBr (2)</td>
<td>A</td>
<td>1.11</td>
</tr>
<tr>
<td>3</td>
<td>LaCl$_3$</td>
<td>LiI (3)</td>
<td>A</td>
<td>0.08</td>
</tr>
<tr>
<td>4</td>
<td>LaCl$_3$</td>
<td>LiOtBu (3)</td>
<td>A</td>
<td>traces</td>
</tr>
<tr>
<td>5</td>
<td>LaCl$_3$</td>
<td>LiOtBu (3)</td>
<td>B</td>
<td>traces</td>
</tr>
<tr>
<td>6</td>
<td>LaCl$_3$</td>
<td>LiBr (3)</td>
<td>B</td>
<td>0.90</td>
</tr>
<tr>
<td>7</td>
<td>LaCl$_3$</td>
<td>LiBF$_4$ (3)</td>
<td>B</td>
<td>0.03$^d$</td>
</tr>
<tr>
<td>8</td>
<td>LaCl$_3$</td>
<td>LiPF$_6$ (3)</td>
<td>B</td>
<td>0.02</td>
</tr>
<tr>
<td>9</td>
<td>LaCl$_3$</td>
<td>LiOTf (3)</td>
<td>B</td>
<td>0.05</td>
</tr>
<tr>
<td>10</td>
<td>LaCl$_3$</td>
<td>LiH (3)</td>
<td>B</td>
<td>0.02</td>
</tr>
<tr>
<td>11</td>
<td>LaCl$_3$</td>
<td>LiBH$_4$ (3)</td>
<td>B</td>
<td>0.03</td>
</tr>
<tr>
<td>Entry</td>
<td>Formula</td>
<td>Additive</td>
<td>Concentration</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------------</td>
<td>----------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>LaCl$_3$</td>
<td>LiNH$_2$ (3)</td>
<td>B</td>
<td>0.03</td>
</tr>
<tr>
<td>13</td>
<td>LaCl$_3$</td>
<td>LiOAc (3)</td>
<td>B</td>
<td>0.01</td>
</tr>
<tr>
<td>14</td>
<td>LaCl$_3$</td>
<td>Li(acac) (1)</td>
<td>B</td>
<td>0.04$^d$</td>
</tr>
<tr>
<td>15</td>
<td>LaCl$_3$</td>
<td>Li(acac) (2)</td>
<td>B</td>
<td>0.04$^d$</td>
</tr>
<tr>
<td>16</td>
<td>LaBr$_3$</td>
<td>LiBr (3)</td>
<td>B</td>
<td>0.50</td>
</tr>
<tr>
<td>17</td>
<td>LaBr$_3$</td>
<td>LiCl (2)</td>
<td>B</td>
<td>0.60</td>
</tr>
<tr>
<td>18</td>
<td>LaBr$_3$</td>
<td>LiCl (3)</td>
<td>B</td>
<td>1.09</td>
</tr>
<tr>
<td>19</td>
<td>La(OTf)$_3$</td>
<td>LiCl (3)</td>
<td>B</td>
<td>0.02</td>
</tr>
<tr>
<td>20</td>
<td>La(OTf)$_3$</td>
<td>LiBr (3)</td>
<td>B</td>
<td>0.53</td>
</tr>
<tr>
<td>21</td>
<td>La$_2$(SO$_4$)$_3$</td>
<td>LiCl (3)</td>
<td>B</td>
<td>0.02</td>
</tr>
<tr>
<td>22</td>
<td>La$_2$(SO$_4$)$_3$</td>
<td>LiBr (3)</td>
<td>B</td>
<td>0.11$^d$</td>
</tr>
</tbody>
</table>

$^a$ Stoichiometry used for the preparation.
$^b$ The value represents the minimally achievable solubility; higher concentrations may be possible.
$^c$ Concentration determined by EDTA-titration of an aliquot in a urotropine-buffered solution using methylthymol blue as indicator.
$^d$ Value obtained from industry collaboration with Chemetall (Frankfurt).
$^d$ ± 0.02; No sharp change of colour in EDTA titration.

summarizes the results. It can be easily seen that LiBr obviously is a very potent additive for LaCl$_3$ (1.11 and 0.90 M, respectively, see entries 2 and 6). Inversely, LiCl is also giving high concentrations with LaBr$_3$ (0.60 and 1.09 M, entries 17 and 18). Interestingly, the considerably higher value is reached using 3 equivalents of LiCl. Furthermore, the combination of LaBr$_3$ and LiBr does not result in high solubility which indicates the importance of the chloride anions for reaching good concentrations. The LaBr$_3$/LiBr and La(OTf)$_3$/LiBr systems display mediocre solubility in the range of LaCl$_3$·2LiCl (see entries 1, 16 and 20). All other tested combinations display tremendously lower concentrations. Summarizing, a mixture of the formal composition Li$_2$LaCl$_3$Br$_2$ obviously represents the optimum combination, giving access to 1.0 M solutions in THF.
To examine its potential, we first used this solution \((\text{LaCl}_3\cdot2\text{LiBr})\) in the addition of \(i\text{-PrMgCl}\cdot\text{LiCl}~(93a)\) to diphenyl acetone \((94b)\); Scheme 50). The desired product \(95b\) was isolated in 95 % yield which illustrates that this new solution displays a similar activity like the solutions of the first generation.

\[
\begin{array}{c}
\text{Ph} \quad \text{CO} \quad \text{Ph} \\
\text{94b} \\
\end{array}
\xrightarrow{1) \text{LaCl}_3\cdot2\text{LiBr (1.0 equiv)}}
\text{THF, rt, 0.5 h}
\xrightarrow{2) i\text{-PrMgCl}\cdot\text{LiCl}~(93a),}
\text{THF, 0°C, 5 min}
\begin{array}{c}
\text{Ph} \quad \text{OH} \quad \text{Ph} \\
\text{95b: 95 %} \\
\end{array}
\]

**Scheme 50:** Addition of \(i\text{-PrMgCl}\cdot\text{LiCl}~(93a)\) to diphenyl acetone \((94b)\) in the presence of \(\text{LaCl}_3\cdot2\text{LiBr}\).

Furthermore, we were interested, if these new solutions might serve to replace the expensive lanthanide triflates in catalytic reactions. Thus, we used our solution as a catalyst for the 1,4-addition of benzyl amine \((106)\) to ethyl-prop-2-enoate \((107)\); Scheme 51). This reaction is known to proceed smoothly in 6 h in the presence of \(\text{Yb(OTf)}_3\) \((10 \text{ mol}%)\) at rt.\(^\text{94}\) The results of first kinetic measurements using \(\text{LaCl}_3\cdot2\text{LiBr}\) are depicted in Figure 7.

\[
\begin{array}{c}
\text{Ph} \quad \text{NH}_2 \\
\text{106} \\
\end{array}
\xrightarrow{\text{Ph} \quad \text{NH} \quad \text{CO}_2\text{Et}}
\begin{array}{c}
\text{Ph} \quad \text{NH} \quad \text{CO}_2\text{Et} \\
\text{108} \\
\end{array}
\xrightarrow{\text{LaCl}_3\cdot2\text{LiBr}}
\text{THF, rt}
\]  

**Scheme 51:** Michael addition catalyzed by \(\text{LaCl}_3\cdot2\text{LiBr}\).

Thus, using 10 mol% \(\text{LaCl}_3\cdot2\text{LiBr}\) in a 2.0 M reaction mixture, the conversion reaches excellent 96 % (line C; conversion determined by GC monitoring). Even lowering the loading of the lanthanide salt to 5.0 mol%, still 83 % conversion can be achieved (D). However, the reaction becomes much slower working in a lower concentration (0.5 M; A, B). Interestingly, the direct comparison between \(\text{LaCl}_3\cdot2\text{LiBr}\) and \(\text{LaCl}_3\cdot2\text{LiCl}\) at the same concentration displays a higher reactivity for the new \(\text{LaCl}_3\cdot2\text{LiBr}\)-solution (compare A, E).

Fig. 7: Kinetic measurements on the Michael addition of benzyl amine (106) to ethyl-prop-2-enoate (107).

A: 10 mol-% \( \text{LaCl}_3\cdot\text{LiBr} \); ca. 0.5 M in THF
B: 5 mol-% \( \text{LaCl}_3\cdot\text{LiBr} \); ca. 0.5 M in THF
C: 10 mol-% \( \text{LaCl}_3\cdot\text{LiBr} \); ca. 2.0 M in THF
D: 5 mol-% \( \text{LaCl}_3\cdot\text{LiBr} \); ca. 2.0 M in THF
E: 10 mol-% \( \text{LaCl}_3\cdot\text{LiCl} \); ca. 0.5 M in THF
4. Summary and Outlook

This work was focused on the synthesis of Grignard reagents bearing unprotected acidic groups as well as the preparation of functionalized cyclopropane derivatives through magnesium carbenoids. Furthermore, the preparation and use of soluble lanthanide species of the type LnX₃·2LiY (Ln = lanthanide; X, Y = anionic complex ligands) was accomplished.

4.1. Halogen/Magnesium Exchange Reactions in the Presence of Unprotected Acidic Groups

The generation of Grignard reagents in the presence of unprotected acidic groups was described. Using the conception of a stepwise deprotonation and exchange reaction, aromatic and heteroaromatic alcohols and carboxylic acid derivatives were successfully metallated. The

![Scheme 52: Functionalization of aromatic and heteroaromatic alcohols and carboxylic acid derivatives (the dotted lines indicate the newly formed bond).](image-url)
reactions with a broad range of electrophiles afford the desired products in good yields (Scheme 52). Furthermore, this conception was successfully transferred to heterocyclic systems like imidazoles and uracils (Scheme 53). First applications to the synthesis of precursors for pharmaceuticals were presented.

Scheme 53: Functionalization of imidazole and uracil derivatives (the dotted lines indicate the newly formed bond).

An extension to CH-acidic compounds might be challenging, as in this case the selective reaction of one of two organomagnesium moieties with the electrophile has to be achieved.
4.2. Diastereoselective Synthesis of Cyclopropane Carbenoids Bearing a Nitrile Function

The synthesis of cyclopropane carbenoids bearing a nitrile function via bromine/magnesium and sulfoxide/magnesium exchange reactions was described. Their reactions with a range of different electrophiles give the desired products in good yields and diasteroselectivities. (Scheme 54). An application to the diastereoselective construction of quaternary centers was achieved.

![Scheme 54: Functionalized cyclopropane carbenoids via bromine/magnesium and sulfoxide/magnesium exchange reactions.](attachment:image)

Further extensions of this methodology could be directed to the functionalization of cyclic systems different from the cyclopropane. Especially the application to cyclobutane derivatives could be rewarding, as the stereoselective preparation of functionalized cyclobutanes is not an easy task up to now.
4.3. Preparation of Soluble Lanthanide Salts and Their Applications in Organomagnesium Chemistry

The preparation of soluble lanthanide species of the type LnX₃·2LiY (Ln = lanthanide; X, Y = anionic complex ligands) was elaborated. The application to the addition of Grignard reagents to carbonyl derivatives was described (Scheme 55).

\[
\text{LnCl}_3\cdot6\text{H}_2\text{O} + 2 \text{LiCl} \rightarrow \text{LnCl}_3\cdot2\text{LiCl} \\
\text{Ln} = \text{La, Ce, Nd}
\]

Products of the addition reactions to different ketones:

- \(92\%\) 3-5\% without additives 72\% with CeCl₃
- \(96\%\) 3\% without additives
- \(86\%\) 37\% without additives 8\% with CeCl₃
- \(73\%\) 0\% without additives 0\% with CeCl₃
- \(69\%\) 22\% without additives 57\% with CeCl₃
- \(81\%\) 35\% without additives

Scheme 55: Preparation of soluble lanthanide salts and application to the addition of Grignard reagents to ketones (the dotted lines indicate the newly formed bond).

An improved solution of type LaCl₃·2LiBr was developed. Thereby, the achievable concentration was increased to around 1.0 M. In first test reactions, this solution showed also high activity in the carbonyl addition reaction and, moreover, promising results were obtained in preliminary studies on a catalyzed Michael addition reaction. Further investigations in the field of catalytic reactions, possibly employing chiral ligands, would be challenging.
C

EXPERIMENTAL SECTION
1. General Considerations

All reactions employing air or moisture sensitive reagents were performed in flame-dried glassware under argon. Syringes which were used for the transfer of such reagents or anhydrous solvents were purged with argon prior to use.

Solvents

Solvents were dried according to standard methods by distillation over drying agents as stated below and stored under argon.

**CH₂Cl₂** was predried over calcium chloride and was distilled from calcium hydride

The solvents used for workups and flash chromatography were distilled at the rotavapor prior to use.

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

**Toluene** was predried over calcium chloride and was distilled from calcium hydride.

**Tetrahydrofuran** (THF) was continuously refluxed and freshly distilled from sodium benzophenone ketyl.

**Diethyl ether** (Et₂O) was predried over calcium hydride and then dried using a solvent-purification device of type SPS-400-2 (Innovative Technologies Inc.).

Reagents

As not otherwise stated, all reagents were obtained from commercial sources. Reagents of >97 % purity were used as obtained, except technical grade tosyl cyanide (purity: 95 %).

Some substrates were additionally purified:

Commercially available 5,7-diiodo-quinolin-8-ol was recrystallized from toluene before use. Benzaldehyde, cyclohexane carbaldehyde, butyraldehyde, benzyol chloride, triisopropyl borate and ethyl chloridocarbonate were distilled under reduced pressure prior to use.

The following substances were prepared according to literature procedures:
2-hydroxy-5-iodo-benzoic acid tert-butyl ester, 2-iodo-pyridin-3-ol, ethyl 2-(bromomethyl)-acrylate, S-phenyl benzenesulfonothioate, S-(4-bromophenyl) benzenesulfonothioate, 3,5-Diodobenzoic acid, 6-iodopurine, 5-methyl-barbituric acid, benzyl (2,2-dibromocyclopropyl)methyl ether, 2,2-dibromo-1-methylcyclopropanecarbonitrile, N-(1H-1,2,3-benzotriazol-1-ylmethyl)-N,N-diethylamine; 6-iodouracil was prepared according to the literature and additionally purified by silica gel filtration (eluent: CH₂Cl₂:MeOH; 19:1).

*i-PrMgCl·LiCl* in THF was either used as solution (1.30 M) purchased from Chemetall or prepared according to the following procedure:

Magnesium turnings (2.64 g, 110 mmol, 1.10 equiv) and anhydrous LiCl (4.20 g, 100 mmol, 1.00 equiv) were placed in an Ar-flushed flask and were flame dried in high vacuum. After cooling to rt and purging with argon, THF (50 mL) was added. A solution of *i-PrCl* (7.85 g, 100 mmol, 1.00 equiv) in THF (50 mL) was slowly added at rt. The reaction starts within a few minutes. After addition, the reaction mixture was stirred for 12 h at rt. The grey solution of *i-PrMgCl·LiCl* was cannulated to another flask under Ar and removed in this way from excess of magnesium.

*PhMgBr·LiCl, PhMgI·LiCl, MesMgBr·LiCl, NaphtMgBr·LiCl* and *c-PentMgBr·LiCl* were prepared according to this procedure from the corresponding bromides.

*PhMgBr* was prepared as follows:

Magnesium turnings (2.64 g, 110 mmol, 1.10 equiv) were placed in an Ar-flushed flask and were flame dried in high vacuum. After cooling to rt and purging with argon, THF (50 mL) was added. A solution of bromobenzene (1.57 g, 100 mmol, 1.00 equiv) in THF (50 mL) was slowly added at rt. The reaction starts within a few minutes. After addition, the reaction mixture was stirred for 12 h at rt. The grey solution of *PhMgBr* was cannulised to another flask under Ar and removed in this way from excess of magnesium.

*i-PrMgCl* (3.0 M in diethyl ether) was prepared according to this procedure from isopropyl chloride and magnesium in diethyl ether.

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PhMgCl (2.0 M), MeMgCl (3.0 M) and i-PrMgCl (1.0 M) in THF were purchased from Chemetall.

**Preparation of LiCl in THF (0.50 M)**
LiCl (5.25 g, 125 mmol) was placed in a 500 mL Schenk flask equipped with a magnetic stirring bar and a glass stopper. For all purposes, Teflon grease should be employed. The salt is heated at 150 °C in an oil bath for 4 h. Then, after cooling to rt, the stopper was changed to a rubber septum and absolute THF (250 mL) was added. Afterwards, the septum was replaced again by a glass stopper and the suspension was left stirring over night at rt. After at least 12 h, the LiCl had completely dissolved, the stirring was stopped and the solution was left for some more time to become completely clear (little particles and insoluble impurities are allowed to settle down by that way). The solution was stored under argon upon use.

**Determination of the Concentration of the Organometallic Reagents:**
Organomagnesium reagents were directly titrated by adding the respective reagent to a known amount of I₂ in a LiCl-solution in THF (0.50 M). The decolourization of the solution was observed. 97

**CuCN·2LiCl (1.00 M solution in THF):**
CuCN (869 mg, 10.0 mmol) and LiCl (848 mg, 10.0 mmol) were placed in a Schlenk-flask, equipped with a stirring bar and a glass stopper and heated at 150 °C under high vacuum. After cooling down to rt, the stopper was replaced with a septum and absolute THF (10 mL) was added under an argon atmosphere. Afterwards, the septum was replaced again by a glass stopper and the suspension was left stirring over night at rt to assure all salts being dissolved.

**CuI·2LiCl (0.75 M solution in THF):**
This solution was prepared analogously from CuI and LiCl.

**Typical procedure for the preparation of LnCl₃·2LiCl-solutions: Preparation of a solution of LaCl₃·2LiCl in THF (0.33 M):**
In a 500 mL Schlenk-flask, commercially available LaCl₃·6H₂O (0.10 mol, 35.3 g) was mixed with LiCl (0.20 mol, 8.40 g) and water (100 mL) was slowly added under vigorous stirring. The resulting slurry was stirred in high vacuum (0.01 mm Hg) at RT for 4 h. Stirring was

continued for 4 h at 40 °C, 4 h at 60 °C, 4 h at 80 °C, 4 h at 100 °C, 4 h at 120 °C, 4 h at 140 °C and finally 4 h at 160 °C. The slow increase of temperature and highly efficient stirring are essential. The resulting solid was cooled to room temperature and THF was added until a total volume of 300 mL was reached. Then, molecular sieves (50.0 g; 4 Å) were added and the resulting mixture was stirred vigorously for 1 d at RT. Finally, all insoluble material (mostly crushed molecular sieves) was filtered over a combined filter system (fresh molecular sieves/filter paper) under an argon atmosphere. By this procedure, a clear and colorless solution of LaCl$_3$·2LiCl was obtained that was stored until use at RT under argon.

**Determination of Concentration of Lanthanide Solutions:**

3.00 mL of the respective solution were evaporated in high vacuum, calcinated using a heat gun. The resulting solid was dissolved in distilled water to reach an overall volume of 10.0 mL. 5.00 mL of this solution were transferred to a 50 mL Erlenmeyer flask, urotropine as a buffer (1.00 M in water) and methylthymolblue (3 dr, 0.05 M solution in MeOH) were added. The deep blue solution was now dropwise titrated using an aqueous solution of EDTA (ethylendiamine tetraacetate; 0.10 M) till the colour changed to yellow.

**Determination of Remaining Protic Impurities Lanthanide Solutions:**

The content of remaining protic impurities was determined by titration with $n$-BuLi using ortho-phenanthroline as indicator, similarly to the method for concentration determination for Li- and Mg-reagents described by Paquette.

**Chromatography**

Thin layer chromatography (TLC) was performed using aluminium plates covered with SiO2 (Merck 60, F-254). Spots were visualized under UV light and/or by staining of the TLC plate with one of the solutions below followed by heating with a heat gun:

1. KMnO$_4$ (0.3 g), K$_2$CO$_3$ (20 g), KOH (0.3 g) in water (300 mL).
2. Phosphormolybdic acid (5.0 g), Ce(SO$_4$)$_2$ (2.0 g), conc. H$_2$SO$_4$ (12.0 mL) in water (230 mL).

Flash column chromatography was performed using SiO2 60 (0.040-0.063 mm, 230-400 mesh ASTM) from Merck.

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Analytical Data

NMR-spectra were recorded on Bruker ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the deuterated solvent peak: CDCl₃ (δ_H = 7.25; δ_C = 77.0), DMSO-d₆ (δ_H = 2.49; δ_C = 39.5).

For the characterization of the observed signal multiplicities, the following abbreviations were used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), quint (quintet), sext (sextet), sept (septet), br (broad). If not otherwise noted, the coupling constants given are (CH)-coupling constants.

Melting points are uncorrected and were measured on a Büchi B.540 apparatus.

Infrared spectra were recorded from 4000-400 cm⁻¹ on a Nicolet 510 FT-IR or a Perkin-Elmer 281 IR spectrometer. Samples were measured either as film between potassium bromide plates (film), as potassium bromide tablets (KBr), or neat (Smiths Detection DuraSamp IR II Diamond ATR).

The absorption bands are reported in wavenumbers (cm⁻¹). For the band characterization, the following abbreviations were used: br (broad), vs (very strong), s (strong), m (medium), w (weak).

Gas chromatography (GC) was performed machines of the types Hewlett-Packard 6890 or 5890 Series II, using a column of the type HP 5 (Hewlett-Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm). The detection was accomplished using a flame ionization detector. Depending on the retention time of the substrate, decane or tetradecane were used as internal standards.

Mass Spectra were recorded on a Finnigan MAT 95Q or Finnigan MAT90 instrument for electron impact ionization (EI). High resolution mass spectra (HRMS) were recorded on the same instrument.

For the combination of gas chromatography with mass spectroscopic detection, a GC-MS of the type Hewlett-Packard 6890 / MSD 5793 networking was used (column: HP 5-MS,
Hewlett-Packard; 5% phenylmethylpolysiloxane; length: 15 m, diameter 0.25 mm; film thickness: 0.25 μm).
2. Typical Procedures (TP)

2.1. Typical procedure for the preparation of the functionalized iodophenols (TP01)

The corresponding functionalized phenol of type 29 (15.0 mmol) was dissolved in ethanol (30 mL), then iodine (7.62 g, 30.0 mmol, 2.00 equiv) and silver(I)sulfate (9.36 g, 30.0 mmol, 2.00 equiv) were added neat to the stirred solution. After the conversion was complete (tlc monitoring), the suspension was filtrated and the solvent was removed in vacuo. The crude product was purified by flash column chromatography.

For the corresponding monoiodinated substrates, just one equivalent of each, iodine and silver(I)sulfate was used.

2.2. Typical procedure for the I/Mg-exchange on unprotected phenols and the reaction with electrophiles (TP02)

In a dry and argon-flushed Schlenk-tube equipped with a septum and a magnetic stirring bar, the iodophenol derivative (30, 1.50 mmol) was dissolved in a solution of LiCl in THF (3.00 mL, 0.50 M, 1.50 mmol, 1.00 equiv) and cooled to -30 °C. Then, MeMgCl (2.80 M THF; 0.54 mL, 1.50 mmol, 1.00 equiv) was added dropwise. The reaction mixture was kept stirring at -30 °C for 40 min, then i-PrMgCl (1.05 M THF; 1.57 mL, 1.65 mmol, 1.10 equiv) was slowly added and the mixture was stirred for 30 min at -30 °C. After the exchange reaction was complete (tlc monitoring, silica plates, CH₂Cl₂ or pentane/CH₂Cl₂), the electrophile was added and the mixture was kept at -30 °C until the conversion was complete. MeOH (1.0 mL) was added, the resulting solution was poured into a mixture of saturated aqueous NH₄Cl and water (1:1; 40 mL) and extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent removed in vacuo. The product was purified by flash column chromatography.

2.3. Typical procedure for the I/Mg-exchange on unprotected 2-iodo-pyridin-3-ol (33a) and the reaction with electrophiles (TP03)

In a dry and argon-flushed Schlenk-tube equipped with a septum and a magnetic stirring bar, 2-iodo-pyridin-3-ol (33a; 332 mg, 1.50 mmol) was dissolved in a solution of LiCl in THF (0.50 M; 3.00 mL, 1.50 mmol, 1.00 equiv) and cooled to -20 °C. Then, MeMgCl (0.54 mL, 2.80 M solution in THF, 1.50 mmol, 1.00 equiv) was added dropwise. The reaction mixture was kept stirring at -20 °C for 40 min, then i-PrMgCl (1.05 M in THF; 1.57 mL, 1.65 mmol, 1.10 equiv) was slowly added and the mixture was stirred for 2 h and warmed up to 0 °C. After the exchange reaction was complete (tlc monitoring), the solution was cooled down again and the electrophile was added at -10 °C. The solution was slowly warmed up to 0 °C and stirring was continued until the conversion was complete. MeOH (1.0 mL) was added and the resulting solution was evaporated to dryness (high vacuum). The crude solid was redissolved (CH₂Cl₂/MeOH), adsorbed on silica and subjected to purification by column chromatography.
2.4. Typical procedure for the I/Mg-exchange on unprotected 5,7-diiodo-quinolin-8-ol (36) and the reaction with electrophiles (TP04)

In a dry and argon-flushed Schlenk-tube equipped with a septum and a magnetic stirring bar, 5,7-diiodo-quinolin-8-ol (36; 596 mg, 1.50 mmol) was suspended in a solution of LiCl in THF (0.25 M in THF; 6.00 mL, 1.50 mmol, 1.00 equiv) and cooled to -30 °C. Then, MeMgCl (2.80 M in THF; 0.54 mL, 1.50 mmol, 1.00 equiv) was added dropwise and a clear solution formed. The reaction mixture was kept stirring at -30 °C for 40 min, then i-PrMgCl (1.05 M in THF; 1.57 mL, 1.65 mmol, 1.10 equiv) was slowly added and the mixture was stirred for 60 min at -30 °C. After the exchange reaction was complete (tlc monitoring), the electrophile was added and the mixture was kept at -30 °C until the conversion was complete. MeOH (1.0 mL) was added and the resulting solution was poured into 60 mL of a slightly acidic aqueous EDTA solution (60 mL, 0.1 M in EDTA plus 1.0 mL 2.0 M HCl), then extracted with ether. The organic layer was dried (Na₂SO₄) and the solvent removed in vacuo. The crude residue was mostly redissolved in diethyl ether using ultrasonication. Insoluble impurities were removed by filtration and the filtrate evaporated to dryness. Recrystallization from chloroform provided the desired products.

2.5. Typical procedure for the double metallation of ortho-, meta-, and para-iodobenzoic acid (40d-40f) (TP05)

The iodobenzoic acid (2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for some minutes at rt., the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Afterwards, i-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. The exchange reaction was monitored by TLC and was usually complete after 45 min. The resulting slurry was cooled to -20 °C and the respective electrophile was added at this temperature, then the mixture was allowed to warm up to rt. The reaction was again monitored using TLC. After the completion of the reaction, the mixture was subjected to workup and purification (see below).

2.6. Typical procedure for the double metallation of functionalized iodobenzoic acids (40g; 40h-40j) (TP06)

The iodobenzoic acid of type 40 (2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 8.00 mL, 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Afterwards, i-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting solution was stirred at the same temperature. After TLC indicated full conversion, the respective electrophile was added at -20 °C and the mixture was allowed to warm up to rt. The reaction was again monitored using
2.7. Typical procedure for the double metallation of 3,5-diiodobenzoic acid (40a) (TP07)

3,5-Diiodobenzoic acid (40a; 748 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 8.00 mL, 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the resulting red solution was cooled to -50 °C. After stirring 15 min at -50 °C, MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -50 °C for further 30 min. Afterwards, \(i\)-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added very slowly, the solution turned dark brown immediately. The mixture was stirred at -50 °C. After TLC indicated full conversion (60 min), the respective electrophile was added at -50 °C, the mixture was stirred 20 min at this temperature and was subsequently allowed to warm up to rt. After the completion of the reaction, the reaction was quenched (MeOH, 2.0 mL), subjected to workup and purification (see below).

2.8. Typical procedure for the double metallation of 5-bromo-2-furoic acid (48a) and 5-bromothiophene-2-carboxylic acid (48b) (TP08)

The carboxylic acid of type 48 (2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for some minutes at rt, the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Afterwards, \(i\)-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. A first check after 30 min did indicate complete conversion. The Grignard reagent did precipitate as a thick, greyish slurry, which was cooled to 20 °C. Subsequently, the respective electrophile was added at this temperature, the mixture was allowed to warm up to rt. The reaction was again monitored using TLC. After the completion of the reaction, the mixture was subjected to workup and purification (see below).

2.9. Typical procedure for the bromine/magnesium-exchange on 4,5-dibromo-2-thiophene-carboxylic acid (48c) (TP09)

4,5-Dibromo-2-thiophene-carboxylic acid (48c; 572 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for some minutes at rt, the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Afterwards, \(i\)-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was and the resulting mixture was stirred at the same temperature. After 60 min, TLC indicated complete conversion. Subsequently the
respective electrophile was added at this temperature and the mixture was allowed to warm up to rt. After the completion of the reaction, the mixture was subjected to workup and purification (see below).

2.10. Typical procedure for the double mettallation of iodoimidazoles of type 52

(TP10)

The iodoimidazole of type 52 (2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. A solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for some minutes at rt, the resulting slurry was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Then, i-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. The exchange reaction was monitored by TLC (samples quenched with MeOH, silica plates; CH₂Cl₂:MeOH; 19:1) versus the starting material and was usually complete after 45 min. As not otherwise stated, the resulting slurry was cooled to -20 °C and the respective electrophile (2.40 mmol, 1.20 equiv) was added, then the mixture was allowed to rt. After the completion of the reaction (TLC monitoring) the reaction mixture was poured on water (20 mL) and sat. aq. NH₄Cl (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. The crude product was subjected to flash column chromatography.

2.11. Typical procedure for the exchange on 4-iodo-5-(phenylthio)-1H-imidazole (54g) (TP11)

4-Iodo-5-(phenylthio)-1H-imidazole (54g; 604 mg; 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. A solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for some minutes at rt., the resulting slurry was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Then, i-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.10 mmol, 1.05 equiv) was added slowly and the resulting mixture was stirred at -20 °C. The exchange reaction was monitored by TLC (samples quenched with MeOH, silica plates; CH₂Cl₂:MeOH; 19:1) versus the starting material and was usually complete after 45 min. The respective electrophile (2.40 mmol, 1.20 equiv) was added, then the mixture was allowed to rt. After the completion of the reaction (TLC monitoring) the reaction mixture was poured on water (20 mL) and sat. aq. NH₄Cl (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. The crude product was subjected to flash column chromatography.

2.12. Typical procedure for the triple mettallation of 5-iodouracil (57a) (TP12)

5-Iodouracil (57a; 476 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Applying vigorous stirring, the substrate was dried for 15 min in high vacuum to exclude the presence of water in the hygroscopic substrate. Then, a solution of LiCl in THF (0.50 M; 8.00 mL; 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the substrate dissolved to give a clear and colorless solution. The solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. Strong bubbling of methane out of the solution
did indicate the proceeding deprotonation. After completion of the addition, the resulting, clear solution was stirred at -20 °C for further 20 min. Afterwards, \(i\)-PrMgCl·LiCl (1.32 M in THF; 1.82 mL, 2.40 mmol, 1.20 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. After one hour, a thick, greyish slurry had formed and the TLC of the mixture did show only traces of 5-iodouracil. The mixture was cooled to –20 °C and the respective electrophile was added at this temperature, then the mixture was allowed to warm up to rt. After the completion of the reaction, it was quenched by addition of MeOH (2.0 mL), the mixture was subjected to workup and purification (see below).

2.13. Typical procedure for the triple metallation of 5-bromouracil (57b) (TP13)

5-Bromouracil (57b; 382 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. A solution of LiCl in THF (0.50 M; 8.00 mL; 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the substrate dissolved to give a clear, pale yellow solution. The solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, clear solution was stirred at -20 °C for further 20 min. Afterwards, \((i\)-Pr\)\(_2\)Mg·LiCl (0.42 M in THF; 5.24 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. After one hour, a clear, greyish solution had formed and the TLC of the mixture did show only traces of 5-bromouracil. The mixture was cooled to –20 °C and the respective electrophile was added at this temperature, then the mixture was allowed to warm up to rt. After the completion of the reaction, it was quenched by addition of MeOH (2.0 mL) the mixture was subjected to workup and purification (see below).

2.14. Typical procedure for the triple metallation of 6-iodouracil (57c) (TP14)

6-Iodouracil (57c; 476 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. A solution of LiCl in THF (0.50 M; 8.00 mL; 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the substrate dissolved to give a clear, slightly yellow solution. The solution was cooled to -25 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, clear solution was stirred at -25 °C for further 20 min. Afterwards, \(i\)-PrMgCl·LiCl (1.32 M in THF; 1.82 mL, 2.40 mmol, 1.20 equiv) was added slowly and the resulting mixture was stirred at the same temperature. After one hour, a clear, greyish solution had formed and the TLC of the mixture did show mainly the exchanged species, traces of 6-iodouracil and traces of an unidentified byproduct. The respective electrophile was added at this temperature, and then the mixture was allowed to warm up to rt. After the completion of the reaction, it was quenched by addition of MeOH (2.0 mL) the mixture was subjected to workup and purification (see below).

2.15. Typical procedure for the synthesis of the Grignard reagents of type 66

(TP15)

The 5-alkyl-6-iodouracil of type 63 was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 2.00 equiv) was added leading to a clear and colorless solution. The solution was cooled to -30 °C and MeMgCl (3.00 M in THF, 2.00 equiv) was added dropwise. Strong bubbling of
methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the resulting, clear solution was stirred at -30 °C for further 20 min. Afterwards, i-PrMgCl·LiCl (1.30 M in THF, 1.30 equiv) was added slowly and the resulting mixture was allowed to stir at -30 °C for 1 h. The exchange reaction was monitored by TLC versus the starting material.

2.16. Typical procedure for the synthesis of functionalized cyclopropane carbonitriles of type 81 (TP16)

i-PrMgCl (2.56 M in Et₂O; 2.20 mmol, 1.10 equiv) was added dropwise to a solution of 2,2-dibromo-1-methylcyclopropanecarbonitrile (76; 2.00 mmol) in dichloromethane (4.0 mL) at -50 °C and stirred for 5 min at this temperature. Then, the electrophile (1.20 equiv) was added neat and the reaction mixture was allowed to warm up to rt. The reaction was followed by GC-MS-analysis of reaction aliquots. After the conversion was complete, sat. aq. NH₄Cl (10 mL) was added, and the resulting mixture was extracted with dichloromethane (4 × 15 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. The crude residue was purified by flash column chromatography.

The d.r. of the reactions was determined by GC-MS analysis of aliquots from the crude reaction mixture. If not otherwise stated, the isolated yields of the main diastereoisomer are given.

2.17. Typical procedure for the exchange on 2-bromo-1-methyl-2-(phenylsulfanyl)cyclopropane-carbonitrile (81e) (TP17)

i-PrMgCl (2.56 M in Et₂O; 5.50 mmol, 1.10 equiv) was added dropwise to a solution of 2-bromo-1-methyl-2-(phenylsulfanyl)cyclopropanecarbonitrile (81e; 1.34 g, 5.00 mmol) in dichloromethane (20 mL) at -50°C and stirred for 10 min at this temperature. Then, the respective allyl bromide and, subsequently, CuCN·2LiCl (1.00 M in THF; 0.05 mL; 0.50 mol%) were added and the reaction mixture was allowed to warm up to rt. The reaction was followed by GC-MS-analysis of reaction aliquots. Isomerization in course of the reaction was not observed. After the conversion was complete, a saturated aqueous solution of ammonium chloride (20 mL) was added, and the resulting mixture was extracted with dichloromethane (4 × 25 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. The crude residue was purified by flash column chromatography.

2.18. Typical procedure for the reactions of Grignard reagents with ketones (TP18)

In a flame dried, argon-flushed 25 mL Schlenk-flask equipped with a septum and a magnetic stirring bar was placed LaCl₃·2LiCl in THF (0.33 M; 6.10 mL, 2.00 mmol, 1.00 equiv). The ketone (2.00 mmol) was added neat and the resulting mixture was stirred for 1 h at rt. The reaction mixture was cooled to 0 °C and the Grignard reagent (solution in THF, 2.10 mmol, 1.05 equiv.) was added dropwise and the reaction mixture was allowed to stir at the same temperature. After GC-analysis of reaction aliquots showed complete conversion, sat. aq. NH₄Cl (2.0 mL) and water (2.0 mL) was added. The aqueous layer was extracted with ether.
(4 × 10 mL), the combined extracts were dried (Na₂SO₄) and evaporated in vacuo. The crude residue was purified by flash column chromatography.

2.19. Typical procedure for the catalytical Michael additions of benzyl amine (106) to ethyl (2Z)-but-2-enoate (107) (TP 19)

In a flame dried, argon-flushed 10 mL Schlenk-flask equipped with a septum and a magnetic stirring bar was placed ethyl (2Z)-but-2-enoate (107; 114 mg, 1.00 mmol) and benzyl amine (106; 161 mg, 1.50 mmol, 1.50 equiv). Then THF was added (the amount was calculated to reach the final concentrations given in Fig. 7). Subsequently, the catalyst, LaX₃·2LiY in THF (LaCl₃·2LiCl: 0.50 M; LaCl₃·2LiBr: 1.00 M) was added to start the reaction. The reaction was stirred at rt and monitored by GC analysis of reaction aliquots versus decane as internal standard.
3. Halogen/Magnesium Exchange Reactions in the Presence of Unprotected Phenol Derivatives

3.1. Starting Material Synthesis

Synthesis of 4-bromo-2,6-diiodophenol (30a)

4-Bromophenol (29a; 2.60 g, 15.0 mmol) was reacted with iodine and silver(I)sulfate according to TP01 and purified chromatographically (silica; CH₂Cl₂). The product was obtained as colorless solid (5.47 g, 12.9 mmol, 86%).

**mp.:** 129.5-131.3 °C

**¹H-NMR (CDCl₃, 300 MHz):** δ [ppm] = 7.78 (s, 2 H); 5.72 (s, 1 H).

**¹³C-NMR (CDCl₃, 75 MHz):** δ [ppm] = 153.1; 140.9; 113.6; 82.4.

**IR (KBr):** ν [cm⁻¹] = 3452 (m); 3066 (w); 1726 (w); 1530 (m); 1436 (s); 1400 (m); 1376 (s); 1328 (w); 1304 (s); 1258 (m); 1230 (s); 1208 (m); 1174 (s); 1144 (s); 1106 (m); 1080 (m); 1046 (m); 874 (w); 856 (vs); 674 (m); 652 (s); 610 (w).

**MS (EI):** m/z (%) = 426 (M⁺; 81Br; 93); 424 (M⁺; 79Br; 100); 298 (2); 296 (2); 271 (5); 269 (5); 218 (4); 212 (3); 189 (3); 172 (16); 170 (17); 143 (5); 141 (5); 127 (6); 91 (6); 62 (13).

**HR-MS (C₆H₄BrI₂O):** calculated: 423.7457 found: 423.7439.

Synthesis of ethyl 4-hydroxy-3,5-diiodobenzoate (30b)

Ethyl 4-hydroxybenzoate (29b; 2.49 g, 15.0 mmol) was reacted with iodine and silver(I)sulfate according to TP01 and purified chromatographically (silica; CH₂Cl₂). The product was obtained as colorless solid (5.80 g, 13.9 mmol, 92%).

**mp.:** 124.0-125.0 °C

**¹H-NMR (CDCl₃, 300 MHz):** δ [ppm] = 8.34 (s, 2 H); 6.12 (s, 1 H); 4.34 (q, ³J = 7.2 Hz, 2 H); 1.37 (t, ³J = 7.2 Hz, 3 H).

**¹³C-NMR (CDCl₃, 75 MHz):** δ [ppm] = 163.5; 157.1; 140.8; 126.4; 81.6; 61.5; 14.3.

**IR (KBr):** ν [cm⁻¹] = 3376 (m); 3075 (w); 2972 (m); 2931 (w); 1784 (w); 1705 (vs); 1581 (m); 1544 (m); 1458 (s); 1395 (m); 1367 (m); 1296 (s); 1255 (vs); 1231 (s); 1174 (m); 1188
MS (EI): m/z (%) = 418 (M⁺; 86); 390 (50); 373 (100); 345 (9); 291 (5); 245 (6); 218 (14); 189 (3); 119 (7); 91 (11); 62 (8),
HR-MS (C₉H₈I₂O₂): calculated: 417.8563  found: 417.8592.

Synthesis of 2,6-diiodo-4-trifluoromethyl-phenol (30c)

\[
\begin{array}{c}
\text{CF}_3 \\
\text{I} \\
\text{OH} \\
\end{array}
\]

4-Trifluoromethylphenol (29c; 2.43 g, 15.0 mmol) was reacted with iodine and silver(I)sulfate according to TP01 and purified chromatographically (silica; pentane/CH₂Cl₂, 1:9). The product was obtained as colorless solid (5.61 g, 13.6 mmol, 90 %).
mp.: 104.0-104.5 °C

\[\text{^1H-NMR (CDCl}_3, \text{ 300 MHz)}: \delta [ppm] = 7.91 (s, 2 H); 6.05 (s, 1 H).\]

\[\text{^13C-NMR (CDCl}_3, \text{ 75 MHz)}: \delta [ppm] = 156.5; 136.4 (q, \text{^3J(CF)} = 3.7 Hz); 126.2 (q, \text{^2J(CF)} = 33.7 Hz); 122.0 (q, \text{^1J(CF)} = 272.5 Hz); 81.8.\]

\[\text{IR (KBr)}: \nu [\text{cm}^{-1}] = 3450 (s); 3390 (w); 2926 (w); 2514 (w); 1784 (w); 1596 (w); 1574 (w); 1596 (w); 1553 (w); 1464 (w); 1404 (m); 1336 (s); 1316 (vs); 1272 (m); 1245 (m); 1200 (s); 1176 (m); 1143 (s); 1124 (vs); 1094 (s); 1049 (w); 889 (s); 765 (w); 716 (m); 706 (m); 644 (s); 599 (w); 531 (w).
\]

MS (EI): m/z (%) = 414 (M⁺; 100); 395 (6); 286 (4); 258 (2); 207 (3); 160 (22); 141 (3); 132 (12); 127 (3); 112 (2); 81 (5); 63 (3); 62 (3); 53 (2); 41 (51).

HR-MS (C₇H₉F₃I₂O): calculated: 413.8225  found: 413.8244.

Synthesis of 4-hydroxy-3-iodo-benzonitrile (30e)

\[
\begin{array}{c}
\text{CN} \\
\text{I} \\
\text{OH} \\
\end{array}
\]

4-Hydroxy-benzonitrile (29d; 1.79 g, 15.0 mmol) was reacted with iodine (3.81 g, 15.0 mmol, 1.00 equiv.) and silver(I)sulfate (4. 68 g, 15.0 mmol, 1.00 equiv) according to TP01 and purified chromatographically (silica; CH₂Cl₂) the product was obtained as colorless solid (2.16 g, 8.85 mmol, 59 %)
mp.: 147.0-148.0 °C (decomposition)

\[\text{^1H-NMR (CDCl}_3, \text{ 400 MHz)}: \delta [ppm] = 10.62 (brs, 1 H); 7.82 (d, \text{^4J} = 2.0 Hz, 1 H); 7.31 (dd, \text{^3J} = 2.0 Hz, \text{^3J} = 8.5 Hz, 1 H); 6.84 (d, \text{^3J} = 8.5 Hz,1 H).
\]

\[\text{^13C-NMR (CDCl}_3, \text{ 100 MHz)}: \delta [ppm] = 160.7; 142.4; 133.2; 117.7; 115.1; 103.6; 83.9.
\]
IR (KBr): $\nu$ [cm$^{-1}$] = 3412 (s); 3272 (s); 2226 (s); 1641 (w); 1592 (s); 1565 (w); 1397 (s); 1295 (m); 1348 (w); 1295 (m); 1134 (w); 1039 (w); 894 (w); 822 (m); 732 (w); 581 (w); 475 (w).

MS (EI): $m/\ell$ (%) = 245 (M$^+$; 100); 127 (5); 118 (8); 9 (15); 63 (15); 53 (3).

HR-MS (C$_7$H$_9$INO): calculated: 244.9338 found: 244.9350.

Synthesis of ethyl 4-hydroxy-3-iodobenzoate (30f)

![Structure of ethyl 4-hydroxy-3-iodobenzoate](image)

Ethyl 4-hydroxybenzoate (29b; 2.49 g, 15.0 mmol) was reacted with iodine (3.81 g, 15.0 mmol, 1.00 equiv) and silver(I)sulfate (4.68 g, 15.0 mmol, 1.00 equiv) according to TP01 and purified chromatographically (silica; CH$_2$Cl$_2$). The product was obtained as colorless solid (2.72 g, 9.32 mmol, 62%).

**mp.:** 119.0-121.3 °C

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ [ppm] = 8.36 (d, $^4J$ = 1.9 Hz, 1 H); 7.92 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.9 Hz, 1 H); 6.99 (d, $^3J$ = 8.3 Hz, 1 H); 6.14 (s, 1 H); 4.34 (q, $^3J$ = 7.1 Hz, 2 H); 1.37 (t, $^3J$ = 7.1 Hz, 3 H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ [ppm] = 165.1; 158.8; 140.3; 131.9; 124.7; 114.6; 85.0; 61.2; 14.3.

IR (KBr): $\nu$ [cm$^{-1}$] = 2986 (w); 2903 (w); 1685 (s); 1596 (m); 1574 (m); 1498 (w); 1477 (w); 1465 (w); 1446 (w); 1416 (w); 1369 (m); 1286 (vs); 1263 (vs); 1175 (w); 1124 (m); 1036 (w); 1020 (w); 908 (w); 870 (w); 828 (w); 766 (m); 706 (w); 670 (m); 632 (m); 465 (w).

MS (EI): $m/\ell$ (%) = 292 (53); 264 (48); 247 (100); 219 (12); 191 (3); 165 (6); 120 (8); 109 (3); 92 (22); 81 (3); 63 (14); 53 (8).


3.2. Iodine/Magnesium Exchange and Reactions with Electrophiles

Synthesis of 4-hydroxy-3-(hydroxy-phenyl-methyl)-5-iodo-benzonitrile (32a)

![Structure of 4-hydroxy-3-(hydroxy-phenyl-methyl)-5-iodo-benzonitrile](image)

According to TP02, the Grignard reagent of type 31 was prepared from 4-hydroxy-3,5-diodo-benzonitrile (30d; 557 mg, 1.50 mmol) and reacted at -30 °C with benzaldehyde (191 mg, 1.80 mmol, 1.20 equiv). Flash column chromatography (silica; CH$_2$Cl$_2$) afforded 32a as a colorless, crystalline solid (421 mg, 1.20 mmol, 80%).
mp.: 131.0-132.0 °C

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ [ppm] = 10.76 (brs, 1 H); 7.76 (d, $^4J = 2.1$ Hz, 1 H); 7.28-7.18 (m, 5 H); 7.00 (d, $^4J = 2.1$ Hz, 1 H); 5.81 (s, 1 H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ [ppm] = 159.1; 141.3; 141.1; 131.7; 128.6; 128.4; 128.0; 126.5; 117.4; 103.9; 85.5; 75.1.

IR (KBr): $\nu$ [cm$^{-1}$] = 3340 (vs); 3066 (m); 2240 (s); 1812 (w); 1602 (m); 1556 (w); 1493 (m); 1467 (vs); 1457 (vs); 1415 (m); 1327 (w); 1281 (m); 1262 (m); 1193 (s); 1008 (m); 1037 (m); 1028 (m); 944 (w); 924 (w); 880 (w); 762 (m); 742 (m); 702 (vs); 644 (w); 622 (w); 598 (w); 483 (w).

MS (EI): m/z (%) = 349 ($[M-2H]^+$; 100); 348 (74); 333 (7); 332 (9); 272 (19); 271 (18); 164 (7); 144 (6); 139(5); 117 (14); 106 (5); 105 (57); 89 (7); 88 (9); 78 (5); 77 (49); 62 (7); 51 (15).

HR-MS (C$_{14}$H$_8$INO$_2$, $[M-2H]^+$): calculated: 348.9600 found: 348.9599.

Synthesis of 4-bromo-2-(hydroxy-phenyl-methyl)-6-iodo-phenol (32b)

According to TP02, the Grignard reagent of type 31 was prepared from 4-bromo-2,6-diiodo-phenol (30a; 636 mg, 1.50 mmol) and reacted at -30 °C with benzaldehyde (191 mg, 1.80 mmol, 1.20 equiv). Flash column chromatography (silica; CH$_2$Cl$_2$) afforded 32b as a colorless, crystalline solid (497 mg, 1.23 mmol, 82 %).

mp.: 154.0-154.5 °C

$^1$H-NMR (CDCl$_3$/dms-d$_6$, 300 MHz): $\delta$ [ppm] = 9.88 (brs, 1 H); 7.65 (d, $^4J = 2.4$ Hz, 1 H); 7.35-7.22 (m, 6 H); 6.96 (d, $^4J = 2.4$ Hz, 1 H); 5.82 (s, 1 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ [ppm] = 154.0; 141.7; 139.1; 130.4; 129.6 ; 128.2; 127.7; 126.4; 111.4; 86.2; 75.1.

IR (KBr): $\nu$ [cm$^{-1}$] = 3388 (vs); 3027 (w); 2901 (w); 1629 (w); 1554 (w); 1494 (w); 1451 (s); 1411 (m); 1332 (w); 1295 (w); 1249 (m); 1230 (m); 1202 (s); 1138 (m); 1030 (w); 1020 (m); 919 (w); 888 (w); 834 (m); 808 (w); 748 (m); 731 (m); 700 (s); 684 (m); 666 (m); 570 (w); 547 (w); 455 (w).

MS (EI): m/z (%) = 402 ([M-2H]$^+$; 100); 326 (30); 199 (5); 197 (5); 172 (9); 170 (10); 168 (5); 143 (5); 139 (23); 105 (84); 91 (7); 77 (83); 74 (6); 63 (16); 62 (14); 51 (20).

HR-MS (C$_{13}$H$_8$BrI$_2$O$_2$, [M-2H]$^+$): calculated: 401.8752 found: 401.8756.

Synthesis of 4-hydroxy-3-(hydroxy-phenyl-methyl)-5-iodo-benzoic acid ethyl ester (32c)
According to **TP02**, the Grignard reagent of type **31** was prepared from 4-hydroxy-3,5-diiodo-benzoic acid ethyl ester (**30b**; 627 mg, 1.50 mmol) and reacted at -30 °C with benzaldehyde (191 mg, 1.80 mmol, 1.20 equiv). Flash column chromatography (silica; CH₂Cl₂) afforded **32c** as a colorless, crystalline solid (435 mg, 1.09 mmol, 73 %).

**mp.**: 147.0-150.0 °C (decomposition)

**1H-NMR (CDCl₃, 300 MHz)**: δ [ppm] = 8.89 (s, 1 H); 8.28 (d, J = 2.0 Hz, 1 H); 7.65 (d, J = 2.0 Hz, 1 H); 7.36-7.29 (m, 5 H); 5.98 (s, 1 H); 4.26 (q, J = 7.1 Hz, 2 H); 3.62 (s, 1 H); 1.32 (t, J = 7.1 Hz, 3 H).

**13C-NMR (CDCl₃, 75 MHz)**: δ [ppm] = 165.2; 157.9; 141.0; 139.9; 130.0; 128.8; 128.5; 127.0; 126.6; 123.7; 85.7; 76.1; 61.2; 14.3.

**IR (KBr)**: ν [cm⁻¹] = 3388 (s); 2984 (w); 2939 (w); 1674 (s); 1577 (w); 1494 (w); 1452 (m); 1395 (m); 1369 (s); 1309 (vs); 1266 (m); 1203 (w); 1153 (w); 1119 (w); 1093 (w); 1023 (m); 917 (w); 872 (w); 834 (w); 767 (m); 702 (s); 663 (w); 634 (w); 572 (w); 530 (w).

**MS (EI)**: m/z (%) = 396 ([M-2H]+; 100); 367 (10); 351 (14); 319 (16); 291 (12); 273 (18); 168 (6); 139 (14); 119 (7); 105 (58); 91 (8); 77 (41); 63 (5); 51 (7).


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**Synthesis of 2-(5-bromo-2-hydroxy-3-iodo-benzyl)-acrylic acid ethyl ester (32d)**

According to **TP02**, the Grignard reagent of type **31** was prepared from 4-bromo-2,6-diiodo-phenol (**30a**; 636 mg, 1.50 mmol). After transmetallation with CuCN·2LiCl (1.00 M in THF; 1.65 mL, 1.65 mmol, 1.10 equiv; 30 min, -30 °C) it was reacted with 2 ethyl 2-(bromomethyl)-acrylate (318 mg, 1.65 mmol, 1.10 equiv) at -30 °C. Flash column chromatography (silica; pentane/CH₂Cl₂, 2:1) afforded **32d** as a colorless oil (382 mg, 0.93 mmol, 62 %).

**1H-NMR (CDCl₃, 400 MHz)**: δ [ppm] = 7.68 (s, 1 H); 7.67 (d, J = 2.5 Hz, 1 H); 7.21 (d, J = 2.5 Hz, 1 H); 6.26 (s, 1 H), 5.77 (s, 1 H); 4.23 (q, J = 7.2 Hz, 2 H); 3.65 (s, 2 H); 1.29 (t, J = 7.2 Hz, 3 H).

**13C-NMR (CDCl₃, 100 MHz)**: δ [ppm] = 168.4; 152.8; 139.0; 138.2; 133.5; 127.8 ; 127.5; 112.9; 87.4; 61.9; 33.6; 14.0.

**IR (KBr)**: ν [cm⁻¹] = 3478 (m); 3234 (m); 2981 (m); 2935 (m); 2870 (w); 1913 (w); 1712 (s); 1682 (vs); 1624 (s); 1584 (w); 1551 (m); 1451 (vs); 1421 (s); 1406 (s); 1373 (s); 1335 (vs); 1304 (s); 1273 (m); 1211 (vs); 1143 (vs); 1095 (m); 1021 (m); 955 (m); 932 (w); 896 (w); 861 (m); 823 (m); 743 (w); 696 (w); 669 (m); 592 (w), 546 (w).

**MS (EI)**: m/z (%) = 412 ([M+81Br]+; 14), 410 ([M+79Br]+; 14), 367 (13); 366 (96); 364 (100); 337 (26); 335 (26); 285 (31); 257 (18); 239 (5); 237 (5); 211 (6); 210 (6); 209 (6); 208 (5); 185 (5); 183 (7); 131 (12); 130 (10); 103 (7); 102 (26); 101 (5); 76 (7); 75 (8); 74 (5); 51 (5).

**HR-MS** (C₁₆H₁₂BrIO₃): calculated: 409.9000 found: 409.9015.
Synthesis of 2-(hydroxy-phenyl-methyl)-6-iodo-4-trifluoromethyl-phenol (32e)

According to **TP02**, the Grignard reagent of type 31 was prepared from 2,6-diiodo-4-trifluoromethyl-phenol (30c; 426 mg, 1.50 mmol) and reacted at -30 °C with benzaldehyde (191 mg, 1.80 mmol, 1.20 equiv). Flash column chromatography (silica; pentane/CH₂Cl₂, 1:1) afforded 32e as a colorless, crystalline solid (426 mg, 1.08 mmol, 72 %).

**mp.:** 146.5-147.0 °C

**¹H-NMR (CDCl₃, 600 MHz):** δ [ppm] = 10.37 (brs, 1 H); 7.77 (d, ⁴J = 1.8 Hz, 1 H); 7.33-7.19 (m, 6 H); 7.06 (d, ⁴J = 1.8 Hz, 1 H); 5.87 (s, 1 H).

**¹³C-NMR (CDCl₃, 150 MHz):** δ [ppm] = 157.8; 141.6; 134.8 (q, ³J(CF) = 4.0 Hz); 128.4; 128.01; 127.9; 126.6; 126.1 (q, ³J(CF) = 3.6 Hz); 124.8 (q, ¹J(CF) = 272.8 Hz); 122.8 (q, ²J(CF) = 32.9 Hz); 85.3; 75.6.

**IR (KBr):** ν [cm⁻¹] = 3424 (s); 2929 (w); 2226 (w); 1614 (s); 1495 (w); 1450 (w); 1423 (w); 1324 (vs); 1266 (w); 1212 (w); 1164 (m); 1114 (s); 1094 (w); 1020 (w); 891 (w); 837 (w); 742 (w); 700 (m); 682 (w); 657 (m); 639 (w); 592 (w).

**MS (EI):** m/z (%) = 392 ([M-2H]+; 100); 391 (76); 364 (29); 363 (11); 188 (8); 187 (9); 160 (15); 132 (9); 131 (5); 106 (6); 105 (59); 81 (5); 77 (47); 63 (7); 51 (12).

**HR-MS (C₁₄H₈F₃IO₂, [M-2H]+):** calculated: 391.9521 found: 391.9526.

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Synthesis of 2-(cyclohexyl-hydroxy-methyl)-6-iodo-4-trifluoromethyl-phenol (32f)

According to **TP02**, the Grignard reagent of type 31 was prepared from 2,6-diiodo-4-trifluoromethyl-phenol (30c; 426 mg, 1.50 mmol) and reacted at -30 °C with cyclohexylaldehyde (202 mg, 1.80 mmol, 1.20 equiv). Recrystallization from heptane afforded 32f as a colorless, crystalline solid (444 mg, 1.11 mmol, 74 %).

**mp.:** 120.5-121.0 °C

**¹H-NMR (CDCl₃, 400 MHz):** δ [ppm] = 8.97 (brs, 1 H); 7.87 (d, ⁴J = 1.6 Hz, 1 H); 7.15 (d, ⁴J = 1.6 Hz, 1 H); 4.57 (d, ³J = 7.1 Hz, 1 H); 2.84 (brs, 1 H); 1.92 (d, ²J = 12.7 Hz, 1 H); 1.80-1.65 (m, 4 H); 1.39 (d, ²J = 12.7 Hz, 1 H); 1.28-0.96 (m, 5 H).

**¹³C-NMR (CDCl₃, 100 MHz):** δ [ppm] = 157.2; 135.2 (q, ³J(CF) = 3.8 Hz); 126.6; 125.6 (q, ³J(CF) = 3.8 Hz); 123.3 (q, ²J(CF) = 33.3 Hz); 123.2 (q, ¹J(CF) = 272.8 Hz); 85.7; 80.3; 43.7; 29.4; 28.2; 26.1.

**IR (KBr):** ν [cm⁻¹] = 3444 (s); 2929 (s); 2856 (m); 1616 (w); 1478 (w); 1451 (w); 1422 (w); 1327 (vs); 1282 (w); 1264 (w); 1204 (m); 1162 (s); 1115 (vs); 1095 (w); 1070 (w); 1012 (w); 964 (w); 904 (w); 890 (w); 748 (w); 680 (w); 656 (m); 546 (w); 578 (w).
MS (EI): m/z (%) = 383 (9); 382 ([M-F]+; 55); 363 (5); 325 (5); 314 (17); 301 (15); 226 (5); 213 (5); 212 (5); 200 (6); 199 (5); 186 (6); 173 (7); 157 (5); 151 (6); 145 (7); 144 (5); 131(5); 115 (7); 81 (100); 80 (10); 79 (9).

HR-MS (C_{14}H_{16}F_{3}O_{2}): calculated: 400.0147 found: 400.0145.

Synthesis of 4-Hydroxy-3-(1-hydroxy-2,2-dimethyl-propyl)-5-iodo-benzonitrile (32g)

According to TP02 the Grignard reagent of type 31 was prepared from 4-hydroxy-3,5-diiodo-benzonitrile (30d; 557 mg, 1.50 mmol) and reacted at -30 °C with pivaldehyde (142 mg, 1.65 mmol, 1.10 equiv). Flash column chromatography (silica; CH_{2}Cl_{2}) afforded 32g as a colorless, crystalline solid (353 mg, 1.07 mmol, 71 %).

mp.: 132-133 °C

^1H-NMR (CDCl_{3}, 400 MHz): δ [ppm] = 9.89 (s, 1 H); 7.88 (d, \(^J=2.0\) Hz, 1 H); 7.15 (d, \(^J=2.0\) Hz, 1 H); 4.54 (d, \(^J=3.6\) Hz, 1 H); 3.46 (d, \(^J=3.6\) Hz, 1 H); 0.94 (s, 9 H).

^13C-NMR (CDCl_{3}, 100 MHz): δ [ppm] = 159.6; 141.7; 133.5; 125.2; 117.8; 103.6; 86.2; 83.6; 37.4; 25.8.

IR (KBr): ν [cm\(^{-1}\)] = 3392 (vs); 3201 (m); 2964 (s); 2905 (w); 2871 (w); 2235 (vs); 1601 (m); 1567 (w); 1465 (vs); 1425 (s); 1386 (m); 1366 (m); 1310 (w); 1286 (m); 1241 (m); 1216 (w); 1192 (m); 1116 (m); 1053 (m); 1088 (m); 958 (w); 933 (w); 898 (w); 880 (w); 817 (w); 785 (m); 758 (m); 730 (w); 698 (m); 608 (w); 546 (w); 477 (w).

MS (EI): m/z (%) = 331 (M\(^+\); 8); 313 (8); 276 (10); 275 (100); 274 (30); 273 (7); 272 (6); 266 (10); 146 (6); 128 (6); 119 (10); 57 (63); 41 (16).

HR-MS (C_{12}H_{14}I_{3}O_{2}): calculated: 331.0069 found: 331.0077.

Synthesis of 3-allyl-4-hydroxy-5-iodo-benzonitrile (32h)

According to TP02, the Grignard reagent of type 31 was prepared from 4-hydroxy-3,5-diiodo-benzonitrile (30d; 557 mg, 1.50 mmol). Then, CuCN·2LiCl (1.00 M in THF; 0.08 mL, 0.08 mmol, 5.00 mol%) and allyl bromide (218 mg, 1.80 mmol, 1.20 equiv) were added at -30 °C. After standard workup, flash column chromatography (silica; pentane:CH_{2}Cl_{2};4:1) afforded 32h as colorless, crystalline solid (351 mg, 1.23 mmol, 82 %).

mp.: 88.0-89.0 °C

^1H-NMR (CDCl_{3}, 400 MHz): δ [ppm] = 7.82 (d, \(^J=2.0\) Hz, 1 H); 7.39 (d, \(^J=2.0\) Hz, 1 H); 6.10-5.92 (m, 2 H); 5.19-5.10 (m, 2 H); 3.43 (d, \(^J=6.6\) Hz, 2 H).
\[ ^{13}\text{C-NMR (CDCl}_3, \ 100 \text{ MHz)}: \delta \text{ [ppm]} = 156.6; 140.1; 134.4; 134.3; 127.9; 117.7; 117.4; 106.0; 85.9; 34.0. \]

\[ \text{IR (KBr): } v \text{ [cm}^{-1}] = 3344 \text{ (vs); 3064 (w); 2902 (w); 2229 (s); 1785 (w); 1643 (w); 1595 (m); 1552 (m); 1459 (s); 1433 (m); 1405 (m); 1343 (w); 1284 (s); 1256 (s); 1215 (m); 1155 (vs); 1099 (s); 1000 (m); 930 (s); 894 (m); 873 (m); 828 (w); 740 (w); 728 (m); 685 (m); 616 (m); 580 (w); 530 (w); 480 (w). \]

\[ \text{MS (EI): } m/z \% = 285 \text{ (M}^+; 100); 300 (11); 258 (8); 257 (8); 158 (16); 130 (35); 115 (5); 103 (35); 102 (17); 76 (11); 77(13); 51 (7). \]

\[ \text{HR-MS (C}_{10}\text{H}_{8}\text{INO): calculated: 284.9651 found: 284.9671.} \]

**Synthesis of 5'-cyano-2'-hydroxy-3'-iodo-biphenyl-4-carboxylic acid ethyl ester (32i)**

![Structural diagram]

According to TP02, the Grignard reagent of type 31 was prepared from 4-hydroxy-3,5-diiodo-benzonitrile (30d; mg, 1.50 mmol). Then, ZnCl\(_2\) (1.00 M in THF; 1.65 mL, 1.10 equiv) was added at -30 °C and the resulting solution was stirred 30 min at -30 °C. This mixture then was slowly added to a preprepared solution of Pd(dba)_2 (43.1 mg, 0.08 mmol, 5.00 mol%), trifuryl phosphine (34.8 mg, 0.15 mmol, 10.0 mol%) and ethyl 4-iodobenzoate (331 mg, 1.20 mmol, 0.80 equiv) in THF (2.0 mL) and the resulting solution was stirred at rt (12h). After standard workup, flash column chromatography (silica; CH\(_2\)Cl\(_2\)) afforded 32i as a colorless, crystalline solid (335 mg, 0.85 mmol, 71%).

\[ \text{mp.: } 172.5-173.0 \text{ °C (decomposition)} \]

\[ ^{1}\text{H-NMR (CDCl}_3, \ 300 \text{ MHz): } \delta \text{ [ppm]} = 8.12 \text{ (d, } ^3J = 8.1 \text{ Hz, } 2 \text{ H}); 7.98 \text{ (d, } ^4J = 1.9 \text{ Hz, } 1 \text{ H}); 7.56-7.51 \text{ (m, } 3 \text{ H}); 6.10 \text{ (brs, } 1 \text{ H}); 4.39 \text{ (q, } ^3J = 7.1 \text{ Hz, } 2 \text{ H}); 1.40 \text{ (t, } ^3J = 7.1 \text{ Hz, } 3 \text{ H).} \]

\[ ^{13}\text{C-NMR (CDCl}_3, \ 75 \text{ MHz): } \delta \text{ [ppm]} = 166.0; 155.5; 141.7; 139.6; 134.7; 130.7; 130.0; 129.0; 128.4; 117.0; 106.5; 86.5; 61.2; 14.3. \]

\[ \text{IR (KBr): } v \text{ [cm}^{-1}] = 3407 \text{ (s); 3070 (w); 2984 (w); 2927 (w); 2229 (m); 1706 (vs); 1610 (m); 1592 (m); 1509 (w); 1457 (s); 1412 (w); 1398 (w); 1368 (w); 1312 (m); 1285 (vs); 1242 (m); 1184 (w); 1135 (s); 1119 (m); 1056 (w); 1022 (w); 883 (w); 862 (w); 774 (w); 739 (m); 705 (m); 618 (w); 608 (w); 508 (w). \]

\[ \text{MS (EI): } m/z \% = 393 \text{ (M}^+; 72); 365 (33); 348 (100); 321 (9); 267 (6); 222 (12); 193 (32); 164 (22); 138 (5); 96 (3). \]

\[ \text{HR-MS (C}_{16}\text{H}_{12}\text{INO): calculated: 392.9862 found: 392.9865.} \]
Synthesis of 3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4-hydroxy-5-iodobenzonitrile (32j)

According to TP02, the Grignard reagent of type 31 was prepared from 4-hydroxy-3,5-diodo-benzonitrile (30d; 7.42 g, 20.0 mmol). Then, B(Oi-Pr)_3 (7.52 g, 40.0 mmol, 2.00 equiv) was added at -20 °C, the solution was stirred for 1 h at this temperature and was then allowed to warm up to rt. After stirring for 1 h, 2,2-dimethyl-1,3-propanediol (7.29 g, 70.0 mmol, 3.50 equiv) was added neat and the resulting solution was stirred for 3 h at rt. After standard workup, recrystallization from MeOH afforded 32j as colorless, crystalline solid (4.32 g, 13.1 mmol, 66 %).

\[ \text{mp.: } 174.3-175.4 ^\circ C \]

\[^1H\text{-NMR (CDCl}_3, 300 MHz): \delta [ppm] = 9.57 (s, 1 H); 8.03 (d, ^4J = 2.1 Hz, 1 H); 7.90 (d, ^4J = 2.1 Hz, 1 H); 3.84 (s, 4 H); 1.04 (s, 6 H). \]

\[^13C\text{-NMR (CDCl}_3, 75 MHz): \delta [ppm] = 165.5; 145.42; 139.9; 117.8; 104.9; 104.7; 72.7; 32.1; 21.7. \]

\[^{1}H\text{-NMR (CDCl}_3, 300 MHz): \delta [ppm] = 9.38 (s, 1 H); 7.28 (d, ^4J = 2.1 Hz, 1 H); 7.02 (d, ^4J = 2.1 Hz, 1 H); 6.01-5.88 (m, 1 H); 5.12-5.02 (m, 2 H); 4.54 (d, ^3J = 3.7 Hz, 1 H); 3.36-3.32 (m, 3 H); 0.95 (s, 9 H). \]

\[^{13}C\text{-NMR (CDCl}_3, 75 MHz): \delta [ppm] = 158.7; 135.3; 132.6; 131.8; 129.8; 124.3; 119.7; 116.6; 101.1; 84.4; 37.3; 33.5; 25.9. \]

Synthesis of 3-allyl-4-hydroxy-5-(1-hydroxy-2,2-dimethyl-propyl)-benzonitrile (32k)

According to TP02, the Grignard reagent of type 31 was prepared from 3-allyl-4-hydroxy-5-iodo-benzonitrile (32h; 428 mg, 1.50 mmol) and reacted at -30 °C with pivaldehyde (142 mg, 1.65 mmol, 1.10 equiv). Flash column chromatography (silica; pentane:CH_2Cl_2; 1:2) afforded 32k as a colorless, crystalline solid (258 mg, 1.05 mmol, 70 %).

\[ \text{mp.: } 131.0-132.0 ^\circ C \]

\[^1H\text{-NMR (CDCl}_3, 300 MHz): \delta [ppm] = 9.38 (s, 1 H); 7.28 (d, ^4J = 2.1 Hz, 1 H); 7.02 (d, ^4J = 2.1 Hz, 1 H); 6.01-5.88 (m, 1 H); 5.12-5.02 (m, 2 H); 4.54 (d, ^3J = 3.7 Hz, 1 H); 3.36-3.32 (m, 3 H); 0.95 (s, 9 H). \]

\[^{13}C\text{-NMR (CDCl}_3, 75 MHz): \delta [ppm] = 158.7; 135.3; 132.6; 131.8; 129.8; 124.3; 119.7; 116.6; 101.1; 84.4; 37.3; 33.5; 25.9. \]
Synthesis of 4-hydroxy-3-(hydroxy-phenyl-methyl)-benzonitrile (32l)

According to TP02, the Grignard reagent of type 31 was prepared from 4-hydroxy-3-iodo-benzonitrile (30e; 368 mg, 1.50 mmol) and reacted at -30 °C with benzaldehyde (191 mg, 1.80 mmol, 1.20 equiv). Flash column chromatography (silica; pentane:CH₂Cl₂; 1:1) afforded 32l as a colorless resin (253 mg, 1.13 mmol, 75 %).

$^{1}$H-NMR (CDCl₃, 300 MHz): $\delta$ [ppm] = 8.96 (s, 1 H); 7.43-7.32 (m, 6 H); 7.08 (d, $J = 2.0$ Hz, 1 H); 6.92 (d, $J = 8.4$ Hz, 1 H); 5.99 (s, 1 H); 3.51 (brs, 1 H).

$^{13}$C-NMR (CDCl₃, 75 MHz): $\delta$ [ppm] = 159.8; 140.7; 133.3; 132.5; 129.0; 128.9; 127.9; 126.8; 119.1; 118.3; 102.7; 76.3.

IR (KBr): $\nu$ [cm⁻¹] = 3321 (vs); 2850 (w); 2227 (m); 1605 (s); 1495 (m); 1453 (w); 1370 (w); 1493 (m); 1350 (w); 1287 (m); 1243 (m); 1208 (w); 1104 (w); 1016 (w); 905 (w); 836 (m); 699 (s); 1037 (m); 1028 (m); 944 (w); 924 (w); 908 (w); 880 (w); 762 (m); 593 (w).

MS (EI): m/z (%) = 225 (M⁺; 1); 224 ([M-H]⁺; 10); 223 ([M-2H]⁺; 69); 222 ([M-3H]⁺; 100); 146 (22); 105 (28); 77 (28); 63 (8); 51 (8).

HR-MS (C₁₅H₁₅NO): calculated: 245.1416 found: 245.1417.

Synthesis of 3-allyl-4-hydroxy-5-iodo-benzoic acid ethyl ester (32m)

According to TP02, the Grignard reagent of type 31 was prepared from 4-hydroxy-3,5-diiodo-benzoic acid ethyl ester (30b; 627 mg, 1.50 mmol). Then, CuCN·2LiCl (1.00 M in THF; 0.08 mL, 0.08 mmol, 5.00 mol%) and allyl bromide (218 mg, 1.80 mmol, 1.20 equiv) were added at -30 °C. After standard workup, flash column chromatography (silica; CH₂Cl₂) afforded 32m as colorless, crystalline solid (351 mg, 1.23 mmol, 74 %).

mp.: 68.5-70.0 °C
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ [ppm] = 8.23 (d, $^4J$ = 2.0 Hz, 1 H); 7.78 (d, $^4J$ = 2.0 Hz, 1 H); 6.02-5.92 (m, 1 H); 5.79 (s, 1 H); 5.14-5.09 (m, 2 H); 4.33 (q, $^3J$ = 7.1 Hz, 2 H); 3.45 (d, $^3J$ = 6.6 Hz, 2 H); 1.41 (t, $^3J$ = 7.1, 3 H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ [ppm] = 165.0; 156.4; 138.1; 135.3; 132.3; 126.4; 124.7; 116.8; 85.7; 61.0; 35.4; 14.3.

IR (KBr): $\nu$ [cm$^{-1}$] = 3294 (s); 3078 (w); 3002 (w); 3977 (w); 3938 (w); 2908 (w); 1848 (w); 1796 (w); 1681 (vs); 1635 (w); 1602 (m); 1557 (m); 1474 (m); 1446 (m); 1418 (w); 1370 (m); 124 (m); 1203 (vs); 1248 (s); 1336 (s); 1293 (w); 1028 (m); 995 (w); 960 (w); 939 (w); 926 (w); 912 (m); 873 (w); 812 (w); 768 (m); 752 (w); 685 (w); 648 (w); 623 (w); 551 (w).

MS (EI): m/z (%) = 332 (M$^+$; 83); 304 (22); 288 (14); 287 (100); 259 (14); 132 (22); 131 (19); 103 (11); 79 (9); 71 (7).

HR-MS (C$_{16}$H$_{13}$O$_3$): calculated: 331.9881 found: 331.9909.

**Synthesis of 4-hydroxy-3-(hydroxy-phenyl-methyl)-benzoic acid ethyl ester (32n)**

According to TP02, the Grignard reagent of type 31 was prepared from 4-hydroxy-3-iodo-benzoic acid ethyl ester (438 mg, 1.50 mmol) and reacted at -30 °C with benzaldehyde (191 mg, 1.80 mmol, 1.20 equiv). Flash column chromatography (silica; CH$_2$Cl$_2$) afforded 32n as a colorless solid (253 mg, 0.93 mmol, 62 %).

mp.: 112.5-114.0 °C

$^1$H-NMR (CDCl$_3$, 600 MHz): $\delta$ [ppm] = 8.76 (brs, 1 H); 7.83 (dd, $^3J$ = 8.5 Hz, $^4J$ = 2.1 Hz, 1 H); 7.60 (d, $^4J$ = 2.1 Hz, 1 H); 7.36-7.28 (m, 5 H); 6.87 (d, $^3J$ = 8.5 Hz, 1 H); 5.98 (s, 1 H); 4.25 (dq, $^3J$ = 7.1 Hz, $^4J$ = 2.8 Hz, 2 H); 3.66 (brs, 1 H); 1.31 (t, $^3J$ = 7.1 Hz, 3 H).

$^{13}$C-NMR (CDCl$_3$, 150 MHz): $\delta$ [ppm] = 166.7; 159.9; 141.4; 131.0; 130.2; 128.8; 128.4; 126.6; 126.4; 121.9; 117.2; 77.1; 60.8; 14.3.

IR (KBr): $\nu$ [cm$^{-1}$] = 3342 (s); 3223 (s); 3057 (m); 3032 (w); 2990 (m); 2942 (w); 2907 (w); 1953 (w); 1902 (w); 1675 (vs); 1614 (m); 1594 (s); 1583 (s); 1499 (s); 1475 (m); 1453 (w); 1395 (s); 1366 (s); 1275 (s); 1250 (s); 121 (s); 1164 (m); 1126 (s); 1108 (m); 1078 (w); 1012 (s); 950 (w); 919 (m); 868 (w); 848 (w); 839 (w); 815 (w); 769 (s); 750 (m); 700 (w); 661 (w); 644 (w); 633 (w); 626 (m); 552 (w); 479 (w).

MS (EI): m/z (%) = 272 (M$^+$; 2); 270 (100); 241 (26); 225 (41); 197 (10); 193 (23); 165 (26); 147 (46); 139 (10); 115 (10); 112 (9); 105 (65); 92 (9); 81 (6); 78 (6); 77 (68); 63 (11); 51 (15).

HR-MS (C$_{16}$H$_{16}$O$_4$): calculated: 272.1049 found: 272.1095.
Synthesis of 5-allyl-2-hydroxy-benzoic acid tert-butyl ester (32o)

According to TP02, the Grignard reagent of type 31 was prepared from 2-hydroxy-5-iodo-benzoic acid tert-butyl ester (30g; 480 mg, 1.50 mmol). Then, CuCN·2LiCl (1.00 M in THF; 0.02 mL, 0.02 mmol, 1.00 mol%) and allyl bromide (218 mg, 1.80 mmol, 1.20 equiv) were added at -30 °C. After standard workup, flash column chromatography (silica; pentane) afforded 32o as colorless oil (264 mg, 1.13 mmol, 75%).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ [ppm] = 10.89 (brs, 1 H); 7.55 (d, $^3$J = 2.1 Hz, 1 H); 7.24 (dd, $^4$J = 2.1 Hz, $^3$J = 8.5 Hz, 1 H); 6.88 (d, $^3$J = 8.5 Hz, 1 H); 6.00-5.87 (m, 1 H); 5.08-5.02 (m, 2 H); 3.31 (d, $^3$J = 6.6 Hz, 2 H); 1.61 (s, 9 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ [ppm] = 169.8; 160.2; 137.4; 135.6; 130.2; 129.5; 117.5; 115.8; 113.5; 82.7; 39.2; 28.2.

IR (KBr): $\nu$ [cm$^{-1}$] = 3155 (w); 3081 (w); 3006 (w); 2980 (m); 2932 (w); 1670 (vs); 1640 (w); 1614 (m); 1595 (m); 1489 (s); 1456 (w); 1394 (w); 1371 (s); 1347 (s); 1303 (m); 1250 (s); 1223 (s); 1157 (s); 1091 (m); 994 (w); 955 (w); 916 (m); 848 (m); 836 (m); 797 (m); 746 (w); 689 (w); 654 (w); 655 (w); 530 (w).

MS (EI): m/z (%) = 234 (M$^+$; 9); 179 (16); 178 (95); 162 (9); 161 (72); 160 (100); 131 (21); 104 (27); 77(23); 57 (20); 51 (6).

HR-MS (C$_{14}$H$_{18}$O$_3$): calculated: 234.1256 found: 234.1245.

Synthesis of 3-benzoyl-4-hydroxy-5-iodo-benzonitrile (32p) (and benzoic acid 4-cyano-2-iodo-phenyl ester (32q))

According to TP02, the Grignard reagent of type 31 was prepared from 4-hydroxy-3,5-diodo-benzonitrile (30d; 557 mg, 1.50 mmol). ZnCl$_2$ (1.00 M in THF; 1.50 mL, 1.00 equiv) is added and the resulting mixture stirred 30 min at –30 °C. Then, CuCN·2LiCl (1.00 M in THF; 0.54 mL, 0.54 mmol, 30 mol%) was added and the resulting mixture stirred 15 min at –30 °C. Afterwards, benzoylchloride (252 mg, 1.80 mmol, 1.20 equiv) was added at –30 °C. The standard workup was modified as follows: The reaction mixture was, after quenching with MeOH, poured on NaOH (1.0 M; 40 mL), and then carefully neutralized by addition of HCl (2.0 M). The aqueous layer was extracted with CH$_2$Cl$_2$, the collected organic layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. Flash column chromatography (silica; pentane/CH$_2$Cl$_2$, 4:1) afforded 3-benzoyl-4-hydroxy-5-iodo-benzonitrile (32p) as yellow needles (330 mg, 0.95 mmol; 63 %).
Omitting the transmetallation to Zn, and applying the standard workup, a mixture of mainly two compounds is obtained. Flash column chromatography (silica; pentane/CH₂Cl₂, 4:1) and recrystallization from heptane afforded 3-benzoyl-4-hydroxy-5-iodo-benzonitrile (32p) as yellow needles (141 mg, 0.40 mmol; 27 %) and benzoic acid 4-cyano-2-iodo-phenyl ester (32q) as a colorless, crystalline solid (132 mg, 25 %).

**Analytical data for 3-benzoyl-4-hydroxy-5-iodo-benzonitrile (32p):**

mp.: 121.5-123 °C

¹H-NMR (CDCl₃, 300 MHz): δ [ppm] = 8.27-8.24 (m, 2 H); 8.16 (d, 4J = 1.9 Hz, 1 H); 7.73-7.66 (m, 2 H); 7.58-7.53 (m, 2 H); 7.39 (d, 3J = 8.5 Hz, 1 H).

¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] = 163.5; 155.0; 143.0; 134.4; 133.2; 130.6; 128.8; 128.3; 123.8; 116.6; 111.6; 90.9.

IR (KBr): ν [cm⁻¹] = 3430 (w); 3054 (w); 2227 (m); 1625 (vs); 1598 (m); 1575 (w); 1435 (s); 1411 (w); 1331 (vs); 1255 (s); 1204 (w); 1175 (M); 1080 (w); 982 (w); 903 (w); 807 (w); 792 (w); 776 (w); 752 (w); 734 (w); 708 (w); 695 (m); 668 (m); 607 (w); 544 (w); 491 (w).

MS (EI): m/z (%) = 349 (M⁺; 2); 245 (2); 221 (1); 193 (1); 170 (1); 105 (100); 77 (25); 51 (6).

HR-MS (C₁₂H₁₄INO₂): calculated: 348.9600  found: 348.9576.

**Analytical data for benzoic acid 4-cyano-2-iodo-phenyl ester (32q):**

mp.: 124.5-125.5 °C

¹H-NMR (CDCl₃, 300 MHz): δ [ppm] = 13.39 (s, 1 H); 8.22 (d, 4J = 2.0 Hz, 1 H); 7.94 (d, 4J = 2.0 Hz, 1 H); 7.71-7.64 (m, 3 H); 7.60-7.53 (m, 2 H).

¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] = 200.0; 165.2; 147.4; 137.9; 135.9; 133.3; 129.3; 128.9; 118.8; 116.8; 104.3; 87.3.

IR (KBr): ν [cm⁻¹] = 3460 (w); 3108 (w); 3086 (w); 2232 (m); 1932 (w); 1742 (vs); 1600 (w); 1586 (w); 1564 (w); 1480 (m); 1450 (m); 1379 (w); 1315 (w); 1257 (s); 1216 (vs); 1175 (m); 1143 (w); 1074 (w); 1052 (vs); 1022 (s); 1002 (w); 938 (w); 888 (w); 882 (w); 820 (w); 797 (w); 752 (w); 707 (m); 699 (m); 674 (w); 658 (w); 586 (w); 562 (w); 457 (w).

MS (EI): m/z (%) = 349 (M⁺; 100); 348 (68); 272 (17); 221 (4); 193 (7); 164 (5); 144 (4); 117 (9); 105 (38); 88/4; 77 (27); 51 (8).

HR-MS (C₁₂H₁₄INO₂): calculated: 348.9600  found: 348.9588.

**Synthesis of 2-(hydroxy-phenyl-methyl)-pyridin-3-ol (35a)**

According to TP03, the Grignard reagent 34a was prepared from 2-iodo-pyridin-3-ol (33a; 332 mg, 1.50 mmol) and reacted with benzaldehyde (191 mg, 1.80 mmol, 1.20 equiv). Flash column chromatography (CH₂Cl₂:MeOH; 19:1) afforded 35a as a colorless, crystalline solid (211 mg, 1.05 mmol, 70 %).

mp.: 130.5-132.0 °C
$^1$H-NMR (CDCl$_3$/dmso-d$_6$, 300 MHz): $\delta$ [ppm] = 7.97 (dd, $^4$J = 1.4 Hz, $^3$J = 4.5 Hz, 1 H); 7.41-7.37 (m, 2 H); 7.14-7.28 (m, 3 H); 7.09 (dd, $^4$J = 1.4 Hz, $^3$J = 8.2 Hz, 1 H); 7.01 (dd, $^3$J = 4.6 Hz, $^4$J = 8.2 Hz, 1 H); 5.96 (s, 1 H).

$^{13}$C-NMR (CDCl$_3$/dmso-d$_6$, 75 MHz): $\delta$ [ppm] = 151.1; 147.7; 142.8; 138.8; 128.0; 127.2; 123.6; 123.2; 73.8.

IR (KBr): $\nu$ [cm$^{-1}$] = 3531 (m); 3463 (m); 3063 (m); 3032 (m); 2916 (m); 2787 (m); 2632 (m); 1953 (w); 1890 (w); 1813 (w); 1601 (w); 1580 (s); 1495 (w); 1458 (vs); 1401 (m); 1364 (m); 1331 (m); 1293 (s); 1219 (s); 1194 (m); 1160 (w); 1116 (w); 1081 (w); 1048 (m); 1021 (m); 973 (w); 920 (w); 881 (w); 828 (w); 805 (m); 753 (w); 744 (m); 700 (s); 656 (m); 613 (m); 577 (w); 558 (w); 537 (w); 506 (w).

MS (EI): m/z (%) = 201 (M$^+$; 20); 184 (100); 168 (12); 154 (31); 95 (7); 91 (14); 77 (13); 58 (6); 51 (6); 43 (15).

HR-MS (C$_{12}$H$_{11}$NO$_2$): calculated: 201.0790 found: 201.0807.

Synthesis of 2-(1-Hydroxy-butyl)-pyridin-3-ol (35b)

According to TP03, the Grignard reagent 34a was prepared from 2-iodo-pyridin-3-ol (33a; 332 mg, 1.50 mmol) and reacted with butyraldehyde (86.0 mg, 1.20 mmol, 0.80 equiv). Flash column chromatography (CH$_2$Cl$_2$:MeOH; 19:1) afforded 35b as a colorless oil (140 mg, 0.84 mmol, 70%).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ [ppm] = 7.87 (dd, $^4$J = 1.4 Hz, $^3$J = 4.6 Hz, 1 H) ; 7.18 (dd, $^4$J = 1.4 Hz, $^3$J = 8.2 Hz, 1 H); 7.06 (dd, $^3$J = 4.6 Hz, $^4$J = 8.2 Hz, 1 H); 6.37 (brs, 2 H); 4.92 (dd, $^3$J = 5.2 Hz, $^4$J = 7.8 Hz, 1 H); 1.67-1.51 (m, 4 H); 0.86 (t, $^3$J = 7.3 Hz, 3 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ [ppm] = 152.6; 148.0; 138.6; 125.0; 123.5; 75.3 (m); 744 (m); 700 (s); 656 (m); 613 (m); 577 (w); 558 (w); 537 (w); 506 (w).

IR (KBr): $\nu$ [cm$^{-1}$] = 3157 (m), 2960 (s); 2933 (s); 2873 (m); 2620 (w); 1580 (m); 1511 (w); 1455 (vs); 1331 (m); 1291 (s); 1271 (m); 1215 (m); 1165 (m); 1100 (m); 1068 (m); 1028 (m); 964 (w); 874 (w); 852 (w); 802 (m); 649 (w); 576 (w).

MS (EI): m/z (%) = 201 (M$^+$; 20); 184 (100); 168 (12); 154 (31); 95 (7); 91 (14); 77 (13); 58 (6); 51 (6); 43 (15).

HR-MS (C$_{12}$H$_{11}$NO$_2$): calculated: 201.0790 found: 201.0790.

Synthesis of 2-allyl-pyridin-3-ol (35c)

According to TP03, the Grignard reagent 34a was prepared from 2-iodo-pyridin-3-ol (33a; 332 mg, 1.50 mmol). Then, CuCN·2LiCl (1.00 M in THF; 15.0 $\mu$L, 15.0 $\mu$mol, 1.00 mol%) and allyl bromide (218 mg, 1.80 mmol, 1.20 equiv) were added at -20 °C. After standard
workup, flash column chromatography (CH₂Cl₂:MeOH; 19:1) afforded 35c as a pale yellow, crystalline solid (150 mg, 1.11 mmol, 74%).

**mp.:** 85.0-87.0 °C

**¹H-NMR (CDCl₃, 300 MHz):**  δ [ppm]= 10.90 (brs, 1 H); 7.97 (dd, 4J = 1.3 Hz, 3J = 4.8 Hz, 1 H); 7.25 (dd, 4J = 1.2 Hz, 3J = 8.2 Hz, 1 H); 7.07 (dd, 3J = 4.8 Hz, 3J = 8.2 Hz, 1 H); 6.13-6.03 (m, 1 H); 5.15-5.06 (m, 2 H); 3.70 (d, 3J = 6.5 Hz, 2 H).

**¹³C-NMR (CDCl₃, 75 MHz):** δ [ppm] = 152.9; 148.1; 138.1; 124.0; 123.8; 123.1; 116.3; 36.6.

**IR (KBr):** ν [cm⁻¹]= 3432 (w); 3075 (w); 3002 (w); 2976 (w); 2925 (m); 2787 (m); 2597 (m); 2509 (m); 1820 (m); 1638 (s); 1601 (w); 1577 (vs); 1459 (s); 1426 (w); 1412 (w); 1359 (s); 1295 (vs); 1282 (vs); 1228 (s); 1207 (m); 1170 (s); 1126 (m); 1082 (w); 1061 (w); 998 (m); 964 (w); 931 (m); 918 (s); 882 (w); 804 (m); 796 (s); 744 (m); 664 (m); 583 (w); 567 (w); 538 (w); 492 (w) 475 (w).

**MS (EI):** m/z (%) = 134 ([M-H]⁺; 100); 120 (10); 109 (10); 92 (3); 80 (9); 67 (4); 53 (4).

**HR-MS (C₈H₉NO, [M-H]⁺):** calculated: 134.0606  found: 134.0596.

Synthesis of 2-(methylthio)pyridin-3-ol (35d)

According to TP03, the Grignard reagent 34a was prepared from 2-iodo-pyridin-3-ol (332 mg, 1.50 mmol). Then, MeSSO₂Me (227 mg, 1.80 mmol, 1.20 equiv) was added at -20 °C. After standard workup, flash column chromatography (CH₂Cl₂:MeOH; 19:1) afforded 35d as a colorless, crystalline solid (87 mg, 0.62 mmol, 41%).

**mp.:** 150.4-152.6 °C

**¹H-NMR (CDCl₃, 300 MHz):**  δ [ppm] = 8.13 (dd, 3J = 4.6 Hz, 4J = 1.2 Hz, 1 H); 7.13 (dd, 3J = 8.0 Hz, 4J = 1.2 Hz, 1 H); 7.02 (dd, 3J = 8.0 Hz, 4J = 4.6 Hz, 1 H); 6.30 (brs, 1 H); 2.57 (s, 3 H).

**¹³C-NMR (CDCl₃, 75 MHz):** δ [ppm] = 14.7; 121.1; 121.8; 141.9; 145.4; 150.7.

**IR (neat):** ν [cm⁻¹]= 2920 (m); 2852 (w); 2710 (w); 2570 (w); 2542 (w); 2470 (w); 1812 (w); 1586 (m); 1564 (m); 1448 (m); 1432 (s); 1360 (s); 1294 (s); 1274 (s); 1194 (s); 1178 (vs); 1132 (s); 1092 (s); 1058 (s); 1016 (m); 974 (m); 956 (m); 910 (m); 890 (m); 788 (vs); 732 (s); 688 (s); 560 (m).

**MS (EI):** m/z (%) = 141 (M⁺; 100); 108 (33); 98 (3); 96 (3); 80 (6); 67 (8); 57 (3); 45 (4).

**HR-MS (C₆H₇NOS):** calculated: 141.0248  found: 141.0229.

Synthesis of 5-allyl-7-iodo-quinolin-8-ol (38a)

According to TP03, the Grignard reagent 34a was prepared from 2-iodo-pyridin-3-ol (332 mg, 1.50 mmol). Then, MeSSO₂Me (227 mg, 1.80 mmol, 1.20 equiv) was added at -20 °C. After standard workup, flash column chromatography (CH₂Cl₂:MeOH; 19:1) afforded 35d as a colorless, crystalline solid (87 mg, 0.62 mmol, 41%).
According to TP04, the Grignard reagent 37 was prepared from 5,7-diiodo-quinolin-8-ol (36; 596 mg, 1.50 mmol). Then, CuCN·2LiCl (1.00 M in THF; 15.0 μL, 15.0 μmol, 1.00 mol%) and allyl bromide (218 mg, 1.80 mmol, 1.20 equiv) were added at –30 °C. After standard workup and recrystallization, 38a was obtained as a pale yellow, crystalline solid (351 mg, 1.13 mmol, 75%).

mp.: 140.0-144.0 °C

$^1$H-NMR (CDCl$_3$, 300 MHz): δ [ppm] = 8.74 (dd, $^4$J = 1.5 Hz, $^3$J = 4.2 Hz, 1 H); 8.27 (dd, $^4$J = 1.5 Hz, $^3$J = 8.6 Hz, 1 H); 7.61 (s, 1 H); 7.47 (dd, $^3$J = 4.2 Hz, $^3$J = 8.6 Hz, 1 H); 6.05-5.95 (m, 1 H); 5.11 (dq, $^4$J = 1.6 Hz, $^3$J = 10.1 Hz, 1 H); 5.03 (dq, $^4$J = 1.6 Hz, $^3$J = 17.1 Hz, 1 H); 3.66 (d, $^3$J = 6.2 Hz, 2 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): δ [ppm] = 151.8; 148.0; 137.7; 136.3; 135.8; 133.3; 128.0; 126.9; 121.8; 116.8; 76.3; 35.6.

IR (KBr): ν [cm$^{-1}$] = 3322 (s); 3084 (w); 3014 (w); 2922 (w); 2892 (w); 2853 (w); 1958 (w); 1928 (w); 2922 (w); 2892 (w); 2853 (w); 1958 (w); 1928 (w); 1863 (w); 1645 (w); 1605 (w); 1574 (w); 1497 (s); 1460 (s); 1429 (w); 1396 (vs); 1372 (s); 1328 (m); 1307 (w); 1293 (w); 1257 (s); 1213 (w); 1198 (m); 1183 (s); 1149 (w); 1178 (w); 1056 (m); 1917 (w); 1000 (w); 928 (m); 868 (w); 851 (w); 808 (w); 785 (m); 720 (m); 684 (w); 667 (w); 646 (m); 608 (w); 566 (w); 507 (w).

MS (EI): m/z (%) = 310 (M$^+$; 100); 284 (30); 184 (15); 154 (14); 129 (12); 102 (4); 77 (4); 51 (2).

HR-MS (C$_{12}$H$_{10}$INO): calculated: 310.9807 found: 310.9787.

Synthesis of 7-iodo-5-methylsulfanyl-quinolin-8-ol (38b)

According to TP04, the Grignard reagent 37 was prepared from 5,7-diiodo-quinolin-8-ol (36; 596 mg, 1.50 mmol) and reacted with MeSSO$_2$Me (227 mg, 1.80 mmol, 1.20 equiv) at –30 °C. After standard workup and recrystallization, 38b was obtained as a pale yellow, crystalline solid (361 mg, 1.14 mmol, 76%).

mp.: 148.5-149.0 °C (decomposition)

$^1$H-NMR (CDCl$_3$, 300 MHz): δ [ppm] = 8.77 (d, $^3$J = 4.3 Hz, 1 H); 8.63 (d, $^3$J = 8.6 Hz, 1 H); 7.85 (s, 1 H); 7.53 (dd, $^3$J = 4.3 Hz, $^3$J = 8.6 Hz, 1 H); 2.46 (s, 1 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): δ [ppm] = 152.5; 148.6; 137.8; 134.4; 128.0; 126.9; 77.0; 18.8.

IR (KBr): ν [cm$^{-1}$] = 3414 (m); 3084 (w); 2913 (m); 1951 (w); 1602 (w); 1565 (w); 1490 (s); 1394 (vs); 1375 (s); 1337 (s); 1271 (m); 1246 (w); 1207 (s); 1140 (w); 1046 (w); 970 (w); 956 (m); 846 (w); 806 (w); 782 (m); 731 (w); 717 (w); 690 (w); 646 (m); 597 (w).

MS (EI): m/z (%) = 310 (M$^+$; 100); 284 (30); 184 (15); 154 (14); 129 (12); 102 (4); 77 (4); 51 (2).

HR-MS (C$_{12}$H$_{10}$INO): calculated: 316.9371 found: 316.9363.
Synthesis of 7-iodo-5-(4-nitrophenyl)quinolin-8-ol (38c)

According to TP04, the Grignard reagent 37 was prepared from 5,7-diiodo-quinolin-8-ol (36; 794 mg, 2.00 mmol). Then, ZnCl2 (1.00 M in THF; 2.40 mL, 1.20 equiv) was added at -30 °C and the resulting solution was stirred for 30 min at -30 °C. To this mixture then was slowly added a preprepared solution of Pd(dba)2 (57.4 mg, 0.10 mmol, 5.00 mol%), trifuryl phosphine (46.4 mg, 0.20 mmol, 10.0 mol%) and 1-iodo-4-nitrobenzene (498 mg, 2.00 mmol, 1.00 equiv) in THF (4.0 mL) (exothermic!) and the resulting mixture was stirred for 3 h at rt. After standard workup and recrystallization from CH2Cl2, 38c was obtained as bright yellow, crystalline solid (548 mg, 1.40 mmol, 70%).

mp.: 194.8-196.7 °C

1H-NMR (CDCl3, 300 MHz): δ [ppm] = 8.82 (dd, 3J = 4.2 Hz, 4J = 1.2 Hz 1 H); 8.36 (d, 3J = 8.6 Hz, 2 H); 8.14 (dd, 3J = 8.6 Hz, 4J = 1.2 Hz, 1 H); 7.81 (s, 1 H); 7.61 (d, 3J = 8.6 Hz, 2 H); 7.50 (dd, 3J = 4.2 Hz, 4J = 8.6 Hz, 1 H).

13C-NMR (CDCl3, 75 MHz): δ [ppm] = 153.6; 152.8; 148.8; 147.4; 144.6; 137.3; 136.9; 134.1; 130.8; 129.8; 126.0; 123.9; 122.8.

IR (KBr): ν [cm⁻¹] = 1592 (m); 1572 (m); 1502 (vs); 1486 (s); 1458 (s); 1404 (s); 1372 (vs); 1310 (m); 1290 (s); 1278 (s); 1264 (s); 1198 (s); 1164 (m); 1124 (m); 1104 (m); 984 (w); 948 (w); 896 (w); 850 (vs); 812 (m); 788 (s); 746 (s); 718 (s); 700 (s); 652 (s); 620 (m); 586 (m).

MS (EI): m/z (%) = 392 (M⁺; 100); 362 (5); 346 (12); 219 (13); 191 (18); 163 (8); 95 (4).

HR-MS (C15H9IN2O3): calculated: 391.9658; found: 391.9649.

Synthesis of 5-(4-bromophenyl)-7-iodoquinolin-8-ol (38d)

According to TP04, the Grignard reagent 37 was prepared from 5,7-diiodo-quinolin-8-ol (36; 794 mg, 2.00 mmol). Then, ZnCl2 (1.00 M in THF; 2.40 mL, 1.20 equiv.) was added at -30 °C and the resulting solution was stirred for 30 min at -30 °C. To this mixture then was slowly added a preprepared solution of Pd(dba)2 (57.4 mg, 0.10 mmol, 5.00 mol%), trifuryl phosphine (46.4 mg, 0.20 mmol, 10.0 mol%) and 1-bromo-4-iodobenzene (566 mg, 2.00 mmol, 1.00 equiv) in THF (4.0 mL) and the resulting mixture was stirred for 3 h at rt. After standard workup (plus additional extraction with 3 × 40 mL EtOAc) and recrystallization from CH2Cl2, 38d was obtained as pale yellow, crystalline solid (508 mg, 1.19 mmol, 60%).
mp.: 186.2-187.2 °C

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ [ppm] = 8.78 (d, $^3J = 3.8$ Hz, 1 H); 8.16 (d, $^3J = 8.5$ Hz, 1 H); 7.75 (s, 1 H); 7.61 (d, $^3J = 8.0$ Hz, 2 H); 7.50 (dd, $^3J = 3.82$ Hz, $^3J = 8.5$ Hz, 1 H); 7.29 (d, $^3J = 8.0$ Hz, 2 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ [ppm] = 152.7; 148.4; 137.3; 136.8; 134.7; 131.8; 131.6; 131.0; 126.3; 122.3; 122.0; 76.2.

IR (KBr): $\nu$ [cm$^{-1}$] = 3360 (w); 1058 (w); 2222 (m); 1602 (w); 1572 (w); 1504 (w); 1486 (m); 1458 (s); 1402 (s); 1368 (m); 1340 (m); 1284 (s); 1266 (m); 1254 (s); 1234 (m); 1188 (s); 1134 (m); 1110 (m); 1014 (w); 940 (w); 924 (m); 896 (m); 870 (w); 846 (m); 832 (s); 814 (s); 788 (s); 718 (s); 682 (w); 650 (vs); 628 (m); 616 (m); 586 (s).

MS (EI): m/z (%) = 427 (M$^+$, $^{81}$Br; 100); 425 (M$^+$, $^{79}$Br; 100); 300 (5); 298 (5); 272 (21); 270 (22); 219 (6); 190 (52); 163 (34); 95 (22); 87 (7); 63 (7).

HR-MS (C$_{15}$H$_9$BrINO): calculated: 424.8912 found: 424.8912.
4. Halogen/Magnesium Exchange Reactions on Unprotected Aromatic and Heteroaromatic Carboxylic Acids

4.1. Starting Material Synthesis

Synthesis of ethyl 3,5-diiodobenzoate (41)

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

\[ \text{I} \quad \text{I} \]

3,5-Diiodobenzoic acid (40a; 1.87 g, 5.00 mmol) was placed under N\(_2\) in a 50 mL Schlenk-flask equipped with a magnetic stirring bar and a reflux condenser. SOCl\(_2\) (5.00 mL, 67.0 mmol, 13.8 equiv) was carefully added and the resulting mixture was heated at reflux for one hour. Then, toluene (30 mL) was added and the excess thionyl chloride was removed by azeotropic distillation. The residue was cooled in an ice bath and dry ethanol (20 mL; excess) was added. Afterwards, the mixture was refluxed for another 15 min. Chilling (ice bath) of the resulting solution resulted in the crystallization of the product. Filtration afforded the product 41 as pale orange, crystalline solid (1.43 g, 3.56 mmol, 71%).

mp.: 90.2-91.6 °C

\[ ^1\text{H-NMR (CDCl}_3, 400 \text{ MHz)}: \delta [\text{ppm}] = 8.31 (s, 2 H); 8.21 (s, 1 H); 4.37 (q, ^3J = 7.2 \text{ Hz, 2 H}); 1.38 (t, ^3J = 7.2 \text{ Hz, 3 H}). \]

\[ ^{13}\text{C-NMR (CDCl}_3, 100 \text{ MHz)}: \delta [\text{ppm}] = 163.7; 149.1; 137.7; 133.7; 94.3; 61.8; 14.3. \]

\[ \text{IR (neat)}: \nu [\text{cm}^{-1}] = 3050 (\text{w}); 2978 (\text{w}); 2935 (\text{w}); 2110 (\text{w}); 1720 (\text{s}); 1674 (\text{w}); 1543 (\text{m}); 1466 (\text{w}); 1448 (\text{w}); 1414 (\text{m}); 1391 (\text{m}); 1364 (\text{m}); 1257 (\text{vs}); 1130 (\text{m}); 1112 (\text{m}); 1104 (\text{m}); 1020 (\text{s}); 911 (\text{w}); 885 (\text{m}); 872 (\text{m}); 862 (\text{m}); 761 (\text{s}); 705 (\text{s}); 659 (\text{m}). \]

\[ \text{MS (EI)}: (m/z) [%] = 401 (M^+; 100); 374 (37); 357 (62); 329 (18); 247 (7); 201 (9); 191 (4); 75 (9). \]

\[ \text{HR-MS (C}_{9}\text{H}_{8}\text{I}_{2}\text{O}_{2}): \text{calculated: 401.8614 \ found: 401.8601.} \]

Synthesis of 3-(ethoxycarbonyl)-5-iodobenzoic acid (40b)

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

\[ \text{I} \quad \text{CO}_2\text{H} \]

Ethyl 3,5-diiodobenzoate (41; 1.21 g, 3.00 mmol) was placed in a dry and argon flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. THF (6.0 mL) was added and the resulting solution was cooled to –50 °C. i-PrMgCl (1.00 M in THF; 3.06 mL, 1.03 equiv) was added dropwise and after 15 min at –50 °C, the GC analysis of reaction aliquots indicated complete conversion to the desired Grignard reagent. Then, predried (CaCl\(_2\)) CO\(_2\) was bubbled through the solution and the reaction mixture was at the same time slowly warmed up to room temperature. The conversion was checked by TLC (silica; CH\(_2\)Cl\(_2\):MeOH, 19:1). When the reaction was complete, the mixture was poured on water.
(50 mL) and the pH of the aqueous layer was adjusted to 3-4 (indicator paper) by addition of
2.0 M HCl. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL), the completeness of
the reaction was checked by TLC of the fractions. The combined organic layers were dried
(Na₂SO₄) and evaporated in vacuo. The resulting solid was covered with heptane and subjected to sonication. After filtration the desired product 40b was obtained as pale orange
solid (604 mg, 1.89 mmol, 63 %).

mp.: 167.5-169.5 °C

¹H-NMR (dmső-d₆, 400 MHz): δ [ppm] = 13.56 (brs, 1 H); 8.43-8.38 (m, 3 H); 4.33 (q,
³J = 7.0 Hz, 2 H); 1.33 (t, ³J = 7.0 Hz, 3 H).

¹³C-NMR (dmső-d₆, 100 MHz): δ [ppm] = 165.1; 163.7; 141.7; 141.1; 133.2; 132.1; 128.8;
94.9; 61.5; 14.0.

IR (neat): v [cm⁻¹] = 3072 (w); 2982 (w); 2872 (w); 2636 (w); 2524 (w); 1724 (s); 1686 (vs);
1598 (w); 1566 (m); 1468 (w); 1446 (m); 1434 (w); 1404 (m); 1394 (m); 1366 (m); 1304 (m);
1246 (vs); 1150 (m); 1116 (m); 1102 (m); 1024 (s); 998 (w); 932 (m); 922 (m); 898 (m); 864
(m); 824 (w); 750 (vs); 730 (w); 718 (m); 696 (s); 658 (m).

MS (EI): (m/z) (%) = 320 (M⁺; 89); 292 (58); 275 (100); 247 (16); 191 (8); 165 (6); 149 (7);
120 (10); 92 (11); 75 (21); 64 (6); 50 (6).

HR-MS (C₁₀H₈IO₄): calculated: 319.9546  found: 319.9549.

Synthesis of 2-[(2,2-dimethylpropanoyl)oxy]-5-iodobenzoic acid (40c)

In a round bottom flask, equipped with a reflux condenser and a magnetic stirring bar, 5-
iodosalicylic acid (42; 3.96 g, 15.0 mmol) was dissolved in pivalic anhydride (6.10 mL,
30.1 mmol, 2.01 equiv). Concentrated sulfuric acid (5 drops) was added as a catalyst and the
resulting mixture was refluxed (110 °C) for 2 h. After cooling to rt, upon careful treatment
with water (5.0 mL), the product precipitated as white solid, which was filtered. After drying
in high vacuum, 2-[(2,2-dimethylpropanoyl)oxy]-5-iodobenzoic acid (40c) was obtained as
colorless, crystalline solid (3.96 g, 11.4 mmol, 76 %).

mp.: 174.3-176.2 °C

¹H-NMR (dmső-d₆, 400 MHz): δ [ppm] = 13.37 (s, 1 H); 8.14 (d, ³J = 2.3 Hz, 1 H); 7.95 (dd,
³J = 8.5 Hz, ³J = 2.3 Hz, 1 H); 6.99 (d, ³J = 8.5 Hz, 1 H); 1.27 (s, 9 H).

¹³C-NMR (dmső-d₆, 100 MHz): δ [ppm] = 175.8; 164.4; 150.0; 142.1; 139.3; 126.7; 126.1;
90.5; 38.4; 26.8.

IR (neat): v [cm⁻¹] = 2972 (m); 2930 (w); 2904 (w); 2868 (w); 2822 (w); 2704 (w); 2656 (w);
2592 (w); 2554 (w); 2518 (w); 1748 (s); 1696 (vs); 1592 (m); 1562 (m); 1472 (m); 1458 (m);
1422 (m); 1394 (w); 1382 (w); 1366 (w); 1300 (s); 1264 (s); 1234 (m); 1202 (s); 1102 (vs);
1090 (vs); 1076 (s); 1028 (m); 968 (m); 932 (m); 892 (s); 864 (m); 838 (m); 808 (m); 776
(m); 748 (m); 682 (s); 640 (m).

MS (EI): (m/z) (%) = 348 (M⁺; 16); 265 (98); 246 (>99); 218 (10); 85 (15); 63 (20); 57 (100);
41 (26).

HR-MS (C₁₂H₁₃IO₄): calculated: 347.9859  found: 347.9840.
Synthesis of 5-cyano-2-hydroxy-3-iodobenzoic acid (43)

\[
\begin{array}{c}
\text{CN} \\
\text{I} \\
\text{OH} \\
\text{CO}_2\text{H}
\end{array}
\]

In a dry and argon-flushed Schlenk-tube equipped with a septum and a magnetic stirring bar, 4-hydroxy-3,5-diiodobenzonitrile (30d; 1.86 g, 5.00 mmol) was dissolved in a solution of LiCl in THF (0.50 M; 10.0 mL, 5.00 mmol, 1.00 equiv) and cooled to -30 °C. Then, MeMgCl (3.00 M in THF; 1.67 mL, 5.00 mmol, 1.00 equiv) was added dropwise. The reaction mixture was kept stirring at -30 °C for 40 min, then i-PrMgCl (1.00 M in THF; 5.50 mL, 5.50 mmol, 1.10 equiv) was slowly added and the mixture was stirred for 30 min at -30 °C. After the exchange reaction was complete (TLC), predried (CaCl₂) CO₂ was bubbled through the solution and the reaction mixture was at the same time slowly warmed up to room temperature. The conversion was checked by TLC (silica; CHCl₃:MeOH, 19:1). When the reaction was complete, the mixture was poured on water (50 mL) and the pH of the aqueous layer was adjusted to 3-4 (indicator paper) by addition of 2.0 M HCl. The aqueous layer was extracted with EtOAc (3 × 50 mL), the completeness of the extraction was checked by TLC of the fractions. The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. The resulting solid was suspended in little CHCl₃ and the slurry was subjected to sonication (30 min). After filtration and washing with small amounts of CHCl₃ and pentane, the desired product (43) was obtained as off-white solid (1.14 g, 3.94 mmol, 79%).

**mp.**: 174.3-176.2 °C

\(^1\text{H}-\text{NMR (dmsod}_6, 400 \text{ MHz}): \delta \text{ [ppm]} = 8.12 (d, J = 2.0 \text{ Hz}, 2 \text{ H}); 7.99 (d, J = 2.0 \text{ Hz}, 2 \text{ H}). \text{ The acidic protons were not detected.}

\(^{13}\text{C}-\text{NMR (dmsod}_6, 100 \text{ MHz)}: \delta \text{ [ppm]} = 168.9; 168.6; 144.3; 134.7; 118.4; 116.4; 98.1; 89.8.

\text{IR (neat): } v \text{ [cm}^{-1} ] = 3057 \text{ (w); 2868 (w); 2233 (m); 1811 (w); 1675 (s); 1579 (m); 1554 (m); 1437 (vs); 1391 (m), 1328 (m); 1300 (w); 1269 (w); 1243 (vs); 1202 (m); 1155 (vs); 1097 (w); 930 (w); 917 (w); 898 (m); 868 (s); 818 (m); 795 (m); 756 (m); 727 (m); 703 (vs); 622 (w).

\text{MS (EI): } (m/z) (%) = 289 (M^+; 62); 271 (100); 245 (94); 144 (24); 128 (50); 127 (43); 117 (9); 90 (15); 88 (21); 63 (13); 44 (42).

\text{HR-MS (C₈H₆INO₃): calculated: } 288.9236 \text{ found: 288.9220.}

4.2. Halogen/Magnesium Exchange and Reactions with Electrophiles

Synthesis of 4-[hydroxy(phenyl)methyl]benzoic acid (45a)

\[
\begin{array}{c}
\text{OH} \\
\text{CO}_2\text{H}
\end{array}
\]
The double magnesiated reagent of type 44 was prepared according to **TP05** from 4-iodobenzoic acid (40d; 496 mg, 2.00 mmol) and reacted with benzaldehyde (254 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo, to give pure 4-[hydroxy(phenyl)methyl]benzoic acid (45a) as a colorless solid (433 mg, 1.90 mmol, 95 %).

**mp.:** 166.8-168.1 °C

**¹H-NMR (dmso-d₆, 300 MHz):** δ [ppm] = 12.25 (brs, 1 H); 7.89 (d, 3J = 8.2 Hz, 2 H); 7.50 (d, 3J = 8.2 Hz, 2 H); 7.39-7.17 (m, 5 H); 6.03 (brs, 1 H); 5.77 (s, 1 H).

**¹³C-NMR (dmso-d₆, 75 MHz):** δ [ppm] = 167.2; 150.6; 145.1; 129.2; 129.2; 126.9; 126.3; 126.2; 73.9.

**IR (KBr):** ν [cm⁻¹] = 3285 (m); 3032 (w); 2898 (m); 2643 (m); 1702 (vs); 1611 (m); 1578 (w); 1509 (w); 1496 (w); 1554 (m); 1416 (m); 1316 (m); 1276 (vs); 1193 (m); 1178 (m); 1172 (w); 1110 (w); 1080 (w); 1034 (s); 1024 (m); 1014 (s); 923 (w); 876 (m); 826 (w); 790 (m); 779 (w); 758 (s); 742 (s); 700 (s); 634 (w); 620 (w); 556 (w); 530 (w); 490 (w).

**MS (EI):** (m/z) (%) = 228 (M⁺; 24); 183 (16); 165 (20); 149 (42); 123 (100); 105 (55); 79 (46); 77 (48); 65 (10); 51 (14).

**HR-MS (C₁₄H₁₂O₃):** calculated: 228.0786 found: 228.0790.

---

**Synthesis of 4-benzoylbenzoic acid (45b)**

![Chemical structure of 4-benzoylbenzoic acid](attachment:image.png)

The double magnesiated reagent of type 44 was prepared according to **TP05** from 4-iodobenzoic acid (40d; 496 mg, 2.00 mmol) and reacted with benzoyl chloride (366 mg, 2.40 mmol 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M; 0.40 mL, 0.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. After recrystallization from MeOH, 4-benzoylbenzoic acid (45b) was obtained as a colorless solid (375 mg, 1.42 mmol, 71 %).

**mp.:** 197.0-198.0 °C

**¹H-NMR (dmso-d₆, 300 MHz):** δ [ppm] = 13.31 (s, 1 H); 8.11-7.55 (m, 9 H).

**¹³C-NMR (dmso-d₆, 75 MHz):** δ [ppm] = 195.7; 167.0; 140.9; 136.8; 134.3; 133.4; 130.1; 130.0; 129.7; 129.0.

**IR (KBr):** ν [cm⁻¹] = 3423 (br); 3058 (br); 2678 (w); 2553 (w); 1962 (w); 1704 (s); 1682 (m); 1681 (vs); 1599 (m); 1579 (w); 1501 (m); 1446 (w); 1430 (m); 1407 (m); 1385 (w); 1320 (m); 1279 (vs); 1226 (m); 1180 (w); 1150 (w); 1110 (m); 1077 (w); 1016 (w); 1000 (w); 978 (w); 942 (m); 928 (m); 872 (m); 809 (w); 792 (w); 766 (m); 710 (s); 692 (m); 656 (w); 578 (w); 524 (w).
MS (EI): (m/z) (%) = 226 (M⁺; 52); 181 (11); 149 (40); 121 (10); 105 (100); 77 (33); 65 (11); 51 (9).

HR-MS (C₁₄H₁₀O₃): calculated: 226.0630 found: 226.0621.

**Synthesis of 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoic acid (45c)**

![Diagram of 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoic acid (45c)]

The double magnesiated reagent of type 44 was prepared according to TP05 from 4-iodobenzoic acid (40d; 496 mg, 2.00 mmol) and reacted with B(Oi-Pr)₃ (451 mg, 2.40 mmol 1.20 equiv) at –20 °C, then the reaction mixture was warmed up to rt and stirred for 1 h. Then, 2,2-dimethyl-1,3-propanediol (270 mg, 2.60 mmol, 1.30 equiv) was added neat at rt, the mixture was stirred for another 2 h. The reaction mixture was poured on water, the aqueous layer carefully acidified by addition of sat. aq. citric acid to reach a pH of 5-6 (indicator paper). The resulting mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. After recrystallization from MeOH, 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoic acid (45c) was obtained as a highly crystalline, colorless solid (234 mg, 1.00 mmol, 50%).

**mp.**: 236.9-238.1 °C

¹H-NMR (dmsö-d₆, 300 MHz): δ [ppm] = 7.92-7.77 (m, 4 H); 3.76 (s, 4 H); 0.94 (s, 6 H).

¹³C-NMR (dmsö-d₆, 75 MHz): δ [ppm] = 167.3; 133.6; 132.6; 128.3; 112.1; 71.4; 39.5; 31.4; 21.2.

IR (KBr): ν [cm⁻¹] = 3434 (w); 2963 (m); 2874 (m); 2674 (w); 2551 (w); 1693 (vs); 1561 (w); 1508 (m); 1479 (m); 1427 (s); 1377 (m); 1342 (m); 1307 (s); 1180 (w); 1135 (s); 1121 (m); 1020 (w); 932 (w); 860 (w); 813 (w); 719 (m); 707 (m); 657 (w); 641 (m); 545 (w); 500 (w).

MS (EI): (m/z) (%) = 234 (M⁺; 74); 191 (23); 163 (6); 149 (11); 135 (5); 103 (5); 56 (100); 41 (15).

HR-MS (C₁₂H₁₃BO₄): calculated: 234.1063 found: 234.1040.

**Synthesis of 3-(1-hydroxy-2,2-dimethylpropyl)benzoic acid (45d)**

![Diagram of 3-(1-hydroxy-2,2-dimethylpropyl)benzoic acid (45d)]

The double magnesiated reagent of type 44 was prepared according to TP05 from 3-iodobenzoic acid (40e; 496 mg, 2.00 mmol) and reacted with pivaldehyde (206 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in...
After recrystallization from MeOH, 3-((1-hydroxy-2,2-dimethylpropyl)benzoic acid (45d) was obtained as colorless solid (300 mg, 1.44 mmol, 72%).

**mp.:** 142.8-144.6 °C (decomposition)

**1H-NMR (dms-o-d6, 300 MHz):** \( \delta \ [ppm] = 12.89 \text{ (brs, 1 H)}; \ 7.79 \text{ (d, } J = 7.5 \text{ Hz, 1 H}); \ 7.88 \text{ (s, 1 H)}; \ 7.49 \text{ (d, } J = 7.5 \text{ Hz, 1 H}); \ 7.39 \text{ (t, } J = 7.5 \text{ Hz, 1 H}); \ 5.25 \text{ (brs, 1 H)}; \ 4.29 \text{ (s, 1 H)}; \ 0.81 \text{ (s, 9 H)}; \)

**13C-NMR (dms-o-d6, 75 MHz):** \( \delta \ [ppm] = 167.6; \ 144.0; \ 132.1; \ 129.7; \ 128.4; \ 127.6; \ 127.2; \ 79.5; \ 35.2; \ 25.9. \)

**IR (KBr):** \( \nu \ [cm^{-1}] = 3393 \text{ (br)}; \ 2958 \text{ (s)}; \ 2908 \text{ (w)}; \ 2872 \text{ (w)}; \ 2668 \text{ (w)}; \ 1693 \text{ (vs)}; \ 1607 \text{ (s)}; \ 1589 \text{ (m)}; \ 1589 \text{ (m)}; \ 1480 \text{ (m)}; \ 1458 \text{ (m)}; \ 1400 \text{ (m)}; \ 1384 \text{ (w)}; \ 1365 \text{ (w)}; \ 1365 \text{ (m)}; \ 1341 \text{ (w)}; \ 1306 \text{ (m)}; \ 1261 \text{ (m)}; \ 1194 \text{ (s)}; \ 1114 \text{ (m)}; \ 1088 \text{ (s)}; \ 1056 \text{ (s)}; \ 1011 \text{ (s)}; \ 881 \text{ (vw)}; \ 822 \text{ (m)}; \ 775 \text{ (m)}; \ 743 \text{ (s)}; \ 696 \text{ (m)}; \ 670 \text{ (s)}; \ 644 \text{ (s)}; \ 575 \text{ (w)}; \ 548 \text{ (w)}.

**MS (EI):** \( (m/z) \ (%) = 208 \text{ (M}^+; \ < 1); \ 175 \text{ (15); } 152 \text{ (100); } 151 \text{ (84); } 123 \text{ (4); } 107 \text{ (32); } 105 \text{ (10); } 79 \text{ (22); } 77 \text{ (15); } 65 \text{ (3); } 57 \text{ (33); } 41 \text{ (11).}

**HR-MS (C12H16O):** calculated: 208.0999 found: 208.1093.

### Synthesis of 3-[2-(ethoxycarbonyl)-2-propenyl]benzoic acid (45e)

![Chemical structure of 3-[2-(ethoxycarbonyl)-2-propenyl]benzoic acid](image)

The double magnesiated reagent of type 44 was prepared according to TP05 from 3-iodobenzoic acid (40e; 496 mg, 2.00 mmol) and treated at -20 °C with CuCN·2LiCl in THF (1.00 M; 2.30 mL, 1.15 equiv) and stirred for 40 min at the same temperature. Afterwards, ethyl 2-(bromomethyl)-acrylate (461 mg, 2.40 mmol, 1.20 equiv) is added and the mixture is allowed to warm up to room temperature. After TLC indicated completion of the reaction, MeOH (2.0 mL) was added and the mixture was transferred to a separation funnel containing sat. aq. NH₄Cl (10 mL). By careful addition of 2.0 M HCl, the pH was adjusted to 5-6. The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL) and EtOAc (3 × 20 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. After flash column chromatography (silica; CH₂Cl₂:MeOH; 19:1), 3-[2-(ethoxycarbonyl)-2-propenyl]benzoic acid (45e) was obtained as a colorless solid (366 mg, 1.56 mmol, 78%).

**mp.:** 93.3-95.8 °C (decomposition)

**1H-NMR (dms-o-d6, 300 MHz):** \( \delta \ [ppm] = 12.91 \text{ (brs, 1 H)}; \ 7.80-7.41 \text{ (m, 4 H)}; \ 6.16 \text{ (d, } J = 1.5 \text{ Hz, 1 H}); \ 5.71 \text{ (d, } J = 1.5 \text{ Hz, 1 H}); \ 4.10 \text{ (q, } J = 6.9 \text{ Hz, 2 H}); \ 3.66 \text{ (s, 2 H)}; \ 1.16 \text{ (t, } J = 6.9 \text{ Hz, 3 H).}

**13C-NMR (dms-o-d6, 75 MHz):** \( \delta \ [ppm] = 167.2; \ 166.2; \ 139.6; \ 133.6; \ 133.2; \ 131.1; \ 129.6; \ 128.9; \ 127.6; \ 127.1; \ 60.8; \ 37.5; \ 14.3. \)

**IR (KBr):** \( \nu \ [cm^{-1}] = 3427 \text{ (w)}; \ 3060 \text{ (w)}; \ 2995 \text{ (m)}; \ 2677 \text{ (w)}; \ 2564 \text{ (w)}; \ 1709 \text{ (vs)}; \ 1695 \text{ (vs)}; \ 1634 \text{ (m)}; \ 1607 \text{ (m)}; \ 1591 \text{ (m)}; \ 1490 \text{ (w)}; \ 1476 \text{ (m)}; \ 1450 \text{ (m)}; \ 1425 \text{ (m)}; \ 1392 \text{ (w)}; \ 1372 \text{ (w)}; \ 1350 \text{ (w)}; \ 1318 \text{ (m)}; \ 1294 \text{ (s)}; \ 1239 \text{ (w)}; \ 1214 \text{ (m)}; \ 1194 \text{ (m)}; \ 1140 \text{ (s)}; \ 1083 \text{ (w)}; \ 1029 \text{ (s)}; \ 948 \text{ (br)}; \ 932 \text{ (m)}; \ 870 \text{ (w)}; \ 820 \text{ (w)}; \ 785 \text{ (m)}; \ 748 \text{ (s)}; \ 708 \text{ (s)}; \ 674 \text{ (w)}; \ 662 \text{ (m)}; \ 650 \text{ (m)}; \ 537 \text{ (w)}; \ 482 \text{ (w).}

**MS (EI):** \( (m/z) \ (%) = 234 \text{ (M}^+; \ 8); \ 216 \text{ (100); } 188 \text{ (51); } 187 \text{ (11); } 171 \text{ (14); } 170 \text{ (10); } 161 \text{ (18); } 160 \text{ (91); } 117 \text{ (32); } 116 \text{ (34); } 115 \text{ (81); } 91 \text{ (13); } 89 \text{ (7); } 77 \text{ (8).}

**HR-MS (C13H10O3):** calculated: 234.0892 found: 234.0892.
Synthesis of 3-cyclohexyl-2-benzofuran-1(3H)-one (45f)

[Diagram]

The double magnesiated reagent of type 44 was prepared according to TP05 from 2-iodobenzoic acid (40f; 496 mg, 2.00 mmol) and reacted with cyclohexane carboxaldehyde (269 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. After recrystallization from MeOH, 3-cyclohexyl-2-benzofuran-1(3H)-one (45f) was obtained as a colorless solid (375 mg, 1.74 mmol, 87%).

mp.: 95.0-97.0 °C

¹H-NMR (dmsod₆, 300 MHz): δ [ppm] = 7.89-7.80 (m, 2 H); 7.72-7.62 (m, 2 H); 5.57 (d, J = 3.3 Hz, 1 H); 2.14-0.98 (m, 11 H).

¹³C-NMR (dmsod₆, 75 MHz): δ [ppm] = 169.9; 148.7; 134.2; 129.1; 125.7; 124.8; 122.8; 84.6; 40.9; 30.6; 28.9; 25.7; 25.6; 25.2.

IR (KBr): ν [cm⁻¹] = 3483 (w); 2932 (s); 2850 (m); 1750 (vs); 1614 (w); 1594 (w); 1466 (w); 1455 (m); 1380 (w); 1350 (m); 1314 (w); 1291 (m); 1272 (w); 1214 (m); 1198 (w); 1098 (m); 1076 (m); 1058 (s); 956 (w); 986 (s); 896 (w); 848 (w); 784 (w); 750 (s); 712 (w); 697 (s); 654 (m); 608 (w); 562 (w); 526 (w); 496 (w).

MS (EI): (m/z) (%) = 216 (M⁺; 5); 135 (74); 134 (90); 133 (100); 105 (78); 83 (25); 77 (41); 55 (56); 51 (11); 41 (29).

HR-MS (C₁₄H₁₆O₂): calculated: 216.1150 found: 216.1157.

Synthesis of 3-bromo-5-[cyclohexyl(hydroxy)methyl]benzoic acid (45f)

[Diagram]

The double magnesiated reagent of type 44 was prepared according to TP06 from 3-bromo-5-iodobenzoic acid (40g; 654 mg, 2.00 mmol) and reacted with cyclohexane carboxaldehyde (269 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. After recrystallization from MeOH, 3-bromo-5-[cyclohexyl(hydroxy)methyl]benzoic acid (45f) was obtained as a colorless solid (570 mg, 1.82 mmol, 91%).

mp.: 179.2-180.3 °C
$^1$H-NMR (dmso-$d_6$, 300 MHz): δ [ppm] = 7.88 (s, 1 H); 7.83 (s, 1 H); 7.67 (s, 1 H); 5.31 (brs, 1 H); 4.34 (d, $^3J = 5.6$ Hz, 1 H); 1.72-0.83 (m, 11 H).

$^{13}$C-NMR (dmso-$d_6$, 75 MHz): δ [ppm] = 166.1; 148.4; 133.4; 132.5; 129.9; 126.4; 121.1; 75.7; 44.6; 28.9; 27.6; 25.6; 25.5; 25.0.

IR (KBr): ν [cm$^{-1}$] = 3386 (s); 3057 (m); 2922 (vs); 2852 (s); 2646 (w); 1685 (vs); 1601 (w); 1575 (m); 1451 (m); 1386 (m); 1365 (w); 1314 (m); 1278 (s); 1265 (s); 1199 (m); 1083 (w); 1028 (m); 972 (w); 909 (w); 893 (m); 843 (w); 772 (m); 686 (m); 658 (w); 572 (w).

MS (EI): (m/z) (%) = 314 (M$^+$; 81Br; 3); 312 (M$^+$; 79Br; 3); 232 (10); 230 (11); 185 (12); 151 (41); 105 (18); 83 (40); 77 (35); 55 (56); 41 (24).

HR-MS (C$_{14}$H$_{17}$BrO$_3$): calculated: 312.0361 found: 312.0367.

**Synthesis of 3-bromo-5-[(4-bromophenyl)(hydroxy)methyl]benzoic acid (45g)**

![Chemical structure](image)

The double magnesiated reagent of type 44 was prepared according to TP06 from 3-bromo-5-iodobenzoic acid (40g; 654 mg, 2.00 mmol) and reacted with 4-bromo-benzaldehyde (444 mg, 2.40 mmol 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca. 1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined CH$_2$Cl$_2$-layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. After recrystallization from MeOH, 3-bromo-5-[(4-bromophenyl)-(hydroxy)methyl]benzoic acid (45g) was obtained as a colorless solid (533 mg, 1.38 mmol, 69%).

mp.: 226.9-228.0 °C (decomposition)

$^1$H-NMR (dmso-$d_6$, 300 MHz): δ [ppm] = 12.72 (brs, 1 H); 7.90 (s, 1 H); 7.88 (s, 1 H); 7.81 (s, 1 H); 7.51 (d, $^3J = 8.0$; 7.35 (d, $^3J = 8.0$; 6.24 (brs, 1 H); 5.80 (s, 1 H).

$^{13}$C-NMR (dmso-$d_6$, 75 MHz): δ [ppm] = 165.8; 148.4; 144.0; 133.0; 133.0; 131.2; 130.2; 128.5; 126.0; 121.5; 120.2; 72.3.

IR (KBr): ν [cm$^{-1}$] = 3436 (br); 3028 (w); 2956 (m); 2835 (m); 2169 (m); 1603 (w); 1495 (s); 1454 (s); 1373 (m); 1361 (m); 1300 (w); 1248 (vs); 1230 (s); 11048 (s); 1077 (m); 1029 (m); 987 (s); 956 (m); 853 (vs); 794 (m); 752 (vs); 699 (vs); 644 (m); 610 (m); 532 (w); 503 (w); 486 (w).

MS (EI): (m/z) (%) = 388 (M$^+$; 2 × 81Br; 18); 386 (M$^+$; 79Br + 81Br; 37); 384 (M$^+$; 2 × 79Br; 23); 307 (30); 305 (30); 247 (20); 229 (100); 227 (95); 203 (37); 201 (42); 199 (19); 187 (26); 185 (61); 183 (38); 157 (35); 105 (16); 77 (64).

HR-MS (C$_{14}$H$_{10}$Br$_2$O$_3$): calculated: 383.8997 found: 383.8974.
Synthesis of 3-bromo-5-cyanobenzoic acid (45h)

The double magnesiated reagent of type 44 was prepared according to TP06 from 3-bromo-5-iodobenzoic acid (40g; 654 mg, 2.00 mmol) and tosyl cyanide (95 %, technical quality; 434 mg, 2.40 mmol, 1.20 equiv) in THF (3.0 mL) was added at -50 °C. The mixture was slowly warmed up to room temperature. The reaction mixture was quenched with MeOH (4.0 mL) and poured on water (20 mL). The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. After gel filtration (silica; CH₂Cl₂:MeOH; 19:1) and subsequent recrystallization from MeOH, 3-bromo-5-cyanobenzoic acid (45h) was obtained as pale rosé solid (181 mg, 0.80 mmol, 40 %).

mp.: 185.5-186.5 °C

¹H-NMR (dmso-d₆, 300 MHz): δ [ppm] = 13.83 (brs, 1 H); 8.40 (s, 1 H); 8.28 (s, 1 H); 8.26 (s, 1 H).

¹³C-NMR (dmso-d₆, 75 MHz): δ [ppm] = 164.5; 138.4; 136.3; 134.0; 131.8; 122.4; 116.7; 113.9.

IR (KBr): ν [cm⁻¹] = 3076 (m); 2812 (w); 2668 (w); 2558 (w); 2240 (w); 1686 (vs); 1598 (w); 1568 (m); 1444 (s); 1428 (w); 1406 (m); 1292 (vs); 1256 (m); 1210 (m); 1124 (w); 944 (m); 932 (m); 914 (m); 890 (s); 816 (m); 772 (s); 754 (w); 704 (s); 668 (vs); 602 (m); 582 (w).

MS (EI): (m/z) (%) = 227 (M⁺, 81Br; 100); 225 (M⁺, 79Br; 100); 210 (74); 208 (77); 182 (24); 180 (24); 100 (25); 75 (22); 50 (23).

HR-MS (C₈H₄BrNO₂): calculated: 224.9425 found: 224.0407.

Synthesis of 3-allyl-5-iodobenzoic acid (45i)

The double magnesiated reagent of type 44 was prepared according to TP07 from 3,5-diodobenzoic acid (40a; 748 mg, 2.00 mmol) and reacted with allyl bromide (290 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%). The reaction mixture was poured on water (40 mL). The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. After gel filtration chromatography (silica; CH₂Cl₂:MeOH; 19:1), 45i was obtained as an off white solid (403 mg, 1.40 mmol, 70 %).

mp.: 115.4-117.8 °C

¹H-NMR (dmso-d₆, 300 MHz): δ [ppm] = 13.22 (s, 1 H); 8.05 (s, 1 H); 7.81 (s, 1 H); 7.75 (s, 1 H); 5.98-5.88 (m, 1 H); 5.05-5.15 (m, 2 H); 3.40 (d, ³J = 6.7 Hz, 2 H).
$^{13}$C-NMR (dmsod$_6$, 75 MHz): $\delta$ [ppm] = 165; 142.9; 141.2; 136.7; 135.4; 132.8; 128.7; 116.8; 94.8; 38.5.

**IR (neat):** $\nu$ [cm$^{-1}$] = 2980 (w); 2808 (w); 2662 (w); 2538 (w); 1692 (vs); 1642 (m); 1594 (m); 1560 (s); 1452 (s); 1412 (s); 1310 (m); 1292 (s); 1276 (vs); 1248 (m); 1196 (m); 1122 (m); 1102 (w); 994 (m); 928 (vs); 890 (s); 862 (s); 798 (m); 766 (vs); 746 (m); 694 (vs); 662 (s).

**MS (EI):** (m/z) (%) = 288 (M$^+$; 100); 242(10); 161(8), 117 (56); 115 (82); 105 (5); 91 (15); 89 (12); 77 (10); 63 (14); 51 (7).

**HR-MS (C$_8$H$_9$O$_2$I):** calculated: 287.9647 found: 287.9665.

**Synthesis of 3-cyano-5-iodobenzoic acid (45j)**

$$\text{CO}_2\text{H}$$

$$\text{ICN}$$

The double magnesiated reagent of type 44 was prepared according to TP07 from 3,5-diiodobenzoic acid (40a; 748 mg, 2.00 mmol) and tosyl cyanide (95 %, technical quality; 434 mg, 2.40 mmol, 1.20 equiv) in THF (3.0 mL) was added at -50 °C. The mixture was slowly warmed up to room temperature. The reaction mixture was quenched with MeOH (4.0 mL) and poured on water. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined CH$_2$Cl$_2$-layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. After gel filtration (silica; CH$_2$Cl$_2$:MeOH; 19:1), 3-cyano-5-iodobenzoic acid (45j) was obtained as pale yellow solid (300 mg, 1.10 mmol, 55 %).

mp.: 169.3-171.2 °C

$^1$H-NMR (dmsod$_6$, 300 MHz): $\delta$ [ppm] = 13.75 (brs, 1 H); 8.49 (s, 1 H); 8.45 (s, 1 H); 8.26 (s, 1 H).

$^{13}$C-NMR (dmsod$_6$, 75 MHz): $\delta$ [ppm] = 164.5; 143.8; 142.0; 133.5; 132.0; 116.6; 113.6; 95.3.

**IR (neat):** $\nu$ [cm$^{-1}$] = 3065 (w); 2956 (w); 2926 (w); 2855 (w); 2667 (w); 2550 (w); 2236 (m); 1831 (w); 1691 (vs); 1593 (w); 1560 (m); 1444 (m); 1427 (m); 1400 (m); 1284 (vs); 1256 (m); 1202 (m); 1122 (w); 997 (w); 930 (m); 900 (s); 823 (w); 796 (m); 768 (s); 756 (m); 700 (s); 668 (vs).

**MS (EI):** (m/z) (%) = 273 (100); 256 (23); 228 (9); 146 (11); 130 (7); 127 (8); 101 (16); 90 (16); 75 (14); 63 (8); 50 (15).

**HR-MS (C$_8$H$_9$O$_2$I):** calculated: 272.9287 found: 272.9293.

**Synthesis of 3-(ethoxycarbonyl)-5-(1-hydroxy-2,2-dimethylpropyl)benzoic acid (45k)**

$$\text{CO}_2\text{H}$$

$$\text{t-Bu}$$

$$\text{OH}$$

$$\text{O}$$

$$\text{O}$$

$$\text{O}$$

125
The double magnesiated reagent of type 44 was prepared according to TP06 from 3-(ethoxycarbonyl)-5-iodobenzoic acid (40h; 654 mg, 2.00 mmol) and reacted with pivaldehyde (206 mg, 2.40 mmol 1.20 equiv). The reaction mixture was poured on water (40 mL), the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined CH$_2$Cl$_2$-layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. After gel filtration (silica; CH$_2$Cl$_2$:MeOH; 19:1) 3-(ethoxycarbonyl)-5-(1-hydroxy-2,2-dimethylpropyl)benzoic acid (45k) was obtained as colorless, crystalline solid (389 mg, 1.39 mmol, 70 %).

\[ \text{mp.: } 167.4-168.7 ^\circ C \]

$^1$H-NMR (dmsso-d$_6$, 300 MHz): $\delta$ [ppm] = 13.25 (s, 1 H); 8.35 (s, 1 H); 8.08 (m, 2 H); 5.43 (s, 1 H); 4.39 (s, 1 H); 4.34 (q, $^3$J = 7.1 Hz, 2 H); 1.33 (t, $^3$J = 7.1 Hz, 3 H); 0.82 (s, 9 H).

$^{13}$C-NMR (dmsso-d$_6$, 75 MHz): $\delta$ [ppm] = 166.7; 165.2; 145.0; 132.8; 132.2; 130.3; 129.3; 128.1; 79.0; 61.0; 35.2; 25.7; 14.1.

IR (neat): $\nu$ [cm$^{-1}$] = 3394 (w); 2966 (m); 2938 (m); 2904 (m); 2874 (m); 1720 (s); 1688 (vs); 1650 (w); 1642 (w); 1602 (m); 1480 (w); 1462 (w); 1446 (w); 1398 (m); 1390 (m); 1366 (m); 1342 (w); 1318 (m); 1262 (s); 1234 (vs); 1200 (s); 1182 (m); 1124 (m); 1106 (m); 1070 (w); 1052 (m); 1012 (s); 976 (w); 954 (w); 946 (w); 934 (m); 916 (m); 876 (w); 862 (w); 772 (m); 748 (s); 692 (m); 684 (m); 670 (s).

MS (EI): (m/z) (%) = 281 ([M+H]$^+$; 3); 273 (8); 265 (13); 235 (9); 224 (100); 195 (57); 150 (15); 121 (4); 105 (6); 79 (11); 57 (23); 41 (11).

HR-MS (C$_{15}$H$_{21}$O$_5$; [M+H]$^+$): calculated: 281.1389 found: 281.1391.

Attempted synthesis of 5-[(4-bromophenyl)thio]-2-[(2,2-dimethylpropanoyl)oxy]benzoic acid; Synthesis of 5-[(4-bromophenyl)thio]-2-hydroxybenzoic acid (45l)

The double magnesiated reagent of type 44 was prepared according to TP06 from 2-[(2,2-dimethylpropanoyl)oxy]-5-iodobenzoic acid (40i; 522 mg, 1.50 mmol) and $i$-PrMgCl·LiCl (1.30 M in THF; 1.21 mL, 1.58 mmol 1.05 equiv) and reacted with S-(4-bromophenyl)benzenesulfonothioate (494 mg, 1.50 mmol 1.00 equiv) in THF (3.0 mL). The reaction mixture was poured on water (20 mL) and sat. aq. NH$_4$Cl (20 mL), the aqueous layer was carefully adjusted to pH 5-6 (indicator paper) by dropwise addition of HCl (2.0 M) accompanied by vigorous shaking and extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined CH$_2$Cl$_2$-layers were dried (Na$_2$SO$_4$) and reduced in vacuo. After flash column chromatography (silica, CH$_2$Cl$_2$:MeOH; 19:1), 5-[(4-bromophenyl)thio]-2-hydroxybenzoic acid (45l) was obtained as wine red solid (263 mg, 0.81 mmol, 54 %).

\[ \text{mp.: } 112.1-114.0 ^\circ C \]

$^1$H-NMR (dmsso-d$_6$, 300 MHz): $\delta$ [ppm] = 7.86 (d, $^4$J = 2.1 Hz, 1 H); 7.44 (d, $^3$J = 8.3 Hz, 1 H); 7.36 (dd, $^3$J = 8.7 Hz, $^4$J = 2.1 Hz, 1 H); 6.98 (d, $^3$J = 8.3 Hz, 2 H); 6.79 (d, $^3$J = 8.7 Hz, 1 H). Both acidic protons were not detected.

$^{13}$C-NMR (dmsso-d$_6$, 75 MHz): $\delta$ [ppm] = 170.5; 164.0; 139.0; 138.9; 137.0; 131.9; 128.4; 120.2; 118.3; 118.2; 116.6.
IR (neat): ν [cm⁻¹] = 3062 (w); 1621 (w), 1579 (m); 1469 (s); 1429 (s); 1369 (m); 1342 (m); 1285 (m); 1242 (m); 1202 (m); 1152 (m); 1109 (w); 1085 (m); 1968 (m); 1006 (s); 955 (w); 884 (w); 806 (vs); 707 (s); 651 (s).

HR-MS (ESI; C₁₃H₉BrO₅S, [M-H]): calculated: 322.9378 found: 322.9396.

**Synthesis of 5-[9-anthryl(hydroxy)methyl]-2-[(2,2-dimethylpropanoyl)oxy]benzoic acid (45m):**

![Chemical structure](image)

The double magnesiated reagent of type 44 was prepared according to TP06 from 2-[(2,2-dimethylpropanoyl)oxy]-5-iodobenzoic acid (40i; 696 mg, 2.00 mmol) and a slight excess of i-PrMgCl·LiCl (1.30 M; 1.60 mL; 1.05 equiv) and reacted with anthraldehyde (453 mg, 2.20 mmol 1.10 equiv) in THF (4.0 mL). The reaction mixture was poured on water (20 mL) and sat. aq. NH₄Cl (20 mL), the aqueous layer was carefully adjusted to pH 5-6 (indicator paper) by dropwise addition of HCl (2.0 M) accompanied by vigorous shaking and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and reduced in vacuo. Then, heptane was added, followed by some drops of diethyl ether. The resulting slurry was sonicated (30 min) and subsequently filtered. The residue was washed with heptane. After drying the crude product in high vacuum, 5-[9-anthryl(hydroxy)methyl]-2-[(2,2-dimethylpropanoyl)oxy]benzoic acid (45m) was obtained as a grey-yellow solid (574 mg, 1.34 mmol, 67 %).

**mp.:** 183.5-185.6 °C

¹H-NMR (dmsø-d₆, 300 MHz): δ [ppm] = 13.01 (brs, 1 H); 8.62 (s, 1 H); 8.51 (d, J= 8.4 Hz, 2 H); 8.10 (d, J= 8.4 Hz, 2 H); 7.83 (s, 1 H); 7.52-7.42 (m, 5 H); 7.31 (s, 1 H); 7.03 (d, J= 8.4 Hz, 1 H); 6.63 (brs, 1 H); 1.24 (s, 9 H).

¹³C-NMR (dmsø-d₆, 75 MHz): δ [ppm] = 176.0; 165.8; 148.5; 135.4; 131.3; 130.4; 129.3; 129.0; 128.1; 127.9; 125.6-125.7 (broad, 2 signals); 125.0; 123.8; 123.3; 67.5; 38.3; 26.8.

IR (neat): ν [cm⁻¹] = 3054 (w); 2976 (w); 2872 (w); 1748 (m); 1684 (s); 1610 (w); 1586 (w); 1492 (w); 1482 (m); 1446 (m); 1426 (w); 1398 (w); 1366 (m); 1280 (w); 1232 (w); 1210 (s); 1124 (vs); 1062 (m); 1022 (m); 1000 (m); 958 (w); 942 (m); 922 (w); 896 (m); 870 (w); 854 (w); 842 (m); 788 (w); 734 (s); 692 (w); 674 (w); 654 (w); 636 (w); 610 (w).

MS (ESI): (m/z) (%) = 428 (M⁺; 44); 344 (10); 324 (13); 252 (11); 207 (18); 205 (24); 194 (9); 179 (74); 165 (17); 152 (18); 147 (11); 120 (16); 85 (10); 57 (100); 41 (30).

HR-MS (C₂₇H₂₄O₈): calculated: 428.1624 found: 428.1646.
The double magnesiated reagent of type 44 was prepared according to TP06 from 3-iodo-4-methylbenzoic acid (40j; 524 mg, 2.00 mmol) and reacted with 4-bromobenzoyl chloride (526 mg, 2.40 mmol 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M; 0.40 mL, 0.20 equiv). The reaction mixture was poured on water (40 mL), the aqueous layer was adjusted to pH 5-6 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The collected organic layers were washed with a saturated aqueous solution of sodium-potassium-tartrate to remove remaining copper. The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. After column chromatography (silica; CH₂Cl₂:MeOH, 19:1), the resulting white solid was subjected to sonication (30 min) in little heptane. After filtration and drying, 3-(4-bromobenzoyl)-4-methylbenzoic acid (45n) was obtained as a white solid (517 mg, 1.62 mmol, 81 %).

mp.: 189.5-190.8 °C

¹H-NMR (dmsö-d₆, 300 MHz): δ [ppm] = 12.99 (brs, 1 H); 8.00 (d, ³J = 7.9 Hz, 1 H); 7.82 (s, 1 H); 7.77 (d, ³J = 8.1 Hz, 2 H); 7.62 (d, ³J = 8.1 Hz, 2 H); 7.50 (d, ³J = 7.9 Hz, 1 H); 2.30 (s, 3 H);

¹³C-NMR (dmsö-d₆, 75 MHz): δ [ppm] = 196.4; 167.0; 141.6; 138.1; 136.2; 132.4; 132.0; 131.9; 131.6; 129.3; 129.0; 128.3; 20.0.

IR (neat): ν [cm⁻¹] = 2968 (w); 2840 (w); 2556 (w); 2546 (w); 1686 (s); 1662 (vs); 1606 (m); 1584 (s); 1566 (m); 1480 (w); 1430 (m); 1396 (m); 1378 (w); 1310 (s); 1294 (s); 1280 (s); 1254 (s); 1176 (m); 1162 (m); 1138 (m); 1110 (w); 1100 (m); 1068 (m); 1034 (w); 1010 (m); 952 (s); 936 (m); 926 (m); 850 (s); 840 (s); 772 (s); 754 (s); 740 (m); 712 (w); 696 (w); 658 (m); 632 (m); 624 (m).

MS (EI): (m/z) (%) = 319 ([M-H]⁺); ³¹Br; 9); 317 ([M-H]⁺; ³⁹Br; 8); 239 (100); 195 (24); 194 (24); 185 (15); 183 (15); 177 (11); 165 (11); 163 (16); 156 (11); 155 (12); 135 (8); 107 (4); 89 (5); 77 (6).


Synthesis of 5-cyano-2-hydroxy-3-(phenylthio)benzoic acid (47a)

5-cyano-2-hydroxy-3-iodobenzoic acid (43; 578 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 8.00 mL, 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. After completion of
the addition, the mixture was stirred at -20 °C for further 40 min. Afterwards, i-PrMgCl-LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added and the resulting mixture was stirred at the same temperature. After 120 min, TLC indicated complete conversion. Subsequently, PhSSO₂Ph (600 mg, 2.40 mmol, 1.20 equiv) in THF (4.0 mL) was added at this temperature, then the mixture was allowed to warm up to rt. After completion of the reaction (TLC), the reaction mixture was poured on water (40 mL) and the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined EtOAc-layers were dried (Na₂SO₄) and evaporated in vacuo. The crude product was purified by flash column chromatography (silica; CH₂Cl₂: MeOH, 19:1) and subsequent recrystallization from MeOH to yield 5-cyano-2-hydroxy-3-(phenylthio)benzoic acid (47a) as crystalline, beige solid (298 mg, 1.10 mmol, 55 %).

**mp.**: 227.4-229.2 °C (decomposition, starting at 200 °C)

**¹H-NMR (dmsö-d₆, 300 MHz)**: δ [ppm] = 7.95 (d, ⁴J = 1.9 Hz, 1 H); 7.43-7.31 (m, 5 H); 7.23 (d, ⁴J = 1.9 Hz, 1 H); the acidic protons were not detected.

**¹³C-NMR (dmsö-d₆, 75 MHz)**: δ [ppm] = 169.5; 167.2; 135.9; 133.4; 133.0; 131.4; 129.6; 127.7; 125.9; 119.1; 116.6; 97.1.

**IR (KBr)**: ν [cm⁻¹] = 3070 (m); 2230. (s); 1652 (m); 1626 (m); 1456 (s); 1440 (s); 1421 (s); 1382 (m); 1354 (m); 1292 (w); 1250 (m); 1183 (s); 1108 (w); 1082 (w); 1068 (w); 1024 (m); 926 (w); 910 (w); 888 (w); 870 (w); 808 (m); 776 (m); 744 (s); 706 (m); 688 (s).

**MS (EI)**: (m/z) (%) = 271 (M⁺; 52); 253 (100); 227 (55); 225 (13); 196 (31); 121 (13); 78 (17); 77 (14); 51 (15).

**HR-MS (C₁₄H₉NO₅S)**: calculated: 271.0303 found: 271.0304.

**Synthesis of 5-cyano-4′-(ethoxycarbonyl)-2-hydroxybiphenyl-3-carboxylic acid (47b)**

5-cyano-2-hydroxy-3-iodobenzoic acid (43; 578 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 8.00 mL, 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt., the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. After completion of the addition, the mixture was stirred at -20 °C for further 40 min. Afterwards, i-PrMgCl-LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added and the resulting mixture was stirred at the same temperature. After 120 min, TLC indicated complete conversion. Then, ZnCl₂ (1.00 M in THF; 2.20 mL, 2.20 mmol, 1.10 equiv) was added and the resulting mixture was stirred at the same temperature. After 30 min at that temperature. Concurrently, Pd(dba)₂ (57.5 mg, 5.00 mol%) and tri-2-furylphosphine (46.4 mg, 10.0 mol%) were placed in a second, dry and argon-flushed Schlenk-flask and dissolved in THF (4.0 mL). After stirring this mixture for 5 min at rt, the colour changed from orange to green. Subsequently, ethyl 4-iodobenzoate (552 mg, 2.00 mmol, 1.00 equiv) was added neat and the resulting solution was stirred for another 10 min at rt. Afterwards, it was cannulated to the zinc reagent prepared above, the mixture was heated at 50 °C for 3 h. Then, MeOH (2.0 mL)
was added and the reaction mixture was poured on water (40 mL). The aqueous layer was carefully adjusted to pH 5-6 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. The crude product was purified by flash column chromatography (silica; CH$_2$Cl$_2$: MeOH, 19:1) and subsequent recrystallization from MeOH to yield 5-cyano-4'- (ethoxycarbonyl)-2-hydroxybiphenyl-3-carboxylic acid (47b) as colorless solid (205 mg, 0.52 mmol, 26 %).

mp.: 254.3-255.9 °C
$^1$H-NMR (dmsO-d$_6$, 300 MHz): $\delta$ [ppm] = 12.74 (brs, 2 H); 8.21 (d, $^3$$J$ = 1.9 Hz, 1 H); 8.01 (d, $^3$$J$ = 1.9 Hz, 1 H); 7.99 (d, $^3$$J$ = 8.1 Hz, 2 H); 7.72 (d, $^3$$J$ = 8.1 Hz, 2 H); 4.32 (q, $^3$$J$ = 7.0 Hz, 3 H); 1.32 (t, $^3$$J$ = 7.0 Hz, 3 H).

$^{13}$C-NMR (dmsO-d$_6$, 75 MHz): $\delta$ [ppm] = 171.1; 165.4; 162.1; 139.6; 138.5; 134.8; 129.6; 129.4; 129.2; 128.9; 118.2; 114.6; 101.8; 60.8; 14.1.

IR (KBr): $\nu$ [cm$^{-1}$] = 3074 (w); 2980 (m); 2908 (w); 2234 (m); 1724 (m); 1680 (vs); 1610 (m); 1604 (m); 1586 (m); 1484 (w); 1460 (m); 1438 (s); 1400 (s); 1368 (m); 1334 (m); 1292 (m); 1270 (vs); 1242 (vs); 1200 (m); 1186 (s); 1148 (s); 1126 (s); 1104 (s); 1024 (m); 938 (m); 920 (m); 858 (m); 844 (w); 802 (s); 788 (m); 770 (m); 744 (s); 726 (s); 702 (vs); 678 (m); 652 (w); 606 (m).

MS (EI): (m/z) (%) = 311 (M$^+$; 64); 293 (100); 266 (16); 237 (6); 164 (29); 124 (6); 63 (1).

HR-MS (C$_{17}$H$_{13}$NO$_5$): calculated: 311.0794  found: 311.0807.

Synthesis of 5-allyl-2-furoic acid (49a)

The double magnesiated reagent was prepared according to TP08 from 5-bromo-2-furoic acid (48a; 382 mg, 2.00 mmol) and reacted with allyl bromide (290 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%). The reaction mixture was poured on water (40 mL). The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH$_2$Cl$_2$(3 × 40 mL). The combined CH$_2$Cl$_2$-layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. Pure 5-allyl-2-furoic acid (49a) was obtained as colorless solid (280 mg, 1.84 mmol, 92 %).

mp.: 195.0-196.0 °C
$^1$H-NMR (dmsO-d$_6$, 300 MHz): $\delta$ [ppm] = 12.86 (s, 1 H); 7.12 (d, $^3$$J$ = 3.2 Hz, 1 H); 6.30 (d, $^3$$J$ = 3.2 Hz, 1 H); 5.98-5.84 (m, 1 H); 5.19-5.10 (m, 2 H); 3.45 (d, $^3$$J$ = 6.5 Hz, 2 H).

$^{13}$C-NMR (dmsO-d$_6$, 75 MHz): $\delta$ [ppm] = 159.2; 158.0; 143.7; 133.2; 118.8; 117.7; 108.4; 32.0.

IR (KBr): $\nu$ [cm$^{-1}$] = 3424 (w); 3121 (m); 3014 (m); 2924 (m); 2681 (m); 2582 (m); 2058 (w); 1861 (w); 1690 (vs); 1645 (m); 1594 (m); 1522 (vs); 1428 (s); 1384 (w); 1292 (s); 1232 (m); 1212 (m); 1161 (s); 1022 (s); 1003 (m); 975 (w); 966 (w); 929 (s); 901 (w); 880 (w); 802 (m); 761 (m); 748 (w); 561 (m).

MS (EI): (m/z) (%) = 152 (M$^+$; 100); 125 (10); 107 (32); 79 (41); 77 (35); 53 (6); 51 (13).

HR-MS (C$_8$H$_8$O$_3$): calculated: 152.0456  found: 152.0445.
Synthesis of 5-{hydroxy[4-(trifluoromethyl)phenyl]methyl}-2-furoic acid (49b)

The double magnesiated reagent was prepared according to TP08 from 5-bromo-2-furoic acid (48a; 382 mg, 2.00 mmol) and reacted with 4-(trifluoromethyl)benzaldehyde (415 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. The crude product is suspended in little heptane and subjected to sonication (3 min). After filtration and washing with pentane, 5-{hydroxy[4-(trifluoromethyl)phenyl]methyl}-2-furoic acid (49b) was obtained as a colorless solid (501 mg, 1.75 mmol, 88%).

mp.: 137.5-139.0 °C

¹H-NMR (dmsö-d₆, 300 MHz): δ [ppm] = 7.73 (d, 3J = 8.1 Hz, 2 H); 7.62 (d, 3J = 8.1 Hz, 2 H); 7.12 (d, 3J = 3.4 Hz, 1 H); 6.40 (d, 3J = 3.4 Hz, 1 H); 5.87 (s, 1 H). Both acidic OH groups can not be detected.

¹³C-NMR (dmsö-d₆, 75 MHz): δ [ppm] = 160.4; 159.3; 146.4; 144.5; 129.6; 128.8; 128.3; 127.9; 127.5; 127.2; 126.0; 125.1-125.2 (q); 122.4; 118.8; 118.2; 108.9.

Thereby, the following assignments can be done:
A: 129.6; 126.0; 122.4; 118.8: q, 3J = 271 Hz;
B: 127.5; 127.9; 128.3; 128.8: q, 3J = 31 Hz;
C: 125.1-125.2; q, 3J = 4 Hz.

IR (KBr): ν [cm⁻¹] = 3402 (m); 2704 (w); 2579 (w); 1689 (vs); 1621 (m); 1594 (m); 1526 (s); 1415 (s); 1329 (vs); 1275 (w); 1211 (w); 1198 (m); 1164 (w); 1124 (m); 1113 (w); 1069 (vs); 1018 (vs); 970 (w); 959 (m); 930 (w); 858 (m); 813 (m); 785 (m); 767 (m); 601 (m); 551 (w); 425 (w).

MS (EI): (m/z) (%) = 286 (M⁺; 24); 284 (6); 269 (14); 267 (11); 242 (14); 241 (100); 225 (6); 223 (7); 217 (7); 213 (17); 195 (10); 173 (22); 165 (13); 146 (21); 141 (8); 139 (22); 128 (19); 123 (15); 113 (38); 95 (13).
HR-MS (C₁₃H₉F₃O₄): calculated: 286.0453  found: 286.0447.

Synthesis of 5-[hydroxy(phenyl)methyl]thiophene-2-carboxylic acid (49c)

The double magnesiated reagent was prepared according to TP08 from 5-bromothiophene-2-carboxylic acid (48b; 414 mg, 2.00 mmol) and reacted with benzyldehyde (254 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.00 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous
layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined CH$_2$Cl$_2$-layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. After recrystallization from MeOH, 5-[hydroxy(phenyl)methyl]thiophene-2-carboxylic acid (49c) was obtained as colorless solid (417 mg, 1.78 mmol, 89%).

mp.: 162.0-163.5 °C
$^1$H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 12.38 (brs, 1 H); 7.54 (d, $^3$J = 3.7 Hz, 1 H); 7.43-7.23 (m, 5 H); 6.90 (d, $^3$J = 3.7 Hz, 1 H); 6.43 (brs, 1 H); 5.94 (s, 1 H).

IR (KBr): ν [cm$^{-1}$] = 3031 (m); 2923 (m); 2805 (m); 2623 (m); 1672 (vs); 1540 (s); 1493 (w); 1465 (s); 1455 (m); 1406 (m); 1334 (m); 1322 (m); 1305 (m); 1264 (s); 1201 (m); 1157 (m); 1109 (m); 1078 (w); 1032 (m); 996 (m); 945 (w); 912 (w); 840 (w); 821 (m); 785 (w); 761 (m); 754 (m); 746 (s); 697 (s); 634 (w); 540 (w); 472 (m).

MS (EI): (m/z) (%) = 234 (M$^+$, 18); 232 (25); 218 (29); 189 (9); 187 (9); 173 (41); 171 (12); 157 (10); 155 (36); 129 (67); 11 (17); 105 (100); 85 (12); 77 (40); 51 (13).

HR-MS (C$_6$H$_6$O$_2$S$_2$): calculated: 234.0351 found: 234.0349.

Synthesis of 5-(methylthio)thiophene-2-carboxylic acid (49d)

The double magnesiated reagent was prepared according to TP08 from 5-bromothiophene-2-carboxylic acid (48b; 414 mg, 2.00 mmol) and reacted with S-methyl methanesulfonothioate (610 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.00 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined CH$_2$Cl$_2$-layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. After gel filtration (silica; CH$_2$Cl$_2$:MeOH; 19:1), 5-(methylthio)thiophene-2-carboxylic acid (49d) was obtained as a pale pink solid (324 mg, 1.86 mmol, 93%).

mp.: 104.4-105.6 °C
$^1$H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 13.06 (brs, 1 H); 7.59 (d, $^3$J = 3.7 Hz, 1 H); 7.06 (d, $^3$J = 3.7 Hz, 1 H); 2.59 (s, 3 H).

IR (KBr): ν [cm$^{-1}$] = 3437 (m); 2926 (m); 2853 (w); 2573 (w); 1658 (vs); 1525 (vs); 1427 (vs); 1405 (vs); 1304 (vs); 1278 (m); 1224 (m); 1106 (vs); 1066 (m); 1009 (m); 966 (m); 915 (br); 800 (s); 764 (m); 748 (s); 670 (w); 533 (m); 490 (m); 469 (m).

MS (EI): (m/z) (%) = 174 (M$^+$, 100); 159 (28); 157 (12); 131 (16); 114 (9); 103 (7); 71 (6); 69 (8); 57 (4); 44 (6).

HR-MS (C$_6$H$_6$O$_2$S$_2$): calculated: 173.9809 found: 173.9803.
Synthesis of 5-[4-(dimethylamino)phenyl]thiophene-2-carboxylic acid (49e)

The double magnesiated reagent was prepared according to TP08 from 5-bromothiophene-2-carboxylic acid (48b; 414 mg, 2.00 mmol). Then, ZnCl₂ (1.00 M in THF; 2.20 mL, 2.20 mmol, 1.10 equiv) was added at -20 °C, the resulting solution was warmed up to room temperature and stirred for 30 min at that temperature. Concurrently, Pd(dba)₂ (57.5 mg, 5.00 mol%) and tri-2-furylphosphine (46.4 mg, 10.0 mol%) were placed in a second, dry and argon-flushed Schlenk-flask and dissolved in THF (4.0 mL). After stirring this mixture for 5 min at rt, the colour changed from orange to green. Then, a solution of 4 iodo-N,N-dimethylaniline in THF [due to the low stability of the iodoarene, it was prepared in situ by quenching 4-(dimethylamino)phenylmagnesium bromide/LiCl (1.10 M; 2.18 mL, 2.40 mmol, 1.20 equiv; prepared by insertion in the presence of LiCl) with I₂ (610 mg, 2.40 mmol 1.20 equiv)] was added via a cannula and the resulting mixture was stirred for 10 min at rt. Afterwards, it was cannulated to the zinc reagent prepared above, the mixture was heated at 50 °C for 3 h. Then, MeOH (2.0 mL) was added and the reaction mixture was poured on water (40 mL). The aqueous layer was carefully adjusted to pH 5-6 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. The residue was suspended in dichloromethane (20 mL) and subjected to sonication (30 min). After filtration and thorough washing with CH₂Cl₂, the desired product 49e was obtained as a solid of intensive green colour (470 mg, 1.90 mmol, 95 %).

\[ \text{mp. : 100.4-202.3 °C} \]

\[ ^1H\text{-NMR (dmsso-d₆, 300 MHz)} : \delta [ppm] = 7.60 (d, J = 4.0 Hz, 1 H); 7.53 (d, J = 8.2 Hz, 2 H); 7.30 (d, J = 4.0 Hz, 1 H); 6.74 (d, J = 8.2 Hz, 2 H); 2.94 (s, 6 H). \]

\[ ^{13}C\text{-NMR (dmsso-d₆, 75 MHz)} : \delta [ppm] = 163.8; 151.6; 151.2; 134.7; 132.0; 127.4; 122.1; 121.3; 112.9; 40.5. \]

IR (KBr): v [cm⁻¹] = 3430 (m); 3044 (m), 2679 (w); 2560 (m); 1660 (s); 1607 (vs); 1540 (m); 1481 (w); 1451 (vs); 1440 (vs); 1366 (s); 1302 (m); 1254 (w); 1230 (w); 1198 (m); 1106 (m); 1044 (w); 960 (w), 945 (w); 809 (m); 758 (s); 671 (w); 580 (w); 524 (w). 

UV/Vis: λ_{max} = 363, 251, 202.

MS (EI): (m/z) (%): 247 (M⁺; 100); 231 (13); 203 (5); 158 (4); 115 (6); 79 (4).

HR-MS (C₁₃H₁₃NO₂S): calculated: 247.0667 found: 247.0652.

Synthesis of 4-bromothiophene-2-carboxylic acid (49g)

The double magnesiated reagent was prepared according to TP09 from 4,5-dibromo-2-thiophenecarboxylic acid (48c; 572 mg, 2.00 mmol). Then, MeOH (2.0 mL) was added. The reaction mixture was poured on water (40 mL) and the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The
combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. After drying in high vacuum (15 min), 4-bromothiophene-2-carboxylic acid (49h) was obtained as a colorless, crystalline solid (412 mg, 1.98 mmol, 99%).

\[ \text{mp.}: 121.2-123.1 \degree C \]

\(^1\)H-NMR (dmso-d₆, 300 MHz): \( \delta [\text{ppm}] = 13.45 \text{ (brs, 1 H)} ; 7.99 \text{ (d, } ^4J = 1.6 \text{ Hz, 1 H)} ; 7.67 \text{ (d, } ^4J = 1.6 \text{ Hz, 2 H)} . \)

\(^1\)H-NMR (CDCl₃, 200 MHz): \( \delta [\text{ppm}] = 12.02 \text{ (brs, 1 H)} ; 7.77 \text{ (d, } ^4J = 1.6 \text{ Hz, 1 H)} ; 7.53 \text{ (d, } ^4J = 1.6 \text{ Hz, 2 H)} . \)

\(^13\)C-NMR (dmso-d₆, 75 MHz): \( \delta [\text{ppm}] = 161.7; 136.1; 134.5; 130.8; 109.5. \)

IR (KBr): \( \nu [\text{cm}^{-1}] = 3103 \text{ (m)}; 2855 \text{ (m)}; 2662 \text{ (m)}; 2552 \text{ (m)}; 1678 \text{ (vs)}; 1524 \text{ (s)}; 1429 \text{ (vs)}; 1338 \text{ (m)}; 1300 \text{ (s)}; 1263 \text{ (s)}; 1185 \text{ (m)}; 1098 \text{ (m)}; 1058 \text{ (m)}; 890 \text{ (w)}; 874 \text{ (m)}; 861 \text{ (m)}; 828 \text{ (m)}; 776 \text{ (s)}; 758 \text{ (m)}; 681 \text{ (m)}; 573 \text{ (m)}; 504 \text{ (m)} . \)

MS (EI): \( \text{(m/z) \%} = 208 \text{ (M}^+; 81\text{Br}; 100); 206 \text{ (M}^+; 79\text{Br}; 100); 191 \text{ (69); 189 (68); 163 (5); 82 (20); 59 (8); 43 (15).} \)

HR-MS (C₁₃H₁₃NO₂S): calculated: 205.9037 found: 205.9028.

The selectivity was confirmed by comparing the \(^1\)H-NMR data in CDCl₃ with the literature data of 4-bromo-2 thiophenecarboxylic acid\(^{99}\) as well as the data for 5-bromo-2 thiophenecarboxylic acid.\(^{100}\) Furthermore, a commercial sample of 5-bromo-2 thiophenecarboxylic acid was measured in dmso-d₆ and was found to be not identical with the product isolated above. Thus, the exchange was clearly assigned to proceed in 5-position.

**Synthesis of 5-allyl-4-bromo-2-thiophenecarboxylic acid (49g)**\(^{101}\)

\[
\text{HO}_2\text{C} \quad \begin{array}{c}
\text{S} \\
\text{Br}
\end{array} \\
\text{CH}_2=\text{CH}
\]

The double magnesiated reagent was prepared according to TP09 from 4,5-dibromo-2-thiophenecarboxylic acid (48c; 572 mg, 2.00 mmol) and reacted with allyl bromide (290 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%). The reaction mixture was poured on water (40 mL) and the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH₂Cl₂ (3 × 40 mL). The combined CH₂Cl₂-layers were dried (Na₂SO₄) and evaporated in vacuo. After drying in high vacuum, 5-allyl-4-bromo-2-thiophenecarboxylic acid (49g) was obtained as a colorless, crystalline solid (477 mg, 1.93 mmol, 97%).

\[ \text{mp.}: 107.3-108.6 \degree C \]

\(^1\)H-NMR (dmso-d₆, 300 MHz): \( \delta [\text{ppm}] = 13.36 \text{ (brs, 1 H)} ; 7.62 \text{ (s, 1 H)} ; 5.99-5.86 \text{ (m, 1 H)} ; 5.23-5.12 \text{ (m, 2 H)} ; 3.53 \text{ (d, } ^3J = 6.4 \text{ Hz, 2 H)} . \)

\(^13\)C-NMR (dmso-d₆, 75 MHz): \( \delta [\text{ppm}] = 161.8; 144.5; 134.9; 134.0; 132.6; 117.9; 109.1; 33.2. \)


\(^{100}\) A. F. M. Kilbinger, W. J. Feast, J. Mat. Chem. 2000, 10, 1777.

\(^{101}\) The analytical data for 5-allyl-4-bromo-2-thiophenecarboxylic acid (49g) were reported in ref. 134.
IR (KBr): $\nu$ [cm$^{-1}$] = 3001 (m); 2671 (m); 1665 (vs); 1528 (s); 1451 (s); 1411 (m); 1390 (m); 1312 (s); 1275 (s); 1151 (m); 1145 (m); 1096 (w); 1046 (w); 996 (m); 922 (s); 868 (m); 801 (w); 771 (m); 751 (m); 688 (w); 589 (w); 512 (m).

MS (EI): (m/z) (%) = 248 (M$^+$; $^{81}$Br; 100); 246 (M$^+$; $^{79}$Br; 95); 231 (6); 229 (5); 221 (20); 219 (19); 167 (25); 149 (5); 132 (82); 95 (7); 79 (18); 77 (12); 69 (7); 51 (7); 45 (21).

HR-MS $(\text{C}_8\text{H}_7\text{BrO}_2\text{S})$: calculated: 245.9350 found: 245.9318.

**Synthesis of 5-bromo-4-(ethoxycarbonyl)-2-thiophenecarboxylic acid (49h)**

The double magnesiated reagent was prepared according to TP09 from 4,5-dibromo-2-thiophenecarboxylic acid (48c; 572 mg, 2.00 mmol) and reacted with ethyl chloridocarbonate (259 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on water (40 mL) and the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined EtOAc-layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. After recrystallization from heptane/EtOAc (4:1), 5-bromo-4-(ethoxycarbonyl)-2-thiophenecarboxylic acid (49h) was obtained as a pale orange, crystalline solid (477 mg, 1.12 mmol, 56%).

**mp.:** 188.2-190.1 °C

$^1$H-NMR (dms o-$d_6$, 300 MHz): $\delta$ [ppm] = 13.81 (brs, 1 H); 7.75 (s, 1 H); 4.31 (q, $^3J$ = 7.1 Hz, 2 H); 1.30 (t, $^3J$ = 7.1 Hz, 3 H).

$^{13}$C-NMR (dms o-$d_6$, 75 MHz): $\delta$ [ppm] = 161.3; 159.5; 139.0; 136.7; 131.6; 115.9; 88.2; 61.8; 39.5; 13.9.

IR (KBr): $\nu$ [cm$^{-1}$] = 3086 (m); 2996 (w); 2984 (w); 2942 (w); 2870 (w); 2566 (w); 1724 (m); 1686 (s); 1658 (s); 1518 (s); 1460 (m); 1412 (s); 1330 (m); 1296 (s); 1276 (m); 1226 (vs); 1160 (m); 1120 (w); 1090 (s); 1080 (m); 1010 (s); 888 (s); 840 (m); 814 (w); 774 (m); 760 (s); 692 (m).

MS (EI): (m/z) (%) = 280 (M$^+$; $^{81}$Br; 47); 278 (M$^+$; $^{79}$Br; 44); 252 (48); 250 (46); 235 (100); 233 (96); 208 (9); 206 (9); 191 (11); 189 (11); 109 (10); 82 (21); 45 (5).

HR-MS $(\text{C}_8\text{H}_7\text{BrO}_4\text{S})$: calculated: 277.9248 found: 277.9242.
5. Iodine/Magnesium Exchange Reactions on Unprotected Imidazole Derivatives

Synthesis of 1-(1H-imidazol-5-yl)-2,2-dimethylpropan-1-ol (54a)

According to TP10, the dimagnesiated imidazole 53a was prepared from 4-iodo-1H-imidazole (52a; 308 mg, 2.00 mmol) and reacted at -20 °C with t-BuCHO (207 mg, 2.40 mmol, 1.20 equiv). After flash column chromatography (silica, CH₂Cl₂:MeOH, 19:1), 54a was obtained as a colorless, crystalline solid (302 mg, 1.96 mmol, 98%).

mp.: 76.3-77.9 °C

$^1$H-NMR (dmsod$_6$, 400 MHz): \( \delta \) [ppm] = 12.48 (brs, 1H); 7.78 (s, 1 H); 7.76 (s, 1 H); 7.63 (s, 1 H); 7.29 (s, 1 H); 1.30 (s, 9 H).

$^{13}$C-NMR (dmsod$_6$, 100 MHz): \( \delta \) [ppm] = 137.8; 136.5; 122.8; 80.5; 42.9; 27.2.

IR (neat): \( \nu \) [cm$^{-1}$] = 3136 (w); 3120 (w); 3082 (w); 2986 (m); 2972 (m); 2952 (m); 2930 (m); 2870 (m); 2790 (m); 2638 (m); 2574 (m); 2382 (w); 2350 (w); 1822 (w); 1644 (s); 1536 (m); 1526 (m); 1518 (m); 1476 (m); 1460 (w); 1432 (m); 1394 (w); 1364 (w); 1308 (m); 1288 (m); 1228 (w); 1184 (m); 1118 (m); 1068 (m); 1042 (m); 1004 (m); 946 (s); 926 (s); 844 (m); 828 (s); 800 (m); 768 (s); 758 (s); 658 (m); 616 (vs).

MS (EI): (m/z) (%) = 125 ([M-2H]$^+$; 37); 97 (25); 96 (32); 95 (100); 68 (45); 57 (40); 41 (11).

HR-MS (C$_8$H$_{12}$N$_2$O; [M-2H]$^+$): calculated: 152.0950 found: 152.0942.

Synthesis of 5-(methylthio)-1H-imidazole (54b)

According to TP10, the dimagnesiated imidazole 53a was prepared from 4-iodo-1H-imidazole (52a; 308 mg, 2.00 mmol) and reacted at -20 °C with MeSSO$_2$Me (302 mg, 2.40 mmol, 1.20 equiv). After flash column chromatography (silica, CH₂Cl₂:MeOH, 19:1), 54b was obtained as a pale yellow, crystalline solid (162 mg, 1.42 mmol, 71%).

mp.: 80.3-81.5 °C

$^1$H-NMR (dmsod$_6$, 400 MHz): \( \delta \) [ppm] = 12.19 (brs, 1H); 7.65 (s, 1 H); 7.05 (s, 1 H); 2.31 (s, 3 H).

$^{13}$C-NMR (dmsod$_6$, 100 MHz): \( \delta \) [ppm] = 137.8; 136.3; 118.8; 17.6.

IR (neat): \( \nu \) [cm$^{-1}$] = 3144 (w); 3108 (m); 3020 (w); 2990 (m); 2922 (m); 2884 (m); 2802 (m); 2678 (m); 2642 (m); 2584 (m); 1824 (w); 1678 (w); 1550 (w); 1530 (m); 1488 (w); 1428 (m); 1418 (w); 1394 (w); 1364 (w); 1330 (m); 1308 (w); 1288 (m); 1228 (w); 1184 (m); 1118 (m); 1068 (m); 1042 (m); 1004 (m); 946 (s); 926 (s); 844 (m); 828 (s); 800 (m); 768 (s); 758 (s); 658 (m); 616 (vs).
1414 (m); 1316 (m); 1292 (m); 1216 (m); 1184 (m); 1168 (m); 1074 (s); 968 (m); 960 (m); 946 (m); 928 (m); 916 (m); 836 (s); 772 (s); 704 (w); 682 (m); 660 (w); 620 (s).

MS (EI): (m/z) (%) = 114 (M^+; 100); 99 (30); 81 (40); 72 (16); 68 (7); 59 (6); 45 (32); 41 (7).

HR-MS (C_4H_6N_2S): calculated: 114.0252  found: 114.0249.

Synthesis of 1-(4-iodo-1H-imidazol-5-yl)-2,2-dimethylpropan-1-ol (54c)

According to TP10, the dimagnesiated imidazole 53b was prepared from 4,5-diiodo-1H-imidazole (52b; 640 mg, 2.00 mmol) and reacted at -20 °C with t-BuCHO (207 mg, 2.40 mmol, 1.20 equiv). After flash column chromatography (silica, CH_2Cl_2:MeOH, 19:1), 54c was obtained as a colorless, crystalline solid (476 mg, 1.70 mmol, 85 %).

mp.: 207 °C (decomposition)

^1H-NMR (dmsO-d_6, 400 MHz): δ [ppm] = 0.87 (s, 9 H); 4.21 (d, J = 3.5 Hz, 1 H); 5.45 (d, J = 3.5 Hz, 1 H); 7.54 (s, 1 H); 12.13 (s, 1 H).

^13C-NMR (dmsO-d_6, 100 MHz): δ [ppm] = 26.1; 36.6; 72.6; 83.9; 133.7; 137.1.

IR (KBr): ν [cm^-1] = 3176 (m); 2961 (s); 2904 (w); 2868 (m); 1626 (w); 1556 (w); 1476 (m); 1424 (m); 1394 (w); 1365 (m); 1338 (w); 1318 (w); 1285 (w); 1236 (m); 1177 (m); 1066 (m); 1012 (s); 947 (m); 896 (m); 813 (m); 788 (m); 652 (w); 566 (w); 482 (w).

MS (EI): (m/z) (%) = 280 (M^+; 9); 223 (100); 97 (13); 95 (9); 68 (8); 57 (6); 41 (9).

HR-MS (C_8H_13IN_2O): calculated: 280.0073  found: 280.0077.

Synthesis of 1-4-iodo-1H-imidazol-5-yl)(phenyl)methanol (54d)

According to TP10, the dimagnesiated imidazole 53b was prepared from 4,5-diiodo-1H-imidazole (52b; 640 mg, 2.00 mmol) and reacted at -20 °C with benzaldehyde (254 mg, 2.40 mmol, 1.20 equiv). After flash column chromatography (silica, CH_2Cl_2:MeOH, 19:1), 54d was obtained as a colorless, crystalline solid (516 mg, 1.71 mmol, 86 %).

mp.: 207 °C (decomposition)

^1H-NMR (dmsO-d_6, 400 MHz): δ [ppm] = 12.43 (brs, 1 H); 7.58 (s, 1 H); 7.39-7.29 (4 H); 7.25-7.20 (m, 1 H); 6.11 (s, 1 H); 5.65 (d, J = 3.6 Hz; 1 H).

^13C-NMR (dmsO-d_6, 100 MHz): δ [ppm] = 143.2; 141.5; 137.8; 128.0; 127.0; 125.8; 67.3.

IR (KBr): ν [cm^-1] = 3435 (m); 3140 (s); 2972 (m); 2856 (m); 2681 (m); 1643 (w); 1566 (m); 1492 (m); 1476 (m); 1449 (s); 1440 (m); 1341 (m); 1326 (w); 1274 (m); 1243 (s); 1186 (s); 1161 (m); 1080 (w); 1052 (m); 1030 (w); 1011 (vs); 954 (s); 920 (w); 877 (w); 846 (w); 802 (m); 723 (vs); 697 (m); 652 (m); 632 (w); 491 (w).

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Synthesis of 5-allyl-4-iodo-1H-imidazole (54e)

According to TP10, the dimagnesiated imidazole 53b was prepared from 4,5-diiodo-1H-imidazole (52b; 640 mg, 2.00 mmol) and reacted at -20 °C with allyl bromide (291 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN⋅2LiCl (1.00 M in THF; 0.02 mL; 1.00 mol%). After flash column chromatography (silica, CH2Cl2:MeOH, 19:1), 54e was obtained as a colorless, crystalline solid (516 mg, 1.71 mmol, 86 %).

mp.: 126.4-128.3 °C (decomposition)

$^1$H-NMR (dmso-d$_6$, 400 MHz): $\delta$ [ppm] = 12.41 (brs, 1 H); 7.63 (s, 1 H); 5.88-5.78 (m, 1 H); 5.05-4.96 (m, 2 H); 3.23 (d, $^3J = 6.3$ Hz, 2 H).

$^{13}$C-NMR (dmso-d$_6$, 100 MHz): $\delta$ [ppm] = 137.4; 134.7; 131.5; 116.3; 81.1; 29.7.

IR (KBr): $\nu$ [cm$^{-1}$] = 3154 (w); 3126 (w); 3068 (m); 3056 (m); 3002 (w); 2944 (m); 2926 (m); 2900 (m); 2868 (m); 2828 (m); 2800 (m); 2750 (m); 2724 (m); 2682 (m); 2644 (m); 2620 (m); 2592 (m); 2336 (w); 1634 (m); 1582 (m); 1486 (w); 1466 (w); 1448 (m); 1418 (m); 1342 (m); 1284 (w); 1246 (m); 1182 (m); 1152 (s); 1104 (w); 1032 (w); 996 (s); 952 (s); 936 (m); 918 (vs); 900 (s); 886 (s); 812 (s); 770 (s); 664 (s); 642 (s); 618 (w).

MS (EI): (m/z) (%) = 234 (M$^+$; 100); 233 (23); 207 (13); 180 (2); 107 (14); 80 (19); 53 (9).

HR-MS (C$_{4}$H$_{7}$IN$_{2}$): calculated: 233.9654 found: 233.9658.

Synthesis of ethyl 2-[(4-iodo-1H-imidazol-5-yl)methyl]acrylate (54f):

According to TP10, the dimagnesiated imidazole 53b was prepared from 4,5-diiodo-1H-imidazole (52b; 640 mg, 2.00 mmol) and reacted at -20 °C with ethyl 2-(bromomethyl)-acrylate (291 mg, 2.40 mmol, 1.20 equiv) after transmetallation using CuCN⋅2LiCl (1.00 M in THF; 2.20 mL, 2.20 mmol, 1.10 equiv; -20 °C, 30 min). After flash column chromatography (silica, CH$_2$Cl$_2$:MeOH, 19:1), 54f was obtained as a colorless, crystalline solid (128 mg, 0.84 mmol, 42 %).

mp.: 103.1-104.2 °C

$^1$H-NMR (dmso-d$_6$, 400 MHz): $\delta$ [ppm] = 12.22 (brs, 1 H); 7.63 (s, 1 H); 6.13 (s, 1 H); 5.37 (s, 1 H); 4.14 (q, $^3J = 7.1$ Hz, 2 H); 3.46 (s, 1 H); 1.21 (t, $^3J = 7.1$ Hz, 3 H).

$^{13}$C-NMR (dmso-d$_6$, 100 MHz): $\delta$ [ppm] = 165.7; 137.6; 137.1; 130.6; 126.0; 81.7 (very weak signal); 60.5; 27.8; 14.0.
IR (KBr): $\nu$ [cm$^{-1}$] = 3404 (w); 3058 (m); 2957 (m); 2799 (m); 2600 (m); 1709 (vs); 1631 (m); 1591 (w); 1458 (m); 1425 (m); 1401 (w); 1370 (w); 1328 (m); 1278 (s); 1251 (m); 1184 (m); 1164 (m); 1156 (m); 1134 (s); 1051 (w); 1023 (w); 963 (m); 873 (w); 820 (m); 670 (w); 654 (w).

MS (EI): (m/z) (%) = 306 (M$^+$; 55); 260 (31); 232 (37); 207 (21); 179 (100); 151 (27); 133 (59); 105 (28); 79 (20); 52 (14).

HR-MS ($C_9H_{11}N_2O$): calculated: 305.9865 found: 305.9850.

Synthesis of 4-iodo-5-(phenylthio)-1H-imidazole (54g)

According to TP10, the dimagnesiated imidazole 53b was prepared from 4,5-diiodo-1H-imidazole (52b; 640 mg, 2.00 mmol) and reacted at -20 °C with PhSSO$_2$Ph (600 mg, 2.40 mmol, 1.20 equiv). After flash column chromatography (silica, CH$_2$Cl$_2$:MeOH, 19:1), 54g was obtained as a colorless, crystalline solid (387 mg, 1.28 mmol, 64%).

mp.: 177.3-179.6 °C (decomposition)

$^1$H-NMR (dmso-d$_6$, 400 MHz): $\delta$ [ppm] = 13.15 (brs, 1 H); 7.95 (s, 1 H); 7.29 (t, $^3J = 7.4$ Hz, 2 H); 7.17 (t, $^3J = 7.4$ Hz, 1 H); 7.03 (d, $^1J = 7.4$ Hz, 2 H);

$^{13}$C-NMR (dmso-d$_6$, 100 MHz): $\delta$ [ppm] = 141.4; 136.4 (br); 129.2; 129.0; 126.1; 125.9. (Only 6 of 7 possible signals were detected)

IR (KBr): $\nu$ [cm$^{-1}$] = 2844 (w); 2772 (w); 2574 (w); 1874 (w); 1852 (w); 1840 (w); 1796 (w); 1680 (w); 1582 (w); 1536 (w); 1478 (m); 1452 (m); 1440 (m); 1426 (w); 1272 (m); 1192 (m); 1164 (m); 1086 (w); 1068 (w); 1024 (m); 988 (w); 954 (m); 924 (m); 902 (w); 894 (w); 840 (m); 734 (vs); 684 (s); 666 (m); 648 (m).

MS (EI): (m/z) (%) = 302 (M$^+$; 100); 175 (20); 148 (79); 104 (16); 77 (27); 65 (7); 51 (20).

HR-MS: (C$_9$H$_{11}$IN$_2$S); calculated: 301.9375 found: 301.9357.

Synthesis of 4-iodo-5-(methylthio)-1H-imidazole (54h)

According to TP10, the dimagnesiated imidazole 53b was prepared from 4,5-diiodo-1H-imidazole (52b; 640 mg, 2.00 mmol) and reacted at -20 °C with MeSSO$_2$Me (302 mg, 2.40 mmol, 1.20 equiv). After flash column chromatography (silica, CH$_2$Cl$_2$:MeOH, 19:1), 54h was obtained as a colorless, crystalline solid (351 mg, 1.46 mmol, 73%).

mp.: 126.1-128.4 °C (beginning decomposition)

$^1$H-NMR (dmso-d$_6$, 400 MHz): $\delta$ [ppm] = 12.85 (brs, 1 H); 7.78 (s, 1 H); 2.29 (s, 3 H).

$^{13}$C-NMR (dmso-d$_6$, 100 MHz): $\delta$ [ppm] = 142.3; 140.7; 65.6; 19.4.

IR (KBr): $\nu$ [cm$^{-1}$] = 3068 (w); 2986 (w); 2954 (w); 2920 (w); 2874 (w); 2772 (m); 2638 (m); 2562 (m); 2384 (m); 1834 (w); 1744 (w); 1714 (w); 1662 (w); 1534 (w); 1452 (s); 1418 (m); 139.
Synthesis of 4-iodo-5-(methylthio)-1H-imidazole (54i):

According to TP10, the dimagnesiated imidazole 53b was prepared from 4,5-diiodo-1H-imidazole (52b; 640 mg, 2.00 mmol) and reacted at -20 °C with 4-bromobenzyl bromide (600 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.40 mL, 20.0 mol%). After flash column chromatography (silica, CH2Cl2:MeOH, 19:1), 54i was obtained as a colorless, crystalline solid (392 mg, 1.08 mmol, 54%).

mp.: 160.8-162.3 °C (beginning decomposition)

1H-NMR (dmso-d6, 400 MHz): δ [ppm] = 12.39 (brs, 1 H); 7.63 (s, 1 H); 7.48 (d, 3J = 8.6 Hz, 2 H); 7.12 (d, 3J = 8.6 Hz, 2 H); 3.80 (s, 2 H).

13C-NMR (dmso-d6, 100 MHz): δ = 142.3; 139.1; 138.5; 132.0; 131.0; 120.0; 82.9; 31.4.

IR (KBr): ν [cm⁻¹] = 3040 (w); 2928 (w); 2818 (m); 2780 (m); 2672 (m); 2584 (m); 2478 (m); 1846 (w); 1642 (w); 1572 (m); 1486 (s); 1470 (m); 1450 (m); 1434 (s); 1404 (m); 1346 (m); 1308 (w); 1240 (m); 1180 (m); 1154 (m); 1096 (w); 1070 (m); 1028 (w); 1012 (s); 956 (vs); 922 (m); 902 (m); 842 (m); 830 (s); 818 (s); 798 (vs); 754 (s); 670 (w); 654 (vs); 606 (m).

MS (EI): (m/z) (%) = 364 (M⁺, 81Br; 75); 362 (M⁺, 79Br; 80); 283 (13); 237 (56); 235 (57); 210 (31); 208 (37); 207 (37); 183 (9); 182 (9); 181 (10); 184 (10); 169 (7); 156 (100); 129 (82); 102 (60); 99 (18); 78 (38); 75 (23); 63 (12); 51 (16).

HR-MS (C10H7BrIN2; [M-H]⁺): calculated: 360.8837 found: 239.9233.

Synthesis of 4-(4-iodo-1H-imidazol-5-yl)benzonitrile (54j):

According to TP10, the dimagnesiated imidazole 53b was prepared from 4,5-diiodo-1H-imidazole (52b; 640 mg, 2.00 mmol). Then, ZnCl₂ in THF (1.00 m; 2.30, 1.15 equiv) was added at -20 °C, the resulting Solution was warmed up to room temperature and stirred for 30 min at that temperature.

Concurrently, Pd(dba)₂ (57.5 mg, 5.00 mol%) and tri-2-furylphosphine (46.4 mg, 10.0 mol%) were placed in a second, dry and argon-flushed Schlenk-flask and dissolved in THF (4.0 mL). After stirring this mixture for 5 min at rt, the colour changed from orange to green. Then, a solution of 4-iodobenzonitrile (504 mg, 2.20 mmol, 1.10 equiv) in THF (2.0 mL) was added
via a cannula and the resulting mixture was stirred for 10 min at rt. The mixture was then cannulated to the Zink reagent prepared above, the mixture was heated at 50 °C over night (14 h). After cooling down to rt, the mixture was subjected to workup. After flash column chromatography (silica, CH₂Cl₂:MeOH, 19:1), 54j was obtained as colorless solid (359 mg, 1.22 mmol, 61 %).

mp.: 215.6-217 °C

$^1$H-NMR (dmso-d$_6$, 400 MHz): $\delta$ [ppm] = 12.99 (brs, 1 H); 8.15-7.85 (m, 5 H).

$^{13}$C-NMR (dmso-d$_6$, 100 MHz): $\delta$ = 140.7; 133.1; 128.9 (weak); 127.3; 119.6; 109.9; 67.7 (weak); (Only 7 of 8 possible signals were detected).

IR (KBr): $\nu$ [cm$^{-1}$] = 3080 (w); 3064 (w); 2970 (w); 2912 (w); 2830 (w); 2228 (m); 1610 (m); 1500 (m); 1438 (m); 1336 (w); 1312 (w); 1244 (m); 1182 (m); 1168 (m); 1152 (m); 1118 (m); 1108 (w); 1022 (w); 964 (w); 950 (s); 932 (m); 850 (s); 830 (vs); 816 (s); 776 (m); 730 (m); 688 (w); 648 (s); 634 (vs).

MS (EI): (m/z) (%) = 295 (M$^+$; 100); 268 (1); 168 (12); 141 (19); 114 (17).

HR-MS (C$_{10}$H$_7$BrIN; [M-H]$^-$): calculated: 294.9606 found: 294.9582.

Synthesis of 5-allyl-4-(phenylthio)-1H-imidazole (56a)

According to TP11, the dimagnesiated imidazole 55 was prepared from 4-iodo-5-(phenylthio)-1H-imidazole (54g; 604 mg, 2.00 mmol) and reacted at -20 °C with allyl bromide (291 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL; 1.00 mol%). After flash column chromatography (silica, CH₂Cl₂:MeOH, 19:1), 56a was obtained as a yellow solid (272 mg, 1.26 mmol, 63 %).

mp.: 139.5-140.5 °C

$^1$H-NMR (dmso-d$_6$, 400 MHz): $\delta$ [ppm] = 12.51 (brs, 1 H); 7.81 (brs, 1 H); 7.23 (t, $^3$J = 7.2 Hz, 2 H); 7.09 (t, $^3$J = 7.2 Hz, 1 H); 7.01 (d, $^3$J = 7.2 Hz, 2 H); 5.84 (brs, 1 H); 4.99-4.95 (m, 2 H); 3.36 (brs, 2 H).

$^{13}$C-NMR (dmso-d$_6$, 100 MHz): $\delta$ [ppm] = 138.4; 134.5; 128.8; 125.8; 125.1; 116.2; 28.7. (Only 8 of 10 possible signals were detected.)

IR (KBr): $\nu$ [cm$^{-1}$] = 3070 (w); 3046 (w); 3008 (w); 2978 (w); 2944 (w); 2912 (w); 2774 (w); 2724 (w); 2680 (w); 2646 (w); 2588 (m); 1852 (w); 1642 (w); 1582 (m); 1478 (m); 1450 (m); 1440 (m); 1424 (m); 1284 (w); 1256 (w); 1186 (m); 1158 (w); 1082 (w); 1072 (w); 1052 (w); 1024 (m); 988 (m); 962 (s); 914 (s); 828 (m); 782 (m); 740 (s); 730 (vs); 688 (s); 648 (m); 616 (w).

MS (EI): (m/z) (%) = 216 (M$^+$; 100); 201 (14); 189 (5); 183 (8); 139 (22); 137 (10); 125 (7); 121 (7); 112 (8); 107 (10); 91 (8); 80 (16); 77 (13); 51 (11).

HR-MS (C$_{12}$H$_{12}$N$_2$S): calculated: 216.0721 found: 216.0716.
Synthesis of 5-allyl-4-(phenylthio)-1H-imidazole (56b)

According to TP11, the dimagnesiated imidazole 55 was prepared from 4-iodo-5-(phenylthio)-1H-imidazole (54g; 604 mg, 2.00 mmol) and reacted at –20 °C with (2E)-hex-2-enal (235 mg, 2.40 mmol, 1.20 equiv). After flash column chromatography (silica, CH₂Cl₂:MeOH, 19:1), 56b was obtained as a colorless, viscous oil (318 mg, 1.16 mmol, 58 %). The compound is quite unstable and prone to polymerization.

$^1$H-NMR (dmso-d$_6$, 400 MHz): δ [ppm] = 12.47 (brs, 1 H); 7.71 (s, 1 H); 7.20 (t, $^3$J = 7.5 Hz, 2 H); 7.08 (t, $^3$J = 7.5 Hz, 1 H); 7.02 (d, $^3$J = 7.5 Hz, 2 H); 5.59 (dd, $^2$J = 15.2 Hz, $^3$J = 6.4 Hz, 1 H); 5.38-5.50 (m, 2 H); 5.21 (d, $^3$J = 5.8 Hz, 1 H); 1.85 (brs, 2 H); 1.22 (sext, $^3$J = 7.4 Hz, 2 H); 0.77 (t, $^3$J = 7.4 Hz, 3 H).

$^{13}$C-NMR (dmso-d$_6$, 100 MHz): δ [ppm] = 13.4; 21.6; 33.5; 65.4; 125.1; 126.1; 128.7; 129.6; 130.2; 131.6; 132.7; 136.7; 138.3.

IR (KBr): ν [cm$^{-1}$] = 3056 (m); 2956 (m); 2928 (m); 2870 (m); 2838 (m); 1666 (w); 1650 (w); 1582 (m); 1478 (s); 1464 (m); 1454 (m); 1440 (m); 1378 (w); 1346 (w); 1298 (w); 1270 (w); 1242 (w); 1204 (w); 1190 (w); 1084 (w); 1070 (w); 1040 (w); 1024 (m); 998 (w); 964 (s); 828 (w); 736 (vs); 688 (s); 650 (w).

MS (EI): (m/z) (%) = 274 (M$^+$; 2); 254 (100); 249 (8); 239 (34); 227 (33); 212 (13); 198 (3); 187 (10); 167 (8); 150 (17); 145 (10); 136 (16); 121 (12); 118 (18); 104 (14); 91 (13); 77 (22); 65 (9); 51 (12).

HR-MS (C$_{15}$H$_{19}$N$_2$OS; [M+H]$^+$): calculated: 275.1218  found: 275.1211.
6. Halogen/Magnesium Exchange Reactions on Unprotected Uracil Derivatives

6.1. Synthesis of Functionalized Uracil Derivatives

Preparation of 5-(1-hydroxy-2,2-dimethylpropyl)pyrimidine-2,4(1H,3H)-dione (59a)

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 476 mg, 2.00 mmol) and reacted with t-BuCHO (224 mg, 2.60 mmol, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and the volume was, after filtration, reduced in vacuo to ca. 30-40 mL giving a suspension of the white product, that was cooled and subsequently filtered. After drying in high vacuum, the product 59a was obtained as a colorless, crystalline solid (307 mg, 1.55 mmol, 77%).

mp.: 256.3-259.0 °C

¹H-NMR (dmsod₂o, 300 MHz): δ [ppm] = 10.86 (brs, 2 H); 7.09 (s, 1 H); 4.87 (brs, 1 H); 4.27 (s, 1 H); 0.79 (s, 9 H).

¹³C-NMR (dmsod₂o, 75 MHz): δ [ppm] = 164.1; 151.0; 139.0; 114.4; 70.9; 35.9; 25.5.

IR (KBr): ν [cm⁻¹] = 3434 (w); 3102 (w); 3080 (w); 2984 (w); 2984 (w); 2952 (m); 2906 (m); 2872 (w); 1702 (s); 1648 (vs); 1500 (w); 1482 (m); 1464 (m); 1446 (m); 1424 (m); 1392 (w); 1376 (w); 1362 (m); 1322 (w); 1206 (m); 1188 (m); 1136 (w); 1050 (m); 1012 (m); 954 (w); 906 (w); 864 (s); 826 (m); 780 (m); 742 (m); 650 (s).

MS (EI): (m/z) (%) = 183 ([M-CH₃]⁺; 1); 165 (8); 142 (85); 141 (100); 137 (5); 124 (9); 113 (7); 98 (18); 70 (8); 57 (16).


Preparation 5-[hydroxy(phenyl)methyl]pyrimidine-2,4(1H,3H)-dione (59b)

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 476 mg, 2.00 mmol) and reacted with benzaldehyde (276 mg, 2.60 mmol, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and the volume was, after filtration, reduced in vacuo to ca. 30-40 mL.
giving a suspension of the white product, that was cooled and subsequently filtered. After

drying in high vacuum, the product 59b was obtained as a colorless, crystalline solid (339 mg, 
1.56 mmol, 78 %).

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\text{mp.: 272.9-274.2 °C}
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^1\text{H-NMR (dmsO-d}_6, 300 MHz): \delta [ppm] = 11.01 (\text{brs, 1 H}); 10.78 (\text{brs, 1 H}); 7.35-7.18 (m, 
6 H); 5.60 (\text{brs, 1 H}); 5.48 (s, 1 H).
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^13\text{C-NMR (dmsO-d}_6, 75 MHz): \delta [ppm] = 163.2; 151.1; 143.9; 137.7; 127.9; 126.9; 126.5; 
116.2; 67.3.
\]

\[
\text{IR (KBr): } \nu [\text{cm}^{-1}] = 3562 (\text{m}); 3472 (\text{w}); 3204 (\text{m}); 3082 (\text{m}); 2876 (\text{m}); 2814 
(\text{m}); 1712 (s); 1698 (\text{s}); 1658 (\text{vs}); 1488 (\text{m}); 1468 (\text{m}); 1466 (\text{m}); 1426 (\text{m}); 1374 (\text{w}); 
1364 (\text{w}); 1338 (\text{w}); 1232 (s); 1220 (m); 1190 (m); 1142 (m); 1130 (w); 1078 (w); 1042 (m); 1024 
(m); 874 (m); 826 (m); 808 (m); 762 (s); 746 (s); 696 (vs); 662 (s); 624 (w); 606 (w).
\]

\[
\text{MS (EI): (m/z) (%): 218 (M}^+; 49); 200 (100); 171 (23); 141 (13); 139 (17); 130 (24); 129 
(37); 112 (15); 105 (10); 102 (37); 98 (8); 78 (8).
\]

\[
\text{HR-MS (C}_{11}\text{H}_{11}\text{NO}: \text{calculated: 218.0691 found: 218.0683.}
\]

Preparation 5-[cyclohexyl(hydroxy)methyl]pyrimidine-2,4(1\text{H},3\text{H})-dione (59c)

\[
\begin{align*}
\text{HN} & \text{N} \\
\text{OH} & \text{O} \\
\text{O} & \text{N} \\
\end{align*}
\]

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 
476 mg, 2.00 mmol) and reacted at -20 °C with cyclohexane carbaldehyde (291 mg, 
2.60 mmol, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a 
separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the 
mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with 
EtOAc, the combined organic layers were dried (Na\text{2SO}_4) and the volume was, after filtration, 
reduced in \text{vacuo} to ca. 30-40 mL giving a suspension of the white product, that was cooled 
and subsequently filtered. After drying in high vacuum, the product 59c was obtained as a 
colorless, crystalline solid (314 mg, 1.40 mmol, 70 %).

\[
\text{mp.: 270.1-273.0 °C}
\]

\[
^1\text{H-NMR (dmsO-d}_6, 300 MHz): \delta [ppm] = 10.94 (\text{brs, 1H}); 10.67 (\text{brs, 1H}); 7.11 (s, 1 H); 
4.72 (d, \text{J} = 5.1 \text{ Hz, 1 H}); 4.18 (t, \text{J} = 5.1 \text{ Hz, 1H}); 1.35-1.70 (m, 6 H); 0.80-1.25 (m, 5 H).
\]

\[
^13\text{C-NMR (dmsO-d}_6, 75 MHz): \delta [ppm] = 163.6; 151.1; 137.8; 115.0; 69.3; 42.3; 29.3; 26.9; 
26.2; 25.9; 25.7.
\]

\[
\text{IR (KBr): } \nu [\text{cm}^{-1}] = 3444 (w); 3158 (m); 3084 (m); 3022 (m); 2920 (s); 2866 (m); 2850 (m); 
2806 (w); 1712 (s); 1650 (vs); 1504 (m); 1466 (m); 1450 (s); 1422 (s); 1380 (m); 1368 (m); 
1344 (w); 1306 (w); 1230 (s); 1210 (m); 1174 (w); 1134 (w); 1092 (w); 1066 (w); 1026 (m); 
956 (w); 890 (m); 850 (s); 814 (m); 786 (s); 774 (s); 756 (m); 680 (s); 620 (w).
\]

\[
\text{MS (EI): (m/z) (%): 218 (M}^+; 49); 200 (100); 171 (23); 141 (13); 139 (17); 130 (24); 129 
(37); 112 (15); 105 (10); 102 (37); 98 (8); 78 (8).
\]

\[
\text{HR-MS (C}_{11}\text{H}_{14}\text{N}_2\text{O}_2; [M-H}_2\text{O}]^+: \text{calculated: 206.1055 found: 206.1044.}
\]

Preparation 5-[hydroxy(2-thienyl)methyl]pyrimidine-2,4(1\text{H},3\text{H})-dione (59d)
According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 476 mg, 2.00 mmol) and reacted at –20 °C with thiophene-2-carbaldehyde (291 mg, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated. After recrystallization from MeOH and drying in high vacuum, the product (59d) was obtained as a pale beige, crystalline solid (246 mg, 1.10 mmol, 55%).

**mp.: 208.6-210.0 °C**

**¹H-NMR (dmsod₂₆, 300 MHz):** δ [ppm] = 5.72 (d, J = 5.1 Hz, 1 H); 5.95 (d, J = 5.1 Hz, 1 H); 6.92 (2 × s, 2 H; overlaid signals); 7.28 (brs, 1H); 7.36 (t, J = 3.1 Hz, 1H); 10.79 (brs, 1H); 11.12 (brs, 1H).

**¹³C-NMR (dmsod₂₆, 75 MHz):** δ [ppm] = 63.4; 115.9; 124.0; 124.5; 126.5; 137.9; 148.5; 151.0; 163.1.

**IR (KBr):** ν [cm⁻¹] = 3472 (m); 3098 (m); 2992 (m); 2954 (m); 2824 (m); 1692 (s); 1652 (vs); 1506 (m); 1452 (m); 1426 (s); 1394 (m); 1360 (m); 1298 (w); 1228 (s); 1210 (s); 1164 (w); 1140 (m); 1018 (m); 1006 (m); 954 (w); 890 (m); 856 (m); 842 (m); 826 (m); 778 (s); 742 (m); 686 (s); 656 (s); 626 (m); 612 (w).

**MS (EI):** (m/z) (%) = 224 (M⁺; 54); 208 (72); 206 (100); 178 (17); 140 (32); 137 (19); 136 (61); 135 (51); 112 (47); 108 (38); 85 (42); 45 (22).

**HR-MS (C₉H₈N₂O₂S):** calculated: 224.0256; found: 224.0235.

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Preparation of 5-(trimethylsilyl)-2,4(1H,3H)-pyrimidinedione (59e)

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 476 mg, 2.00 mmol) and reacted at chlorotrimethylsilane (719 mg, 6.60 mmol, 3.30 equiv). Afterwards, the mixture was warmed up to rt and stirred at that temperature till TLC indicated completion of the reaction. It was quenched by addition of MeOH (2.0 mL) and transferred to a separation funnel containing a mixture of HCl (1.0 M; 20 mL) and sat. aq. NH₄Cl (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL) and EtOAc (3 × 40 mL), the combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. Recrystallization from MeOH afforded 59e as a colorless, crystalline solid (286 mg, 1.45 mmol, 72%).

**mp.: 339.3-346.6 °C (decomposition)**

**¹H-NMR (dmsod₂₆, 300 MHz):** δ [ppm] = 10.89 (brs, 2 H); 7.12 (s, 1 H); 0.13 (s, 9 H).

**¹³C-NMR (dmsod₂₆, 75 MHz):** δ [ppm] = 166.6; 151.7; 146.1; 107.0; -1.6.
IR (KBr): ν [cm\(^{-1}\)] = 3214 (m); 3088 (m); 2956 (m); 1721 (vs); 1661 (vs); 1614 (s); 1438 (m); 1348 (m); 1248 (m); 1162 (w); 1071 (m); 1012 (w); 843 (s); 785 (m); 756 (w); 697 (w); 667 (w); 614 (m); 554 (m); 473 (m).

MS (EI): (m/z) (%) = 184 (M\(^+\); 4); 169 (100); 100 (7); 83 (4); 74 (29); 43 (4).

HR-MS (C\(_7\)H\(_{12}\)SiN\(_2\)O\(_2\)): calculated: 184.0668 found: 184.0648.

**Preparation of 5-allylpyrimidine-2,4(1H,3H)-dione (59f)**

![Structure Image]

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 476 mg, 2.00 mmol) and reacted with allyl bromide (315 mg, 2.60 mmol, 1.30 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%) (the catalyst was added first). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 6-7 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na\(_2\)SO\(_4\)) and the volume was, after filtration, reduced in vacuo to ca. 30-40 mL giving a suspension of the crystalline product, that was cooled and subsequently filtered. After drying in high vacuum, the product 59f was obtained as a colorless, crystalline solid (256 mg, 1.68 mmol, 84%).

mp.: 279.5-281.3 °C (decomposition)

\(^1\)H-NMR (dmso-d\(_6\), 300 MHz): δ [ppm] = 10.99 (brs, 1 H); 10.67 (brs, 1 H); 7.14 (s, 1 H); 5.89-5.76 (m, 1 H); 5.06-4.96 (m, 2 H); 2.90 (d, \(^3\)J = 6.4 Hz, 2 H).

\(^13\)C-NMR (dmso-d\(_6\), 75 MHz): δ [ppm] = 164.1; 151.3; 138.2; 135.9; 115.9; 110.3; 29.9.

IR (KBr): ν [cm\(^{-1}\)] = 3216 (m); 3152 (m); 3074 (m); 3016 (m); 2896 (m); 2864 (m); 2826 (m); 1792 (w); 1728 (m); 1700 (m); 1660 (vs); 1484 (s); 1448 (s); 1428 (s); 1372 (m); 1338 (w); 1284 (w); 1234 (s); 1190 (s); 1130 (w); 1116 (w); 1006 (m); 996 (w); 976 (w); 952 (w); 930 (m); 918 (s); 898 (m); 864 (m); 820 (m); 796 (m); 776 (m); 758 (s); 746 (s); 656 (m); 612 (w).

MS (EI): (m/z) (%) = 152 (M\(^+\); 40); 137 (10); 109 (26); 94 (10); 80 (100); 66 (17); 54 (12); 53 (21); 52 (22); 51 (12).

HR-MS (C\(_7\)H\(_8\)N\(_2\)O\(_2\)): calculated: 152.0586 found: 152.0595.

**Preparation of 5-(2-methyl-2-propenyl)-2,4(1H,3H)-pyrimidinedione (59g)**

According to TP13, the trimagnesiated reagent 58b was prepared from 5-bromouracil (57b; 382 mg, 2.00 mmol) and reacted at –20 °C with 3-bromo-2-methyl-1-propene (743 mg, 5.50 mmol, 2.75 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%). After quenching with MeOH, the mixture was transferred to a separation funnel
containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was
adjusted to ca 6-7 (indicator paper). The aqueous layer was extracted with EtOAc, the
combined organic layers were dried (Na₂SO₄) and the volume was, after filtration, reduced in
vacuo to ca. 30-40 mL giving a suspension of the crystalline product, that was cooled and
subsequently filtered. The residue was washed with little cold CH₂Cl₂, and after drying in
high vacuum, a first batch of the product (59g) was obtained. Reducing the volume of the
mother liquor and cooling of the same did give another crop of the crystalline, colorless
product (allover 180 mg, 1.08 mmol, 54 %).

mp.: 271.3-274.0 °C

¹H-NMR (dmso-d₆, 300 MHz): δ [ppm] = 10.68 (brs, 1 H); 10.01 (brs, 1 H); 7.16 (s, 1 H);
4.71 (s, 1 H); 4.62 (s, 1 H); 1.84 (s, 2 H); 1.64 (s, 3 H).

¹³C-NMR (dmso-d₆, 75 MHz): δ [ppm] = 164.3; 151.4; 143.4; 138.9; 111.2; 109.7; 33.4;
22.2.

IR (KBr): ν [cm⁻¹] = 3204 (m); 3164 (m); 3126 (m); 3066 (m); 3026 (m); 2968 (m); 2934 (m);
2906 (m); 2868 (m); 2820 (m); 2724 (w); 1728 (m); 1660 (vs); 1650 (vs); 1488 (m);
1448 (s); 1424 (s); 1374 (m); 1342 (m); 1244 (s); 1228 (m); 1206 (s); 1138 (w); 1014 (w);
950 (w); 918 (m); 902 (s); 834 (w); 804 (w); 765 (w); 742 (w); 640 (w).

MS (EI): (m/z) (%) = 166 (M⁺, 100); 151 (28); 123 (82); 108 (24); 94 (52); 81 (31); 80 (68);
55 (13); 41 (15).

HR-MS (C₈H₁₀N₂O₂): calculated: 166.0742  found: 166.0734.

Preparation of 5-(phenylsulfanyl)-2,4(1H,3H)-pyrimidinedione (59h)

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a;
476 mg, 2.00 mmol) and reacted at –20 °C with S-phenyl benzenesulfonothioate (650 mg,
2.60 mmol, 1.30 equiv; in 4.0 mL THF). After quenching with MeOH, the mixture was
transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl,
the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was
extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated in
vacuo. The crude product was suspended in little heptane, some drops of EtOAc were added
and the suspension was sonicated for 30 min. After filtration and drying in high vacuum, the
product 59h was obtained as an off white solid (337 mg, 1.53 mmol, 77 %; purity by ¹H-
NMR: 92 %, impurity: 8 % 5-iodouracil).

mp.: 273.0-274.2 °C

¹H-NMR (dmso-d₆, 400 MHz): δ [ppm] = 11.37 (brs, 2H); 7.91 (s, 1 H); 7.30-7.12 (m, 5 H).
¹³C-NMR (dmso-d₆, 100 MHz): δ [ppm] = 162.2; 151.2; 148.9; 136.7; 128.9; 126.3; 125.5;
101.9.

IR (KBr): ν [cm⁻¹] = 3164 (m); 3058 (m); 2876 (m); 1744 (vs); 1679 (vs); 1610 (m);
1480 (m); 1438 (m); 1423 (m); 1326 (w); 1220 (m); 1175 (w); 1075 (w); 1025 (w) 998 (w);
815 (w); 786 (w); 760 (m); 733 (m); 686 (m); 615 (w); 551 (w).

MS (EI): (m/z) (%) = 220 (M⁺; 100); 177 (4); 149 (36); 121 (29); 117 (7); 105 (5); 77 (10);
51 (7).
Preparation of 5-(methylthio)pyrimidine-2,4(1H,3H)-dione (59i)

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 476 mg, 2.00 mmol) and reacted at -20 °C with S-methyl methanesulfonothioate (328 mg, 2.60 mmol, 1.30 equiv). Afterwards, the mixture was warmed up to rt and stirred at that temperature till TLC indicated completion of the reaction. After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca. 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated. Recrystallization from MeOH afforded the product 59i as a colorless, crystalline solid which was dried in high vacuum (202 mg, 1.28 mmol, 64 %).

mp.: 303.7-304.9 °C

¹H-NMR (dmsø-d₆, 400 MHz): δ [ppm] = 11.26 (s, 1H); 11.03 (s, 1 H); 7.41 (s, 1 H); 2.20 (s, 3 H).

¹³C-NMR (dmsø-d₆, 100 MHz): δ [ppm] = 163.1; 151.7; 141.4; 108.4; 16.5.

IR (KBr): ν [cm⁻¹] = 3447 (w); 3204 (m); 3014 (s); 2819 (m); 1728 (vs); 1664 (vs); 1612 (s); 1474 (m); 1427 (s); 1353 (m); 1316 (w); 1244 (m); 1158 (w); 1090 (m); 1018 (w); 985 (w); 964 (w); 899 (w); 868 (m); 810 (m); 778 (m); 758 (m); 677 (s); 624 (w); 551 (m).

MS (EI): (m/z) (%) = 158 (M⁺; 100); 125 (42); 115 (15); 88 (12); 72 (18); 69 (24); 60 (9); 45 (23).

HR-MS (C₅H₅N₂O₂S): calculated: 158.0150 found: 158.0153.

Preparation of ethyl 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (59j)

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 476 mg, 2.00 mmol) and reacted at -20 °C with ethyl chloroformate (283 mg, 2.60 mmol, 1.30 equiv). Afterwards, the mixture was warmed up to rt and stirred at that temperature till TLC indicated completion of the reaction. After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca. 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated. Column chromatography (silica; CH₂Cl₂:MeOH, 19:1) afforded the product 59j as a colorless, crystalline solid which was dried in high vacuum (74 mg, 0.40 mmol, 20 %).
mp.: 132.3-234.8 °C

\[ ^1H-NMR \text{ (dmso-}d_6, 400 \text{ MHz)}: \delta \text{ [ppm] } = 11.54 \text{ (brs, 1 H); 11.26 \text{ (brs, 1 H); 8.09 \text{ (s, 1 H); }} 4.14 \text{ (q, } ^3J = 7.0 \text{ Hz, 2 H); 1.21 \text{ (t, } ^3J = 7.0 \text{ Hz, 3 H).} \]

\[ ^{13}C-NMR \text{ (dmso-}d_6, 100 \text{ MHz)}: \delta \text{ [ppm] } = 162.5; 160.0; 150.6; 149.3; 103.1; 59.9; 14.13. \]

IR (KBr): \( \nu \text{ [cm}^{-1}] = 3306 \text{ (w); 3078 \text{ (w); 3034 \text{ (m); 2984 \text{ (m); 2848 \text{ (w); 1736 \text{ (s); 1694 \text{ (vs); 1678 \text{ (vs); 1620 \text{ (s); 1480 \text{ (s); 1440 \text{ (m); 1368 \text{ (m); 1346 \text{ (m); 1330 \text{ (m); 1304 \text{ (m); 1282 \text{ (s); 1216 \text{ (s); 1164 \text{ (s); 1154 \text{ (s); 1090 \text{ (s); 1010 \text{ (m); 988 \text{ (m); 862 \text{ (s); 846 \text{ (s); 788 \text{ (s); 756 \text{ (s); 738 \text{ (s); 718 \text{ (m); 638 \text{ (s); 610 \text{ (m); 570 \text{ (m); 554 \text{ (s).} \]

MS (EI): \( m/z \) (%) = 184 (M+; 29); 157 (23); 156 (12); 139 (100); 112 (71); 96 (16); 85 (7); 69 (17); 53 (3).

HR-MS (C7H8N2O4): calculated: 184.0484; found: 184.0486.

Preparation of 5-(1-benzyl-1-hydroxy-2-phenylethyl)pyrimidine-2,4(1H,3H)-dione (59k):

According to TP12, the trimagnesiated reagent 58a was prepared from 5-iodouracil (57a; 476 mg, 2.00 mmol). Concurrently, diphenyl acetone (546 mg, 2.60 mmol, 1.30 equiv) and CeCl3·2LiCl (0.33 M in THF; 6.06 mL, 2.00 mmol, 1.00 equiv) were mixed under argon and stirred for 30 min at rt. This mixture was then added at 0 °C to the above prepared Grignard reagent and stirred for 1 h at this temperature. Then, the mixture was warmed up to rt and stirred at that temperature till TLC indicated completion of the reaction. After quenching with MeOH, the mixture was transferred to a separation funnel containing diluted HCl (1.0 M; 40 mL). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na2SO4) and evaporated. Column chromatography (silica; CH2Cl2:MeOH, 19:1) afforded the product 59k as a colorless, crystalline solid which was dried in high vacuum (89 mg, 0.28 mmol, 14 %).

mp.: 292.6-294.5 °C

\[ ^1H-NMR \text{ (dmso-}d_6, 400 \text{ MHz): } \delta \text{ [ppm] } = 11.0 \text{ (s, 1 H); 10.28 (d, } ^3J = 5.8 \text{ Hz, 1 H); 7.22-7.05 \text{ (m, 10 H); 6.49 (d, } ^3J = 5.8 \text{ Hz, 1 H); 5.01 (s, 1 H); 3.45 (d, } ^2J = 13.3 \text{ Hz, 2 H); 2.90 (d, } ^2J = 13.3 \text{ Hz, 2 H).} \]

\[ ^{13}C-NMR \text{ (dmso-}d_6, 100 \text{ MHz): } \delta \text{ [ppm] } = 151.7; 139.4; 138.8; 130.8; 126.4; 114.9; 75.2; 45.8. \]

IR (KBr): \( \nu \text{ [cm}^{-1}] = 3566 \text{ (w); 3218 \text{ (w); 3096 \text{ (m); 3022 \text{ (m); 2902 \text{ (w); 2828 \text{ (w); 1704 \text{ (s); 1666 \text{ (vs); 1602 \text{ (m); 1580 \text{ (m); 1492 \text{ (m); 1450 \text{ (m); 1426 \text{ (m); 1368 \text{ (w); 1350 \text{ (w); 1228 \text{ (s); 1182 \text{ (m); 1156 \text{ (w); 1138 \text{ (m); 1080 \text{ (m); 1056 \text{ (w); 1034 \text{ (w); 1018 \text{ (w); 980 \text{ (w); 962 \text{ (w); 868 \text{ (m); 830 \text{ (m); 790 \text{ (m); 762 \text{ (m); 750 \text{ (s); 694 \text{ (vs); 636 \text{ (s); 602 \text{ (m); 558 \text{ (m).}} \]

MS (EI): \( m/z \) (%) = 304 (8); 231 (100); 213 (32); 139 (7); 115 (5); 91 (15); 65 (3).

HR-MS (C19H18N2O3): calculated: 322.1317; found: 322.1322.

Preparation of 6-allylpyrimidine-2,4(1H,3H)-dione (59l):
According to TP14, the trimagnesiated reagent 58c was prepared from 6-iodouracil (57c; 476 mg, 2.00 mmol) and reacted with allyl bromide (315 mg, 2.60 mmol, 1.30 equiv) in the presence of CuCN·2LiCl (1.00 m in THF; 0.02 mL, 1.00 mol%). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 m HCl, the pH of the mixture was adjusted to ca 6-7 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated. Column chromatography through a short column (l = ca. 6 cm, Ø = ca. 3 cm; silica; CH₂Cl₂:MeOH; 19:1) afforded the desired product (59l) as a colorless, crystalline solid (195 mg, 1.28 mmol, 64 %).

**mp.: 188.2-190.1 °C**

**¹H-NMR (dmsø-d₆, 400 MHz):** δ [ppm] = 10.90 (brs, 1 H); 10.83 (brs, 1 H); 5.90-5.80 (m, 1 H); 5.27 (s, 1 H); 5.22-5.13 (m, 2 H); 3.05 (d, J = 6.8 Hz, 2 H).

**¹³C-NMR (dmsø-d₆, 100 MHz):** δ [ppm] = 164.12; 154.6; 151.6; 132.4; 118.8; 98.1; 35.8.

**IR (KBr):** ν [cm⁻¹] = 2982 (m); 2932 (m); 2854 (m); 2810 (m); 1712 (s); 1640 (vs); 1530 (m); 1504 (s); 1450 (s); 1422 (vs); 1372 (s); 1322 (m); 1282 (m); 1238 (m); 1168 (m); 1046 (w); 1020 (m); 992 (m); 970 (m); 942 (s); 924 (m); 904 (m); 850 (s); 816 (vs); 728 (m); 616 (s).

**MS (EI):** (m/z) (%) = 152 (M⁺; 100); 124 (36); 109 (34); 81 (42); 80 (46); 68 (48); 67 (35); 53 (8); 41 (10).

**HR-MS (C₇H₈N₂O₂S):** calculated: 152.0586 found: 152.0581.

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**Preparation of 6-(1-hydroxy-2,2-dimethylpropyl)pyrimidine-2,4(1H,3H)-dione (59m)**

According to TP14, the trimagnesiated reagent 58c was prepared from 6-iodouracil (57c; 476 mg, 2.00 mmol) and reacted with t-BuCHO (224 mg, 2.60 mmol, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 m HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the completeness of the reaction was checked by TLC of the fractions. The combined organic layers were dried (Na₂SO₄) and evaporated. Column chromatography through a short column (l = ca. 6 cm, Ø = ca. 3 cm; silica; CH₂Cl₂:MeOH; 19:1) afforded the desired product (59m) as a colorless, crystalline solid (253 mg, 1.28 mmol, 64 %).

**mp.: 188.2-190.1 °C**

**¹H-NMR (dmsø-d₆, 400 MHz):** δ [ppm] = 10.94 (s, 1 H); 10.48 (s, 1 H); 5.57 (d, J = 4.6 Hz, 1 H); 5.33 (s, 1 H); 3.90 (d, J = 4.6 Hz, 1 H); 0.86 (s, 9 H).

**¹³C-NMR (dmsø-d₆, 100 MHz):** δ [ppm] = 164.0; 158.0; 151.2; 97.9; 75.6; 35.1; 25.7.
IR (KBr): $\nu [\text{cm}^{-1}] = 3154 (\text{m}); 2976 (\text{m}); 2964 (\text{m}); 2954 (\text{m}); 2904 (\text{m}); 2870 (\text{m}); 2824 (\text{m}); 1694 (\text{vs}); 1672 (\text{s}); 1642 (\text{vs}); 1614 (\text{s}); 1496 (\text{s}); 1480 (\text{m}); 1464 (\text{m}); 1422 (\text{vs}); 1386 (\text{m}); 1366 (\text{m}); 1304 (\text{m}); 1234 (\text{m}); 1158 (\text{w}); 1088 (\text{s}); 1056 (\text{m}); 1016 (\text{m}); 966 (\text{m}); 876 (\text{m}); 840 (\text{m}); 828 (\text{s}); 792 (\text{m}); 766 (\text{s}); 748 (\text{m}); 714 (\text{w}); 620 (\text{m}); 604 (\text{w}).$

MS (EI): (m/z) (%) = 198 (M$^+$; 8); 142 (100); 125 (4); 114 (7); 98 (4); 71 (9); 68 (13); 57 (64).

HR-MS ($C_{9}H_{15}N_{2}O_{3}$; [M+H$^+$]): calculated: 199.1083 found: 199.1075.

**Synthesis of 6-(phenylthio)-9H-purine (62)**

6-iodopurine (60; 246 mg, 1.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Applying vigorous stirring, the substrate was dried for 15 min in high vacuum, to exclude the presence of water in the hygroscopic substrate. Then, a solution of LiCl in THF (0.50 M; 2.00 mL; 1.00 equiv) and dry THF (2.00 mL) was added and the resulting suspension was cooled to -30 °C. Then, MeMgCl (0.33 mL, 3.00 M in THF, 1.00 equiv) was added dropwise. Bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the resulting, clear yellow solution was stirred at -20 °C for further 20 min. Afterwards, $i$-PrMgCl·LiCl (0.80 mL, 1.32 M in THF, 1.05 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. After one hour, an orange slurry had formed and the TLC of the mixture did show only traces of the starting material and traces of an unidentified byproduct. The mixture was cooled to –30 °C again and $S$-phenyl benzenesulfonothioate (275 mg, 1.10 mmol, 1.10 equiv; in 2.0 mL THF) was added at this temperature, then the mixture was allowed to rt. The reaction was monitored using TLC. After the completion of the reaction, it was quenched by addition of sat. aq. NH$_4$Cl (2.0 mL, not more!), which resulted in the precipitation of the contained salts. The slurry was, directly in the Schlenk-tube, extracted with EtOAc until TLC of the organic layer did not show any content under UV (10 times, 10 mL each). The combined organic layers were dried and evaporated in vacuo. Column chromatography (silica; CH$_2$Cl$_2$:MeOH, 19:1) afforded 62 as a yellow, crystalline solid (125 mg, 0.55 mmol, 55 %).

**mp.:** 231.5-233.2 °C

$^1$H-NMR (dmoso-d$_6$, 400 MHz): $\delta$ [ppm] = 13.59 (brs, 1 H); 8.50 (2 × s, 2 H); 7.61 (m, 2 H); 7.49 (m, 3 H).

$^{13}$C-NMR (dmoso-d$_6$, 100 MHz): $\delta$ [ppm] = 158.0; 151.6; 149.7; 143.5; 135.5; 129.7; 129.5; 129.4; 127.0.

IR (KBr): $\nu [\text{cm}^{-1}] = 3122 (\text{w}); 3076 (\text{w}); 3064 (\text{w}); 2960 (\text{m}); 2816 (\text{m}); 2800 (\text{m}); 2696 (\text{w}); 2658 (\text{w}); 2522 (\text{w}); 1590 (\text{m}); 1560 (\text{vs}); 1472 (\text{m}); 1444 (\text{w}); 1434 (\text{m}); 1418 (\text{m}); 1384 (\text{m}); 1320 (\text{m}); 1278 (\text{w}); 1234 (\text{vs}); 1218 (\text{m}); 1176 (\text{w}); 1166 (\text{w}); 1150 (\text{w}); 1070 (\text{w}); 1024 (\text{w}); 994 (\text{s}); 948 (\text{w}); 920 (\text{s}); 888 (\text{m}); 856 (\text{vs}); 838 (\text{s}); 792 (\text{m}); 750 (\text{s}); 704 (\text{m}); 686 (\text{s}); 670 (\text{m}); 640 (\text{vs}); 632 (\text{s}); 608 (\text{s}).

**MS (EI):** (m/z) (%) = 227 ([M-H$^+$]; 100); 207 (23); 200 (4); 146 (4), 109 (5); 77 (5); 65 (4); 44 (4).
HR-MS (C_{11} H_{7} N_{4}S; [M-H]^+): calculated: 227.0384  
found: 227.0391.
6.2. Synthesis of the Precursors for \textit{HEPT} (69) and \textit{Emivirine} (70)

**Synthesis of 6-chloro-5-methylpyrimidine-2,4(1H,3H)-dione (65a)**

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

5-Methyl-barbituric acid\(^{102}\) (64a; 7.10 g, 50 mmol) was placed under N\(_2\) in a Schlenk-flask equipped with a magnetic stirring bar, a reflux condenser and a bubbler on top. POCl\(_3\) (45.0 mL, 75.2 g, 490 mmol, 9.80 equiv) was carefully added, the substrate suspended and then, H\(_3\)PO\(_4\) (85 %; 3.50 mL) was carefully added. The resulting mixture was then refluxed (100 \(^\circ\)C) for 45 min. \textbf{Note: Longer reaction times have to be strictly avoided}, as in this case big amounts of 2,4,6-trichloro-5-methylpyrimidine are formed as side product and, by that way, the yield of the desired product is drastically diminished (3h \(\rightarrow\) 10 %!). Then, the mixture was shortly left for cooling and was poured portionwise on ice. The resulting slurry was than subjected for 30 min to sonication which led to the formation of a fine, white solid that was subsequently filtered and washed with little water. Cooling of the mother liquor afforded another 2-3 crops of the crude product. As TLC of the crops showed, the very first fraction usually only contains the byproduct, whereas the later ones contain the already nearly clean product. The collected product ‘fractions’ were washed with diethylether (400 mL; to remove 2,4,6-trichloro-5-methylpyrimidine). After recrystallization from MeOH and drying in high vacuum, the desired product 65a was obtained as a crystalline powder (5.23 g, 32.7 mmol, 65 %). From the ether eluate of the washing, the solvent was removed and 2,4,6-trichloro-5-methylpyrimidine was received as a colorless, crystalline solid (1.85 g, 9.40 mmol, 19 %, identified by \(^1\)H-NMR and GC-MS measurements.). (So, the total recovery is 84 %)

\begin{align*}
\text{mp.:} & \quad 273.8-275.0 \, ^\circ\text{C (decomposition)} \\
\text{\(^1\)H-NMR (dmsso-d\(_6\), 400 MHz):} & \quad \delta [\text{ppm}] = 11.77 (\text{brs, 1 H}); 11.26 (\text{s, 1H}); 1.78 (\text{s, 3 H}). \\
\text{\(^13\)C-NMR (dmsso-d\(_6\), 100 MHz):} & \quad \delta [\text{ppm}] = 163.1; 149.6; 140.6; 105.9; 10.7. \\
\text{IR (KBr):} & \quad \nu [\text{cm}^{-1}] = 3072 (\text{m}); 2990 (\text{m}); 2912 (\text{m}); 2820 (\text{m}); 2768 (\text{m}); 1708 (\text{s}); 1646 (\text{vs}); 1624 (\text{vs}); 1510 (\text{s}); 1482 (\text{s}); 1428 (\text{vs}); 1382 (\text{s}); 1286 (\text{s}); 1226 (\text{m}); 1210 (\text{m}); 1184 (\text{m}); 1062 (\text{s}); 1010 (\text{m}); 872 (\text{s}); 778 (\text{s}); 754 (\text{vs}); 728 (\text{s}); 610 (\text{m}). \\
\text{MS (EI):} & \quad (m/z) (%) = 162 (M^+, 37\text{Cl}, 29); 160 (M^+, 35\text{Cl}, 54); 117 (17); 82 (100); 52 (26); 44 (18). \\
\text{HR-MS (C\(_5\)H\(_2\)ClN\(_2\)O\(_2\))}: & \quad \text{calculated: 160.0040} \quad \text{found: 160.0026.}
\end{align*}

\(^{102}\) Also, the dihydrate, which primarily is obtained by the reaction of urea and diethyl-2-methylmalonate as described in ref., can be used directly. The addition of H\(_3\)PO\(_4\) is then unnecessary. However, the addition of POCl\(_3\) in this case should be conducted very carefully.
Synthesis of 6-chloro-5-isopropylpyrimidine-2,4(1H,3H)-dione (65b)

5-Isopropyl-barbituric acid (64b; 4.25 g, 25.0 mmol) was placed under N₂ in a Schlenk-flask equipped with a magnetic stirring bar, a reflux condenser and a bubbler on top. POCl₃ (11.3 mL, 18.9 g, 124 mmol, 4.96 equiv) was carefully added, the substrate suspended and then, carefully H₃PO₄ (85 %; 1.75 mL,) was added. The resulting mixture was then refluxed (100 °C) for 3 h. Then, the mixture was shortly left for cooling and was poured portionwise on ice. The resulting slurry was then subjected for 30 min to sonication which led to the formation of a fine, white solid that was subsequently filtered and washed with water (20 mL). Recrystallization from EtOH gave the desired product 65b as a colorless plates (3.00 g, 15.9 mmol, 63 %).

mp.: 242.3-245.2 °C

¹H-NMR (dmso-d₆, 400 MHz): δ [ppm] = 11.69 (s, 1 H); 11.19 (s, 1 H); 3.00 (sept, 3J = 7.1 Hz, 1 H); 1.17 (d, 3J = 7.1 Hz, 6 H).

¹³C-NMR (dmso-d₆, 100 MHz): δ [ppm] = 162.2; 149.5; 140.1; 113.9; 27.1; 19.7.

IR (KBr): ν [cm⁻¹] = 3020 (m); 2978 (m); 2966 (m); 2928 (m); 2900 (s); 2874 (s); 2846 (s); 2770 (m); 1722 (s); 1702 (s); 1670 (vs); 1650 (vs); 1606 (vs); 1494 (s); 1470 (m); 1446 (s); 1424 (vs); 1380 (s); 1364 (m); 1352 (m); 1306 (w); 1278 (s); 1224 (m); 1196 (w); 1184 (m); 1154 (m); 1110 (w); 1054 (s); 1036 (s); 910 (s); 852 (m); 788 (s); 758 (vs); 728 (vs); 670 (m).

MS (EI): (m/z) (%) = 190 (M⁺; 37Cl; 14); 188 (M⁺; 35Cl; 38); 175 (35); 173 (100); 159 (19); 153 (18); 132 (24); 130 (74); 115 (7); 94 (22); 68 (9); 66 (9).

HR-MS (C₇H₇ClN₂O₂): calculated: 188.0358 found: 188.0362.

General Information on the iodinations of 65a and 65b: As mentioned in the discussion, we found these reactions to be strongly dependent on the quality of the hydriodic acid used. Even though the reactions proceed always in a spot-to-spot manner (as seen by TLC), iodine and other impurities contained in the acid decrease the quality of the crude product dramatically. Thus, the purification becomes more difficult, resulting in lower yields. The hydriodic acid employed should be therefore absolutely clean to receive optimum results. The optical appearance of the reagent should be that of a light yellow, clear solution, smoking at the air. Purification of contaminated solutions can be achieved, for example, by stirring the respective solution over red phosphorus until the upstanding solution shows the desired colour and storing the resulting mixture overnight in the fridge, to allow the phosphorus to settle down.

Synthesis of 6-iodo-5-methylpyrimidine-2,4(1H,3H)-dione (63a)
6-Chloro-5-methylpyrimidine-2,4(1H,3H)-dione (65a; 1.44 g, 9.00 mmol), NaI (6.75 g, 45.0 mmol, 5.00 equiv) and HI (54 %, 23.0 mL) are placed in a tube equipped with a magnetic stirring bar and a Teflon stopper. The resulting mixture was stirred for 1 d at rt. Then, the suspension was filtered employing reduced pressure, washed with EtOAc and water until a pale yellow to white solid was obtained (crude yield 2.00 g, 88 %). Recrystallization from EtOAc:MeOH (ca. 9:1) afforded 63a as off white solid (1.61 g, 6.39 mmol, 71 %).

**mp.**: 250.0 °C (decomposition)

$^1$H-NMR (dmsod$_6$, 400 MHz): δ [ppm] = 11.30 (s, 1 H); 11.19 (s, 1 H); 1.89 (s, 1 H).

$^{13}$C-NMR (dmsod$_6$, 100 MHz): δ [ppm] = 160.9; 150.5; 114.2; 110.9; 17.8.

IR (KBr): ν [cm$^{-1}$] = 3148 (w); 3006 (m); 2810 (m); 1702 (s); 1658 (s); 1634 (vs); 1598 (s); 1494 (m); 1470 (m); 1426 (s); 1378 (s); 1274 (m); 1212 (m); 1200 (m); 1180 (m); 1038 (s); 986 (m); 856 (s); 840 (s); 760 (s); 750 (vs); 710 (s); 646 (m); 632 (m).

MS (EI): (m/z) (%) = 252 (M$^+$; 100); 207 (6); 127 (10); 82 (47); 52 (15); 44 (40).

HR-MS (C$_{5}$H$_{13}$INO): calculated: 251.9396  found: 251.9378.

**Synthesis of 6-iodo-5-isopropylpyrimidine-2,4(1H,3H)-dione (63b)**

![Image of 6-iodo-5-isopropylpyrimidine-2,4(1H,3H)-dione (63b)]

6-Chloro-5-isopropylpyrimidine-2,4(1H,3H)-dione (65b; 3.12 g, 16.5 mmol), NaI (12.4 mg, 82.5 mmol, 5.00 equiv) and HI (54 %, 41.3 mL) are placed in a tube equipped with a magnetic stirring bar and a Teflon stopper. The resulting mixture was stirred for 3 d at rt. Then, the suspension was filtered employing reduced pressure, washed with water and CH$_2$Cl$_2$ until a white solid was obtained (crude yield 3.83 g, 83 %). It was dissolved in EtOAc, dried (Na$_2$SO$_4$) and evaporated in vacuo. Recrystallization from heptane:EtOAc (ca. 2:3) afforded 63a as a colorless, crystalline solid (3.50 g, 12.5 mmol, 76 %)

**mp.**: 251.3-255.2 °C

$^1$H-NMR (dmsod$_6$, 400 MHz): δ [ppm] = 11.69 (s, 1 H); 11.19 (s, 1 H); 2.83 (sept, $^3$J = 7.0 Hz, 1 H); 1.15 (d, $^3$J = 7.0 Hz, 6 H).

$^{13}$C-NMR (dmsod$_6$, 100 MHz): δ [ppm] = 159.3; 150.3; 121.5; 110.9; 35.7; 19.8.

IR (KBr): ν [cm$^{-1}$] = 3110 (m); 2996 (m); 2976 (m); 2956 (m); 2922 (m); 2844 (m); 1720 (s); 1666 (s); 1648 (vs); 1582 (s); 1484 (m); 1466 (m); 1446 (s); 1418 (vs); 1376 (m); 1358 (m); 1348 (m); 1302 (w); 1266 (m); 1220 (m); 1178 (m); 1148 (m); 1108 (w); 1044 (s); 1024 (s); 892 (m), 866 (m); 840.00 (s); 784 (m); 752 (s); 722 (s); 652 (m).

MS (EI): (m/z) (%) = 252 (M$^+$; 100); 265 (100); 251 (16); 222 (27); 153 (21); 110 (10); 94 (24); 68 (6); 52 (4).

HR-MS (C$_{7}$H$_{15}$IO$_2$N$_2$): calculated: 279.9709  found: 279.9700.
Synthesis of 5-methyl-6-(phenylthio)pyrimidine-2,4(1H,3H)-dione (67)

The Grignard reagent 66a was synthesized according to TP15 from 6-iodo-5-methylpyrimidine-2,4(1H,3H)-dione (63a; 504 mg, 2.00 mmol). Then, S-phenyl benzenesulfonothioate (700 mg, 2.80 mmol, 1.40 equiv) in THF (4.0 mL) was added dropwise and the resulting mixture was warmed up to rt. After 1 h, TLC monitoring showed nearly complete consumption of the Grignard reagent (Note: Longer reaction times should be avoided, as the product obviously decomposes by time in this mixture at rt). MeOH (2.0 mL) was added and the mixture was transferred to a separation funnel containing water (30 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 6-7 (indicator paper). The aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. Column chromatography (silica; CH₂Cl₂:MeOH, 19:1) afforded 67 as a colorless, crystalline solid (187 mg, 0.80 mmol, 40 %)

mp.: 244.6-245.8 °C

1H-NMR (dmsø-d₆, 400 MHz): δ [ppm] = 11.23 (s, 1 H); 10.92 (s, 1 H); 7.41-7.32 (m, 5 H); 1.89 (s, 3 H);

13C-NMR (dmsø-d₆, 100 MHz): δ [ppm] = 164.3; 151.2; 143.5; 132.1; 130.4; 130.3; 128.3; 113.8; 12.7.

IR (KBr): ν [cm⁻¹] = 3204 (m); 1700 (s); 1652 (s); 1634 (s); 1590 (s); 1574 (s); 1470 (s); 1440 (s); 1418 (s); 1386 (s); 1376 (s); 1328 (m); 1304 (m); 1280 (m); 1202 (m); 1174 (m); 1156 (m); 1066 (m); 1044 (s); 1026 (m); 1004 (m); 980 (m); 886 (m); 842 (m); 816 (s); 768 (m); 754 (m); 740 (vs); 706 (s); 684 (vs); 644 (s); 614 (m).

MS (EI): (m/z) (%) = 234 (M⁺; 100); 207 (10); 201 (12); 156 (34); 110 (28); 109 (14); 82 (35); 44 (16).

HR-MS (C₁₁H₁₀N₂O₂S): calculated: 234.0463 found: 234.0454.
Synthesis of 6-benzyl-5-isopropylpyrimidine-2,4(1H,3H)-dione (68)

The Grignard reagent 66b was synthesized according to TP15 from 6-iodo-5-isopropylpyrimidine-2,4(1H,3H)-dione (63b; 560 mg, 2.00 mmol). Then, Cu-2LiCl\textsuperscript{103} (0.75 M in THF; 3.47 mL, 2.60 mmol, 1.30 equiv) was slowly added and the resulting mixture was warmed up to rt. After 0.5 h, the mixture was cooled again to -30 °C, then benzyl bromide (479 mg, 2.80 mmol, 1.40 equiv) was added slowly and after 20 min at -30 °C, the solution was allowed to warm up to rt. After 3 h, TLC monitoring showed nearly complete consumption of the Grignard reagent. MeOH (2.0 mL) was added and the mixture was transferred to a separation funnel containing water (20 mL) and sat. aq. NH\textsubscript{4}Cl (20 mL). The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 40 mL), the completeness was checked by TLC of the fractions. The combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}) and evaporated in vacuo. Column chromatography (silica; CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 19:1) afforded 68 as a colorless, crystalline solid (278 mg, 1.14 mmol, 57 %)

mp.: 231.5-233.2 °C

\textsuperscript{1}H-NMR (dmsod\textsubscript{6}, 400 MHz): \(\delta [ppm] = 10.88 \text{ (s, 1 H)}; 10.70 \text{ (s, 1 H)}; 7.34-7.20 \text{ (m, 5 H)}; 3.75 \text{ (s, 2 H)}; 2.80 \text{ (sept, } ^3J = 6.9 \text{ Hz, 1 H)}; 1.05 \text{ (d, } ^3J = 6.9 \text{ Hz, 6 H)}.

\textsuperscript{13}C-NMR (dmsod\textsubscript{6}, 100 MHz): \(\delta [ppm] = 163.8; 150.9; 148.4; 137.0; 128.6; 128.0; 126.6; 113.9; 35.2; 26.4; 20.1.

IR (KBr): \(\nu [cm^{-1}] = 3108 \text{ (m)}; 3090 \text{ (m)}; 3068 \text{ (m)}; 3034 \text{ (m)}; 2980 \text{ (m)}; 2958 \text{ (m)}; 2942 \text{ (m)}; 2926 \text{ (m)}; 2868 \text{ (w)}; 2826 \text{ (w)}; 1726 \text{ (s)}; 1682 \text{ (m)}; 1640 \text{ (vs)}; 1620 \text{ (s)}; 1604 \text{ (s)}; 1586 \text{ (m)}; 1506 \text{ (m)}; 1496 \text{ (m)}; 1460 \text{ (s)}; 1440 \text{ (s)}; 1410 \text{ (s)}; 1376 \text{ (m)}; 1358 \text{ (m)}; 1328 \text{ (w)}; 1314 \text{ (w)}; 1290 \text{ (m)}; 1278 \text{ (m)}; 1242 \text{ (w)}; 1192 \text{ (m)}; 1170 \text{ (w)}; 1156 \text{ (m)}; 1112 \text{ (w)}; 1086 \text{ (m)}; 1046 \text{ (w)}; 1032 \text{ (m)}; 986 \text{ (w)}; 934 \text{ (w)}; 898 \text{ (w)}; 802 \text{ (s)}; 776 \text{ (s)}; 756 \text{ (s)}; 724 \text{ (s)}; 702 \text{ (vs)}; 640 \text{ (m)}; 626 \text{ (w)}; 612 \text{ (m)}.

MS (EI): \(m/z (\%) = 244 (M^+; 51); 299 (100); 186 (14); 153 (4); 118 (4); 91 (13); 69 (11).

HR-MS (C\textsubscript{14}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2}): calculated: 244.1212 found: 244.1222.

\textsuperscript{103} Prepared in analogy to CuCN-2LiCl from CuI and LiCl.
7. Diastereoselective Synthesis of Cyclopropane Carbenoids Bearing a Nitrile Function

7.1. Exchange on 2,2-Dibromo-1-methylcyclopropanecarbonitrile (76) and Subsequent Reactions with Electrophiles

Synthesis of 2-bromo-1-methylcyclopropanecarbonitrile (81b)

According to TP16, the magnesium carbenoid 80 was prepared from 2,2-dibromo-1-methylcyclopropanecarbonitrile (76; 478 mg, 2.00 mmol) and at -50 °C quenched by addition of sat. aq. NH₄Cl (2.0 mL, then workup as described in TP16). Flash column chromatography (silica; CH₂Cl₂) afforded 81b as a colorless oil (243 mg, 1.52 mmol, 76%; d.r.: > 99:1).

\[\text{Me} \text{ NC} \text{Br}\]

1H-NMR (CDCl₃, 300 MHz): \(\delta\) [ppm] = 3.45 (dd, \(^3J = 5.7\) Hz, \(^2J = 8.4\) Hz, 1 H); 1.86 (dd, \(^2J = 6.9\) Hz, \(^3J = 8.4\) Hz, 1 H); 1.53 (s, 1H); 1.09 (dd, \(^2J = 6.9\) Hz, \(^3J = 5.7\) Hz, 1 H).

13C-NMR (CDCl₃, 75 MHz): \(\delta\) [ppm] = 121.4; 25.6; 23.6; 18.4; 9.7.

The relative configuration was determined by 2D NMR experiments (HSQC, NOESY), see also discussion.

IR (KBr): \(\nu [\text{cm}^{-1}] = 3452\) (w); 3093 (m); 3065 (m); 2979 (m); 2939 (m); 2876 (w); 2239 (vs); 1725 (m); 1600 (w); 1458 (s); 1434 (s); 1386 (m); 1310 (s); 1273 (m); 1212 (s); 1087 (m); 1052 (m); 936 (m); 893 (s); 832 (m); 665 (m); 639 (s); 536 (m).

MS (EI): (m/z) [%] = 162 ([M+1H]+; 81 Br; 1); 160 ([M+1H]+; 79 Br; 1); 146 (5); 144 (5); 108 (2); 106 (2); 95 (2); 93 (2); 81 (6); 80 (100); 64 (4); 53 (76); 52 (5); 51 (6).

HR-MS (C₅H₇BrN; [M+1H]+): calculated: 159.9762; found: 159.9756.

Synthesis of 2-bromo-1-methyl-2-(phenylsulfanyl)cyclopropane-carbonitrile (81e)

According to TP16, the magnesium carbenoid 80 was prepared from 2,2-dibromo-1-methylcyclopropanecarbonitrile (76; 478 mg, 2.00 mmol) and at -50 °C reacted with PhSSO₂Ph (600 mg, 2.40 mmol, 1.20 equiv). Column chromatography (silica; CH₂Cl₂/pentane 1:1) afforded 81e as a colorless, crystalline solid (461 mg, 1.72 mmol, 86%; d.r.: 95:5).

\[\text{Me} \text{ NC} \text{SPh} \text{Br}\]

mp.: 65.0-66.0 °C

1H-NMR (CDCl₃, 300 MHz): \(\delta\) [ppm] = 7.57 (m, 5 H); 2.07 (d, \(^3J = 7.0\) Hz, 1 H); 1.71 (s, 3 H); 1.65 (d, \(^3J = 7.0\) Hz, 1 H).

13C-NMR (CDCl₃, 75 MHz): \(\delta\) [ppm] = 132.0; 130.9; 129.1; 128.2; 119.4; 42.9; 32.7; 23.0; 22.1.

IR (KBr): \(\nu [\text{cm}^{-1}] = 3131\) (w); 3080 (m); 3066 (w); 3001 (w); 2981 (w); 2934 (w); 2234 (s); 1949 (w); 1884 (w); 1866 (w); 1799 (w); 1733 (w); 1642 (w); 1584 (s); 1483 (s); 1450 (m); 1441 (m); 1430 (m); 1384 (m); 1302 (m); 1249 (w); 1185 (w); 1159 (w); 1087 (m); 1075 (m);
1048 (m); 1025 (m); 986 (m); 967 (m); 952 (m); 899 (w); 831 (w); 742 (vs); 699 (m); 690 (s); 673 (m); 616 (w); 608 (w); 480 (w); 460 (w).

**MS (EI):** (m/z) (%) = 269 (M⁺); 267 (M⁺); 189 (14); 188 (100); 173 (5); 172 (5); 161 (33); 154 (6); 135 (7); 134 (31); 131 (8); 130 (70); 129 (4); 121 (42); 111 (5); 109 (32); 91 (12); 87 (11).

**HR-MS** (C₁₁H₁₀BrNS): calculated: 266.9717  found: 266.9745.

**Synthesis of 2-bromo-2-[(diethylamino)methyl]-1-methylcyclo-propanecarbonitrile (81f)**

According to TP16, the magnesium carbenoid 80 was prepared from 2,2-dibromo-1-methylcyclopropanecarbonitrile (76; 478 mg, 2.00 mmol) and at -50 °C reacted with N-(1H-1,2,3-benzotriazol-1-ylmethyl)-N,N-diaethylamine (490 mg, 2.40 mmol, 1.20 equiv). Column chromatography (silica; pentane/Et₂O 9:1) afforded 81f as a colorless oil (389 mg, 1.58 mmol, 79 %; d.r.: 96:4).

**¹H-NMR (CDCl₃, 300 MHz):** δ [ppm] = 3.02 (d, ²J = 14.7 Hz, 1 H); 2.88 (d, 1 H, ²J = 14.7 Hz); 2.66 (q, ³J = 7.2 Hz, 4 H); 1.79 (d, ³J = 6.8 Hz, 1 H); 1.65 (s, 3 H); 1.29 (d, ³J = 6.8 Hz, 1 H); 1.02 (t, ³J = 7.2 Hz, 6 H).

**¹³C-NMR (CDCl₃, 75 MHz):** δ [ppm] = 120.3; 60.9; 46.1; 42.9; 28.4; 15.5; 21.4; 11.1.

**IR (KBr):** ν [cm⁻¹] = 3086 (w); 271 (vs); 2936 (s); 2874 (m); 2812 (m); 2236 (m); 1455 (m); 1385 (m); 1344 (w); 1295 (w); 1207 (m); 1184 (m); 1145 (w); 1070 (s); 1004 (w); 955 (w); 898 (w); 771 (m); 680 (w); 663 (w); 575 (w).

**MS (EI):** (m/z) (%) = 246 (M⁺); 244 (M⁺); 231 (21); 229 (24); 149 (3); 135 (7); 92 (3); 87 (4); 86 (100); 65 (3); 58 (12); 56 (5); 42 (5).

**HR-MS** (C₁₁H₁₀BrNS): calculated: 244.0575  found: 244.0574.

**Synthesis of 2-allyl-2-bromo-1-methylcyclopropanecarbonitrile (81a)**

According to TP16, the magnesium carbenoid 80 was prepared from 2,2-dibromo-1-methylcyclopropanecarbonitrile (76; 478 mg, 2.00 mmol) at -50 °C, allyl bromide (290 mg, 2.40 mmol, 1.20 equiv) and subsequently CuCN·2LiCl (1.0 M in THF; 0.01 mL; 0.50 mol%) was added. After 5 min at -50 °C, the solution was warmed up to rt; after standard workup, column chromatography (silica; pentane/CH₂Cl₂ 9:1) afforded 81a as a colorless oil (311 mg, 1.56 mmol, 79 %; d.r.: > 99:1).

**¹H-NMR (CDCl₃, 300 MHz):** δ [ppm] = 5.93 (m, 1 H); 5.25 (m, 2 H); 2.76 (d, ³J = 6.7 Hz, 2 H); 1.65 (s, 3 H); 1.59 (d, ³J = 7.0 Hz, 1 H); 1.29 (d, ³J = 7.0 Hz, 1 H).

**¹³C-NMR (CDCl₃, 75 MHz):** δ [ppm] = 133.3; 120.8; 119.5; 45.2; 43.4; 30.0; 21.8; 16.9.

**IR (KBr):** ν [cm⁻¹] = 3084 (m); 2981 (m); 2937 (s); 2237 (vs); 1644 (m); 1430 (s); 1385 (m); 1320 (w); 1290 (w); 1259 (w); 1146 (m); 1041 (m); 993 (s); 926 (s); 898 (w); 771 (m); 641 (w).
**MS (EI):** (m/z) (%) = 200 (M⁺; 3); 160 (5); 158 (5); 134 (91); 132 (100); 120 (9); 104 (5); 93 (19); 91 (11); 77 (12); 67 (7); 65 (7); 53 (15); 41 (7).

**HR-MS (C₈H₁₀BrN):** calculated: 198.9997    found: 198.9984.

### 7.2. Reactions of Carbenoid 80 with Different Benzaldehydes

**General:** The ring closure in case of products of type 83 and the uncyclized alcohol in case of products of type 84 are clearly shown by $^{13}$CNMR data (signal of the carbonyl group at around 174 ppm (83) compared to the nitrile signal at 113 ppm (84)) and high resolution mass spectra. In the IR experiments in both cases the nitrile function (expected at around 2200 cm$^{-1}$) is missing and the spectrum shows instead a strong bend in the carbonyl-region. Presumably, in case of the free alcohols, this is due to cyclization of the compound during preparation of the KBr pellet, induced by humidity in the KBr and mechanical energy.

For the reactions, it should be pointed out that vigorous stirring is essential as after addition of the aldehydes a slurry forms immediately and one may loose conversion if the reaction is not well mixed all the time.

**Reaction of carbenoid 80 with benzaldehyde: synthesis of 83a and 84a**

According to TP16, the magnesium carbenoid 80 was prepared from 2,2-dibromo-1-methylcyclopropanecarbonitrile (76; 478 mg, 2.00 mmol) and at −50 °C reacted with benzaldehyde (254 mg, 2.40 mmol, 1.20 equiv). Column chromatography (silica; CH$_2$Cl$_2$/Et$_2$O gradient 99:1 to 1:1) affor ded the products 83a and 84a as colorless, crystalline solids (83a: 176 mg, 0.66 mmol, 33%; 84a: 186 mg, 0.70 mmol, 35%).

**Analytical data of compound 83a:**

mp.: 98.3-98.8 °C

$^1$H-NMR (CDCl$_3$, 300 MHz): δ [ppm] = 7.43 (m, 5 H); 5.76 (s, 1 H); 1.56 (m, 4 H); 1.27 (d, J = 6.4 Hz, 1 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): δ [ppm] = 174.5; 134.8; 128.9; 128.7; 125.7; 83.7; 41.3; 29.9; 24.6; 13.2.

**IR (KBr):** ν [cm$^{-1}$] = 3523 (w); 3079 (m); 3057 (m); 3033 (m); 2979 (m); 2938 (m); 1963 (w); 1889 (w); 1790 (vs); 1605 (w); 1585 (w); 1500 (m); 1451 (m); 1442 (m); 1386 (w); 1361 (w); 1350 (w); 1308 (s); 1294 (s); 1204 (w); 1162 (w); 1127 (s); 1084 (w); 1059 (w); 1043 (m); 1036 (m); 1020 (s); 972 (w); 920 (w); 885 (m); 865 (w); 830 (w); 780 (w); 762 (w); 745 (s); 702 (s); 678 (w); 632 (m); 618 (w); 600 (m); 481 (m).

**MS (EI):** (m/z) (%) = 268 (M$^+$; $^{81}$Br; 7); 266 (M$^+$; $^{79}$Br; 7); 187 (43); 160 (6); 159 (56); 141 (11); 131 (9); 129 (8); 128 (27); 127 (6); 118 (11); 115 (15); 105 (16); 91 (8); 81 (13); 77 (18); 69 (100); 53 (22); 51 (11); 41 (13).

**HR-MS (C$_{12}$H$_{11}$BrO$_2$):** calculated: 265.9942    found: 265.9914.
Analytical data of compound 84a:
mp.: 110.0-111.5°C

$^1$H-NMR (CDCl$_3$, 300 MHz): δ [ppm] = 7.36 (m, 2 H); 7.17 (m, 3 H); 5.32 (s, 1 H); 1.63 (d, $^3$J = 5.8 Hz, 1 H); 1.60 (s, 3 H); 1.47 (d, $^3$J = 5.8 Hz, 1 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): δ [ppm] = 138.6; 129.2; 128.5; 127.2; 112.6; 85.9; 43.3; 29.7; 28.3; 14.4.

IR (KBr): ν [cm$^{-1}$] = 3284 (m); 3060 (w); 3032 (w); 2968 (w); 2927 (w); 1783 (w); 1702 (vs); 1654 (w); 1496 (w); 1456 (w); 1388 (w); 1366 (m); 1350 (m); 1322 (m); 1272 (w); 1194 (s); 1074 (w); 1052 (w); 1012 (s); 970 (m); 951 (s); 914 (m); 864 (m); 823 (w); 774 (m); 752 (m); 715 (m); 699 (m); 624 (w); 589 (w); 545 (w); 493 (w); 418 (w).

MS (EI): (m/z) (%) = 267 (M$^+$+Br; 81); 265 (M$^+$+Br; 79; 14); 200 (100); 198 (99); 186 (68); 158 (24); 143 (53); 142 (14); 141 (27); 133 (15); 128 (62); 118 (41); 105 (16); 91 (14); 80 (15); 77 (24); 68 (16); 53 (19); 51 (16).

HR-MS (C$_{12}$H$_{12}$BrNO): calculated: 265.0102 found: 265.0097.

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Reaction of carbenoid 2 with 4-cyanobenzaldehyde: synthesis of 83b and 84b

According to TP16, the magnesium carbenoid 80 was prepared from 2,2-dibromo-1-methylcyclopropanecarbonitrile (76; 478 mg, 2.00 mmol) and at –50 °C reacted with para-cyanobenzaldehyde (314 mg, 2.40 mmol, 1.20 equiv). Column chromatography (silica; CH$_2$Cl$_2$/Et$_2$O gradient 39:1 to 1:1; afterwards washing with EtOAc) afforded 83b as a colorless, crystalline solid and 84b as a very viscous, colorless resin (83b: 185 mg, 0.64 mmol, 32 %; 84b: 204 mg, 0.70 mmol, 35 %).

Analytical data of compound 83b:
mp.: 130-132.5 °C

$^1$H-NMR (CDCl$_3$, 300 MHz): δ [ppm] = 7.72 (d, $^3$J = 8. 5 Hz, 2 H); 7.59 (d, $^3$J = 8. 5 Hz, 2 H); 5.76 (s, 1 H); 1.55 (s, 3 H); 1.44 (d, $^3$J = 6.5 Hz, 1 H); 1.27 (d, $^3$J = 6.5 Hz, 1 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): δ [ppm] = 173.7; 140.1; 132.5; 126.4; 118.2; 113.0; 82.6; 40.5; 30.0; 24.4; 13.1.

IR (KBr): ν [cm$^{-1}$] = 3094 (w); 3072 (w); 2980 (w); 2230 (m); 1784 (vs); 1610 (m); 1544 (w); 1504 (w); 1460 (w); 1442 (w); 1413 (w); 1384 (w); 1358 (w); 1302 (m); 1207 (w); 1124 (s); 1066 (w); 1042 (w); 1026 (s); 1015 (s); 972 (w); 922 (w); 896 (m); 868 (w); 841 (w); 826 (m); 773 (m); 736 (w); 677 (w); 608 (w); 597 (w); 549 (m); 514 (w); 428 (w).

MS (EI): (m/z) (%) = 293 (M$^+$+Br; 81); 291 (M$^+$+Br; 79; 14); 212 (25); 184 (100); 168 (25); 166 (12); 153 (28); 143 (32); 140 (16); 130 (30); 102 (15); 81 (12); 69 (84); 53 (25); 41 (11).

HR-MS (C$_{12}$H$_{10}$BrNO$_2$): calculated: 265.0102 found: 265.0097.

Analytical data of compound 84b:

$^1$H-NMR (CDCl$_3$, 300 MHz): δ [ppm] = 7.67 (d, $^3$J = 8.7 Hz); 7.29 (d, $^3$J = 8.7 Hz); 5.35 (s, 1 H); 1.65 (d, $^3$J = 6.0 Hz, 1 H); 1.57 (s, 3 H); 1.49 (d, $^3$J = 6.0 Hz, 1 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): δ [ppm] = 143.6; 132.3; 127.8; 118.2; 113.0; 112.5; 84.5; 42.6; 29.5; 28.3; 14.3.
IR (KBr): ν [cm⁻¹] = 3284 (m); 3060 (w); 3032 (w); 2968 (w); 2927 (w); 1783 (w); 1702 (vs); 1654 (w); 1496 (w); 1456 (m); 1441 (w); 1388 (w); 1366 (m); 1350 (m); 1322 (m); 1272 (w); 1194 (s); 1074 (w); 1052 (w); 970 (m); 951 (s); 914 (m); 864 (m); 823 (w); 774 (m); 752 (m); 699 (m); 624 (w); 589 (w); 545 (w); 493 (w); 418 (w).

MS (EI): (m/z) (%) = 293 ([M+1H]+; 81Br; 4); 291 ([M+1H]+; 79Br; 4); 212 (13); 184 (51); 168 (18); 166 (12); 162 (7); 156 (7); 153 (23); 143 (24); 141 (10); 140 (16); 130 (23); 115 (8); 102 (18); 81 (17); 69 (100); 53 (38); 51 (10); 41 (21).

HR-MS (C₁₃H₁₂BrN₂O; [M+1H]+): calculated: 291.0133 found: 291.0109.

Reaction of carbenoid 80 with 4-bromobenzaldehyde: synthesis of 83c and 84c

According to TP16, the magnesium carbenoid 80 was prepared from 2,2-dibromo-1-methylcyclopropanecarbonitrile (76; 478 mg, 2.00 mmol) and at –50 °C reacted with para-bromobenzaldehyde (444 mg, 2.40 mmol, 1.20 equiv). Column chromatography (silica; CH₂Cl₂/Et₂O gradient 39:1 to 1:1) afforded the products 83c and 84c as colorless, crystalline solids (83c: 222 mg, 0.64 mmol, 32 %; 84c: 201 mg, 0.58 mmol, 35 %).

Analytical data of compound 83c:
mp.: 78.0-79.5 °C.

¹H-NMR (CDCl₃, 300 MHz): δ [ppm] = 7.54 (d, 3J = 8.5 Hz, 2 H); 7.32 (d, 3J = 8.5 Hz, 2 H); 5.69 (s, 1 H); 1.53 (s, 3 H); 1.48 (d, 3J = 6.8 Hz, 1 H); 1.27 (d, 3J = 6.8 Hz, 1 H).

¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] = 174.1; 133.8; 131.9; 127.3; 123.0; 83.0; 40.9; 29.9; 24.4; 13.1.

IR (KBr): ν [cm⁻¹] = 2927 (w); 2854 (w); 1775 (vs); 1678 (br); 1593 (w); 1487 (m); 1444 (w); 1410 (w); 1365 (w); 1311 (m); 1279 (w); 1104 (s); 1072 (m); 1039 (m); 991 (s); 945 (w); 873 (w); 835 (m); 776 (w); 743 (w); 665 (w); 604 (w); 542 (w); 505 (w); 428 (w).

MS (EI): (m/z) (%) = 348 (M⁺; 2 × 81Br; 41); 346 (M⁺; 79Br + 81Br; 89); 344 (M⁺; 2 × 79Br; 43); 280 (39); 278 (82); 276 (41); 266 (35); 264 (32); 239 (84); 237 (88); 196 (23); 185 (42); 183 (41); 158 (37), 142 (83); 141 (50); 115 (40); 69 (100); 53 (50).

HR-MS (C₁₂H₁₀Br₂O₂): calculated: 343.9048 found: 343.9037.

Analytical data of compound 84c:
mp.: 80.0-81.0 °C.

¹H-NMR (CDCl₃, 300 MHz): δ [ppm] = 7.54 (d, 3J = 8.2 Hz, 2 H); 7.08 (d, 2 H, 3J = 8.2 Hz); 5.32 (s, 1 H); 1.66 (d, 1 H, 3J = 6.0 Hz); 1.61 (s, 3 H); 1.50 (d, 1 H, 3J = 6.0 Hz).

¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] = 137.6; 131.7; 128.8; 123.3; 112.6; 85.11; 43.0; 29.7; 28.3; 14.4.

IR (KBr): ν [cm⁻¹] = 3282 (w); 2927 (w); 1780 (w); 1694 (vs); 1591 (w); 1487 (m); 1442 (w); 1410 (w); 1364 (m); 1321 (m); 1196 (m); 1071 (m); 1025 (m); 1010 (s); 970 (m); 954 (m); 937 (m); 870 (m); 826 (s); 753 (w); 594 (w); 493 (w).

MS (EI): (m/z) (%) = 347 (M⁺; 2 × 81Br; 13); 345 (M⁺; 79Br + 81Br; 26); 343 (M⁺; 2 × 79Br; 13); 280 (46); 278 (100); 276 (48); 266 (33); 264 (34); 236 (11); 198 (11); 196 (13); 185 (15); 157 (15), 142 (62); 141 (32); 115 (27); 80 (13); 68 (20); 53 (14).
7.3. Diastereoselective Constructions of Quarternary Centers

Synthesis of allyl-1-methyl-2-(phenylsulfanyl)cyclopropanecarbonitrile (85a)

Synthesized according to TP17 using allyl bromide (726 mg, 6.00 mmol, 1.20 equiv) as electrophile. After flash column chromatography (silica; pentane/Et₂O 19:1), the product (85a) was isolated as a colorless oil (813 mg; 3.55 mmol; 71%).

¹H-NMR (CDCl₃, 300 MHz): δ [ppm] = 7.47 (m, 2 H); 7.30 (m, 3 H); 5.93 (m, 1 H); 5.09 (m, 2 H); 2.39 (m, 1 H); 2.25 (m, 1 H); 1.59 (d, 3J = 6.1 Hz, 1 H); 1.56 (s, 3 H); 1.06 (d, 3J = 6.1 Hz, 1 H).

¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] = 133.9; 132.9; 131.5; 129.1; 127.5; 122.2; 118.0; 36.5; 36.0; 27.3; 20.5; 17.9.

The relative configuration was determined by 2D NMR experiments (COSY, NOE); see also discussion.

IR (KBr): ν [cm⁻¹] = 3436 (br); 3078 (m); 3003 (m); 2979 (m); 2938 (m); 2235 (s); 1738 (w); 1642 (m); 1584 (m); 1480 (w); 1440 (w); 1386 (w); 1261 (w); 1150 (w); 1084 (m); 1075 (m); 995 (m); 964 (w); 919 (s); 742 (vs); 692 (vs); 568 (w).

MS (EI): (m/z) (%) = 229 (M⁺; 59); 214 (21); 196 (17); 188 (15); 175 (16); 161 (38); 149 (30); 147 (21); 135 (25); 134 (32); 131 (21); 130 (24); 129 (23); 128 (18); 120 (64); 110 (100); 109 (57); 104 (16); 99 (27); 93 (30); 91 (36); 85 (50); 77 (49); 65 (31); 51 (14); 41 (16).

HR-MS (C₁₂H₁₁Br₂NO): calculated: 342.9207  found: 342.9197.

Synthesis of 1-methyl-2-(2-methyl-2-propenyl)-2-(phenylsulfanyl)cyclopropane-carbonitrile (85b)

Synthesized according to TP17 using methallyl bromide (810 mg, 6.00 mmol, 1.20 equiv) as electrophile. After flash column chromatography (silica; pentane/Et₂O 19:1), the product (85b) was isolated as a colorless oil (851 mg; 3.50 mmol; 70%).

¹H-NMR (CDCl₃, 300 MHz): δ [ppm] = 7.45 (m, 2 H); 7.30 (m, 3 H); 4.99 (s, 1 H); 4.66 (s, 1 H); 2.43 (d, 1 H, 3J = 16.2 Hz); 2.19 (d, 1 H, 3J = 16.2 Hz); 1.76 (s, 3 H); 1.64 (d, 1 H, 3J = 6.1 Hz); 1.55 (s, 3 H); 1.10 (d, 1 H, 3J = 6.1 Hz).

¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] = 141.1; 133.2; 131.4; 127.4; 122.3; 114.2; 39.3; 35.0; 27.5; 22.5; 20.5; 19.0; 18.1.
The relative configuration was determined by 2D NMR experiments (COSY, NOE); see also discussion.

**IR (KBr):** \( \nu \text{[cm}^{-1}] = 3077 \text{ (m); 2970 (m); 2938 (m); 2235 (s); 1953 (w); 1798 (w); 1798 (w); 1731 (w); 1651 (m); 1584 (m); 1480 (s); 1440 (vs); 1375 (m); 1286 (w); 1260 (w); 1228 (w); 1156 (w); 1082 (m); 1025 (m); 959 (w); 895 (w); 741 (vs); 692 (vs); 610 (w); 566 (w). \\

**MS (EI):** (m/z) (%) = 243 (M\(^+\); 18); 229 (7); 228 (48); 201 (8); 188 (10); 161 (17); 147 (9); 135 (11); 134 (14); 130 (10); 118 (16); 113 (21); 111 (20); 109 (19); 107 (55); 99 (32); 91 (24); 79 (28); 77 (22); 65 (12).

**HR-MS (Cl\(_3\)H\(_7\)NS):** calculated: 243.1082 found: 243.1059.

**Synthesis of 2-allyl-1-methyl-2-(phenylsulfinyl)cyclopropanecarbonitrile (86a)**

\[
\text{Me}\_3\text{C} \quad \begin{array}{c|c} \text{NC} & \text{SOPh} \\ \hline \text{meta-ClO}_{2}\text{C} \quad \text{SO}_{2}\text{Ph} \\ \end{array}
\]

Meta-chloroperbenzoic acid (1.12 g, 3.68 mmol, 1.05 equiv; wet, 75% w/w) was dissolved in dichloromethane (7 mL). The resulting solution was cooled to 0 °C and at this temperature dried 20 min over anhydrous sodium sulfate under vigorous stirring. The solution was filtered and subsequently added dropwise to a solution of allyl-1-methyl-2-(phenylsulfanyl)cyclopropanecarbonitrile (85a; 802 mg, 3.50 mmol) in dichloromethane (3.5 mL) at -50 °C. After addition, the reaction was allowed to warm up to room temperature. TLC monitoring showed complete conversion after 30 min. 2 M NaOH (10 mL) was added and the aqueous layer was extracted with ethyl acetate (4 x 10 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo. The crude product was subsequently subjected to column chromatography (silica; gradient CHCl\(_3\)/EtOAc, 39:1 to 19:1; two diastereoisomers are obtained due to the unsel ective formation of the sulfoxide, both showing cis-configuration of the cyano- and the sulfur substituent). The product (86a) was obtained as a very viscous, colorless oil (660 mg, 2.70 mmol, 77%).

**1H-NMR (CDCl\(_3\), 300 MHz)** (mixture of two diastereoisomers; the signals of these compounds are assigned as (d1) and (d2)); \( \delta \text{[ppm]} = 7.83 \text{ (m, 2 H, (d1)); 7.66 (m, 2 H, (d2)); 7.54 (m, 3 H, (d1)+(d2)); 5.37 (m, 1 H, (d1)+(d2)); 4.90 (m, 2 H, (d1)); 4.74 (m, (d2)); 2.89 (m, 1 H, (d2)); 2.53 (m, 1 H, (d1)); 2.15 (m, 2 H, (d1)+(d2)); 1.79 (d, 3\(^J\) = 6.7 Hz, 1 H, (d1)); 1.51 (s, 3 H, (d2)); 1.45 (s, 3 H, (d1)); 1.29 (d, 3\(^J\) = 6.7 Hz, 1 H, (d1)); 1.10 (d, 3\(^J\) = 6.7 Hz, 1 H, (d2)).

**13C-NMR (CDCl\(_3\), 75 MHz):** \( \delta \text{[ppm]} = 141.0 \text{ (d2); 140.0 (d1); 133.7 (d2); 133.7 (d1); 131.6 (d2); 131.6 (d1); 129.3 (d1); 129.2 (d2); 124.9 (d1); 24.8 (d2); 121.0 (d1); 120.0 (d2); 118.6 (d1); 118.2 (d2); 49.1 (d2); 48.9 (d1); 28.2 (d1); 25.9 (d2); 23.7 (d1); 21.5 (d2); 17.9 (d2); 17.6 (d2); 17.4 (d1); 14.8 (d1). \\

The cis-configuration of the cyano- and the sulfur substituent was proven by 2D NMR experiments (COSY, NOESY); see also discussion.

**IR (KBr):** \( \nu \text{[cm}^{-1}] = 4057 \text{ (w); 3493 (br); 3079 (m); 2999 (m); 2980 (m); 2939 (m); 2603 (w); 2326 (w); 2234 (s); 2132 (w); 1979 (w); 1897 (w); 1834 (w); 1729 (w); 1640 (m); 1582 (m); 1478 (m); 1456 (m); 1444 (s); 1428 (m); 1387 (m); 1330 (w); 1289 (w); 1260 (w); 1175 (w); 1159 (w); 1127 (w); 1987 (vs); 1049 (vs); 1022 (m); 999 (s); 968 (m); 922 (s); 866 (w); 785 (w); 752 (vs), 714 (m); 692 (s); 666 (w); 596 (m); 571 (m); 522 (m); 461 (m).

**MS (EI):** (m/z) (%) = 245 (M\(^+\); 1); 228 (2); 204 (2); 196 (3); 181 (1); 169 (6); 154 (14); 135 (7); 130 (12); 129 (9); 127 (14); 126 (100); 125 (97); 120 (10); 117 (12); 110 (13); 109 (14); 97 (21); 93 (37); 91 (33); 78 (64), 77 (65); 67 (11); 66 (18); 65 (20); 53 (17); 51 (26); 41 (44).
Synthesis of 1-methyl-2-(2-methyl-2-propenyl)-2-(phenylsulfinyl)cyclopropane-carbonitrile (86b)

86b was prepared according to the oxidation procedure described above starting from 1-methyl-2-(2-methyl-2-propenyl)-2-(phenylsulfanyl)cyclopropane-carbonitrile (85b; 648 mg, 2.50 mmol) and was obtained as a viscous, slightly yellow oil (571 mg, 2.20 mmol, 88%; two diastereoisomers are obtained due to the unselective formation of the sulfoxide, both showing cis-configuration of the cyano- and the sulfur substituent).

\[ \begin{align*}
\text{Me}_2\text{C} & \text{NC} & \text{SO}_\text{Ph} \\
\text{Me} & & \\
\end{align*} \]

\[ \text{i-PrMgCl (2.56 M in Et}_2\text{O; 0.55 mL, 1.43 mmol, 1.10 equiv) was added dropwise to a solution of 2-allyl-1-methyl-2-(phenylsulfanyl)cyclopropanecarbonitrile (86a; 350 mg, 1.30 mmol) in dichloromethane (4.0 mL) at -50°C and stirred for 10 min at this temperature. Then, methallyl} \]
bromide (243 mg, 1.56 mmol, 1.20 equiv) and subsequently CuCN·2LiCl (1.0 M in THF; 5.00 μL; 0.50 mol%) were added and the reaction mixture was allowed to warm up to rt. The reaction was followed by GC-MS-analysis of reaction aliquots. After the conversion was complete, a saturated aqueous solution of ammonium chloride (4.0 mL) was added, and the resulting mixture was extracted with dichloromethane (4 × 5.0 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo. The crude residue was purified by flash column chromatography (silica; pentane:Et₂O, 39:1). The product (87a) was obtained as a volatile, colorless oil (166 mg, 0.94 mmol, 73%; single distereoisomer).

1H-NMR (CDCl₃, 300 MHz): δ [ppm] = 5.71 (m, 1 H); 5.08 (m, 2 H); 4.78 (s, 1 H); 4.87 (s, 1H); 2.47 (d, 2J = 15.2 Hz, 1 Hz); 2.20 (m, 2 H); 2.00 (m, 1 H); 1.75 (s, 3 H); 1.46 (s, 3 H); 1.18 (d, 3J = 5.2 Hz, 1 H); 0.75 (d, 3J = 5.2 Hz, 1 H).

13C-NMR (CDCl₃, 75 MHz): δ [ppm] = 141.9; 134.4; 123.3; 117.8; 113.5; 42.3; 34.4; 28.5; 26.7; 22.5; 17.2; 14.3.

The relative configuration was determined by 2D NMR experiments (COSY, NOE); see also discussion.

IR (KBr): ν [cm⁻¹] = 3078 (m); 2972 (s); 2939 (s); 2231 (vs); 1738 (w); 1642 (m); 1440 (s); 1377 (m); 1288 (w); 1083 (m); 996 (m); 897 (vs); 620 (w); 567 (w).

MS (EI): (m/z) (%) = 174 ([M-1H]+; 2); 160 (5); 134 (7); 119 (5); 118 (5); 108 (19); 107 (11); 105 (4); 104 (6); 93 (100); 91 (27); 80 (16); 79 (31); 77 (17); 66 (5); 41 (8).


Synthesis of 2-allyl-1-methyl-2-(2-methyl-2-propenyl)cyclopropanecarbonitrile (87b)

87b was prepared starting from 1-methyl-2-(2-methyl-2-propenyl)-2-(phenylsulfanyl)cyclopropanecarbonitrile (86b; 319 mg, 1.30 mmol) according to the method described above for 87a, using allyl bromide (189 mg, 1.56 mmol, 1.20 equiv) instead of methallyl bromide. The product was received as a volatile, colorless oil (157 mg, 0.90 mmol, 69%).

1H-NMR (CDCl₃, 300 MHz): δ [ppm] = 5.82 (m, 1 H); 5.11 (m, 2 H); 4.88 (s, 1 H); 4.78 (s, 1 H); 2.30 (brd, 3J = 7.0 Hz, 1 H); 2.16 (d, 2J = 15.7 Hz, 1 H); 2.03 (d, 2J = 15.7 Hz, 1 H); 1.70 (s, 3 H); 1.42 (s, 3 H); 1.19 (d, 3J = 5.3 Hz, 1 H); 0.72 (d, 3J = 5.3 Hz, 1 H).

13C-NMR (CDCl₃, 75 MHz): δ [ppm] = 141.9; 134.8; 123.8; 118.4; 113.8; 39.3; 38.2; 29.2; 27.2; 23.11; 17.9; 14.6.

The relative configuration was determined by 2D NMR experiments (COSY, HSQC, NOESY); see also discussion.

IR (KBr): ν [cm⁻¹] = 3079 (m); 2972 (m); 2939 (s); 2231 (vs); 1722 (w); 1643 (m); 1438 (s); 1376 (m); 1288 (w); 1231 (w); 1083 (m); 996 (m); 895 (vs); 760 (w); 618 (w).

MS (EI): (m/z) (%) = 174 ([M-1H]+; 2); 160 (7); 134 (7); 119 (5); 118 (5); 108 (22); 107 (11); 105 (6); 104 (5); 93 (100); 91 (25); 80 (20); 79 (36); 77 (21); 66 (6); 55 (5); 41 (15).

8. Reactions of Grignard Reagents with Carbonyl Compounds Mediated by LnCl·2LiCl

Throughout the following procedures, LaCl·2LiCl is always used as the lanthanide source. Of course, CeCl·2LiCl or NdCl·2LiCl can be used analogously. The results are comparable in all cases (see discussion).

Synthesis of 1-isopropyl-cyclopentanol (95a)

According to TP18, i-PrMgCl (93a; 1.00 M in THF; 3.30 mL, 3.30 mmol, 1.10 equiv) was reacted with cyclopentanone (94a; 252 mg; 3.00 mmol) in the presence of LaCl·2LiCl (0.33 M; 9.09 mL, 3.00 mmol, 1.00 equiv), the conversion was complete after 5 min (GC monitoring). After workup and careful evaporation of the solvents under reduced pressure, the desired product (95a) was obtained as a colorless oil (353 mg, 2.76 mmol, 92%).

^1H-NMR (dms-o-d₆, 300 MHz): δ [ppm] = 1.81-1.52 (m, 9 H); 1.05 (s, 1 H); 0.93 (d, J = 6.8 Hz, 6 H).
^13C-NMR (dms-o-d₆, 75 MHz): δ [ppm] = 85.2; 38.2; 37.1; 24.0; 17.8.
MS (EI): (m/z) (%) = 128 (M⁺; 2); 110 (1); 99 (15); 95 (5); 100 (85); 71 (13); 67 (43); 57 (23); 55 (10).
The analytical data were found to be in accordance with the literature data.¹⁰⁴

Synthesis of 2-benzyl-3-methyl-1-phenyl-butan-2-ol (95b)

According to TP18, i-PrMgCl (93a; 1.00 M in THF; 1.10 mL, 1.10 mmol, 1.10 equiv) was reacted with 1,3-diphenylacetone (94b; 210 mg; 1.00 mmol) in the presence of LaCl·2LiCl (0.33 M; 3.00 mL, 1.00 mmol, 1.00 equiv), the conversion was complete after 5 min (GC monitoring). After workup and careful evaporation of the solvents under reduced pressure, the desired product (95b) was obtained as a colorless solid (241 mg, 0.95 mmol, 95 %).

mp.: 52–53 °C
^1H-NMR (CDCl₃, 300 MHz): δ [ppm] = 7.36-7.26 (m, 10 H); 2.95 (d, J = 13.8 Hz, 2 H); 2.69 (d, J = 13.8 Hz, 2 H); 1.77 (sept, J = 6.8 Hz, 1 H); 1.33 (s, 1 H); 1.08 (d, J = 6.8 Hz, 1 H).
^13C-NMR (CDCl₃, 75 MHz): δ [ppm] = 137.5; 130.8; 128.1; 126.3; 76.1; 41.5; 33.9; 17.4.

Synthesis of 4-(1-benzyl-1-hydroxy-2-phenyl-ethyl)-benzoic acid ethyl ester (95c)

According to TP18, the Grignard reagent 93c (freshly prepared via iodine-magnesium exchange from ethyl-4-iodobenzoate (607 mg, 2.20 mmol, 1.10 equiv) and i-PrMgCl·LiCl (1.00 M in THF; 2.16 mL, 2.16 mmol, 1.08 equiv) at -20 °C) was reacted with diphenylacetone (420 mg; 2.00 mmol) in the presence of LaCl₃·2LiCl (0.33 M; 6.06 mL, 2.00 mmol, 1.00 equiv), the conversion was complete after 20 min (GC monitoring). The crude product was recrystallized from heptane to give 4-(1-benzyl-1-hydroxy-2-phenyl-ethyl)-benzoic acid ethyl ester (95c) as a crystalline, colorless solid (662 mg, 1.84 mmol, 92 %).

mp.: 126–128 °C

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 7.94 (d, \(^3\)J = 8.5 Hz, 2 H); 7.34 (d, \(^3\)J = 8.5 Hz, 2 H); 6.95 (m, 4 H); 7.15 (m, 6 H); 4.37 (q, \(^3\)J = 7.1 Hz); 3.32 (d, \(^2\)J = 13.5 Hz, 2 H); 3.13 (d, \(^2\)J = 13.5 Hz, 2 H); 1.99 (s, 1 H); 1.39 (t, \(^3\)J = 7.1 Hz, 3 H).

¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 166.6; 150.5; 135.8; 130.6; 129.1; 128.7; 128.0; 126.7; 125.9; 77.2; 60.9; 48.7; 14.3.

IR (KBr): ν/cm⁻¹ = 3500 (m); 3061 (w); 3030 (w); 2978 (w); 2920 (w); 1700 (vs); 1607 (s); 1571 (w); 1499 (m); 1477(m); 1454 (m); 1405 (m); 1371 (s); 1316 (m); 1283 (vs); 1245 (s); 1204 (m); 1185 (m); 1160 (m); 1132 (s); 1113 (s); 1092 (s); 1066 (w); 1038 (m); 1020 (s); 992 (m); 919 (w); 902 (w); 884 (m); 851 (m); 777 (s); 754 (m); 722 (m); 700 (s); 698 (s); 664 (w).

MS (EI): m/z (%) = 361 ([M+H]⁺; < 1); 315 (5); 270 (19); 269 (100); 241 (3); 197 (6); 177 (22); 149 (6); 121 (3); 105 (10); 91 (14); 65 (3).


Synthesis of 4-(1-benzyl-1-hydroxy-2-phenyl-ethyl)-benzonitrile (95d)

MS (EI): (m/z) (%): 254 (M⁺; < 1); 236 (< 1); 211 (6); 193 (9); 163 (74); 145 (23); 129 (2); 119 (26); 105 (7); 91 (100); 77 (4); 71 (13); 65 (12); 51 (2).

The analytical data were found to be in accordance with the literature data.¹⁰⁵

According to TP18, the Grignard reagent 93d (freshly prepared via bromine-magnesium exchange\textsuperscript{30} from 4-bromo-benzonitrile (182 mg, 1.00 mmol) and i-PrMgCl·LiCl (1.00 M in THF; 1.05 mL, 1.05 mmol, 1.05 equiv) at -20 °C) was reacted with diphenylacetone (94b; 210 mg; 1.00 mmol) in the presence of LaCl\textsubscript{3}·2LiCl (0.33 M in THF; 3.03 mL, 1.00 mmol, 1.00 equiv). The crude product was recrystallized from heptane to give the desired product (95d) as a white solid, (268 mg, 0.86 mmol, 86 %).

\textbf{mp.}: 152.8-153.1°C

\textbf{\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3})}: δ [ppm] = 7.54 (d, \textsuperscript{3}J = 8.4 Hz, 2 H); 7.38 (d, \textsuperscript{3}J = 8.4 Hz, 2 H); 7.20-7.15 (m, 6 H); 6.95-6.90 (m, 4 H); 3.28 (d, \textsuperscript{2}J = 13.7 Hz, 2 H); 3.13 (d, \textsuperscript{2}J = 13.7 Hz, 2 H); 2.02 (brs, 1 H).

\textbf{\textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3})}: δ [ppm] = 193.7; 150.9; 135.4; 131.6; 130.5; 128.2; 126.9; 126.7; 110.4; 76.8; 48.5.

\textbf{MS (EI)}: m/z (%) = 313 (M\textsuperscript{+}; < 1); 222 (100); 204 (3); 130 (39); 116 (15); 105 (17); 102 (14); 91 (25); 65 (6); 51 (2).

The analytical data were found to be in accordance with the literature data.\textsuperscript{106}

\textbf{Synthesis of 4-(1-hydroxy-cyclopentyl)-benzonitrile (95e)}

\begin{center}
\begin{tikzpicture}
\node[draw] (a) {OH};
\node[draw, anchor=north west] (b) at (a|-a) {NC};
\end{tikzpicture}
\end{center}

According to TP19, the Grignard reagent 93d (freshly prepared via bromine-magnesium exchange\textsuperscript{30} from 4-bromo-benzonitrile (400 mg, 2.20 mmol, 1.10 equiv) and i-PrMgCl·LiCl (1.00 M in THF; 2.16 mL, 2.16 mmol, 1.08 equiv) at -20 °C) was reacted with cyclopentanone (94a; 168 mg; 2.00 mmol) in the presence of LaCl\textsubscript{3}·2LiCl (0.33 M; 6.06 mL, 2.00 mmol, 1.00 equiv). The crude product was purified by flash column chromatography (silica; pentane:Et\textsubscript{2}O, 7:3) to give the desired product (95e) as a colorless oil (355 mg, 1.90 mmol, 95 %).

\textbf{\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3})}: δ [ppm] = 7.57 (s, 4 H); 2.04 (s, 1 H); 1.89 (m, 8 H).

\textbf{\textsuperscript{13}C-NMR (300 MHz, CDCl\textsubscript{3})}: δ [ppm] = 152.3; 131.9; 125.8; 118.9; 110.2; 83.1; 42.4; 24.0.

\textbf{IR (KBr)}: ν/cm\textsuperscript{-1} = 3436 (br); 2964 (s); 2874 (m); 2229 (vs); 1928 (w); 1725 (w); 1608 (s); 1503 (m); 1449 (w); 1402 (m); 1323 (w); 1183 (w); 1092 (w); 1040 (w); 1010 (s); 960 (w); 906 (w); 884 (w); 837 (s); 567 (s).

\textbf{MS (EI)}: m/z (%) = 187 (M\textsuperscript{+}; 27); 168 (9); 159 (12); 158 (100); 154 (6); 145 (41); 140 (9); 130 (55); 116 (7); 89 (4); 76 (4); 63 (2); 55 (7); 51 (3).

\textbf{HR-MS (C\textsubscript{12}H\textsubscript{13}NO)}: calculated: 187.0997 found: 187.0982.

Synthesis of 2-(6-bromo-pyridin-2-yl)-1-phenyl-propan-2-ol (95f)

According to TP19, the Grignard reagent 93e (freshly prepared via bromine-magnesium exchange from 2,5-dibromopyridine (391 mg, 1.65 mmol, 1.10 equiv) and i-PrMgCl·LiCl (1.00 M in THF; 1.62 mL, 1.62 mmol, 1.08 equiv) at -10 °C) was reacted with 1-phenyl-propan-2-one (94c; 201 mg, 1.50 mmol) in the presence of LaCl₃·2LiCl (0.33 M; 4.55 mL, 1.50 mmol, 1.00 equiv). The crude product was purified by flash column chromatography (silica; pentane:Et₂O, 9:1, 0.20 % (v/v) NEt₃) to give the desired product (95f) as a colorless oil (355 mg, 1.22 mmol, 81 %).

\[
\begin{align*}
\text{H-NMR (300 MHz, CDCl₃): } & \delta \text{ [ppm]} = 7.47 (t, ^3J = 7.8 \text{ Hz}, 1 \text{ H}); 7.34 (d, ^3J = 7.8 \text{ Hz}, 1 \text{ H}); 7.23 (d, ^3J = 7.8 \text{ Hz}, 1 \text{ H}); 7.19 (m, 3 \text{ H}); 6.98 (m, 2 \text{ H}); 3.16 (d, ^2J = 13.5 \text{ Hz}, 1 \text{ H}); 3.03 (d, ^2J = 13.5 \text{ Hz}, 1 \text{ H}); 1.55 (s, 3 \text{ H}). \\
\text{C-NMR (75 MHz, CDCl₃): } & \delta \text{ [ppm]} = 166.7; 140.5; 138.8; 136.6; 130.4; 127.9; 126.5; 126.1; 118.4; 74.8; 49.5; 27.6. \\
\text{IR (KBr): } & \nu/\text{cm}^{-1} = 4062 (w); 3444 (br); 3085 (m); 3062 (m), 3028 (m); 2977 (m), 2922 (m); 2851 (w); 1950 (w); 1885 (w); 1808 (w); 1674 (w); 1581 (s); 1555 (s); 1496 (s); 1454 (s); 1430 (s); 1400 (s); 1307 (s); 1232 (m); 1198 (m); 1159 (s); 1128 (s); 1080 (m); 1055 (m); 1031 (w); 987 (m); 951 (m); 909 (w); 872 (w); 797 (s); 781 (s); 739 (s); 676 (m); 659 (m); 643 (w); 624 (w); 566 (m); 463 (m). \\
\text{MS (EI)}: m/z (%) = 292 (M⁺; < 1); 274 (2); 260 (1); 202 (95); 200 (100); 184 (15); 182 (14); 158 (6); 120 (4); 102 (12); 92 (39); 91 (39); 78 (25); 65 (13); 51 (5). \\
\text{HR-MS (C₁₄H₁₅BrNO)}: \text{calculated} = 292.0337 \text{ found} = 292.0325.
\end{align*}
\]

Synthesis of ethyl 4-(1-hydroxy-1-methyl-2-phenylethyl)-3-nitrobenzoate (95g)

According to TP19, the Grignard reagent 93f (freshly prepared via iodine-magnesium exchange from ethyl-4-iodo-3-nitrobenzoate (353 mg, 1.10 mmol, 1.10 equiv) and PhMgBr·LiCl (0.95 M in THF; 1.13 mL, 1.07 mmol, 1.07 equiv) at -50 °C) was reacted with 1-phenyl-propan-2-one (94d; 134 mg; 1.00 mmol) in the presence of LaCl₃·2LiCl (0.33 M in THF; 3.03 mL, 1.00 mmol, 1.00 equiv). The crude product was purified by flash column chromatography (silica; pentane:Et₂O, 19:1) to give the desired product (95g) as a yellow oil (231 mg, 0.73 mmol, 73 %).

\[
\begin{align*}
\text{H-NMR (300 MHz, CDCl₃): } & \delta \text{ [ppm]} = 8.20 (m, 2 \text{ H}); 7.80 (d, ^3J = 8.1 \text{ Hz}); 7.27 (m, 5 \text{ H}); 4.40 (q, 2 \text{ H}, ^3J = 7.1 \text{ Hz}); 3.66 (s, 1 \text{ H}); 2.00 (s, 3 \text{ H}); 1.39 (t, 2 \text{ H}, ^3J = 7.1 \text{ Hz}). \\
\text{C-NMR (75 MHz, CDCl₃): } & \delta \text{ [ppm]} = 164.1; 145.7; 144.4; 132.4; 131.1; 129.2; 128.4; 127.8; 126.0; 125.3; 112.6; 75.9; 61.9; 42.0; 31.0; 14.2. \\
\text{IR (KBr): } & \nu/\text{cm}^{-1} = 2982 (s); 1724 (vs); 1617 (m); 1542 (vs); 1494 (m); 1448 (m); 1370 (s); 1289 (vs); 1131 (s); 1019 (s); 912 (m); 861 (m); 837 (m); 767 (s); 735 (m); 701 (s); 671 (w). \\
\end{align*}
\]
Synthesis of 2-(2,4,6-trimethyl-phenyl)-propan-2-ol (95h)

(a) From MeMgCl (93g) and 1-(2,4,6-trimethyl-phenyl)-ethanone (94e):
According to TP19, MeMgCl (93g; 2.90 M; 0.76 mL, 2.20 mmol, 1.10 equiv) was reacted with 1-(2,4,6-trimethyl-phenyl)-ethanone (94e; 324 mg, 2.00 mmol) in the presence of LaCl$_3$·2LiCl (0.33 M in THF; 6.06 mL, 2.00 mmol, 1.00 equiv). Flash column chromatography (silica; pentane:Et$_2$O, 9:1) afforded the desired product (95h) as a colorless, crystalline solid, (217 mg, 1.22 mmol, 61 %).

(b) From mesitylmagnesium bromide (93h) and acetone (94h):
Mesitylmagnesium bromide (93h; 1.20 M in THF; 1.83 mL; 2.20 mmol; 1.10 equiv) was placed in a flame dried Schlenk-flask under an argon atmosphere and cooled to 0 °C. At this temperature, LaCl$_3$·2LiCl (0.33 M; 6.06 mL, 2.00 mmol, 1.00 equiv) was slowly added. The resulting mixture was allowed to warm up to room temperature and stirred for 4 h. Then, after cooling to 0 °C, acetone (94h; 116 mg; 2.00 mmol) was added and the reaction was warmed up to room temperature and stirred for another hour at this temperature. When the end of the reaction was reached (GC-monitoring of aliquots), sat. aq. NH$_4$Cl (2.0 mL) and water (2.0 mL) were added. The aqueous layer was extracted with ether (4 × 10 mL), the combined extracts were dried (Na$_2$SO$_4$) and evaporated in vacuo. Column chromatographical purification (silica; pentane:Et$_2$O 9:1) afforded the desired product (95h) as a colorless, crystalline solid (245 mg, 1.38 mmol, 69 %).

mp.: 106-107 °C
$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ [ppm] = 6.83 (s, 2 H); 2.51 (s, 6 H); 2.24 (s, 3 H); 1.72 (s, 6 H).$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ [ppm] = 142.4; 135.8; 135.3; 131.8; 75.8; 31.7; 25.0; 20.2.

MS (EI): (m/z) (%) = 178 (M$^+$; 9); 163 (52); 161 (15); 160 (100); 145 (73); 130 (16); 129 (16); 128 (19); 121 (25); 119 (17); 117 (11); 115 (18); 105 (41); 91 (21); 77 (16); 65 (7); 59 (15); 51 (6).

The analytical data were found to be in accordance with the literature data.$^{107}$

Synthesis of 1-tert-butyl-cyclohexanol (95i)

According to TP19, $t$-BuMgCl·LiCl (93i; 1.01 M in THF 2.18 mL; 2.20 mmol; 1.10 equiv) was reacted with cyclohexanone (94i; 178 mg; 2.00 mmol) in the presence of LaCl$_2$·2LiCl (0.33 M in THF; 6.06 mL, 2.00 mmol, 1.00 equiv). Flash column chromatography (silica; pentane:Et$_2$O, 9:1) afforded the desired product (95i) as colorless oil, which started to crystallize after being chilled (287 mg, 1.84 mmol, 92%).

mp.: 49–50 °C

$^1$H-NMR (dmsos-d$_6$, 300 MHz): $\delta$ [ppm] = 1.64-0.99 (m, 11 H); 0.91 (s, 9 H).

$^{13}$C-NMR (dmsos-d$_6$, 75 MHz): $\delta$ [ppm] = 74.9; 37.7; 30.8; 25.8; 25.0; 22.0.

MS (EI): (m/z) (%) = 156 (M$^+$; < 1); 141 (1); 123 (3); 113 (6); 99 (100); 81 (60); 57 (13); 55 (11).

The analytical data were found to be in accordance with the literature data.  

Synthesis of 1,7,7-trimethyl-2-phenyl-bicyclo[2.2.1]heptan-2-ol (95j)

According to TP19, PhMgBr·LiCl (93k; 1.00 M in THF 1.10 mL, 1.10 mmol, 1.10 equiv) was reacted with 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (94j; 152 mg, 1.00 mmol) in the presence of LaCl$_2$·2LiCl (0.33 M; 3.03 mL, 1.00 mmol, 1.00 equiv) at room temperature. Flash column chromatography (silica; pentane:Et$_2$O, 9:1) afforded the desired product (95j) as colorless oil that solidified upon being chilled (211 mg, 0.92 mmol, 92%).

mp.: 41- 42 °C

$^1$H-NMR (dmsos-d$_6$, 300 MHz): $\delta$ [ppm] = 7.57 (d, $^3$J = 7.8 Hz, 2 H); 7.39-7.27 (m, 3 H); 2.37 (d, $^2$J = 13.9 Hz, 1 H); 2.23 (brd, $^2$J = 13.9 Hz, 1 H); 1.96-1.71 (m, 3 H); 1.32 (s, 3 H); 1.31-1.15 (m, 2 H); 0.96 (t, 6 H); 0.93-0.89 (m, 1 H).

$^{13}$C-NMR (dmsos-d$_6$, 75 MHz): $\delta$ [ppm] = 146.1; 127.5; 126.8; 126.7; 83.6; 53.5; 50.4; 45.6; 45.5; 31.2; 26.6; 21.7; 21.6; 9.8.

MS (EI): (m/z) (%) = 230 (M$^+$; 1); 212 (1); 197 (2), 169 (5); 129 (5); 120 (100); 108 (9); 105 (34); 95 (58); 91 (10); 77 (18); 67 (6); 55 (7).

The analytical data were found to be in accordance with the literature data.  

Synthesis of 1-cyclopentyl-cyclohex-2-enol (97)

According to TP19, cyclopentylmagnesiumbromide/LiCl (1.00 M in THF; 2.10 mL, 2.10 mmol, 1.05 equiv) was reacted with cyclohexenone (96; 192 mg, 2.00 mmol) in the

presence of LaCl$_3$:2LiCl (0.33 M in THF; 6.06 mL, 2.00 mmol, 1.00 equiv). Flash column chromatography (silica; pentane:Et$_2$O 9.1, 0.5 vol-% NEt$_3$) afforded 1-cyclopentyl-cyclohex-2-enol (97) as a colorless oil (306 mg, 1.86 mmol, 93 %).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ [ppm] = 5.82 (m, 1 H); 5.65 (brd, 1 H; J = 10.2 Hz).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ [ppm] = 131.6; 130.4; 112.6; 71.0; 49.7; 41.7; 34.6; 26.9; 26.5; 26.0; 25.4; 18.7.

IR (KBr): $\nu$/cm$^{-1}$ = 3430 (br); 3023 (m); 2948 (vs); 2867 (s); 2833 (m); 1647 (w); 1452 (m); 1438 (m); 1402 (w); 1321 (w); 1172 (m); 1099 (w); 1063 (m); 966 (m); 930 (m); 884 (w); 851 (w); 734 (m); 533 (w).

MS (EI): m/z (%) = 166 (M$^+$; 0.1); 149 (4); 138 (3); 97 (100); 79 (5); 77 (2); 69 (5); 67 (4).

HR-MS (C$_{18}$H$_{18}$O): calculated: 166.1358 found: 166.1363.

Synthesis of 1-(1-naphthyl)cyclopent-2-en-1-ol (99)

According to TP19, naphthylmagnesiumbromide/LiCl (1.00 M in THF; 2.10 mL, 2.10 mmol, 1.05 equiv) was reacted with cyclopentenone (98; 164 mg, 2.00 mmol) in the presence of LaCl$_3$:2LiCl (0.33 M in THF; 6.06 mL, 2.00 mmol, 1.00 equiv). Flash column chromatography (silica; pentane:Et$_2$O 9:1, 0.5 vol-% NEt$_3$) afforded 1-(1-naphthyl)cyclopent-2-en-1-ol (99) as a colorless solid (251 mg, 1.20 mmol, 60 %).

mp.: 111.0-112.0 °C

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ [ppm] = 8.61 (d, $^3$J = 7.9 Hz, 1 H); 7.88-7.85 (m, 1 H); 7.77 (d, $^3$J = 8.0 Hz, 1 H); 7.55-7.45 (m, 2 H); 7.07 (t, $^3$J = 7.9 Hz, 1 H); 6.19 (s, 2 H); 2.75-2.40 (m, 4 H); 2.16 (s, 1 H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ [ppm] = 141.7; 136.6; 134.8; 134.5; 130.8; 128.8; 128.5; 127.0; 125.5; 125.3; 124.7; 122.9; 88.1; 40.2

IR (KBr): $\nu$/cm$^{-1}$ = 3228 (w); 3050 (w); 2970 (w); 2852 (w); 1596 (w); 1508 (w); 1392 (w); 1354 (w); 1260 (w); 1246 (w); 1234 (w); 1182 (w); 1179 (w); 1122 (w); 1106 (m); 1082 (w); 1048 (s); 1020 (w); 990 (w); 968 (m); 948 (w); 916 (m); 868 (m); 830 (w); 780 (s); 768 (s); 756 (m); 744 (m); 684 (w); 662 (m); 628 (w); 574 (m); 562 (m).

MS (EI): m/z (%) = 210 (M$^+$; 72); 192 (100); 191 (94); 181 (9); 178 (8); 165 (56); 155 (10); 128 (13); 127 (13); 95 (17); 82 (8).

HR-MS (C$_{18}$H$_{18}$O): calculated: 210.1045 found: 210.1053.

Control experiment: Synthesis of cyclohex-2-en-1-ol (100)
Cyclopentylmagnesiumbromide/LiCl (1.00 M in THF; 2.10 mL, 2.10 mmol, 1.05 equiv) was added to a solution of cyclohexenone (96; 192 mg, 2.00 mmol) in absolute THF at 0 °C. After 15 min, GC and GC/MS monitoring indicated complete conversion to the reduction product, cyclohexenol (100). Sat. aq. NH₄Cl (2.0 mL) and water (2.0 mL) were added and the aqueous layer was extracted with ether (4 × 10 mL). The combined extracts were dried (Na₂SO₄) and carefully evaporated under reduced pressure. Gel filtration (silica; pentane:Et₂O, 9:1) afforded cyclohex-2-enol (100) as a colorless oil (151 mg, 1.54 mmol, 77 %).

**1H-NMR (CDCl₃, 200 MHz)**: δ [ppm] = 5.88-5.69 (m, 2 H); 4.18 (brs, 1 H); 2.09-1.46 (m, 7 H).

**13C-NMR (CDCl₃, 75 MHz)**: δ [ppm] = 130.3; 130.0; 65.4; 32.0; 25.1; 19.1.

**MS (EI)**: (m/z) (%) = 98 (M⁺; 40); 97 (45); 83 (49); 79 (22); 77 (13); 70 (100); 55 (26).

The analytical data were found to be in accordance with the literature data.¹⁰⁹

9. Data of the X-ray Analysis

Crystallographic data for the cyclopropane 83a
(The crystal was grown by sublimation of the clean product after column chromatography at 50 °C in high vacuum (10⁻² mbar)).

CCDC 275461 contains the supplementary crystallographic data for this compound. These data can be obtained online free of charge from the Cambridge Crystallographic Data Centre (postal address: 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

![Image of cyclopropane 83a structure]

Empirical formula: C₁₂H₁₁BrO₂; \( M_r = 267.12 \), orthorhombic, space group Pna₂₁, \( a = 7.0914(14) \) Å, \( b = 24.615(5) \) Å, \( c = 6.3857(13) \) Å, \( V = 1114.7(4) \) Å³, \( Z = 4 \), \( \rho_{calc} = 1.592 \) g/cm³, MoKα radiation (\( \lambda = 0.71073 \) Å), \( \mu = 3.664 \) mm⁻¹. Data were collected on a NONIUS MACH3 system at 295 K. The structure was solved by direct methods (SHELXS-90, SHELXL-97). All non-hydrogen atoms were refined anisotropically. \( R_1 = 0.0340 \), \( \omega R_2 = 0.0780 \) for all data with \( I > 2\sigma(I) \).
D

APPENDIX
1. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>Ac</td>
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<tr>
<td>Ar</td>
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<td>boiling point</td>
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<td>broad</td>
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<td>Ts</td>
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2. Curriculum Vitae

Felix Kopp

Citizenship: German

Marital Status: single

Languages: German (mother tongue)
            English (fluently)

*27.10.1978 in Augsburg

1984-88 Primary school “Maria Stern/St. Ursula” in Augsburg.

1989-97 High school “Gymnasium bei St. Stephan” in Augsburg.
            06/1997 Graduation (Abitur; main subjects: biology/music;
                        average grade: 1.7)

10/1997-05/2002 Studies in Chemistry at the Ludwig-Maximilians-University,
                    Munich, diploma examinations in 05/2002

05/2002-01/2003 Diploma thesis on the “Synthesis of Functionalized Amines by
                  Reaction of Grignard Reagents with Nitrosobenzene-
                  derivatives” in the group of Prof. Dr. P. Knochel.
                  (Allover diploma average grade: 1.4)

03/2003-02/2007 PhD thesis in the group of Prof. Dr. P. Knochel on the
                  “Preparation and Reactions of Polymagnesiated Aromatics and
                  Heteroaromatics, Functionalized Cyclopropane Carbenoids and
                  Soluble Lanthanide Reagents”
Extracurricular activities: - Music education (violin, viola, concert guitar).

Publications:

Communications


Reviews and Book Chapters


Patent Application

**Poster Presentations**


2. F. Kopp, P. Knochel, “Halogen-Magnesium Exchange on Substrates Bearing Acidic Functionalities” (Poster 14) at the **109th International Summer Course**, July 17th to 13th **2005**, at the **BASF AG** Ludwigshafen, Germany.

**Oral Presentations**

